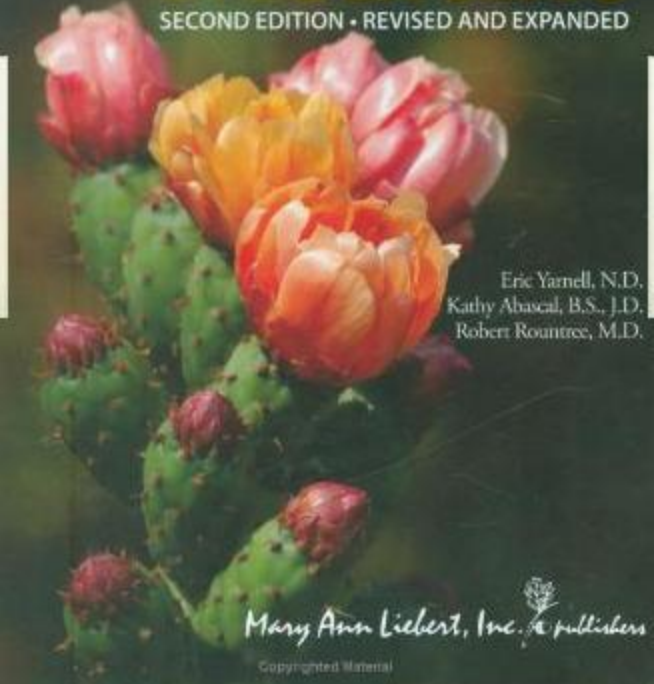
Clinical Botanical Medicine

SECOND EDITION • REVISED AND EXPANDED



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Preface

We have significantly expanded how herbs can be used effectively in common clinical conditions in this second edition of *Clinical Botanical Medicine*. Our objective in the second edition has been to refine and expand the presentation of clinically relevant information on the use of botanicals. Much of the material is entirely new. All material retained from the first edition has been updated, reviewed, and made current. In support of our decision to enhance the clinical relevance of this edition, we deleted all monographs on herbs and focus exclusively on health challenges. Although much can be learned by exploring the whole range of herbal actions that particular herbs possess, we are convinced that busy clinicians are better served if they can focus on herbs that are useful for specific clinical conditions in a way that makes it easier to apply the information provided. Our goal is to enable practitioners to quickly "get up to speed" on herbs that may serve them well in practice. We also include detailed information on the potential synergy that can be obtained by combining herbs with conventional medicines, as there are strong indications that herbs can help overcome drug resistance, an issue of great concern at this time. To strengthen the clinical relevance of this book, we have expanded examples of herbal formulas, dosing tables, and full references to underlying literature.

However, the objectives and philosophy set out in the Introduction, written for the first edition of *Clinical Botanical Medicine*, remain unchanged and are set out in full in this second edition in chapter 1. We are grateful to Mary Ann Liebert, Inc., for the opportunity to refine and update this reference book, and hope that it will serve clinicians well and encourage the incorporation of herbal remedies in everyday practice.

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1

INTRODUCTION

This book explores some aspects of the multifaceted nature of botanical medicine. It consists of articles published over the years in *Alternative and Complementary Therapies*, with all but the most recent articles thoroughly revised and updated. The resurgence of interest in this and related aspects of natural medicine has had both exciting and disturbing results. It is exciting that many people are reclaiming the responsibility and power of self-healing. It is exciting that many health care professionals are breaking away from dogma to expand their therapeutic medicine chest. It is disturbing that this often translates into simply using herbs or their constituents as drugs. This use certainly has a place at times but it ignores the facts that whole herbs are not drugs and offer an important and expanded way of promoting health and healing. The herbs or plants used in botanical medicine are living beings, part of the incredibly complex web we call Earth. One of our central goals is to serve as a counterpoint to the many recent botanical texts that increasingly explain the use of herbs based solely on a constituent-based approach. We illustrate that botanical medicine is and should be much deeper and more complex.

We honor that the knowledge of herb as drug has a living place in botanical medicine, and is actually the historical foundation of all pharmacological medicine. But we always find ourselves circling back to show how a Western science-based understanding of herbs can benefit from acknowledging an approach that treats herbs as a whole, living part of healing. Even the simplest plant contains a huge number of distinct compounds, compounds made by the plant for its own needs. In turn, these many compounds are metabolized in the human body to a vastly greater number of metabolites with a multitude of actions on existing systems and compounds. We have a shocking lack of understanding of the nature and degree of interactions between these multitudes of molecules and our physiology, although the clues scattered throughout the historical and scientific literature are intriguing.

As the published studies tend to focus on drug discovery among herbal compounds and metabolites, it is easy to forgot the many other poorly explored aspects of botanical medicine, such as therapeutic synergy among compounds within a plant and between multiple plants and how use of the whole plant can modify the potential toxicity of some of its constituents. An example that comes to mind is *Andrographis paniculata* (kalmegh). Relatively high concentrations of isolated andrographolide from kalmegh were hepatotoxic in animals, whereas the whole leaf was hepatoprotective.[1] In addition, clinical trials support the idea that whole kalmegh leaf is safer and more effective than isolated andrographolide—the whole leaf has proven useful in at least one clinical trial for viral hepatitis, whereas a study of isolated andrographolide for treatment of patients infected with human immunodeficiency virus showed a tendency toward increasing serum transaminase levels.[2,3]

The time of harvest and method of preparation can alter solubility, pharmacokinetics, and other important factors in botanical medicines. Historically, combinations of herbs (usually referred to as formulae, in some cases combining as many as 20–30 herbs) were commonly employed. This exponentially increases the range of possible interactions between the constituents in the various herbs themselves as well as in the human body. Only the Asian scientists have begun to investigate this vast array of interactions. An example of this research: *Panax*

ginseng (Asian ginseng) has been shown to enhance absorption of saikosaponins from *Bupleurum chinensis* (Chinese thorowax) in a formula.[4] Previously, science questioned the importance of the saikosaponins because they did not appear to be bioavailable.

These intriguing results lead us back to another tenet of our understanding of botanical medicine: Traditional knowledge is more than a free guide to sources of patentable plant derivatives. It is important to acknowledge that traditional medicine, whether obtained intuitively or by trial-and-error, has a vast, unexplored body of knowledge that we need to integrate into our practice. We must move beyond simply understanding plants based on pharmacological studies of single constituents or patented extracts that exclude many potentially important compounds from the source herb.

Finally, in this book we also attempt to shed some light on the difficult interactions between the human body, pharmaceutical drugs, and plants. We have empirical knowledge of plants based on millennia of use. Our knowledge of what our modern drugs are doing in the body is less encompassing. Our knowledge of how plants and drugs may interact is a brand new arena. We approach this arena by making sure that we provide as much information as is possible on the potential for negative interactions between drugs and herbs. At the same time, we also bring to the fore information that shows that we cannot assume that these interactions are necessarily always negative: Plants often have a positive synergistic effect on medicines such as antibiotics and chemotherapeutic agents.

The complexity of botanical medicine is ultimately a delight. It is not merely a frustrating obstacle in the way of solidly designed double-blind, randomized, placebo-controlled studies. The full benefit of botanical medicine will be ours only if we are willing to rise to the intellectual challenge that plant use presents. We hope you will enjoy joining us in our attempt to find a wise, knowledgeable way to live with the many unanswered questions botanical medicine offers modern medicine.

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2

HERBAL MEDICINE FOR ACNE VULGARIS

Acne vulgaris remains a common condition in industrialized societies, with many mainstream treatment options available. However, all such treatments carry risks and none is completely satisfactory. Natural alternatives are gaining greater research support, and have much to offer clinically in this disorder.

Antibiotic resistance in *Propionibacterium acnes* and *Staphylococcus epidermidis* has been rising steadily since the 1980s. In one analysis covering 10 years in the United Kingdom, carriage of resistant bacteria was noted in over 50% of acne patients treated with antibiotics, with most patients carrying multiple different resistant strains on different parts of their bodies.[1] Similar trends have been reported in many other industrialized nations.[2] Despite some efforts by drug manufacturers to inform consumers, the incidence of women exposed to oral tretinoin, a known teratogen, during pregnancy has been increasing, possibly due to direct-to-consumer drug advertising.[3] These and other concerns including cost underscore the need for safer, effective, less expensive approaches to acne, including those offered by herbal medicine.

This chapter focuses primarily on herbal treatments for acne. Few botanical medicines have been systematically evaluated in clinical trials, and there is virtually no research on the common approach of natural medicine practitioners for acne: the use of multiple lifestyle changes along with multiple natural products. Nonetheless, biological plausibility has been demonstrated for many therapies in isolation.[4]

DIET, DIGESTION, ACNE, AND HERBS

Mainstream dermatology has long maintained that "diet is not related to acne" based on outdated, low-quality, and rather sparse research. Mounting modern research supports that diet does in fact affect acne in multiple ways.[5] Most recently, a controlled trial in male acne patients has shown that eating a low-sugar diet significantly reduced acne lesions over a three-month period compared to eating a high-sugar diet.[6] If nothing else, it is quite clear that people living in "Stone Age societies" have no acne, compared to rates as high as 95% in adolescents in industrialized societies.[7] Though diet is not the only difference between traditional and industrial societies, it is one of the major differences between them.

Changes in diet and lifestyle are therefore critical to any natural approach to acne. It is a tenet of natural medicine that poor digestion may exacerbate poor dietary intake and contribute to acne. Several studies demonstrate that low stomach acid is a common finding in acne patients.[8,9] This suggests that the traditional use of bitter herbs, which act by stimulating digestive function including acid secretion, may be useful and important in correcting acne vulgaris (see Sidebars 2-1 and 2-2). Some common bitter herbs used include *Taraxacum officinale* (dandelion) leaf and root, *Achillea millefolium* (yarrow) flowering top, *Artemisia absinthium* (wormwood) leaf, *Gentiana lutea* (gentian) root, and *Mahonia aquifolium* (Oregon grape) root.

The belief in natural medicine that liver function is also critical to avoiding diet-induced acne is more theoretical. The idea is that if the liver and its detoxification and excretory functions are

2–1. *Proposed Acne Vulgaris Protocol*

Increase omega-3 fatty acid, fruit, and vegetable intake.

Eliminate or greatly reduce trans-fatty acid and simple carbohydrate intake. Reduce or eliminate animal product ingestion, and use only organic animal products if any are taken to avoid exogenous hormones. Avoid iodized salt and swimming in chlorinated water.

Use bitter herbs before meals for any suspected or documented problems with malabsorption, hypochlorhydria, or other digestive atony.

Cleanse the skin with nonmedicated soap gently on a daily basis.

Apply 5–50% tea tree oil diluted in jojoba oil topically one to two times daily as needed. Apply after skin cleansing.

Use natural skin moisturizers as needed for dry skin.

As needed, use inflammation-modulating (IM), antimicrobial (AM), and anti-comedogenic (AC) herbs internally and topically. Following is a typical formula.

Mahonia aquifolium (Oregon grape) fresh root tincture, 20–30% (IM, AM, AC, bitter)
Scutellaria baicalensis (scute) decocted dried root tincture, 20–30% (IM, AC)
Achillea millefolium (yarrow) fresh-flowering top tincture, 10–20% (IM, AM, bitter)
Curcuma longa (turmeric) fresh root tincture, 10–20% (IM)
Commiphora mukul (gugul) resin tincture, 5–10% (AC? IM?)
Glycyrrhiza glabra (licorice) dried-root fluid extract, 5–10% (IM, AM, flavor enhancer)
Oplopanax horridum (devil's club) fresh root bark glycerite, 5–10% (where stress is a problem)
Vitex agnus-castus (chaste tree) mature fruit tincture, 10–20% (hormone balancing)
Serenoa repens (saw palmetto) mature fruit tincture, 10–20% (where androgens are a factor)

Dose: 1 tsp three times per day in water sipped before meals

not functioning optimally, the body will attempt to compensate by eliminating toxic compounds through other routes in the body, including the skin. It is also possible that the liver herbs commonly used, such as *Arctium lappa* (burdock) root, actually work because of their bitter digestive stimulant actions. Sufficient clinical research has not been done on this hypothesis to allow a reasoned analysis of the approach.

Antimicrobial Herbs

Various bacteria play a role in the pathogenesis of acne with *Propionibacterium acnes* and *Staphylococcus epidermidis* most often studied. Both of these microbes, and others potentially related to acne pathogenesis, are present on normal skin and none has been definitively shown to cause acne.[10] Once either excess sebum production or inflammatory changes begin, these microbes can and often do overgrow and worsen inflammation.

2–2. *Case Study: Digestive Herbs for Acne*

A 23-year-old with mild-to-moderate papulopustular acne on the face, back, and chest that had not responded to systemic erythromycin treatment sought care. He also complained of clay-like stools. He was vegan (and had been for seven years) except for occasional dairy product intake and was in a stressful educational program. He used no medication but was taking a multivitamin and vitamin C. Blood tests revealed that he had low-grade macrocytic anemia. Stool fecal fat analysis indicated elevated fecal fat levels. Celiac disease was excluded by a negative serum anti-endomysial antibody test.

The initial treatment included:

Increase omega-3 fatty acid-rich foods into his diet, particularly flax oil.
Elimination/challenge diet (which revealed that he had various negative reactions to dairy products, avocados, and chocolate).
One intramuscular (IM) vitamin B12 shot weekly for six weeks.

After three months on this protocol, the patient saw a moderate reduction in the number of acne lesions and his anemia was resolved, though his stools had not improved much. Therefore a bitter tincture formula containing 50% *Gentiana lutea* (gentian) root, 30% *Taraxacum officinale* (dandelion) leaf, and 20% *Mahonia aquifolium* (Oregon grape) root was prescribed at a dose of two droppers full before meals. The patient also decided to start eating fish and began taking 6 g fish oil daily.

Three months of this program led to near total resolution of all lesions as well as normalization of his stools. The bitters were discontinued after one more month, and the acne remained almost entirely resolved.

After one year, associated with a severe time of stress, some acne lesions recurred, but improved as the stress passed. Reinstituting bitters, occasional use of topical tea tree oil in jojoba, and stress reduction were sufficient to control these episodes. After four years of this the patient would often go months with no lesions and acute outbreaks would consist of no more than four to five lesions on the back and face.

Given these facts, antimicrobial herbs have a role to play in acne treatment. The best supported natural treatment in this regard is steam-distilled volatile oil of *Melaleuca alternifolia* (tea tree) leaf. A single-blind trial was conducted comparing a 5% gel of tea tree oil with 5% benzoyl peroxide lotion in 124 patients with mild-to-moderate acne.[11] The two treatments were ultimately equally effective at clearing comedones, though the tea tree oil took longer to show efficacy. Tea tree oil caused significantly less skin irritation than benzoyl peroxide in this trial. In vitro, microemulsified and liposomally dispersed formulations of tea tree oil at pH 6.5 have shown optimal follicular penetration and antimicrobial activity, though it is unclear if these products are clinically more effective than direct application of the oil.[12,13]

We have found that 25–50% tea tree oil diluted in jojoba oil applied twice daily is highly tolerable and effective for most patients, though occasionally the strong scent of the tea tree oil is unacceptable for daytime application. In such instances, a 5% dilution is usually acceptable scent-wise for application in the morning and the stronger application can be used in the evening or at bedtime, or else switch to using 25–50% *Santalum album* (sandalwood) oil. Because

Figure 2–1. *Taraxacum officinale* (dandelion)

excessive organic matter can interfere with the activity of tea tree oil (and because mild cleansing seems to be helpful empirically),[14] it is recommended that patients *gently* cleanse their skin with soap or other cleansers that do not contain any pharmaceutical active ingredients prior to applying the tea tree oil. Jojoba oil is used because it is noncomedogenic and has demonstrated its own inflammation-modulating effects in animal studies.[15]

There is also a clinical trial that apparently showed that steam-distilled volatile oil of *Ocimum basilicum* (basil) leaf was effective for patients with acne, but full details of the study could not be obtained.[16] Basil oil is both antimicrobial and inflammation modulating.[17]

In vitro, a methanol–dichloromethane extract of the leaves of *Eucalyptus globulus*, *E. maculata*, and *E. viminalis* (various species of eucalyptus) all showed potent anti–*P. acnes* activity.[18] This activity was strongly associated with flavonoids and chalcones (flavonoid precursors) in *E. maculata*, which is surprising as these compounds are not normally antimicrobial. Eucalyptus steam-distilled volatile oils have been used successfully and safely for skin infections such

Figure 2–2. *Arctium lappa* (burdock)

as scabies in pilot clinical trials.[19] Thus the potential for eucalyptus volatile oil to help acne patients is good.

Oregon grape crude root extracts and its alkaloids berberine and jatrorrhizine all showed minimum inhibitory concentrations (MIC) of 5–50 mcg/ml against *P. acnes* in vitro.[20] Oregon grape is often used as an antimicrobial clinically, and has at least two other properties that make it particularly compelling for acne patients: It is a bitter digestive stimulant and an inflammation modulator.

Ultimately, the antimicrobial approach does not cure most cases of acne, and the organisms involved are almost certainly responding to other pathological processes. Thus, a broader approach to using herbs in acne is logical and necessary.

Inflammation-Modulating Herbs

Inflammation plays a major role in the pathogenesis of acne. As microcomedones form, a lymphocytic infiltrate occurs and triggers inflammation.[21] This tends to further trigger follicular keratinocytes to produce more keratin, as well as stimulate increased sebum production and a reduced linoleic acid content in the sebum generated by the sebaceous glands. Most westernized people have experienced the inflammatory nature of acne vulgaris, given the various red, swollen, tender lesions associated with it, particularly papules, pustules, nodules, and cysts.

Herbs that relieve inflammation could therefore also be useful in limiting or resolving acne. Berberine-containing herbs, besides their antimicrobial action already discussed, have been

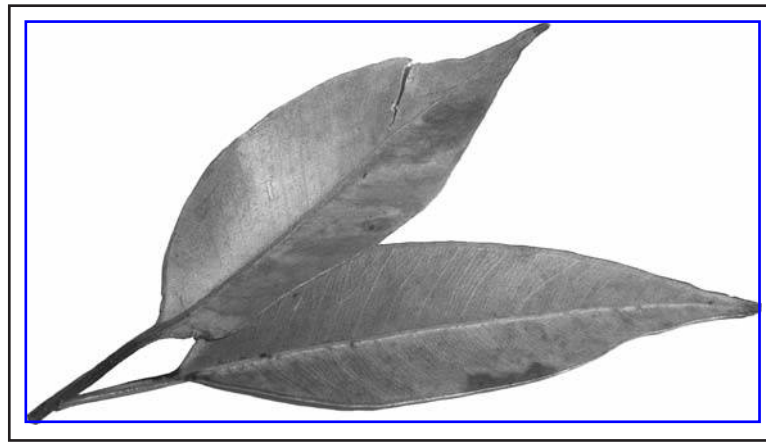

Figure 2–3. Extract of the leaves of *Eucalyptus globulus, E. maculata,* and *E. viminalis* (various species of eucalyptus) all showed potent anti–*P. acnes* activity.

shown to be inflammation modulating.[22] Besides Oregon grape, *Berberis vulgaris* (barberry), *Coptis chinensis* (goldthread), *Hydrastis canadensis* (goldenseal), and *Xanthorrhiza simplicissima* (yellowroot) all contain berberine and similar alkaloids. Oregon grape has been shown repeatedly to be helpful in clinical trials for patients with psoriasis, another inflammatory skin condition.[23] Acne clinical trials are still lacking and sorely needed.

Scutellaria baicalensis (Asian skullcap, scute) root extracts are well-established inflammation modulators from traditional Asian medicine.[24] Attention has focused on its flavonoids, wogonin and baicalein in particular, as potent inflammation modulators.[25,26] The potential for internal and topical administration of this herb to help with acne is great, though clinical trials are unfortunately lacking.

Magnolia spp. (magnolia) stem bark is used quite frequently in traditional Asian medicine. Its diphenylpropanid constituents honokiol and magnolol have low MICs against *P. acnes* in vitro.[27] The compounds also reduced inflammatory reactions to the microbe in this study, and were nonirritating when applied to the skin of healthy human volunteers. The inflammation-modulating effects of magnolol and honokiol have been shown to be related to their ability to suppress the critical inflammatory mediator NF-kappaB.[28] Clinical trials are needed on this promising herb and its constituents.

Preliminary evidence looks promising, but much work remains to be done to prove the value of inflammation-modulating herbs for acne. Many inflammation-modulating herbs or herbal compounds have additional actions, including the antimicrobial effects discussed above. They often also appear to affect comedone formation.

Anti-Comedogenic Herbs

A comedone arises when a hair follicle is blocked by excess keratin and sebum. If the lipids and/or sebum involved are exposed to air they oxidize, turning black (the infamous blackhead). If the follicle is completely closed and an anaerobic environment forms, the material is cream-colored (thus, a whitehead). Several natural keratolytics such as glycolic acid or salicylic acid are well established to treat comedones. However, they tend to be painful when applied and can

cause bizarre whitening patterns of the skin. They also do not resolve the underlying causes of the comedones.

In contrast, several natural products have been shown to directly and significantly inhibit abnormal lipogenesis in hamster sebaceous glands.[29] Berberine and wogonin were the most active in this study. In a separate study, a crude extract of goldthread root (which contains berberine alkaloids) at a concentration of just 0.01% also had a strongly antilipogenic effect in sebaceous glands.[30] While no further work has been done to clarify the clinical relevance of these findings, it is yet another way in which the herbs containing these compounds may operate in acne. Thus one cannot focus too closely on any single action for most herbs that could be beneficial for acne, as research continually shows they have multiple ways of affecting the disease.

In a double-blind clinical trial, tetracycline 500 mg twice daily or an extract of *Commiphora mukul* (guggul) providing 25 mg guggulsterone twice daily was compared in 20 patients with nodulocystic acne.[31] After three months, all subjects had similar reductions in the number of inflammatory lesions (approximately 65%). Three months after discontinuation of therapy, four patients previously on tetracycline and two on guggul relapsed. The authors suggested that patients with more oily skin reacted best to the guggul, raising the possibility that this agent works by addressing comedogenesis. Guggul also may have antimicrobial and inflammation-modulating activities.

Multiherbal Approaches from Traditional Asian Medicine

In traditional Asian herbal medicines, the standard approach is to combine multiple herbs into a formula suited to an individual patient. While this approach is also used by many herbal practitioners in the western world, it is a difficult approach for mainstream health care providers to understand. Being schooled in a system of medicine that focuses on single molecular entities to treat disease in broad groups of people, and also having been taught that combining multiple agents is potentially dangerous polypharmacy, makes the use of polyherbal formulas seem quite foreign. Nevertheless, ample experience and published clinical trial data support that this approach can be quite effective.

In a double-blind trial, four different herbal and mineral combinations were compared to a charcoal placebo in Indian patients with acne vulgaris. Only one of the formulae, Sunder Vati, showed a significant improvement in inflammatory and noninflammatory lesions compared to baseline or a placebo.[32] Sunder Vati contains *Holarrhena antidysenterica* (kutaj) stem bark 180 mg, *Emblica officinalis* (amalaki) fruit 30 mg, *Embelia ribes* (vidanga) fruit 30 mg, and *Zingiber officinale* (ginger) rhizome 10 mg for a total of 250 mg, administered at a dose of 500 mg three times per day.

A similar double-blind trial compared various combinations of internal and external herbal formulas. A combination of *Aloe barbadensis* (aloe vera), *Azardirachta indica* (neem), *Curcuma longa* (turmeric), *Hemidesmus indicus* (Indian sarsparilla), *Terminalia chebula* (chebulic myrobalan), *Terminalia arjuna* (arjun), *Withania somnifera* (ashwagandha), and *Piper longum* (long pepper) was given orally combined with either a gel or cream of the same formula but without long pepper (which is used orally to increase absorption of other herbs). One group took herbs orally and applied a placebo topically and one group took an oral placebo and an active topical treatment.[33] All patient groups receiving the herbal preparation showed improvement, compared to no improvement in the placebo group. The active cream preparation combined with oral herbs was judged the most effective. These inflammation- and immune-modulating herbs definitely should be investigated further for helping acne patients.

Figure 2–4. *Terminalia chebula* (chebulic myrobalan)
Drawing ©2006 by Kathy Abascal, BS, JD.

One preparation, known as Compound Oldenlandia Mixture (COM) in Chinese medicine, was compared with Angelica and Sophora Root Pills (ASRP) in 120 acne patients.[34] COM led to a cure rate of 73% compared to 47% for the ASRP. While the full details of what was in these formulas are not available, and though arguably a known active treatment was not used as a control, this study still provides some evidence that multiple herbs working in synergy can be quite effective for acne patients.

In a similar trial, a topical formula known as xiao cuo fang (full details of what this contains were not available) was combined with 0.1% adapalene (a synthetic retinoid) gel and compared to topical 0.03% retinoic acid cream in 133 patients with acne.[35] The adapalene and herbal combination was significantly more effective at reducing the number of acne lesions compared to retinoic acid. Adverse effects due to the herbal formula were minimal. More rigorous follow-up research is necessary but this trial again shows the potential benefit of polyherbal formulas applied topically in acne vulgaris patients.

Hormonal Acne

Very often acne flares up related to the impending onset of menses. This particular type of acne highlights the fact that acne is often affected by hormone balance in the body. Much work has focused on the potential negative impact of androgens on acne; estrogen and progesterone can definitely also be involved.[36]

Two herbs are commonly used for hormonal acne. The first is *Vitex agnus-castus* (chaste tree) fruit. This plant acts in the pituitary to balance secretion of luteinizing and follicle-stimulating hormones, thus regulating estrogen and progesterone levels.[37] Preliminary German research confirms that chaste tree can help moderate hormonal acne.[38] Chaste tree should be taken throughout the menstrual cycle for optimal effects. Chaste tree is often used together with vitamin B6, which has also proven quite helpful in resolving hormonal acne, though one comparative trial found that chaste tree was superior to B6 for helping with symptoms of premenstrual syndrome.[39]

When androgens are a problem in acne vulgaris, *Serenoa repens* (saw palmetto) fruit is the first herb most clinicians use. If polycystic ovarian syndrome or documented high-serum androgens are present, saw palmetto should be considered to help offset the negative effects of excessive androgens. Saw palmetto does this by moderately inhibiting 5-alpha reductase (which activates testosterone to the much more potent dihydrotestosterone form) and by antagonizing the androgen receptor.[40] No clinical trials were located on the efficacy of saw palmetto in acne. The only other well-documented anti-androgenic herb is *Glycyrrhiza glabra* (licorice), though it also has not been studied for acne in clinical trials.[41,42]

Other hormone-balancing herbs may have a role in acne vulgaris, including but not limited to *Medicago sativa* (alfalfa), *Chamaelirium luteum* (false unicorn root), *Verbena* spp. (vervain), and *Mitchella repens* (partridge berry). This is yet another fruitful area for more study.

CONCLUSION

Much disparate and introductory research exists on the effects of herbs on multiple aspects of acne (see Sidebar 2-3). A comprehensive approach combining multiple herbs as well as lifestyle and dietary changes has been documented to help people with acne in preliminary clinical trials. The continued resistance of mainstream dermatology to the possibility of this approach

2–3. *Clinical Trial on Combination Therapies for Acne*

In an open clinical trial, 90 of 98 patients had significant improvement on the following protocol over six or more months' time, and 42 had 90–100% lesion clearance within 2 months. While this trial did not incorporate herbal medicine, it is still important to recognize that dietary approaches to acne are reasonable, safe, and effective, and complement an herbal approach.

Supplements:

Vitamin A, water-soluble form, 50,000 IU bid, tapered gradually over the course of the trial
Vitamin E 400 IU bid
Pyridoxine 50 mg qd-bid (in women with perimenstrual acne flares only)
Benzoyl peroxide 5% gel topical at night after gently washing with nonmedicated soap
Vitamin B12 was avoided as it can occasionally exacerbate acne.

(*continued*)

2–3. *Clinical Trial on Combination Therapies for Acne (continued)*

Diet:

A "well-balanced diet" low in fat and simple sugars was recommended. Processed grain flours with added inorganic iron, thought to bind and inactivate vitamin E, were proscribed. Iodized salt, kelp, soft drinks, and milk were proscribed due to their associations with acne.

Exogenous estrogens were also to be avoided.

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does not optimally serve patients who might be significantly helped by natural therapies. There are sufficient pilot data to warrant larger trials on various herbal medicines in isolation and combined with each other and other natural therapies. The data are also sufficient to support a recommendation for their use in clinical practice. This is particularly true given how safe they are. Overall, herbal medicine has much to offer to improve our ability to deal with the complex issues acne presents.

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3

ADAPTOGENS

Adaptogenic herbs are used to strengthen the body's immune response and increase the individual's ability to cope with physical and mental stress. They are also used to increase overall vitality. Adaptogens are generally not used to treat specific ailments but are used fairly long term to help the patient achieve a more healthful state. Pharmaceutical drugs are different as they instead target specific symptoms or disease states. At present, the concept of using a medicine other than as a solution for a specific ailment is quite foreign to the Western medical model. To further confound the picture, adaptogens often have measurable effects in different disease states. For example, *Panax quinquefolius* (American ginseng) has been shown to have a hypoglycemic effect in diabetes. This often leads Western researchers to try to confirm its use as a medicine for patients with diabetes rather than as an adaptogen that may benefit both those with and without diabetes. The failure of these experiments to satisfy fully this Western model often leads researchers to erroneously conclude that there is a "lack of evidence of efficacy" for adaptogens.[1]

Adaptogens benefit people who constantly suffer minor ailments, such as colds. They also greatly benefit those struggling with chronic ailments, such as autoimmune disease. Because they help the individual cope with physical and mental stress, they are highly useful in people who are feeling tired, run-down, "stressed-out," "burned-out," and ill. For example, Asian ginseng (*Panax ginseng*) is used in traditional Chinese medicine (TCM) to restore qi, or the functioning of the person as a whole. This replenishment is not an energy boost similar to that of caffeine or amphetamine where the boost ultimately further depletes the strength of the patient. Instead, it is an aid during convalescence, a prophylactic to build resistance, reduce susceptibility to illness, and promote health.

HOW ADAPTOGENS WORK

Unfortunately, few studies have tested the traditional uses of adaptogens. Most of the research focuses on isolated properties of these herbs in animals and in vitro, such as investigating their hypoglycemic, antimicrobial, or specific immune system–enhancing effects. There are some clinical studies but much of the research continues to be published in Asian and Slavic languages, preventing a thorough analysis of the study results. As a result, there is surprisingly little solid information on how adaptogens work.

One postulate is that adaptogens act by stimulating the patient's nonspecific stress response through the hypothalamic–pituitary–adrenal axis. This axis acts to increase cortisol when animals and humans are subjected to stress, with a reduced sensitivity to feedback down-regulation and a disruption in the circadian rhythm of cortisol secretion. Central nervous system changes include a stress-induced depletion of catecholamine neurotransmitters (norepinephrine and dopamine), and an acute increase in beta endorphin levels. Recent studies indicate that the urinary content of tribulin (a monoamine oxidase A and B inhibitor) increases in patients and animals in response to physical stress (such as illnesses like cancer) as well as to emotional stress.[2] Increased urinary tribulin is thus a marker for stress. In one study the adaptogenic herb ashwagandha (*Withania somnifera*) reduced urinary tribulin in stressed animals.[3] It is possible

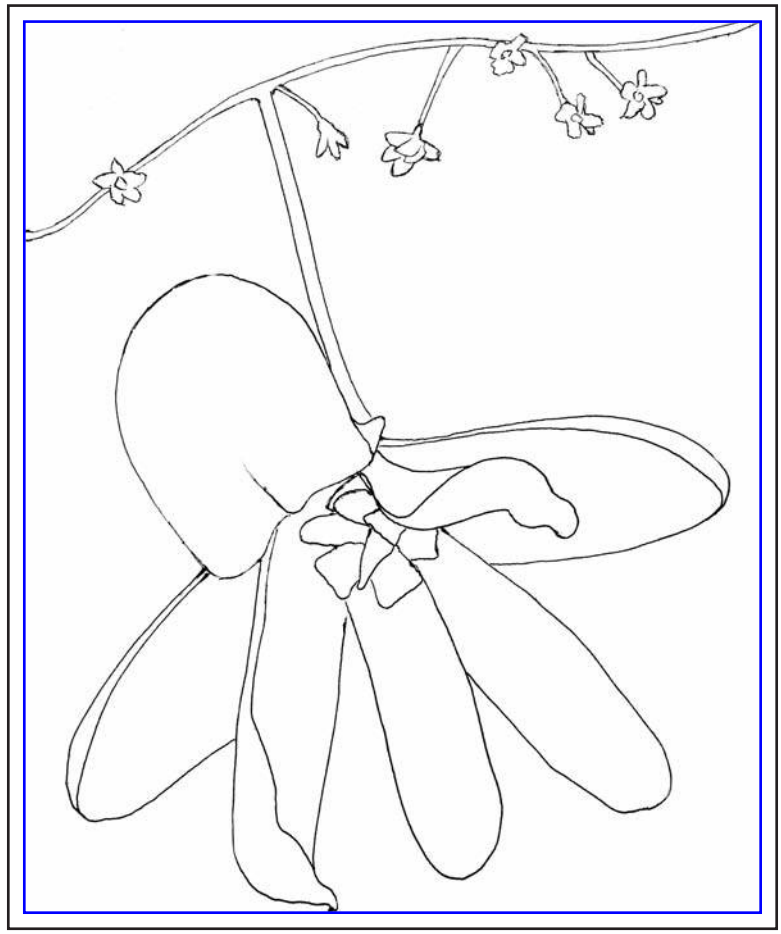

Figure 3–1. *Schisandra chinensis* (schisandra)
Drawing ©2003 by Kathy Abascal, BS, JD.

that this branch of research may some day explain the action of adaptogens in scientific terms. Another study postulated that an adaptogen (*Schisandra chinensis*) protected the qi, or body energy, by fortifying the antioxidant status of mitochondria, offering a generalized protection against both internal and external challenges.[4]

COMMON ADAPTOGENS AND THEIR USE

Following is a discussion of some of the adaptogens we use most frequently, with a summary of the scientific data on their actions, and a description of a type of patient who in our opinion might benefit from using that particular adaptogen. Our opinions are intended only as a general guideline based on our clinical experience rather than an exhaustive analysis of all known adaptogens.

American Ginseng (*Panax quinquefolius*)

American ginseng was used as a tonic and a panacea—a remedy used in serious illness when other remedies failed—by many Native American tribes.[5] It is a graceful plant with bright red

berries and is indigenous to Eastern hardwood forests. American ginseng is under tremendous pressure in the wild due to habitat loss and overharvesting. Fortunately, many organic, woods-cultivated products (simulating the way American ginseng naturally grows) are now on the market. American ginseng cultivated in other conditions is usually exposed to high levels of fungicides and other chemicals and in our opinion should be avoided.[6]

American ginseng has shown a definite hypoglycemic action in clinical studies of type 2 diabetes, as well as having other beneficial effects in this population including improving lipid status.[7–12] A proprietary extract of the root (COLD-fx) was found to prevent upper respiratory tract infections in healthy adults. In this randomized, double-blind, placebo-controlled trial, 323 participants took 400 mg of COLD-fx per day or placebo for four months and maintained assessment records of cold-related symptoms; 279 completed the study. The ginseng extract reduced the risk of recurrent colds by 12.8% and significantly reduced the severity of symptoms and length of colds as well.[13]

American ginseng, combined with ginkgo (*Ginkgo biloba*), reduced hyperactive impulses and social problems in children with attention deficit hyperactivity disorder (ADHD).[14] In a randomized, double-blind, crossover study of 13 healthy males, 1600 mg of American ginseng per day for four weeks prior to an exhaustive running exercise improved a marker of muscle damage (creatine kinase) but did not enhance aerobic workout ability.[15]

In vitro and animal studies show American ginseng to have antioxidant and immuno-enhancing properties. In mice, its saponins had an anxiolytic effect equal to that of diazepam but did not negatively affect locomotor function as diazepam did.[16] It has neuroprotective and memory-enhancing effects in animals, and may be beneficial in Parkinson's disease. It has antineoplastic effects and enhanced the efficacy of most breast cancer chemotherapy drugs in vitro. American ginseng is cardioprotective and blocked the development of reverse tolerance to morphine and inhibited morphine-induced memory impairment. It also facilitated male copulatory behavior in rats. Finally, low-dose (35 mg/kg bw) American ginseng enhanced the course and magnitude of antibody response to vaccination in horses.[17]

In our practice, we primarily use American ginseng as a strengthening herb in men and women in their middle age (40–65). It helps individuals in this age range handle common midlife stressors such as teenage children, elderly parents, peak career demands, and the physical stressors of poor lifestyle choices beginning to manifest in elevated blood lipids and pressure. American ginseng is not as stimulating as Asian ginseng, which we prefer for frailer individuals (see discussion below). We find it of particular value in menopausal women and in women with breast cancer because it appears to cool hot flashes and support chemotherapy drugs. While the studies indicate its potential usefulness in type 2 diabetes, we often turn to devil's club (*Oplopanax horridum*, discussed hereafter) as the adaptogen of choice in that ailment.

The breadth of research and clinical use of this herb is part of why it is considered an adaptogen. American ginseng affects many body systems—perhaps all of them—both directly and indirectly. Like other adaptogens, its effects are gentle, appearing gradually but acting deeply. Rarely will it alter a symptom immediately, but instead digs into root causes and helps eliminate underlying problems, particularly chronic uncompensated stress reactions that are now so clearly linked to many acute and chronic illnesses. Because growing conditions may significantly affect the medicinal qualities of American ginseng,[18] because it is challenged in the wild, and because many preparations claiming to contain American ginseng actually do not, we carefully source our American ginseng. High-quality, organically woods-cultivated ginseng is available, and is our preference. For a discussion of the safety of American ginseng, see Asian ginseng below.

Asian Ginseng (*Panax ginseng*)

Asian ginseng, like its relative, American ginseng, likes to grow in the shade of trees. Asian ginseng even looks very much like American ginseng. The main difference is said to be that Asian ginseng's berries are held 8–12 inches above the leaves while American ginseng's grow at or just below leaf level. However, James Duke, PhD, claims that interbreeding and the extreme similarity between the two species make it nearly impossible to tell the two apart.[19] Nonetheless, traditional wisdom has distinct uses for the two plants, and a few chemical studies indicate that the two plants have different ginsenoside profiles as well as differences in their actions.

There are some interesting studies on Asian ginseng. However, a meta-analysis of these data concluded that its efficacy has yet to be established beyond reasonable doubt for any condition.[20] This, of course, is true to varying degrees of all of the adaptogens.

The incidence of cancer is low in areas of China and Korea where Asian ginseng is consumed as a food.[21,22] Fresh Asian ginseng extracts in particular reduced stomach, lung, and liver cancer rates in a case-controlled study in Korea.[23] Asian ginseng combined with other herbs and conventional treatment improved survival in a study of 54 patients with small-cell lung cancer.[24] In a review of clinical studies, Asian ginseng was found to consistently demonstrate some degree of quality of life improvement but this effect was deemed not well established.[25]

Asian ginseng's ability to enhance physical endurance has received mixed results in studies. In three fairly well-designed studies, Asian ginseng enhanced parameters of physical endurance.[26–28] In another four studies, Asian ginseng failed to improve the exercise performance of healthy adults.[29–31] A double-blind trial showed a benefit on mental and physical fatigue after 42 days of use.[32] However, it had no effect on the mood or general well-being of healthy young adults in another study.[33] In yet another, it was found to improve reaction time and abstract thinking.[34]

In a study of healthy volunteers, Asian ginseng's effect on blood glucose was quite different from that of American ginseng in diabetic patients. In two placebo-controlled crossover studies, Asian ginseng significantly lowered glucose levels in healthy volunteers. Conversely, when taken with glucose, it raised blood glucose levels.[35] At the same time, both Asian ginseng and glucose enhanced cognitive performance and reduced the subjective sense of mental fatigue during demanding tasks.[36] Other studies show that Asian ginseng improved cognitive performance.[37,38] American ginseng has been shown to reduce postprandial glycemia in healthy

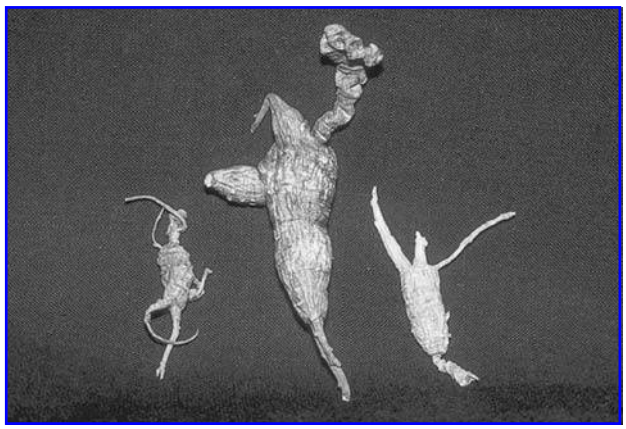

Figure 3–2. *Panax ginseng* (Asian ginseng)

people and those with type 2 diabetes in some but not all trials, as discussed above.[39,40] The effect of taking American ginseng with or without glucose has not been evaluated.

A study comparing eight types of ginseng (Asian, steamed Asian or red ginseng, American wild, American cultivated, eleuthero, *Panax japonicus* or Japanese ginseng, *Panax vietnamensis* or Vietnamese ginseng, and *P. notoginseng* or sanchi ginseng) in healthy volunteers found that cultivated American and Vietnamese ginseng lowered postprandial blood glucose, whereas wild American and Asian ginseng and eleuthero raised it significantly compared to placebo.[41] Asian ginseng raised plasma insulin levels; no other herb had a significant effect on plasma insulin levels except that Vietnamese ginseng lowered it (but only in overweight subjects). The presence of certain ginsenosides was associated with differences in effects between species.

Asian ginseng has a reputation as a libido enhancer, and one study found it superior to trazodone for erectile dysfunction.[42] Its saponins raise sperm counts in men with normal amounts of sperm, with oligospermia, and with asthenospermia.[43] Asian ginseng alleviated menopausal symptoms in two studies.[44] However, in a study of postmenopausal women, a combination of 120 mg of ginkgo and 200 mg Asian ginseng for 12 weeks did not have a significant effect on ratings of mood, menopausal symptoms, or cognitive function.[45]

There is a long-term controlled study showing that Asian ginseng was beneficial in human immunodeficiency virus (HIV) infection, and a randomized study showing a synergistic effect with zidovudine (AZT) as well as effectiveness when used alone.[46,47] Several preclinical studies support Asian ginseng's immunomodulatory effects. It potentiated the action of vaccination for cold and/or influenza and it also reduced the bacterial count in patients in an acute attack of chronic bronchitis.[48]

Asian ginseng extract (6 g/day) for eight weeks reduced cholesterol and triglyceride levels while increasing high-density lipoprotein in human volunteers.[49] Another human study found that it directly modulated cerebro-electrical activity and to a greater extent than ginkgo did.[50] Numerous animal and in vitro studies show that Asian ginseng and/or its constituents have an antineoplastic effect, enhance the effectiveness of chemotherapy agents, improve brain metabolism, are immunomodulatory, have an antiulcerogenic effect, and protect from radiation damage. One interesting study showed that ginseng, combined with brewers' yeast, improved both the mental and physical status of elderly dogs compared to placebo without changing blood or urine analyses or causing any side effects.[51]

It is reported that 1,075 volunteers have participated in Asian ginseng studies without any reports of side effects except for minor events (acne, diarrhea, etc.) that were equally common in those taking the placebo.[52] A study on its effect on the P450 enzymes showed Asian ginseng to inhibit CYP2D6 but at a magnitude that was deemed clinically irrelevant.[53]

Asian ginseng is our adaptogen of choice for those weakened by either age or serious disease, such as HIV or cancer. Following traditional practice, we do not use Asian ginseng as a treatment for acute infections, nor do we use it in individuals in good general health and strength with a lot of body heat. Many advise against the use of Asian ginseng in patients with hypertension. The belief that ginseng promotes hypertension, however, is not supported by available clinical trial data showing that Asian ginseng actually tends to lower blood pressure.[54] Thus, it is, in our opinion, a suitable adaptogen for an elderly, frail, cold person who also has high blood pressure. Asian ginseng is a difficult plant to cultivate, and the amount of fungicide and pesticide residue in commercial products is of concern.[4] Unfortunately, organically grown Asian ginseng is practically unknown. In sourcing Asian ginseng, we look to companies with substantial experience buying and selling Chinese herbs in general, and Asian ginseng in particular because these companies are likely to have access to higher quality herb.

The ginsengs are very safe. Some sensitive people, particularly when very stressed and when they first start taking the herb, may have an overreaction to the invigorating effects of these herbs, most commonly leading to insomnia. If insomnia does occur, then the dose should be reduced and no doses should be taken after lunch. Neither American nor Asian ginseng is considered indicated in pregnancy or lactation, though there is no clear contraindication to their use either. There are no well-documented adverse drug interactions. One case study suggests they may potentiate warfarin,[55] though this hardly proves a causal connection. Caution is warranted when combining the ginsengs with anticoagulants or antiplatelet drugs until more information is available.

Eleuthero (*Eleutherococcus senticosus*)

Eleuthero is a shrub/small tree native to central Eastern Asia. It is widespread in Russia and is entering cultivation in various western states of the United States. The root is used medicinally. Formerly, eleuthero was often called *Siberian ginseng*, a name that was dropped because eleuthero belongs to the Araliaceae family but is not in the *Panax* genus. Traditionally, eleuthero was used to increase vital energy, to improve quality of sleep in those bothered by many dreams, to improve appetite, for lower back and kidney pain, and for rheumatoid arthritis.[56]

Eleuthero may be the best studied of the adaptogens, although most of these studies are not available in English. Russian studies of over 6,000 patients tested its ability to improve mental alertness, work output, and work quality in individuals subjected to heat, noise, exercise, and heavy work loads. The results were reported to be generally positive with minimal side effects.[34] Several studies show that it improved athletic performance;[57,58] two showed that it did not.[59,60] A recent review of the studies on the benefits concluded that the positive trials had methodological flaws, whereas the rigorous studies showed no benefit on performance.[61]

In a study of 100 children with acute dysentery, children on a combined treatment of monomycin and eleuthero recovered more quickly than children on monomycin alone.[62] This may seem somewhat surprising because, just like the ginsengs, eleuthero is not traditionally used as a treatment for acute infections. However, the results likely simply reflect the benefit of using an adaptogen to strengthen a weakened individual (often needed in a person struggling with a disease) rather than its benefit as a treatment for acute dysentery. It increased T lymphocytes significantly compared to placebo in healthy individuals.[63] Other studies indicate that eleuthero may be of benefit in stress,[64–68] pneumonia,[69] pyelonephritis,[70] cancer,[71] and as an adjunct to oncologic therapy.[72–74] However, a randomized controlled study on the use of eleuthero for one to two months in patients suffering from substantial, unexplained fatigue or diagnosed with chronic fatigue syndrome found only a suggestion of benefit for those with moderate fatigue.[75] Yet another study comparing eleuthero with Asian ginseng in club-level endurance athletes found that eleuthero actually tended to increase stress hormone levels rather than reduce them.[76]

Most studies indicate that eleuthero is a very safe herb although there is a case report of a patient whose serum digoxin levels were elevated (but without toxic effects) due to his intake of eleuthero, an effect that was tested on rechallenge.[77]

We tend to choose eleuthero for younger individuals suffering from stress and for athletes searching for a safe alternative to hormones. In contrast to rhodiola (see discussion below), which we use for patients suffering from mental stress, we prefer eleuthero for patients suffering from physical stress from work or exercise. Eleuthero has a similar safety profile to Asian ginseng.

Schisandra (*Schisandra chinensis*)

Schisandra is a lovely vine native to Eastern Asia. Its berries are used medicinally. Its Chinese name means "five-taste fruits" because the berries taste sweet, sour, bitter, pungent, and salty. Schisandra is considered nourishing and helpful when spontaneous sweating and night sweats cause a depletion of body fluids. It is a traditional remedy for nervous conditions, coughs, and liver ailments. It enhances immune response and reduces fatigue and sleeplessness. It is both calming and stimulating.

There are reports that schisandra lowered serum glutamic–pyruvic transaminase (SGPT) levels in 87–98% of 5,000 cases of hepatitis.[34,78] A review article reports that Russian studies show that schisandra reduces fatigue and increases endurance in athletes.[79] This research has not been followed up with further clinical studies but some interesting research on horses supports schisandra's beneficial physical effects. Schisandra fed to thoroughbred, racer, polo, and jumper horses typically reduced indices of muscle fatigue and damage while improving performance.[80–82] Another study abstract indicates that schisandra combined with Asian ginseng and *Ophiopogon japonicus* (ophiopogon) injected intravenously into 22 patients with primary dilated cardiomyopathy improved myocardial performance.[83]

There are many in vitro and in vivo studies of schisandra. These studies show schisandra and its constituents have neuroprotective, hepatoprotective, cardioprotective, renal protective, antineoplastic, antioxidant, and immune-enhancing effects. They stimulated liver regeneration post-partial hepatectomy, had strong anti-hepatitis C activity, enhanced cognition and memory in animals, and enhanced physical endurance. Schisandra lignans appear to be able to reverse P-glycoprotein-mediated multidrug resistance in cancer cells.[84]

Schisandra makes a delightful tasting glycerite, and is a good choice for children in need of an adaptogen. It is also our first choice as a strengthening tonic in patients with chronic liver and heart ailments. Based on indications for use from traditional medicine, we recommend it to menopausal women and other patients suffering from night sweats. Schisandra has no known or reported adverse effects. One study showed a related species, *S. sphenanthera*, increased the oral bioavailability of tacrolimus in healthy volunteers.[85] On the other hand, an herbal formula containing schisandra strongly inhibited CYP3A4, confirming other in vitro studies showing schisandra's inhibitory effect to be equal to that of grapefruit juice. However, in in vivo rats the formula did not affect the serum concentration of the drug nifedipine as grapefruit juice did.[86] In rats, both schisandra and licorice increased the metabolism of coadministered warfarin.[87] Schisandra may also help protect against the side effects of some pharmaceuticals. Thus, schisandrin B protected against tacrine-induced hepatotoxicity in mice.[88]

Ashwagandha (*Withania somnifera*)

Ashwagandha is an evergreen shrub found in the arid parts of India. Its range extends as far west as Israel. It has been described as looking like a very large potato plant and it is in the Solanaceae family. The root is the primary part used medicinally. The Latin name for the plant translates to "sweat of a horse," some claim because the root smells like a damp horse.

Historically used as a general tonic to enhance energy and health, ashwagandha is used in a variety of Ayurvedic formulae prescribed for arthritis and rheumatism, and to prevent disease in the elderly as well as in pregnancy.

In a double-blind, placebo-controlled crossover study of 42 patients with osteoarthritis, ashwagandha combined with other herbs significantly reduced pain and disability.[89] In another

study, ashwagandha, again in a formula, proved superior to placebo for treatment of osteoarthritis of the knees.[90] Ashwagandha appeared to increase body weight and hemoglobin in a study of 60 healthy children,[91] and it improved hemoglobin levels and hair melanin in a one-year-long study of 101 healthy males.[92]

Ashwagandha stimulated neurite outgrowth in human brain cells that may compensate for damaged neuronal circuits in the dementia brain. In animals and in vitro, it stimulated thyroid function and increased physical endurance; had strong hepato- and renal-protective, and antineoplastic effects; and was cardioprotective, anti-inflammatory, antioxidant, and immunomodulating. It significantly inhibited parasitemia in mice innoculated with *Plasmodium berghei* compared to negative controls with a maximum inhibition at a dose of 600 mg/kg.[93]

Although lacking complete studies, ashwagandha appears quite safe.[92] One study, however, found that compounds in ashwagandha interfered with serum digoxin measurements.[94] There is also a case report of ashwagandha precipitating in thyrotoxicosis in a patient taking the herb for chronic fatigue. This report is unfortunately in Dutch so relevant details needed to assess it are not available.[95] On the other hand, ashwagandha also appears able to offset the side effects of some medicines. It reversed haloperidol-induced catalepsy in mice,[96] and reduced reserpine-induced orofacial dyskinesia and cognitive dysfunction in rats.[97]

We use ashwagandha for low libido in stressed patients as well as in anxious patients because it is not associated with insomnia, unlike the ginsengs or eleuthero. It is a good choice in arthritic patients. Finally, ashwagandha is a good choice in elderly patients suffering from various degrees of dementia.

Rhodiola, Golden Root (*Rhodiola rosea*)

Rhodiola was the subject of an exhaustive and interesting review.[98] The fragrant root of rhodiola is used in mainstream Russian medicine for fatigue and infectious illnesses, and in psychiatric and neurological conditions. In healthy individuals, it is used to relieve fatigue and improve concentration, memory, and productivity. In smaller doses, the herb had a stimulating effect on laboratory animals; in larger doses it had a more sedative effect. Its dual action of cognitive stimulation and emotional calming enhances learning and memory while delivering beneficial antioxidant effects to the brain.

In an open study of 53 healthy subjects and 412 patients with a variety of neuroses and debilities (such as recovering from illness and infection), rhodiola improved symptoms of fatigue, insomnia, irritability, weakness, and headaches.[99–101] In another open study, 21 physicians and doctors took rhodiola before embarking on intense intellectual work. In all cases, the amount and quality of work increased and fatigue diminished.[102] At a relatively high dose (300 mg/day), rhodiola improved the accuracy of proofreaders although it did not increase the number of errors caught.[103] A lower dose (170 mg/day) improved the functioning of 56 physicians on prolonged night duty during a two-week period but was not as effective during the last two weeks of a six-week duty.[104] In a double-blind 20-day study of 60 medical students studying for final exams, well-being, physical fitness, mental fatigue, and final exam grades were improved by a relatively low dose of rhodiola.[57] In another double-blind study, rhodiola increased general well-being while decreasing psychic fatigue and situational anxiety in high school students.[105] In a 12-week study, rhodiola along with vitamins and minerals improved symptoms such as exhaustion, forgetfulness, daytime sleepiness, irritablity, and other similar complaints. Greater improvements were found in those who took a full dose of rhodiola in the morning rather than a divided dose over the day. This study was not placebo controlled.[106] In a six-week

study of 79 patients with mild to moderate depression, rhodiola (340 or 680 mg/day) improved significantly depression, insomnia, and emotional stability but not self-esteem compared to placebo.[107]

A recent study reported that rhodiola did not affect muscle recovery time or time to exhaustion in 12 resistance-trained men taking 1500 mg rhodiola/day for four days.[108] Of course, this study looked at a relatively high dose given for a very short period of time and does not shed much light on how the herb is used in practice. Finally, a small study found that rhodiola reduced levels of C-reactive protein and creatinine kinase in healthy untrained volunteers after exhaustive exercise.[109]

Animal and in vitro studies show that rhodiola, like most of the adaptogens, has antioxidant, cardioprotective, anticarcinogenic, and strengthening effects. Rhodiola has a very low level of toxicity with an LD_{50} in rats equating to a dose of 235,000 mg in an average-sized man. As a typical dose is less than 600 mg/day, there is a large margin of safety.

In our opinion, rhodiola is an excellent choice for individuals bogged down in the stress and fatigue of demanding intellectual work. An example would be a generally healthy patient who cannot get over a cold—the latest in a series of colds—and who is unable to rest and cannot "afford to be sick." We also use it for students of any age who are frazzled and fatigued from studying too hard. It is a good choice for individuals who have trouble concentrating while awake, and trouble sleeping at night. Rhodiola's traditional use also includes enhancing fertility, improving adaptation to high altitude, and treating gastrointestinal ailments and infections. We have little experience using rhodiola in these ways.

Aralia spp.

Aralias and the ginsengs are closely related, and most botanists consider that they are all in the same family.[110] Species of aralia are found in the United States and various parts of Asia. Their adaptogenic properties are neither well-known nor well studied. Michael Moore, director of the Southwest School of Botanical Medicine (Bisbee, Arizona), states that aralia moistens dried mucus membranes and is useful in bronchiectasis and early emphysema. He uses the root as a pulmonary tonic to smooth out variations in pulmonary secretions in smokers and individuals with many allergies and a chronic moisture in the respiratory organs. He has had success using both the root and the berries as an adaptogen, and states that the berry tincture, in particular, is helpful in moving individuals out of a panic state. Aralia has a gentler, milder adaptogenic action than Asian ginseng and eleuthero.

3–1. Aralia *species*

Michael Moore, who has been using aralia as a medicine for decades, considers *Aralia californica, A. humulus, A. racemosa*, and *A. nudicalis* to have interchangeable medicinal properties.[a] In his opinion, the spiny *A. hispida* has too much heat to be used as a tonic adaptogen. However, all of the North American aralia, including *A. hispida*, were used as diaphoretics, expectorants, and tonics by Native Americans.[b]

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[b]Duke JA, Bogenschutz-Godwin MJ, duCellier J. *Handbook of medicinal herbs*, 2nd ed., Boca Raton, FL:CRC Press 2002.

We have not found any scientific data on the North American aralia species. Their Asian cousins have received slightly more research attention. Unfortunately, we do not know enough about American aralia's constituents to determine whether the results on the Asian plants apply to them as well. However, it is quite possible that they do. These results include a strong ability to induce phase II enzymes in vitro, an antioxidant effect; and the ability to normalize abnormal kidney function in diabetic rats, a hypoglycemic effect. One species protected mice from radiation damage.

We do not have a vast experience with aralia. The berry tincture has a pleasant taste, and we tend to use it more often than the root, which has a vaguely unpleasant taste. We use aralia as the adaptogen for patients who have chronic lung issues that can range from asthma to emphysema or simply a tendency to frequently have colds move deeper into the chest. It has no known adverse effects.

Devil's Club (*Oplopanax horridum*)

Devil's club is a member of the Araliaceae family. Unlike its other ginseng relatives, devil's club's properties remain largely unexplored. It was used by Native Americans as a treatment for rheumatism, as an analgesic for stomach and bowel cramps, and as a purgative. It was also used for colds, coughs, and various pulmonary disorders. Some tribes also used it as a tonic, to promote weight gain, and as a blood cleanser. Some tribes used it to treat diabetes.[3]

There is little research on devil's club. It completely inhibited the growth of *Mycobacterium tuberculosis* and *M. avium* in vitro. The plant contains polyynes, each of which exhibited anticandidal, antibacterial, and antimycobacterial activity in vitro including an ability to kill *Mycobacterium tuberculosis* and isoniazid-resistant *M. avium*. It also partially inhibited respiratory syncytial virus in vitro.

Its Asian cousin, the species *O. elatus*, has a high content of essential oil that has antifungal activity against *Trichophyton rubrum*, *T. verrucosum*, and other fungi.[111] In another study a cream containing 1% essential oil of *O. elatus* purportedly had a 90% effectiveness rate in patients with dermatomycoses.[112]

Devil's club's clinical use is largely guided by the knowledge and insight of Michael Moore.[113] Moore recommends devil's club as a reliable and safe expectorant and respiratory stimulant, and as an aid in rheumatoid arthritis and other autoimmune disorders. In autoimmune conditions, it is not used as a treatment in acute phases but rather as a tonic to reduce the number and intensity of flare-ups of the underlying conditions. Moore also recommends it as a tonic treatment in type 2 diabetes where he finds it works best in stocky, mesomorphic patients with elevated blood lipids and blood pressure. He reports on older studies that validate its use in type 2 diabetes that we have not reviewed.

Devil's club is the adaptogen we most typically pick for patients with type 2 diabetes. We also tend to choose devil's club for thin, young women who feel scattered and frazzled, particularly when they have a tendency to indulge in sugary foods, often manifesting in recurrent *Candida albicans* infections.

There are no known adverse effects, and in our experience devil's club does not cause hypoglycemia in people without blood sugar dysregulation problems. It is not known to interact with any drugs, though there is obviously a potential for synergy with insulin or oral hypoglycemic drugs.

COMBINATIONS AND COMPARISONS

Although an early Russian study suggested that adaptogens may function better singly than in combination, there are a few studies that show that combinations of adaptogens certainly can work well. We, however, did not find any studies showing that combining several adaptogens works better than using them singly. In our practice, we tend to select an appropriate adaptogen and then combine it with other herbs that address the patient's symptoms rather than rely more heavily on a combination of adaptogens. For more information on the value of combining adaptogens with nervines and other herbs, we recommend David Winston's recent text on adaptogens.[102]

In a double-blind, placebo-controlled, randomized phase III study, a combination of rhodiola, schisandra, and eleuthero (dubbed Chisan) was tested in a study of 60 patients with acute nonspecific pneumonia. All were given a standard treatment of cephazoline, bromhexine, and theophylline. Half were given placebo and the other half Chisan for 10 to 15 days. Time to recovery was two days shorter in those taking Chisan. In addition, the patients taking Chisan scored higher on subjective quality of life criteria.[114]

In another study, 270 mg/day of a combination of rhodiola, eleuthero, schisandra, and *Leuzea carthamoides* (maral root) was administered for four weeks after 28 patients with stage III–IV ovarian cancer completed chemotherapy with cisplatin and cyclophosphamide. That adaptogens increased the mean numbers of T cells compared to placebo and also increased the amounts of IgG and IgM, indicating a positive effect on chemotherapy-suppressed immunity.[115] Twenty-four children with familial Mediterranean fever were treated with a combination of schisandra, eleuthero, *Andrographis paniculata* (andrographis), and *Glycyrrhiza glabra* (licorice) for a month while ten patients were given placebo. Duration, frequency, and severity of attacks improved in the active group with the severity of attacks showing the greatest improvement.[116]

A combination of ashwagandha, *Ocimum sanctum* (holy basil), *Asparagus racemosus* (shatavari), and *Emblica officinalis* (amla) used to treat stress-related disorders normalized neurotransmitter levels and tribulin activity in rats.[117]

Finally, one study compared single-dose administration of rhodiola, schisandra, and eleuthero in humans, measuring mental performance and physical working capacity. Rhodiola was found to have the greatest effect, producing within 30 minutes a stimulating effect that lasted at least four to six hours.[118]

CONCLUSION

Stress is a root cause of many ailments afflicting modern humans. Adaptogens help individuals cope with stress and are highly beneficial in most, if not all, patients. Adaptogens differ from each other in subtle ways, and we do not claim to have a definitive answer on each one's most appropriate use (see Table 3-1). Ultimately, adaptogens are in many respects interchangeable, and a high-quality but less specific adaptogenic product will usually work better than a lower quality product that more exactly matches the specifics of the patient's condition. In the final analysis, any of the adaptogens will ultimately help your patient better cope with life's stressors.

Table 3–1. Overview of Uses and Doses of Adaptogens

Plant	*Indications*	*Dose**
Asian ginseng	Frailty/physical weakness in elderly or in patients with serious ailments (e.g., cancer, HIV). A synergizer in formulas. Main picture: An older man at high risk of cancer who is tired, is losing muscle mass, has diabetes or diabetic tendencies, is facing a life of chronic stress, and tends to have chronic diseases or ailments that linger.	Decocted crude root: 1–2 g three times per day Tincture: 2–3 ml three times per day Capsules standardized to 4% Ginsenosides: 200 mg three times per day
American ginseng	Middle-aged individuals (40–65), menopausal women, individuals with breast cancer	Tincture: 3–5 ml three times per day Capsule: 1–3 g three times per day
Eleuthero	Athletes, body builders, young men. Do not tend to use in diabetes.	Tincture or fluid extract: 3–5 ml three times per day
Rhodiola	Individuals stressed by demanding intellectual endeavors	Tincture or fluid extract: 3–5 ml three times per day Capsules: 170–300 mg four times per day
Schisandra	Patients with kidney and/or liver problems such as chronic renal failure, mildly elevated liver enzymes, hepatitis, cirrhosis. Menopausal women or individuals suffering from night sweats. Any individual who rejects other adaptogens based on taste	Glycerite or tincture: 3–7 ml three times per day
Ashwagandha	Stressed patients presenting with low libido. Anxious or excitable individuals. Elderly patients with a degree of dementia. A truly sedating adaptogen that will not increase blood pressure or cause insomnia.	Tincture or fluid extract: 3–5 ml three times per day
Aralia	Strengthening tonic in individuals with pulmonary concerns (e.g., asthma, emphysema, frequent chest colds)	Tincture: 3–5 ml three times per day
Devil's club	Type 2 diabetes or hypoglycemia, particularly in stocky individuals; it greatly reduces their chance of infection. Ectomorphic individuals with a tendency to overindulge in hyperglycemic foods with frequent *Candida albicans* infections. We prefer devil's club prepared as a glycerite.	Tincture or glycerite: 5 ml three times per day

*All for average-sized adults. A child's dose is determined by using any standard formula based on their smaller body size.

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4

ALZHEIMER'S DISEASE: BOTANICAL TREATMENTS

There is no proven treatment for Alzheimer's disease, conventional or alternative. Most of the government-approved Alzheimer's drugs are acetylcholinesterase inhibitors. Although widely prescribed, these drugs are of questionable efficacy and are associated with substantial adverse effects. The belief that estrogen replacement therapy might limit Alzheimer's disease in women has been thoroughly disproved in double-blind clinical trials.[1] Thus, Alzheimer's is a difficult condition to treat effectively.

We begin by discussing the biology of Alzheimer's and review some of the cholinesterase-inhibiting botanicals used in treatment of the disease. Then, we present a botanical treatment plan for Alzheimer's disease premised on the concept that, especially in the early stages of the disease, best results will be obtained through the use of effective antioxidants. This protocol includes *Ginkgo biloba, Salvia lavendufolia, Melissa officinalis, Rosmarinus officinalis*, and *Withania somnifera* along with a diet rich in fruits and vegetables, particularly blueberries and beets, and vitamins C and E. (See Sidebar 4-1.) Scientific studies and historical data supporting the treatment plan are analyzed.

4–1. *Protocol for Alzheimer's Disease*

1. *Ginkgo biloba* leaf extract standardized to contain 24% ginkgo flavonoid glycosides, 6% terpene lactones, and no more than 5 ppm ginkgolic acids; 120–240 mg daily taken in divided doses
2. 10 ml of the following formula, taken in divided doses three times daily

   a. *Curcuma longa* (turmeric), fresh rhizome tincture; 30%
   b. *Salvia* spp. (sage), tincture of fresh leaf; 15%
   c. *Melissa officinalis* (lemon balm), fresh leaf tincture; 15%
   d. *Rosmarinus officinalis* (rosemary), fresh herb tincture; 10%
   e. *Withania somnifera* (ashwagandha), fresh root tincture; 30%

3. Vitamin E, 400 IU, with vitamin C, 1,000 mg; may be taken in divided doses but should be taken together
4. Blueberries, approximately 1 cup/day as berries or juice
5. Beets, daily or every other day, ½ cup serving
6. Regular physical and mental exercise

INTRODUCTION

Alzheimer's has become a growing problem because humans routinely live more than 70 years and are exposed to a multitude of toxic substances over their life. Those who have the condition and those who have watched friends or family members struggle with the disease know how horrific it can be. Though several acetylcholinesterase-inhibiting drugs are approved by the U.S. Food and Drug Administration (FDA) and other governmental agencies around the world for treatment of Alzheimer's disease, their utility is questionable, especially given the high incidence of adverse effects. Botanical medicine offers an array of options to modify the progress and symptoms of Alzheimer's disease.

BIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive disease that causes memory loss, disorientation, depression, loss of control over bodily functions, and death. The condition was first described by the German neurologist Alois Alzheimer in 1907. It currently afflicts about 12 million people worldwide but is expected to affect more than 22 million people by the year 2025. The pathological features associated with Alzheimer's disease are senile plaques and neurofibrillary tangles, oxidative and inflammatory processes, and neurotransmitter disturbances.

Senile plaques are composed of parts of neurons surrounding a group of proteins called beta-amyloid deposits. Beta-amyloid is a normal breakdown product of beta-amyloid precursor protein (BAPP) via alpha- or beta-secretase and then gamma-secretase. Less than 10% of the ultimate metabolites of BAPP are the potentially toxic beta-amyloid form (C42-BAPP fragment); the remainder is the nontoxic C40-BAPP fragment. The presenilin gene associated with some cases of Alzheimer's disease may code for gamma-secretase; mutations in this gene are associated with increased risk of Alzheimer's disease, possibly by forming abnormal gamma-secretase.

One of the earliest events in Alzheimer's is oxidative damage to the brain.[2] The brain is particularly vulnerable to oxidative damage due to its large demand for oxygen; the presence of large amounts of easily oxidized, polyunsaturated, fatty acids in neuron and Schwann cell membranes; the abundance of redox-active transition metal ions; and the relatively low antioxidant defense systems in the brain.

Increases in metal ion accumulation and oxidative stress in the brain are associated with changes in the deposition of beta-amyloid.[2] Although these deposits are devastating in Alzheimer's disease, beta-amyloid actually has a neuroprotective function at physiological concentrations and reflects an attempt by the brain to reduce oxidative damage by chelating metal ions, sealing vessels, and promoting neurite outgrowth. When beta-amyloid interacts with metal ions, it generates toxic reactive oxygen species. This toxicity is abolished in vitro in the presence of superoxide dismutase, synthetic hydrogen peroxide scavengers, and chain-breaking antioxidants like vitamins E and C. It is the lack of competent peroxide-clearing mechanisms in the brain that appears to transform beta-amyloid from a neuroprotectant to a neurotoxin. Indeed, pharmacological research suggests that a focus on curtailing beta-amyloid in the brain will have substantial negative side effects. Instead, research is increasingly focused on providing the aging patients' brain with suitable antioxidants to moderate the damage of beta-amyloid metabolites.

Epidemiological studies show that high cholesterol is associated with Alzheimer's with a latency period of 15 to 30 years, and is an independent risk factor for the disease.[3] Apolipoprotein

E (apoE) normally functions in transport of cholesterol within high-density lipoprotein (HDL). However, three forms of apoE exist—ε (epsilon) 2, ε3, and ε4. Roughly one-third of people have the ε4 form, which increases the risk of developing Alzheimer's disease.[4] It is postulated this may be because it competes with beta-amyloid for removal from the intercellular spaces in the brain. Experimental studies suggest that the statin drugs, such as pravastatin and lovastatin, may act to prevent or delay Alzheimer's onset.[5] To date, studies have failed to demonstrate that statins are a clinically important treatment but they are increasingly prescribed as a treatment nonetheless. For a botanical statin alternative, see Sidebar 4-2.

Neurofibrillary tangles are composed of tau protein, coded for by a gene on chromosome 17. It is not known what provokes production and accumulation of these tangles. As the tangles become more dense, tubulin in neurons and other cells becomes damaged, and the cells die. Neurofibrillary tangles are directly correlated with disease severity, whereas beta-amyloid plaque density is not, and neurofibrillary tangles are seen in other brain diseases, whereas beta-amyloid plaques have only been found in brains of people with Alzheimer's disease.

Neuronal death also occurs due to the presence of free radicals (possibly related to beta-amyloid plaques, as noted above) and direct action of various putative neurotoxins. The resulting cellular debris triggers chronic inflammation with recruitment of microglia into the brain. This process does not resolve the problem but instead perpetuates further inflammation, greater neuronal damage, and ultimately worsening of the disease.

4–2. *Policosanol*

A botanical product, policosanol, has in many studies been shown to reduce cholesterol equally or more effectively than statin drugs such as simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and atorvastatin.[a,b,c,d,e] In addition, policosanol has stronger inhibitory effects on lipid peroxidation and is not associated with side effects in a study of over 6,000 patients lasting for five years.[f] Although recent studies put in question its ability to lower cholesterol,[g] policosanol is a good candidate for investigation as it may offer a potential benefit in Alzheimer's.

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ACETYLCHOLINE AND ALZHEIMER'S

The concentration of acetylcholinesterase diminishes 85–90% in the hippocampus and cerebral cortex in late-stage Alzheimer's patients due to death of cholinergic neurons in these regions.[6] The neurotransmitter acetylcholine plays an important role in memory and cognition in these brain regions. Once acetylcholine binds to muscarinic (M1) receptors, it is rapidly broken down by acetylcholinesterase. Unfortunately, simply supplementing choline, the precursor to acetylcholine, is ineffective because there are simply not enough neurons present to synthesize sufficient acetylcholine, and because the enzyme necessary for this process, choline acetyltransferase, becomes progressively nonfunctional as the disease worsens.

Most of the government-approved drugs for Alzheimer's disease are acetylcholinesterase inhibitors.[7] The four primary drugs in this category available in the United States are tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®). These drugs help maintain acetylcholine levels in the synapses and reduce some symptoms of Alzheimer's disease. They do nothing to halt the loss of cholinergic neurons, and thus do not affect progression of the disease. They are also associated with significant adverse effects including gastrointestinal distress and liver damage (observed in up to 50% of people taking tacrine in particular).

Recent investigations indicate that a cholinergic deficit occurs only late in the disease progression; in the earliest stages there may even be an up-regulation of cholinergic activity.[8] A postmortem comparison of brains and cholinergic activity showed that a cholinergic deficit correlated only with advanced stages of Alzheimer's disease. A cholinergic deficit was not found in those with mild-to-moderate Alzheimer's disease, based on rigorous documentation of cognitive status prior to death, although senile plaques and tangles were evident on autopsy.[9] Thus, the data increasingly suggest that cholinesterase inhibitors should not be used in early stages of Alzheimer's disease but perhaps should be reserved for the very advanced stages of the disease. One analysis of clinical trials of three of these drugs (all except tacrine) found that the benefits at any stage in the disease were "small and may not be clinically relevant."[10]

ALKALOIDAL ACETYLCHOLINESTERASE INHIBITORS

Natural acetylcholinesterase inhibitors are well-known and predated creation of tacrine, the first synthetic acetylcholinesterase inhibitor. Physostigmine (see Figure 4-1) is an indole alkaloid from the seed of *Physostigma venenosum* (Calabar bean) and is a reversible inhibitor of acetylcholinesterase. The alkaloid is easily destroyed by light and is fairly toxic. It is generally

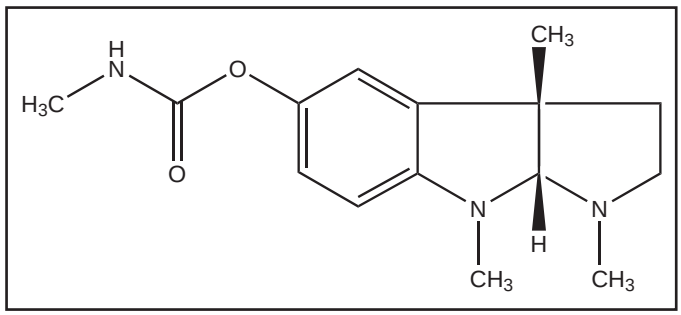

Figure 4–1. Physostigmine

not considered sufficiently safe or effective for clinical use. However, naturopathic physician Bill Mitchell, ND, one of the cofounders of Bastyr University, Washington, recommends use of tincture of Calabar bean, 5 drops twice daily, for patients with Alzheimer's disease.[11] Early signs of overdose are dizziness, nausea, vomiting, diarrhea, salivation, miosis, dyspnea, and dysphagia. Calabar bean is contraindicated in asthma and mechanical obstruction of the gastrointestinal or genitourinary tracts.

The approved drug galantamine (see Figure 4-2) is an alkaloid naturally occurring in *Galanthus nivalis* (snow drop), *Narcissus tazetta* (daffodil), and *Leucojum aestivum* (snowflake), all in the Amaryllidaceae family. It was originally discovered and tested in Bulgaria in the 1950s for use by anesthesiologists to reverse effects of curare-like muscle relaxants.[12] Eventually it was discovered that galantamine was beneficial in people with Alzheimer's disease at a dose of 8–24 mg daily.[13] In vitro research suggests that galantamine has some antioxidant activity.[14] How important this is in its clinical effects remains unknown.

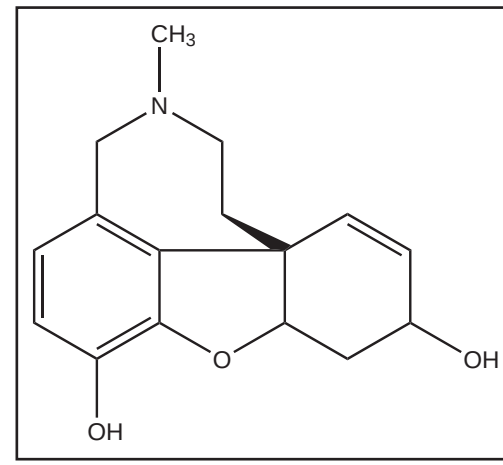

Figure 4–2. Galantamine

Galantamine causes nausea in up to 10% of people who take it, and more serious adverse effects such as vomiting or weight loss in up to 5%. It does not appear to be a problem in people with cerebrovascular atherosclerosis according to the results of clinical trials.[15] It is unknown what the effects would be of whole herb or whole herb extracts of the herbal sources of galantamine, though the herb, extract, and isolated compound are all considered moderately toxic and do not have a well-established history of use.

Excitement in the news media has focused on huperzine A (see Figure 4-3), an alkaloid isolated from *Huperzia serrata* (toothed clubmoss). This alkaloid is a potent, reversible, natural acetylcholinesterase inhibitor. Toothed clubmoss has a long tradition of use in Chinese herbal medicine for fevers, inflammation, blood disorders, and schizophrenia.[16] Huperzine A has shown promising results in Chinese clinical trials for people with Alzheimer's disease.[16,17] In rats, huperzine A produced a more prolonged increase of acetylcholine levels than did tacrine or physostigmine.[16] The effective dose and toxicity have not yet been clarified in the Western world but human pharmacokinetic studies indicate a daily dose schedule of two or three daily administrations might be optimum. No "notable" side effects were observed with doses between 0.18 and 0.54 mg. Secondary effects observed in the clinical trials were mainly cholinergic and, with the exception of nausea, were significantly milder than with neostigmine. We have talked with practitioners who have experimented with low doses of toothed clubmoss tincture, 1–5 drops three times daily, in patients with dementia with some initially beneficial responses. Much more research is needed on both the whole herb and its alkaloid.

Pilocarpine (see Figure 4-4) is an imidazole alkaloid found in the leaves of *Pilocarpus jaborandi* (Pernambuco jaborandi) and related species in the genus, native to South America. Unlike the other two natural products described earlier, pilocarpine is a muscarinic receptor agonist or cholinomimetic agent. This novel therapy does not appear to have been tested in clinical trials for Alzheimer's disease. Dr. Mitchell suggests using a dose of 2 mg pilocarpine twice daily. R. F. Weiss, MD, the late, great German physician and phytotherapist, suggests that whole plant extracts of jaborandi are superior to pilocarpine, at least when used as diaphoretics.[18]

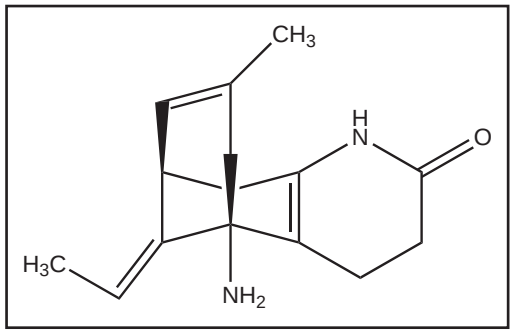

Figure 4–3. Huperzine A

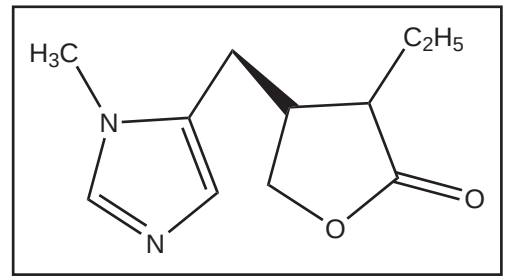

Figure 4–4. Pilocarpine

Weiss suggests a dose of 1 tsp herb made into tea (steep 5–10 min in hot water) as a diaphoretic but does not give a dose for regular use. Overdose of pilocarpine causes all the same symptoms as with physostigmine.

ANTIOXIDANT BOTANICALS

Cholinesterase-inhibiting botanicals may be very helpful in the later stages of Alzheimer's disease. However, as mentioned above, it appears that botanicals with greater antioxidant properties may be more useful in the early to middle stages of Alzheimer's, especially when combined with good nutrition and supplements.

Ginkgo biloba (Ginkgo)

Ginkgo is a monoecious tree with ancient roots. It is the last surviving member of its family, Ginkgoaceae. The fruits are fairly commonly eaten in Asia as food, and have long been used as medicine in traditional Chinese herbal medicine. Though there are hints of the use of the leaves in Chinese medicine, they only became widespread in use as a result of research conducted in Germany beginning in the twentieth century.

Ginkgo is popular in Europe as a treatment of the symptoms of early-stage Alzheimer's disease and vascular dementias. There is good evidence that ginkgo has at least modest effects on improving symptoms of dementia and cerebral insufficiency.

Thus a recent clinical trial shows that ginkgo is significantly superior to placebo for symptoms of apathy/indifference, anxiety, irritability, depression, and nighttime behavior.[19] Meta-analyses and systematic reviews indicate that ginkgo has an effect equal to ergoloid mesylates (Hydergine®), an uncommonly used drug believed to increase cranial blood flow, and donepezil in people with Alzheimer's disease. Deductive analysis of research data suggests that ginkgo may delay the progression of Alzheimer's disease by nine months compared with placebo.[20] A similar analysis of donepezil indicated a delay in progression of about 6–10 months compared to placebo. Another trial comparing ginkgo and donepezil found ginkgo was clinically equal to the drug and tended to show that it also might be as effective in moderately severe stages of the disease.[21] A review of clinical studies at least six months in duration demonstrated that ginkgo was as effective as second-generation cholinesterase inhibitors in the treatment of Alzheimer's disease. A Cochrane meta-analysis of 33 clinical trials concluded that ginkgo appeared safe

and showed promising evidence of improvement in cognition and function in Alzheimer's patients.[22] However, one well-designed study of patients with age-associated memory impairment or very mild dementia failed to show a benefit for ginkgo.[23] Several large studies are in progress that should shed more definitive light on ginkgo's potential benefit in Alzheimer's disease. In 2006, a five-year study of ginkgo's ability to prevent dementia in the elderly was begun, the GEM study.[24]

Ginkgo is often preferred over the acetylcholinesterase inhibitors because of the substantially lower adverse-effect risk with the herb. In fact, one reviewer suggests that trials on the acetylcholinesterase inhibitors are flawed because the common adverse effects of nausea and vomiting unblind the studies.[20] Another reviewer noted that all positive studies on tacrine were funded by the industry, whereas negative studies were independently funded (though the sample sizes in the independent studies were smaller than those in the industry studies).[25] Ginkgo is rarely associated with adverse effects such as stomach or intestinal upsets, dizziness, and palpitations. It has been associated with two reports of subdural hematoma but at least one of these was in a patient who also suffered a fall and the role of ginkgo, if any, is unclear.

Almost all clinical studies use a concentrated ginkgo extract standardized to contain 24% ginkgo flavonoid glycosides, 6% terpene lactones, and no more than 5 parts per million ginkgolic acids. A typical dose of ginkgo consists of 120–240 mg daily taken in divided doses. Ginkgo should be used cautiously in patients taking drugs that affect hemostasis, although a recent study of the interaction of ginkgo and warfarin showed no change in the international normalized ratio.[26] It is recommended that ginkgo not be administered prior to surgery. Although bleeding is unlikely, patients should be advised to report an increase in the tendency to bruise while taking ginkgo.

OTHER BOTANICAL ANTIOXIDANTS

As mentioned, the deposition of beta-amyloid is associated with the generation of reactive oxygen species in a brain that lacks sufficient antioxidants to cope with the resulting oxidative stress. Almost all plants contain antioxidants—as does ginkgo—and some of its benefit in Alzheimer's may be due to that action. Some plants combine a confirmed antioxidant action with a long tradition of use as memory aids. The following herbs are included in our Alzheimer's treatment plan primarily in deference to traditional knowledge but also because there is some science that confirms their potential benefit.

Curcuma longa (Turmeric)

Curcuma longa (turmeric) hails from the tropical regions of India and Southeast Asia and is in the same family as ginger, Zingiberaceae. The rhizome is traditionally used as medicine. Though familiar to most as the golden color in various curry blends, turmeric has long been an important medicine in Ayurveda and other traditional herbal systems in Asia.

Two factors speak strongly for the potential benefit of turmeric in Alzheimer's disease: Epidemiologic studies show a 77% lower incidence of the disease in places like India where turmeric is commonly part of the diet.[27] Other epidemiological studies indicate that non-steroidal anti-inflammatory drugs (NSAIDs) are associated with reduced risk of Alzheimer's disease.[28] In animal studies, NSAIDs significantly suppressed inflammation and the development of beta-amyloid pathology. However, NSAID use is also associated with gastrointestinal, kidney, and liver toxicity. Studies suggest that turmeric provides the anti-inflammatory benefits of

NSAIDs without their side effects.[29,30] Of particular note is that turmeric does not promote ulcer formation, and has even been tested (unsuccessfully) as a therapy for peptic ulcers.[31] Unfortunately, there are no clinical studies on turmeric's benefit in Alzheimer's disease.

There are, however, interesting results from animal and in vitro studies suggesting turmeric might be of great benefit in a protocol for Alzheimer's disease. In a transgenic mouse study, a very low dose of turmeric (160 ppm) reduced a pro-inflammatory cytokine that is linked to neuro-inflammatory cascades involved in neuritic plaque pathogenesis.[32] Turmeric decreased insoluble beta-amyloid, soluble alpha-amyloid, and plaque burden in the brains of these animals by 43–50%. Interestingly, this latter effect was not seen when high doses (5,000 ppm) were administered. The intraperitoneal injection of curcumin, a compound that gives turmeric its yellow color, significantly diminished markers of oxidative stress in the brains of rats with surgically induced forebrain ischemia.[33] Curcumin's in vitro ability to inhibit lipid peroxidation and neutralize reactive oxygen species is several times more potent than that of vitamin E.[34]

Turmeric has low toxicity and produced no mortality at doses of 2,000 mg/kg in mice. A 5,000 ppm (0.5%) diet of turmeric showed no central nervous system (CNS) toxicity in a mouse study.[32] Rats can tolerate turmeric (80% curcumin) as 5% of their diet for prolonged periods of time.[35] Humans regularly consume significant quantities of turmeric in the diet with no adverse effects.

A typical dose of turmeric tincture in isolation is 5 ml three times daily. Crude turmeric powder can be added to the diet at a dose of 1–3 tsp daily, or taken in capsules (500 mg three times daily). The powder should ideally be less than six months old and should be kept refrigerated. However, because studies suggest that turmeric has a beneficial effect in Alzheimer's disease at low doses, we use a lower dose of the tincture of turmeric in the formula and prefer that to an extract designed to increase the delivery of curcuminoids at the expense of other potentially valuable constituents.

Melissa officinalis (Lemon Balm)

Lemon balm leaves have a long history of use as anxiolytics and memory support. This fragrant herb is in the Lamiaceae (mint) family and is frequently found in gardens. Lemon balm is also useful for treating herpes and other viral infections, and its pleasant lemony flavor often makes it useful as a taste enhancer in formulations.

Several clinical trials indicate that lemon balm might be of benefit in Alzheimer's disease. These trials were undertaken based on the historical use of lemon balm combined with pharmacological studies indicating that it acts on acetylcholine receptors and has some antioxidant activity. In a randomized, placebo-controlled, double-blind, crossover trial of 20 healthy volunteers, lemon balm showed a sustained improvement in accuracy of attention and calmness at the lowest dose (300 mg/day) and a reduction of alertness and memory decrements at the highest dose (900 mg/day).[36] The study failed to confirm a significant effect on cholinergic binding. The researchers noted that the lowest dose of lemon balm appeared most efficacious and also noted that the low cholinergic binding properties might have been a result of the loss of volatile components in the product used. We and many other practitioners prefer to use only products made from fresh lemon balm to preserve these vital components.

Another study tested a fluid extract (1:1 weight to volume) of lemon balm.[37] In this double-blind, randomized, placebo-controlled trial, 42 patients with mild-to-moderate Alzheimer's disease were given a daily dose of 60 drops of lemon balm over a four-month period. Lemon balm significantly improved cognitive function compared to placebo with significant improvement in cognition seen after 16 weeks of treatment. In addition, agitation was more frequent in the placebo group. This correlated with another clinical trial that indicated that lemon balm

essential oil had a calming effect on Alzheimer's patients.[38] A significant calming effect resulted when lemon balm oil was applied topically twice daily. However, the placebo consisted of sunflower oil, and it is likely that both staff and the patients could detect which treatment was placebo and which was active, thus unblinding the study.

Lemon balm is exceedingly safe and is often used in children because of this. There are no known drug interactions or contraindications. A typical adult dose of the fresh herb tincture is 2–5 ml three times daily. Because the studies suggest that lemon balm at lower doses may be more effective in Alzheimer's disease and because we combine lemon balm with two other members of the mint family in our formula, we use a lower dose of fresh plant tincture in the formula.

Salvia spp. (Sage)

Sage is another member of the Lamiaceae family that was used traditionally to support memory. The leaves are typically used. There are many species of sage. The European standard, native to the Mediterranean region, is known as *Salvia officinalis*, but many other species have been used similarly and effectively. Pharmacological studies show that many sage species possess significant antioxidant and anti-inflammatory activity as well as an ability to inhibit acetylcholinesterase and some potentially estrogenic action.[39] Though true *Salvia* should not be confused with various members of the *Artemisia* genus sometimes referred to as "sage," some plants such as *A. vulgaris* (mugwort) also have a history of use in improving or protecting memory.

There are some small clinical trials that indicate sage's potential benefit in Alzheimer's disease. Two of these studied the effects of the essential oil of *S. lavandulaefolia* (Spanish sage), a species that is naturally very low in thujone, a potentially toxic compound. In a pilot study, 11 patients with a diagnosis of mild-to-moderate probable Alzheimer's disease were given capsules containing 50 microliters of essential oil of sage over a six-week period.[39] There was a mean decrease in acetylcholinesterase as well as trends toward improvements in memory and attention. Bilirubin levels increased in the sage oil group, though nonsignificantly compared to controls. Two patients with a history of hypertension showed an increase in blood pressure when on the highest dose of sage oil.

In 20 healthy young volunteers, single doses of Spanish sage essential oil (5–10 microliters) significantly improved immediate word-recall skills in a placebo-controlled, double-blind, balanced, crossover methodology.[40] Doses of 25–150 microliters did not significantly improve these skills. The study suggested that improvement might be greater where the initial baseline performance is low.

A tincture of sage had a significant positive effect on cognitive function in 42 elderly patients diagnosed with mild-to-moderate Alzheimer's disease (60 drops/day, 1:1 ethanolic extract).[41] No adverse effects were noted in the four-month-long study except that agitation was more common in the placebo group.

Sage has a long history of use as a food flavoring agent and spice. Some species, such as *S. officinalis*, contain a significant amount of thujone. Thujone has a reputation as a toxic compound but, in fact, has been poorly studied. It has been connected with seizures when consumed in large amounts (e.g., 20 drops/day of thuja oil).[42] As mentioned above, many studies have chosen to work with Spanish sage because of its low thujone content, which makes sense especially where the herb will be used long term. One animal study showed that sage (*S. fruticosa*) may decrease fertility but it did not show any reproductive toxicity.[43]

A typical dose of *S. officinalis* or *S. lavandulaefolia* tincture is 3–5 ml three times daily for chronic use. We use a lower dose in the formula because it is combined with other herbs with overlapping action and to mirror more closely doses used in studies on sage and Alzheimer's

disease. The essential oil can be taken internally with caution at a dose of 1–2 drops three times daily. Thujone-free products may be preferable. As with all mints, it may possibly worsen existing gastroesophageal reflux in some people. People with a history of seizure disorders should use caution when taking sage.

Rosmarinus officinalis (Rosemary)

Rosemary has the best-defined historical use as a memory aid of the different mint family herbs. Despite rosemary's historical background indicating a strong potential for benefit in dementias, it has received little scientific attention. Rosemary's benefits extend to the cardiovascular system and it is particularly indicated for vascular dementias.

In one study of 144 healthy individuals, airborne rosemary essential oil significantly enhanced cognitive performance and mood although it impaired speed of memory.[44] We include it in the treatment plan because of its strong historical reputation as a memory aid and because it contains a variety of compounds with actions potentially beneficial in people with Alzheimer's disease, particularly its antioxidant effects.[45]

The leaves are the part used. The dose of a fresh plant tincture used alone is 3–5 ml three times daily. We use a lower dose in the formula for the reasons previously stated. The volatile oil can be applied topically and is particularly helpful when applied over arthritis joints. The oil can be taken internally at a dose of 1–2 drops three times daily. Overall, rosemary is a very safe herb but the volatile oil should not be taken in excess.

Lavandula angustifolia (Lavender)

Lavender is another member of the Lamiaceae family of interest in patients with Alzheimer's disease. Like its cousins sage, rosemary, and lemon balm, it contains antioxidant cichoric acid derivatives as well as neuromodulating low-molecular-weight terpenoids. It is traditionally used as a nervine and burn remedy among many other things.

Four clinical trials have assessed the efficacy of aromatherapy or lavender essential oil massage on aggressive and agitated behavior in people with dementia. The first study was a double-blind trial that used 2% lavender oil aerosolized for two hours compared to aerosolized water in patients with severe dementia and agitated behavior.[46] The lavender treatment was more effective than water at modestly reducing agitation. However, a trial in seven patients using oil saturated in cloth worn attached to the shirt did not find any effect on behavior.[47] An open trial of hand massage using lavender oil found it more effective than no massage or massage with just jojoba oil over two weeks' time for reducing aggressiveness in Korean dementia patients.[48] In the most recent controlled trial, inhalation of lavender oil reduced agitation significantly better than inhalation of sunflower oil in Chinese dementia patients.[49]

The majority of data appears to support the efficacy of lavender volatile oil for reducing aggressive behavior and agitation in Alzheimer's patients. Its extremely low rate of adverse effects (occasional respiratory irritation being the only effect noted in most cases) and low cost are major advantages.

Withania somnifera (Ashwagandha)

Many of the plants listed on Dr. James Duke's phytochemical database[50] that are high in constituents that have shown a potential benefit in Alzheimer's disease are adaptogens. Adaptogens nonspecifically strengthen both the body and the mind, particularly counteracting the negative

effects of stress, and historically were used to slow or offset the negative symptoms of aging. For a more in-depth discussion of adaptogens, see chapter 3. We strongly recommend the use of adaptogens in Alzheimer's disease, particularly *Withania somnifera* (ashwagandha).

Ashwagandha ("horse sweat," from the characteristic odor of the freshly dug root) hails from India and neighboring regions and has a very long tradition of use in Ayurvedic medicine. It is a member of the Solanaceae (nightshade) family, unlike many other adaptogens that are found in the Araliaceae (ginseng) family. The root is the part used.

Ashwagandha stimulated neurite outgrowth in human brain cells; this may compensate for damaged neuronal circuits in the dementia brain.[51] In animals and in vitro, ashwagandha stimulated thyroid function, increased physical endurance, and had strong hepato- and renal-protective, antineoplastic effects, as well as cardioprotective, anti-inflammatory, antioxidant, and immunomodulating effects.

Human trials of ashwagandha in dementia are lacking. Ashwagandha appears very safe based on historical information and limited clinical trial data.[52] Unlike other adaptogens, which tend to be stimulating, ashwagandha has a calming effect and thus may be particularly indicated in people with Alzheimer's disease and agitation. For those who are more catatonic, one of the Araliaceae adaptogens (*Panax ginseng* [Asian ginseng] root, *P. quinquefolius* [American ginseng] root, *Aralia californica* [California spikenard] root, *Oplopanax horridus* [devil's club] root bark, or *Eleutherococcus senticosus* [eleuthero] root) is possibly more appropriate. Both American and Asian ginseng have improved memory deficits in animal studies, and Asian ginseng has shown some preliminary but positive effects on cognition in humans.[53]

DIET

The risk of developing dementia is lower in subjects having a diet rich in flavonoids.[54] Therefore, a diet rich in a variety of fruits and vegetables should be part of any Alzheimer's disease regimen. We consistently recommend that an Alzheimer's patient's diet emphasizes two foods in liberal quantities: blueberries and beets.

Figure 4–5. *Vaccinium myrtillus* (blueberry)

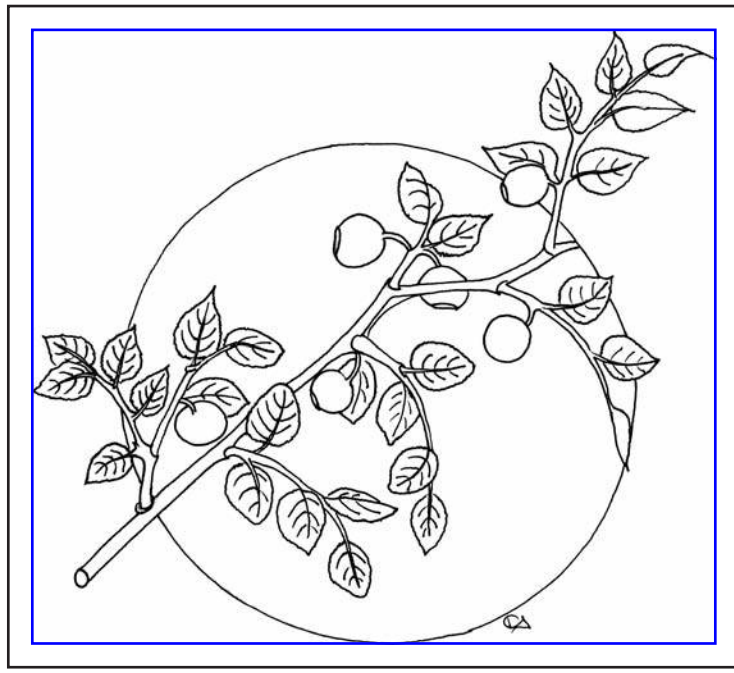

Figure 4–6. *Vaccinium myrtillus* (blueberry)
Drawing ©2004 by Kathy Abascal, BS, JD.

Anthocyanins from blueberries display strong vasoprotective and anti-inflammatory properties. Blueberries are rich in anthocyanins and top the list of foods containing constituents that may enhance neuronal function.[55] In aged rats, blueberry extracts reversed age-related decline in cognitive, motor, and neuronal effects.[54] At the equivalent of 1 cup/day of blueberries in a human, blueberries increased the release of dopamine in the rat brain. The dopaminergic system is impaired in Alzheimer's, there is some evidence showing a related loss of cognitive function (verbal memory and naming performance), and it has been suggested that dopamine agonists may be helpful in early Alzheimer's.[56]

A history of hypertension may be an independent risk factor for Alzheimer's.[57] The connection is complex as the hypertensive episodes may precede the onset of dementia by a decade or more and because the onset of dementia is often preceded by a hypotensive period. However, research is beginning to indicate that homocysteine levels may some day help explain the link between hypertension and dementia.[58] It has been estimated that elevated homocysteine accounts for about 15% of the population's risk for Alzheimer's.[55] Beets are rich in betaine (named for beets, in fact), and betaine may help lower homocysteine levels although this is far from fully established.[59] However, beets are rich in antioxidant compounds that certainly will be useful in Alzheimer's patients.

CONCLUSION

There are many botanicals that have shown a potential benefit in Alzheimer's disease.[60] This is particularly promising because current drug treatments are inadequate and fairly toxic.

4–3. *Nutrients and Alzheimer's Disease*

Vitamins and nutritional supplements should be part of any treatment plan for Alzheimer's disease but their role is beyond the scope of this article. However, we wish to make one strong recommendation about vitamins here. We urge our patients to make sure they take both vitamin E and vitamin C *at the same time* and consistently. Vitamin C (1,000 mg) had a synergistic effect with vitamin E (400 IU) in a human study rendering cerebrospinal fluid and plasma lipoproteins less susceptible to in vitro oxidation.[a] A large-scale, double-blind trial, once randomization problems were corrected, found vitamin E significantly delayed time to nursing-home placement of people with Alzheimer's disease.[b]

Two other nutrients with a large amount of research support for treating Alzheimer's disease are phosphatidyl serine[c] and acetyl-L-carnitine.[d]

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Preliminary clinical trials suggest herbs may have a useful role to play in treating people with Alzheimer's disease, though much more research is needed to fill in the gaps in our knowledge. The treatment plan described in this article is one example of how a practitioner might combine strongly antioxidant herbs that have a historical usage as memory aids with adaptogens and a varied diet rich in plant nutrients to prevent or retard the progression of Alzheimer's disease. (See Sidebar 4-3.)

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5

NERVINE HERBS FOR ANXIETY, INSOMNIA, AND ADDICTION

Nervine herbs are commonly used to help people cope with stress, anxiety, insomnia, mild depression, and similar problems. These herbs have a long history of traditional use, and appear to be safe and effective. Unfortunately, they have not received much scientific attention. A recent French clinical study pointed out the great need for serious research on the use of nervines. The authors explained that patients frequently consult their physicians about anxiety disorders, and estimated that 25% of adult French patients suffer from some type of anxiety disorder.[1] The statistics also reflect that anxiety disorders are equally common in American patients.[2]

Typically, anxiolytic or hypnotic drugs are prescribed for these patients, most commonly benzodiazepines, though these agents are problematic. For short-term use, these sedatives can cause a loss of memory, disturb balance in elderly patients, degrade sleep quality, and diminish alertness in drivers leading to accidents and injuries. They can also cause rebound insomnia and anxiety after discontinuation or paradoxical worsening of anxiety during use. For long-term use, the drugs can lead to dependence and withdrawal symptoms as well as side effects such as somnolence, fatigue, gastrointestinal upset, and vertigo.

It makes much greater sense to use herbs as an initial prescription for most of these patients, reserving pharmaceuticals for patients with more difficult and persistent cases of anxiety. This chapter describes how nervines are commonly used in practice and attempts to clarify some of their clinical distinctions. Where relevant research is available it is noted, but because such research is limited, mostly clinical pictures are provided. A few botanicals, such as *Hypericum* spp. (St. John's wort) for mild to moderate depression, *Piper methysticum* (kava) for mild to moderate anxiety, and *Valeriana* spp. (valerian) for insomnia have a substantial amount of research support and those uses are not discussed here. Instead we discuss some commonly used but less popular nervines. However, St. John's wort, kava, and valerian should be considered as options in any treatment plan as they are quite effective. Tables 5-1 and 5-2 provide additional information on most of the nervines in use, including some of their specific uses and dosages.

Hawthorn

In a French study, patients were administered a tablet combining 75 mg dried hydro-alcoholic extract of *Crataegus oxyacantha*, now known as *C. laevigata* (hawthorn) flower; 25 mg dried aqueous extract of *Eschscholzia californica* (California poppy) flower; and 75 mg elemental magnesium. Patients took two tablets twice daily for three months. Two-hundred sixty-four patients participated in this multicenter study, which measured changes in the Hamilton Anxiety Scale (HAM-A), change in patient self-assessment, number of responsive subjects (defined as at least a 50% reduction in Hamilton or self-assessment scale), and the physician's clinical global impression. Only physicians specializing in the evaluation of drugs in mental disorders participated. As in most anxiety studies, the placebo response was high (40%). However, the decrease in HAM-A and the self-assessment of anxiety were both significantly greater in the herb group than in the placebo group. The physicians rated the combination formula with 90%

Table 5–1. Other Common Clinical Uses of Nervines

Herb	*Easily Fatigued, Mildly Depressed*	*Anger Issues*	*Trouble Concentrating*	*Sleep Problems*	*Heart Palpitations, Nonorganic*	*Panic*	*Other Major Indications*
Eschscholzia californica (California poppy)				Yes		Yes	Pain
Matricaria recuita (chamomile)		Yes	Yes	Yes			Indigestion, inflammation
Crataegus spp. (hawthorn)					Yes		Cardiovascular disease
Piper methysticum (kava)			Yes	Yes		Yes	Pain, addiction
Lavandula spp. (lavender)	Yes			Yes			Infections
Melissa officinalis (lemon balm)	Yes		Yes			Yes	Viral infections
Tilia spp. (linden)				Yes	Yes		Viral infections
Leonuris cardiaca (motherwort)			Yes	Yes	Yes		Uterine weakness
Avena spp. (oats)	Yes	Yes	Yes			Yes	Addiction
Passiflora incarnata (passionflower)			Yes	Yes	Yes	Yes	Pain
Scutellaria lateriflora (skullcap)		Yes					Pain
Hypericum spp. (St. John's wort)	Yes		Yes				Neuropathy, viral infections
Valeriana spp. (valerian)				Yes		Yes	Pain
Verbena spp. (verbena)		Yes					Hormonal imbalance, indigestion

Note: Each herb is used as a nervine for general anxiety and irritability.

Table 5–2. Doses for Nervines and Possible Safety Considerations

Herb	*Adult Dose, Tincture*	*Negative Drug Interactions*	*Safety Concerns*
Eschscholzia californica (California poppy)	0.5–1 ml four times per day	Theoretical concern that it may potentiate MAO inhibitors	None known; considered safe in pregnancy
Matricaria recuita (chamomile)	4–6 ml three times per day		None known; considered safe in pregnancy
Crataegus spp. (hawthorn)	4–5 ml three times per day		None known; considered safe in pregnancy
Piper methysticum (kava)	3–5 ml three times per day	Theoretical concern that it may increase toxicity of hepatotoxic drugs	Not safe in pregnancy; not for use in patients with liver ailments, on drugs that tax the liver, or in patients who frequently consume alcohol; not for long-term use
Lavandula spp. (lavender)	1–2 ml three times per day		None known; considered safe in pregnancy
Melissa officinalis (lemon balm)	2–5 ml three times per day		None known; considered safe in pregnancy
Tilia spp. (linden)	3–5 ml tid		None known; considered safe in pregnancy
Leonuris cardiaca (motherwort)	1–2 ml four times per day		None known; considered safe in pregnancy
Avena spp. (oats)	Tincture 1–5 ml four times per day		None known; considered safe in pregnancy
Passiflora incarnata (passionflower)	3–5 ml three times per day		None known; considered safe in pregnancy; isolated reports of tachycardia and pancreatitis
Scutellaria lateriflora (skullcap)	3–5 ml three times per day		None known; considered safe in pregnancy
Hypericum spp. (St. John's wort)	Tincture 2–5 ml four times per day	Can decrease blood levels of many prescription medications, including birth control pills, protease inhibitors, warfarin, and digoxin	Possible photosensitization but likely rare; otherwise none known; considered safe in pregnancy
Valeriana spp. (valerian)	48 ml three to four times per day		None known; considered safe in pregnancy
Verbena spp. (verbena)	1–3 ml three times per day		None known; not safe in pregnancy

Note: Most nervines are poorly studied, and their possible interactions with drugs are not fully known.

in favor of the combination as opposed to 80% for placebo. They concluded that the combination formula was an effective and safe treatment for mild to moderate anxiety states.

Hawthorn is not typically considered a nervine. Instead, it is primarily viewed as a heart medicine and is fairly well researched as such. Many herbal practitioners have noted that hawthorn has a calming effect, and that it can also help alleviate cardiac symptoms of anxiety such as palpitations and increased blood pressure. In Chinese medicine, *Crataegus pinnatifida* (shan zha) fruit is recognized primarily for disturbed shen, which is very similar to the Western conception of anxiety. A combination of hawthorn and *Passiflora* spp. (passionflower) reduced patient scores on the HAM-A index compared to placebo.[3] There is also a clinical study reportedly showing that combinations of hawthorn and passionflower (*P. incarnata*) combined either with *Erythrina* spp. or *Salix alba* (willow) worked well in a multicenter, prospective, randomized, double-blind, comparative study of patients with insomnia and mild anxiety.[4]

Crataegus monogyna (one-seed hawthorn) as well as *C. laevigata* are medicinally active. Though both are native to Eurasia and are members of the Rosaceae family, *C. monogyna* has naturalized in the United States. *C. douglasii* (blackthorn) is a native Northwest alternative. Other local species may also be medicinally active—generally this appears to be true where the tree has thorns and white or pink flowers (as opposed to red), and the flowers have a disagreeable fishy odor.

California Poppy

Unlike hawthorn, the lovely California poppy is primarily used as a nervine. It and the *Papaver somniferum* (opium poppy) are in the Papaveraceae family, though only opium is narcotic. California poppy, native to the southwestern United States but naturalized as far north as Washington state, will not produce a high and helps normalize psychological function. It has mild analgesic effects and is a gentle calmative. Low-dose opium appears to have similar effects to California poppy, having been described as an antidepressant and hypnotic by German physicians who used primarily herbal medicines.[5] Only at high doses or as purified heroin or morphine does it dull consciousness, cause euphoria, and induce sleep.

There are anecdotal reports that California poppy used alone has helped individuals overcome their fear of flying or fear of public speaking. Clinicians seldom use California poppy alone, instead using it to harmonize or boost efficacy of other nervines. In a lower dose in a mood formula, it makes life seem a little better and a little more manageable. In a higher dose in a sleep formula, it makes the patient more ready to fall asleep. Mixed with valerian or other herbs, it creates a sleep mixture that works if pain, say from a sprained ankle, is interfering with sleep.

Studies show that California poppy tea reduces anxiety, acts as a mild analgesic, and helps prevent drug-induced memory loss in mice.[6] Animal studies confirm that an aqueous-alcoholic extract of California poppy has sedative effects at higher doses and anxiolytic effects at lower doses.[6] California poppy contains protopine, a compound that is suggested to have both anti-acetylcholinesterase and antiamnesic properties.[7] The extracts injected intraperitoneal. did not induce any acute toxic effects and its LD_{50} was over 5,000 mg/kg.

Native Americans claimed that even the scent of California poppy was poisonous to pregnant women. Some texts advise that it may be contraindicated in pregnancy because its constituent allocryptopine (and possibly other alkaloids) has an oxytocic effect, whereas other practitioners consider the herb safe for short-term use in pregnancy.[8] There are no other known adverse effects, contraindications, or interactions.

Immature Oat Seed

One of the safest and most popular nervines is *Avena* spp. (oat) immature or milky seed, a Poaceae family member native to Asia and now spread globally in temperate climates. The seed is very distinct from the largely lifeless oat straw or stem. Immature oat seed is prescribed for acute and chronic anxiety, stress and excitation, neurasthenic and pseudoneurasthenic syndromes, skin diseases, connective tissue deficiencies, and weakness of the bladder, and as a tonic and roborant. The German Commission E, however, concluded that its effectiveness for these conditions had not been established.[9] The Eclectics considered tincture of oat seed to be a mild stimulant and nerve tonic, and many Eclectics considered it of some importance for nervous debility and for affections bordering closely upon nervous prostration. It was deemed useful for headaches from exhaustion or overwork or the nervous headache of menstruation. But they cautioned that it was not a remedy of great power and would not always be useful. They did not consider its use in morphine addiction to be substantiated.[10]

Many Western herbalists prefer to use oat seed tincture as a simple to quiet temporary, mild anxiety or to take the edge off moods that might otherwise express themselves as angry outbursts or loss of self-control. We have also used it in pet dogs to calm and avert seizures. Oat seed tincture is frequently included as an ingredient in formulas intended to help patients quit cigarette smoking. This aspect of oats has been the subject of some research, mostly with negative results.[11,12] These results mirror the conclusion of the Eclectics: oat seed is not strong enough to have a substantial effect on serious addictions like cigarette smoking, although its calming effect may be somewhat helpful as a component of a treatment for these addictions. It is, however, safe for use in essentially anyone, with no known contraindications (except that some patients with celiac disease cannot tolerate it), adverse effects, or interactions.

Passionflower

Passiflora incarnata (passionflower) leaf (Passifloraceae family) comes from a vining plant native to the southeastern United States and produces one of the truly most visually stunning flowers of all. Passionflower may be particularly useful in formulas for addiction and is traditionally used in herbal sleep formulas as well as in calming formulas for anxiety. The German Commission E has approved the use of passionflower for nervous restlessness.[9] For the Eclectics, passionflower was specifically indicated for irritation of brain and nervous system, with atony; insomnia from worry or overwork, or from febrile excitement; sleeplessness of the young and aged; convulsive movements; hysteria; infantile nervous irritability; dyspnea; or heart palpitations from excitement or shock.[10] It was considered a very effective remedy for whopping cough and spasmodic asthma.

In heroin addicts, passionflower significantly enhanced the effect of clonidine in reducing withdrawal symptoms.[13] In this study, 65 opiate addicts were randomly assigned to take either clonidine and 60 drops of passionflower extract (further details not provided) or clonidine and 60 drops of placebo liquid three times daily for 14 days. The Short Opiate Withdrawal Scale was used to assess the benefit of adding passionflower to the regimen.

Passionflower was as effective as oxazepam in the treatment of 36 patients with generalized anxiety disorder, and was preferred over the drug by the researchers because it did not impair job performance.[14] The patients (20 women and 16 men) who met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria for a diagnosis of generalized anxiety disorder with a duration of at least six months participated in this four-week-long trial. A proprietary liquid extract of *P. incarnata* (45 drops/day) was used in the study, and a psychiatrist assessed

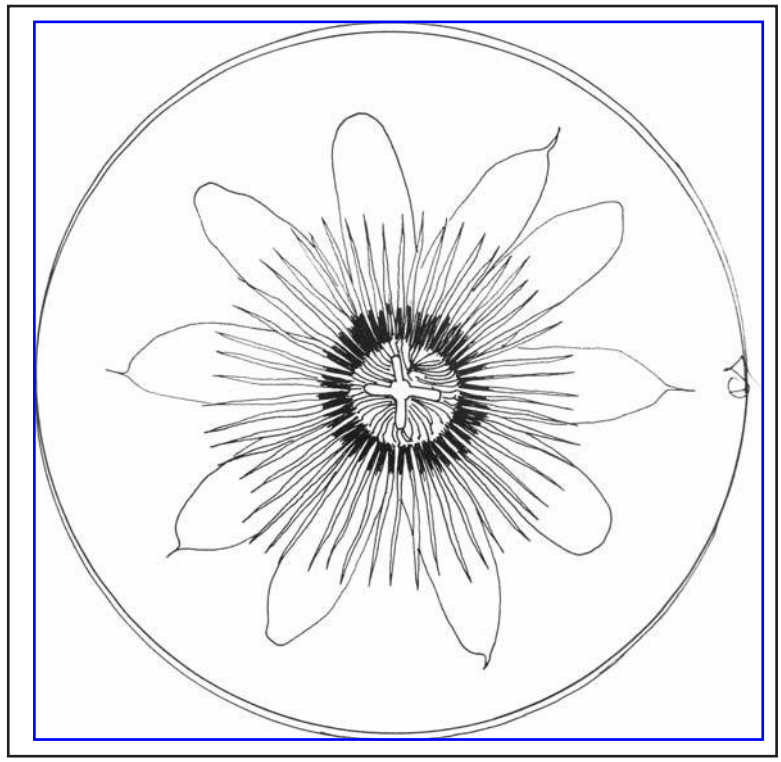

Figure 5–1. *Passiflora* spp. (passionflower)
Drawing ©2004 by Kathy Abascal, BS, JD.

the patients using the HAM-A on six occasions during the study. A study of 111 menopausal women found that *P. incarnata* reduced the frequency of "unpleasant behaviors" of the "socio-sexual behavioral disturbances" found in 80% of these women. This quaint and inappropriate nomenclature referred to symptoms such as irritability, anxiety, stress, and depression.[15] In children and teens with attention-deficit hyperactivity disorder, passionflower (0.08/mg/kg/day) was compared with, and rated as effective as, methyphenidate by teachers and parents.[16]

A benzoflavone from passionflower reversed tolerance and dependence on several psychotropic drugs in rats, including morphine, nicotine, ethanol, diazepam, and delta-9-tetrahydrocannabinol.[17] It enhanced libido and reduced the libido-depressing action of the psychotropic drugs in animals.[17,18] Passionflower had an anxiolytic effect in mice at doses of 50–150 mg/kg.[19] Passionflower had a synergistic effect when administered with kava to mice.[20] Kava had a more pronounced effect on reducing amphetamine-induced hypermotility, whereas passionflower prolonged barbiturate-sleeping time more than kava did. However, another study found that passionflower reduced the hexobarbital sleeping time of mice. One pharmacological study failed to show that passionflower bound to benzodiazepine, dopaminergic, or histaminergic receptors in vitro.[21]

Numerous species of *Passiflora* have been considered for use as medicine, primarily *P. incarnata* and *P. edulis*. One animal study found that while *P. incarnata* was active as an anxiolytic, *P. edulis* was devoid of any activity.[22] Other animals studies, however, show various species (e.g., *P. alata, P. quadrangularis,* and *P. actinia*), including *P. edulis,* to have anxiolytic effects.[23–27] Interestingly, in the study on *P. quadrangularis*, the alcoholic extract worked about as well as diazepam, whereas the aqueous extract lacked an anxiolytic action.[28] In

contrast, the study of *P. edulis* found the aqueous extract to be anxiolytic without an effect on the motor system, whereas the total flavonoid fraction was anxiolytic but compromised motor activity.[26] *P. incarnata* is the species most commonly referenced by older herbals in the West and the one we continue to prefer.

There are reports of passionflower causing tachycardia but its overall safety profile is very high and it can be used in pregnancy.[29] There are lingering concerns that aqueous passionflower extracts can increase serum amylase levels, presumably due to pancreatic damage, as has been observed in clinical trials.[30] Actual pancreatitis has only been reported very rarely; these laboratory changes are of unknown importance and have never been seen in our clinical practices.

Lemon Balm

Melissa officinalis (lemon balm) leaves (Lamiaceae family) have a long history of use as anxiolytics and memory support. Back in the eighth century, Razes described lemon balm as a "great help for sorrow and troubles." According to Paracelcus, "amongst all that the earth produces, it has the best effect on the heart," and French physicians have long used lemon balm to bring happy dreams and drive out sadness.[31]

The German Commission E has approved the use of lemon balm for nervous sleeping disorders and functional gastrointestinal complaints. Clinicians often prescribe lemon balm as a mild mood elevator and calming herb in anxiety. In a randomized, placebo-controlled, double-blind, crossover trial of 20 healthy volunteers, lemon balm showed a sustained improvement in accuracy of attention and calmness at the lowest dose (300 mg/day) and a reduction of alertness and memory decrements at the highest dose (900 mg/day).[32] The study failed to confirm a significant effect on cholinergic binding. The researchers noted that the lowest dose of lemon balm appeared most efficacious and also noted that the low cholinergic binding properties might have been a result of the loss of volatile components in the product used. We and many other practitioners prefer to use only products made from fresh lemon balm to preserve these vital components.

In a double-blind, randomized, placebo-controlled trial, 42 patients with mild to moderate Alzheimer's disease were given a daily dose of 60 drops of lemon balm tincture over a four-month period.[33] Lemon balm significantly improved cognitive function compared to placebo with significant improvement in cognition seen after 16 weeks of treatment. In addition, agitation was more frequent in the placebo group. This correlated with another clinical trial that indicated that lemon balm essential oil had a calming effect on Alzheimer's patients.[34] In an open, multicenter study of 918 children (less than 12 years old), a combination of valerian root (160 mg) and lemon balm (80 mg) substantially reduced dyssomnia and restlessness.[35] In healthy volunteers the combination was anxiolytic at the lowest dose (600 mg) but less so at the highest dose (1,800 mg).[36]

At low doses, lemon balm was said to have a sedative effect on mice (it increased their comfort at being in open spaces, which is interpreted as an anxiolytic effect); at higher doses, the extract had a peripheral analgesic effect and potentiated the sedative effect of pentobarbital.[37] Lemon balm has a thyroid-inhibiting action (by acting both on thyroid-stimulating hormone and on the cellular TSH receptor) in vitro.[38] Lemon balm is today sometimes used clinically to treat hyperthyroidism based on these in vitro studies. Still, the general practitioner consensus is that the herb can be used safely in patients with low thyroid function. It may be that other constituents in the plant offset the effects of the isolated constituent in vitro. Lemon balm is also useful for treating herpes and other viral infections, and its pleasant lemony flavor often makes it useful as a taste enhancer in formulations.

Lemon balm is exceedingly safe and is often used in children. There are no known drug interactions or contraindications. A typical adult dose of the fresh herb tincture is 2–5 ml three times daily.

Vervain

Verbena spp. (verbena or vervain) flowering top has a widespread and very long history of use. The Druids considered it sacred and used it in ceremonies and religious rites. The name *vervain* comes from the Celtic *ferfaen*, "to drive away a stone," referring to a traditional use of verbena for bladder problems and urinary stones. The physicians of Myddfai in 13th-century Wales recommended it for all diseases, but especially for those of the liver, lungs, and kidneys.[39] It was widely used in various traditions for colds, dyspepsia, weak nerves, and liver disorders. In South America, it continues to be used to stimulate milk production, especially in an overly stressed new mother.[40] Vervain is in the Verbenaceae family.

As a nervine, the leaves and flowers of *Verbena* species are often used where there is a component of anger or agitation present in the patient. Michael Moore, director of the Southwest School of Botanical Medicine, gives the following clinical picture of a patient likely to benefit from the use of verbena:[41] verbena is useful in a flushed, red-faced, or angry person; it is a menopausal nervine that chills and calms, allowing sleep; it also quiets those sudden angry outbursts that frequently occur in perimenopause. It will have the same effect on younger women with outbursts related to premenstrual syndrome. He also considers verbena a great occasional herb for children who are worked up, red in the face, overexcited, and unable to calm down.

The German Commission E concluded that the evidence did not establish the effectiveness of verbena for ailments of the oral and pharyngeal mucosa (angina, sore throats), of the respiratory tract (coughs, asthma, whooping cough), pain, spasms, exhaustion, nervous conditions, digestive disorders, liver and gallbladder diseases, jaundice, diseases and ailments of the kidneys and lower urinary tract, menopausal complaints, irregular menstruation, or lactation.[9] The Commission does consider verbena to be secretolytic.

Verbena's use as a nervine has not been researched. Several constituents in *V. littoralis* H. B. K. enhanced the activity of nerve growth factor (NGF)—mediated neurite outgrowth in vitro.[42–44] The various verbena species are considered largely interchangeable in clinical practice.[41] Verbena in vitro showed novel neuroprotective effects, including the ability to attenuate the toxicity of beta-amyloid.[45] Verbena, in vitro, displayed a higher degree of binding to progesterone receptors and increased the progestin activity of saliva to a greater degree than did 150 other herbs and spices. Information on whether this activity constituted a significant effect was not available.[46] An abstract reports that verbena combined with many other herbs (*Acatea racemosa* [black cohosh], *Trifolium* spp. [red clover], *Dioscorea villosa* [wild yam], *Salvia* spp. [sage], *Vitex agnus-castus* [chasteberry], *Astragalus membranaceus* [astragalus], *Leonurus cardiaca* [motherwort], and soy isoflavones) in an open-label study dramatically decreased menopausal symptoms of tiredness, absentmindedness, and lack of energy as well as the typical menopausal symptoms of hot flashes, heart palpitations, and night sweats.[47]

Lavender

Lavandula spp. (lavender) leaf is a nervine with stronger sedative effects. Lavender is a Lamiaceae family member native to the Mediterranean region.

Figure 5–2. *Lavandula* spp. (lavender)

The German Commission E has approved the use of lavender flowers for mood disturbances such as restlessness or insomnia, functional abdominal complaints (nervous stomach irritations, intestinal gas), and nervous intestinal discomfort.[9]

The Eclectics considered it an agreeable and soothing lotion for the headache of debility and in fevers.[10] It was an ingredient in a soothing syrup prescribed for nervous irritability in children. Practitioners today often add lavender as a component in a nervine formula, and consider it helpful but tend not to use the herb as a stand-alone treatment. The essential oil is commonly used as a calmative to relieve mild headaches, an antimicrobial, and to treat minor burns. Lavender aromatherapy has shown the ability to lessen agitation in agitated elderly patients suffering from dementia.[48] In one clinical trial it was just as effective as the tricyclic antidepressant imipramine for adults with mild to moderate depression.[49] In gerbils, lavender aromatherapy was as anxiolytic as diazepam (1 mg/kg, i.p.) and was especially effective in female gerbils.[50]

Linden

Tilia spp. (linden) flowers were used in many parts of the world as a hypnotic, diaphoretic, and diuretic. Linden, sometimes slightly confusingly called lime flower, is in the Tiliaceae family and is not in any way related to true lime. Today, the primary use of linden is as a treatment for colds and flu. Herbalists and other natural medicine practitioners also use linden flowers to relax blood vessels and it is often used in small doses to calm older, nervous people and high blood pressure. In larger doses, the flowers are used to bring on a good, restful sleep.

Animal studies tend to confirm these uses as they show that linden flowers reduce anxiety in mice, reduce blood pressure, and have a sedative effect at higher doses. The flowers contain mucilages, flavonoids, phenolic carbon acids, and essential oils.[51] It has been reported that fresh infusions of linden prolonged the swimming time of mice in a forced swimming test that is interpreted to indicate an antistress effect.[52] A flavonoid complex injected intraperitoneally in mice had a clear anxiolytic effect.[53] Another study reports that freeze-dried aqueous extract of linden showed sedative effects in mice at doses ranging from 10 to 100 mg/kg.[54] Linden extracts injected into rabbits produced a hypotensive effect with a large drop in diastolic arterial pressure, indicating vasodilation.[55] An aqueous extract of linden flowers stimulated lymphocyte production in vitro, with an action mimicking that of two drugs that act as agonists of the peripheral benzodiazepine receptor, perhaps suggesting that linden also is an agonist of this receptor.[56] In another mouse study, both the hexane and methanol extracts of linden were anxiolytic and sedative and elicited behavior similar to that caused by diazepam.[57]

Some concerns have been raised that, because linden contains vitamin K, it may lessen the effect of warfarin or related anticoagulant therapy. However, the usual tincture doses of linden are far too low to contain sufficient vitamin K to interfere (tea doses may be sufficient to cause a problem). Generally, linden is considered a safe herb that can be used in pregnancy.

CONCLUSION

The nervines discussed here have a long history of use in many different folk traditions to improve mental functioning, moods, and sleep. They often work well as simples but have interesting and synergistic effects when combined. In fact, there are glimmerings of scientific support for this concept. Thus, kava and passionflower quieted amphetamine-induced hypermotility in mice more effectively than either herb alone.[58] Most practitioners end up developing nervine mixtures that work especially well for particular mood states or disorders. One of our favorite formulae is given in Sidebar 5-1.

5–1. *A Nervine Formula*

One of our favorite nervine formulae combines equal parts of St. John's wort, lemon balm, and a less well-known plant, *Corydalis aureus* (golden smoke). This formula has proved highly useful in stressed-out, anxious individuals in difficult emotional circumstances. It tends to help them avoid spiraling into depression, instead being able to acknowledge their difficulties without becoming emotionally overwhelmed.

There is little research on this member of the Fumariaceae family. The root of a related species is widely used in Chinese medicine and alkaloids from related species have shown strong anticholinesterase activity,[a,b] to reduce cocaine cravings in addicted rats,[c] to inhibit drug-induced seizures in rats,[d] and to alleviate scopolamine-induced memory impairment in mice.[e] California poppy combined with *C. cava* is used in a product called Phytonoxon N, intended for nervousness-induced insomnia, agitation, and/or anxiety.[f] Another product combines California poppy, *Leonurus cardiaca* (motherwort), *C. cava*, and passionflower.[g] In mice, the combinations prolonged hexobarbital-induced sleeping

(*continued*)

5–1. *A Nervine Formula (continued)*

time while *C. cava* alone had a yet stronger effect. *C. cava* also decreased the exploratory activity of mice, whereas California poppy did not affect this parameter. The combination improved alcohol-impaired balance but did not work effectively when passionflower was taken out of the combination.

Dose: 20–30 drops as needed. Because little is known about golden smoke, we recommend against its use in pregnancy and lactation and do not use it in combination with prescription drugs.

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6

NATURAL APPROACH TO CHRONIC PROSTATITIS AND CHRONIC PELVIC PAIN SYNDROMES

Chronic prostatitis is a surprisingly common set of conditions affecting men in the Western world (and possibly elsewhere). While early on most believed chronic prostatitis was a bacterial infection, over time it became clear that some men had inflammation without infection and some had pain without inflammation or infection. The latter condition is now generally referred to as prostatodynia or chronic pelvic pain syndrome (CPPS). Even in men with chronic prostatitis who have bacteria in their prostatic secretions, antibiotics often induce only temporary relief. This supports the idea of a complex, multifactorial etiology and pathophysiology for all forms of chronic prostatitis. See Table 6-1 for the present official distinctions among prostatitis syndromes.

The need for different therapeutic options and a fresh, holistic, philosophical approach goes beyond the fact that bacteria are not the simple cause of many cases of chronic prostatitis and probably all cases of CPPS. Troubling studies have documented that a substantial proportion of men who are treated with powerful antibiotics long term for chronic bacterial prostatitis develop dysbiosis or abnormal gut flora.[1] This may in fact prolong, aggravate, or otherwise maintain the pathological process of prostatitis by suppressing healthy gut flora and allowing abnormal, disease-promoting strains to predominate. This adverse drug effect also highlights that there is a gut–prostate axis to be considered. Here we consider natural therapies to address the multiple aspects of various chronic prostatitis and CPPS syndromes that may avoid the adverse effects of mainstream therapy (see Table 6-2).

THE INFECTION CONNECTION

The normal prostate is considered sterile. This is supported by polymerase chain reaction studies of prostate samples obtained from healthy men during biopsies and at radical prostatectomy.[2] However, men with chronic bacterial prostatitis have gut flora colonizing their prostates. This is surprising given the long male urethra and its relative distance from the anus, compared to the short female urethra and its close proximity to the anus. Nevertheless, based on research in men with acute prostatitis, it is clear that gut bacteria (either the man's own or from a sexual partner) can ascend the male urethra and infect the prostate in generally healthy men.[3] Though acute prostatitis is distinct from chronic bacterial prostatitis, it does show that gut bacteria can and do ascend the male urethra. To some extent this suggests that chronic bacterial prostatitis is a type of urinary tract infection, supported by evidence that *Escherichia coli* strains causing both acute and chronic prostatitis have virulence markers similar to those seen in women who develop pyelonephritis (but not cystitis).[4]

Complicating this straightforward-seeming picture are a number of lines of evidence. Various studies looking for bacteria deoxyribonucleic acid (DNA) fragments or unusual microbes have found evidence for stealth infection.[5] There is also the potential that a prior infection, whether symptomatic or not, induced an immune or autoimmune reaction. This is discussed in

Table 6–1. National Institute of Health Definitions of Prostatitis Syndromes

Type	*Name*	*Symptoms*	*Findings in Urine and/or EPS*
I	Acute bacterial prostatitis	Acute pain and dysuria, fever	Bacteria, WBC
II	Chronic bacterial prostatitis	Chronic, recurrent pain	Bacteria, WBC
III-A	Chronic abacterial prostatitis, inflammatory CPPS	Chronic, recurrent pain	WBC, no bacteria
III-B	Noninflammatory CPPS	Chronic, recurrent pain	Normal
IV	Asymptomatic inflammatory prostatitis	None	WBC, no bacteria

CPPS: chronic pelvic pain syndrome; EPS: expressed prostatic secretions; WBC: white blood cell.

Table 6–2. Dr. Yarnell's ProstInflanix Formula

This is a general formula developed by Dr. Yarnell as a starting point for patients with chronic prostatitis. It can be individualized to the specifics of any particular patient.

Herb	*Form*	*Percentage in Formula (%)*	*Major Actions*
Echinacea angustifolia	Fresh root tincture	10–20	Antimicrobial, immune stimulant, inflammation modulating
Serenoa repens	Dried fruit tincture	10–20	Tonic, inflammation modulating
Betula spp.	Fresh leaf tincture	10–20	Anodyne, inflammation modulating
Glycyrrhiza glabra	Dried-root fluid extract	10–15	Immunomodulating, gut healing, inflammation modulating, adaptogen
Aesculus hippocastanum	Dried fruit tincture	5–10	Inflammation modulating, anti-edema
Eryngium yuccifolium	Fresh root tincture	5–10	Inflammation modulating
Fouquieria splendens	Fresh bark tincture	5–10	Pelvic lymphagogue
Eleutherococcus senticosus	Dried-root fluid extract	5–10	Immunomodulator, adaptogen
Piper methysticum	Fresh root tincture	5–10	Nervine, pelvic organ sedative, anodyne
Equisetum arvense	Fresh sterile stems glycerite, tincture, or syrup	5–10	Tonic, mucous membrane restorative
Pulsatilla patens	Fresh flower tincture	2–3	Pelvic anodyne

All percentages assume a dose of 1 tsp (5 ml) three times per day, for an average-sized adult male (200 lbs or 90 kg).

more depth below. Different camps conclude from these data that one cannot be certain that the absence of bacteria in urine or expressed prostatic secretions rules out their involvement in chronic prostatitis or CPPS.

Whenever microbial involvement is suspected or documented and antibiotics do not seem to be sufficient, botanical antimicrobial agents should be considered. Though untested in clinical trials, they have a long reputation of helping with numerous infections. It is not known which herbs are most effective but two candidates based on their historical use as urinary tract anti-infectives are *Juniperus communis* (juniper) leaf and *Arctostaphylos uva-ursi* (uva ursi) leaf. Herbs that are more generally used as antimicrobials without a strong history of urinary tract use include *Rosmarinus officinalis* (rosemary) leaf, *Mahonia aquifolium* (Oregon grape) or *Berberis haematocarpa* (desert barberry) root, *Camellia sinensis* (green tea) leaf, *Allium sativum* (garlic) bulb, and *Hypericum perforatum* (St. John's wort) flowering top. All of the herbs in the latter category are also particularly noted here because of in vitro evidence that they reduce antibiotic resistance, a concern in men who have often been treated with multiple or chronic courses of potent antibiotics.[6] The most specific recent research shows that catechin, a key component in green tea, can enhance the efficacy of ciprofloxacin in a rat model of chronic bacterial prostatitis.[7] Probiotics should also be supplemented in such instances due to the damage to the gut-flora antibiotics as mentioned at the beginning of the article.

LEAKY PROSTATE SYNDROME

Ever since the advent of prostate surgery and possibly before this during anatomical dissections, it has been noted that some men have stones in their prostates. A recent, large-scale screening of 1,374 young Greek men revealed that 101 of them had stones detectable by ultrasound.[8] Of these, 71% had microscopic stones and 29% had large stones. CPPS symptoms were far more likely to occur in those men who had large stones. Even more telling is a study in which men with chronic prostatitis had carbon particles instilled in their bladder, and over 70% had particles present throughout their prostates just hours later as detected during transuretheral resection of the prostate operations.[9]

Normally, urine elements are not supposed to enter the prostate tissue. This urine–prostate barrier, however, appears to break down in some men. Minor leakage and microscopic stone formation appear common, at least according to one series that found that 75% of middle-age and older men had prostate stones of some kind.[10] But it does appear to be the case that at least some men with chronic prostatitis have a weakened or abnormal urine–prostate barrier, or leaky prostate syndrome.[11]

This hypothesis has languished for many years until recently. Researchers and clinicians began to pay more attention to the similarities between chronic prostatitis, CPPS, and interstitial cystitis. All three are chronic conditions of uncertain etiology, but which seem to share the hallmark of epithelial-barrier dysfunction. Such dysfunction may also underlie chronic idiopathic gut inflammations such as Crohn's disease, which also shares some pathophysiological features with chronic prostatitis and interstitial cystitis.[12] A new test for sensitivity to a potassium solution instilled into the bladder has highlighted that in all these conditions, as well as the urethral syndrome, patients do have problems with urine–tissue barriers.[13]

Some men note that they have particular dietary sensitivities that activate or irritate their prostate symptoms. To date, no patterns have emerged, leading some to conclude the dietary reactions either are the result of patients conflating actually unrelated events (given the normal waxing and waning of the condition) or are so idiosyncratic as to be unimportant. In our view,

these sensitivities support the leaky prostate theory. Food antigens passing through the urine and able to enter the prostate may exacerbate symptoms, with the high variability coming from individual immunological and inflammatory responses to different antigens, possibly even at different times or dose levels. Research should be undertaken to clarify the role of diet in chronic prostatitis patients.

There is unfortunately little research available about which herbs might help repair the damaged epithelium in the prostate. We have used various herbs renowned for their connective tissue tonifying properties and that have been used in other settings where tissue needs to be restored, particularly in the urinary tract.

Centella asiatica (gotu kola) leaf and root and *Equisetum arvense* (horsetail) sterile shoots are two such plants. Gotu kola is frequently employed in situations where there is connective tissue weakness, dysfunction, or disarray. It has not been explicitly studied in men with chronic prostatitis or prostatodynia to our knowledge. However, studies have looked at its ability to regulate fibrosis in patients with conditions such as progressive systemic sclerosis and keloid scars.[14,15] Laboratory studies clearly show it can regulate collagen synthesis.[16] The side benefits of gotu kola are stress relieving, inflammation modulating, and immune modulating, making it a broad-acting, potentially very beneficial herb in patients with chronic prostatitis. There are no known adverse effects beyond occasional digestive problems. Typical doses of fresh plant tincture or glycerite are 3–5 ml three times daily, though lower amounts are often given when combined with other herbs in individualized formulae. Clinical trials have focused on using 60–120 mg daily of triterpenoid extracts of gotu kola but we have not found these superior to tinctures or other whole-plant preparations.

Horsetail has received little research attention but has been used historically for connective tissue problems and as a urinary tract tonic in Europe.[17] Related species, particularly *Equise-*

Figure 6–1. *Crataegus monogyna* (hawthorn)

tum hymenale and *Equisetum telamateia*, can also be used. Some patients may develop brisk diuretic responses to all medicinal species of horsetail,[18] though in our experience it is generally a fairly gentle diuretic and should not cause any significant irritation. Otherwise this gentle herb has no known adverse effects. Some species of *Equisetum* are contaminated with toxic heavy metals, so substitutions should not be undertaken unless a definitive clinical source states they are safe. Doses of fresh plant tinctures, glycerites, or syrups are the same as for gotu kola.

Both of these herbs and potentially other connective tissue tonifiers like *Crataegus monogyna* (hawthorn) leaf, flower, and fruit are frequently combined with glycosaminoglycan supplements to provide ample precursors for proper bladder wall construction and repair. N-Acetylglucosamine (NAG) is considered by most the best precursor to give in cases of urinary tract epithelial dysfunction. There is an astonishing lack of study of this practice despite its widespread use and recommendation.[19] Typical doses of NAG are 500 mg twice daily. Adverse effects have not been reported but based on the results of people using the related glucosamine sulfate, it should be used with caution in those with diabetes mellitus as it may worsen glycemic control.

THE INFLAMMATORY SPIRAL

Many forms of chronic prostatitis and CPPS are inflammatory in nature. It is not clear in cases where infection has been established if the bacteria came first and incited an inflammatory reaction, or if something else triggered inflammation and thereby created an environment that somehow promoted bacteria growth.[20] The presence of WBC in expressed prostatic secretions is considered definitive that inflammation is occurring though many other markers are usually also present.[21]

Increased oxidation has also been shown to be a part of the pathogenesis of chronic prostatitis.[22] This is likely related to inflammation, as activated leukocytes produce many free radicals during this process, though radical oxygen species have also been detected in the absence of WBC in expressed prostatic secretions.[23] Treatment with antioxidant nutrients such as vitamin E has been helpful according to preliminary Russian studies.[24] Antioxidant botanicals may also be useful.

Most studies that have investigated the effect of natural products in patients with chronic prostatitis have involved inflammation-modulating herbs or supplements. The most current and rigorous trial compared 500 mg quercetin to placebo in men with chronic nonbacterial prostatitis or CPPS.[25] Though only 28 men were ultimately evaluable, there was a significant improvement in symptoms in the quercetin group compared to placebo. This study used the current gold standard evaluation tool, the National Institutes of Health (NIH) chronic prostate symptom score or index. There were no significant adverse effects. The dose used was actually fairly low, with many naturopathic physicians and herbalists suggesting 1,000 mg three or four times daily. Often this is combined with 1,000 mg of 3,200 mcu-strength bromelain or another digestive enzyme complex and taken away from food to enhance absorption and because bromelain is a synergistic inflammation modulator. Unfortunately it has not been studied specifically in men with prostatitis.

At least one double-blind and one so-called partly double-blind trial have evaluated the efficacy of *Secale cereale* (rye flower) pollen extracts in men with various chronic prostatitis syndromes.[26] Both were conducted in the 1960s and their methodological rigor was weak. However, both found that the pollen extract was superior to placebo at relieving symptoms without causing adverse effects.[27,28] Typical doses were 1–2 tablets three times per day.

Aesculus hippocastanum (horse chestnut) seed extract has also been evaluated in an uncontrolled trial in Russia for men with chronic prostatitis.[29] Though details are not available this extract was apparently effective at relieving symptoms. Horse chestnut is an inflammation modulator with anti-edema and vein-strengthening properties. It can occasionally cause nausea.

Eryngium yuccifolium (rattlesnake master) root is considered a urinary tract–specific inflammation modulator in traditional medicine including by Cherokee herbalists.[30] Though it has not been the subject of clinical trials we have found it clinically very useful. Animal studies confirm the inflammation-modulating potency of the closely related herb *E. maritimum* (eryngo).[31] Herbals as ancient as Dioscorides' *De Materia Medica* mention the use of eryngo for urinary tract conditions. Rattlesnake master also has an antihemorrhagic character that may help if there is concomitant hematuria or other excessive bleeding.

Fouquieria splendens (ocotillo) bark has proven to be another extremely useful and powerful herb in men with all types of chronic pelvic conditions. It has not been the subject of research yet is held in high esteem by Southwestern herbalists, Latino curanderas, and native people in the Southwest.[32] It is often described as a pelvic lymphagogue, though its exact mechanism of action is unknown. It does appear to be particularly helpful when there is stagnation or congestion in the pelvis, perhaps a traditional description of chronic inflammation. Regardless of how it works, we have found it effective and include it in every formula for men with chronic prostatitis or CPPS.

There are many other herbal inflammation modulators to consider. *Betula* spp. (birch) bark or leaf are considered the most specific to the urinary tract among the various salicylate-containing members of the Salicaceae family. Birch is also anodyne. *Solidago canadensis* (American goldenrod) flowering tops are urinary tract–specific inflammation modulators that are also diuretic. However, patients who have urinary frequency may worsen if they take this herb in excessive doses. *Achillea millefolium* (yarrow) flowering tops are generally inflammation modulating, astringent, and tonifying to the gut. Yarrow may be particularly useful when a gut connection is suspected. *Houttuynia cordata* (yu xing cao) leaf and flower is a member of the unusual Saururaceae, like its cousin *Anemopsis californica* (yerba mansa) root. Both herbs are inflammation modulating, antimicrobial, and astringent. In traditional Asian herbal medicine, yu xing cao is used for urinary tract infections and chronic nephritis. Though the herb may cause a fishy odor it is otherwise extremely safe. We also recommend topical application of *Larrea tridentata* (chaparral) leaf and flower infused into castor oil over the pelvic area once or twice a day as another anti-inflammatory therapy. An even longer list could be given but these herbs should be tried first given their historical affinity for the prostate or urinary tract.

Hydrotherapy is frequently recommended for men with chronic prostatitis and CPPS in natural medicine. Most commonly, sitz baths are recommended. Herbal infusions and decoctions can be used as bath water to enhance the efficacy of treatment. Often during acute flare-ups cold sitz baths (with cold tap water, staying immersed as long as is tolerated up to 15 minutes twice daily) with inflammation-modulating herbs will be most helpful. For chronic or low-grade symptoms, alternating hot and cold baths (start hot and end cold, 3 minutes in hot then 30 seconds in cold, repeated three times, using water as hot as can be withstood without burning and ice water) are recommended with the tonic herbs discussed in the leaky prostate syndrome section above.

For immediate symptom relief, we have also found that suppositories with inflammation-modulating herbs can be very dramatic. We have used a combination of vitamin A and calendula (*Calendula officinalis*) with some patients to good effect. Other potential options would be *Echinacea angustifolia* root or any of the other anti-inflammatory herbs mentioned above. The usual dose is one suppository in the morning and one in the evening.

Figure 6–2. *Calendula officinalis* (calendula)

AUTOIMMUNITY

Various studies have found evidence that chronic prostatitis can include an autoimmune component. In a cohort of Argentinian men with chronic prostatitis, those with noninfectious disease were demonstrated to have lymphocytes that reacted to multiple normal prostate antigens such as PSA.[33] This same group has now demonstrated that patients with autoimmune, noninfectious, chronic prostatitis also have highly elevated pro-inflammatory semen cytokine levels and greatly impaired sperm quality.[34]

The herbs that are generally used for autoimmune conditions are known as immunomodulators. These herbs can both stimulate underactive immune cells and suppress overactive ones, apparently by modulating cytokine secretion, particularly by T lymphocytes. Though no trials have been conducted with such herbs in men with chronic prostatitis, there is clinical research supporting the efficacy of these herbs in autoimmune diseases.[35]

Classic examples of immune modulators include *Panax ginseng* (Asian ginseng) root, *Panax quinquefolius* (American ginseng) root, *Schisandra chinensis* (schisandra) fruit, *Eleutherococcus senticosus* (eleuthero) root, *Trametes versicolor* (yun zhi, cloud mushroom) mushroom, *Lentinula edodes* (shiitake) mushroom, and *Withania somnifera* (ashwagandha) root among many others. All of these herbs are very safe. They may have to be taken for a long time to obtain full benefits. Because all of these herbs are also adaptogenic, helping to relieve and prevent the negative effects of stress, they are doubly indicated in men with chronic disease. Much

work remains to be done to validate the efficacy of these herbs but we have seen them be very helpful in some cases.

NEUROLOGICAL ISSUES

The most recent theory to surface about the etiology of CPPS in particular is the so-called myoneurological theory. Its champions cite evidence that the underlying problem is one of abnormal neurological activity. For example, it has been demonstrated that there is incomplete toe spreading much more commonly in men with CPPS than those without.[36] One case series has documented that a program integrating trigger-point release in the myofascia of the perineum with relaxation training can achieve significant pain relief.[37]

This theory is corroborated by the historical use of *Piper methysticum* (kava) root as a bladder and urinary tract sedative. Kava has many actions on the central nervous system and is considered a general nervine. It is often helpful particularly in patients who exhibit overt anxiety or have strong depressive symptoms clinically. Other nervine herbs should also be considered in any protocol for patients with CPPS, including but not limited to *Passiflora incarnata* (passionflower) leaf, *Scutellaria lateriflora* (skullcap) leaf and flower, *Valeriana sitchensis* (Pacific valerian) root, and *Hypericum perforatum* (St. John's wort) leaf and flower as discussed in chapter 5. All these herbs are also indirectly anodyne and relaxing and may also help offset the negative effects of chronic stress where those appear to play a role in the chronic prostatitis disease process.

CONCLUSION

There is enormous potential for natural therapies in men with CPPS or chronic prostatitis. Given the complex, multifactorial nature of these syndromes, any one single agent is unlikely to be effective. Given the costs and adverse effects of current pharmceutical therapies and the lack of any consistent demonstrable efficacy, especially in CPPS patients, alternatives need to be urgently explored with much greater rigor. In the meantime, clinicians can enhance their effectiveness by expanding their horizons to incorporate a natural medicine philosophy and therapeutics.

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7

HERBS FOR CHRONIC RENAL FAILURE

Chronic renal failure due to gradual destruction of sufficient nephrons represents a massive problem in the developed world. Diabetic nephropathy is the major culprit, but lupus nephritis and other immunologic nephritides, chronic urinary tract obstruction (such as by benign prostatic hypertrophy (BPH)), and chronic overuse of nonsteroidal anti-inflammatory drugs and aspirin are also significant contributors. Hypertension is believed to contribute to renal failure though this has not been proven in controlled, prospective clinical trials. Regardless of the causes, chronic renal failure is a major burden.

The development of dialysis has allowed people to survive much longer with renal failure than they would have in the past, creating an enormous pool of patients with a severe chronic illness. Though extending life is beneficial to those affected by renal failure, it comes with high costs, both in terms of money and quality of life. Botanical medicine has much to offer not only to help forestall the need for dialysis by treating the causes and effects of renal failure, but also to reduce the many adverse effects of dialysis itself.

Human beings are born with an enormous excess of nephrons—on the order of twice as many as are needed for day-to-day survival.[1] This appears to be due to the fact that hunter–gatherers (and presumably prehuman omnivorous ancestor species) would have periods of massive intake of protein when a large animal was killed and eaten (essentially all at once due to a lack of an efficient way to preserve meat), and thus the kidneys would periodically have to activate far more nephrons to handle the excess nitrogen intake.[2] In most parts of the developed world, our diets have changed radically, now including high intakes of animal protein essentially every day. This leaves little reserve nephron mass to handle additional challenges, and increases the potential development of renal failure. Therefore, lifestyle and dietary changes are critical in preventing renal failure. The connection between high animal protein intake and kidney disease provides yet another reason to recommend a move toward a more vegetarian diet for the large majority of people.

Rhubarb Root

Several herbal medicines appear to have the ability to protect nephrons against a wide range of insults. *Rheum palmatum* (Chinese rhubarb, da huang) root is an interesting example. Traditionally, people looked at this member of the Polygonaceae family as a cathartic laxative. Sufficient doses of the anthraquinone glycoside-rich root definitely can provoke a bowel movement. To the consternation of the pharmacological model (i.e., looking for one herb with one active constituent having one effect on one disease), Chinese rhubarb can, and traditionally has, also been used to treat diarrhea. This is particularly true of the cooked root. The explanation is that the root also contains significant quantities of astringent tannins that can bind up discharges, and heat tends to inactivate its anthraquinone glycosides. Thus, depending on the exact dose and preparation of Chinese rhubarb root, it can have opposite effects on the gut.

The same anthraquinone glycosides that in higher doses can cause catharsis have nephroprotective effects at lower doses. Emodin, for instance, has been shown to inhibit renal tubular cell

proliferation, a key pathologic process in various nephritides that can lead to renal failure.[3] The tannins of rhubarb block the actions of uremic toxins and reduce protein catabolism, thus protecting the kidneys.[4,5] Preclinical studies on other tannin-rich herbs, including *Ephedra distachya* (ephedra) stem,[6] *Geranium thunbergii* (Thunberg's cranesbill) root, and *Cinnamomum cassia* (cassia) bark, have shown that they too can protect nephrons and reduce the effects of uremic toxins.[7,8,9]

Many clinical trials have been conducted in China on various preparations and doses of Chinese rhubarb root in patients with chronic renal failure.[10] These studies have consistently shown a range of benefits, including lowering serum creatinine levels (a major surrogate marker for renal function) and offsetting metabolic dysfunction related to kidney failure. Details of most of these trials are not available as they have not been published in English. However, some are available and illustrate the point.

In one open trial, 56 patients with chronic renal failure were treated with either bao yuan da huang tang or standard supportive measures.[11] Bao yuan da huang tang is a decoction of *Panax ginseng* (Asian ginseng) root, *Astragalus membranaceus* (astragalus) root, cassia bark, *Glycyrrhiza uralensis* (Chinese licorice) root, and Chinese rhubarb. Symptom scores improved significantly more in the herbal therapy group than in controls. Serum BUN and creatinine were significantly lowered by the formula compared to the conventional therapy group.

In 38 patients with moderate chronic renal failure, 1 g of Chinese rhubarb root extract per day led to significant decreases in serum BUN and creatinine.[12] In a comparison group of five healthy patients, the same extract had no effect on these parameters.

In one controlled clinical trial, 42 patients with terminal renal failure either took Chinese rhubarb root extract or had no additional treatment.[13] While serum BUN and creatinine were not affected in either group, serum HDL cholesterol and albumin levels rose significantly, whereas serum total and LDL cholesterol levels fell significantly in the rhubarb group compared to the control group.

Rhubarb, along with the formula known as tong mai san, has been shown helpful in combination with hemodialysis at lowering serum nitrogen levels and reducing protein loss.[14] Rhubarb has also been shown to be more effective combined with captopril than captopril alone for reducing renal inflammation in patients with chronic kidney failure.[15]

Typical doses of Chinese rhubarb root are 300–3,000 mg three times per day. The root should be simmered for at least one hour to reduce cathartic activity. If patients develop loose stools on the dose they are prescribed, the dose should be reduced or the root cooked longer. If taken as tincture of simmered root, the dose is 2–3 ml three times per day, or whatever dose is subcathartic. At these doses no adverse effects are usually observed except, rarely, mild constipation.

Round-Headed Lespedeza

A bushy plant native to the southeastern United States known as *Lespedeza capitata* (round-headed lespedeza) has also attracted attention for patients with chronic renal failure. For unknown reasons, French and Italian researchers have done most of the work on this plant, and unfortunately none of it is very recent. This member of the Fabaceae family deserves more widespread use.

Lespedeza is loaded with proanthocyanidins, which give its extracts a vibrant purple-red color. These compounds have been shown to have angiotensin-converting enzyme (ACE)–inhibiting effects in the lab.[16]

Though the full text or even an abstract could not be located, at least three European clinical trials have been conducted on extracts of lespedeza for patients with chronic renal failure.[17,18,19] At least one of these utilized an injectable extract that is not available in North America. Rudolf Fritz Weiss commented that he often would see benefit with tinctures of lespdeza for both acute and chronic renal failure patients.[20]

Typically the flowering tops of the plant are used. A dose of a tincture of fresh plant would be 3–5 ml three times per day for adults. There is no known toxicity from this plant. It may also have phytoestrogenic effects, so in overdose situations it might cause estrogen-excess symptoms such as moodiness or fluid retention. It is also not known if the many other species in this genus are interchangeable.

Other Renoprotective Herbs

A variety of other herbs have been used for their renoprotective effects (see Table 7-1), though none have been as well researched as Chinese rhubarb and round-headed lespedeza. *Silybum marianum* (milk thistle) seed is generally thought of as a liver-supporting herb, but actually has all the same actions on the kidney as it has on the liver.[21] With one minor exception, milk thistle has not been the subject of clinical trials to validate its effect in renal failure patients. One small trial found that milk thistle seeds could improve the observed imbalance in thiols in patients with end-stage diabetic nephropathy.[22] Milk thistle is very safe so it can be used with the comfort of knowing it is extremely unlikely to make patients worse. Typical doses of standardized extracts of milk thistle seeds are 140 mg three times per day. Crude, ground seeds can also be taken in the amount of 5 g three times per day. The dose of fluid extract is 3–5 ml three times per day.

Urtica dioica (stinging nettle) seed has been recommended as a renoprotective agent. Stinging nettle leaf is relatively well-known as a diuretic and inflammation modulator, and the root

Table 7–1. Summary of Putative Renoprotective Herbs

Herb	*Part Used*	*Family*	*Level of Support**	*Notes*
Lespedeza capitata (round-headed lespedeza)	Flowering top	Fabaceae	PCT	Extremely safe
Orthosiphon stamineus (Java tea)	Leaf	Lamiaceae	H	Extremely safe; uncertain ecological status
Parietaria judaica (pellitory-of-the-wall)	Flowering top	Urticaceae	H	Extremely safe
Rheum palmatum (Chinese rhubarb)	Cooked root	Polygonaceae	PCT	Constipation or catharsis in overdose
Silybum marianum (milk thistle)	Seed	Asteraceae	PCT	Extremely safe
Urtica dioica (stinging nettle)	Seed	Urticaceae	A, H	Not significantly diuretic, unlike leaf

*A: anecdotal, case studies; H: historical use; PCT: preliminary clinical trials.

Figure 7–1. *Silybum marianum* (milk thistle)

Figure 7–2. *Urtica dioica* (stinging nettle)

as a remedy for BPH.[23] However, the seed is much less diuretic and does not seem to affect the prostate, but instead seems to have a direct supportive effect on nephron function. Two published case studies by the herbalist Jonathan Treasure, MNIMH, RH (AHG), illustrate that nettle seed can be quite effective at lowering serum creatinine levels and improving symptoms in patients with chronic renal failure.[24] In an interesting twist on the milk thistle story, nettle seeds appear to also be hepatoprotective based on studies in rodents.[25] Clinical trials are definitely warranted with this completely safe herbal medicine. The dose of tincture is 3–5 ml three times per day.

Parietaria judaica (pellitory-of-the-wall) herb is a relative of stinging nettle native to northern Eurasia without any stingers. It has historically been considered a kidney tonic. Though no published reports have been located on the effects of this plant, clinically it seems very effective and completely safe in patients with chronic renal failure. Typical doses of tincture are 3–5 ml three times per day.

Orthosiphon stamineus (Java tea) is a magnificent flower native to Indonesia. This tropical mint has a long tradition of use as a diuretic, and has demonstrated this and a uricosuric action in preclinical testing.[26]

ADAPTOGEN AND TONIC RENAL PROTECTORS

Besides herbs that seem to directly protect nephrons, there are also those that act in a more general way to strengthen the body and in particular strengthen the kidneys. These include tonic herbs, used to normalize functions of specific systems, as well as adaptogenic herbs that

Figure 7–3. *Orthosiphon stamineus* (Java tea)

help the body cope very generally with all types of stressors (see chapter 3). These herbs can be used to help the kidneys cope with whatever stressors are causing renal failure, as well as help the rest of the body deal with the consequences of renal failure. (See Table 7-2.)

Cordyceps chinensis (cordyceps, Chinese caterpillar fungus) is a remarkable fungus used in traditional Asian medicine to support the kidneys. It is a wonder that it was ever decided to use this fascinating organism, known in Chinese as *duong chong xiao cao* ("summer grass, winter worm"). In the wild, spores from cordyceps are carried by rainwater to underground bat moth caterpillars, which it parasitizes. The caterpillars eat the roots of a particular plant's roots. In late autumn, the spores sprout into a mycelium that overwhelms the caterpillar by the next summer, eventually sprouting fruiting bodies up to 5 cm tall that were the principal parts used. In modern times, cordyceps from the wild has been vastly overharvested, and is seriously threatened as a result. Most cordyceps on the market today is mycelium grown in culture in the laboratory, which although not exactly the same as the original medicine (in particular because the original often contained some caterpillar that might also be medicinal), is a much more

Table 7–2. Summary of Renoprotective Adaptogenic/Tonic Herbs

Herb	*Part Used*	*Family*	*Notes*
Astragalus membranaceus (astragalus)	Root	Fabaceae	Very safe
Cordyceps chinensis (cordyceps)	Cultivated mycelium	Clavicipitaceae	Best studied for renal failure patients
Glycyrrhiza uralensis (licorice, gan cao)	Root	Fabaceae	Can promote hypertension and edema in overdose
Panax ginseng (Asian ginseng)	Root	Araliaceae	Very safe
Panax quinquefolius (American ginseng)	Root	Araliaceae	Very safe

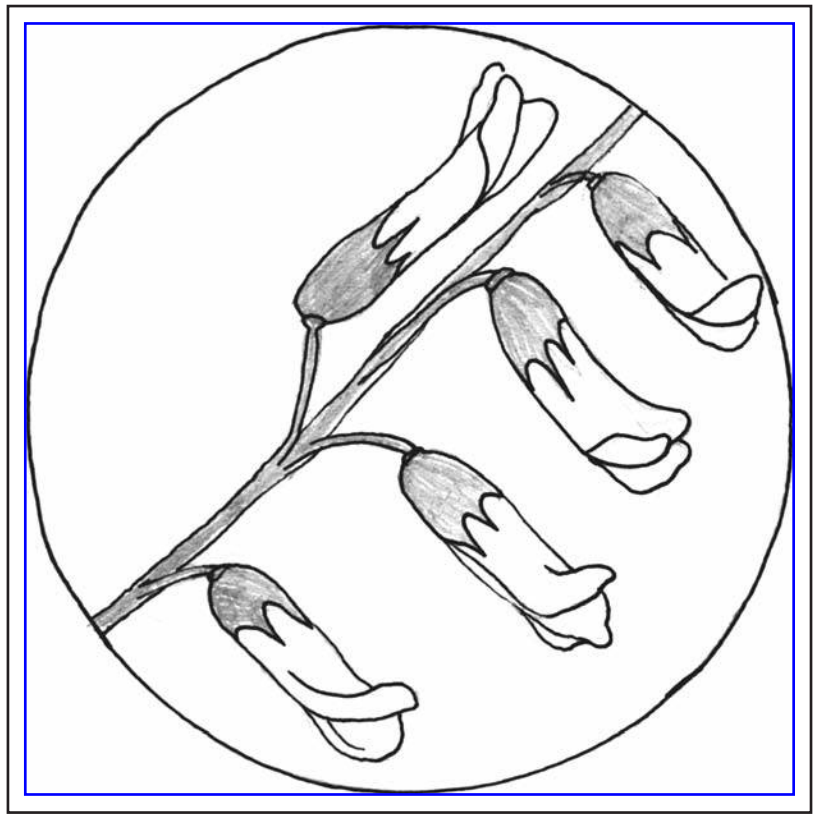

Figure 7–4. *Astragalus membranaceus* (astragalus)
Drawing © 2004 by Kathy Abascal, BS, JD.

sustainable method of production. Only cultivated cordyceps mycelium (also known as jin shui bao) should be used due to its precarious environmental status.

Numerous clinical trials have been conducted on cordyceps in patients with renal failure. The longest trial ran for 10–12 months and used 3–5 g of natural cordyceps daily.[27] It showed a significant improvement in renal and immune function in kidney failure patients. In a one-month trial comparing natural cordyceps fruiting bodies to cultivated cordyceps mycelium, both were able to lower serum BUN and creatinine and improve anemia, with no significant difference between the two.[28] This supports that mycelium can be used effectively in place of the traditional fruiting bodies.

One trial lasting one month used 5 g of cultivated cordyceps mycelium.[29] It showed reduced serum BUN and creatinine and improved symptoms. Enhanced immune function and improved T lymphocyte subset composition coinciding with the renoprotective effects have also been documented with cordyceps mycelium as well.[30] Typical doses of mycelium have been 5–9 g per day, with essentially no adverse effects being reported.

Astragalus membranaceus (astragalus) root has been used in traditional Asian medical systems to support patients with chronic renal failure. As noted above, the formula bao yuan da huang tang, which has been shown to help renal failure patients, contains not only Chinese rhubarb but also astragalus as well as two adaptogens (Asian ginseng and licorice). Another formula containing astragalus, tang fu kang, has also been shown helpful in protecting rodents against diabetic nephropathy.[31] Astragalus compounds have been shown to have angiotensin

receptor down-regulating effects, which though shown in this particular study to protect the hearts in diabetic rats could also protect the kidneys.[32] More thorough research is needed but astragalus appears promising. Typical doses of the root are 3–5 g three times per day; of tincture or glycerite, 3–5 ml three times per day or more frequently.

Other adaptogenic and tonic herbs are almost certainly beneficial in renal failure patients; these are just a few that have been looked at to some degree in this specific setting.

FORMULATING FOR RENAL FAILURE PATIENTS

When working with an individual patient with renal failure, it is important to assess the specific details of that case, though basically all patients will benefit from renoprotective herbs. In practice, we have tended to combine a variety of renoprotective herbs, believing that they will act synergistically to provide a better result than any one in isolation. Other practitioners prefer to use a single renoprotective herb; this can also be helpful. (See Sidebar 7-1.)

Patients who are very fatigued, have low libido, and serious immune dysfunction should have adaptogens emphasized in their herbal formula. If they are particularly having trouble

7–1. *Case Study*

A 36-year-old African American woman was diagnosed with idiopathic glomerulonephritis 13 years prior. Her initial symptoms were nausea and vomiting, which were believed to be due to secondary hyperparathyroidism due to renal failure. She was started on continuous ambulatory peritoneal dialysis and has been on it ever since. The patient ate a standard American diet, drank heavily, and did not exercise at the time. She had not produced any urine in the past two years.

On her own and with the support of her mother, she chose to switch to a vegetarian diet and began walking regularly. She was able to discontinue taking erythropoietin and iron supplements after this switch. She continued to take calcitriol.

She then saw one of us (EY) and started on 1 tsp three times per day of the following tincture formula:

Panax quinquefolium (American ginseng)	Root	20%
Parietaria judaica (pellitory)	Leaf	20%
Astragalus membranaceus (astragalus)	Root	15%
Lespedeza capitata (round-headed lespdeza)	Herb	15%
Rheum palmatum (Chinese rhubarb)	Root	10%
Glycyrrhiza uralensis (Chinese licorice)	Root	10%
Cinnamomum aromaticum (cassia)	Bark	5%
Urtica dioica (stinging nettle)	Seed	5%

Within one month on this formula the patient's serum creatinine fell from 10.5 to 9.7 mg/dl, the first time it had done so since her original diagnosis. She also developed a slight discharge of urine. After three months, her serum creatinine fell further to 9.3 mg/dl. After nine months (the most recent information available), it was down to 8.9 mg/dl. She also had better energy and mood over this time, and did not have to use erythropoietin.

with osteodystrophy, then *Centella asiatica* (gotu kola), a connective tissue-supportive herb, along with nutritional and lifestyle treatments will need to be included. If itching is a serious problem, then topical *Capsicum* spp. (cayenne) has been shown helpful in clinical trials. If dyslipidemia is serious, then *Allium sativum* (garlic) or other lipid correctives are warranted. If low appetite is causing problems, then bitter herbs such as *Achillea millefolium* (yarrow), or aromatic digestive stimulants such as *Zingiber officinale* (ginger) should be included in the formula.

CONCLUSION

Botanical medicine offers many interesting possibilities to help patients prevent or treat chronic renal failure. It is unfortunate that many of these herbs are overlooked, and that the initial exciting research findings have not been followed up with larger, more rigorous trials. It is highly unlikely that nephroprotective herbs can bring back completely destroyed nephrons, but they are very promising for keeping existing nephrons working and possibly reviving partially damaged nephrons. Though this has yet to be definitively proven, we have seen patients develop modest improvements in glomerular filtration rates that would suggest nephron recovery. Adaptogens and other tonic herbs also offer a completely different approach to the immunological aspects of renal failure, while simultaneously appearing to have nephroprotective benefits compared to anything available in conventional medicine.

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8

BOTANICALS FOR CHRONIC VENOUS INSUFFICIENCY

Chronic venous insufficiency (CVI) is a disorder that affects 10–35% of the U.S. population.[1] The major clinical features of CVI are dilated veins, edema, leg pain, and changes in the skin of the legs. Edema begins in the ankle region and ascends up the leg as fluid continues to accumulate. The leg pain or discomfort is usually described as heaviness or aching and often occurs after prolonged standing. The discomfort may be relieved by elevating the leg(s). When the deep venous system is involved, venous claudication or intense leg cramping with ambulation may occur. Advanced CVI can cause lymphedema and slow healing ulcers.[2]

CVI arises in a state of chronic venous hypertension that alters the permeability of the skin's microcirculation.[2] The movement of protein and other matter from the blood vessels into the interstitium leads to endothelial activation, white blood cell chemotaxis, and inflammation-induced injury. The end result is fibrotic and edematous skin with injury to nutrient and exchange capillaries. The mainstay of allopathic treatment of CVI is the use of compression therapy to control edema and venous hypertension.[2] In Europe, botanicals are commonly added as an adjunct therapy and have shown great benefit. Given the prevalence of the disorder, poor patient follow-through with compression therapy, and the complete lack of established drug protocols for this disorder, botanicals should be much more widely prescribed for these patients in this country as well.

Most of the herbs used for CVI are rich in interesting flavonoids and other substances that protect capillaries. Their mechanisms of action vary but all activate venous and lymphatic return. The use of herbs in CVI is supported by research showing that they improve venous tone, venous blood flow, capillary permeability, and lymphatic drainage.

Ruscus aculeatus (Butcher's Broom) Root

Butcher's broom is a prickly, berry-producing shrub in the Liliaceae family. It has a wide growth range (from Egypt and Turkey through the Mediterranean countries and up through France, Spain, and England) and prefers to grow on the outskirts of dry woods. It thrives on moist, uncultivated ground especially where the soil contains chalk. Its berries are reported to be somewhat toxic. Although the plant could easily be cultivated in many parts of the United States, most of the herb in commerce is imported. Butchers at one time used branches of the shrub to clean meat stalls and keep flies at bay, giving rise to its common name. The whole plant contains steroidal saponins and ruscinogens—the compounds deemed most active—but only the dried rhizomes are used medicinally.

Ancient Greek physicians used the plant as a laxative and diuretic. In Europe, a decoction of the root in wine was used as a diuretic to remove urinary obstruction, kidney stones, and gravel. The plant was also used to regulate menses, ameliorate jaundice, and headache, and a poultice of the berries was used to help heal broken bones and dislocated joints. In South America, the root was roasted, ground, and drunk like coffee for prostate tumors. Today, the plant is little used for most of these indications.

Figure 8–1. *Ruscus aculeatus* (butcher's broom)
Drawing © 2004 by Kathy Abascal, BS, JD.

Instead, butcher's broom is frequently used to relieve symptoms of CVI such as edema of the ankles, itching, tension, and cramping of the legs and related symptoms. Both animal and human studies support its benefit in CVI, and the German Commission E has affirmed butcher's broom's value as an adjunct treatment for this condition.[3] The human studies investigating butcher's broom in CVI are given in Table 8-1. All of the studies showed it to have a positive effect, and in one multicenter study its efficacy in CVI was rated as excellent by 81.6% of the treating physicians and as good by the other 18.4%.[4] Even though the products used and the methodological rigor of the studies vary, a clear picture emerges from clinical and in vitro studies showing that butcher's broom improves venous circulation, perhaps most strongly when that circulation is deficient. However, some researchers caution that the disease should not have progressed to a point where venous wall receptor activity has been compromised.[5]

In one study, veins from patients treated with butcher's broom prior to vein-stripping surgery showed greater fibrinolytic activity than did placebo controls.[6] In another trial, patients with CVI and healthy patients were given butcher's broom in a random, double-blind fashion, and were subjected to treatment-simulating venous stasis. The patients with CVI had hematological abnormalities compared to normal patients (e.g, disturbances in parameters of blood viscosity) that were exacerbated in conditions of venous stasis.[7] Butcher's broom significantly reduced these abnormalities. A number of in vitro animal vein studies confirm that butcher's broom and its ruscinogens have a vasoconstrictive effect and reduce vascular permeability.[8] Butcher's broom protected human endothelial cells from hypoxia[11] and exhibited significant anti-elastase

Table 8–1. Studies on Butcher's Broom in CVI

Study	*No Participants*	*Type*	*Product*	*Focus*	*Result*	*Length*
Cappelli[a]	40	Double-blind, crossover, placebo-controlled prospective	2 capsules (16.5 mg ruscinogens, 75 mg hesperidin, 50 mg ascorbic acid) 3 times per day	CVI, varicosities	Itching, edema, and paraesthesia improved greatly	2 month with 15-day washout and 2-month crossover
Rudofsky[b]	141 plus 20 healthy volunteers	Randomized, double-blind, multicenter	2 capsules* 3 times per day for 4 weeks; 2 capsules 2 times per day for 8 weeks * Not clearly stated but appeared to be using a capsule containing 150 mg Ruscus, 150 mg hesperidin methylchalchone, 100 mg ascorbic acid	CVI	Continuous decrease in foot and ankle volume, decrease in leg swelling, improved venous pumping	2-week washout followed by 12-week treatment
Haas[c]	20	Placebo-controlled, double-blind	1 capsule (150 mg Ruscus, 150 mg methylhesperidin chalcone) 3 times per day	CVI stage I and II; scheduled for surgery	Significantly increased fibrinolytic activity of removed great-saphenous vein	14 days
Kiesewetter[d]	30	Random selection, noncontrolled	3×2 Ruscus capsules for 5 weeks then 2 ×2 capsules per day; amount of Ruscus not stated	CVI	Reduced circumferences of lower legs, malleoli, and subjective complaints; greater rheological improvement in patients with advanced stages of CVI	5 months

Beltramino[e]	80	Open-label, randomized, multicenter	2 capsules per day of 150 mg Ruscus, 150 mg hesperidin methylchalchone, 100 mg ascorbic acid; Control: 2 tablets of 500 mg hydroxyethyl rutoside per day	CVI; heavy, tired, swollen, or painful legs	Significant improvement in symptoms, reduction in limb circumference; physicians and patients had a more favorable opinion of Ruscus than of rutoside	90 days
Le Devehat[f]	60 plus 7 healthy volunteers	Random, double-blind, placebo-controlled	2 capsules per day of 150 mg Ruscus, 150 mg hesperidin methylchalchone, 100 mg ascorbic acid	CVI; blood samples drawn from foot before and after provoked venous stasis	Improved blood viscosity disturbances caused by venous stasis	4 weeks
Seydewitz[g]	36	Randomized, double-blind, placebo-controlled	3 capsules per day (150 mg Ruscus, 150 mg trimethylhesperidinchalcone)	Stage IV varicosities with stage I or stage II CVI; scheduled for vein stripping	Increase in enzyme activity in the proximal segment of the vein; distinctly higher incidence of subjective improvement of symptoms	4 weeks

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activity in vitro.[10] A reviewer of 24 pharmacological studies concluded that butcher's broom should be the treatment of choice for CVI.[11]

Butcher's broom is generally considered a safe herb, although it occasionally causes gastrointestinal distress.[3,12] Side effects have not been noted in most of the clinical studies. However, one study of 124 patients with hemorrhoids noted a 2.4% incidence of negative gastrointestinal (GI) symptoms (primarily epigastric burning and pain),[13] and in a second study of lymphedema 3.5% of the participants experienced significant nausea and abdominal pain.[14] In addition, there are reports in the French medical literature suggesting that butcher's broom may cause lymphocytic colitis in some patients.[15–17] We have not been able to review those articles but we suggest that practitioners discontinue the use of butcher's broom if diarrhea is severe or persistent. It might also be wise to advise patients not to combine butcher's broom with nonsteroidal anti-inflammatory medications that also may cause GI upset and lymphocytic colitis.

One text cautions against the use of butcher's broom in patients using alpha-antagonistic therapy for benign prostatic hypertrophy or hypertension, and against its use in patients taking monoamine oxidase-inhibiting medications.[18] The reviewer cites no references for these recommendations that may be based on the theoretical possibility that the tyramine contained in the herb might precipitate a hypertensive crisis, that it might reduce the effectiveness of alpha-adrenergic-blocking antihypertensives, or might reduce the effectiveness of benign prostatic hyperplasia treatment. While one in vitro study showed that alpha-adrenergic and calcium antagonists reduced butcher's broom' venoconstrictive effect, there are no studies showing that butcher's broom diminished the action of those drugs. In fact, in one very small study, butcher's broom reduced edema of ankles and legs secondary to calcium-antagonist treatment for hypertension. The study description is poor but nonetheless four of the nine patients showed complete improvement, and no adverse effects were noted. While caution is needed when we combine herbs and pharmaceutical medications, we also need to remember that botanicals can counteract the adverse effects of drugs and sometimes improve their actions. Many cases of edema are going to be found in patients who are also hypertensive, and butcher's broom should not automatically be ruled out as a treatment in patients who are medicated for hypertension.

The same authors also caution against the use of butcher's broom in pregnancy and lactation based on a lack of proof of safety;[18] however, most authors consider butcher's broom safe in pregnancy and lactation.[3,12] Although not large enough to be conclusive, an open study of 20 pregnant women taking butcher's broom daily for venous insufficiency followed both fetal and postbirth indices. No embryotoxic effects were observed, and postbirth indices were normal in all instances.[12] We reviewed two studies on pregnancy-related venous insufficiency, and both showed improvement in maternal symptoms without any negative effects on the fetus.[19,20] Two other European studies, one a multicenter study of 124 patients, are reported to show a similar improvement of symptoms in pregnant women.[21,22] While these studies do not conclusively establish the safety of butcher's broom in pregnancy, both animal and human studies indicate a high degree of safety. Finally, a few cases of hypersensitivity to its ruscinogens have been reported,[23] and there is one reported case of a severe allergic reaction to butcher's broom.[24]

Butcher's broom is a sustainable medicine, largely obtained from cultivated sources. Dose: dried root: 300–450 mg/day; in most studies, butcher's broom is paired with trimethylhesperidin chalcone and ascorbic acid. (See Table 8-1). Tincture: 2–3 ml three times per day.

Aesculus hippocastanum (Horse Chestnut) Seed

Horse chestnut is also a widely used treatment for CVI. Two of its main constituents are aesculin, a coumarin derivative, and aescin. Aescin stands for the total saponin content of the seeds,

which actually consists of more than 30 derivatives of triterpenoids, protoaescigenin, and barringtogenol C.[25] It also contains a number of flavones. The renowned German phytotherapist, Dr. R. F. Weiss, stated that horse chestnut's anti-edema action was 600 times that of rutin in animals.[26] Horse chestnut was introduced to Europe in the 1600s and has been widely used since that time. It is gaining in popularity in the United States as a treatment for varicose veins and CVI. In Germany, it is the most widely prescribed botanical for venous edema and has been approved by the German Commission E for CVI including heaviness, nocturnal leg cramping, itching, and swelling of the legs.[3] A recent Cochrane Review on the use of horse chestnut found it to be an efficacious and safe short-term treatment for CVI.[27]

In studies, horse chestnut was anti-edemic,[28] improved vein function, inhibited vasodilation, modulated inflammation, and had an antioxidant action.[3] It reduced lysosomal enzymes that break down mucopolysaccharides (e.g., hyaluronidase) in the region of the capillary wall and inhibited filtration of small molecules, electrolytes, and water into the interstitium by reducing vascular permeability.[29] In one study it inhibited induced leg edema in patients with CVI.[30] *The ABC Clinical Guide to Herbs* lists 18 studies of its use in CVI.[31] These studies range in length from 6–12 weeks and uniformly show a reduction in ankle circumference and improvement in symptoms. In an observational study of more than 5,000 patients, horse chestnut improved all of the symptoms investigated (pain, tiredness, tension and swelling of the leg, and itching) and had the advantage over compression stockings of better patient compliance.[32] In one systematic review of clinical trials, horse chestnut reduced leg volume, reduced the likelihood of leg pain four-fold, and improved itching and edema 1.5 fold. It was found to be safe with no adverse effects.[33] As with butcher's broom, horse chestnut appears to be far more effective in the early stages of the disorder. Thus, one study found horse chestnut effective in stage I but far less effective in stage III.[34] Finally, one study found that after eight weeks, the dose of horse chestnut could be cut in half and still maintain its effect.[35]

In rare cases, horse chestnut may cause pruritus, nausea, and gastric complaints. One of its constituents may slow gastric emptying. There is speculation that it may interfere with anticoagulants but this may pertain only to a compound found in the bark and not in the part used medicinally, the seeds. There are no known contraindications to its use in pregnancy and lactation, and it has been used in some studies involving pregnant women with no reports of adverse effects.[31] The potential toxicity of injected aescin has been associated with significant problems, but these are of no relevance when using the whole-plant extract orally.

Horse chestnut is a highly sustainable medicine as it grows readily in many temperate climates and harvesting the seed does not harm the tree.

The initial dose of the dried seed is 250–300 mg twice per day (100 mg aescin daily); of the fresh seed, 120–180 mg four times per day (120 mg aescin daily). Using a tincture, administer 2–3 ml three times per day. All doses may be cut in half after the first eight-week period.

Centella asiatica (Gotu Kola) Herb

An herb of increasing interest and use in CVI is gotu kola. There is evidence that gotu kola is effective in venous insufficiency and, given the apparent ability of the herb to promote wound healing, adding gotu kola to a regimen containing either butcher's broom or horse chestnut (or both) may prove synergistic in preventing or healing venous ulcers.

Most of the clinical studies have been on the isolated total triterpenic fraction of gotu gola. In a test using a vacuum suction chamber that produces swelling when applied to the ankle skin, those with CVI had a relatively slow reabsorption of the fluid compared to controls. However, after taking gotu kola for two weeks, the time required to reabsorb the leaked fluid improved

significantly.[36] In another small study, patients on 90 and 180 mg of gotu kola/day for four weeks showed various measurements of vein function improved in a dose-related fashion. Another study compared 60 and 120 mg, again with a dose-related improvement in discomfort, edema, and sense of leg heaviness.[37] Its triterpenic fraction prevented microcirculatory changes in adults with mild to moderate superficial venous disease during flights lasting over three hours.[38]

Gotu kola is well-known for its wound-healing abilities. The herb and its constituents are beneficial in promoting wound healing and have been used to treat people with keloids,[39] phlebitis, and venous hypertension,[40,41] leprosy,[42] stretch marks in pregnancy,[43] and a variety of other ailments. In wound studies, gotu kola increased antioxidants in newly formed tissue while greatly reducing toxic lipid peroxide levels.[44] Gotu kola and its flavonoids increased tensile strength, collagen content, and epitheliazation in many types of wounds when used internally or topically.[45–47] Gotu kola had different actions at different stages of wound healing, and consistently increased collagen synthesis at the wound site.[48,49] Most herbalists think that gotu kola should be used or prepared fresh for optimal effectiveness. It has no known adverse effects.

Gotu kola grows in tropical areas and is readily cultivated. Though the entire plant is often harvested to make medicine, it is sufficiently easy to grow and is for the most part very sustainable. The usual adult dose of the standardized extract of the dried herb is 90–180 mg/day. The dose of a fresh-plant glycerite or tincture is 3–5 ml three times per day.

Oligomeric Proanthocyanidins

Oligomeric proanthocyanidins, referred to as OPCs, are found in the heartwood and bark of some trees as well as in some seeds and most berries. Pycnogenol® (Horphag Research, Geneva, Switzerland), extracted from grape seeds or *Pinus maritimus* (maritime pine) trees, is a relatively well-researched OPC in CVI. Most berries, ranging from hawthorn to blueberries, have OPCs that vary in composition from plant to plant.

OPCs are primarily known for their antioxidant activity. However, these compounds also appear to have inflammation-modulating, antiallergic, and vasodilatory actions. In addition, they have been found to inhibit lipid peroxidation, platelet aggregation, capillary permeability, and fragility, and to affect enzyme systems including cyclooxygenase and lipoxygenase.[50] Based on these findings, OPCs may be a useful component in the treatment of a number of conditions including venous insufficiency, varicose veins, capillary fragility, and diabetic retinopathy.

The most common sources of OPCs on the market are either extracted from grape seeds or maritime pine. When individual molecules bind together, the result is collectively called procyanidolic oligomers (PCO). They have a broad range of pharmacologic activity through increasing vitamin C levels, decreasing capillary permeability and fragility, scavenging free radicals, and inhibiting destruction of collagen. The latter occurs through the ability to cross-link collagen fibers, which prevents free-radical damage, inhibits enzymatic cleavage of collagen, and prevents the synthesis and release of inflammatory mediators.

One study compared a horse chestnut seed extract with Pycnogenol in CVI. In an open, controlled comparative study 40 patients were treated either with 600 mg chestnut seed extract per day or 360 mg Pycnogenol per day over a period of 4 weeks. Circumference of the lower legs and rating of subjective symptoms of pain, cramps, nighttime swelling, feeling of "heaviness," and reddening of the skin were followed. Pycnogenol significantly reduced the circumference of the lower limbs and significantly improved subjective symptoms. Furthermore, Pycnogenol significantly decreased cholesterol and LDL values in the blood, whereas HDL remained unaffected. Horse chestnut only moderately, but not significantly, reduced the circumference of the lower limbs and marginally improved symptoms. Both Pycnogenol and horse chestnut were equally well tolerated.

Unlike butcher's broom and horse chestnut, Pycnogenol has been shown to provide a benefit in advanced stages of CVI. One study looked at 39 patients with severe chronic venous insufficiency. Pycnogenol (50 mg, three times daily) improved capillary filtration, symptomatic score, and reduced edema.[51] In another study, 86 patients with severe CVI were given either 150 or 300 mg Pycnogenol or 1,000 mg Daflon. (Daflon is a micronized, purified flavonoid mixture.) Ankle swelling was measured early in the morning before the swelling effect of standing could come into play and again after 30 minutes of resting with feet elevated. Measurements were taken at the beginning of the study and after four and eight weeks of treatment. A composite, analog score based on signs and symptoms (edema, pain, restless limbs, subjective swelling, and skin alterations/redness) was recorded by patients. A second evaluation of edema was made by another physician. After eight weeks of treatment, Pycnogenol decreased ankle swelling by 35%, whereas Daflon treatment decreased it by 19%. Pycnogenol decreased a composite score for edema including pain, restless legs, feeling of heavy swollen legs, and skin alterations by 64%, whereas Daflon was only half as effective, lowering the composite edema score by 32%. The transdermal oxygen and carbon dioxide concentration in the lower legs was estimated with small sensors attached to the skin. Pycnogenol treatment was found to significantly increase tissue oxygen and lower CO_2, suggesting a considerable improvement in blood circulation to the legs. Daflon, in contrast, did not yield any significant effect on tissue oxygenation and apparently does not improve blood circulation to the legs. In this study, only the composite edema score was benefited by the higher dose of Pycnogenol.[52]

Like butcher's broom, Pycnogenol has been studied somewhat for its ability to offset edema secondary to treatment with calcium antagonist or angiotensin-converting enzyme-inhibiting drugs.[53]

The trees from which Pycnogenol is obtained are grown in plantations and its use is thus sustainable. The usual dose is 50–350 mg/day.

Vitis vinifera (Grape)

While grape seed is used as a source of OPCs and a substitute for Pycnogenol in practice, there is little research on this use of the grape seed in CVI. We located one French study in which 45 mg of grape OPCs improved CVI symptoms in 108 patients, particularly the symptom of heavy legs.[54] However, extracts of grape leaf (or red vine leaf) have been studied as a treatment for chronic venous insufficiency. One 12-week, double-blind, placebo-controlled study followed 219 individuals with CVI. In this study, daily doses of 360 and 720 mg red vine leaf extract both proved significantly more effective than placebo in reducing edema as well as improving pain and other symptoms. The researchers concluded that the higher dosage resulted in a slightly greater, more sustained improvement.[55] Benefits were also seen in a much smaller study of 39 patients taking 360 mg/day in two doses. A significant improvement in subjective criteria as well as lower leg volume was seen after two weeks of treatment.[56] In another crossover study of 71 patients with CVI, a daily dose of 360 mg red vine leaf extract decreased leg circumference and increased microvascular blood flow values.[57] In the double-blind study first described above, side effects were largely limited to mild gastrointestinal distress and occasional reports of headaches. Blood tests and physical examination did not reveal any harmful effects.[55] However, comprehensive safety studies have not yet been performed, and red vine leaf is not at present recommended for pregnant or nursing women, or individuals with severe liver or kidney disease.

Grapes, as well as their seeds and leaves, are widely available and highly sustainable. The usual dose of an extract of the dried herb is 370–720 mg/day.

Figure 8–2. *Vitis vinifera* (grapes)

CONCLUSION

The herbs discussed in this chapter are useful in the treatment of CVI, both to treat the disorder and to prevent its worsening. (See Table 8-2.) Because many different flavonoids appear to have a beneficial effect on CVI, patients should also be advised to increase the amount of berries in their diet as well as to increase their intake of other fruits and vegetables. Where patients are willing, better progress can be made if these treatments are combined with the use of compression therapy, frequent elevation of the legs, appropriate exercise, and where needed, weight loss. (See Sidebar 8-1.)

Table 8–2. Dose and Potential Safety Concerns of Herbs Used to Treat CVI

Herb	*Dose*	*Potential Safety Concerns*
Ruscus aculeatus (butcher's broom) root	Dried root: 300–450 mg/day In most studies, butcher's broom is paired with trimethylhesperidin chalcone and ascorbic acid. (See Table 8-1.) Tincture: 2–3 ml three times per day	May cause GI upset, take with meals. May cause lymphatic colitis (rare), do not combine with NSAIDs. Theoretical: May interact with MAO-inhibiting drugs (no references supporting theory); herb's action may be decreased when combined with alpha-adrenergic or calciumantagonists. Not sufficiently studied in pregnancy but appears to be safe based on existing data.
Aesculus hippocastanum (horse chestnut) seed	Dried seed: 250–300 mg two times per day; (100 mg aescin daily) Fresh seed: 120–180 mg four times per day; (120 mg aescin daily)	Use with caution in chronic kidney failure. Do not apply topically to broken or ulcerated skin. May cause GI upset—take with meals. Theoretical concern that it may affect anticoagulant drugs.

(*continued*)

Table 8–2. (*continued*)

	Dose may be cut in half after the first 8-week period. Tincture: 2–3 ml three times per day	
Pycnogenol; extract from maritime pine or grape seeds	50–350 mg/day	Not recommended in pregnancy or lactation. May cause mild GI upset. Theoretical concern that as an immune enhancer it should not be combined with immunosuppressive therapies.
Centella asicatica (gotu kola) herb	Dried herb: 90–180 mg/day Tincture: 2–4 ml three times per day	No known contraindications.
Vitis vinifera (red grape) leaf	Dried herb: 370–720 mg/day	No known contraindications.

8–1. *Case Study, CVI*

The patient is a 53-year-old woman, postmenopausal, with a history of gastric bypass surgery and arthroscopic surgery on both knees. She has low-normal blood pressure, suffers from seasonal affective disorder, and is taking an SSRI antidepressant. Her upper body is slender with a small waist and flat stomach. Her legs, however, are quite stocky and swollen. Her skin is a mottled red from midcalf to ankle on both legs, ankle bones are not visible, and pitting edema is present. The tops of feet and toes are swollen. The tiniest scratch on her legs causes a "leaking" of a clear fluid that persists for hours, completely wetting her socks. It can eventually be stopped by applying continuous pressure. She does a lot of physical work, loves to garden, and feels fine as long as she is moving. She is presently unable to sit for other than very short periods because resting causes cramping or pain. This is worsened when she elevates her legs. The patient has had restless leg syndrome in the past and describes her current symptoms as entirely different. The greatest pain comes from one ankle radiating over the top of the foot. Her physician has told her she will simply have to get used to her current circumstances. She has been prescribed full-leg compression stockings that provided some relief but they apparently fit poorly and would slide down over her hips. She no longer uses them.

Her diet is small and not optimal. She primarily eats Lean Cuisine spa meals, does not eat many vegetables, but does drink a spinach drink and V8, imbibes minimal alcohol, and drinks plenty of water. She eats few sweets; some chicken, nuts, and seeds; but little meat or fish. She is not taking any supplements. We discussed the need to increase her intake of flavonoids and other antioxidants by eating as many fruits and vegetables as possible. She is unwilling to take tinctures and unable to spend a great deal of money on supplements.

8–1. *Case Study, CVI (continued)*

INITIAL TREATMENT

Pycnogenol, 100 mg, once a day
Butcher's broom, 470 mg, 1 capsule/day
Horse chestnut cream, (horse chestnut seed, bark extract (Standardized to 20% aescin), also contains butcher's broom, witch hazel, white oak, myrrh gum, and rosemary extracts in a cream preserved with parabens). Applied gently twice daily.

Telephone consult after one week. The patient was taking Pycnogenol every other day because of cost. Disliked the cream as it ran, was green, sticky, and messy.

MODIFIED TREATMENT

Pycnogenol, 100 mg, every other day
Butcher's broom, 470 mg, 1 capsule/day
Horse chestnut, 250 mg seed extract standardized to 20% aescin, 1 capsule/day

Met three weeks later; she is working on including more vegetables and fruit in diet. She thinks she is improving.

RESULTS

After five weeks, the patient's ankle and calf circumferences have decreased and the tops of her feet and toes are no longer swollen. Her ankle bone is now visible.

	Initial	*5 weeks*		*Initial*	*5 weeks*
Right ankle	10.75"	10"	Right calf	17.25"	16.5"
Left ankle	10.25"	9.75"	Left calf	15"	14.5"

The patient still leaks fluid when scratched and still has some pitting edema. She says she feels much better and can fit into pants she could not wear previously because her knees and calves were too large (she wears loose men's pants). She continues to have pain when sitting or being still. It hurts more when she elevates her legs. She agrees to try a pair of air boots and subsequently reports that they enable her to sit comfortably and completely quiet her ankle pain. However, the boots are one-size-fits-all and are too snug for her at times. Skin is still mottled looking but is not worsening or showing signs of breakdown.

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9

BOTANICAL MEDICINE FOR CYSTITIS

Plant medicines are used around the world to prevent and treat cystitis. Some of the specific medicinal herbs used for this purpose have been investigated by scientific means, whereas others are known to be effective and safe on the basis of a long history of use. This chapter discusses general information about infectious and interstitial cystitis, and explores the qualities of the most important botanical medicines used to treat these conditions.

INFECTIOUS CYSTITIS

Bacterial infections of the urinary bladder continue to plague women in particular, although uncircumcised men also have a tendency to develop such infections. Enteric pathogens, particularly *Escherichia coli*, cause almost all cases of bacterial cystitis. These pathogens express a number of molecules that allow them to adhere to different cell types on their journey from the bowel to the bladder, and such bacterial adhesion probably constitutes the first step toward establishing a urinary tract infection (UTI).[1]

In the case of most strains of *E. coli* and other cystitis-causing Enterobacteriaceae, binding occurs through the linkage of bacterial type 1 fimbriae to mannose residues on host mucous or cell membranes. The fimbriae play a crucial role in bacterial adhesion to cells of the perineum, vagina, and foreskin.[2] However, type 1 fimbriae do not appear to play an important role once the bacteria are established in the urinary bladder; rather, research implicates P fimbriae and afimbrial adhesin molecules as the main culprits in allowing gut bacteria to cling to bladder epithelial surfaces.[1] Adherent bacteria can then initiate the steps that lead to bladder inflammation and clinical symptoms. Fimbriae, particularly P fimbriae, also play an important role in the progression of cystitis to pyelonephritis.[3] As subsequently discussed, there are botanical remedies that can interfere with this critical step in the pathogenesis of UTI.

Many antibiotics including trimethoprim-sulfamethoxazole (TMP-SX), commonly used to treat UTI, exert a weak-to-nonexistent effect on bacteria that have adhered to the bladder epithelium.[4] Although antibiotics are often effective in relieving symptoms of acute cystitis, they may not be very effective at eliminating colonization, and may also adversely affect the vaginal and urethral flora, facilitating the establishment of uropathogens.[5] A vicious cycle can ensue when antibiotics used to treat UTI cause gut, vaginal, or periurethral dysbiosis and thereby set the stage for new or recurrent UTI.[6] Antibiotics also induce a high level of antibiotic resistance among bladder bacteria, arguing for greater caution in their use.[4,7] Probiotic supplementation is recommended during and after antibiotic use of any kind, to prevent or correct dysbiosis induced by these drugs.[8]

Other host factors contributing to the pathogenesis of lower UTIs depend on age. In children, congenital anomalies of the urinary tract and vesicoureteral reflux contribute to many instances of cystitis. Sexual abuse may also occasionally be a factor in UTI during childhood. In adults, inadequate urine output secondary to insufficient water intake, various sexual practices (particularly those involving the anus), and spermicide use are all risk factors for lower UTI. Spermicide, especially nonoxynol-9, appears to disrupt the normal vagina flora and normal vaginal pH, thereby removing two of the normal female defenses against bacterial colonization of the

bladder.[9] Among the elderly, urolithiasis, prostatic obstruction of urinary outflow, and confinement to bed may be involved in UTI. Frequent or recurrent catheterization strongly predisposes to infectious cystitis. Patients with P1, a blood cell surface marker not usually measured clinically, are also at greater risk of colonization, in that they produce receptors to which bacterial fimbriae adhere avidly.

Cranberry

Vaccinium macrocarpon and *V. oxycoccos* (cranberry) is a member of the heath (Ericaceae) family and grows in bogs in the northeastern United States and eastern Canada. European colonists adopted it from the indigenous peoples of North America. Besides the use of cranberry as a food, it was applied to treat urolithiasis and several other conditions, and cranberry juice historically found use as a folk remedy for UTI.

Initial clinical reports suggested that cranberry was effective either because it acidified the urine or through its content of benzoic acid, which is converted to hippuric acid in the urine and which may be antimicrobial.[10,11] However, it would be necessary to drink at least 1,500 ml of cranberry juice a day to consistently maintain the urinary pH of 5.5 that is associated with an antibacterial effect.[12] For most people, this volume of cranberry juice is simply too great to consume on a daily basis.

The mechanism by which cranberry exerts an antibacterial effect has been elaborated in the past 20 years. It appears to interrupt the binding of bacterial type 1 and P fimbriae in both the

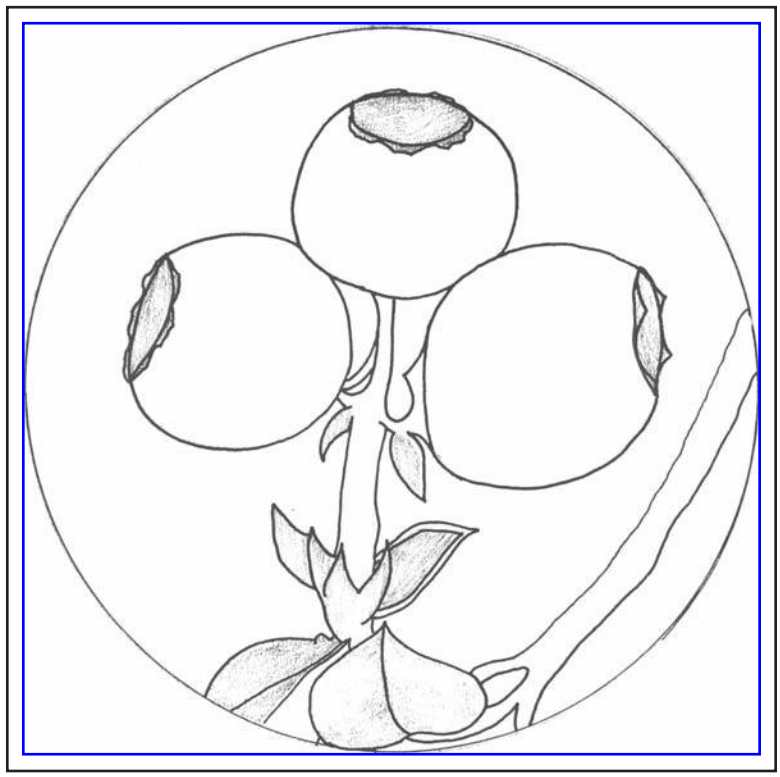

Figure 9–1. *Vaccinium* spp. (cranberry)
Drawing by Kathy Abascal, BS, JD.

urinary bladder and the gut.[13] The effect is to block microbial adhesion rather than to directly kill microbes, although there is some evidence that cranberry also has mild, direct antimicrobial activity.[14] However, if bacteria cannot adhere to the urothelium of the bladder, there is no reason to kill them, since they will be removed with the urine and be unable to initiate infection. This also avoids disruption of the normal urinary flora.

In laboratory experiments, cranberry prevented adhesion of uropathogens (*Proteus* spp., *Pseudomonas* spp., and *E. coli*) to bladder epithelial cells.[15,16] The major anti-adhesive constituents of cranberry have been identified as proanthocyanidins.[17,18] These protective substances are not present in most other fruits, including guava, mango, orange, grapefruit, or pineapple,[19] although they are present in the cranberry-related blueberry or bilberry (*Vaccinium myrtillus*).

In a large, double-blind study, 153 women with a mean age of 78 years, who had bacteriuria and pyuria, were given 300 ml of saccharin-sweetened cranberry juice daily or a placebo juice.[20] Significantly more women drinking cranberry juice developed a sterile urine than did those taking the placebo juice. This study did not show a protective effect of cranberry against new bacterial colonization, but only a conversion from colonized to non-colonized status. However, reduction or elimination of bacteria, which cranberry juice achieved to a clinically relevant degree, is an important step toward preventing frank cystitis. In another, smaller study involving 12 women who had had at least 6 UTIs in the preceding year, none of those taking 400 mg of cranberry extract daily for 12 weeks experienced a UTI. Eight of the women continued taking the extract after the study ended, and two years later, none had experienced an infection.[21] A systematic review found that the prophylactic use of cranberry in individuals with recurrent UTIs significantly reduced the incidence of such infections at 12 months.[22]

Cranberry juice has also been found to reduce odor and to yield a clearer urine in children required to regularly catheterize themselves,[23] and has proven useful in reducing catheter-obstructing mucous production in patients with entero-urocystoplasties.[23,24] Additionally, an open trial found that 250 ml of cranberry juice taken three times daily reduced bacterial biofilms in patients with spinal cord injuries affecting bladder function.[24] However, a double-blind trial involving children with neurogenic bladder and requiring intermittent catheterization failed to find that cranberry concentrate reduced bacteriuria to a greater extent than did an artificially flavored cranberry drink.[25] Also, in a randomized, double-blind trial of 305 patients with neurogenic bladder following spinal cord injury, an 800-mg cranberry capsule taken twice daily failed to prevent UTI.[26]

The relationship between cranberry and kidney stones is often discussed, though there is little solid information to suggest that it has either a beneficial or a detrimental effect. Sufficient intake of cranberry to chronically acidify the urine may help prevent some types of urinary stones (e.g., struvite and calcium phosphate) from forming, but again, the volume required is impractical for most people. Moreover by far the most common type of uroliths in the developed world, calcium oxalate stones, tend to occur in acidic urine, suggesting that high-dose intake of cranberry would actually promote stone formation. A study comparing 12 healthy individuals with 12 patients having a tendency to calcium oxalate stone formation found that 1 liter of cranberry juice per day had a mixed effect on stone formation, but increased the overall risk of calcium oxalate and uric acid stone formation while decreasing the risk of brushite stones.[27] Another human trial found that cranberry tablets increased urinary oxalate levels in five healthy volunteers, leading the authors to conclude, "Physicians and manufacturers of cranberry products should make an effort to educate patients at risk for nephrolithiasis against ingestion of these dietary supplements."[28] However, these latter authors' own study contradicts their conclusion, for they found that urine levels of magnesium and potassium rose with cranberry intake, an effect that is associated with a reduction in the risk of kidney stones. Overall, their findings were based only on indirect measures that do not necessarily equate to stone

formation, and on a very small sample size. To make a sweeping statement against use of cranberry based on such weak data is irrational. Unbiased research is needed on the effect of cranberry on the risk of urolithiasis. In the meantime, blanket statements for or against cranberry based on the existing, highly incomplete data should be condemned.

Although cranberry in therapeutic doses has no known toxicity and is safe for use by pregnant women, it may cause mild gastrointestinal upset in a few people. Sweetening of the juice should be avoided or minimized. Cranberry in therapeutic dose does not decrease the effectiveness of *Arctostaphylos uva-ursi* (uva ursi) or antibiotics because it rarely acidifies the urine enough to interfere with uva ursi's action. (See discussion below.) Capsules providing at least 400 mg of cranberry extract prevent problems for patients with blood sugar imbalances who need to avoid sweetened juice yet dislike the taste of unsweetened cranberry. They can be used in a dosage of 2 or 3 capsules per day (higher doses may be needed for acute UTIs). Overall, cranberry is an excellent agent for preventing the adhesion of uropathogens in in most patients with UTI or related conditions.

Urinary Antiseptics

A variety of botanicals other than cranberry can prevent and treat cystitis. Although many have not been investigated systematically with modern methods, the long history of their use strongly indicates that they should be examined in controlled clinical studies. The three main categories of herbs used medicinally for the urinary tract are urinary antiseptics, diuretics (technically aquaretics, as will be explained), and demulcents. The following sections cover only those in wide use.

Some urinary antimicrobial botanicals commonly used in North America are *Arctostaphylos uva-ursi* (uva ursi) leaf, *Agathosma* (formerly *Barosma*) *betulina* (buchu) leaf, *Tropaeolum major* (nasturium) leaf, *Armoaracia rusticana* (horseradish) root, and berberine-containing herbs including *Hydrastis canadensis* (goldenseal) root, *Mahonia aquifolium* (Oregon grape) root, *Berberis vulgaris* (barberry) root, and various species of *Coptis* (gold thread).

The first of these, uva ursi (also known as bearberry or kinnickinick), is native to North America, where it grows as a low shrub. Its leaves contain relatively high levels of the phenolic glycoside arbutoside (also known as arbutin), which is cleaved by normal flora of the gut to glucose and hydroquinone, the aglycone of arbutoside. The hydroquinone is absorbed and conjugated in the liver to glucuronic acid (and probably also acquires sulfate groups), making it water soluble. The hydroquinone–glucuronide complex is then excreted into the urine. In alkaline urine (pH 8 and above),[29] the complex dissociates spontaneously, releasing free hydroquinone, which has antimicrobial activity.[30] However, a study of three persons has suggested that the recommended dose of uva ursi (3 g uva ursi in 150 ml of water administered four times per day (the equivalent of 400–840 mg arbutin per day) results only in minimal excretion of hydroquinone,[31] although it is possible that undissociated complexes of hydroquinone also contribute to the antimicrobial activity of the herb. Maximum urinary antiseptic activity of uva ursi occurs three to four hours after oral ingestion. A high intake of fruits and vegetables will sufficiently alkalinize the urine for efficacy of uva ursi in some people; others may have to take 6–8 g of sodium bicarbonate daily for this, although this will also reduce stomach acidity, which is usually an undesirable action.

The alkalinity required to produce the antimicrobial hydroquinone from uva ursi has raised concern that it not be combined with cranberry, because the latter can supposedly acidify the urine to an extent that renders the hydroquinone ineffective. However, it is now known that a volume of cranberry of more than 1,500 ml/day is probably needed for such urinary acidification, indicating that most people can safely use uva ursi together with cranberry.

Figure 9–2. *Berberis vulgaris* (barberry)

A double-blind trial of one month's use of an uva ursi extract standardized to arbutin and methylarbutin in women with recurrent cystitis, defined as three or more infections in the previous year, found that it stopped further episodes of cystitis in the year following the study.[32] In contrast, 23% of women in a placebo group in the study experienced at least one further episode of cystitis in the year after conclusion of the study. The difference between the groups was both statistically and clinically significant.

Uva ursi also contains tannins, which can cause nausea. Two methods of avoiding this are to take uva ursi with meals or to make a cold infusion of the herb, into which the tannins are poorly extracted. A typical regimen of uva ursi involves adding 4–5 tbsp of the leaves of the herb to 1 qt water and allowing this preparation to steep overnight. The preparation should then be strained and the fluid consumed in divided doses throughout the next day. Larger quantities can be made ahead of time but should be kept in the refrigerator because they will otherwise rapidly decompose.

The hydroquinone generated from uva ursi has a number of potentially dangerous effects including suppression of B lymphocyte maturation and nephrotoxicity.[33,34] Hydroquinone is

Figure 9–3. *Tropaeolum major* (nasturtium)

also a known mutagen, and is one of the many toxins in cigarette smoke that contribute to cancer. This suggests that uva ursi should not be used over the long term, though the absolute levels of free hydroquinone that it generates in the urine are exceedingly small (or entirely absent according to one pharmacokinetic study in humans).[35] At least one double-blind trial has shown no short-term adverse effects of up to one month of continuous use of uva ursi.[32]

Among other herbal products for UTI, a German clinical trial found a combination of horseradish root extract and nasturtium leaf to be just as effective as antibiotics, and significantly safer than the latter, in curing uncomplicated UTIs.[36] In a double-blind follow-up trial involving 219 adults, the rate of UTI was roughly halved with this same herbal extract as compared to placebo.[37] No difference in adverse effects was seen in the herb and placebo groups. Both horseradish root and nasturtium are traditionally also used for infections in other parts of the body than the urinary tract.

Buchu leaves, obtained from the South African plant *Agathosma betulinum* and several related species, contain various terpenes, flavonoids, and other substances. *A. betulinum* has a long history of use as an antiseptic in UTI,[38] and is also used in gout, rheumatism, and mild gastrointestinal upsets. Because its efficacy has not been confirmed in any clinical trial, it should probably be regarded as a second-line treatment for UTI, behind other herbs with known efficacy. It is also generally better, both economically and ecologically, to avoid using herbs from outside North America if there are acceptable local alternatives.

Herbs containing berberine are used for treating many types of infection throughout the body. This alkaloid is clearly antimicrobial in sufficiently high concentrations, and like cranberry may also be important as a microbial anti-adhesive agent. Berberine has been shown to decrease the expression of fimbriae by *E. coli*, hence preventing their adhesion to the bladder epithelium.[39] Berberine also blocks adhesion of *Streptococcus pyogenes* at concentrations insufficient to inhibit growth and interferes with the lipotechoic acid complexes that allow streptococcal adhesion to fibronectin.[40]

Berberine has proven useful and well tolerated as a treatment for intestinal *E. coli* infections,[41] and has been shown in vitro to inhibit adhesion of uropathogenic strains of *E. coli*.[39] However, while herbs containing berberine have been used empirically with success, they yield only minute urinary levels of this alkaloid when administered orally in humans,[42] raising doubt that they would influence UTIs, and no clinical trials have examined whether administration of berberine-containing plants can prevent or alter the course of cystitis. Historically, treatment has consisted of 1 tsp (5 ml) of a tincture of any of the above berberine-containing plants, taken three times daily. Standardized extracts usually contain 5–10% berberine, and one 250–500 mg capsule is taken three times daily.

Goldenseal, Oregon grape, barberry, and gold thread are the major medicinal herbs containing berberine, and all are very safe. All are digestive bitters, which means that they stimulate the entire digestive tract and may in some instances cause nausea. As a result, they should be used with caution, if at all, in conditions of hyperchlorhydria and increased gut motility, especially as evidenced by diarrhea. (Of course, berberine-containing plants are indicated in conditions of infectious diarrhea.)

There is also some preclinical evidence that berberine displaces bilirubin from albumin, suggesting that it should be avoided in late pregnancy.[43]

Aquaretic Herbs

According to the late pharmacognocist Varro Tyler, most botanicals used for UTIs and other conditions are not technically diuretics but aquaretics.[44] This means that plants traditionally referred to as diuretics may not act by interfering with the renal handling of ions, but instead may act to increase blood flow to the kidneys and thereby raise the glomerular filtration rate. Whether aquaretics or diuretics, these agents can benefit patients with UTI, in which increased urine flow helps wash bacteria out of the urinary bladder.

Some major, traditional phytoaquaretics are *Solidago* spp. (goldenrod) herb, *Levisticum officinale* (lovage) root, *Betula* spp. (birch) bark, *Taraxacum officinalis* (dandelion) leaf, *Zea mays* (corn) silk, *Agropyron repens* (couch grass) rhizome, buchu, *Apium graveolens* (celery) seed, and *Juniperus communis* (juniper) leaf. Tyler reviews research showing goldenrod, buchu, parsley, juniper, and birch to be aquaretic, at least in animals.[44] A double-blind, placebo-controlled trial, conducted in Vietnam, failed to show any increase in urine output after intake of corn silk.[45] Dandelion leaves were shown to have a diuretic effect in rats.[46] A recent abstract reported that a combination of birch leaves, hawthorn (*Crataegus* spp.) berries, strawberry (*Fragaria* spp.) leaves, corn silk, chamomile *(Matricaria recutita*) flowers, and horsetail *(*Equisetum spp.) had a 47% greater diuretic effect than horsetail alone and 34% greater effect than a hydrochlorothizide suspension in rats.[47] This suggests that combining herbs with medicinal foods will often work better than using an herb alone. Celery, parsley, and carrots should be emphasized in the diet because they promote urine flow and generally support the urinary tract. Ultimately, effective treatment of cystitis requires at least eight glasses a day (part of which is often replaced by unsweetened cranberry juice or herbal teas).

No research has been done on the aquaretic action of couch grass, but in one study it failed to prevent kidney stone formation in rats,[48] and because increased urine flow is known to help prevent kidney stones, couch grass appears not to be a very potent aquaretic. The herb does, however, appear to contain enough mannose to prevent uropathogen adhesion to the bladder mucosa via type 1 fimbriae. Jonathan Wright, MD, of Kent, Washington, uses 0.25–1 tsp of mannose dissolved in water and given three or four times a day to prevent mucosal adhesion of

Figure 9–4. *Taraxacum officinalis* (dandelion)

bacteria in cystitis. The mannose in corn silk may help explain its traditional use in treating cystitis.[49] The efficacy of mannose is, however, still uncertain, because it has not yet been examined in a clinical trial.

The Australian herbalist Nicolas Burgess recommends celery seed as a useful diuretic in UTI, and also observes that celery seed is rapidly becoming a major remedy for osteoarthritis in Australia. In Britain, celery seed is considered only a mild diuretic and is largely recommended for rheumatic conditions and gout.[50] It should not be used in persons with renal disease because its volatile oils may "irritate" the kidney with prolonged administration. Light-skinned persons may also want to avoid excessive intake of celery seed because of a slight risk that it may induce photosensitivity.

Figure 9–5. *Fragaria* spp. (strawberry) leaf

Figure 9–6. *Betula* spp. (birch) bark

Juniper offers a very appealing herbal "package" for patients with UTIs. Besides its potent diuretic activity, it is strongly antimicrobial and inflammatory.[51,52] It is surprising that all of these properties have not led to a published clinical trial of juniper for UTI. The reputation of juniper as dangerous to the kidneys is of dubious accuracy, and one text that attempted to trace the origin of this belief could find only that it was due to confusion of the essential oil of

Figure 9–7. *Crataegus* spp. (hawthorn)

J. sabina (savin) with that of juniper.[53] In a study with rats, high doses of juniper oil produced no nephrotoxicity.[54] However, juniper should be used with caution in pregnancy on the basis of unconfirmed historical reports of its having uterine-stimulating effects.

Demulcent Herbs

There is a significant overlap between the aquaretic botanicals and those said to soothe irritated urothelial surfaces. The latter phytomedicines include corn silk, couch grass, *Althaea officinalis* (marshmallow) leaf and root, *Ulmus rubra* (slippery elm) bark, *Sphaeralacea* spp. (globemallow) leaf, and *Alcea rosea* (hollyhock) leaf and root. Although all clearly contain significant mucilaginous material, no research has been done on their therapeutic benefit in cystitis; however, all are exceptionally safe.

It is thought that demulcent agents work via a reflex action: As they pass through the digestive tract they are believed to provoke neurologic reflexes that in turn stimulate production of mucus in the respiratory and urinary tracts. This has not been confirmed in the urinary tract, though it has been shown to occur in the respiratory tract in animals.[55] This increased mucous production is thought to relieve inflammation and soothe pain. Whatever the mechanism of their effect, it is clear that in clinical practice demulcent herbs help relieve symptoms of irritation.

Demulcents are usually used in the form of cold infusions because other extracts are difficult to prepare and administer. A typical dose is prepared from 1 tbsp herb per cup of water (often an entire day's dose is prepared at once), with at least 3 cups consumed per day, although higher doses may be needed to alleviate acute symptoms.

Figure 9–8. *Zea mays* (corn silk)

INTERSTITIAL CYSTITIS

While interstitial cystitis (IC) was first described about 100 years ago, little has been elucidated about its etiology or pathogenesis.[56] It affects middle-age white women almost exclusively. Clinically, its most common symptoms are urinary frequency and urgency, pelvic pain or pressure, and burning on urination.[57]

A number of theories have ben advanced for the pathogenesis of IC, with significant but imperfect evidence supporting each major theory.[58] Although researchers initially described ulcerations of the bladder in most affected patients, it is now known that approximately 80% of patients with IC lack such ulcers. In many patients mast cells infiltrate the bladder wall, although their exact role in the disease is still unclear. High levels of histamine and methylhistamine are found in the urine of IC patients as compared to controls,[59] suggesting that mast cell degranulation may contribute to the inflammatory process in the bladder in IC. Other inflammatory mediators derived from bladder epithelial cells, such as interleukin-6, have also been found in the urine in IC.[60]

The glycosaminoglycan (GAG)-rich bladder epithelium may be disrupted in patients with IC, allowing toxic substances in the urine to damage the bladder wall.[61–63] This has prompted a likening of IC to intestinal hyperpermeability. Morphologically, the GAG-rich mucous barrier has a similar appearance in people with IC and those without.[64] However, there may be a difference in the composition, quality, or rate of turnover of the mucous. This was confirmed in a study that found less type IV collagen in the basement membrane of the bladder epithelium of patients with IC.[65] A large clinical trial found that GAG replacement therapy, using sodium pentosanpolysulfate, was no better than placebo.[66] Directly applied heparin, a naturally occurring GAG, was successful in a separate study.[67]

The occurrence of IC primarily in women initially raised the idea that the disease might be an autoimmune condition, as women are also the population chiefly affected by most other autoimmune diseases. Studies of this intriguing theory have found an association between Sjögren's syndrome and IC, increased levels of complement component C3 in patients with IC, and a variety of other features resembling those in other autoimmune diseases.[56] Another finding has been that of unique anti-nuclear antibodies (ANAs) in the sera of IC patients.[68] An uncontrolled study found that low-dose cyclosporine, an immunosuppressant, was of benefit in IC patients.[69] More clarifying research needs to be conducted in this area, but a case can be made for an autoimmune component in IC.

The role of microbes in the etiology of IC remains uncertain. DNA from Gram-negative bacteria can be isolated in as many as 30% of IC patients but not from controls, suggesting that IC may be a form of infectious cystitis.[70] However, the majority of patients with IC have sterile urine.

NATURAL INTERVENTIONS FOR INTERSTITIAL CYSTITIS

Given the complexity of IC, particularly the variety of pathologic factors involved, no single "magic bullet" exists. Formulae including a number of different plants are therefore utilized. Each can address different aspects that contribute to IC. Often, botanicals are combined with other treatment modalities to enhance efficacy.

Solidago virgaurea (Goldenrod) Herb and *Populus tremuloides* (Quaking Aspen) Bark

Inflammation-modulating botanicals are a component in every IC formula. *Solidago virgaurea* and related species (goldenrod) herb and *Populus tremuloides* (quaking aspen) bark are common choices in this regard. The traditional understanding that goldenrod has aquaretic properties has been confirmed in human studies.[71] It also has anti-inflammatory and spasmolytic activities according to animal studies.[72] It is generally safe though it can provoke allergic reactions in susceptible persons. Use caution if prescribing it for patients with renal disease. Quaking aspen is less thoroughly studied, though it and birch both are useful for reducing symptoms of cystitis. A typical dose of goldenrod, quaking aspen, or birch tincture is 3–5 ml three times daily. Quaking aspen and birch both contain salicylates.

Glycyrrhiza glabra (Licorice) Root

Glycyrrhiza glabra (licorice) root is also a good choice for the inflammation-modulating component in formulas, acting by sparing endogenous cortisol.[73] Licorice exerts other effects that might benefit patients with IC. Licorice has been shown to reduce complement levels, a known pathogenetic factor in IC.[74] Although licorice's constituent glycyrrhetinic acid appears to act primarily on the early complement component C2, it may also affect C3, another inflammation-related complement component that appears to be commonly deranged in IC patients.[56] Licorice is also demulcent according to empirical information. Long-term use of high doses can lead to hypokalemia, hypertension, metabolic acidosis, and other problems.[75] Concomitant supplementation with potassium, consuming a high-potassium diet (i.e., high in fruits and vegetables), and possibly glycine may reduce the risk of such complications. Licorice should not be administered concomitantly with potassium-wasting diuretics, as they increase the toxicity of licorice. Deglycyrrhizinated licorice extracts would not likely be effective for interstitial cystitis. A usual dose of licorice fluid extract is 3–5 ml three times per day.

Quercetin

The ubiquitous, inflammation-modulating plant flavonoid quercetin has also been shown, in an open trial, to reduce symptoms of interstitial cystitis.[76] The dose used was a relatively low 500 mg twice daily. Quercetin has already proved efficacious in a double-blind trial in patients with chronic prostatitis, a condition closely allied and commonly confused with IC.[77] Quercetin-rich foods include green tea, apples, and onions.

Botanical Aquaretics

Botanical aquaretics are standard features in most IC formulas. However, this can be extremely counterproductive as most patients have a primary symptom of urinary frequency, and the last thing they want or need is to urinate even more. That said, tonic herbs that are mildly aquaretic at most may still have a place in therapy as they are primarily building. An example of such an herb is *Equisetum arvense* (horsetail) herb. It is very safe, but it is unclear whether its active constituents are extracted in alcohol.

Antimicrobial Herbs

Antimicrobial herbs are included because part of the pathogenesis may involve bacteria. Uva ursi is sometimes used, or possibly the more soothing arbutin-containing herb *Chimaphila umbellata* (pipsissewa) leaf. It is very mild in its action and almost never causes adverse reactions.

Table 9–1. Summary of Major Botanicals Used for Cystitis

Botanical Name	*Common Name*	*Main Constituent(s)*	*Main Action in Urinary Tract*
Agathosma betulina	Buchu	Terpenoids, mucilage, flavonoids	Antibacterial
Agropyron repens	Couchgrass	Mucilage, terpenoids, glycosides	Soothing, possibly prevents bacterial adhesion
Althea officinalis	Marshmallow	Mucilage	Soothing
Apium graveolens	Celery	Terpenoids	Aquaretic, inflammation modulating
Arctostaphylos uva ursi	Uva ursi	Arbutin	Antibacterial
Betula spp.	Birch	Salicylates, terpenoids	Aquaretic, inflammation modulating
Chimaphilla umbellata	Pipsissewa	Arbutin	Antibacterial
Equisetum arvense	Horsetail	Saponins, alkaloids	Aquaretic
Glycyrrhiza glabra	Licorice	Glycyrrhizin, flavonoids	Inflammation modulating, soothing
Hydrastis canadensis	Goldenseal	Berberine, hydrastine, and related alkaloids	Antibacterial, immuno stimulant
Juniperus communis	Juniper	Terpenoids	Aquaretic, antimicrobial, inflammation modulating
Levisticum officinale	Lovage	Coumarins	Aquaretic
Piper methysticum	Kava	Kava lactones, resin	Sedative
Populus tremuloides	White poplar	Glycosides	Inflammation modulating
Scutellaria spp.	Skullcap	Favonoids	Sedative
Solidago virgaurea	Goldenrod	Flavonoids, glycosides, saponins	Aquaretic, inflammation modulating
Taraxacum officinale	Dandelion	Glycosides, terpene lactones	Aquaretic
Vaccinium macrocarpon	Cranberry	Proanthocyanidins	Prevents bacterial adhesion
Zea mays	Corn silk	Mannose, mucilage	Aquaretic, possibly prevents bacterial adhesion

Sedative Herbs

Finally, sedative herbs such as *Piper methysticum* (kava) and *Scutellaria* spp. (skullcap) should be employed. Studies demonstrate that kava is analgesic by nonopioid pathways, which might benefit IC patients with significant pain.[78–81] Clinical trials also show kava helps alleviate anxiety.[82] Future studies on the efficacy of kava in patients with IC are warranted. Use of therapeutic doses is generally not associated with toxicity. Kava administration should probably be carefully monitored if the patient is taking dopamine-antagonist anti-psychotic medications or any medications that may adversely affect liver function. A typical dose of kava tincture is 3–5 ml three times per day. Extracts standardized to 30% kava lactones, 70 mg per capsule, are available. The usual dose is 1 capsule three times per day. Extracts standardized to greater than 30% kava lactones are not recommended as they may crowd out other important constituents besides kava lactones.

CONCLUSION

The majority of patients will benefit most if a multifaceted botanical formula is combined with other therapies. Self-care and behavioral techniques help patients understand and cope with symptoms as well as reduce their intensity.[83,84] Various medications including dimethylsulfoxide (DMSO) are instilled directly into the bladder by urologists. Eating a whole-foods diet and avoiding stress are generally recognized as beneficial. (See Table 9-1.)

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10

BOTANICAL TREATMENT OF DEPRESSION

Depression ranks as one of the most widespread mental health problems in the world. Besides causing significant morbidity and mortality (through suicide), depression also contributes to or is associated with several other serious problems. Depression may contribute to atherosclerosis, perhaps by impairing glucose tolerance,[1] and depression has been repeatedly linked to depressed immune function.[2] In fact, over half of people with chronic or severe illnesses may suffer from depression. Depression can strike at any age, but depression in the elderly is a particularly significant problem. The surgeon general of the United States recently noted that suicide rates increase with age and that nearly 5 million of the 32 million Americans over 65 suffer from some form of depression. Natural medicine offers many options for helping cope despite the enormity of the problem of depression at any age.

Today, allopathic antidepressant drugs are all too often prescribed and dispensed without a second thought as a treatment for depression. The decision to institute or maintain patients on these drugs should be made much more cautiously. The profitable new antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and atypical agents) have not been shown to be more effective than older drugs, and have not been shown to be more effective than psychotherapy or cognitive behavioral therapy.[3] Newer drugs may not even have fewer adverse effects than some older agents,[4] and reports about unforeseen negative consequences of these drugs, such as upper-gastrointestinal bleeding (increased by concomitant non-steroidal anti-inflammatory drug use),[5] are emerging.

Antidepressant drugs have strong placebo effects, and placebo itself is very effective for people with depression.[6,7] Depression also resolves on its own in up to 50% of people affected. It has also recently become clear that negative trials on these drugs have been actively suppressed by the drug companies, and when they are included in meta-analyses, antidepressants are in fact no more effective than placebo.[8] Furthermore, it has been alleged that some drug makers hid evidence that some antidepressants actually increase the risk of suicide, at least in teenagers and children.[9] According to a review of trials by independent researchers and clinicians in the United Kingdom, trial results of antidepressants in children have exaggerated the benefits of the drugs that the investigators rate as having "doubtful clinical significance," adverse effects have been downplayed, and that these drugs cannot be recommended for childhood depression.[10]

Therefore, in mild cases it is critical to support the mind–body as opposed to ruthlessly suppressing any sign of depression. Ultimately, antidepressants should be reserved for more serious cases of depression that do not respond to safer natural treatments, and even in those cases the practitioner should continue to look for and treat the cause of the depression.

From a holistic perspective, treating depression is not about substituting St. John's Wort for an allopathic antidepressant medication. Instead, therapies should be chosen that will strengthen the individual so as to eliminate the core cause of the depression while using botanicals to palliate symptoms (in this case, elevating mood). Here we focus on botanicals for treating the causes and symptoms of depression, but it is critical to remember that diet and lifestyle issues must be addressed to effectively help people with this condition. Also, we focus primarily on major depression rather than helping patients cope with temporary and normal feelings of sadness or despondency in response to life's trials and tribulations.

BITTERS, THE GUT, AND DEPRESSION

As with many health problems, depression is frequently the result of processes that involve the gut and its accessory organs (particularly the liver). This is often a particularly important aspect in the elderly because gut function declines with age. It is known that a significant percentage of people over 50 have abnormally low levels of gastric acidity.[11] There is also epidemiological data linking food allergies to depression and anxiety, which could support a common digestive problem causing both.[12] Lack of sufficient saliva, inadequate bile production, and less acidic gastric pH can lead to abnormal bowel flora and poor nutrient absorption. Many elderly (and increasingly large numbers of younger) patients are also maintained on various allopathic medications that significantly and adversely affect salivation and digestion generally (e.g., anticholinergics; acid-blockers).

Malabsorption of nutrients is a serious concern and possible cause of depression because numerous nutrient deficiencies, even if marginal, have been linked to depression. Acute depletion of tryptophan (the precursor of serotonin) as well as phenylalanine and tyrosine (the precursors of norepinephrine and dopamine) have been repeatedly shown in experimental studies in humans to depress mood.[13,14] Rat studies have linked chronic tyrosine deficiency to depressed mood, although rigorous data on the tyrosine-mood connection in humans are not available. Thus, it is quite possible that low-grade protein malnutrition, due either to low intake or poor absorption, may aggravate or precipitate depression. Ensuring optimal nutrition and digestion are critical to avoid and correct this problem.

Low vitamin B12 and folic acid levels contribute to depression, again a particular concern in the elderly where age-related hypochlorhydria can decrease vitamin B12 absorption. One study found that vitamin B12 deficiency doubled the risk of depression in noninstitutionalized women.[15] Vitamin B12 and folic acid are critical intermediates in the methylation process necessary for formation of catecholamine neurotransmitters. These neurotransmitters in general elevate mood. Vitamin B12 and folic acid also maintain normal homocysteine levels. When these two vitamins are deficient, even marginally, homocysteine levels rise and atherosclerosis is promoted. Atherosclerosis can impair blood flow to the brain and promote depression. Therefore, maintaining optimal levels of these two B vitamins is critical. These vitamins may need to be supplemented in some people with depression and many elderly people, but is equally important to also ensure the gut is functioning properly to prevent future deficiency.

Bitter herbs are central to the botanical approach to promoting optimal gastrointestinal function. Historically, an atonic gastrointestinal tract was associated with depression, and bitters were used to stimulate the immune system in patients who were pale, lethargic, or prone to infection. Rudolf Fritz Weiss, MD, stressed that tonic effects of bitters became stronger with prolonged use, and claimed that bitters would neutralize the negative influence of chronic stress on digestion.[16] Numerous modern practitioners also use bitters to stimulate hepatic function and general digestion as a key component to addressing depression in some people.[17]

Bitters are substances capable of stimulating digestive powers and appetite in cachexic, debilitated, and healthy people alike. The quinoline alkaloids of *Cinchona* spp. (Peruvian bark), monoterpene secoiridoid glycosides of *Gentiana* spp. (gentian), and the sesquiterpene lactone dimers of *Artemisia absinthium* (wormwood) are some of the most bitter substances known, and these herbs are among the most frequently used bitters. Early studies established that

Table 10–1. Choosing a Bitter Herb

*Patient Features**	*Herb*	*Dose*
Recovering from chronic or acute illness, elderly, cachexic, immunodepressed, strong effect desired	*Gentiana lutea* (gentian) root**	Tea: 1 tsp (5 g)/cup water simmered 10–15 min, sipped 10–15 min before meals Tincture: 2–4 ml in 2–4 oz water, sipped 10–15 min before meals
Same as gentian but milder effect desired	*Taraxacum officinale* (dandelion) leaf	Tea: 1 tsp(5 g)/cup water steeped 10–15 min, sipped 10–15 min before meals Tincture: 2–4 ml in 2–4 oz water, sipped 10–15 min before meals
Gallbladder problems prominent or chronic gastrointestinal infection present	*Artemisia absinthium* (wormwood) root	Tea: 1 tsp (5 g)/cup water simmered 10–15 min, sipped 10–15 min before meals Tincture: 0.5–1 ml in 2–4 oz water, sipped 10–15 min before meals
Liver problems prominent, cholestasis, or chronic gastrointestinal infection present	*Berberis aquifolium* (Oregon grape) root	Tea: 1 tsp (5 g)/cup water simmered 10–15 min, sipped 10–15 min before meals Tincture: 2–4 ml in 2–4 oz water, sipped 10–15 min before meals
Liver damage, peptic ulcer, inflammation, otherwise same as for gentian	*Swertia chirata* (chiretta) root	Tea: 1 tsp (5 g)/cup water simmered 10–15 min, sipped 10–15 min before meals Tincture: 2–4 ml in 2–4 oz water, sipped 10–15 min before meals
Fever, inflammation, hemorrhagic tendency, cardiovascular problems	*Achillea millefolium* (yarrow) herb	Tea: 2 tsp (10 g)/cup water steeped 10–15 min, sipped 10–15 min before meals Tincture: 3–5 ml in 2–4 oz water, sipped 10–15 min before meals
Non-tolerance of bitter taste, inflammation, nausea, arthritis	*Zingiber officinale* (ginger) rhizome	Tea: 1 tsp (5 g)/cup water simmered 10–15 min, sipped 10–15 min before meals Tincture: 1–3 ml in 2–4 oz water, sipped 10–15 min before meals
Menopausal symptoms, hormonal imbalance	*Marrubium vulgare* (horehound) herb	Tea: 2 tsp (10 g)/cup water steeped 10–15 min, sipped 10–15 min before meals Tincture: 3–5 ml in 2–4 oz water, sipped 10–15 min before meals

* Other herbs in this table or otherwise may also be appropriate for patients with the features listed.

** Note that there are concerns about the sustainability of this herb in the wild given current trends of use. Use cultivated or ethically wild-crafted herb. *Taraxacum officinale* (dandelion) leaf is a highly sustainable and reasonably similar substitute.

Figure 10–1. *Achillea millefolium* (yarrow)

bitters worked by taste, and did not appear to affect digestive function in healthy animals. Human studies have demonstrated that gentian and wormwood can increase salivation as well as gastric and bile secretion when taken five minutes before meals.[18] Though bitters can stimulate digestion without being tasted,[19] their effects are probably optimized by allowing the bitter taste to stimulate the cephalic as well as intestinal phases of digestion. Direct connections between bitters and the mind have not been studied. To choose a bitter, refer to Table 10-1.

ESSENTIAL FATTY ACIDS, OXIDATION, AND DEPRESSION

Essential fatty acids, particularly in the omega-3 family, exert a multifactorial influence on mood. Omega-3 fatty acids have been shown to have a regulatory influence on serotonin release and degradation.[20,21] Studies have repeatedly found that omega-3 fatty acid levels are decreased in the serum and cell membranes of a significant proportion of people with depression.[22,23] Higher intake of omega-3 fatty acids is protective against depression in most epidemiologic studies.[24] Existing trials, though limited, also show they may help treat people with depression.[25] There is concern that desaturation of omega-3 fatty acids from precursors as well as excessive dietary omega-6 intake (which can compete for desaturase enzymes shared with omega-3 fatty acids and further decrease levels of omega-3s) may play a significant role in these deficiencies. Impaired absorption due to gut compromise may also reduce essential fatty acid levels, suggesting once again that bitters may be necessary and helpful.

Botanical sources of essential fatty acids thus may provide a benefit for some people with depression. Omega-6 fatty acids, particularly gamma linolenic acid (GLA), are rich in the seeds of *Oenothera biennis* (evening primrose) and related species, *Borago officinalis* (borage), and *Ribes nigrum* (black currant). Controlled clinical trials have suggested that evening primrose oil might be helpful for relieving depression related to premenstrual syndrome,[26] but not all studies have agreed with these findings. Dr. James Duke points out that evening primrose seeds contain the highest tryptophan content of any herb encountered in his extensive survey of the topic. However, tryptophan is not present in evening primrose oil, and patients would have to eat quite a large quantity of seeds (several grams three or more times per day or more) to obtain sufficient tryptophan to influence mood, a regimen unlikely to be practical or affordable for most patients.

The U.S. diet is already fairly high in omega-6 oils (from sunflower, safflower, and canola oils) and there is some concern that further omega-6 supplementation may only exacerbate omega-3 fatty acid problems. Therefore, *Linum usitatissimum* (flax), *Cucurbita pepo* (pumpkin), or *Cannabis sativa* (hemp) seed oils might be considered as all are sources of the omega-3 fatty acid alpha linolenic acid (ALA). Unfortunately, this will not be effective if the patient's ability to desaturate them to active omega-3 fatty acids is impaired. Thus, fish oil- or algae-derived docosahexaenoic acid (DHA) might be the best initial supplements if essential fatty acid problems are suspected. These both contain large quantities of preformed, active omega-3 fatty acids.

Essential fatty acids should always be supplemented with antioxidants. This is because they are sensitive to oxidation and need to be protected. There is evidence that people with major

depression have deficiencies of some antioxidants, particularly vitamin E.[27] This deficiency offers a separate potential explanation of the essential fatty acid problem: If the fatty acids are being oxidized and damaged, they could be unable to perform their mood-normalizing actions. Chronic inflammation might also promote depression by raising levels of inflammatory cytokines and other chemical mediators that have neurological effects because they deplete zinc, a nutrient essential for desaturation of essential fatty acids to their active forms.[16] Oxidative damage of essential fatty acids, rendering them not only inactive but damaging to neurons, might also be a source of the problem. Botanical antioxidants and anti-inflammatories such as *Curcuma longa* (turmeric) rhizome, *Rosmarinus officinalis* (rosemary) leaf, *Ginkgo biloba* (ginkgo), and quercetin may be good supplements along with traditional vitamin and mineral antioxidants to ensure better utilization of essential fatty acids.

CEREBROVASCULAR INSUFFICIENCY AND DEPRESSION

Atherosclerosis of the vasculature feeding the brain can lead to a condition known as cerebrovascular insufficiency. This chronic low-grade ischemia can impair memory or otherwise mimic dementia. It can also produce a syndrome resembling depression. This syndrome is surprisingly little discussed in the United States but is much more widely recognized in Europe. The treatment is obviously the same as for atherosclerosis anywhere in the body—elimination of the underlying dietary and lifestyle causes (especially sedentariness) and addition of supportive nutrients and practices (like meditation).

Ginkgo biloba (ginkgo) leaf extracts have been very rigorously shown to help alleviate cerebrovascular insufficiency symptoms.[28] This is almost certainly due to ginkgo's ability to reduce the underlying atherosclerosis and improve neuron function despite ischemia. It also seems to stimulate blood flow to the brain, perhaps by acting on blood vessels. The usual dose of ginkgo standardized extract is 80–160 mg two or three times per day. It should be used attentively in patients taking anticoagulants as the combination occasionally but rarely may have a synergistic effect and cause bleeding.

Gingko has also been shown to improve mood and depression in the elderly. Gingko's effect in depression is "semi-hidden" in studies that on the surface deal more with cognitive function but mental depression and mood are shown to improve. One study of 60 hospitalized patients with cerebral insufficiency and the leading symptom of depressive mood showed significant improvements in a double-blind study of ginkgo extract lasting six weeks.[29] Limited data suggest that depression in dementia responds to antidepressant medication, perhaps including ginkgo.[30] At least one trial has shown that ginkgo can directly relieve depression not necessarily related to cerebrovascular insufficiency in the elderly.[31] There is no evidence that ginkgo is useful for idiopathic major depression in younger persons. Indeed, one study of ginkgo in younger adults with seasonal affective disorder found it useless.[32] However, it might be useful as an adjunct therapy to prevent sexual side effects of allopathic antidepressant drugs. Other botanicals that help in atherosclerosis and may relieve cerebrovascular insufficiency with concomitant depression in the elderly include *Allium sativum* (garlic) bulb, *Rosmarinus officinalis* (rosemary) leaf, and *Zingiber officinale* (ginger) rhizome. None of these have been specifically studied for this particular syndrome.

St. John's Wort

German and now U.S. research has established beyond a doubt that extracts of *Hypericum perforatum* (St. John's wort) flowering tops are effective antidepressants. A meta-analysis of

clinical trials confirmed that St. John's wort extracts are as effective as several synthetic antidepressant drugs and superior to placebo for people with mild to moderate depression.[33] There is also at least one study showing that relatively high doses of St. John's wort extract is helpful for people with severe depression.[34] St. John's wort was also found effective in people with seasonal affective disorder in an open clinical trial, and combining it with phototherapy was not dangerous (though it did not enhance the benefits of that therapy).[35] It has shown promise for relieving depression in alcoholics with gastritis in a preliminary Russian clinical trial.[36]

A large share of the highly limited resources for research on botanical medicines is being focused on St. John's wort, including a large double-blind study funded by the National Center for Complementary and Alternative Medicine (NCCAM). Many studies firmly establish St. John's wort efficacy, and only the most conservative would claim it is ineffective. It is unfortunate that research resources were not instead invested in studies on other interesting botanical remedies for depression. We believe the only areas of research that are truly needed for St. John's wort at this point are more definitive studies on its mechanism of action, the efficacy of other similar species (e.g., *Hypericum calycinum* or rose of Sharon), and the best way to administer it.

The optimal dose form of St. John's wort is unknown. Prior research focused on extracts standardized to 0.3% hypericin, pseudohypericin, and related dianthrones.[33] However, it has recently become clear that hyperforin and possibly flavonoids in St. John's wort are just as important as hypericin in the antidepressant activity of the herb, if not more important.[37] In addition, red food color can be added to the extract to fool the usual standardization assay for hypericin that assays the red color of this compound. Unscrupulous manufacturers thus were selling far inferior encapsulated extracts almost devoid of hypericin. Extracts standardized to 5% hyperforin are starting to become popular and common. The dose of standardized extracts is 300 mg three times per day (up to double this dose in severe cases). The usual dose of tincture is 3–5 ml three times per day. There are almost no studies on the efficacy of crude extracts like tinctures of infusions of St. John's wort. Although claims are often made that standardized extracts are superior to crude extracts, no direct comparative data currently exist to support those claims. Given the multifactorial nature of St. John's wort's active constituents and mechanisms of action, it is entirely possible that a crude extract would be comparable to or better than a standardized extract in efficacy.

St. John's wort is generally very safe. In a systematic review of its adverse effects in a pool of 35,562 patients it ranged from 0 to 5.75, which was comparable to placebo.[38] In a review of 16 postmarketing studies, it was deemed to be significantly safer than synthetic antidepressants.[38] The risk of phototoxicity at antidepressant doses is minimal to nil, as was shown in a study in people using phototherapy combined with St. John's wort, discussed above. *Hypericum*'s constituents do induce cytochrome P450 enzymes, possibly CYP 3A4 or 2D6, though study results have not been consistent on this point.[39] Nevertheless, there are case studies suggesting St. John's wort may interfere with cyclosporine (Sandimmune), digoxin (Lanoxin), indinavir (Crixivan), warfarin (Coumadin), and theophylline. There is some weak evidence for the danger of combining St. John's wort with pharmaceutical antidepressants,[40] and it may be wiser to have the patient choose one or the other rather than combining the two. Based on the fact that SSRIs can affect thyroid levels, a study attempted to look at St. John's wort's effect on thyroid function. In 74 patients (half with elevated thyroid-stimulating hormone [TSH] levels, half with normal levels), six had taken St. John's wort regularly before a TSH test. Four had elevated TSH levels and two had normal levels. The researchers acknowledged that no link between St. John's wort and thyroid dysfunction had been shown but considered the data to suggest that it, like SSRs, might cause a thyroid-related adverse effect when used long term.[41]

TSH levels rose in these individuals; two were diagnosed as hypothyroid and two already taking levothyroxine required a dose increase.

Saffron

Crocus sativus (saffron), aside from being a popular spice, has a long history of use as an excellent digestive aid that reduces stomach aches, increases appetite, and has antispasmodic effects on both the intestines and the kidneys. In Persian folk medicine, it is also used as an antidepressant.

In one study of 40 people with mild to moderate depression, 30 mg of extracted saffron was compared with 20 mg/day of fluoxetine for six weeks. The drug and the herb had similar effects and showed no differences in terms of side effects.[42] Another randomized, double-blind study compared 30 mg/day saffron with 100 mg/day of imipramine, again for six weeks. Both groups showed significant improvement with symptoms of dry mouth and sedation being greater in the imipramine group.[43] Since these, three other double-blind trials used the same dose of saffron compared to placebo or various antidepressants, again showing good efficacy and a lack of adverse effects.[44–46]

Saffron has also shown an antidepressant effect in animal studies.[42] Saffron capsules do not appear to be readily available commercially in the United States at this time. In the clinical studies, a tincture of saffron was prepared (120 g saffron percolated in 80% ethanol and dried by evaporation to a powder). The Eclectics also prepared a tincture of saffron. They macerated 100 g saffron in 100 ml diluted alcohol and then percolated it until they obtained 1 L of tincture. The tincture was used as an emmenagogue, as a diaphoretic, and for hysteria at a dose of 1–3 drams. It may not have been widely used as a medicine in the United States because much of the saffron on the market was reportedly adulterated.[47]

Saffron may inhibit platelet adhesion so it is contraindicated in pregnancy and should be used with caution in patients on anticoagulant therapy.

THE OVERLOOKED HERBS

A variety of gentle plants are continually overlooked by both pharmacological medicine and clinical practitioners. This happens because it is easy to fall into the trap of looking for rapid-acting, potent plants with a specificity for a particular disease state. It is all too easy to overlook plants that act slowly and nonspecifically but in the end help address the root cause of the problem. Throughout history herbal practitioners have emphasized the importance of these "tonics" (sometimes referred to as neurotrophorestoratives) to help support the patient's own healing process. Herbs that support the integrity and function of the nervous system are almost universally indicated for people with depression. Moreover, nervine tonics are usually called for because depression often exists as "a comorbid condition," very often with anxiety or other mood disorders.

Avena sativa (oats) seeds (picked during the so-called milky stage) are one of the most highly reputed and gentle nerve tonics among the Eclectic physicians as well as European herbalists.[48] Oat seed also has a reputation, however poorly substantiated, for relieving depression and thus cravings in people attempting to break their addiction to nicotine. It might be somewhat surprising to think of various hypnotic herbs as being helpful for depression. Logically one might assume that an herb that induces sleep would only worsen depressed moods. However, many such herbs were used traditionally for melancholic patients. This would include herbs like *Melissa officinalis* (lemon balm) leaf, *Valeriana officinalis* (valerian) root, *Eschscholzia californica* (California poppy) flower, *Scutellaria lateriflora* (skullcap) herb (must be fresh),

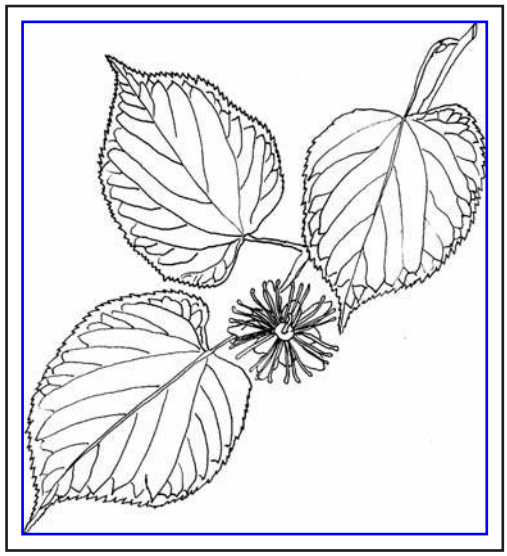

Figure 10–2. *Tilia cordata* (linden)
Drawing © 2004 by Kathy Abascal, BS, JD.

Tilia cordata (linden) flower, *Stachys betonica* (wood betony) herb, and *Passiflora incarnata* (passionflower) herb.

It is possible that in higher doses these herbs are hypnotic but in lower doses more stimulating. However, it is more likely that the herbs are acting as tonics regardless of dose, and help bring the nervous system back into balance in a way that pharmacological medicine presently cannot comprehend or explain. With so many active constituents interacting with a multitude of cells, receptors, neurotransmitters, and other structures, it is not surprising that a complex result would occur. *Actaea racemosa* (black cohosh) root, *Leonurus cardiaca* (motherwort) herb, and *Verbena* spp. (vervain) herb were also traditionally used as nervines but are relatively specific for depression or other disturbances related to the menstrual cycle or menopause in women. A recent open clinical trial confirmed that black cohosh helps relieve mood symptoms related to menopause, and that this benefit was magnified by combination with St. John's wort.[49] Though fluoxetine was superior to black cohosh for relieving postmenopausal moodiness, black cohosh was still helpful and had a better effect on relieving hot flashes in a double-blind trial.[50] All three work as mild nervines in men as well.

All of these herbs can be administered as teas, tinctures, or in capsules. Capsules and herbs for teas should be no more than six months old, ideally, and should have been stored in airtight containers, in cool temperatures, and out of light prior to use. Usually, only small, local herb producers are reliable sources for herbs that have not been stored too long, it is otherwise difficult to assess the freshness of most commercial herbs and tea preparations on the market. Skullcap is far less active dried than fresh in the opinion of many practitioners, and should only be used as a tincture made from fresh plant or as a tea made from fresh leaf. As a tea, 2–3 tsp (5–10 g) of any of the herbs should be added to a cup of water and either simmered for 10–15 minutes (for roots) or steeped in hot water for 10–15 minutes (for soft parts of plants). The patient should drink at least 3 cups a day on a very regular basis, flavored if desired by mixing in some peppermint, ginger, or hibiscus. The usual tincture dose is 3–5 ml three times per day. Two approximately 500 mg capsules would be taken three times per day. All the herbs are completely safe. Rarely, patients may experience sleepiness or excessive stimulation, in which case the dose can usually be lowered without difficulty.

A far more powerful nerve tonic with definite dose-dependent effects is *Pulsatilla* spp. (pasque flower, pulsatilla) herb. In overdose this herb can cause extreme nervous system and cardiovascular suppression including coma and hypotension. In small doses, it is a mildly stimulating nervine and heart tonic with a strong reputation for relieving abnormal menstruation, nervous exhaustion, and melancholy. In slightly higher doses it becomes mildly sedative and significantly analgesic with an affinity for the gonads. As an antidepressant, mother tincture (1:10 weight:volume dilution) is recommended in the amount of 1–3 drops three times per day along with other supportive measures. Somewhat similar to skullcap, only fresh plant should be used as the dried plant is far less active.

Finally, *Piper methysticum* (kava) root is used as a nerve trophorestorative or tonic in people with depression manifesting primarily as anxiety. Kava has repeatedly been shown effective for relieving anxiety, as evidence by a meta-analysis of clinical trials.[51] Unlike benzodiazepines used to treat patients with anxious depression, kava actually improves mental function.[52] It is unknown how effective kava is for depression without anxiety, but Weiss does mention it for this situation.[53] The usual dose of tincture is 3–5 ml three times per day. Extracts standardized to 30% kavalactones are also available; the usual dose is 70 mg three times per day.

BOTANICAL STIMULANTS

Occasionally it may be necessary to temporarily boost the energy of someone who is feeling depressed. The German Commission E has approved the use of *Cola nitida* (kola nut) as an adjunct therapy in depression, and *Camellia sinensis* (tea), *Coffea arabica* (coffee), and *Ilex paraguayensis* (yerba maté) may be useful stimulants due to their caffeine content. However, this is rarely an effective long-term therapy, and entirely fails to address the underlying causes of depression. Certainly, botanical stimulants should not be part of a standard regimen for depression, and it is in fact often recommended that the nearly ubiquitous stimulant caffeine be removed from the diet to stop masking symptoms and allow the person to deal with the real issues of depression.

Instead, we recommend using adaptogens to provide stimulation. These do not contain caffeine and do not appear to have the suppressive effect of the caffeine alkaloid. Instead, they tend to stimulate the entire nervous system. On rare occasions, this may manifest as insomnia, agitation, or mild anxiety but usually adaptogens increase the person's sense of well-being and energy without negatively affecting mood. That said, there is a case report of a woman, taking clomipramin and haloperidol, who added Asian ginseng to her regimen and became manic. Lorazepam was substituted for the clomipramin and Asian ginseng and her mania dissipated (she otherwise suffered from major depressive disorder). The clomipramin was subsequently reintroduced without sequelae.[54] More typical are the results of a phase III clinical trial of *Rhodiola rosea* L. In a six-week study, patients took either 340 or 680 mg/day of rhodiola or placebo. Rhodiola reduced overall depression and insomnia while increasing emotional stability compared to placebo.[55]

In an animal model of depression, many plants were shown to have an antidepressant effect, such as *Eleutherococcus senticosus* (eleuthero, Siberian ginseng) root, *Schisandra chinensis* (schisandra), rhodiola, *Echinacea purpurea* (purple coneflower), and *Syringa vulgaris* (lilac). Eleuthero had the most pronounced effect, one comparable to amitriptyline. Rhodiola was a close second followed by echinacea. Interestingly, *Melissa officinalis* (lemon balm) did not have a positive effect in this study.[56] Many people suffering from depression will find that adaptogens alleviate their symptoms, and where the depression is caused by a poor ability to cope with stress, their use may address the underlying cause of depression. In other patients, their effect will be mostly palliative. Depression that accompanies diseases characterized by immune compromise such as cancer is a strong indication for all these herbs. For more information on adaptogens, see chapter 3.

Peganum harmala (Syrian rue) seed and root is a less well-known stimulant. Though originally from northern India and southern Russia, it has since become naturalized in the western United States. It is completely unrelated to *Ruta graveolens* (rue). Syrian rue contains the indole alkaloids harmaline and harmine among others. These are a classic inhibitor of monoamine

oxidase (MAO) in vitro. Herbalist Michael Moore of Bisbee, Arizona, put the indications for Syrian rue best when he wrote, "The seeds . . . are a useful antidepressant and mood elevator for folks with mopey dragass depressions, not the nervous, peripatetic, manic depression. People who sit in front of the television all day (whether or not they turn it on) and don't want to go out or be visited usually find that Syrian rue and a noisy friend can shake them out of their malaise."[57] The generally safe dose is 1–1.5 ml (approximately 40 drops) of tincture three times per day. Syrian rue should only be used in the short term (a few days to weeks). It should not be taken with tyramine-containing foods (particularly aged cheeses, fermented foods, and wine). Syrian rue will tend to slow and strengthen the pulse while lowering blood pressure. If blood pressure becomes excessively low (to the point of causing dizziness) or if hallucinations occur, Syrian rue use should be discontinued.

The more famous harmine alkaloid-containing plant is *Banisteriopsis caapi* (ayahuasca), the hallucinogenic vine from South America. This use suggests that native peoples were taking advantage of MAO inhibitors long before they were discovered by pharmaceutical science.[58] Unlike ayahuasca, Syrian rue is only hallucinogenic at high, nearly toxic doses, far greater than usual clinical doses. Interestingly, Syrian rue was traditionally used as a vermifuge and amebicidal agent long before it was brought to the New World, and it has shown antimicrobial activity in vitro.[59]

VOLATILE OILS FOR DEPRESSION

A number of volatile oils have been recommended for people with depression. There are varying opinions about which oils are useful, although there is near agreement on a handful of oils. The volatile oil of *Jasminum officinale* (jasmine) is claimed by one author to be among the longest used for depression in Asia,[60] and this author also suggests the use of volatile oils of *Matricaria recutita* (German chamomile), *Rosmarinus officinalis* (rosemary), and *Rosa* spp. (rose). Chamomile is also mentioned in a classic work by the French aromatherapist, Jean Valnet, MD, as being particularly indicated for depression.[61] He further mentions borneol (extracted from *Dryobalanops camphora* or Borneol camphor), lavender, and thyme as useful antidepressants. He suggests 2–5 drops of volatile oil two to three times per day of lavender and thyme as internal doses, but does not give doses for chamomile and borneol. This text does not discuss molecular mechanisms of action for any of the oils, only reporting traditional actions.

Lavandula officinalis (lavender) is perhaps one of the most widely known psychoactive volatile oils. Lavender oil aerosolized in the air was reported to be more effective than pharmaceutical drugs for relieving insomnia in one study.[62] No studies were located on the effect of lavender oil on people with depression but there is a preliminary randomized, controlled study of lavender tincture in mild to moderate depression. It was far less effective than the drug imipramine but greatly enhanced the antidepressive effect of the drug when the two were combined.[63] As mentioned in chapter 5 on anxiety, lavender aromatherapy reduced agitation in elderly patients with dementia.[64] This suggests that lavender might be best indicated in people with agitated depression.

More research on the efficacy of volatile oils in people with depression is needed but, in the meantime, they should not be overlooked as potentially very valuable therapies, in particular considering that inhaled volatile oils pass through the olfactory nerve directly to the cerebrum.

LOW-DOSE HERBS FOR DEPRESSION

Historically, several potentially toxic herbs have been used for depression. It is unlikely that modern practitioners will find much use for them as they are only indicated for the most serious cases of depression, where the better studied, more reliable synthetic drugs are more appropriate. Nevertheless, we briefly discuss these herbs, one of which still has a potential place in the treatment of people with depression.

Papaver somniferum (opium) is highly recommended by the late Dr. Weiss as the safest and most effective botanical for therapy-resistant, severe depression.[65] Mu opioid receptor agonists like morphine induce euphoria. However, it is clear from Weiss's description that opium is only palliative, and he says that symptoms will return unless the opium is used long term. Weiss states that opium is best for endogenous depression, particularly in perimenopausal women and in elderly patients with atherosclerosis causing cerebrovascular insufficiency. He recommends extremely small doses of whole plant extracts (5 doses of tincture three times per day titrated slowly up to 20 drops three times per day), which in his experience are not addictive. Perhaps even more controversial is his suggestion that the patient be misled as to the nature of the medicine (he suggests calling it "tincture thebaica," an antiquated term), because once the patient knows it is opium, the fear of addiction may become a complicating factor.[65] Morphine or other isolated opiates are not recommended for treatment of depression due to their much higher risk of addiction and adverse effects.

Opium tincture may rarely have a place in the treatment of people with depression unrelieved by any other intervention, natural or pharmaceutical. It is clearly not indicated for milder cases or in people who respond to other therapies. Tincture of opium (also known as laudanum or ladanum) and deodorized tincture of opium (opium combined with camphor, also known as paregoric) are schedule III drugs in the United States and can only be prescribed by physicians registered with the Drug Enforcement Agency (DEA). In contrast, morphine, codeine, and other isolated opium alkaloids are schedule II drugs and clearly much more addictive than the whole plant. Weiss recommends combining tincture thebaica with *Rheum palmatum* (rhubarb) root if constipation is a problem (and suggests this will usually pass in a few days) or *Mentha* x *piperita* (peppermint) and bitters if gastrointestinal upset is a problem.[65] Opium should be avoided in people with compromised lung function or intestinal obstruction and is contraindicated in pregnancy and lactation.

Strychnine and brucine are two alkaloids found in such plants as *Ignatia amara* (St. Ignatius bean, ignatia) and *Strychnos nux-vomica* (ordeal bean). Strychnine and brucine act as glycine receptor antagonists, thereby blocking the normally inhibitory effects of the amino acid glycine on neurotransmission. As a result, the entire nervous system is indirectly stimulated by strychnine and brucine. If the dose of these agents is too high, a highly characteristic seizure and diaphragmatic paralysis results. Because of these potentially lethal effects, strychnine-containing herbs are no longer recommended for use, except perhaps in the form of homeopathic remedies. Advanced practitioners might consider using a single drop of ignatia mother tincture (1:10 weight:volume) per 5 ml dose of St. John's wort tincture or an individualized tincture formula as an "activator" or "synergizer."

COMBINING HERBS AND ANTIDEPRESSANTS

Generally speaking, herbs should be combined cautiously with antidepressants and patients should be monitored carefully after starting combination therapy. There are few studies on

whether herbs and antidepressant drugs work together well or might cause adverse effects. As cited above, St. John's wort has been considered a potential threat in combination with antidepressant drugs, though very little evidence of difficulties has been documented. St. John's wort should be used with caution with all types of antidepressant drugs but is not absolutely contraindicated in all cases. Table 10-2 reviews potential interactions of antidepressant drugs and herbs.

Ginkgo has been successfully combined with antidepressants in one study. The goal of this uncontrolled study was to offset the very common incidence of reduced libido caused by SSRIs, tricyclic antidepressants, and MAO-inhibitor drugs.[66] Ginkgo standardized extract at a dose of 60–120 mg two times per day was effective at preventing reduction of libido in 84% of people in the study. Women responded better than men. A further controlled clinical trial is

Table 10–2. Antidepressant Drug–Herb Interactions

Herb	*Antidepressant Drug(s)*	*Nature of Interaction*
Hypericum perforatum (St. John's wort)	All types (SSRI, MAO, tricyclic)	Unknown, potentially unsafe, do not combine without careful and close professional monitoring.
Ginkgo biloba	All types	Preliminary study shows reduction in sexual side effects.
Pausinystalia yohimbe	Fluvoxamine (Luvox)	Potentiated benefits in one clinical trial.
	Desipramine	No negative or positive interaction in clinical trials.
Bitters	All types	No known or anticipated interaction.
EFAs	All types	No known or anticipated interaction.
Nervines	All types	Anticipated beneficial interaction, no reports of adverse interactions.
Stimulants	All types	Avoid combination, theoretical anticipation of potential adverse interactions.
Stimulating immunomodulators	All types	No known or anticipated interactions.
Peganum harmala (Syrian rue)	MAOIs	Combine with great caution (potential synergism due to similar mechanisms of action).
	Tricyclics, SSRIs	Theoretical potential for adverse interactions.
Banisteriopsis caapi (ayahuasca)	MAOIs	Combine with great caution (potential synergism due to similar mechanisms of action).
	Tricyclics, SSRIs	Theoretical potential for adverse interactions.
Volatile oils	All types	Unknown.
Papaver somniferum (opium)	All types	Unknown (serious potential for adverse interaction).
Ignatia amara and *Strychnos nux-vomica*	All types	Unknown (serious potential for adverse interactions).

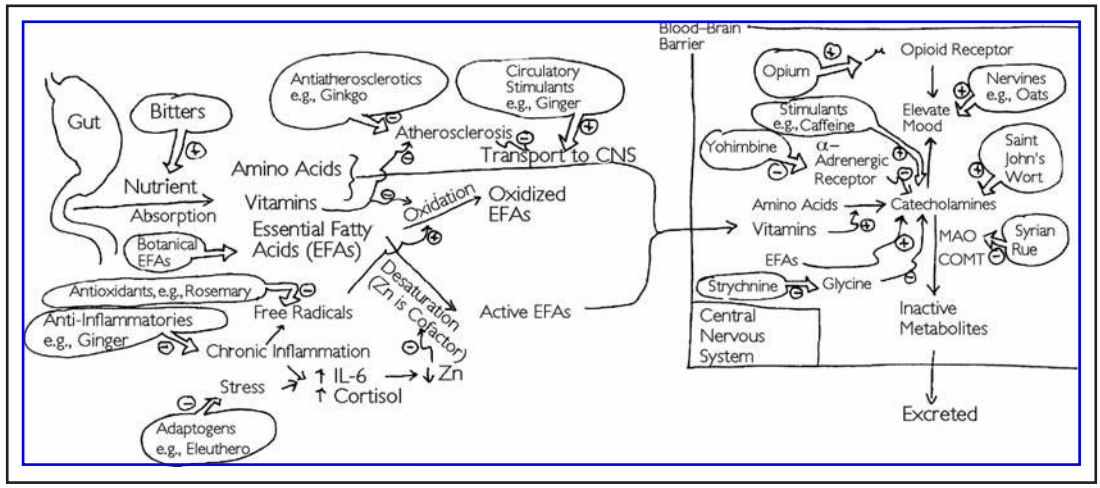

Figure 10–3. Summary Model of Effects of Botanicals on Depression
Abbreviations in Figure 10-3: COMT: catechol-O-methyltransferase, CNS: central nervous system, EFA: essential fatty acid, IL-6: interleukin-6, MAO: monoamine oxidase, Zn: zinc. Schematic designed by Eric Yarnell, ND, RH.

warranted, though reducing side effects of antidepressant drugs should not be used as an excuse to avoid locating and treating the cause of depression.

Yohimbine is an alkaloid derived from the African plant *Pausinystalia yohimbe* (yohimbe) bark. It antagonizes alpha-2 adrenergic receptors. This is important in depression because alpha-2 receptors tend to exert a regulatory role that inhibits release of norepinephrine and possibly other catecholamines. It is believed that tricyclic antidepressants' effects are delayed at least in part due to up regulation of alpha-2 adrenergic receptors to compensate for the increased level of catecholamines induced by these nonselective catecholamine reuptake-inhibiting drugs. One study has shown that yohimbine (5–30 mg three times per day) can enhance the antidepressant activity of the drug fluvoxamine (Luvox), whereas another study did not find yohimbine alone or combined with desipramine (Norpramin) effective in people with severe, refractory depression.[67,68] Thus, there is a potential role for use of standardized extracts of yohimbe providing 5–10 mg three times per day of yohimbine alkaloid to augment antidepressant drugs in severe situations, but this is not an herb that should be dispensed in most cases. Yohimbe is absolutely contraindicated in people with panic disorder or posttraumatic stress disorder, both of which can be worsened by this herb. Above 10 mg three times per day of yohimbine, hypertension, agitation, and other adverse effects become much more common and disturbing, and such high doses are generally best avoided. See Figure 10-3.

GENERAL APPROACH TO PEOPLE WITH DEPRESSION

Obviously there are many potential routes to helping people with depression, some better documented than others. In holistic medicine, it is always critical to attempt to find the underlying cause of the disorder as well as palliate symptoms. Nervine herbs to rebalance or normalize mood are almost always indicated, as well as some degree of gastrointestinal balancing because people in Western society so commonly have disordered digestion (which then affects the rest of their mind–bodies). Counseling and mind–body work is also usually very important.

Table 10–3. A Basic Depression Formula Template

Herb	*Dose Form*	*Amount in Formula*	*Function*
Stachys betonica (wood betony) herb	Fresh or dry plant tincture	35%	Nervine, tonic
Hypericum perforatum (St. John's wort) flowering top	Fresh plant tincture	35%	Symptom palliation
Rosmarinus officinalis (rosemary) leaf*	Fresh plant tincture	15%	Nervine, anti-atherosclerotic, antioxidant, circulatory stimulant
Rosmarinus officinalis (rosemary) volatile oil	Volatile oil	3–5 drops	Antidepressant, nervine
Achillea millefolium (yarrow) flowering top	Fresh plant tincture	10%	Bitter digestive tonic
Peganum harmala (Syrian rue) seed	Dry plant tincture	5%	Symptom palliation, stimulant
Zingiber officinale (ginger) rhizome	Fresh or dry plant tincture	1%	Synergizer, mildly stimulating, circulatory stimulant, digestive tonic
Ignatia amara (St. Ignatius bean) seed	Dry plant tincture	1 drop	Synergizer

*Use ginkgo standardized extract capsules along with this formula in anyone where cerebrovascular insufficiency is a suspected contributor to depression. Dose: 5 ml three times per day.

Except in mild cases of depression, some degree of symptom control is also indicated to improve quality of life and avoid the real possibility of suicide. There are numerous natural products that can be used for this purpose. The best supported and most generally applicable is St. John's wort. For severe cases, pharmaceutical intervention is obviously necessary, but this does not mean that other treatments should be dropped.

Table 10-3 proposes a basic formula that can be used as a base for prescribing an individualized combination for people with depression. This is not intended as a simple recipe or magic bullet that will help everyone, but as a learning tool to help pull together a complex set of information for practitioners. This formula, individualized to meet the patient's needs, along with appropriate dietary, lifestyle, mind–body, and nutritional supplement work, can provide an important base for helping people heal themselves of depression.

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11

INTEGRATING BOTANICALS INTO DIABETES TREATMENT PROTOCOLS

Diabetes is a complex disease that exists in two major forms: insulin-dependent diabetes (IDDM) and non-insulin-dependent or type 2 diabetes mellitus (NIDDM). The vast majority of people with diabetes have NIDDM and presently almost 20% of Americans over the age of 65 suffer from this disorder. It is a growing epidemic and by the year 2010, this percentage is expected to rise to 30%.[1] In addition, it is increasingly affecting younger people and can no longer accurately be referred by its old common name of age-onset diabetes. NIDDM is a progressive disease that shows a consistent deterioration in glycemic control over time, and it is estimated that at least a third of patients with NIDDM will ultimately require insulin therapy.

This chapter primarily focuses on herbs that are useful in NIDDM. These are used to help patients with this diagnosed disease reduce, delay, or avoid entirely oral hypoglycemic drugs and to avoid developing a need for insulin therapy. They can also be used to help individuals with impaired glucose tolerance (IGT) from manifesting NIDDM.[2] While the pathophysiology and pathogenesis of the NIDDM is not fully understood, it is clear that IGT often develops into NIDDM. Moreover, about 11% of American adults (18% of those over 65) suffer from IGT so interventions that may delay or prevent the progression are desperately needed in our society.

Most of the herbs we discuss are established traditional treatments for diabetic patients, and many are being confirmed effective in modern clinical trials. However, some very promising treatments are covered that have slight to no investigation. It must be noted that there are other well-established treatments, such as *Trigonella foenum-graecum* (fenugreek), *Panax quinquefolius* (American ginseng), *Oplopanax horridum* (devil's club), and many others that we do not discuss in this chapter. Thus, this chapter is meant to open the door to treatment possibilities, not to be an exhaustive description of any and all possible botanical treatments for diabetes.

It should also be noted that the precise mechanisms of action, major active constituents, optimal dose and dose form, and safety for the medicinal plants discussed have not been worked out in a rigorous fashion. Finally, we do not suggest that the herbs in this chapter should be relied upon as the sole treatment for anyone with diabetes. Obviously, lifestyle interventions such as changes in diet and exercise patterns are a critical component of both treatment and prevention but these are beyond the scope of this book. And in many cases, antidiabetic medications are necessary. For patients with IDDM, of course, insulin can never be discontinued. However, there are certainly cases of IDDM and NIDDM where botanicals can be used to reduce doses of insulin or other prescription medication. There are also cases of NIDDM where botanicals may be able to supplant entirely these medications, at least for a while. However, combining these, or any other herbs, with antidiabetic medication will require close monitoring of serum glucose levels to maintain appropriate glycemic control, something that should be done regularly in these patients in any event. It is only with close monitoring that the success or failure of a chosen botanical treatment be evaluated. Thus, any practitioner working with these therapies must be able to monitor and address the medical issues and tests associated with treating diabetes.

OPUNTIA SPP. (PRICKLY PEAR)

Prickly pear often goes by its Spanish name, *nopal*. This word comes from the Aztec word for cactus, *nocheznopalli* or *no palli*. Its red, sweet fruits are called tunas in Spanish, another word with an Aztec connection.[3] The Aztecs used prickly pear with *Geranium* spp. (cranesbill) to mitigate fever, alleviate hernias, and soothe irritated livers. The fruit, with seeds, was used to prevent diarrhea especially if caused by "heat." The peoples on the Yaqui River used the extracted fluid from roasted pads to relieve pain.[4] Prickly pear remains turn up so regularly at Anasazi sites that archeologists suggest that their diet, believed to have consisted primarily of corn, beans, and squash, probably included more prickly pear than squash. In New Mexico, prickly pear pads were used as a poultice in painful, inflamed skin injuries, rheumatic inflammations, for swollen glands in the neck, and for congested, purplish breasts in lactating women. The pads were also used as emollients for tumors, warts, and calluses, and fried, mashed pads applied with *Malva* spp. (mallow) reportedly healed fissures of the palms and feet.[5]

The Yaqui and the Hispanics in New Mexico today continue to soak diced pads in water and drink the liquid for thirst and diabetes. The pad is also used to cure diabetic infections. The tip of the pad is skinned and roasted, and the cut surface is applied to the wound and covered, a process that is repeated three times a day.[4]

Botany and Safety of *Opuntia* spp.

There are a multitude of prickly pear species with hundreds documented in Mexico and the Southwestern United States alone. Conclusive data comparing the qualities of the many prickly pear species do not exist, and there is presently no indication that any particular species is a better medicinal plant. The species that have been studied for medicinal qualities include *Opuntia streptacantha, O. ficus-indicus, O. vulgaris, O. inermis, O. megacantha, O. dillenii*, and *O. fulginosa*.

Prickly pear pads and fruits have a long history of use in the human diet without any reports of toxic effects, and most researchers praise the plant's lack of toxicity. However, one researcher has raised a possible adverse effect on kidney and liver function that deserves further study. For the most part, the side effects of prickly pear involve contact with its tiny spines (glochids) and the dermatological reaction that can ensue, especially in agricultural workers harvesting prickly pear fruits. In one study, prickly pear significantly increased blood urea and creatinine levels in both diabetic and nondiabetic rats compared to untreated controls ($p < 0.001$), and increased urinary creatinine clearance rates in diabetic animals only. The authors expressed concern that prickly pear perhaps caused an early stage of kidney dysfunction in both normal and diabetic rats.[6] The same researchers reported that prickly pear changed blood mineral, aspartate aminotransferase, and alkaline phosphatase levels in rats.[7]

In contrast, a safety study of prickly pear in mice, horses, and human patients found no side effects from its use.[8] No adverse effects were observed in human volunteers who took 6 g of prickly pear extract per day for one month or 3 g per day for six months. High doses of intraperitoneal prickly pear extract in mice caused only minor symptoms that disappeared within two days of injection. Horses fed 27 g of extract daily for two to four weeks showed no adverse clinical effects and no abnormalities in laboratory measurements of liver, kidney, or hematological function. Unfortunately, the laboratory blood results were not detailed in the article.

Prickly Pear in Diabetes

Prickly pear is best known for its use in adult-onset NIDDM. Research groups headed by Dr. Alberto Frati-Munari (Hospital de Especialidades, Centro Médico de la Raza, México City, México) have conducted a series of studies on prickly pear's hypoglycemic effect in human volunteers. These studies present evidence that prickly pear has a hypoglycemic action in NIDDM patients despite design flaws such as small sample size, the use of an inadequate control substance (water), and short duration (all of the trials essentially studied only the acute effects of prickly pear intake). Some of the studies were randomized and some were crossover, but none were double-blinded. A preliminary meta-analysis of six of these studies concluded that the control data was insufficient for a full meta-analysis but the intervention data showed prickly pear to lower blood glucose levels by 10–30 mg/dl in NIDDM patients and supported the likelihood that prickly pear has a true metabolic effect in diabetics.[9] A more recent analysis of the human studies found that prickly pear produces a sustained reduction in high glucose levels in diabetics given an oral glucose load. The benefits of prickly pear thus increases over time compared to nontreated volunteers.[10]

A statistically significant reduction of blood glucose and insulin levels (when tracked) were seen consistently where broiled prickly pear was administered to volunteers with NIDDM.[9,11–16] Glucose levels dropped in the first hour after ingestion but typically reached significance two to three hours after ingestion with one study indicating an action that was measurable over a span of six hours. The magnitude of effect ranged from mild to moderate depending on the dose of prickly pear used. For example, one study found that 300-g broiled prickly pear acutely lowered blood glucose levels by an average of 30 mg/dl in eight NIDDM subjects, while 500 g acutely lowered blood glucose levels by an average of 45 mg/dl in these same subjects.[17]

Initially, it appeared that heating was necessary to activate the plant's hypoglycemic activity as homogenized prickly pear did not show a hypoglycemic effect.[16] However, a subsequent study found that pads ground in a regular blender (but not ultrahomogenized) had an effect equivalent to that of broiled prickly pear.[18] Dried capsules did poorly in a crossover, single-blind study where a single dose of 30 capsules of dried prickly pear extract had no hypoglycemic action. Only a mild hypoglycemic action was observed in volunteers taking 30 capsules per day for 10 days—a rather impractical dose in any event.[19] Besides the studies headed by Frati-Munari, there is a case report involving an NIDDM patient, poorly controlled with chlorpropamide, who showed significant improvement in symptoms and blood values after taking prickly pear sap before meals three times a day over an eight-week period.[20]

The animal studies generally confirm a hypoglycemic effect in diabetic rats[6,21] and rabbits,[22] although one study showed no hypoglycemic effect in rabbits where pancreatic beta cells were completely obliterated.[8] Prickly pear and insulin equivalently reduced, but did not normalize, glucose and insulin levels in diabetic rats. Interestingly, diabetic rats given insulin and prickly pear together rapidly achieved normal glucose levels, and at seven weeks became hypoglycemic. At that point, prickly pear alone was able to maintain normal glucose levels.[21] Thus, prickly pear may also have a role to play in patients with IDDM.

Prickly Pear in Normal Individuals

Prickly pear is said to have no hypoglycemic effect in healthy individuals. Dr. Frati-Munari has also headed a number of studies on this aspect of the plant. These studies again suffer from the defects of small size, poor choice of controls, short duration, and multiple variables. Nonetheless,

it appears the plant at most affects glucose levels mildly in normal individuals while significantly reducing glucose levels in volunteers made artificially hyperglycemic.

Prickly pear did not reduce glucose and insulin levels at all in healthy volunteers in two studies.[11,17] In a third study, nondiabetic individuals who ate broiled prickly pear before meals for 10 days showed a mild but significant reduction in fasting glucose levels.[13] A slight drop in glucose and insulin levels was also seen in a study of healthy volunteers before glucose was administered to the volunteers to make them artificially hyperglycemic.[23]

In contrast, prickly pear typically showed a significant hypoglycemic action effect in most volunteers in a hyperglycemic state. In three studies using oral glucose loading, the volunteers' glucose levels dropped significantly, and the area under the glucose tolerance curve was reduced.[15,24,25] But in one test where the glucose was administered intravenously, prickly pear had no hypoglycemic effect.[17] Prickly pear also had a hypoglycemic effect in dogs, rats, and rabbits in a state of hyperglycemia.[8,26–28] In animals, a hypoglycemic effect was seen even where glucose loading was induced by subcutaneous injection as well as in cases where prickly pear either was not heated or was given as a purified, dried extract.

In summary, prickly pear's hypoglycemic action appears significant but, unlike pharmaceutical medications, appears to significantly and consistently reduce glucose and insulin levels only in individuals with diabetes or in a hyperglycemic state, not in normoglycemic volunteers. While prickly pear may mildly affect glucose levels in normal individuals, it was never noted to cause hypoglycemia in any of the volunteers. Researchers suggest that prickly pear may slow down the absorption of glucose in the intestine, increase cellular sensitivity to insulin, and/or increase cellular utilization of glucose but prickly pear's mode of action in NIDDM and hyperglycemia remains unknown.

Preparing Prickly Pear

In many traditions, diabetics cut up the inner part of the prickly pear pad, soak it in water, and drink the liquid over the day. Alternatively, they juice the inner pad, drinking the juice as a slurry or after filtering to make the drink more palatable.[4,29] Prickly pear studies have used a variety of preparation methods. Most of them have used broiled or grilled pads. Initially, heating appeared to be essential, however, a later study showed that pads juiced in a regular blender, rather than an ultrahomogenizing lab blender, had an action equivalent to broiled pads. Ground prickly pear (presumably a juiced slurry) reduced glucose levels in hyperglycemic volunteers, and one man was able to control his diabetic symptoms by eating fresh prickly pear sap before meals. The studies achieved good results using 100–500 g pads three times a day before meals. Although not well studied, dried preparations had negligible or no hypoglycemic effects in human volunteers. A purified extract of prickly pear did produce good results in rats at low doses but the extraction method was not described.

Spineless pads are often available in Hispanic grocery stores and health food markets, and can easily be broiled and mixed with seasonings to make a palatable dish. In our experience however, few patients will consistently eat enough prickly pear as part of their diet. As a result, we recommend that patients prepare and drink a cold infusion of prickly pear until further research validates the effectiveness of purified extracts. See Sidebar 11-1.

Effects of Prickly Pear on Body Weight

Prickly pear significantly reduced body weight of obese and diabetic volunteers in one study, even though they remained on their usual diet. In the human study, 8 healthy, 14 obese, and

11–1. *Recommendations for Use of Prickly Pear*

PAD OR FRUIT, INTERNAL

Preparation: Remove all spines and glochids, either by purchasing pads or fruits precleaned, carefully peeling the flesh, or burning them off by searing the pad over an open flame. Consume approximately one to three pads or fruits per meal either boiled, broiled, or juiced.
Indications: NIDDM, hyperlipidemia, obesity
ons: BPH, capillary fragility, easy bruising, systemic inflammatory disorders

7 type 2 diabetic individuals ate 100 g broiled pads before meals three times a day for 10 days. Each group showed a mean reduction of 1.5 kg (approximately 3 lb) in body weight. The weight loss achieved statistical significance in the obese and diabetic volunteers.[13] Prickly pear's effect on body weight in animals is more confusing although it typically reduced weight gain in normal animals and sometimes prevented weight loss in diabetic animals. Of course, humans have different growth and weight gain patterns than rats, so animal studies may not provide any particular insight into the potential use of prickly pear as an aid in obesity and in heavy-set diabetic patients. However, as obesity plays a significant role in the progression of IGT to NIDDM, it makes sense to have patients incorporate prickly pear as a preventative measure.

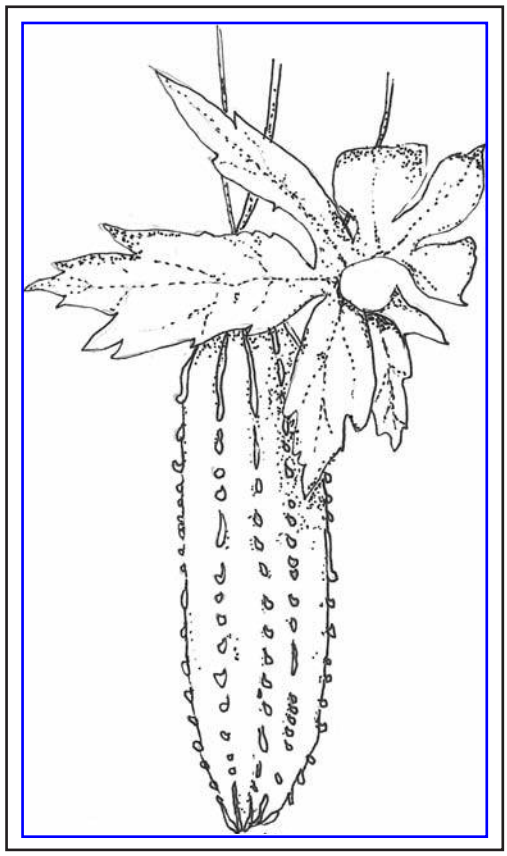

Figure 11–1. *Momordica charantia* (bitter melon)
Drawing ©2005 by Eric Yarnell, ND, RH.

MOMORDICA CHARANTIA (BITTER MELON)

Bitter melon is a complex plant medicine that has a remarkably long history of use both as a food and as a medicine. Many plants are used this way, and typically, plants used both as food and as medicine tend to be supportive, tonic, and nourishing in nature. They work effectively and seldom have strong hypoglycemic properties or strong effects on the reproductive tract. Bitter melon is unusual because it is widely consumed as food but also has a long history of use for issues such as diabetes, psoriasis, infections, menstrual cycle regulation, infertility, and abortion. Modern science is just beginning to investigate its many uses, and much remains to be learned about this fascinating vine.

11–2. *Bitter Gourd Dish*[a]

Cut bitter melon into fine pieces. Add salt and turmeric powder and let sit for 15 minutes. Heat oil in a saute pan, add mustard seeds, and when they pop, add asafoetida. Squeeze out the water from the bitter melon and add it to the oil mixture. Add red chili powder and saute well until fully cooked.

- ½ kg bitter melon
- 2 tsp salt
- 2 tsp turmeric powder
- ½ tsp mustard seeds
- 1 tsp red chili powder
- ¾ tsp asafoetida
- 6 tsp oil

[a]www.webindia123.com/health/disease/diab/recipes.htm.

The native habitat for bitter melon is not known. It is cultivated throughout the tropics, especially in China, India, East Africa, Central America, and South America.[30] Bitter melon has many different common names, reflecting its widespread use in numerous cultures. The fruit of bitter melon has a bitter taste (as its name clearly conveys) and for the most part its palatability is said to be "an acquired taste." In southern China, it is commonly eaten to cool the body.[31] Recipes for its use abound (see Sidebar 11-2) but it is difficult to find data that illuminate with what frequency the plant is eaten. Although common, bitter melon does not appear to be a daily staple. It does, however, appear to be eaten several times a week when it is in season.[32] This is important information because plants that are widely consumed as foods have a built-in safety test by hundreds of generations of people. It seems that bitter melon is sufficiently common in the diet to provide some evidence of its safety for general use. When prepared as a food, only the fruit is eaten; seeds are discarded.[33]

As mentioned above, bitter melon is used for many different ailments in many different traditions. See Table 11-1. This chapter reviews only the information on its use in diabetes, one of its most common traditional uses. We touch upon its effects on the reproductive tract because the plant's qualities in this arena may have significant implications on its appropriateness as a daily medicine in diabetes.

Bitter Melon's Role in Diabetes

Bitter melon may have a valuable role to play in both forms of diabetes. However, there are only a few clinical studies on bitter melon in diabetes and the studies are small and do not meet the criteria for reliability. Nonetheless, they consistently appear to confirm the widespread folk use of bitter melon in diabetes. See Table 11-2.

In an open-label crossover trial, 27 patients with NIDDM were randomly assigned to two groups.[34] One group drank 200 ml of dried fruit tea (with seeds) after each major meal while the other group drank black tea. Crossover began at the end of 12 weeks without a washout period. Fasting blood sugar and elevated liver transaminase (SGPT) levels decreased but without statistical significance. Glycosylated hemoglobin (HbA1C) decreased significantly in the active group. Adverse effects consisted of an increase in frequency and softness of stools.

Figure 11–2. *Momordica charantia* (bitter melon)

In another study, 5 patients with NIDDM were given 15 g of powdered dried fruit in three equal doses/day and 7 patients were given 100 ml of decocted fresh fruit (100g/100ml) once daily for 21 days. The postprandial blood sugar levels of the patients on powdered fruit dropped 25% but this was without statistical significance. The fall in blood sugar was 54% in the aqueous group, a highly significant drop, and blood sugar levels were restored to normal within three to seven weeks. Patients in this group had mild (fasting blood glucose or FBG of 260 mg%) to severe (FBG of 433 mg%) diabetes at the start of the trial. The researchers noted that there appeared to be a time-related cumulative response to the aqueous extract. Glycosylated hemoglobin decreased in both groups. The researchers noted that the hypoglycemic properties of bitter melon could not be attributed to a single principle.

Nine patients whose diabetes was controlled by diet (1), chlorpropamide (3), tolubamide (3), glibenclamide (1), or glymidine (1) were given glucose tolerance tests.[35] The first was standard, the second after taking fried bitter melon (0.23 kg/day) for 7–11 weeks. Patients discontinued any drugs 48 hours before the test, and fasted and refrained from smoking the night before each test. In addition, two patients underwent a third test after taking bitter melon juice (0.9 kg fresh fruit, seeds removed, yielding 200–250 ml fresh juice). The study showed that the juice significantly, and the fried melon somewhat, improved glucose tolerance. Serum insulin levels did not increase suggesting that bitter melon may have directly influenced hepatic or peripheral

Table 11–1. Partial List of Traditional Uses of Bitter Melon

Traditional Uses	*Country*
Abortifacient	Australia, Bahamas, Bimini, Brazil, East Africa, India, Philippines
Anthelmintic	Australia, Brazil, Fiji, India, Iraq
Anti-inflammatory	Thailand
Aphrodisiac	Africa, Brazil, Mexico
Appetite, stimulate	Haiti
Colds	Brazil
Diabetes	Asia, Belize, Bimini, England, Fiji, Guadeloupe, India, Mexico
Dysentery	Fiji, Mexico
Emetic	Australia, Brazil, India
Emmenagogue	Bahamas, Costa Rica, Cuba, India, Philippines
Eye infections	Haiti
Fevers	Bimini, Brazil, Haiti
Fungal disease, skin	Guatemala
Galactagogue	India
Insecticide	Brazil
Jaundice	India
Leprosy, to reduce pain	Brazil, India, Iraq
Liver ailments	Haiti, India, Panama
Malaria	Brazil, Ghana, Togo, Venezuela
Menstrual irregularities	Congo
Pneumonia	India
Rheumatism	Brazil, India
Vulnerary	Brazil, Guam, Philippines

Ross IA. *Medicinal Plants of the World*. Totowa, NJ: Humana Press 1999.

glucose disposal. This is doubly important because any agents that stimulate insulin release (so-called insulin secretagogues) may potentially worsen insulin resistance in patients with NIDDM and accelerate beta-cell loss in patients with IDDM. Glycosylated hemoglobin also decreased, suggesting an extra-pancreatic action.

Eighteen patients recently diagnosed with NIDDM but not yet prescribed medication fasted overnight and drank 100 ml water before taking a standard glucose tolerance test (50 g glucose).[36] The next day, again after an overnight fast, the patients drank 100 ml of homogenized bitter melon fruit juice prepared without the seeds. The patients fell into two groups: responders and nonresponders. The total data showed that the area under the glucose tolerance curves was significantly lower, although complete data were not provided in the study report. The researchers concluded that the results nonetheless gave some scientific validity to the use of bitter melon as an oral hypoglycemic agent by traditional Sri Lankan practitioners.

Table 11–2. Miscellaneous Pharmacological Studies on Bitter Melon

Extract	*Model*	*Effect*
75–80% mogroside* extracts of *M. grosvenori* fruit[a]Multiple in vitro assays; iron-induced epileptic rat model	Antioxidant in general and against lipid peroxidation specifically at various concentrations	
Dried, de-seeded, *M. charantia* unripe fruit extracted with benzene, methanol, or 50% ethanol[b]	Writhing and tail–clip assays in rats and mice	Methanol extract (10:1) an effective analgesic
Fresh *M. charantia* fruit juice (apparently without seeds)[c]	Assays of enzyme activity from livers of streptozotocin-diabetic rats	Increased CYP1A1, 2B1, 2E1, 3A4, 4A2 expression, increased phase II enzyme activity (glutathione-S-transferase and others)
Dried, powdered, de-seeded *M. charantia* fruit mixed with equal parts dried, powdered *Emblica officinalis* (amla) and *Curcumin longa* (turmeric)[d]	In vitro cup-plate antibacterial assay; streptozotocin-diabetic rats	Combination more effective than single herbs at inhibiting *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, and *E. coli* and at improving blood glucose in all but one case (*E. officinalis* more effective alone against *B. subtilis*)
Dried whole *M. charantia* fruits then powdered (some extracted in honey and other solvents), freeze-dried, or extracted in olive oil (fresh fruit)[e]	Rat ulcerogenesis by administration of 96% ethanol, indomethacin, hydrochloric acid, and/or diethyldithiocarbamate	Honey extract, olive oil extract, and dried-fruit tincture (95% ethanol) had significant antiulcerogenic activity
Protein extract of seeds of *M. charantia*[f]	In vitro HIV and reverse transcriptase	Ribosome inactivating protein MRK29 inhibited reverse transcriptase and HIV p24 expression; some immunomodulatory effects noted
Dried whole fruit *M. charantia* powder[g]	Liver cancer cells in vitro	Inhibited cancer cell growth

* Sweet-tasting glycosides.

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g. West ME, Sidrak GH, Street SPW. The antigrowth properties of extracts from Momordica charantia. *West Indian J Med* 1971;20:25–34.

An abstract reports that bitter melon seeds were investigated in the hope that they could substitute for the fruit that is seasonal. The seeds (dose not stated) reduced postprandial blood glucose levels (from approximately 350 to approximately 150 mg%) in patients with IDDM (n = 6) and NDDM (n = 20) but that the fasting blood glucose returned to normal by the next day. Adverse effects were minor and consisted of headaches.

Bitter melon contains a protein that is structurally and pharmacologically similar to bovine insulin.[37] It is often referred to as "v-insulin" and research is ongoing to determine if this type of insulin may be suitable for patients who do not tolerate, or for philosophical reasons prefer not to use, animal-sourced insulin. In a small study, nine patients (six with juvenile onset, one with maturity onset, and two with asymptomatic IDDM) were administered v-insulin subcutaneously. Five healthy and five patients with overt diabetes served as controls and were given a placebo injection. A hypoglycemic effect was observed that started 30–60 minutes after injection but peaked after 4–12 hours (compared to 2–3 hours for regular insulin). In another study, subcutaneous v-insulin showed a hypoglycemic effect in a small controlled study (n = 19) of juvenile and maturity onset IDDM.[38] One juvenile patient who suffered side effects when on bovine insulin (swelling, stomach pain, and bouts of hypoglycemia) was maintained on v-insulin for five months without experiencing any adverse effects.

Finally, it was reported that a patient on chlorpropamide noticed a synergistic effect when consuming a curry made with bitter melon and garlic.[36] Bitter melon tea had a significant hypoglycemic effect in two small children (three and four years old) who drank a tea of the leaves and vine on an empty stomach. An hour or two after ingestion, the children suffered convulsions followed by coma. Their blood sugar was about 1 mM (normal 3.8 to 5.5); both children recovered.[39]

Animal Studies on Bitter Melon

There are many animal studies on bitter melon's effect on the course of diabetes. These studies are usually of better design than the clinical studies. However, they too suffer from certain flaws. In the pharmacological studies, bitter melon was also prepared and dispensed in a variety of ways, reflecting its use as a traditional diabetes medicine. In some cultures, the fruit was crushed and strained to produce a juice. Sometimes the fruit was fried and consumed. In many cultures, the fruit was chopped and soaked in water, sometimes cold, sometimes decocted; sometimes with seeds, sometimes without. In others, the whole plant was used similarly.[30] The heterogeneity in forms of bitter melon studied makes it difficult to draw firm conclusions about its mode of action, best form, and dose. However, the overwhelming majority of studies tend to confirm traditional wisdom as far as using bitter melon in diabetes regardless of dose form.

These animal studies show variously that bitter melon inhibits glucose absorption, promotes glucose utilization in the liver, contains an insulin-like polypeptide, increases pancreatic insulin secretion, and may increase beta-cell production in the pancreas.[40,41] However, an increase in blood levels of insulin has not been observed, and the exact mechanism whereby bitter melon affects blood sugar remains unclear. Overall, the combined observations made traditionally in clinical and animal studies strongly suggest that bitter melon has a role to play in diabetes.

Another facet of bitter melon is that it may have a positive effect on diabetic complications. Diabetes is associated with irreversible functional and structural changes in the kidneys, eyes, nerves, and blood vessels, and bitter melon appeared to potentially have a positive effect on aspects of these complications in various animal models. These results are very preliminary

and cannot support a recommendation for use to prevent diabetic complications. Nonetheless, although highly preliminary, they are promising and additional research is definitely needed to investigate this aspect of bitter melon. It should also be noted these benefits may be secondary to improved blood glucose control.

For instance, diabetes is the leading cause of end stage renal disease.[42] Mice with streptozotocin-induced diabetes have elevated serum creatinine, urinary albumin, urine volume, and renal weight compared to normal mice. Mice treated with bitter melon showed significantly improved albeit not normalized values. Diabetic neuropathy causes limb pain and sexual dysfunction as well as other negative symptoms. Tail-flick latency increases substantially (by 74%) in diabetic mice. A mouse study showed that an aqueous extract of bitter melon (200 mg/kg) significantly reduced this increase, raising the possibility that future research may some day reveal bitter melon to provide a benefit in diabetic neuropathy.[42]

Another diabetic complication is diabetic enteropathy that results in a syndrome of dyspepsia, heartburn, nausea, vomiting, abdominal pain, constipation, diarrhea, and fecal incontinence. Bitter melon was used in traditional medicines to improve gastrointestinal function, and it may provide some benefit in diabetic enteropathy. The transit time of diabetic mice was reduced by 83% compared to normal mice in one animal study.[42] Aqueous bitter melon extract almost re-normalized the animals' transit time while also reducing their blood glucose levels. In a rat model of syndrome X (hyperglycemia associated with hyperinsulinemia, hypertriglyceridemia, and obesity), aqueous bitter melon extract (400 mg/day) fed to rats on a fructose-rich diet prevented hyperinsulinemia and hyperglycemia compared to controls.[42]

Finally, diabetes is an important risk factor for cataracts. In one experiment, aqueous bitter melon extract delayed somewhat the onset of cataracts in rats with alloxan-induced diabetes (120 days to onset compared to 100 days in controls).[43] In a second study, high doses of bitter melon fruit (4 g/kg) for 2 months also delayed the onset in diabetic rats (140–180 days compared to 90–100 days).

Bitter Melon's Reproductive Effects and Other Safety Issues

Bitter melon was used to treat a seemingly contradictory range of reproductive issues in traditional medicine. It is reported to have been used as an aphrodisiac, to treat infertility, as an emmenagogue, as a galactogogue, and as an abortifacient. Often, the leaves, vine, and seeds were used for these purposes.[44] In considering whether and how to use bitter melon in diabetes, it is important to consider research showing that it has definite although poorly elucidated negative reproductive effects. These effects must also be evaluated in light of the fact that bitter melon is frequently consumed as a food but does not have any reputation of being an inappropriate food for pregnant women or individuals planning to have children.

Mice fed bitter melon juice daily exhibited a decline in fertility rate from 90 to 20%. Those mice that did conceive bore normal litters and normal fertility rates returned when the bitter melon was not administered.[45] Bitter melon extract (1.75 g/day for 60 days) inhibited spermatogenesis in dogs and was associated with testicular lesions. After 60 days, the semniferous tubules were completely devoid of sperm.[46]

Bitter melon contains several proteins, alpha- and beta-momorcharins that induce midterm abortion and terminate early pregnancy in mice.[47–49] The early termination results from negative effects on embryo implantation and the endometrium. Embryos that did implant showed retarded development. Bitter melon juice (6 ml/kg by mouth) caused uterine hemorrhage and death in two pregnant female rabbits but did not have that effect in nonpregnant rabbits.[50] How-

ever, the majority of rabbits fed bitter melon juice continuously died within 23 days, and rats administered the juice intraperitoneally (15–40 ml/kg) died within 6–18 hours.[31]

In patients using bitter melon's antiviral properties in human immunodeficiency virus (HIV), no apparent toxicity was observed even with long-term treatment (n = 3).[31] One patient showed no change in blood chemistries or any adverse symptoms after taking bitter melon daily for over three years. These patients were taking a powder that combines the water and alcohol soluble parts of the whole plant where1 g of powder is equal to 25 g of fresh plant. The actual dose taken by the patients was not disclosed.

Vicine is a compound that can induce favism in genetically susceptible individuals. Vicine (or a vicine-like) compound has been isolated from bitter melon seed and caution should be used in individuals who may be predisposed to favism.[41] There are, however, no reports of favism induced by the ingestion of bitter melon.

There are strong indications that bitter melon may be highly useful in diabetes. The seeded fruit has a long history of use as a food eaten with some frequency, and aqueous extracts of bitter melon appear to have a significant hypoglycemic effect. In addition, there are some (albeit very weak) indications that bitter melon extracts may protect against some of the complications of diabetes. We feel comfortable recommending seeded bitter melon as a food or as a tea to older patients with NIDDM. A daily dose of bitter melon tea may be prepared by boiling 100 g of diced fruit in 200 ml of water until the liquid is reduced by half. However, given its potential abortifacient effects and ability to reduce fertility in animals, we would not at this time recommend daily use of bitter melon to younger patients or patients possibly interested in having children.

GYMNEMA SYLVESTRE (GYMNEMA)

G*ymnema sylvestre* (gymnema) is a woody climber that reportedly has been used to treat diabetes in India for over 2,000 years.[51] The plant is known for reducing the taste of sweet, and in humans, gymnema reduced the taste stimuli of sweetness by an average of 77% regardless of the type of sweetener used (acesulfame K, aspartame, sodium cyclamate, fructose, glucose, sucrose, stevia, and xylitol were tested).[52] Gymnema also has a reputation for aiding in weight reduction.[53,54] Most people with IGT and NIDDM have substantial dietary and weight issues that need to be addressed, and gymnema can be used to help effectuate needed changes in these areas by reducing sugar cravings as well as weight. However, we in the West have a tendency to use herbs and drugs in the hope of achieving health and weight loss without changing our dietary habits. In our experience, this never works for long and often creates additional health issues as the herbs and/or drugs are taken in excess to compensate for the failure to change diet. Thus, the use of gymnema to effectuate weight loss in IGT and diabetes may prove to be a double-edged sword unless in the hands of a skilled practitioner who can motivate needed lifestyle changes.

Another concern is research showing that while gymnema reduces blood glucose levels, it also may simultaneously raise blood insulin levels. Insulin-resistance with high circulating levels of insulin is an important problem in both IGT and NIDDM, and further raising insulin levels in these patients may be highly detrimental. However, it is entirely unclear whether this research on gymnema suggests that it is inappropriate because of this effect. Practitioners report good success in using gymnema in NIDDM but further clinical studies are definitely needed on this issue before gymnema can unequivocally be recommended in diabetes.

Generally, existing research shows gymnema to increase blood insulin levels but does not show this to be a problem. One article reports that gymnema raised the circulating insulin levels in a single patient with NIDDM.[51] In 22 NIDDM patients on oral diabetic drugs, gymnema significantly reduced blood glucose levels permitting a reduction in the dose of the oral drugs. In five of those patients, oral medications could be entirely discontinued. At the same time, gymnema raised insulin levels in these patients.[55] In 27 patients with IDDM, gymnema reduced the need for exogenous insulin and appeared to enhance endogenous insulin.[56] In alloxan-diabetic rats, blood glucoseand glycoproteins increased while insulin levels decreased. The ethanol extract of the leaves of *G. montanum* reversed these changes and raised insulin levels.[57] Glibenclamide, the reference drug, had a similar effect. In neither case were insulin levels raised to that of normal rats.[57] In another rat study, *G. montanum* leaves reduced blood glucose levels at all doses tested. At the highest dose (200 mg/kg), it also significantly increased plasma insulin levels.[58] G. sylvestre leaves also increased plasma insulin levels in stretozotocin-diabetic mice.[59] Pharmacological data suggest that gymnema increases plasma levels by increasing the membrane permeability of pancreatic cells rather than by increasing insulin production.[60] In genetically obese-hyperglycemic rats, the water extract of *G. sylvestre* leaves induced a weight loss and reduced or normalized the blood glucose increase caused by an oral sucrose tolerance test without altering blood insulin levels.[61]

Other preliminary studies indicate that gymnema may be particularly beneficial in steroid-induced hyperglycemia.[62] In one animal study, gymnemic acids (percentage-wise) reduced blood glucose level almost three times more than the drug ketoconazole.[63]

EUGENIA JAMBOLANA (JAMBUL)

Eugenia jambolana (also known as *Syzygium jambolanum* and *Syzygium cumini*) or jambul is a plant native to India, ranging from the foot of the Himalayas southward. It grows readily in other tropical climates and has been carried to eastern Africa, Brazil, and southeast Asia. Jambul is in the Myrtaceae family. It is a relative of *Syzygium aromaticum* (cloves) but cloves are apparently not utilized to treat diabetes in traditional herbal medical systems. The area of origin may make a huge difference as one study showed that eugenia fruit grown in Brazil lacked the hypoglycemic effect found in Indian jambul.[64]

Traditionally the jambul fruits, leaves, seeds, and bark are all used in ayurvedic medicine. The tasty fruits are also consumed as food. The bark contains tannins and carbohydrates, accounting for its long-term use as an astringent to combat ailments like dysentery.[65] A glycoside in the seed, jamboline, is considered to have antidiabetic properties.[65] Older French research shows that the seeds have a significant hypoglycemic effect in diabetic rabbits.[66] The seeds have also shown anti-inflammatory effects in rats and antioxidant properties in diabetic rats.[67,68] Older reports from Indian medical journals suggest jambul seed and bark can be beneficial in humans with diabetes.[69,70] Controlled clinical trials are awaited to determine more completely the mechanism of action of jambul, its degree of efficacy, and to confirm its safety. *E. jambolana* Lam., *E. uniflora* L., and *E. puncifolia* (Humb., Bonpl L and Kunt) DC are used in traditional medicine for diabetes. Older studies report that water extracts of jambul leaves do not lower serum glucose levels in diabetic rats or in normal humans.[71,72] This may be why most of the reports on traditional use of jambul in diabetic patients in India focus on use of the seeds or bark or it may reflect the extractability of particular constituents. For instance, the aqueous

extract of *E. puncifolia* leaves had an anorexic effect, whereas the alcohol extract improved the diabetic state in streptozotocin-induced rats.[73] But, in another study, *E. jambolana* leaf extract also had a hypoglycemic action in diabetic rats.[74] In any event, the seed powder of *E. jambolana* had a hypoglycemic action in streptozotocin-diabetic rats.[75,76] Its effect may be persistent, as in one study, homeostasis was maintained in the rats for two weeks after the cessation of treatment.[77]

In alloxan-diabetic rabbits the water extract of *E. jambolana* fruit pulp was more effective than the ethanol extract at reducing fasting blood glucose and improving blood glucose levels in the glucose tolerance test. *E. jambolana* also increased blood insulin levels in both diabetic and severely diabetic rabbits.[78,79] Another study also found that *E. jambolana* seed extract reduced blood glucose, glycosylated hemoglobin, and increased plasma insulin.[80] However, yet another study found that *E. jambolana* fruit combined with bitter melon decreased insulin levels that were raised in diabetic rats fed a fructose diet.[81]Again, as mentioned above in the discussion of gymnema, the importance of this effect in patients with insulin resistance is unknown.

Ayurvedic texts suggest that 1–3 g of seed powder per day is an average dose.[82] Additionally, juice of ripe fruits in the amount of 0.5–2 tsp (2.5–10 ml) at least three times daily have been recommended for treatment of diabetes.[65] A tincture of bark or seed might be attempted at a dose of 3–5 ml three times daily, though the optimal extract and dose are unknown. No side effects are mentioned in the traditional reports, but high-tannin bark extracts may cause mild gastrointestinal upset in some people unless taken with food.

CINNAMOMUM ZEYLANICUM (CINNAMON)

One widely used cooking spice has potentially significant hypoglycemic effects: *Cinnamomum zeylanicum* (cinnamon) bark and other species of cinnamon. Like jambul, cinnamon trees are native to southern Asia. However, they are in the Lauraceae family. The bark is the portion of the plant that is used as food and medicine. In the Western world, true cinnamon (i.e., *C. zeylanicum*) is rarely available. Instead, most cinnamon is actually *C. cassia*, although *C. aromaticum* and *C. burmanii* are also sold as cinnamon. Many, if not most, studies fail to identify which "cinnamon" they are using, as do most products on the market. Thus, it is unclear if the results attributed to cinnamon actually relate to true cinnamon or the more common cassia. We found only one comparative animal study that concluded that *C. cassia* was superior to *C. zeylanicum*.[83]

In a small study of women with polycystic ovary syndrome, cinnamon (333 mg of extract three times/day for eight weeks) significantly reduced insulin resistance.[84] In 14 healthy adults, the addition of 6 g of cinnamon to a meal of rice pudding significantly reduced postprandial glucose levels and somewhat reduced gastric emptying.[85] In 60 patients with NIDDM not taking insulin, *C. cassia* (1, 3, or 6 g/day for 40 days), significantly reduced blood glucose levels after 40 days (18–29% decrease). Those taking 6 g/day had reduced glucose levels after 20 days but only those taking 1 g/day maintained lower glucose levels 20 days after stopping the regimen. There were no significant changes in the placebo group. Cinnamon also reduced triglyceride, LDL cholesterol, and total cholesterol levels in these patients.[86] On the other hand, in 58 people with NIDDM, 1 g/day of cinnamon had no significant effect on any relevant parameters. One notable difference between this and other studies showing a benefit was that the majority of the volunteers were taking some type of antidiabetic medication.[87] Similarly, 1 g of cinnamon

a day for 90 days did not in any way improve glycemic control in teenagers with IDDM.[88] A literature review found that cinnamon was well tolerated and that the data suggest that it has a modest glucose lowering effect in poorly controlled NIDDM.[89]

In vitro, cinnamon has been shown to potentiate the effects of insulin in rat adipocytes.[90] It is not clear if this is an effect at the glucose receptor or on postreceptor glucose utilization. If postreceptor effects could be demonstrated in diabetic patients, cinnamon would represent a simple and cheap way of helping overcome insulin resistance. Albumin can interfere with cinnamon's insulin-like activity, however, casting doubt on its ability to act in vivo.[90]

It is not known what the active insulin-potentiating constituents of cinnamon are, though some suggest it may be methyl hydroxy chalcone polymer. No information was retrieved from any of several sources suggesting that cinnamon has been used by traditional herbal systems as a therapy for patients with diabetes. However, many cultures use cinnamon in the diet, which may reflect the wisdom of the old adage of "Let your food be your medicine." The potential of using cinnamon as a diabetes treatment generated much interest in the Western world as it is a popular spice, making patient compliance much easier. Unfortunately, not all studies have supported its benefit. Of course, these studies are not definitive and given the safety and popularity of the spice, again, there is little reason not to incorporate it in a treatment plan. An effective dose is uncertain; 1 tsp of powdered bark (straight or in capsules) three times daily with food is one way to start. Monitor serum glucose levels closely and increase or decrease the dose as is appropriate.

PSACALIUM DECOMPOSITUM (MATARIQUE)

Psacalium decompositum (psacalium, matarique, maturín), formerly known as *Cacalia decomposita*, is a beautiful plant in the Asteraceae family found primarily in the high deserts of southern Arizona and New Mexico and northern Mexico. The plant is relatively uncommon and thus there is concern about overharvesting. It can withstand removal of a few plants from each stand but probably not any stronger pressure than that. Matarique grows reasonably well from seeds and could conceivably be replenished by intentional wild planting. It could also be cultivated, although this may reduce the quality of the medicine if grown outside of its natural habitat. Future research will need to clarify these issues.

The rhizome and root gathered in the autumn are used to prepare the medicine. Only its antidiabetic effects, a narrow portion of its other medicinal benefits, are discussed here.[91] Little is known about matarique's mechanism of action, though animal studies clearly show it is hypoglycemic.[92,93] A related species, *P. paltatum*, also was hypoglycemic in animals.[94,95] A constituent (ulopranose) isolated from the water extract had hypoglycemic activity comparable to tolbutamide and insulin in alloxan-diabetic mice.[96] Another related species, *P. palladium*, also used to treat diabetes in Mexico, found the aqueous extract of the plant was cytotoxic, whereas other fractions were cytostatic.[97] It has been said to prevent gluconeogenesis in the liver by herbalist Michael Moore.[29] Ethanol has a similar effect, blocking conversion of amino acids into glucose.[98] This is generally a beneficial action, because low insulin levels in diabetic patients will cause the liver to inappropriately engage in gluconeogenesis, raising serum glucose levels even when fasting. However, this requires any insulin-dependent diabetic to take into account that protein consumed in a meal may not be converted to glucose if matarique (or ethanol) is ingested along with it, and thus should alter insulin doses accordingly. Because no direct

research has confirmed this action, this should only be considered a highly speculative discussion of matarique's effects.

Regardless of how matarique accomplishes the feat, it has a dramatic serum glucose-lowering effect. Generally, the root tincture is dosed at 1–2 ml taken before lunch and dinner for one to two weeks. Fresh root is usually more potent than dry. This is considered an induction program soon after type 2 diabetes is diagnosed. Matarique should not be used in type 1 diabetics, in anyone using insulin, in those with active peptic ulcers or severe hepatic or renal disease, or during pregnancy. Use for more than two to four weeks consecutively is not recommended, particularly as variable amounts of potentially hepatotoxic pyrrolizidine alkaloids have been detected in matarique.[99] Rapid induction of normal or near-normal serum glucose levels can cause the sensation of hypoglycemia (anxiety, shaking, sweating) in people with diabetes who have become accustomed to high serum glucose levels. Therefore, it may be necessary to use a smaller dose of matarique for the first few days until the patient accommodates. Matarique will also cause hypoglycemia in nondiabetics and should be used cautiously, if at all, or in patients with mild IGT. Ultimately, the best use of matarique appears to be a short-term course for those who either need to come off oral diabetic medications quickly or who need to quickly normalize blood sugar levels using only botanicals, transitioning into other treatments for the long term.

BRICKELLIA GRANDIFLORA (HAMULA)

Brickellia grandiflora (hamula, prodigiosa, bricklebush) is another Asteraceae plant used differently from matarique. Hamula is found in a much more diverse bioregion extending from California to Arkansas. It is less showy than matarique and has a sticky texture to its leaves, unlike other members of the genus. *B. incana* and *B. californica* may be interchangeable species.[29] A hexane extract of *B. veronicaefolia* was shown to have a substantial hypoglycemic effect in diabetic and healthy mice.[100] The mechanism of action was not elucidated but based on historical accounts of long-term, safe use of the plant; it is most likely an insulin sensitizer. An additional benefit of hamula is that its flavonoids have been demonstrated to inhibit aldose reductase,[101] suggesting it could have a benefit beyond normalization of blood sugars toward inhibiting neuropathy and cataract development.

Hamula is much safer than matarique, and contains no pyrrolizidine alkaloids. The aboveground parts in the flower of the plant are used dry or fresh. Generally 1–3 tsp of the leaves are steeped in 1 cup hot water for 15–20 minutes, then 1 cup is drunk in the morning and 1 cup in the evening. Alternately, a tincture can be used at a dose of 1–3 ml twice a day (again, morning and afternoon). Like matarique, it can stimulate digestive function and therefore should not be taken by those with active peptic ulcers. It may also precipitate acute cholecystitis if given to someone who has an active gallstone.

Table 11–3. Speculative Actions of Novel Antidiabetic Botanicals

Mechanism of Action, Purported	*Botanicals*
Gluconeogenesis inhibition	*Cacalia decomposita* (matarique)*

* This is poorly documented.

Table 11–4. Summary of Doses of Antidiabetic Botanicals

Botanical	*Dose and Dose Form*
Eugenia jambolana (jambul) seed	1 g powder three times daily
Eugenia jambolana (jambul) fruit	0.5–2 tsp (2.5–10 ml) juice two to four times daily
Cinnamomum zeylanicum (cinnamon) bark	1 tsp powder three times daily (initial dose only, modify based on blood sugar readings)
Cacalia decomposita (matarique) root	1–2 ml tincture two times daily
Brickellia grandiflora (hamula) herb	1 cup tea twice daily (1–3 tsp herb/cup) or 1–3 ml tincture two times daily

CONCLUSION

Poor glycemic control and frank diabetes are common issues in our culture, issues that are on the rise and will increasingly need to be addressed in practice. Botanicals have a long history of use in this arena, and there are many herbs that can be used to normalize blood sugar control, reduce the need for oral antidiabetic medications, help prevent the progression from oral medications to insulin therapy in NIDDM, and help moderate insulin need in some patients. The botanicals covered in this chapter work well. However, there are other botanicals that are also useful and, as is often the case, the botanicals may be more effective if combined in a formula. As we mentioned earlier, our review is not exhaustive, and those treating patients with blood sugar issues should not consider this chapter the "end all, be all" of managing diabetes with botanicals.

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12

BOTANICAL MEDICINES FOR HEADACHE

Various types of headaches are common in our culture. Given that herbal remedies historically were used to remedy headache pain, it is likely that headaches were common in the past as well. These remedies continue to have a place of importance in treating headaches. In fact, two of the oldest and still quite effective drugs for alleviating acute headache pain, aspirin and ergotamine, are derived from natural products. Unfortunately, these more modern treatments are not without significant adverse effects. Many of the most common headache medications, including aspirin, acetaminophen, and codeine, can all cause rebound headaches when stopped.[1,2] This leads to the lose–lose proposition of suffering the headache without the medicine or fixing the headache only to suffer it again when the medicine is stopped. Worse still is the headache that is directly caused by overuse of headache medications.[3] There is clearly a need for better treatments both to avoid these problems and to provide options to those not helped by medications. This chapter reviews botanical options to help patients with three major types of headache: tension, migraine, and cluster.

TYPES OF HEADACHES

Tension-type headache is the most common type of headache by many estimates. The official diagnostic criteria are given in Sidebar 12-1. It is not associated with any significant chronic morbidity in most patients, though an occasional patient may react to the recurrent pain by developing depression or low energy. It is important to rule out various potential contributing factors before treating patients. Stress (emotional, mental, or physical), menstrual symptoms, sleep disturbance, eye strain, muscle tension, poor posture, food allergies, and caffeine withdrawal all occasionally can cause these types of headaches. Only after the potential contributors have been removed or mitigated should herbal therapies be considered.

Migraine headaches are more complex and can either be preceded by an aura or not (see Sidebar 12-1 for definitions). Migraines appear to be due to a complex interplay of neurological and vascular changes. Waves of neurological changes can be observed washing over the brain during a migraine, which can then trigger vascular changes. Decreased blood flow may account for aura symptoms, or possibly the neurological changes themselves. Regardless, again, the causative factors leading to the neurovascular alterations must be sought out and eliminated. Hormonal factors, food reactions (including to any numbers of allergens, dietary monoamines, and dietary tannins), and stress must all be ruled out as playing a role.

Cluster headaches are a type of trigeminal autonomic phenomenon, and are unusual in that they are much more common in men than women. It is now believed that they are neurological pain syndromes that trigger a normal parasympathetic reflex with subsequent abnormal sympathetic responses.

12–1. *Definition of Headaches*

Cluster Headache
At least five attacks
Unilateral severe pain lasting 15–180 minutes
At least one of the following along with headache (each occurring on the same side as the headache): conjunctivitis or tearing, nasal congestion or rhinorrhea, eyelid edema, sweating, miosis or ptosis, or restlessness/irritation (generalized)
Frequent; every other day up to eight headaches per day

Migraine Without Aura
At least five attacks
Duration 4–72 hours
Nausea/vomiting and/or photophobia and phonophobia
At least two of the following: unilateral, pulsatile, moderate-or-severe pain, and aggravation of (or causing avoidance of) routine activities
Not caused by any other disorder

Migraine with Aura (General)
At least two attacks with one of the following: fully reversible flickering lights or loss of vision, fully reversible paresthesias, or fully reversible dysphasia
At least two of the following: homonymous visual symptoms, unilaterial sensory symptoms, development over 5 minutes, and duration 5–60 minutes
As migraine without aura but headache begins during or within 60 minutes of aura
Many subtypes exist

Tension-Type Headache
At least 10 attacks
Duration 30 minutes to 7 days
Headaches on fewer than 12 days a year
No nausea or vomiting present (though loss of appetite can occur)
Photophobia or phonophobia alone, but not both, or the absence of both
At least two of the following: bilateral location, nonpulsatile pain, mild to moderate intensity (not prohibiting normal activities of daily living), and no aggravation by continuing routine activities

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COUNTERIRRITANTS

Topical application of counterirritant botanicals is one of the simplest, safest, and most effective therapies for aborting a developing headache or stopping a headache in progress. These remedies include many steam-distilled volatile oils, notably of *Mentha* x *piperita* (peppermint),

Rosmarinus officinalis (rosemary), and *Juniperus communis* (juniper). They appear to work in part by directly penetrating the skin and reducing muscular and possibly vascular spasms, and also by affecting nerve function. Topical application of peppermint and *Eucalyptus globulus* (eucalyptus) volatile oils was shown, in 32 healthy subjects, to relax the mental process, relax muscles, and increase cognitive performance without decreased pain sensitivity compared to placebo.[4] A combination of the two oils reduced pain sensitivity. This supports the historical tradition of applying these oils to reduce pain.

This age-old practice has also been confirmed in one clinical trial. Topical application of a combination of camphor, menthol, *Melaleuca leucodendron* (cajeput) volatile oil, and *Syzygium aromaticum* (clove) volatile oil three times 30 minutes apart was just as effective as acetaminophen and more effective than placebo at reducing pain.[5]

Another potent counterirritant is *Capsicum* spp. (cayenne) fruit, known to everyone who has ever eaten spicy food. Capsaicin and related compounds that activate vanillinoid receptors are responsible for the burning sensation cayenne causes. Capsaicin initially stimulates pain-sensing C nerve fibers, but soon depletes these nerves of their neurotransmitters. The ultimate result is reduced pain.[6]

Clinical trials have been conducted with capsaicin in patients with migraine and cluster headaches. At least two trials have shown that applying a capsaicin cream intranasally three times a day can dramatically decrease the pain of cluster headaches.[7,8] This treatment can initially be irritating and cause burning but these sensations are quickly replaced by relief of the

Figure 12–1. *Mentha* x *piperita* (peppermint)

Figure 12–2. *Rosmarinus officinalis* (rosemary)

headache, which is always vastly more severe than the initial mild discomfort caused by the treatment. An additional trial found that application of capsaicin in the nostril on the same side as the headache could reduce recurrence of cluster headaches, whereas applying it to the opposite nostril had no effect.[9] One preliminary double-blind trial used intranasal capsaicin for patients with migraines. This trial found that, compared to an acidic placebo that also caused burning, capsaicin dramatically reduced migraine pain (only one patient on placebo improved).[10] Further research is definitely warranted on this inexpensive, harmless, yet quite effective treatment. See Sidebar 12-2 for a quick and easy way to apply cayenne for headache relief.

Counterirritants mix very well with hydrotherapy and massage treatments, which by themselves have great potential to relieve headache pain and possibly treat underlying causes.[11] It is common to use volatile oils mixed into massage oils, and if appropriate ones are chosen, they could be beneficial in headache sufferers.

Another traditional counterirritant is *Sinapis alba* (mustard) powder. This can be nearly as potent as cayenne, though it seems to have fallen out of favor since research support for capsaicin began to accumulate. One traditional approach to using mustard powder is presented in Sidebar 12-3.

ORAL SPASMOLYTIC NERVINES

Not every patient is helped by, or is willing to attempt to use, topical therapies. There are many choices for oral herbal treatment as well, to both prevent and abort headaches of various types.

12–2.

CAYENNE FOR HEADACHES

Place 0.25 tsp of good-quality cayenne powder in hot water. Old powder loses its potency and will not burn when applied (nor will it relieve pain effectively). Allow the powder to settle at the bottom of the cup. Dip a cotton swab in the extract and apply to the nasal mucosa on the same side as the headache (both sides for bilateral problems). Repeat every 30 minutes if necessary.

Alternatively, a few drops of tincture of cayenne can be placed in 1 oz of water and this solution swabbed into the nose.

In both cases, there should be initial burning for approximately 10 minutes, though this will cease after repeated applications.

As suggested by Agatha Thrash, MD.

12–3.

MUSTARD FOOT BATH FOR ACUTE HEADACHES

Have the patient prepare a foot bath as hot as possible, keeping hot water nearby to add to the bath to keep it hot. Add 1–2 tbsp mustard powder (or cayenne if that is what is available) to the water. It will initially sting and feel like it is burning and turn the feet red (in a light-skinned patient), but an actual burn is very unlikely. The patient should maintain their feet in the water for 15–20 minutes, and keep ice on the neck the whole time.

As suggested by Silena Heron, ND.

One of the most common and useful treatments employs herbs that are known both for relaxing smooth muscle and relieving anxiety. Many of these herbs are also covered in chapter 5 on herbs as agents for relief of various nervous conditions. Here we focus on them as headache remedies.

Perhaps the most familiar nervines in North America have not been studied as headache remedies, but were traditionally used this way. Some examples, in order from mildest to strongest, include *Eschscholzia californica* (California poppy), *Passiflora incarnata* (passionflower), *Scutellaria lateriflora* (skullcap), *Valeriana* spp. (valerian), and *Piscidia piscipula* (Jamaica dogwood). The strongest of these, Jamaica dogwood, is potentially potent enough to abrogate even a strong migraine or cluster headache at a tincture dose up to 1–2 ml every two to three hours. Other herbs may be effective in milder headaches or to reduce severity of other headaches.

Pueraria montana var *lobata* (kudzu) root is a spasmolytic used in traditional Asian medicine. There are older reports of its effective use for patients with migraine.[12] It has reportedly been shown effective for relieving cerebral artery spasms in Chinese trials.[13] Kudzu is also a rich source of phytoestrogenic isoflavones, so it is likely useful in menstrual or menopausal migraines. A previous trial involving soy isoflavones and two hormone-modulating herbs not currently considered to be phytoestrogenic, *Angelica sinensis* (dang gui) and *Actaea racemosa* (black cohosh), found that these herbs were significantly more effective than placebo at relieving menstrual migraines.[14] Although it is not proven kudzu would have the same benefit, it is a good possibility.

Kudzu's greatest benefit probably lies in prevention of headaches, but it can also reduce or eliminate headaches in progress. A typical dose of a kudzu root glycerite or tincture is 3–5 ml three times per day (or more often during acute attacks). If the powder is used only unbleached or brown, medicinal-grade powder should be used (not the bleached, white form often used as a cooking starch); the dose is 3–5 g three times per day.

The latest spasmolytic herb popular for headache is *Petasites hybridus* (butterbur). Butterbur does not have a strong history of use as a nervine but two double-blind trials have investigated the efficacy of a standardized extract of butterbur root for patients with migraine.[15] Both trials found a 150 mg twice daily dose significantly more effective than placebo at reducing frequency of migraine attacks over a three- to four-month period. Since butterbur contains unsaturated pyrrolizidine alkaloids that are potentially hepatotoxic, only extracts that have removed these compounds should be used for more than two weeks consecutively. The exact mechanisms of this herb have not been determined, though butterbur clearly has smooth muscle-relaxing effects.

INFLAMMATION MODULATORS

Inflammation and inflammatory intermediates undoubtedly play a significant role in many types of headache. Therefore, many herbs that modulate inflammation have had a prominent place in the treatment of patients with headaches.

Perhaps most notable in this regard are the salicylate-rich herbs, including *Salix* spp. (willow), *Populus tremuloides* (aspen), and *Betula* spp. (birch). These herbs have a long history of use in all types of headaches as well as rheumatic diseases, low back pain, and arthritides. Of course modern-day aspirin is a semisynthetic variant of salicylic acid, and is a well-documented quick fix for headache pain. Salicylate-containing herbs can prevent and decrease headache pain, but do not seem to have the potential for the rebound headaches that aspirin can cause. A typical dose of the tincture of any of these three herbs is 3–5 ml every two to three hours during an acute attack for an average-sized adult.

Surprisingly, only one modern trial has bothered to look at the efficacy of these herbs for headache. This trial used topical salicin, a glycoside found in *Salix* spp., along with a mask, compared to the same mask with a placebo, in patients with tension or migraine headaches.[16] Topical salicin was significantly more effective at reducing headache pain than placebo. It is much more common to use willow internally.

Another well-known inflammation-modulating botanical for headache is *Tanacetum parthenium* (feverfew). Some meta-analyses of clinical trials support that regular intake of the leaves can reduce the frequency of migraines, whereas others conclude the existing evidence is inconclusive.[17,18] The trials that have been conducted have used many different types of products.

Figure 12–3. *Salix* spp. (willow)

The positive trials all used whole-leaf products—either dried or freeze-dried. Extracted products have generally not done well in clinical trials. The traditional approach is to eat one leaf per day fresh off the plant, though a greater number of leaves might be more effective. The dose of dried or freeze-dried encapsulated leaf is 500–1,000 mg two to three times per day. Contrary to many reports, there is no evidence that feverfew causes mouth ulcers with any greater frequency than placebo; feverfew is extremely safe.

A combination of feverfew and willow, 300 mg of each twice daily, has been studied in an open trial and was found to reduce migraine headache frequency significantly compared to baseline.[19] When headaches did occur they were of reduced intensity. A controlled trial is clearly warranted to find out if these two really have a synergistic action when combined.

A related, double-blind trial compared the efficacy of feverfew (100 mg), magnesium (300 mg), and riboflavin (400 mg) to 25 mg of riboflavin.[20] The two treatments were equally effective. This strongly suggests that the trial was poorly designed because the higher dose of riboflavin at least should have been more effective than the lower doses. Another possibility is that the two treatments interfered with each other.

Two other inflammation modulators often recommended, particularly for migraine sufferers, are *Ginkgo biloba* (ginkgo) and *Zingiber officinale* (ginger). Neither appears to have been studied but their various mechanisms of actions, and historical use in the case of ginger, recommend them as potentially valuable treatments.

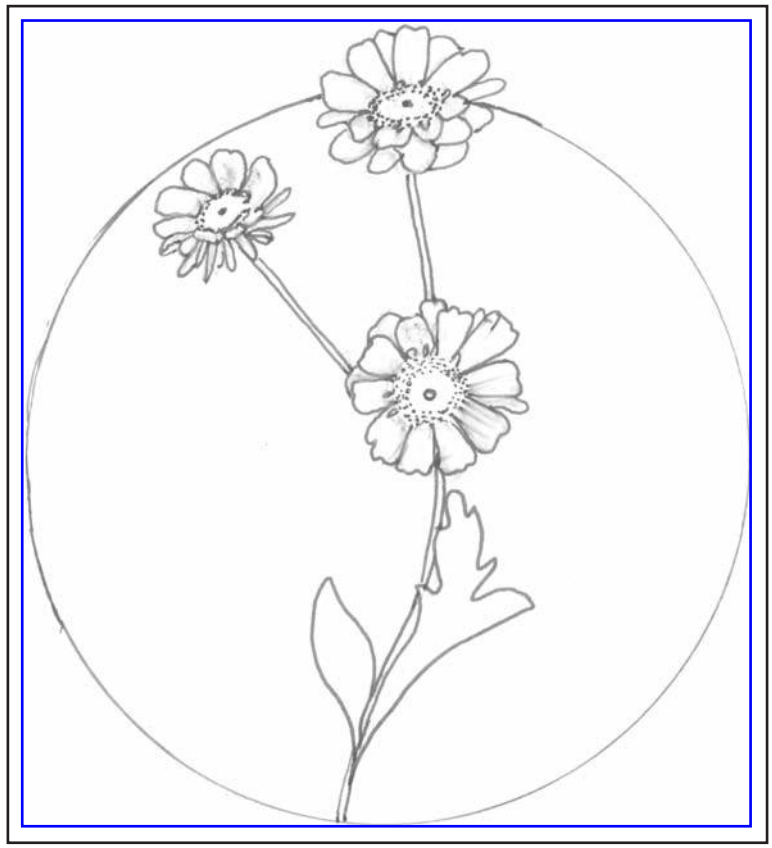

Figure 12–4. *Tanacetum parthenium* (feverfew)
Drawing by Kathy Abascal, BS, JD.

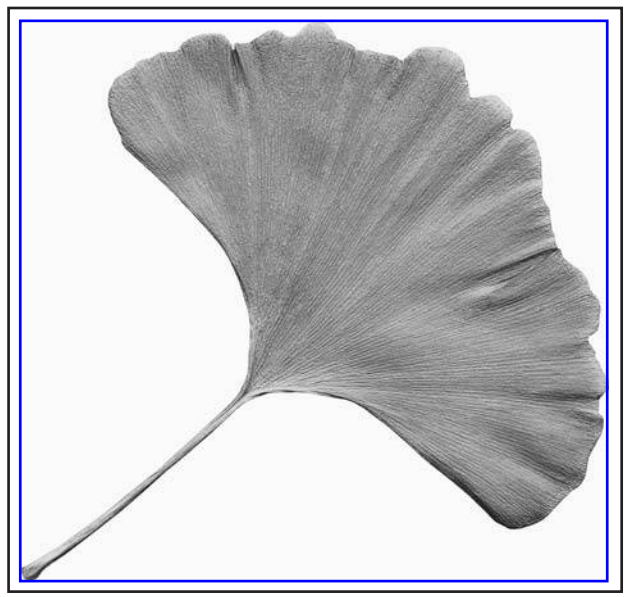

Figure 12–5. *Ginkgo biloba* (ginkgo)

CONCLUSION

There are many herbal medicines available to help patients with the three major types of headaches (tension-type, migraine, and cluster). Historical and preliminary modern evidence support the efficacy of many of these remedies. Further research is clearly needed. Sometimes a simple topical counterirritant can make a world of difference typically without any adverse effects. Other times, complex formulas with herbs of various actions are needed to help patients. These herbs and others should continue to be used and researched to determine their full potential.

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13

BOTANICALS THAT REGULATE HEART RHYTHM

Clinicians often encounter patients with cardiac arrhythmias. Many of these are minor and represent no danger to patients, but some may cause sufficient palpitations and distress or hemodynamic effects to warrant treatment. As always, the cause or causes of any arrhythmia should be investigated and treated directly if possible. Sometimes the cause is not immediately or ever apparent, however, and therapy to control symptoms may be necessary. Because antiarrhythmic drugs all have adverse effects, some of them quite serious including worsening of arrhythmias by flecainide and encainide, safer botanical options can be useful. This chapter reviews the clinical use of herbs that can beneficially modulate heart rhythms.

The more serious an arrhythmia, the more careful one has to be in deciding on botanical treatment. Atrial flutter and atrial fibrillation are associated with increased risk of thromboembolism and if not quickly responsive to botanical therapy should be treated medically as well. Any recurrent or chronic arrhythmia associated with other symptoms, particularly ventricular ectopic beats (premature ventricular contractions) and ventricular tachycardia, may herald underlying pathologic causes of the arrhythmia that should be thoroughly investigated.

SIMPLE SEDATIVES FOR MINOR ARRHYTHMIAS

Arrhythmias not related to underlying heart or systemic pathology but that are sufficiently strong to cause palpitations and/or anxiety can be quite debilitating. In these circumstances, the costs and hazards of drug therapy or pacemaker implantation make them treatments of last resort. Numerous botanicals are available for precisely these circumstances to safely and more cost-effectively reduce or eliminate the problem.

Leonurus cardiaca (motherwort), a humble mint of Eurasia origin, stands preeminently among botanical remedies for nonpathologic arrhythmias. The prickly flowering tops of the herb are used, preferably fresh. Its active and supportive constituents have not been well characterized, though it has long been used as a tea effectively, suggesting that the most important compounds are water soluble. Labdane diterpenoids are gaining increasing attention as critical components of motherwort.

Rudolf Fritz Weiss, MD, hailed motherwort as a remedy for, "functional heart complaints due to autonomic imbalance."[1] Eclectic practitioners, including Harvey Wickes Felter, MD, have written about the sedative nature of this herb.[2] It is possible that motherwort acts in part simply by calming the patient, reducing anxiety induced by fear of heart disease or the strangeness of the sensation of palpitations. Some very preliminary studies from Russia support this contention.[3,4] People under heavy, poorly compensated for stress may also benefit from motherwort. Motherwort is considered by many clinicians specific for palpitations secondary to hyperthyroidism. Palpitations that interfere with sleep or concomitant smooth muscle spasms in the gut or reproductive tract may also be counteracted by motherwort.

A typical adult dose of motherwort is 1–2 tsp/cup of water infused for 15–20 minutes, three cups daily. A glycerin extract (75% glycerin) has also proved useful at a dose of 3–5 ml three

times per day or in lower quantities when combined with other herbs in formulations. The herb is completely safe with no known contraindications. Ethanolic extracts are dosed similarly.

Valeriana officinalis (valerian) root, *V. sitchensis* (Pacific valerian) root, *Scutellaria lateriflora* (skullcap) herb, *Passiflora incarnata* (passionflower) leaf, *Zizyphus jujuba* (jujube), and *Piper methysticum* (kava) root are some of the other choices for problems such as this. These herbs do not have the historical specific indications that motherwort does but they can all aid heart arrhythmias causing or secondary to anxiety, uncompensated stress, or unknown but non-pathologic causes. All have a long history of safe use and have not shown adverse effects in clinical trials. There is preclinical evidence of an antiarrhythmic effect for valerian.[5] The recent concern over the hepatotoxicity of kava is based on no more than a handful of cases, most of which do not even support the connection due to interfering factors such as concomitant use of hepatotoxic drugs.[6]

One of the safest among these herbs, though poorly researched, is skullcap. A member of the Lamiaceae family like motherwort, there are species in the genus native to both Eurasia and North America. It is a very broadly applicable nervine, used effectively in clinical practice for patients with anxiety, insomnia, seizure disorders, attention deficient hyperactivity disorder, and similar problems. Additionally, many practitioners have found it useful for patients with minor arrhythmias. This herb is an excellent candidate for clinical trials given its widespread use and general appreciation by practitioners. It is imperative that it be used fresh or prepared from fresh plant, as the dried plant material loses much of its activity. A typical dose of glycerite (75% glycerin) or tincture is 3–5 ml three times per day for adults.

Queen of the Night

Several botanicals are considered specific for treatment of patients with arrhythmias in general. One of the most promising yet often forgotten is *Selenicereus grandiflorus* (formerly *Cactus grandiflora*), known colloquially as night-blooming cereus. This climbing member of the Cactaceae family is unusual in that it is native to the rain forests of Central America, Mexico, and the Caribbean, and not the desert. This cactus produces an enormous, incredibly fragrant, white flower in a very narrow window late at night once each year, earning it another common name: queen of the night.

The Eclectic physicians used night-blooming cereus extensively. It was considered a nervine with exceptional specificity for regulating the conductive activity of the heart.[2] Though mainly considered helpful for tachyarrhythmias, some practitioners noted that it could counteract bradycardic problems as well. It was also recommended for counteracting problems associated with valvular regurgitation, particularly aortic regurgitation and mitral-valve prolapse. However, Felter wrote that it was contraindicated in cases of stenotic valves. Night-blooming cereus is useful for palpitations related to menopause and anxiety. It can also be beneficial in patients with mild congestive heart failure, though it does not contain cardioactive glycosides.[7] The nature of its action is gentle—it takes fairly consistent use over several months to obtain the full benefit.

It is reported that the Shoshone of Death Valley called the plant "pain in the heart," and that natives of the Caribbean Islands used fresh extracts of the plant to treat dropsy. In Mexico, related species were used for kidney and bladder problems, intermittent fevers, coughs, and difficulty breathing.[8,9] Night-blooming cereus contains cactoic and cactine, tyrosine (a positive inotropic), and biogenic amines.[10,11] Older in vitro studies showed it to have a positive inotropic effect on isolated frog heart and papillary muscle (probably from guinea pigs). In theory, this could be due to its tyramine content but the actually concentrations of tyramine and its two derivatives in the plant appear to be too low to exert any pharmacological effects.[10] Cactine (better

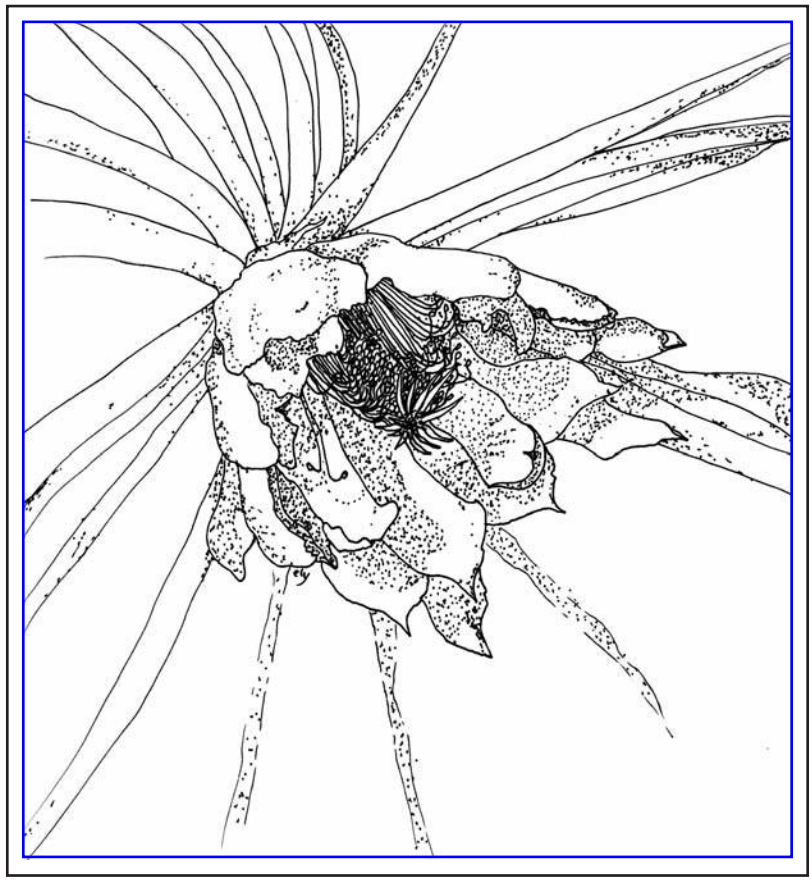

Figure 13–1. *Selenicereus grandiflorus* (night-blooming cereus or queen-of-the-night)
Drawing ©2003 by Eric Yarnell, ND, RH.

known as hordenine) injected intraveneously into horses (200 mg/animal) caused an insignificant rise in heart rate for 90 seconds. Oral administration (500 mg/animal) reportedly had no effect on circulation.[10] Hordenine is a constituent in some plants used as animal feed, for example, sprouting barley. Pharmacological models show that hordenine is an indirectly acting adrenergic compound that liberates norepinephrine from stores. Experiments in intact animals (rats, dogs) show that hordenine has a positive inotropic effect on the heart, increases systolic and diastolic blood pressure, and peripheral blood flow. It has no effect on the psychomotorical behavior of mice. All of these effects are short-lived and only possible after high doses.[12]

Use of a fresh plant tincture is recommended. The usual dose ranges from the low end in the Eclectic tradition of 10–30 drops diluted in 4 oz water; then take 1 tsp three times per day up to a more pharmacologic dose of 5–15 gtt three times per day. Though generally considered an herb to treat with caution, Felter does not mention any serious adverse effects and Ellingwood stated that he had never seen any unpleasant effects from overdoses and was "growing in the belief that we will yet learn that there are cases where we now obtain indifferent results, or where the agent is not now advised, in which good results will be secured by much larger dosage than is now given."[13] Michael Moore, on the other hand, reports that in excess, the herb is

too slowing: "All you can do is watch cartoons."[14] It should probably be avoided in pregnancy and lactation due to lack of information.

A similar vine-like jungle cactus is known as *Hylocereus undatus*. These two cacti are sufficiently morphologically similar that some professionals in the field consider them to be frequent adulterants of one another. Dr. Yarnell's mentor, the late Silena Heron, ND, sent tinctures made from *Selenicereus grandiflorus* and *Hylocereus undatus* to the late John Bastyr, ND, DC, without saying which was which. He eventually reported back that the bottle that contained *Hylocereus* tincture was more effective. However, because no formal testing or botanical keying confirmed the identity of the plants and no voucher specimens were retained, it is possible that they were mislabeled. The Eclectic pharmacist John Uri Lloyd cautioned against substituting other species for *Selenicereus*.[13]

A Weed for All Seasons

A better-researched, relatively strong, generally antiarrhythmic herb is *Cytisus scoparius* (Scotch broom), formerly known as *Sarothamnus scoparius*. This Fabaceae family member originated in northern Europe, but has since naturalized to many parts of the world. It is a pernicious weed in the Pacific Northwest where it grows rapidly, crowding out native plants. This makes it a very sustainable source of medicine.

The constituents of greatest interest in Scotch broom are quinolizidine alkaloids, particularly sparteine. According to Weiss, Scotch broom acts very similarly to quinine and quinidine, though it is much safer.[15] He recommends it for patients with congestive heart failure to help regulate heart rhythm and indirectly improve venous return. He cites it as a specific treatment for atrial or ventricular fibrillation and extrasystoles. These indications are echoed in other modern sources that also cite it as specific for sinus tachycardia and post–myocardial infarction arrhythmias.[16]

Modern investigation has revealed that sparteine and related alkaloids antagonize potassium channels.[17] There is also evidence of sodium channel antagonism.[18] There is a definite positive inotropic action from sparteine, apparently due to its concomitant actions on sodium and potassium channels[19]—unlike many standard class I antiarrhythmic drugs (quinidine, mexilitene) that also inhibit calcium channels and are actually negative inotropic.

No published clinical trials were located on the efficacy of Scotch broom or sparteine. The recommended dose of Scotch broom herb tincture made from fresh or dry material for an average-sized adult is 0.5–1 ml three times per day. The standard pharmacological dose of isolated sparteine is 100–200 mg daily in divided doses. Unfortunately the average content of sparteine in crude Scotch broom could not be confirmed. Since 1977, the Food and Drug Administration (FDA) has made injectable sparteine unavailable due to unpredictability of effects and propensity to cause tetanic uterine contractions.[20]

Whole plant extracts of Scotch broom at usual therapeutic doses are essentially without adverse effect, and even overdose is rarely a problem.[15] The most likely adverse effects, if any, are bradycardia, indigestion, loose stools, and hypertension. It is contraindicated in pregnancy (though it does have some application during labor as an oxytocic) and atrioventricular block (which it can readily exacerbate).[21] Some also consider it contraindicated in hypertension due to its vasoconstrictive properties.[22]

Much is known about the pharmacokinetics of sparteine because it is thoroughly and specifically oxidized by hepatic CYP 2D6. Approximately 5% of people of European descent are poor metabolizers of sparteine due to inefficiency or lack of CYP 2D6.[23] In these patients, sparteine levels may build up to toxic levels. Arguably CYP 2D6 function should be assessed prior to administration of this herb, though the cost–effectiveness of this approach is questionable.

Scotch broom or sparteine should not be administered simultaneously with drugs that inhibit CYP 2D6 function, including cimetidine and many selective serotonin reuptake inhibitors including fluoxetine and paroxetine, thioridazine, haloperidol, propoxyphene, and ritonavir. Even more important is the fact that many anti-arrhythmic drugs are CYP 2D6 inhibitors including quinidine, flecainide, and amiodarone. Caution is warranted in combining Scotch broom with other anti-arrhythmics for this reason. It should also be noted that approximately 1% of populations of European descent are hypermetabolizers of sparteine due to excessive CYP 2D6 activity, and these people would be unlikely to respond to Scotch broom therapy.[24]

Other drugs should not be combined with Scotch broom. Due to the presence of simple amines in the plant, it may cause problems if combined with monoamine oxidase inhibitors. It should also not be given with epinephrine due to potential synergy of effects, particularly in vasoconstriction and uterine contraction.

Indian Snakeroot

Another potent, specific anti-arrhythmic herb that comes from India is *Rauvolfia serpentina* (rauwolfia), formerly known as Indian snakeroot. The root of this herb contains many interesting alkaloids. Of particular interest in the case of arrhythmias is ajmaline. Ajmaline is said to have been isolated by Dr. Salimuzzaman Siddiquil and named after Hakim Ajmal Khan, a strong advocate for Unani-Tib (Arab traditional medicine).[25]

In animal studies, isolated ajmaline has shown particular efficacy in preventing arrhythmias due to cardiac ischemia.[26] Clinical trials have repeatedly shown that ajmaline is effective for patients with various arrythmias including atrial fibrillation and ventricular tachycardia, often more effectively than synthetic drugs.[27,28] Russian clinicians have found various rauwolfia preparations containing ajmaline to be effective at preventing supraventricular arrhythmias.[29] Because other lines of research support the concept that the combined alkaloids of the plant are more effective than any alkaloid in isolation, the whole plant or whole plant extracts are recommended. The usual dose of a tincture standardized to 0.1–0.125% reserpine (as a quality control) is 3–5 gtt three times per day for an average-sized adult. For more information on rauwolfia, see chapter 18 on hypertension.

Lily-of-the-Valley

The third, relatively strong herb for intervention in more serious arrhythmias is *Convallaria majalis* (lily-of-the-valley). This herb has a long history of use for people with mild congestive heart failure, and it contains cardioactive glycosides.[30] Unlike the much stronger and more dangerous plant *Digitalis* spp. (foxglove), lily-of-the-valley glycosides do not accumulate and are vastly safer, though milder in their effects. Lily-of-the-valley flavonoids are also considered important for the activity of the herb and this supports the use of the whole plant and not just the cardiac glycosides in isolation.[31] This is supported by a study on a related species, *C. keiskei*.[32] The aqueous extract of the whole plant increased atrial stroke volume, pulse pressure, and cAMP efflux in rabbit atrea. It also markedly increased potassium concentration in the atria-derived perfusate. Convallatoxin also increased atrial stroke volume and pulse pressure but did not alter the cAMP efflux level. So, whereas convallatoxin definitely contributes to the plant's digitalis-like activity, the whole plant acts somewhat differently than the isloated constituent.

Lily-of-the-valley has long been recognized by clinicians to have an anti-arrhythmic effect. Felter found it particularly useful for tachycardia and mitral insufficiency.[2] He found it less

useful for aortic valve problems. Animal studies support that lily-of-the-valley has a positive inotropic effect, and that it is a moderately strong vasoconstrictor.[33] In a bizarre twist, human identical progesterone has been found in lily-of-the-valley, presumably in quantities too minute to be relevant to medicine, but suggesting humans and plants may have more hormonal regulation systems in common than was once thought.[34]

The usual dose of lily-of-the-valley fresh plant tincture is 0.5–1 ml three times per day for an average-sized adult. Though lily-of-the-valley is very safe, it should not be taken in excess and the patient should maintain a high intake of fruits and vegetables to guard against hypokalemia, which potentiates the toxicity of other cardiac glycosides. Also, it should not be combined with potassium-wasting drugs such as loop diuretics and corticosteroids without careful monitoring of potassium levels. Onset of severe nausea, vomiting, or atrial fibrillation are all indications for discontinuation of the herb.

Hawthorn the Tonifier

No discussion of plants for patients with arrhythmias would be complete without mentioning the ultimate cardiac tonic, *Crataegus laevigata* (hawthorn) and its close relative *C. monogyna*. This herb is so safe it has no known overdose level. Its effects are very gentle, often taking weeks or months to become fully noticeable. For this reason, it is advocated as a long-term treatment to both prevent and treat essentially all types of arrhythmias.

There is much less research on the anti-arrhythmic activity of hawthorn than its many other actions. However, some animal research has shown directly that the hawthorn species *Crataegus meyeri* is anti-arrhythmic.[35] In rats a standardized hawthorn extract (WS 1442) diminished the incidence of ventricular fibrillations during prolonged heart ischemia.[36] Surprisingly, one rat study actually found *C. laevigata* standardized extract to be pro-arrhythmic in ischemic

Figure 13–2. *Crataegus laevigata* (hawthorn)
Photograph by Holly Shull Vogel, Frost Flower Farm.

hearts.[37] It appeared that the calcium channel antagonist activity of the herb was causing the problem. The extract was also administered by injection. A similar study using the same methodology but using oral pretreatment with hawthorn found that it greatly reduced the incidence of postischemic fibrillation in rats.[38]

Clinical trials of hawthorn in patients with congestive heart failure (CHF) have often reported secondary outcomes involving cardiac rhythm. In one large open trial (n = 3,664), hawthorn was found to be particularly useful in CHF patients with tachycardic arrhythmias.[39] In another large open trial (n = 1,011), the incidence of arrhythmias and ventricular extrasystoles was notable and appeared to coincide with improved myocardial perfusion.[40] A prospective study of 130 patient pairs taking hawthorn for CHF stage II supports the tonic use of hawthorn. After two years of treatment the cardinal symptoms of heart failure (fatigue, stress dyspnea, and palpitations) were significantly reduced in the hawthorn cohort.[41] To confirm the antiarrhythmic nature of hawthorn, arrhythmia types and incidence should be assessed in future trials involving hawthorn as primary or secondary measures, both in patients with CHF and with non-CHF-related arrhythmias.

Hawthorn can be taken in many forms. The leaves, flowers, and haws (fruit or berries) are all utilized. An infusion of 2–3 tsp/cup, steeped for 10–15 minutes, can be drunk three times daily. A tincture or glycerite is dosed at 3–10 ml three times per day for adults depending on severity of the disease and body size. The usual dose of extracts standardized to 1.8% vitexin-4'-rhamnoside or 10% procyanidins is 100–250 mg three times per day. As noted above, there are few adverse effects of this herb and no contraindications. A recent meta-analysis looked specifically at the plants adverse-event profile, and in data from 5,577 patients found only 8 serious adverse events with dizziness/vertigo being the most common.[42]

Ginkgo biloba (Ginkgo)

One of the main concerns in patients with atrial fibrillation is the increased risk of clot formation that may result when the blood does not completely empty out of the rapidly beating atria. To prevent strokes, most of the patients are treated with anticoagulants. Some patients either cannot tolerate or refuse this treatment, and *Ginkgo biloba* (ginkgo) is sometimes prescribed to reduce the risk of clotting in these patients. Ginkgo may also have direct effects on arrhythmias. A systematic review of ginkgo studies and cardiovascular function, unfortunately available only in Chinese, concluded that ginkgo had the pharmacological ability to prevent arrhythmias and protected cardiovascular function through its action on platelet-activating factor.[43]

In rats, ginkgo (EGb 761) dose dependently mitigated drug-induced ventricular arrhythmias.[44,45] Another animal study found that ginkgo (EGb 761) combined with a calcineurin inhibitor reduced the incidence of reprefusion-induced ventricular fibrillation more effectively than ginkgo alone.[46] Injected, ginkgo (EGb) protected dogs fom ventricular premature beats and on reperfusion protected them from ventricular fibrillation.[47] On the other hand, an abstract of an Italian article reports that ventricular arrhythmias resolved in a patient on two occasions when the patient ceased taking ginkgo.[48] Finally, in rats ginkgo (EGb 761) administered ip somewhat diminished doxorubicin-induced cardiomyopathy.[49]

One of our patients ended up in constant atrial fibrillation not controlled by his prescription medicines (atenolol and lanoxin). He refused the suggested additional treatment (sotalol and warfarin) and instead sought a holistic treatment. We prescribed standardized ginkgo (150 mg/day), magnesium (500 mg/day) and 1 tsp fish oil/day. Within two days of beginning this regimen, he converted to normal rhythm, a change that now has persisted for almost a year.

Table 13–1. Summary of Major Antiarrhythmic Herbs

Latin Name	*Common Name*	*Part Used*	*Typical Adult Dose*	*Warnings*
Leonurus cardiaca	Motherwort	Leaf and flower	1–2 tsp/cup of water infused for 15–20 minutes, 1 cup three times per day; fresh plant glycerin extract 3–5 ml three times per day	Occasional mild sedation
Scutellaria lateriflora	Skullcap	Leaf and flower	Fresh plant glycerite or tincture, 3–5 ml three times per day	Occasional mild sedation
Cytisus scoparius	Scotch broom	Leaf and flower	Fresh or dry plant tincture 0.5–1 ml three times per day	Avoid in pregnancy, AV block, hypertension; many drug interactions; may cause bradycardia
Selenicereus grandiflorus or *Hylocereus undatus*	Night-blooming cereus	Stem and flower	Fresh plant tincture 5–15 gtt three times per day	Do not overdose
Rauvolfia serpentina	Rauwolfia	Root	Dry plant tincture standardized to 0.1–0.125% reserpine 3–5 gtt three times per day	Minor nasal stuffiness and loose stools common; avoid in depression; do not overdose; many drug interactions
Convallaria majalis	Lily-of-the-valley	Root	Fresh plant tincture 0.5–1 ml three times per day	May cause nausea; hypokalemia potentiates toxicity
Crataegus laevigata	Hawthorn	Leaf, flower, and haws	Infusion of 2–3 tsp/cup, steeped for 10–15 minutes three times per day. Fresh or dry plant tincture or glycerite 3–10 ml three times per day; extracts standardized to 1.8% vitexin-4'-rhamnoside or 10% procyanidins 100–250 mg three times per day	None
Ginkgo biloba	Ginkgo	Leaf	Standardized extract (24% ginkgo flavone glycosides, 6% terpene lactones), 60–180 mg/day	Caution indicated when combined with anticoagulants; should be discontinued prior to surgery

CONCLUSION

Numerous herbs are useful in treating patients with a wide range of arrhythmias. In all cases, *Crataegus laevigata* is recommended for prevention and treatment as a gentle tonic. For mild arrhythmias not related to demonstrable heart pathology, simple sedatives such as *Leonurus cardiaca* and *Scutellaria lateriflora* are recommended. In more serious cases or when milder remedies are not sufficient, *Selenicerus grandiflorus* or *Hylocereus undatus*, *Cytisus scoparius*, *Rauvolfia serpentaria*, and *Convallaria majalis* offer more potent though also potentially more dangerous options. Careful monitoring and proper dosing usually allow even these strong herbs to be utilized safely. See Table 13-1.

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14

BOTANICAL TREATMENTS FOR HEMORRHOIDS

Hemorrhoids are an understudied and often an undertreated condition. It is estimated that about one half of all Americans have some discomfort from hemorrhoids by the time they are 50, but only a much smaller percentage (around 4%) seek medical treatment for their condition.[1] Hospital-based proctoscopy studies show prevalence rates of up to 86% with many patients in an asymptomatic state.[2] Clinical experience suggests that botanical treatments and lifestyle changes can relieve hemorrhoid symptoms in the early stages and can provide significant benefit as an adjunct treatment in the later stages of the ailment. Unfortunately, science has barely begun investigating these fairly ancient treatments.

Hemorrhoidal tissue, cushions of tissue within the anal canal that contain blood vessels and supporting tissue made up of muscle and elastic tissue, are present in all individuals.[2] There are usually three major hemorrhoidal cushions oriented right posterior, right anterior, and left lateral. There is a rich network of arteries around the anal canal, providing a ready supply of arterial blood to hemorrhoidal blood vessels. It is only when these cushions enlarge, causing negative symptoms, that hemorrhoids in the vernacular sense are present. Negative symptoms typically include the passage of bright red blood that can occasionally be severe and result in anemia.

If the hemorrhoid originates at the top of the anal canal, it is referred to as an internal hemorrhoid. If it originates at the lower end, near the anus, it is referred to as an external hemorrhoid. Internal hemorrhoids are usually painless (because this area of the body lacks pain receptors) but they may bleed when they are irritated. Untreated, sufficiently large internal hemorrhoids can lead to prolapse, where the distended internal hemorrhoids protrude outside of the anus, causing discomfort. If the sphincter spasms, the blood supply to the prolapsed hemorrhoid can be cut off, leading to a strangulated hemorrhoid. External hemorrhoids occur outside the anal verge. They can be painful, swollen, and irritated. Itching can be due to external hemorrhoids although typically itching is due to skin irritation. The stages of internal hemorrhoids are given in Table 14-1. Obviously, pain, bleeding, and problems passing stool can be caused by conditions other than hemorrhoids. We presuppose that such conditions have been ruled out before any hemorrhoid treatment is undertaken.

The actual cause of hemorrhoids is not known.[2] Genetic predisposition, straining during bowel movements, obesity, a sedentary lifestyle, pressure on the rectal veins due to poor posture and/or muscle tone, and pregnancy are believed to be causes. Hemorrhoids are common in spinal cord injuries. Constipation, chronic diarrhea, poor bathroom habits (such as overzealous cleaning and wiping), postponing bowel movements, and a fiber-poor diet are considered to be contributing causes.[3] Alcoholic cirrhosis or other causes of portal obstruction can cause severe hemorrhoids.

Though botanical treatments for hemorrhoids are poorly researched, preliminary trials show promise for several agents. Below we review both internal and topical herbal therapies.

INTERNAL THERAPIES

Butcher's Broom

Ruscus aculeatus (butcher's broom), Liliaceae, is related to asparagus and hails from the Mediterranean region. The tough mature stems and leaves of the plant were apparently used

Table 14–1. Staging of Internal Hemorrhoids

Stage	*Symptoms*
I	Occasional discomfort and/or bleeding but no obvious external abnormality
II	Hemorrhoids protrude with defecation but reduce spontaneously
III	Hemorrhoids protrude and require digital reduction
IV	Hemorrhoids protrude and cannot be reduced

Adapted from Anon. American Gastroenterological Association Medical position statement: Diagnosis and treatment of hemorrhoids. *Gastroenterol* 2004; 126(5):1461–1462.

historically as brooms, hence the common name. Butcher's broom rhizomes contain steroidal saponins known as ruscinogens, considered the most active compounds. The dried rhizomes are used medicinally. Butcher's broom is typically administered in capsule form, and is frequently paired with trimethylhesperidin chalcone (a flavonoid complex) and ascorbic acid.[4] However, the plant is also available as a tincture and a tea. There are also numerous topical preparations, often combining butcher's broom with sweet clover (*Melilotus* spp.).

Butcher's broom has a long clinical history of use as a treatment for hemorrhoids, a use for which it has been approved by the German Commission E.[5] In one open-label multicenter study of 124 patients with hemorrhoids, 69% of the patients rated butcher's broom as having good or excellent efficacy.[6] Seventy-five percent of the treating physicians rated its efficacy similarly. Ninety-two percent of the physicians rated butcher's broom as safe and well tolerated. Patients took six capsules per day of a product containing 150 mg of butcher's broom for three days, and then reduced their dose to four capsules daily. Statistically significant improvement in a variety of symptoms (such as pain, local signs, overall severity, etc.) was seen after seven days of treatment. While a single study does not prove efficacy, the very favorable observations of treating physicians combined with a long history of clinical use are reasons to recommend that patients consider using butcher's broom as an internal treatment for hemorrhoids.

Butcher's broom has been studied for use in pregnancy-related varicosities. Two studies on pregnancy-related venous insufficiency both showed improvement in maternal symptoms without any negative effects on the fetus.[7,8] Two additional European studies, one a multicenter study of 124 patients, are reported to show a similar improvement of symptoms in pregnant women.[9,10] These studies do not conclusively establish the safety of ruscus in pregnancy, but both animal and human studies indicate a high degree of safety. Based on these studies, we favor butcher's broom when an internal remedy is needed for hemorrhoids in pregnant women (where surgical treatments are often contraindicated).

Most clinical studies administered 150 mg butcher' broom three times daily with meals. The typical tincture dose is 30–60 drops (1.5–3 ml) three times daily.[11]

Horse Chestnut

Horse chestnut (*Aesculus hippocastanum*) is a beautiful, Eurasian deciduous tree that produces large chestnut-like seeds that are dried for medicinal use. The seeds contain a complex mixture of triterpene saponins collectively referred to as escins (or aescins, as the British prefer to spell it).[12] It also contains flavonoids and tannins.[13] The German Commission E has approved the use

Figure 14–1. *Aesculus hippocastanum* (horse chestnut)

of a standardized horse chestnut extract (containing 16–20% anhydrous escin) in chronic venous insufficiency (CVI).

There are European publications from the late 1800s and early 1900s reporting that horse chestnut benefits hemorrhoids, but there are no recent studies on the use of the whole botanical medicine in hemorrhoids. One double-blind, placebo-controlled study of 80 patients suffering from acute symptomatic hemorrhoids showed that 40 mg of aescin administered three times per day for up to two months improved symptoms in 81% (compared to 11% in placebo group) and a notable improvement in bleeding (95% vs. 62%) and swelling (87% vs. 38%) on endoscopic examination.[14] Symptom improvement typically was reported after six days of treatment and endoscopic improvement after two weeks. As an added benefit, there is preliminary evidence from animal trials that beta-escin from horse chestnut may have cancer-preventative effects in the colon.[15]

Michael Moore, Director of the Southwest School of Botanical Medicine, considers horse chestnut the preferred remedy for hemorrhoids in individuals who are highly active physically. High levels of physical activity moves more blood to the skeletal muscles reducing the flow of blood to the gastrointestinal tract. Moore says this can lead to malabsorption, constipation, and hemorrhoids, and he has found horse chestnut combined with increased dietary flavonoids to be particularly helpful in these cases.

A typical dose of horse chestnut is 250 mg (corresponding to 100 mg escin) twice daily with meals. Delayed-release formulations have not been shown to have any different bioavailability in humans compared to standard encapsulated forms.[16]

Stone Root

Many American herbalists favor the nonaromatic mint family plant *Collinsonia canadensis* (stone root) as a treatment for symptomatic hemorrhoids. The Eclectic physicians found this herb particularly useful in those with signs of congestion (dark red or purple tissue) and hemorrhoids.[17] Overweight, physically inactive individuals who eat a diet high in fats and sugars and low in fruits, vegetables, and grains tend to develop this state of congestion. In our experience, stone root will often rapidly resolve hemorrhoid symptoms and we favor its use in this type of individual. There is virtually no research on stone root, except for constituent studies showing that it contains flavonoids and saponins.[18,19] Of course, isolated flavonoids have shown benefit

in hemorrhoids,[20] and both butcher's broom and horse chestnut contain flavonoids and saponins. These data lend some very vague support for the use of stone root. The Eclectics used a fairly low dose of stone root (1–30 drops), presently a typical dose of stone root tincture is 2–4 ml, three times per day.[11,17]

Witch Hazel

Hamamelis virginiana (witch hazel) also has a long history of use as a hemorrhoid treatment. Witch hazel is a shrub or small tree indigenous to North America. Its yellow flowers appear in the fall, and its leaves and bark are harvested for medicine. Both the leaves and the bark contain tannins, primarily hamamelitannins, but they also contain catechins. The leaves contain more flavonoids than the roots, and both contain a small amount of volatile oil.[13]

Today, many people think of witch hazel primarily as a topical treatment (see section below). However, European and American herbalists typically use witch hazel both as an internal and topical remedy for hemorrhoids. Thus both the European Scientific Cooperative on Phytotherapy (ESCOP) and the French government have approved its combined use for hemorrhoids.[13] Witch hazel is frequently prescribed as a decoction or an alcohol-preserved decoction. This makes sense as tannins are highly soluble in hot water. Witch hazel extract has displayed inflammation-modulating, astringent, and vasoconstrictive properties in pharmacological studies.[13] Its astringency is of help in bleeding hemorrhoids, and the Eclectics favored it for such hemorrhoids as well as for any type of passive bleeding.[17] The dose for an infusion is 2–3 g of

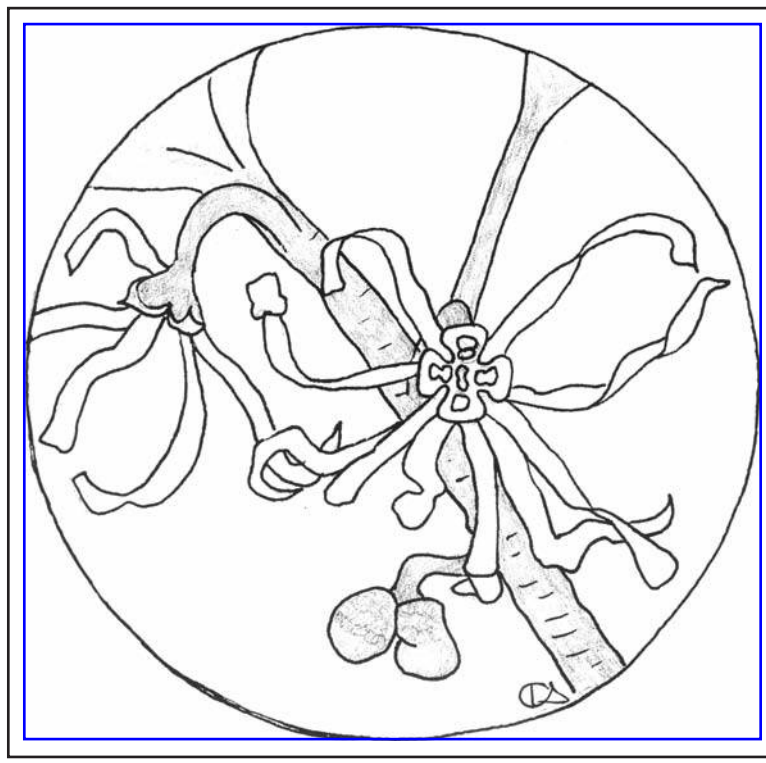

Figure 14–2. *Hamamelis virginiana* (witch hazel) flowers
Drawing © by Kathy Abascal BS, JD.

leaf or bark steeped in 150 ml boiled water taken two to three times daily between meals. The tincture dose is 2–4 ml, three times per day. It can cause nausea, which is usually easily relieved by administering witch hazel with food.

TOPICAL TREATMENTS

Topical treatments to assist locally in calming inflammation and stopping bleeding and swelling are important in hemorrhoid treatment. According to the late Rudolf Fritz Weiss, acute hemorrhoidal inflammation is best treated with wet compresses.[21] In addition, ointments can be applied but he did not consider them sufficient if used alone. He recommended that the compresses be cool, below room temperature, but not so cold as to induce rectal spasm. Dr. Weiss recommended that the wet compresses be applied for at least an hour, morning and night, or that a sitz bath be used. A hemorrhoid ointment should then be applied after each treatment and after every bowel movement. As a practical matter, only a client with severe symptoms is likely to dedicate that amount of time to treatment. Milder cases may be effectively dealt with by a shorter compress application and an occasional sitz bath with regular application of ointment. Suppositories also work well.

Dr. Weiss favored *Arnica* spp. (arnica) compresses, which he considered one of the fastest remedies for acute hemorrhoid inflammation. He recommended using 1–2 tsp (5-10 ml) of arnica tincture per ½ l (½ quart) of water for compresses. Alternatively, he recommended the use of an *Quercus* spp. (oak) bark decoction or a *Matricaria recutita* (chamomile) infusion. He typically followed the application of compresses with a witch hazel ointment.

Figure 14–3. *Matricaria recutita* (chamomile)

Topical application of witch hazel alone will often suffice to soothe minor symptoms of acute inflammation. No doubt its effectiveness explains why witch hazel remains a common ingredient in over-the-counter hemorrhoidal preparations. Preparation H® Hemorrhoidal Cooling Gel, for instance, contains 50% witch hazel. It is witch hazel's tannins that provide many aspects of its healing power, and the clear witch hazel distillate so readily available is *not* the medicine of choice as it is almost completely devoid of tannins.[13] Instead, a more colorful tea or tincture should be used.

Figure 14–4. *Calendula officinalis* (calendula)

We tend to prefer combining several herbs in the compresses, sitz baths, or ointments to provide a broader range of actions. Any of the herbs used internally (e.g., stone root, butcher's broom, horse chestnut, and witch hazel) can be combined effectively for topical application. We also like to include herbs that are noted for their wound-healing properties such as *Centella asiatica* (gotu kola), chamomile, or *Calendula officinalis* (calendula). If needed, tinctures of these herbs can be worked into a cream base for topical application.

CONCLUSION

Addressing hemorrhoids should go beyond simply prescribing the botanicals discussed above. Dietary issues, while beyond the scope of this book, are of great importance. Surprisingly little research has been done on the connection between diet and hemorrhoids given the prevalence of the disorder and the fact that isolated flavonoids have shown substantial benefit in the treatment of hemorrhoids.[22] Adding soluble fiber has shown benefit in hemorrhoid treatment, at least where constipation is an aggravating factor.[23] As a general rule, we consistently recommend that our clients increase their intake of fruits and vegetables with an emphasis on foods containing soluble fiber. Where constipation is an issue, we often recommend *Plantago ovata* (psyllium) seed husks. Lifestyle changes that include increasing water intake and exercise to increase muscle tone also help effect a long-term improvement in hemorrhoid symptoms.

As mentioned above, using botanicals both internally and topically will speed healing. Botanicals such as gotu kola or *Ginkgo biloba* (ginkgo), used to increase peripheral circulation, can act synergistically with herbs used specifically for hemorrhoids.[24] For instance, gotu kola and its isolated triterpenic fraction improve microcirculation, decrease capillary permeability, and improve symptoms of chronic venous insufficiency.[25,26] It also has been shown to increase tensile strength, collagen content, and epithelialization in many types of wounds when used internally or topically.[27–29]

Dr. Weiss commented that it is important to address adequately the constipation and pain that accompanies many hemorrhoids as well.[21] He typically prescribed a tea that combined laxative, inflammation-modulating, and antispasmodic herbs with a bitter herb to tone the plexus hemorrhoidalis and an astringent to relieve bleeding. One of his tea formulas is given in Sidebar 14-1.

A comprehensive treatment plan will work effectively on hemorrhoids in the early stages. More complicated or advanced hemorrhoids likely will require allopathic intervention. None-

14–1. *Dr. Weiss's Hemorrhoid Tea*

Matricaria recutita (chamomile) flowers	20%
Acorus calamus (calamus) root	20%
Foeniculum officinalis (fennel) seed	20%
Senna spp. (senna) leaves	20%
Frangula alnus (frangula) bark	20%

1–2 tsp (5–10 g) in a cup of boiling water infused for 10 minutes; 1 cup morning and night. This should only be used for a few days consecutively to avoid inducing rebound constipation due to the presence of cathartic laxatives in the formula.

theless, botanicals as an adjunct to ligation and surgery are helpful in healing and preventing recurrences, as has been demonstrated at the very least with the use of *Plantago ovatum* (psyllium) after hemorrhoidectomy in one controlled clinical trial.[30]

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15

HERBS FOR HERPES SIMPLEX INFECTIONS

Herpes simplex viruses (HSV) infect an extraordinary number of people. In one study looking at a large sample of the U.S. population from 1976 to 1994, 68% of the population 12 years and older had HSV-1 antibodies with little change during the period of the study.[1] Although HSV infections are rarely life threatening, they are associated with a high morbidity and the rashes they cause are usually quite painful. Genital herpes ulcers may be a risk factor for transmission of human immunodeficiency virus.[2] In patients who develop severe immune suppression, HSV encephalitis can occur and is life threatening. Exposure of neonates to genital HSV can cause serious disease such as keratitis.[3] Though acyclovir and related drugs (famciclovir, valacyclovir) are now widely available to suppress HSV, cheap and effective natural prevention and treatment options are still sorely needed. This is particularly a concern as the risk of development of drug resistance exists with single-chemical agents. A recent study in the Netherlands, for example, found that 7% of immunocompromised patients had acyclovir-resistant HSV infections.[4] Clinical aspects of HSV and infections by these viruses are reviewed in Sidebar 15-1.

15–1. *Clinical Review of Herpes Simplex*

Types of Herpes Viruses

HSV-1: primarily infects by direct contact with saliva above the waist, but can cause genital infections. Goes dormant in sensory ganglion cells of trigeminal ganglia in the brainstem. Infection reactivated by stress (physical or mental), immune suppression, menses and other hormonal shifts, and/or environmental fluctuations.

HSV-2: infects by direct sexual contact below the waist, but can cause oral lesions. Transmission of both types can occur when there are no visible lesions present. Goes dormant in sacral or lumbar ganglia. Reactivation similar to HSV-1.

Signs and Symptoms

Herpes labialis or genitalis: prodromal tingle or itch for 1–2 days followed by crops of painful, fluid-filled vesicles on erythematous bases. The vesicles burst after 5–7 days creating yellow-crusted lesions that heal 12–21 days after the outbreak begins without treatment. Scarring may occur if outbreaks affect the same area repeatedly.

Initial infection may cause more severe symptoms and fever and systemic myalgia.

Can also cause ophthalmitis or central nervous system disease in neonates or immunsuppressed people.

Diagnosis

Generally by clinical examination but can be confirmed by rising viral titers, Tzanck smear, or viral culture when presentation is unusual.

MINTS AGAINST HERPES

Various members of the Lamiaceae (mint) family of herbs offer safe and effective topical treatment for HSV outbreaks. The best-studied mint, *Melissa officinalis* (lemon balm), has been shown effective as a concentrated extract in a cream base for relieving symptoms of acute herpes labialis in one open-controlled and three double-blind clinical trials.[5–8] The most recent and largest of these studies also found that prolonged use of the product increased the interval between acute outbreaks.[7] It has unfortunately not been tested directly in comparison to acyclovir or related drugs. What is clear is that except for some generic brands of acyclovir from some suppliers, lemon balm cream is significantly less expensive. See Table 15-1.

Lemon balm leaf contains a variety of compounds that have shown anti-HSV activity in vitro. Earlier studies suggested that rosmarinic, caffeic, and ferulic acids were responsible for blocking activity of HSV-1.[9] More recently the terpenoids of lemon balm have been shown to inhibit HSV-2 replication.[10]

In another double-blind clinical trial, a cream formula that combined aqueous extracts of the mint family plant *Salvia officinalis* (sage) leaf with *Rheum palmatum* (Chinese rhubarb) root was just as effective as acyclovir cream and significantly more effective than sage cream by itself at healing herpes labialis.[11] Average time to complete healing with the combined cream was 6.7 days compared to 6.5 days for acyclovir. No significant adverse effects were reported. The trial was fairly large (total 145 immunocompetent participants), making the results fairly

Table 15–1. Cost of Typical Course of Treatment for a Recurrent Outbreak of Herpes Labialis

Drug and Form	*Unit Cost*	*Dose (Total Dose)*	*Cost of Course*
Drugs			
Acyclovir,* 200 mg capsule	$0.21–$1.67	1 capsule 5 times per day for 5 days (25 capsules)	$6.30–$50.10
Acyclovir,* 500 mg tablet	$0.25–$2.16	1 tablet 3 times per day for 5 days (15 tablets)	$3.75–$32.40
Famciclovir (Famvir), 125 mg tablet	$2.90–$5.20	1 tablet 2 times per day for 5 days (10 tablets)	$29.00–$52.00
Valacyclovir (Valtrex), 500 mg tablet	$2.89–$6.17	1 tablet 2 times per day for 5 days (10 tablets)	$28.90–$61.70
Natural Products			
Lemon balm cream* (70:1 extract) (Cold Sore Relief), 5 g (0.18 oz) tube	$5.32–$9.95	3–4 applications per day for 5 days (1 tube)	$5.32–$9.95

*Generic brands available.
Note: None of this information is to imply support for any particular brand; it is only to show relative cost between products. The authors have no financial interest in any of the products listed.
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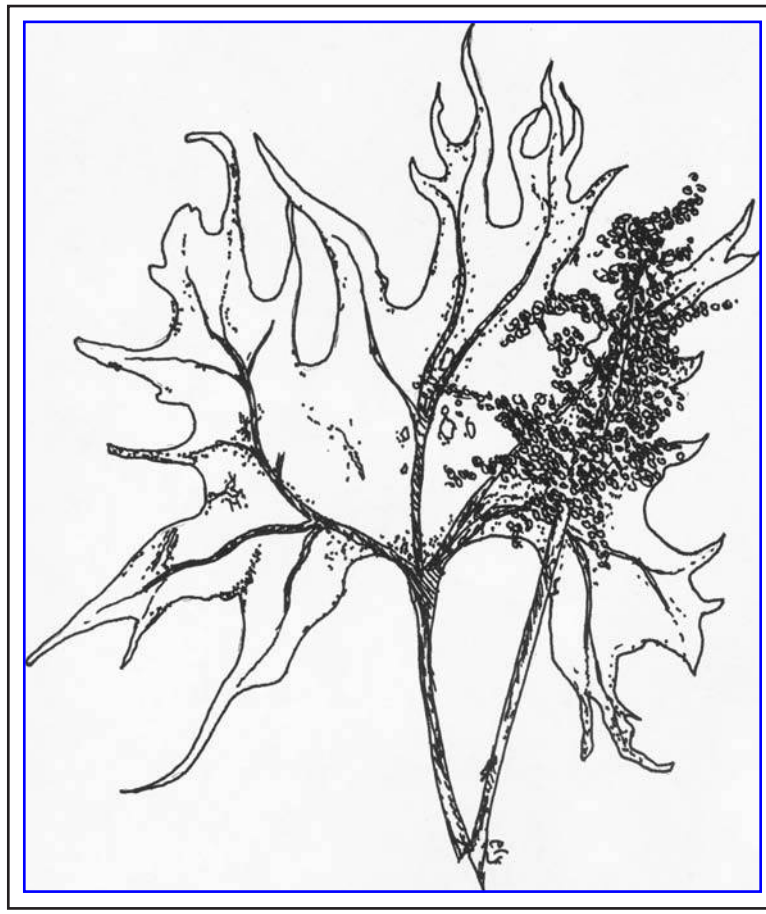

Figure 15–1. *Rheum palmatum* (Chinese rhubarb)
Drawing © Eric Yarnell, ND, RH.

strong. The mechanisms of action of sage have not been clarified though this herb is definitely antioxidant and has a long history of use for treating infections of all sorts.[12] An early study was reported to have found that rhubarb cream alone was ineffective.[13]

No other clinical trials of mint family plants were identified. Other potentially useful herbs in this category to consider are *Prunella vulgaris* (heal all) aerial parts, *Thymus serpyllum* (wild thyme) leaf, *Nepeta cataria* (catnip) leaf, *Origanum vulgare* (oregano) leaf, and *Mentha* spp. (mint) leaf. In one study of traditional Mexican HSV remedies, mint (*Mentha piperata*) and basil (*Ocimum basilicum Lineo*) displayed the strongest activity in vitro.[14] A study of aqueous extracts of a number of mints (lemon balm, peppermint, heal all, rosemary, sage, and thyme) all showed strong antiviral activity against HSV-1 in vitro. This study concluded that the mints exert their effect on HSV before adsorption and should work well topically.[15] Another study of basil fractions found that its ursolic acid had the strongest activity against HSV-1 in vitro.[16] We often combine lemon balm with another mint family plant in our antiherpes topical formulas.

Heal all has a long history of use for viral infections and its anti-HSV mechanisms have been studied more closely than that of other mints. In guinea pigs, a cream made from a semipurified

fraction (lignin-polysaccharide complex) from heal all significantly reduced skin lesions and inhibited viral binding and penetration into the host cell.[17] Heal all inhibits HSV by a different mechanism than acyclovir, potentially via suppression of antigen expression.[18] Polysaccharides seem critical to the antiherpetic efficacy of this herb and have also been shown to block HSV entry into cells, possibly through receptor blockade.[19] However, other constituents in mints may be equally important to their activity.

THE ROLE OF TANNINS

Tannins come in two forms, condensed and hydrolyzable. Condensed tannins are large flavonoid polymers, whereas hydrolyzable tannins have a glucose core with attached gallic or ellagic acid units. Older studies focused on the tannins in mints as important antiviral constituents.[20,21]

More recent laboratory studies have found that simple hydrolyzable tannins are potent antiherpetic agents and act by blocking viral adsorption to human cells.[22] Many tannin-rich herbs have been shown to inhibit HSV in vitro. For instance, *Punica granatum* (pomegranate) pericarp blocked HSV replication as well as adsorption.[23] *Geranium sanguineum* (bloody cranesbill) aqueous root extract, rich in tannins, blocked HSV replication and cytopathogenicity in vitro and delayed vesiculation when administered orally to guinea pigs after primary infection.[24] A close relative of this herb is frequently used in the West, *Geranium maculatum* (cranesbill) in a similar fashion. *Crataegus sinaica* (Chinese hawthorn) contains proanthocyanidins, flavonoid oligomers that are precursors to condensed tannins, and was shown to inhibit HSV activity in vitro.[25] Other species of hawthorn (*C. aronia, C. monogyna, C. pseudoheterophylla*) also have shown strong HSV inhibitory activity in vitro.[26] There are other but these suggest that tannins have relevant anti-HSV activity.

One clinical trial investigating a method of assessing efficacy of antiherpes drugs studied a topical combination of isolated tannic acid and salicylic acid.[27] The authors found that the study medication greatly speeded reduction in size of lesions compared to baseline, whereas placebo was much weaker in this regard. Although this proof-of-concept study was small and did not use true between-group comparisons, it does give some initial sense that tannins can be therapeutically useful when applied topically.

In clinical practice, it is observed that tannin-rich herbs are particularly useful topically when vesicles are starting to burst and weep. The tannins adsorb proteins in the exudates and help relieve symptoms. We often include tannin-rich herbs in topical formulas for these and their antiviral effects.

INTRIGUING ANTIVIRALS FROM CHINA

Numerous other herbs have shown potential as antiherpes treatments. As mentioned above, Chinese rhubarb root is one of these that has been shown effective, combined with sage, for treating patients with herpes labialis. Though Chinese rhubarb contains tannins that might explain its activity, most research has focused on the anthraquinones in this plant most renowned for their cathartic laxative properties in higher doses. One study found that anthraquinones from Chinese rhubarb as well as several other herbs, including *Frangula purshiana* (cascara sagrada) bark, *Rhamnus frangula* (alder buckthorn) root, *Senna alexandrina* (cassia) leaf, and *Aloe barbadensis* latex, were virucidal to HSV and other enveloped viruses in vitro.[28] Injection

of an ethanolic extract of Chinese rhubarb, presumably low in tannins (as the compounds are quite toxic when present in high concentrations in the body) in mice infected with HSV, was as effective as acyclovir in one Chinese study.[29] Ethanol extract of Chinese rhubarb blocked HSV attachment and penetration in vitro.[30]

Melia azedarach (China tree, chinaberry) root bark and fruit are traditional Chinese remedies for many infectious diseases. A limonoid compound from the leaves of this tree was shown to inhibit HSV in vitro.[31] A protein from the leaves, meliacine, has been more extensively studied and shown to interfere with HSV–DNA synthesis and viral maturation and envelope formation.[32] This protein inhibited formation of herpetic keratitis in a mouse study when applied topically, whereas placebo had no protective effect.[33] A compound in the fruit, 28-deacetylsendanin, has been shown to block HSV replication and to reduce HSV thymidine kinase production.[34] Another study concluded that chinaberry compounds not only inhibit replication but also act as immunomodulators.[35] We believe whole herb extracts of this plant need to be studied to find out if synergy among the various constituents provide equally or more effective results. At least one study of an aqueous extract of a close relative, *Melia toosendan*, has shown that it can prevent viral attachment in vitro.[30]

OTHER ANTIHERPETIC HERBS

The volatile oil of *Melaleuca alternifolia* (tea tree) leaf is popular as an antifungal. However, in vitro, it is also a potent blocker of HSV adsorption.[36] Tepinen-4-ol was found to be a stronger antiherpetic than total volatile oil of tea tree, apparently because other terpenoids in the mixture were reducing its water solubility significantly.[37] A preliminary, single-blind clinical trial of a gel product containing 6% tea tree volatile oil in immunocompetent patients with recurrent herpes labialis found some improvement with the gel but statistical significance compared to placebo was not achieved.[38] This is not surprising given the very small sample size of the study (n=20). Further study of tea tree and other antiviral volatile oils is warranted to determine their efficacy.

Propolis is a mixture of compounds harvested by bees from the resin of various trees, most notably members of the Salicaceae (willow) family. Propolis mixtures have been shown more active against HSV in vitro than single propolis flavonoids.[39] A minor caffeic acid derivative in propolis has been shown to inhibit HSV–DNA synthesis in vitro.[40] In a single-blind clinical trial, topical application of 3% propolis ointment was found to be significantly more effective than acyclovir or placebo at resolving lesions and symptoms of genital herpes in men and women.[41] Unlike acyclovir or placebo, the propolis ointment was also effective at treating vaginal superinfections in those women with intravaginal or cervical herpetic lesions. These promising results should be confirmed in larger clinical trials.

Hypericum perforatum (St. John's wort) is a traditional treatment for herpes and other viral infections. A number of in vitro studies have found that various species in the *Hypericum* genus inhibit HSV, though one concluded this activity was much weaker than the other two.[42–45] Different extracts, concentrations, cell models, and timings of application could easily explain the variability of these preclinical studies. St. John's wort has also shown wound-healing activity that makes it particularly suitable for topical administration.[46]

The final group of antiviral herbs we mention are various algae (seaweeds) that contain sulfated polysaccharides such as *Prionitis lyallii* (red dulse). It is believed that these compounds act by blocking viral adsorption to cells. For a list of selected studies on various red

Table 15–2. Selected Antiherpetic Seaweeds

Name	*Type*	*Research*
Pterocladia capillacea	Uruguay	Blocks HSV adsorption in vitro[a]
Grymnogongrus griffithsiae and *Cyrptonemia crenulata*	Brazil	Blocks HSV adsorption in vitro and in murine vaginal model[b]
Nothogenia fastigiata	Argentina	Blocks HSV adsorption in vitro[c]
Bostrychia montagnei	South American coast	Blocks HSV adsorption in vitro, no effect on blood clotting[d]
Gracilaria corticata	India	Inhibits HSV adsorption[e]

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algae and seaweeds that have been shown to have antiherpetic effects, see Table 15-2. We have encountered many patients with excellent results both from topical and oral preparations of various red algae products. Unfortunately no clinical trials were located but are urgently needed.

It should be emphasized that, although most recent HSV studies investigate topical preparations or the antiviral activities of plants in vitro, most practitioners use plants both internally and topically in HSV. Although there are some studies indicating the benefit of orally administered herbs to prevent or mitigate HSV eruptions, most of these studies are in relatively obscure foreign journals and their abstracts provide little information. Reportedly, an orally administered St. John's wort extract (LI 160) showed some benefit in two placebo-controlled, double-blind studies.[47] It was also reported that an infusion of various Japanese herbs was an "effective treatment for herpes genetialis and herpes labialis."[48] In addition, studies indicate that a number of herbs of botanicals arrested or delayed the formation of vesicles and prolonged survival times when administered to animals coinfected with HSV and HIV.[49–52]

We have frequently used herbs internally with some success, often in formulas that include both lemon balm and St. John's wort. If a patient notices the onset of an acute outbreak and begins taking a combination of antivirals right away, he or she can sometimes abort the attack entirely. Other patients have significantly extended the time between attacks or had much milder attacks by using a formula that includes both antiviral and adaptogenic herbs (see below).

Finally, another area ripe for further research is the use of herbs as synergists to pharmaceutical antivirals or as a treatment in drug-resistant HSV infections. There are preliminary studies that indicate that several herbs potentiated the action of acyclovir in in vitro and in vivo studies.[53]

IMMUNE THERAPIES FOR HERPES

A complete, holistic treatment of a patient with HSV requires the use of herbs that directly interfere with HSV and herbs that support the immune system. This is particularly important in patients who are immunesuppressed due to chemotherapy or HIV infection. Of course, patients who are on immunosuppressive drugs must be approached much more cautiously as immunomodulating herbs may interfere with these drugs and cause organ rejection.

In this context, we suggest herbs that have a tonic (or long-term) immune-building effect rather than herbs that are typically used for acute issues. *Echinacea* spp. is an example of the latter. Besides being a macrophage stimulator, various extracts of various species have been shown to be anti-HSV in vitro, with the presence of alkenes and alkylamides being most associated with inhibition.[54] A clinical trial compared the leaf and flower juice of *Echincea purpurea*, which is relatively low in alkylamides compared to the root of *E. angustifolia* or *E. pallida*, with placebo in a double-blind, crossover trial.[55] Over one year's time, there was no difference in the number or severity of infections found between the groups.

In contrast are herbs that have a broader effect on the immune system mediated by their effects on CD4+ T helper lymphocytes, such as *Astragalus membranaceus* root. In a clinical trial conducted in China, patients with herpetic keratitis were treated with either astragalus or ribavirin with uncertain blinding conditions.[56] Those who received astragalus had a definite improvement in immune parameters not seen during ribavirin treatment. Results on actual

Figure 15–2. *Echinacea* spp. (echinacea)

progression of the infection were not reported, as the full text of this Chinese-language study was not available for complete assessment. A topical formulation of astragalus combined with interferon has been shown to be more effective than interferon alone at inhibiting HSV in vitro.[57] At fairly high concentrations astragalus is directly anti-HSV in vitro.[58] Taken together these studies suggest that more work should be done to determine whether astragalus would be a good immune tonic for preventing or treating herpes infections.

Adaptogens are herbs that are used to strengthen individuals contending with chronic conditions. They include plants such as *Eleutherococcus senticosus* (eleuthero) root, *Rhodiola rosea* (goldenroot) root, medicinal mushrooms, *Schisandra chinensis* (wu wei) fruit, and others discussed in chapter 3 on adaptogens. We highly recommend the inclusion of individually chosen adaptogenic herbs to lessen the severity and frequency of outbreaks in patients with HSV.

CLINICAL APPLICATION

Several herbal medicines have been shown effective and safe for treatment of patients with herpes simplex in clinical trials, most notably lemon balm, sage, Chinese rhubarb, propolis, and tea tree. These antiviral herbs, or ones similar to them, form an important basis to natural regimens for patients with herpes. Tannin-rich herbs are also frequently used topically to help relieve symptoms, and have many documented anti-HSV effects. We have also had many good results using several antiherpetic herbs internally as well as topically, though this has not yet been the subject of rigorous clinical trials.

We have generally found that creams are acceptable and can be effective for relieving herpes outbreaks, but that topical application of tinctures can be even more immediately helpful. This is because ethanol has a drying effect that quickly reduces pain. Unfortunately, this is not as cosmetically acceptable and may even stain the skin for several hours' time, and thus most patients opt to apply tincture in the evening when not at work and to use cream throughout the day. It cannot be sufficiently stressed that multiple applications of any topical herbal compounds are necessary for full efficacy, and that they should be started as soon as prodromal symptoms are noted or lesions appear, whichever comes first. Oils and ointments are not as effective and may actually spread the lesions.

Added to topical antivirals are various adaptogenic, immunomodulating herbs that potentiate the patient's own ability to fight the virus. While not as well documented to be effective, we have consistently found them helpful. They are particularly vital in immunosuppressed patients, but should not be combined with immunosuppressive drugs.

We have found that a full herbal protocol coupled with nutritional recommendations and stress reduction can cost-effectively and safely help most patients with herpes infections.

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16

HERBS FOR HERPES ZOSTER INFECTIONS

Varicella-zoster virus (VZV) causes chicken pox and shingles. Like its close cousin herpes simplex, it can go dormant in nerve ganglia and reemerge later. With the advent of VZV vaccine being routinely administered to children, it is expected that cases of VZV-induced disease will decline. Nevertheless, there is still a large pool of infected people in the developed world who are susceptible to developing shingles and its dreaded complication, postherpetic neuralgia (PHN). Though rarely life threatening, VZV reactivation syndromes such as shingles, Ramsay-Hunt syndrome, ophthalmic herpes zoster, and PHN can cause pain, paralysis, chronic or even permanent neuropathies, depression, and other morbid states.

Conventional treatments for these two conditions are not satisfactory and thus there is a need for natural treatments and prevention. Western herbal medicine offers a lot of potential benefit, though local herbal treatments in other settings have also shown at least preliminary value.[1] Though our focus here is on botanical therapies for shingles and PHN, diet, lifestyle, nutritional supplements, and other modalities are useful and often combined with herbs.

PREVENTING SHINGLES

The emergence of dormant VZV is correlated with depressed cellular immune function, such as is seen with aging, in organ transplant patients, in cancer patients, or in AIDS patients.[2] Stressful situations such as social distress (e.g., divorce), surgery, or space flight are also associated with VZV activation.[3,4] Therefore, it is logical (though unproven) that herbs that support cellular immune function and counteract stress will help prevent shingles and PHN.

The major category of herbs that fit this description are known as adaptogens or immunomodulators. These are discussed in chapter 2, so only a brief review is included here. By multiple mechanisms, adaptogens help support normal immune function and diminish the potential negative effects of stress. Some commonly used adaptogens are *Panax ginseng* (Asian ginseng) root, *P. quinquefolius* (American ginseng) root, *Eleutherococcus senticosus* (eleuthero) root, *Schisandra chinensis* (schisandra) fruit, *Withania somniferum* (ashwagandha) root, *Astragalus membranaceus* (astragalus) root, and various medicinal mushrooms such as *Lentinula edodes* (shiitake). All of these appear to be safe for long-term use based on historical records as well as the fact that many are consumed as food (such as Asian ginseng and shiitake mushrooms). Patients who are on immunosuppressive drugs are advised to avoid these herbs due to the *theoretical* risk of causing organ rejection or autoimmune disease reactivation.

Asian ginseng in a multiherb formula has shown benefit in PHN and is discussed below. We have already discussed the research on the potential impact of immunomodulating herbs on herpes simplex reemergence, which may have some implications for this closely related situation as well.

ANTI-VZV HERBS

Several herbs can be used to suppress the VZV virus once it reactivates, and may also have a role to play in preventing reactivation. The only clinical trials located on the use of a topical

herbal preparation to treat shingles used a 5% cream of the leaf of the Thai herb *Clinacanthus nutans* (bi phaya yaw). Details of both trials are lacking but they appear to have been double-blind, placebo-controlled, randomized trials, one of which involved 51 patients.[5,6] Speed of healing and reduction in symptoms were significantly better in the Clinacanthus groups compared to the placebo groups in both. Monoglycosylated diglycerides from this herb have shown anti-HSV-1 activity in vitro.[7] An extract of Clinacanthus was also found to have immunomodulating properties in vitro.[8]

Glycyrrhiza glabra (licorice) and its relative *G. uralensis* (Chinese licorice, gan cao) root both contain the triterpenoid saponin glycyrrhizin, which has been shown to have excellent anti-VZV activity in human fibroblasts.[9] This same study showed the glycyrrhizin had an additive to mildly synergistic activity with several antiherpetic drugs including acyclovir. Evidence from this and other studies of the antiviral effect of glycyrrhizin suggests the benefit comes from preventing penetration of the viral particles into cells.[10] Polysaccharides in Chinese licorice have also been shown to prevent cellular penetration of various viruses including VZV.[11] No clinical trials have been found on the efficacy of oral licorice or Chinese licorice for shingles. One Russian study apparently found some benefit from topical applications of licorice liniments but no details are available in English.[12]

Extracts of juice of *Sambucus* spp. (elder) fruit and *Ribes nigrum* (black currant) fruit both showed anti-VZV activity in vitro.[13] Black currant was somewhat more active than elder. Both appeared to inhibit viral entry into cells but may have limited viral protein synthesis as well. Black currant showed an additive effect with acyclovir against herpes simplex. The authors questioned whether the phenolic compounds found in the extract would be absorbed from the gut, and noted that the extracts caused fairly significant death among healthy cells in their assays. Both elder and black currant fruits are considered extremely safe and are eaten regularly as food. They should be studied in humans to determine if they are effective anti-VZV treatments.

Other anti-VZV herbs are based on historical treatments and extrapolation from their antiherpes simplex activity. Three herbs we consider useful in this regard are *Hypericum perforatum* (St. John's wort) flowering tops, *Larrea tridentata* (chaparral) leaf, flower, and seed, and *Melissa officinalis* (lemon balm) leaf. Besides being antiviral St. John's wort is also traditionally considered to be antineuropathic, though one clinical trial involving patients with polyneuropathies (not PHN) found no benefit of standardized extracts compared to placebo.[14] Tinctures should be taken internally and applied directly on the lesions to both relieve symptoms and maximize antiviral activity. Inflammation-modulating herbs such as *Curcuma longa* (turmeric) rhizome, *Calendula officinalis* (calendula) flower, and licorice should be combined topically and internally to help relieve symptoms.

TOPICAL CAPSAICIN

Once shingle lesions clear, postherpetic neuralgia may continue to trouble the patient. The best and most widely studied herbal remedy for this problem is topical application of the hot principle of *Capsicum* spp. (cayenne) fruit, capsaicin. This treatment appears to work by overactivating the peripheral C fibers so much that the neurotransmitter substance P is depleted, interrupting transmission of pain.

Several open clinical trials initially reported on the success of this approach.[15,16,17] A large, double-blind trial involving 143 patients with PHN lasting at least 6 months (and some more than 12 months) found that topical application of 0.075% capsaicin significantly reduced pain severity compared to total lack of activity of placebo.[18] It is difficult to conduct truly blind

studies on capsaicin as the active medication causes burning and itching the first few times it is applied. Though this effect fades with repeated application, it means people in the active group can easily deduce their treatment status. Nonetheless, capsaicin cream has shown enough evidence of benefit to be included as part of conventional medical treatments.[19,20]

Patients must be cautioned to either wear gloves while applying capsaicin or to thoroughly wash their hands afterward with hot water and soap. Otherwise it can easily be transmitted to the eyes or genitals and cause burning and itching there. It has no other known adverse effects other than in the occasional patient who is allergic.

Another herb that is potentially useful in the same way is *Euphorbia resinifera* (resin spurge) latex, a native Moroccan plant. Its constituent resiniferatoxin activates the same receptor as capsaicin, known as the vanillinoid receptor. Clinical trials are apparently in progress for using refiniferatoxin to treatment patients with PHN though results are not yet available.[21]

MISCELLANEOUS HERBS

Topical volatile oil of *Pelargonium* spp. (geranium) or 50% or 10% dilutions (in mineral oil) thereof showed significant pain-relieving ability compared to placebo in one small, double-blind clinical trial.[22] These treatments were equally effective as 0.025% capsaicin ointment applied topically. Minor irritation occurred in a few cases. A number of our patients have reported positively on this treatment, which should be more thoroughly investigated.

Figure 16–1. *Scutellaria lateriflora* (skullcap)
Drawing ©2005 by Kathy Abascal, BS, JD.

Figure 16–2. *Passiflora incarnata* (passionflower)

Hot water extracts of *Ganoderma lucidum* (reishi) mushroom (36–72 g/day taken orally) have been reported effective for PHN in several cases.[23] A formula containing *Wisteria floribunda, Trapa natans, Miristica agrans, Coix semine,* reishi, *Elfuiinga applanata,* Asian ginseng, and *Punica granatum* was tested in five cases of PHN. The formula provided rapid pain relief. Based on earlier studies, the researchers suggested that the formula might enhance natural killer-cell activity with a possible direct inhibitory effect on VZV.[23]

Traditional but untested therapies for PHN include *Avena sativa* (oat) milky seed, *Passiflora incarnata* (passionflower) leaf, *Scutellaria lateriflora* (skullcap) leaf, *Valeriana sitchensis* (Pacific valerian) root, and *Piper methysticum* (kava) root, used internally. According to the Eclectics, *Atropa belladonna (*belladonna) and *Aconitum* spp. (aconite) applied topically and internally were indispensible for any painful blistering of the skin.[24] Michael Moore recommends 2–4 drops combined with a dose of skullcap internally along with a topical application of aconite for HVZ and PHN.[25] Both belladonna and aconite are toxic in inappropriate doses and should only be considered by professionals trained in their use.

CLINICAL FORMULATING

A combination of internal immune support, internal antivirals and inflammation modulators, and topical antivirals and inflammation modulators is usually used to treat shingles. The specific details of each patient's case will determine which actions need to be emphasized and which herbs are most useful. For someone with nonintentional immune suppression, immune herbs will be emphasized. For immunocompetent patients, antiviral herbs are likely more relevant. If PHN develops after shingles clears, then the various antineuropathic herbs discussed are employed. See Sidebar 16-1.

One case series has reported on the efficacy of an integrative approach for PHN. Though this approach employed various modalities based on traditional Chinese medicine, it supports that combinations of natural therapies can be effective. Pain relief was on average 72% in patients treated with acupuncture, local nerve block, cupping, meditation, and traditional Chinese herbal formulas.[26] As mentioned above, practitioners should combine herbal treatments with supplements and other healing modalities in order to most effectively help advance the healing of patients with this painful, potentially debilitating condition.

16–1. *Summary of Herbs for Shingles and Postherpetic Neuralgia*

Adaptogens, Immunomodulators
- *Astraagalus membranaceus* (astragalus) root
- *Eleutherococcus senticosus* (eleuthero) root
- *Glycyrrhiza glabra* (licorice) root
- *Glycyrrhiza uralensis* (Chinese licorice) root
- *Panax ginseng* (Asian ginseng) root
- *Panax quinquefolius* (American ginseng) root
- *Schisandra chinensis* (schisandra) fruit
- *Withania somniferum* (ashwagandha) root

(*continued*)

16–1. *Summary of Herbs for Shingles and Postherpetic Neuralgia (continued)*

Antiviral

- *Clinacanthus nutans* (bi phaya yaw) leaf
- *Glycyrrhiza glabra* (licorice) root
- *Glycyrrhiza uralensis* (Chinese licorice) root
- *Hypericum perforatum* (St. John's wort) flowering tops
- *Larrea tridentata* (chaparral) flowering tops
- *Melissa officinalis* (lemon balm) leaf

Inflammation Modulating

- *Achillea millefolium* (yarrow) flower
- *Calendula officinalis* (calendula) flower
- *Curcuma longa* (turmeric) rhizome
- *Glycyrrhiza glabra* (licorice) root
- *Glycyrrhiza uralensis* (Chinese licorice) root
- *Matricaria recutita* (chamomile) flower
- *Populus tremuloides* (aspen) bark
- *Tanacetum parthenium* (feverfew) leaf

Antineuralgic and Analgesic

- *Atropa belladonna* (belladonna) leaf (use caution)
- *Avena sativa* (oat) milky seed
- *Capsicum* spp. (cayenne) fruit or capsaicin
- *Euphorbia resinifera* (resin spurge) latex (use caution)
- *Geranium* spp. (cranesbill) volatile oil
- *Passiflora incarnata* (passionflower) leaf
- *Piper methysticum* (kava) root
- *Scutellaria lateriflora* (skullcap) leaf
- *Valeriana sitchensis* (Pacific valerian) root

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17

UPDATE ON IMMUNOMODULATORS AND HIV INFECTION

The advent of highly active antiretroviral therapy (HAART), or combination therapy with three different classes of antiretroviral drugs, has been a great boon to people infected with human immunodeficiency virus (HIV). However, the lengthening of life and decrease in HIV-related complications associated with HAART comes at a high price.[1] HIV rapidly evolves resistance to these agents unless they are taken precisely on schedule—even short lapses in taking the pills can lead to resistance. Additionally, these drugs cause a variety of minor and serious adverse effects. For example, in the case of indinavir (Crixivan), the drug crystallizes in the urine causing kidney stones, proteinuria, hematuria, and pyuria. It can also cause azotemia and renal atrophy with long-term use in some cases.[2] A lipodystrophy syndrome occurs with use of various protease inhibitors, in which subcutaneous fat is lost in the extremities while central obesity develops along with various abnormalities of serum lipid levels and glucose tolerance.[3] It has been clearly shown that protease inhibitors significantly increase the risk of myocardial infarction.[4] Up to 73% of patients in one study of an HAART combination suffered mild-to-moderate nervous system side effects (anxiety, agitation, etc.) and a third had loose stools.[5] The drug stavudine has been associated with severe liver damage.[6]

Hence, the development of effective adjuncts and alternatives to antiretroviral drugs remains a priority. This chapter reviews the evidence that herbs that improve immune function may be beneficial in people infected with HIV or suffering from acquired immunodeficiency syndrome (AIDS). See Table 17-1 for a complete list of immunomodulators that might potentially be of benefit for people infected with HIV.

ECHINACEA: THEORY VERSUS REALITY

Echinacea purpurea (purple coneflower or echinacea) is a popular herb used originally by Native Americans and known to have immune-enhancing effects in humans. In the test tube, echinacea flower and leaf extracts, particularly polysaccharides, can be shown to increase production of tumor necrosis factor (TNF).[7] TNF has been shown to contribute to the pathogenesis HIV-related disease in complex ways.[8] Interestingly, HAART has been shown to cause an imbalance in TNF production that is believed to contribute to lipodystrophy.[9] However, large polysaccharides are poorly absorbed when given orally to humans. Studies on oral dosing of echinacea in people operated on for cancer have not documented an increase in serum TNF levels.[10] This is particularly true when root extracts of *Echinacea purpurea*, *Echinacea angustifolia*, or *Echinacea pallida* are given, as polysaccharide levels are not as high as in the above-ground parts of the plant. Additionally, roots were traditionally and are often still given as tinctures with high ethanol content, which do not extract those polysaccharides very well. In any event, the old theory that echinacea should not be given to people infected with HIV does not appear valid.

Table 17–1. Immunomodulators Potentially Beneficial for People Infected with HIV

Category	*Examples*	*Notes*
Echinacea	*Echinacea angustifolia* (narrow-leaf coneflower) *Echinacea pallida* (pale coneflower) *Echinacea purpurea* (purple coneflower)	Preliminary clinical trial results promising.
Araliaceae family	*Aralia racemosa* (California spikenard) *Eleutherococcus senticosus* (eleuthero) *Panax ginseng* (Asian ginseng) *Panax quinquefolius* (American ginseng)	Eleuthero looks promising in preliminary clinical trials. Asian ginseng shows benefits in vitro. Other herbs have not been studied.
Polysaccharide-containing	*Althea officinalis* (marshmallow) *Althea rosea* (hollyhock) *Symphytum officinale* (comfrey)	Purely theoretical.
Mushrooms	*Coriolus versicolor* (cloud mushroom) *Ganoderma lucidum* (reishi) *Grifola frondosa* (maitake) *Lentinula edodes* (shiitake)	Reishi shows effects in vitro; all are theoretical, clinically speaking.
Miscellaneous	*Andrographis paniculata* (andrographis) *Astragalus membranaceus* (huang chi) *Commiphora molmol* (myrrh) *Eupatorium perfoliatum* (boneset) *Glycyrrhiza glabra* (licorice) *Ligusticum porteri* (oshá) *Ligustrum lucidum* (privet) *Schisandra chinensis* (schisandra) *Withania somnifera* (ashwagandha)	Licorice repeatedly helpful in clinical trials (also antiviral and hepator-estorative). European mistletoe promising in early clinical trials. All others are purely theoretical.

The question remains: what is the effect of echinacea on people infected with HIV? When white blood cells (particularly monocytes, natural killer cells, and other lymphocytes) from people with AIDS are incubated with echinacea extracts, a definite stimulation of their activity is detected.[11] Because the activity of these cells is decreased in people infected with HIV, it makes sense that agents that can stimulate activity of the cells might be beneficial.

A double-blind trial is in progress to determine what happens when echinacea is given to people infected with HIV. Preliminary results involving 12 patients taking 1 g three times daily of an unspecified *Echinacea angustifolia* extract or placebo have shown that those taking the

echinacea have dramatic improvements in immune function.[12] Those taking placebo did not have noticeable changes in immune function. The duration of the study was 16 weeks. Subjects were either on a stable drug treatment regime or no treatment prior to enrollment in the study.[12] The study is slated to enroll 60 patients; total and final results are eagerly anticipated. This study provides some of the strongest information yet that echinacea, and possibly other immune herbs, may be extremely beneficial to people living with HIV. Note that the results of this study also run counter to the *theoretical* contraindication of using echinacea in HIV infection and AIDS listed in the German Commission E monograph.[13]

EUROPEAN MISTLETOE: DRUIDIC REMEDY GOES MODERN

Viscum album (European mistletoe) leaf has been used since ancient times for a variety of ailments. European mistletoe parasitize oak trees (among other tree species) and were long considered a sacred symbol and potent medicine by the druids. Similar to the situation with echinacea, in vitro studies originally found that European mistletoe increased TNF production by leukocytes. Unlike echinacea, European mistletoe also induces TNF secretion when given intravenously and orally to humans.[14] Thus there has been a warning that European mistletoe is theoretically contraindicated in HIV-infected persons. However, this is counterbalanced by the results of test tube studies showing that aqueous European mistletoe extracts inhibit the toxicity of HIV toward human cells and inhibit reverse transcriptase.[15]

An uncontrolled preliminary trial showed that regular subcutaneous injection of European mistletoe extracts has no negative effects in people infected with HIV. In fact, the 12 people with initially symptomatic infection followed in this study for six years were found to have stable CD4+ lymphocyte counts and signs of clinical improvement.[16] These encouraging clinical results hardly suggest that European mistletoe's TNF-increasing effects make it contraindicated for HIV+ persons.

A follow-up dose escalation study in 40 HIV+ patients also found strong signs of immune enhancement, including a 20% or greater increase in CD4+ lymphocyte levels in 28 of 36 (77%) participants after 12 weeks of therapy.[17] This study also employed subcutaneous injection of special European mistletoe extracts (sold under the trade name Iscador in Europe), 0.01–10 mg twice weekly for 18 weeks. Subjects tended to have mild, transient fever and erythema and pruritus at the injection site on the day of injection but no other signs of adverse effects. Another study has confirmed that the only significant adverse effects are local irritation, and that there are important immunological effects in HIV+ patients using subcutaneous European mistletoe injections.[18] Whether oral European mistletoe would have the same effects as subcutaneous injections is unknown but appears unlikely. Further study is warranted using injectable European mistletoe extracts as an adjunct therapy to antiretroviral drugs and natural therapies.

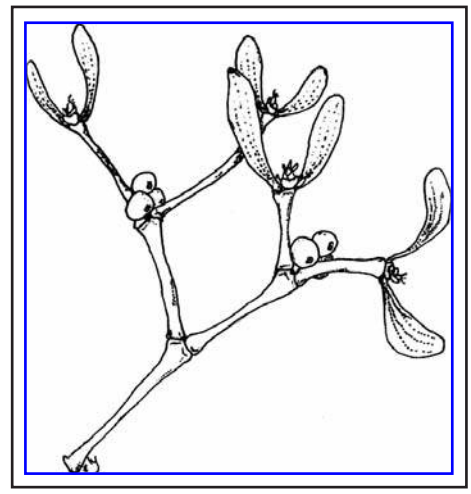

Figure 17–1. *Viscum album* (European mistletoe)
Drawing ©2000 by Eric Yarnell, ND, RH.

MISCELLANEOUS IMMUNOMODULATORS

Results with most other immunomodulating herbs are more preliminary than for echinacea and European mistletoe. For example, Russian research on *Eleutherococcus senticosus* (eleuthero or Siberian ginseng) root and rhizome have reportedly been studied in a handful of people with AIDS.[19] Profound increases in CD4+ lymphocyte levels were noted after regular oral ingestion of an eleuthero extract known as PCM-4. It is surprising that no published reports have since been issued on the use of eleuthero in people infected with HIV. We have used eleuthero and other Araliaceae family immunomodulators, particularly *Panax ginseng* (Asian ginseng), in HIV+ patients with good success. Asian ginseng extracts have proven to be immune stimulating when incubated with the leukocytes of people infected with HIV. A double-blind trial of eleuthero and/or Asian ginseng is definitely warranted.

Ganoderma lucidum (reishi) mushroom is one of several fungal immunomodulators in use for thousands of years or more in Asia. There are preliminary data that reishi stimulates activity of T helper cells taken from people infected with HIV or with AIDS.[20] Several constituents have been identified in reishi that are HIV protease inhibitors in vitro.[21] No clinical trial results were located in the literature. One of the authors, Dr. Yarnell, has often included reishi and related mushroom immunomodulators in complex treatment protocols for HIV-infected patients and seen good results. Double-blind clinical trials of mushroom immunomodulators alone, combined with other immunomodulators and natural antivirals, and antiretroviral drugs are definitely indicated.

LICORICE: ANTIVIRAL, IMMUNOMODULATOR, OR BOTH?

Two of the most thoroughly studied botanical immunomodulators in HIV-infected individuals are the European plant *Glycyrrhiza glabra* (licorice) and its close Asian cousin *Glycyrrhiza uralensis* (gan cao). Licorice, particularly its main active glycoside known as glycyrrhizin, appears to act both as an immunomodulating agent and an antiviral, an ideal combination when addressing HIV infection. Additionally, intravenous glycyrrhizin has been shown to improve liver function in uncontrolled clinical trials when it is compromised in HIV-infected individuals.[22]

Intravenous glycyrrhizin has been used in Japan to treat people infected with HIV since the 1980s. Early uncontrolled clinical trials found that this therapy was very effective at suppressing levels of HIV.[23] Intravenous glycyrrhizin in combination with glycine and cysteine (known as Stronger Neo-Minophanen C or SNMC in Japan) was also effective in combination with didanosine (ddI) in two patients.[24] SNMC was later demonstrated beneficial in a longer term but still uncontrolled study.[25]

Intravenous glycyrrhizin is clearly not optimal therapy given the inconvenience and expense of intravenous injection. At least three long-term studies conducted in Japan have shown that oral administration of glycyrrhizin is also effective at maintaining immune function and suppressing HIV replication in those infected with the virus.[26–28] Though most of these trials were uncontrolled, at least one compared glycyrrhizin therapy to no treatment. In this trial, none of the 10 patients taking glycyrrhizin progressed over one year's time, whereas two patients receiving no treatment developed AIDS and died. Another study followed 16 asymptomatic HIV-infected patients for 3–7 years. None of the participants progressed clinically and lymphocyte levels remained stable. No adverse effects were noted. Similar results were seen in the other trial involving oral glycyrrhizin.

The dose of glycyrrhizin employed in these studies was 150–225 mg daily in divided doses. This dose is sufficient to induce the pseudoaldosteronism syndrome in some patients. Because glycyrrhizin suppresses cortisol catabolism by the liver and kidney, cortisol levels increase during therapy with this agent. Cortisol weakly agonizes mineralocorticoid receptors, leading to increased potassium excretion by the kidney. If this process lasts too long, hypertension, edema and related weight gain, and more serious problems can develop. The risk of all of these side effects can be reduced by administering potassium concomitantly with glycyrrhizin, including eating a diet high in fruits and vegetables. Blood pressure can be monitored to detect early onset of pseudoaldosteronism, which should be confirmed in more serious cases by serum cortisol and potassium measurements. Note that none of the three trials of oral glycyrrhizin led to the development of pseudoaldosteronism.

The results from these trials on licorice are perhaps the most exciting of any immunomodulating botanical. Double-blind trials of whole licorice extracts providing 150–225 mg glycyrrhizin per day are urgently needed. Extracts of this sort are widely available. Because licorice contains other potential constituents besides glycyrrhizin, whole plant extracts should be studied and not just isolated glycyrrhizin. The two should be compared head-to-head to determine relative efficacy and safety. Note that deglycyrrhizinated licorice (DGL), popular and effective for treating peptic ulcer and aphthous stomatitis, would be very unlikely beneficial for inhibiting HIV or stimulating the immune system.

CONCLUSION

In sum, botanical immunomodulators are mostly in infant stages of clinical research as therapy for people infected with HIV. HAART therapy carries a high risk of toxicity and induction of drug resistance. Additionally, its high cost makes it almost completely unavailable to the vast majority of HIV-infected people around the globe. Therefore safe, inexpensive new therapies are needed. Licorice, echinacea, European mistletoe, eleuthero, reishi, and other immunomodulating natural products alone, combined with one another, and combined with antiretroviral drugs should all be studied as they are quite promising therapeutic options.

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18

TREATING ESSENTIAL HYPERTENSION BOTANICALLY

Many individuals worldwide suffer from elevated blood pressure that increases their risk of numerous serious conditions including atherosclerosis, myocardial infarction, stroke, and renal failure. There is no single treatment for hypertension because there are many subcategories of hypertension based on etiology and risk factors as well as the unique constitution of the individual. This chapter deals with the treatment of people suffering so-called essential hypertension. We focus on specifically reducing blood pressure readings and clinical symptoms, and touch on the use of botanicals to address either the underlying causes of hypertension or to strengthen other systems that are taxed in the hypertensive patient.

A single blood pressure reading should never be used to diagnose chronic hypertension. Instead, at least three readings on different days are required. To reduce error, these readings should be conducted by the same person using the same equipment, at the same time of day, and in the same setting. The official criteria defining hypertension in the United States are set by the Joint National Committee (JNC) on detection, evaluation, and treatment of high blood pressure. Table 18-1 shows the official criteria set by JNC in 1993 and their revision downward in 2003.

It should be noted that all of the 11 lead authors/main members of the Joint National Committee VII have been paid, in one form or another, by pharmaceutical companies that sell antihypertensive medications.[1,2] Clearly the guidelines are politically influenced and may not represent the best interests of patients (to the JNC's credit, however, their guidelines were not directly funded by the drug companies). Despite these guidelines and the existence and widespread prescription of over 100 antihypertensive drugs, as many as one in three Americans still has hypertension and the number who have it under control has only improved slightly in the past 10–20 years.[3] One analysis found that 40% of prescription antihypertensives are incorrect based on published guidelines.[4] The pharmacological approach used in most conventional medical settings leaves much to be desired, and leaves ample room for natural alternatives.

IMPORTANCE OF LIFESTYLE CHANGES

Essential hypertension largely results from various lifestyle abuses. These include excessive salt consumption; borderline micronutrient intake (calcium, magnesium, antioxidants, etc.); excessive simple carbohydrate, fat, and calorie intake; and a sedentary lifestyle.[5–7] These factors lead to glucose intolerance, hyperinsulinemia, atherosclerosis, sodium retention, obesity, and other problems that seem to work together to produce essential hypertension.

Drug therapy has been the mainstay for combating essential hypertension in most allopathic settings. This is unfortunate because dietary therapies, exercise, and weight loss are often able to correct the problem without medication. This approach does require a lot of patient motivation and support, because it usually represents a significant change in lifestyle, a difficult (but not impossible) feat for everyone. One highly telling illustration of the power of lifestyle in eliminating hypertension was a study known as the Dietary Approaches to Stop Hypertension.[8] This study randomized 459 adults with hypertension to a diet rich in fruits and vegetables but not re-

Table 18–1. Changing Standards for Hypertension

JNC V Stage	*Systolic (mmHg)**	*Diastolic (mmHg)*	*JNC VII Stage*	*Systolic (mmHg)*	*Diastolic (mmHg)*
Normal	<130	<85	Normal	<120	<89
High Normal	130–139	85–89	Pre-hypertension	120–139	80–89
1 (mild)	140–150	90–99	1	140–159	90–99
2 (moderate)	160–179	100–109	2	>159	>99
3 (severe)	180–209	110–119			
4 (very severe)	>209	>119			

*Note: All blood pressure readings must be elevated on three separate occasions.

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duced in fat content; a diet rich in fruits, vegetables, low-fat dairy products, and low total and saturated fat; or no change from their usual diet. The reductions in blood pressure were substantial in the altered diet groups, particularly the low-fat diet. Sodium chloride intake and physical activity were not modified in this trial, which would likely have added even greater benefits. A recent review article provides interesting detail on the obesity–hypertension connection.[9]

Every patient with essential hypertension should first be approached in terms of helping him or her change lifestyles. Additional measures to lower blood pressure are needed in many cases. In a patient with mild or moderate hypertension that fails to fully respond to lifestyle changes, botanical therapies can be of great benefit. Additionally, some people improve partially with lifestyle changes, but continue to have mild hypertension or high normal blood pressure. In such cases, mild, safe botanical medicines often result in complete normalization of blood pressure. Prescription medications should be reserved for cases of malignant hypertension (when severe or very severe hypertension exists), and for cases where lifestyle changes and botanicals fail to bring about a change in blood pressure. Extra caution is needed in the elderly (over 70 years old) as the cardiovascular benefit of these drugs may come at the expense of increased overall mortality.[10]

IN THE BEGINNING, THERE WAS SNAKEROOT

One botanical medicine actually helped launch the pharmacological approach to patients with hypertension, and has quite a strong physiologic effect. This plant is *Rauvolfia serpentaria* (Indian snakeroot, or rauwolfia) of the Apocynaceae family and grows primarily in southern Asia, particularly India. Known as sarpagandha or chandrika in Sanskrit, it has long been used in Ayurvedic medicine as a remedy for among other ailments, insanity, snake bite, and dysentery.[11]

The story of rauwolfia is a classic tale of how a botanical medicine can be preempted by pharmacological medicine, be turned into a drug, find great utility, then ultimately be maligned and rejected in favor of more expensive but not safer or more effective synthetic drugs. The

reality is that rauwolfia is one of the most effective therapeutic options in patients, with mild to moderate essential hypertension not improved by lifestyle changes.

The Latin name *Rauvolfia* is taken from the 16th century German botanist and adventurer Leonhard Rauwolf. The plant was named after Rauwolf nearly a century after his death based on his popular exploits traveling around Asia exploring the use of indigenous plants. Already in wide use in India and possibly already known in Europe and China as well, rauwolfia would over time come into wider and wider use. Though rauwolfia appears to have initially been used primarily to treat people with schizophrenia, the doses involved were high and often led to adverse effects. Apparently the antihypertensive actions of rauwolfia were noted incidentally during European use of rauwolfia. It is not entirely clear if rauwolfia was used to treat patients with hypertension in Ayurvedic medicine, both because Ayurvedic conceptions of disease differ from those in modern biomolecular medicine, and because hypertension was far less common prior to the modern industrial revolution.

Rauwolfia contains several alkaloids, particularly reserpine (first isolated in 1952) and ajmaline. Reserpine and other rauwolfia alkaloids bind irreversibly to catecholamine storage granules in neurons, primarily those in the midbrain autonomic centers and cells in the adrenal medulla.[12] They then cause a depletion of catecholamines and 5-hydroxytryptamine from those granules. The result is a lessening of systemic sympathetic tone and reduction in blood pressure. This is an entirely central mechanism of action—there is no effect directly on the blood vessels or heart. Ajmaline and possibly other rauwolfia alkaloids also have an antiarrhythmic action.[13]

THE ABSURD DOWNFALL OF RESERPINE

Initially, whole extracts of rauwolfia root were used clinically for their antihypertensive effects. The growing dominance of the reductionist model, however, pushed chemists to isolate reserpine and its use was then promoted as a drug. The heroic medical model pushed clinicians to think that if a low dose of the new drug reserpine could lower blood pressure somewhat, then a higher dose could lower it even more. The ultimate result was overdosing and induction of severe adverse effects leading to the erroneous view that neither low-dose reserpine nor whole rauwolfia should be used, despite critical differences between high-dose reserpine and these treatments.[14]

In fact, low-dose reserpine (meaning 0.05–0.25 mg once daily) combined with a thiazide diuretic was the first therapeutic combination shown to reduce the various adverse effects of chronic hypertension including stroke in large, double-blind trials.[15,16] In these and other large-scale clinical trials, adverse effects were relatively mild. The most common was nasal stuffiness, which was reported by up to 20% of participants. Transient loose stools were also occasionally encountered. Depressed mood was encountered only extremely rarely. Low-dose reserpine was frequently combined with a thiazide diuretic in clinical trials. This category of drug is associated with hypokalemia, hypomagnesemia, and dyslipidemia. However, the adverse effects of thiazides on minerals can usually be overcome by increasing fruits and vegetables in the diet and taking a potassium–magnesium supplement. In addition, low-dose reserpine has been shown to counteract the adverse effects of thiazides on lipid levels in some trials.[17]

In contrast, high-dose reserpine (0.5–1 mg or higher daily) is associated with frequent adverse effects of a more serious nature. Depletion of catecholamines by excessive reserpine can cause impotence, depression, Parkinsonism, and peptic ulcer. Low-dose reserpine has been repeatedly shown to be unrelated to impotence,[18] depression or Parkinsonism,[19,20] or peptic

18–1. *Rauwolfia, Reserpine, and Drug Interactions*

Reserpine is highly protein bound and may interact with other protein-bound drugs. These include aspirin, most nonsteroidal anti-inflammatory drugs, all HMG CoA reductase-inhibitors except pravastatin, loop diuretics, paroxetine, penicillin, phenytoin (Dilantin), propranolol, sulfonylureas, thyroxine, triiodothyronine, and warfarin (Coumadin). If reserpine or rauwolfia is combined with these drugs, one or the other may be displaced from albumin, leading to increased activity and/or toxicity. Caution is warranted.

Reserpine is synergistic and safe combined with thiazide diuretics and hydralazines. However, it may cause hypotension when combined with any antihypertensive agent. Monoamine oxidase inhibitors, tricyclic antidepressants, and possibly selective serotonin-reuptake inhibitors and related agents may all interfere with the efficacy of reserpine. Actions of direct-acting sympathomimetics are prolonged by reserpine, whereas those of indirect-acting agents are inhibited.

ulcer.[21] A reported association between reserpine and breast cancer in case-control studies reported in 1974 was ultimately proven spurious after 10 subsequent rigorous studies found no connection.[22] The original studies had design flaws that caused the false connection between reserpine and cancer, but unfortunately the connection stuck and the subsequent proof of its falsity was largely ignored. The theory that sympathetic blockade due to reserpine could lead to difficulties if the patient went into shock or was hemorrhaging have not been investigated in any rigorous way.

In sum, low-dose reserpine is extremely safe, as well as far cheaper than any synthetic antihypertensive drug.[18] There are some drug interactions with reserpine that should be carefully noted (see Sidebar 18-1). It is effective in a wide range of race and age groups with hypertension, particularly when combined with a thiazide diuretic (and a potassium–magnesium supplement to offset mineral losses from the diuretic). Reserpine has a long half-life, so convenient once-daily dosing is appropriate. A trial of reserpine should almost universally be given to patients before other, more expensive antihypertensive drugs are explored as long as the patients do not have a history of depression or Parkinson's disease, and are not allergic to reserpine, pregnant, or lactating.[23] If reserpine alone is insufficient, an herbal diuretic should be added, if that is insufficient, a thiazide diuretic and potassium–magnesium supplement should be added,[24] and a synthetic antihypertensive resorted to only if these options fail.

WHOLE RAUWOLFIA VERSUS ISOLATED RESERPINE

Whole rauwolfia root extracts contain multiple alkaloids and other constituents and may be comparable or superior to isolated reserpine. Several old reports suggest that crude extracts of rauwolfia are comparable to isolated reserpine.[25] Dr. Weiss, with vast experience using plants, felt that the whole plant had better overall efficacy and was safer than isolated reserpine.[26] Unfortunately, modern science without investigation decided that such extracts were unreliable and thus not worth pursuing, instead opting for the single-agent drug model. While the reserpine content of older extracts may have varied too much, this single-agent method threw out the important concept and potential benefits of synergism of action of multiple compounds within

the plant without adequate study. Today, newer technologies allow for more rigorous control over crude extracts by sampling marker compounds in each batch to ensure that a set range or critical compounds are always present.

In the case of rauwolfia, the marker compound is obvious: reserpine. This marker compound has the advantage that it is clearly a critical component in the efficacy of rauwolfia. Thus, extracts standardized to reserpine content can allow for exact, reliable dosing without losing the other active and supporting constituents in rauwolfia. Because of the potential adverse effects of excessive reserpine, and because an inadequate dose will not adequately lower blood pressure, nonstandardized rauwolfia extracts are not recommended.

The best standardized product in the United States that we are aware of is a tincture of the root made by HerbPharm of Williams, Oregon. This product contains 0.1 mg reserpine per 4 drops of tincture. The initial loading dose is approximately 4 drops two or three times a day for a week. The dose should then be decreased to 4 drops once a day. In cases of mild hypertension, 2 drops once a day may be sufficient. The dose may have to be adjusted until blood pressure is normalized. A maximum of 5 drops twice a day (i.e., 0.25 mg reserpine per day) is recommended to avoid serious adverse effects. If this dose is not sufficient, then a thiazide diuretic should be added along with potassium–magnesium, and possibly *Allium sativum* (garlic) if the thiazide causes prolonged dyslipidemia not offset by the rauwolfia. Note that because of the long half-life of reserpine, its effects will not wear off immediately upon discontinuation, and it will take some time (a few days) for its effects to be noticed. Thus, rauwolfia is not appropriate for the immediate blood pressure lowering needed in cases of malignant hypertension.

UNCERTAINTY ABOUT EUROPEAN MISTLETOE

No botanical remedy for hypertension besides rauwolfia has been subjected to repeated, rigorous, large-scale clinical trials. Hence, no botanical remedy has consistently shown antihypertensive effects across a broad range of the population with hypertension. Nevertheless, many other botanical medicines have some potential efficacy and deserve further research. *Viscum album* (European mistletoe) leaf is one such remedy, though its effects in hypertensive patients have probably been overstated.

European mistletoe has a long history of ritual and medicinal use, as evidenced by the modern continuation of the pagan ritual of kissing someone caught standing under mistletoe at winter solstice (adopted at Christmas by Christianity). The use of European mistletoe for hypertension is not as ancient, only having been accepted to any large degree in Europe just after the turn of the century.[27]

In a case series involving 100 patients with hypertension, 2.5–5 ml of a tincture of dry mistletoe three times daily lowered blood pressure significantly in 25% of the study participants.[28] Interestingly, 75% of study participants reported improvement in headache and dizziness. Most practitioners recommend use of a cold infusion of European mistletoe leaf, not the alcoholic tincture used in the study that may have affected the results.[29] The crude aqueous extract of the leaf has an antihypertensive effect in spontaneously hypertensive rats.[30,31] Flavonoid and other extracts of European mistletoe were weakly vasodilating in vitro.[32]

Still, drastic changes in blood pressure in response to European mistletoe are rare. However, thoroughly controlled trials have not been conducted, and no definite conclusions regarding its benefits can be drawn at this point in time. In our opinion, European mistletoe may have some role in reducing symptoms of hypertension, but cannot be relied upon as a single therapy.

The toxicity of European mistletoe has been greatly exaggerated. Clinically, no adverse effects are associated with use of the cold infusion prepared by steeping 2–4 tsp (5–20 g) of the leaf in water overnight (or throughout the day) in 250 ml of water. The dose is 250 ml twice per day. American mistletoe, *Phoradendron* spp., a close cousin of *Viscum*, is a very different plant that appears to have a hypertensive effect.[33] Nevertheless, the toxicity of American mistletoe has been exaggerated as well. One study found that 96% of people who reported accidental ingestion of mistletoe of any kind had no symptoms without receiving any therapy, 99% had no long-term effects, and there were no deaths.[34]

HIBISCUS

Hibiscus sabdariffa (hibiscus, sour tea, roselle, flor de jamaica) is a plant much loved for its beauty as well as the flavor of its flower in beverage teas. In a recent trial, hibiscus extract (250 mg anthocyanins/dose) was compared with a 10 mg dose of lisinopril in a randomized, controlled, double-blind clinical trial. A total of 168 patients completed the four-week long trial. Hibiscus reduced blood pressure to, on average, 130/86, whereas lisinopril reduced it to

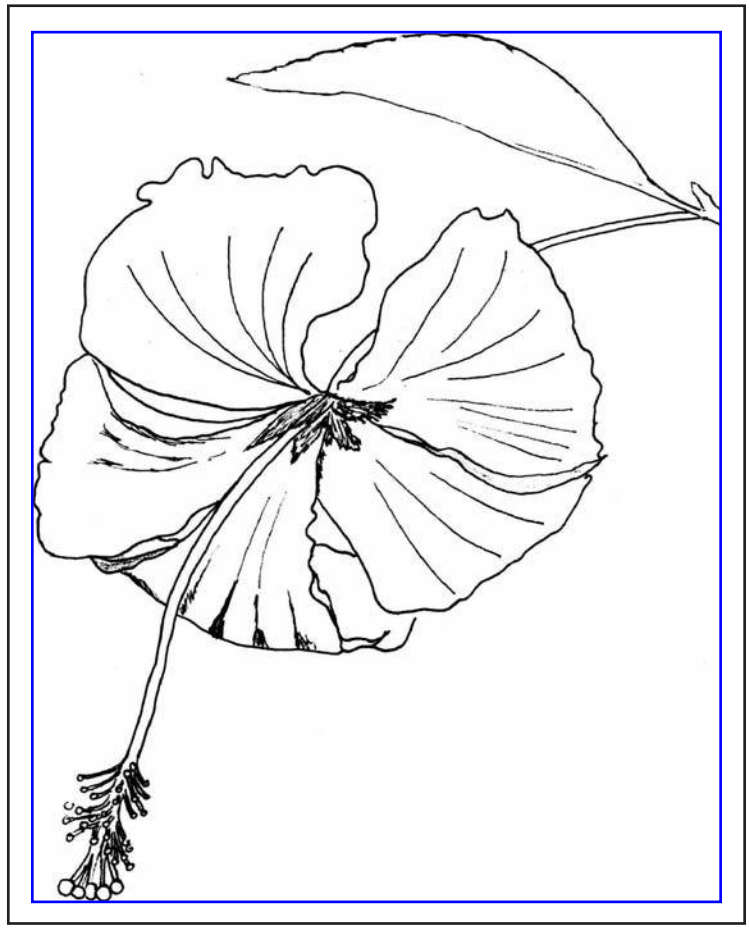

Figure 18–1. *Hibiscus rosa-sinensis* (Chinese hibiscus)
Drawing by Eric Yarnell, ND, RH.

122/82. Hibiscus was deemed to have both a potassium-sparing diuretic and an ACE-inhibitory action as well as some hypocholesterolemic and antiatherosclerotic actions.[35] To evaluate the traditional reputation of hibiscus flower as a hypotensive, a randomized, controlled clinical trial was conducted in 54 men and women with hypertension in Tehran, Iran.[36] Volunteers took either hibiscus tea or black tea (*Camellia sinensis*) in the very low dose of 1 cup (250 ml) of tea daily (2 tbsp (10 g) herb/cup of water) for 12 days. Though the trial was supposedly double blind, it is hard to imagine that the subjects were not able to tell by taste which tea they were drinking. There was a significantly greater drop in blood pressure in the hibiscus group compared to the regular tea group. There were no adverse effects. In another trial, 39 patients were given a daily dose of 10 g hibiscus in 0.5 L water before breakfast while another 36 patients were given captopril (25 mg twice daily). Both treatments reduced blood pressure similarly.[37] The results of these initial trials suggest that this benign, tasty botanical medicine will prove highly useful in patients diagnosed with mild to moderate hypertension. More research is needed to determine if *H. rosa-sinensis* is a possible substitute for *H. sabdariffa*.

REISHI, AN ANTIHYPERTENSIVE MUSHROOM

Ganoderma lucidum, G. japonicum, or *G. tsugae*, known as reishi in Japanese and ling zhi in Chinese, is a medicinal mushroom of great importance in traditional Asian medicine.[38] The fruiting body has been adopted by Western herbal practitioners as an immunomodulator, hypnotic, hepatoprotectant, and antihypertensive. There are at least two classes of major active constituents in reishi polysaccharides, believed to primarily affect the immune system and liver, and triterpenoids, believed to lower blood pressure and affect the nervous system.

The triterpenoids (the ganoderic acids) have shown angiotensin-converting enzyme-inhibiting effects in vitro.[39] An animal study suggested reishi might also work through central inhibition of sympathetic outflow, somewhat similar to reserpine.[40] The latter study utilized an extract of the mycelium of reishi, suggesting that extracts combining fruiting body and mycelium might be optimal to achieve all that reishi has to offer.

At least two controlled clinical trials have assessed the efficacy of reishi as a hypotensive (some trials not available in English also appear to show efficacy in this area).[41] In the most recent trial, 54 men and women with moderate hypertension who had not responded to captopril or nimodipine alone after one month were randomized to receive 55 mg of reishi extract three times daily or placebo (the synthetic drugs were continued simultaneously).[42] Reishi significantly lowered blood pressure compared to baseline, whereas placebo had no such effect. A less rigorous prior trial showed that 240 mg of a different reishi extract six times daily had hypotensive effects.[41] No adverse effects were encountered in either trial. More research is obviously needed to confirm these preliminary results, but it appears that reishi's reputation as a mild, completely safe hypotensive is deserved.

THE STINKING ROSE

Allium sativum (garlic) bulb's primary uses continue to be countering of atherosclerosis and dyslipidemia. There are surprisingly few trials that have specifically addressed whether garlic lowers blood pressure. A meta-analysis of three trials that specifically included hypertensive subjects as well as four others that included some patients with hypertension incidentally, found that garlic had a mild hypotensive effect overall.[43] The authors of this meta-analysis state that

most of the trials they looked at were relatively small; some had inappropriate randomized methodologies, did not last very long, and had other problems. This increased the likelihood that the apparent hypotensive effect of garlic was the result of chance. All of the studies assessed used a dried garlic powder standardized to allicin content (amount unspecified), 300 mg two to three times per day, equivalent to a single clove of fresh garlic per day.

Garlic is obviously widely consumed as food, and has almost no adverse effects. Some people dislike the body odor associated with garlic use, and some develop gastrointestinal irritation and, in extremely rare instances, easy bleeding. Garlic should be a component of the diet of any hypertensive patient. Uncooked, chopped, fresh garlic appears to be most effective. If the patient is unwilling to eat raw garlic, then encapsulated products containing allicin can be used. Enteric coating reduces odor with these products, but "odorless" products devoid of allicin (e.g., garlic oil or aged garlic extract) have not been demonstrated to have the same effects as allicin-containing products except at exorbitant doses and should be avoided.

HAWTHORN, OLIVE LEAF, AND HYPERTENSION

Crataegus laevigata (hawthorn), formerly *C. oxyacantha*, and its close cousins *C. monogyna*, *C. piperi*, *C. rivularis*, and *C. douglasii* commonly find their way into hypertension formulae prescribed by botanical medicine practitioners. The leaf, flower, and fruit of this Rosaceae family plant are all utilized. There is little human research documenting an antihypertensive effect of hawthorn, though it may have some beneficial effects on the hearts of patients affected by hypertension.[44,45] Some older case studies suggest hawthorn may be hypotensive,[46] but apparently no one has attempted to confirm these results in controlled trials. Hawthorn is completely nontoxic and may be useful as a cardiovascular tonic in the overall treatment of patients with hypertension but used alone is extremely unlikely to lead to major, measurable decreases in blood pressure in all but the rarest patient.

The oil of *Olea europaea* (olive) is well known to most, but it is the leaf of this important plant that primarily finds use as medicine. The leaf is rich in flavonoids, bitter terpenoids, and glycosides, all of which may be clinically active. Extracts of olive leaf have been touted for treatment of hypertensive patients, though there is little research support for this idea. One double-blind trial conducted for three months apparently found no difference between 400 mg olive leaf extract four times daily and placebo in lowering blood pressure.[47] Because the original trial was published in French, we had trouble obtaining details about the exact nature of this study or its exact results. For example, some but not all of the subjects in the trial apparently continued to take synthetic antihypertensive medications during the trial. Isolated triterpenoids from three species of olive leaf prevented the development of severe hypertension and atherosclerosis and improved insulin resistance in a rat model of salt-sensitive, insulin-resistant hypertension leading to speculation that olive leaf might provide an inexpensive treatment for the common salt-sensitive hypertension typically found in the African population.[48] However, pending publication of positive controlled clinical trials, there is little basis on which to recommend olive leaf for people with hypertension.

THE PRIMACY OF THE KIDNEY

It has becoming increasingly clear that patients with essential hypertension often have a disordered renin-angiotensin-aldosterone (RAA) system (see Figure 18-2). As clinicians begin to

measure plasma aldosterone and renin levels, and compare their ratio, they have found that 8–15% of hypertensive people and randomly screened adults have elevated aldosterone levels.[49–51] This points strongly to the kidneys and adrenal glands as major sources of causative processes in essential hypertension.

It has been proposed, in particular by the original discoverer of the RAA system's role in regulating blood pressure, Dr. John Laragh, that by assessing RAA system metabolites, treatment of people with hypertension can be better individualized.[52] This hypothesis has only been applied to drugs and lifestyle, though some aspects of herbal therapy may also be guided by this system. According to the renin hypothesis, plasma renin activity (not the less accurate direct plasma renin levels) is measured, and if it is below 0.65 ng/ml/hr, the patient is said to have low-renin or sodium-volume hypertension.[53] When the value is above 0.65, the patient is said to have high-renin or vasoconstrictive hypertension. Low-renin hypertensives should be evaluated for the possibility of an adrenal cortex adenoma causing surgically curable primary aldosteronism (fairly rare).

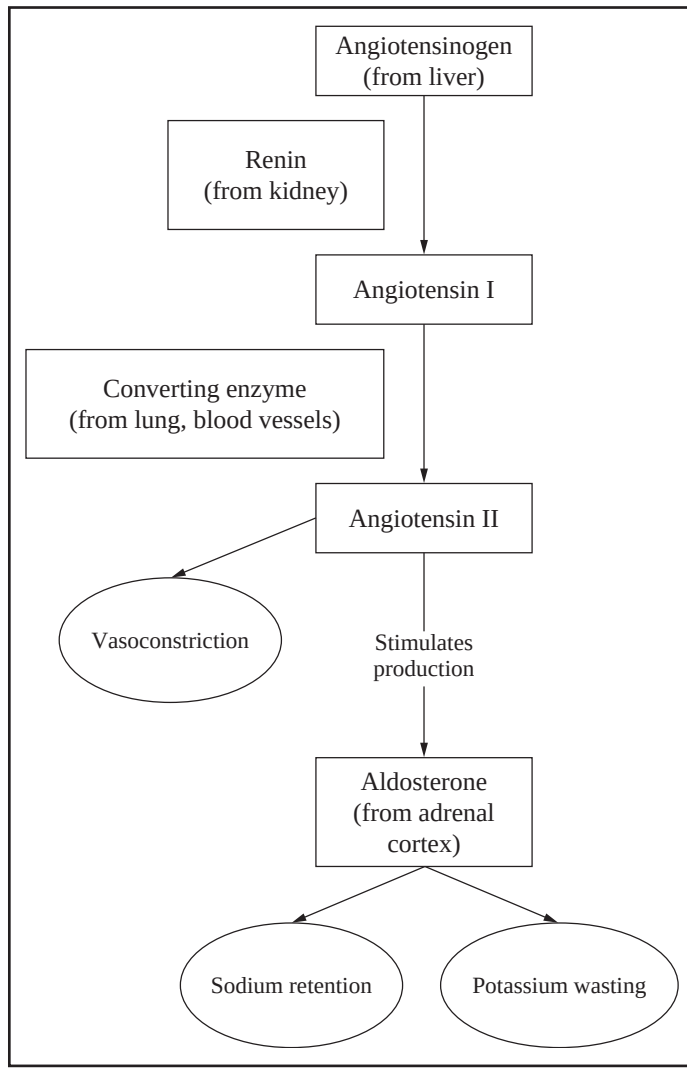

Figure 18–2. RAA Axis

Patients with sodium-volume hypertension are believed to respond best to dietary salt restriction (and presumably increased water intake), though this has not been systematically evaluated. Most studies on salt restriction have not checked renin levels to determine if this can predict who will respond.[54] Diuretic herbs, all of which appear to be potassium-sparing and themselves to contain significant potassium (if taken as teas, powders, or food), would be most indicated, such as *Taraxacum officinale* (dandelion) leaf, *Apium graveolens* (celery) seed or root, *Solidago canadensis* (goldenrod) flower top, *Urtica dioica* (nettle) leaf, or *Levisticum officinale* (lovage) leaf. Patients with low-renin hypertension are much less likely to suffer disastrous consequences of their hypertension, as borne out in large-scale clinical trials.[55]

Patients with vasoconstrictive or high-renin, high-angiotensin hypertension are most likely to respond to *Rauvolfia serpentaria* (Indian snakeroot), a vasodilator with unique actions as discussed above. Angiotension converting-enzyme (ACE) inhibitors are also generally more effective. A total flavonoid extract of *Astragalus complanatus*, a relative of *Astragalus membranaceus*, has been shown to lower blood pressure in rats by antagonizing angiotensin II.[56] In a rodent study, *Salvia miltiorrhiza* has demonstrated ACE inhibiting activity leading to reduced blood pressure.[57] Similar reports exist for *Allium sativum* (garlic) and *A. ursinum* (wild garlic); *Crataegus* spp. (hawthorn); *Vaccinium macrocarpon* (cranberry)—particularly when coupled with *Rosmarinus officinalis* (rosemary); *Panax ginseng* (Asian ginseng); *Rhodiola crenulata* (rhodiola); and *R. rosea* (rose root) among many others.[58–62] One of the clinical trials conducted on hibiscus discussed above found that it was a significantly active ACE inhibitor in humans.[35] Because high-renin hypertensives are at the greatest risk for catastrophic complications including myocardial infarction and strokes, they should be monitored carefully.

The interconnection between the kidney and systemic blood pressure should not be overlooked. Further effort is needed to determine which herbs that affect blood pressure do so by affecting the kidney. This understanding opens up a significant and important area for future research on hypotensive botanicals.

CONCLUSION

Lifestyle changes is the treatment of choice in patients with essential hypertension. However, because many patients are at best only partially successful at making these changes, botanical medicines should play a wider role in their treatment. Various phytomedicines are likely to prove useful to these patients (see Table 18-2). The best studied and most effective is rauwolfia or isolated reserpine. Used in the appropriate dose, this therapy is quite safe and much more cost-effective than synthetic antihypertensives. Other less well-supported but still relevant botanical remedies include reishi mushroom, garlic, and hibiscus. European mistletoe and hawthorn may have some secondary benefits for people with hypertension, but do not seem to clearly lower blood pressure directly in most patients. Olive leaf extracts have not shown efficacy in the limited clinical trial data available. Assessing the renin–angiotension–aldosterone axis may help target herbal and other therapies to underlying, important renal factors in hypertension. Prescription antihypertensives should be reserved for those patients who are not adequately benefited by lifestyle changes, nutritional supplements, and/or botanicals.

Table 18–2. Botanical Antihypertensive Agents (Sorted by Level of Support)

Botanical Agent	*Common Name**	*Part Used*	*Family*	*Level of Supporting Evidence***
Rauwolfia serpentina	Rauwolfia, Indian snakeroot	Root	Apocynaceae	1
Hibiscus sabdariffa	Roselle, sour tea	Flower	Malvaceae	1
Ganoderma lucidum	Reishi, ling zhi	Fruiting body and mycelium	Polyporaceae	2
Allium sativum	Garlic	Bulb	Liliaceae	2
Viscum album	European mistletoe	Leaf	Loranthaceae	3
Crataegus laevigata	Hawthorn	Leaf, flower, and fruit	Rosaceae	4
Olea europaea	Olive	Leaf	Oleaceae	5

*In all cases, the first or single name given is the official one listed in McGuffin M, Kartesz JT, Leung AY, et al. *American Herbal Product Association's Herbs of Commerce* 2nd ed. Silver Springs, MD:American Herbal Products Association 2000.
**1 = multiple positive controlled clinical trials; 2 = limited controlled clinical trial evidence; 3 = uncontrolled clinical trial evidence; 4 = traditional/empirical support only; and 5 = negative clinical trial evidence.

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19

IRRITABLE BOWEL SYNDROME

Botanical medicines can be a useful primary therapy for patients with irritable bowel syndrome (IBS). A meta-analysis recently concluded that all IBS treatments—allopathic and alternative—only have level B scientific support.[1] The benefit of choosing a botanical therapy is that there is a tradition going back centuries supporting the safety and efficacy of the herbs typically used in IBS along with some scientific evidence showing benefit. This chapter covers how to combine various categories of herbs into effective IBS formulas.

Patients with irritable bowel syndrome usually present with a variety of symptoms but the classic symptoms are abdominal pain, abdominal distention, and alternating periods of constipation and diarrhea. In general, constipation is more common than diarrhea but over half of IBS patients report fecal or mucous incontinence. Other common symptoms include nausea, fatigue, low-back pain, and a variety of the nonspecific gastrointestinal and extra-intestinal problems.[2] The Rome II criteria currently used to diagnose the condition are given in Sidebar 19-1. These strict criteria are used in clinical trials and are not necessarily appropriate for clinical practice, as they tend to exclude people with mild or atypical presentations.

Given the multiplicity of symptoms even in a single patient, a single herb can rarely be relied on to provide relief in clinical reality, though research trials have shown that they can improve symptoms in many patients. Examples would be *Mentha* x *piperita* (peppermint)[3] and *Cynara scolymus* (artichoke) leaf.[4] Instead, it is more effective to combine herbs with properties that

19–1. *Rome II Criteria for IBS*

Irritable Bowel Syndrome can be diagnosed based on at least 12 weeks (which need not be consecutive) in the preceding 12 months, of *abdominal discomfort or pain that has two out of three of these features*:

1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool.

Other symptoms that support the diagnosis of IBS:

Abnormal stool frequency (may be defined as greater than three bowel movements per day and less than three bowel movements per week); abnormal stool form (lumpy/hard or loose/watery stool); abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); passage of mucus; bloating or feeling of abdominal distension; fewer than three bowel movements a week; more than three bowel movements a day; hard or lumpy stools; loose (mushy) or watery stools; straining during a bowel movement; urgency (having to rush to have a bowel movement); feeling of incomplete bowel movement; passing mucus (white material) during a bowel movement; and/or abdominal fullness, bloating, or swelling.

address the varying symptoms and causes that predominate in the individual patient with IBS. Here we categorize the various types of actions desired and a selection of herbs within each from which a clinician can choose to develop the most effective, individualized formula.

BITTERS

Herbalists, both Western and Asian, usually include bitters in IBS formulas. Bitters are herbs that stimulate the function and motility of the gastrointestinal (GI) tract. They tend to increase gastric secretions, have a tonic action on the GI generally, and stimulate the exocrine pancreas.[5] In IBS, bitters are used to increase digestive function, which in turn tends to balance the intestinal flora and reduce flatulence and bloating. Patients with predominant constipation tend to respond well to bitter herbs.

Most herbs categorized as bitters have a pronounced bitter taste. This highlights that the term *bitter* refers both to flavor and activity. Some "bitters," however, do not taste bitter at all. So-called aromatic or pungent bitters, such as *Zingiber officinale* (ginger) rhizome, are also digestive stimulants but taste very pleasant. Bitters also are choleretics and cholagogues, notably *Taraxacum officinalis* (dandelion) leaf and *Fumaria officinalis* (fumitory) leaf, and may have antimicrobial actions, such as *Artemisia* spp. (wormwood and related species) herb. In our experience, these more complex bitters often work better than what are termed *simple bitters*, such as *Gentiana* spp. (gentian) root, or the pungent, warming bitters. Artichoke leaf (as mentioned above) and *Iberis amara* (bitter candytuft) herb are two other complex bitters that have benefited some patients with IBS in preliminary studies.[6]

Bitters are usually taken shortly before meals (10–30 minutes) and can be effective at fairly low doses as part of a formula. In general, a better result is obtained where the patient tastes the bitter flavor, creating a reflex digestive response that begins with increased salivary secretions. Although many Americans initially balk at the taste of bitter, most patients will accept them (and some actually come to like them) once they have experienced the benefit of improved digestion and had some time to adapt. It has been shown, interestingly, that people in closer connection with their traditional heritage often equate bitterness with medicinal actions and are more accepting of bitter tastes.[7] Although all bitter-tasting herbs are mildly laxative, they are *not* contraindicated, even in the diarrhea phase of IBS, because of their tonifying effects.

CHOLAGOGUES

Herbs that affect the gallbladder and bile release are often neglected in IBS formulas. Research, however, suggests that cholagogues (herbs that increase the flow of bile by stimulating gall bladder contraction) and choleretics (herbs that increase bile synthesis) may provide substantial benefits in IBS.

One study found that 40% of gallbladder patients had IBS symptoms before undergoing a cholecystectomy but only 33% of this subgroup had persistent symptoms a year later.[8] All patients with gallstones showed poor gallbladder contractility. In addition, IBS patients had abnormal patterns of gallbladder emptying. This fits with a pattern of general dysfunction of regulation of gastrointestinal function theorized to play a critical role in causing IBS.

Cholecystokinin (CCK) is a major hormonal regulator of gallbladder motility. A small placebo-controlled study found that IBS patients had exaggerated and prolonged CCK release and reduced motilin secretion after fatty meals and after water intake.[9] Motilin is another hormone

19–2. *Iberogast Formula*

Iberis amara (bitter candytuft) herb
Matricaria recuitita (German chamomile) herb
Mentha x *piperita* (peppermint) herb
Carum carvi (caraway) fruit
Glycyrrhiza glabra (licorice) root
Melissa officinalis (lemon balm) herb
Angelica archangelica (angelica) root
Chelidonium majus (celandine) root
Silybum marianum (milk thistle) seed

In a randomized, double-blind, multicenter study of 208 patients diagnosed with IBS, patients were randomized to receive either the commercial preparation; an identical preparation made by the researchers that excluded celandine, angelica, and milk thistle; a single constituent of the formula (bitter candytuft); or placebo. The dose was 20 drops three times daily for four weeks. The formula was made with tinctures, but proportions were not provided. Both Iberogast and the research preparation demonstrated efficacy in this trial. Bitter candytuft as a single herb did not.

Madisch A, Holtmann G, Plein K, et al. Treatment of irritable bowel syndrome with herbal preparations: Results of a double-blind, randomized, placebo-controlled, multicenter trial. *Alimentary Pharmacol Ther* 2004;19:271–279. Iberogast is manufactured by Steigerwald Arzneimittlwerk GmbH, Darmstadt, Germany.

that regulates gall bladder function. Currently, research into CCK receptor antagonists as a drug treatment, particularly for constipation–predominant IBS, is underway.[10,11]

Based on what we know about IBS, the gallbladder, and CCK, we strongly recommend the use of cholagogues, particularly in patients with a history of forming gall stones, who have confirmed lack of biliary activity (known as biliary dyskinesia), or who complain of right upper-quadrant gastrointestinal discomfort or intolerance of fatty foods. The Iberogast formula that has been studied in IBS (see Sidebar 19-2) contains a relatively strong cholagogue, *Chelidonium majus* (celandine) leaf and flower. Celandine has been associated with isolated cases of acute hepatitis.[12,13] It can also provoke nausea more readily than other cholagogues. Though celandine is still extremely safe, particularly compared to many drugs, milder cholagogues such as fumitory, dandelion and/or artichoke are better initial therapeutic choices. These herbs have a gentler action and may be taken on a daily basis for a prolonged period of time. Stronger herbs such as celandine should only be used by practitioners familiar with their specific use indications, and should be reserved for patients who do not respond to milder herbs.

CARMINATIVES

Flatulence, abdominal distention, and associated symptoms are common in IBS. The bitters discussed above will substantially help reduce flatulence by improving digestion, but herbs with carminative activity will help moderate these common symptoms. *Carum carvi* (caraway) is

commonly used, and its volatile oil combined with *Mentha* x *piperita* (peppermint) oil was as effective as cisapride in one study of dyspeptic patients.[14] Other studies confirm that peppermint oil is beneficial in IBS.[15,16] Because dyspepsia is also a functional disorder of the gastrointestinal tract, many treatments that help in dyspepsia will also alleviate IBS symptoms. See Sidebar 19-3.

19–3. *Case Study*

A 48-year-old yoga instructor, very restrained, was seeking help for IBS-type symptoms, including several years of severe bloating some time after meals, requiring her to lie down and loosen clothes; burping; and flatulence. These symptoms worsen when flying and are helped by simethicone. She also has a problem with vomiting. Once triggered, it becomes persistent. She saw a GI specialist who diagnosed her with IBS, and recommended she work on food allergies; she quit milk and wheat for a week but is not inclined to continue in that direction. She experiences bad breath in the morning, intestinal bloating, and creamy tongue coating (scrapes tongue daily) and has bouts of diarrhea alternating with constipation although she has a daily bowel movement. She has hemorrhoids that come and go; one was removed when she was younger. She also had an operation in her twenties to remove an anal stricture.

TREATMENT:

1 tbsp psyllium seed husks and 1 tbsp flax seed, ground, daily. The following formula was also recommended at a dose of 1 tsp 5–10 minutes before main meals.

Herb	*Form*	*Parts (percent)*	*Action(s)*
Nepeta cataria (catnip) leaf	T	21	Carminative
Dioscorea villosa (wild yam) root	T	17	Antispasmodic
Mahonia aquifolium (Oregon grape) root	T	13	Bitter, antimicrobial, liver stimulant
Fumaria officinalis (fumitory) herb	T	13	Gall bladder balance
Foeniculum vulgaris (fennel) fruit	T	13	Carminative
Matricaria recutita (chamomile) flower	T	8	Carminative, antispasmodic, nervine
Salvia officinalis (sage) leaf	T	8	Astringent; drying for night sweats
Mentha x *piperita* (peppermint) leaf	S	7	Antispasmodic

S = spirits (volatile oil in alcohol), T = tincture.

Within days the patient reported that symptoms had been alleviated. She continues to use the formula a year later but at a lower dose (approximately 15 drops before meals). No recurrence of symptoms has occurred with the exception of a case of severe flatulence during a long airplane trip.

Peppermint is typically found in Western IBS formulae, and there are a number of clinical trials that tend to validate the benefit of peppermint oil in IBS.[3] Almost all of those studies have looked at peppermint volatile oil, often in enteric-coated capsules. However, while the essential oil is presumed to be *the* active ingredient, one study indicates that some of peppermint's more polar (or water soluble) compounds show antiulcerogenic and cholagogue effects.[17] The researcher posits that these compounds may contribute to peppermint's spasmolytic effect in the intestines and bowel. Side effects of peppermint oil use are pyrosis and rectal burning from the unabsorbed oil. It is possible that an ethanolic extract that combines some of the plant's oils and some of its hydrophilic compounds may work effectively with fewer side effects than pure peppermint oil. This has not been studied but the Iberogast formula (see Sidebar 19-2) includes an alcoholic extract of peppermint with apparent success.

Patients should also be encouraged to drink a carminative, antispasmodic herbal tea of their choice, such as *Matricaria recutita* (chamomile) throughout the day in addition to taking an IBS formula. Carminatives such as caraway, *Anethum graveolens* (dill) fruit, *Foeniculum vulgare* (fennel) fruit, *Pimpinella anisum* (anise) fruit, peppermint leaf, and chamomile flower have been used for millennia in cooking and as teas to enhance digestion. Their excellent safety profiles make them appropriate for long-term use and may help gain the patient sufficient symptomatic relief to pursue deeper therapies to relieve the causes of IBS. See Sidebar 19-4.

SPASMOLYTICS

Abdominal pain and cramping are predominant symptoms in IBS, and antispasmodic herbs are highly indicated when such symptoms are present. Given the dominance of these symptoms, we usually include several antispasmodics in IBS treatment. The carminatives discussed above all have a spasmolytic effect. In fact, although the Eclectics and German physicians like Dr. Weiss considered carminatives and antispasmodics to possess distinct differences, many today believe that carminatives provide a benefit solely through their spasmolytic action. This has not been sufficiently studied, and it remains possible that carminatives also act to reduce flatulence by other means.

19–4. *Carmint Formula*

Melissa officinalis (lemon balm)
Mentha spicata (spearmint)
Coriandrum sativum (coriander)

Proportions not stated, 30 "herbal drops" given three times a day after meals to 32 patients diagnosed with IBS according to Rome II criteria. If patients had diarrhea-predominant IBS, 2 mg loperamide twice per day given; if constipation predominant, 1 spoonful of psyllium powder once per day. Severity of pain and bloating diminished in carmint group beginning in week 2.

Vejdani R, Shalmani HRM, Mir-Fattahi M, et al. The efficacy of an herbal medicine, carmint, on the relief of abdominal pain and bloating in patients with irritable bowel syndrome: A pilot study. *Dig Dis Sci* 2006;51:1501–1507.

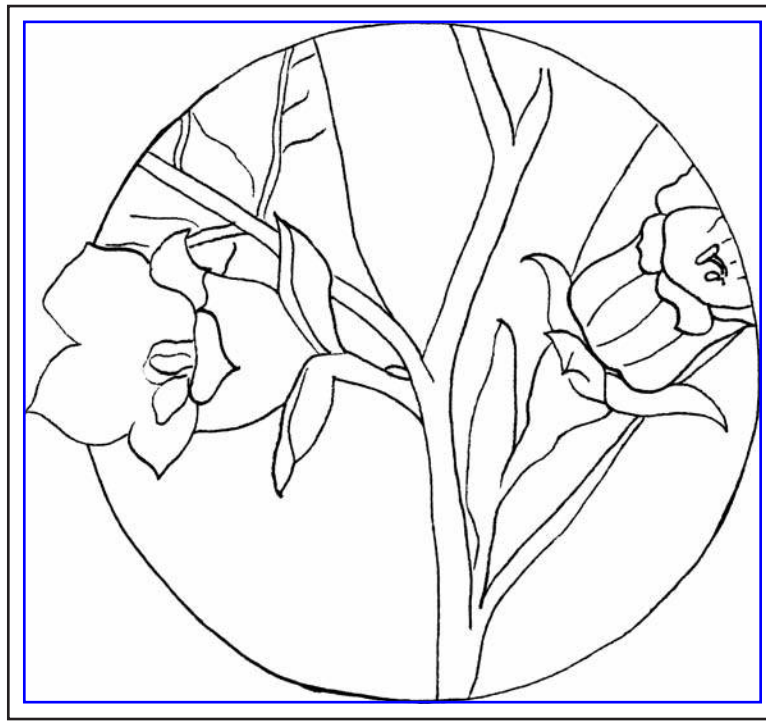

Figure 19–1. *Atropa belladonna* (belladonna)
Drawing by Kathy Abascal, BS, JD.

In addition to peppermint and chamomile, both of which are spasmolytic, we recommend the use of stronger, more specific antispasmodics in IBS. Antispasmodics like *Dioscorea villosa* (wild yam) root and *Viburnum* spp. (crampbark or blackhaw) bark tend to have an excellent effect in IBS formulas. Unfortunately, little research has been done on the spasmolytic effect of these plants despite their long history of use. One animal study showed viburtinosides from a crampbark had a significant and rapid spasmolytic effect on isolated rabbit jejunum.[18]

Dr. Weiss, a physician highly experienced in the clinical use of botanicals, favored the use of *Atropa belladonna* (belladonna) as an antispasmodic for the GI tract.[19] He states, "The gastrointestinal antispasmodic outranking all others is belladonna." He found it to be equally effective in all conditions of the stomach, intestine, and bile ducts involving spasms. Dr. Weiss often dispensed belladonna with chamomile, peppermint, and/or wormwood, which he considered to enhance the plant's action. Belladonna contains the tropane alkaloids atropine and hyoscyamine, which are potent anticholinergic agents. Belladonna is used in drop doses (typically 5–8 drops depending on the patient). It has a potential for toxicity and is only safe for use by a trained and experienced practitioner. However, in the hands of such a clinician, belladonna often proves to be highly useful for more difficult and painful IBS cases.

ANTIMICROBIALS

Research indicates that infection is probably an issue in at least a subset of patients with IBS as up to one third of patients with bacterial enteritis may end up with "postinfectious" IBS.[20] A recent

Table 19–1. Sample Formula 1

Name	*Amount (percent)*	*Action*
Fumitory (*Fumaria officinalis*) herb	20	Bitter, cholagogue, antidiarrheal, aperient
Wild yam (*Dioscorea villosa*) root	20	Antispasmodic
Schisandra (*Schisandra chinensis*) fruit	20	Antidiarrheal, adaptogen
Oregon grape (*Mahonia aquifolium*) root	15	Bitter, cholagogue, antimicrobial, anti-inflammatory
Peppermint (*Mentha* x *piperita*) herb	10	Cholagogue, carminative, antispasmodic, antimicrobial, anti-inflammatory
Chamomile (*Matricaria recuitita*) herb	10	Antispasmodic, anti-inflammatory, carminative, antimicrobial
Lemon balm (*Melissa officinalis*) herb	5	Antispasmodic, nervine

Herbs that might be combined for a hypothetical patient with IBS primarily complaining of mild bouts of diarrhea and abdominal pain, who also is slightly depressed and fatigued.
Dose: 5 ml, three times per day before meals.
Additions: Flax seed (*Linum usitatissimum*), 3 tbsp per day (antidiarrheal, aperient). Chamomile tea, drink liberally (spasmolytic, inflammation modulating, carminative).

study concluded that most patients diagnosed with symptomatic *Giardia lamblia* actually are suffering from IBS and are not helped by antiparasite treatment.[21] It is not clear at this time to what extent there is a pathogenic component to IBS. However, in our opinion, it makes sense to include a berberine-containing plant, at least for a period of time, in IBS formulas, particularly for patients in a predominantly diarrhea phase of the ailment. See Table 19-1.

Goldenseal is an excellent intestinal antimicrobial, and is a very good choice if there is an active intestinal infection. However, it is not the best choice for long-term use because of its strength and because it is challenged in the wild. We usually prefer *Mahonia aquifolium* (Oregon grape). Oregon grape contains berberine, is strongly antimicrobial, and is bitter, and herbalist Michael Moore recommends it as a liver tonic for people with sluggish digestion.[22] Thus, it has several aspects that will be of value in IBS.

INFLAMMATION MODULATORS AND VULNERARIES

IBS is not considered an inflammatory condition per se but gastrointestinal infection with its consequent mucosal inflammation does appear to play a role in a subset of patients with IBS. One reviewer comments that "postinfectious IBS is one of many disorders that leads to chronic inflammation of the GI tract, and in this fashion, causes symptoms of IBS."[23] Many of the carminative, antispasmodic, and antimicrobial herbs will also have anti-inflammatory properties. Thus, a formula using chamomile, Oregon grape, wild yam, peppermint, caraway, and other herbs in those categories will provide an inflammation-modulating action as well.[2]

One textbook recommends adding *Ulmus rubra* (slippery elm) in cases where there is excess mucus production because the presence of mucus indicates a localized inflammation of the intestinal lining.[24] Demulcents are common components in IBS formulas, and can help bind up

diarrhea or stimulate the gut in cases of atonic constipation, though we typically recommend people use food sources such as *Linum usitatissimum* (flax) seed. Licorice is a mild demulcent with more pronounced inflammation-modulating activity. If a demulcent appears appropriate, we would use licorice. Of course, as licorice is an aldosterone synergist, care must be taken to ensure that it is appropriate for long-term use in the individual patient. It should also be noted that in a tincture, it is unlikely that demulcent effects will be active, as insufficient levels of the complex carbohydrates that mediate this action are delivered by tincture except at doses high enough to risk inebriating the patient.

Another text states that a vulnerary (wound-healing herb) may also be needed in an IBS formula.[25] In our experience, IBS patients do not need strong vulneraries. Instead, the inflammation-modulating herbs discussed above are quite sufficient for patients with IBS.

ASTRINGENTS AND ANTIDIARRHEA HERBS

From the patient's perspective, diarrhea possibly causing fecal incontinence is one of the most troubling aspects of IBS. In a TCM formula, more than half of the 20 herbs in the formula are used to treat diarrhea arising from a variety of causes.[26] This formula worked well in a study that included patients with a more constipation-dominated form of IBS. (See Table 19-2.) In fact, there are a number of plants that work well for both constipation and diarrhea. In our opinion, all IBS formulas should always include some type of herb effective for diarrhea.

Indian fumitory is a plant that is traditionally used for both diarrhea and constipation.[27] Preliminary pharmacological and animal studies tend to support both uses. As discussed above, fumitory has a positive effect on the gallbladder. It thus may be an excellent choice in IBS.

Table 19–2. Formula Sample 2

Name	*Amount (percent)*	*Action*
Fumitory (*Fumaria officinalis*) herb	20	Bitter, cholagogue, antidiarrheal, aperient
Cramp (*Viburnum* spp.) bark	15	Antispasmodic, nervine
Licorice (*Glycyrrhiza glabra*) root	15	Aperient, adaptogen
Oregon grape (*Mahonia aquifolium*) root	15	Bitter, cholagogue, antimicrobial, anti-inflammatory
Peppermint (*Mentha* x *piperita*) herb	10	Cholagogue, carminative, antispasmodic, antimicrobial, anti-inflammatory
Yellow dock (*Rumex crispus*) root	10	Bitter, aperient
Chamomile (*Matricaria recuitita*) herb	10	Antispasmodic, anti-inflammatory, carminative, antimicrobial
Valerian (*Valeriana sitchensis*) root	5	Bitter, antispasmodic, nervine

For a hypothetical IBS patient, slightly anxious with dominant symptoms of constipation with flatulence and some abdominal pain; patient is not hypertensive.

Dose: 5 ml three times per day before meals.

Additions: Flax seed (*Linum usitatissimum*), 3 tbsp per day (antidiarrheal, aperient). Chamomile or peppermint tea, drink liberally (spasmolytic, inflammation modulating, carminative).

Plantago spp. (psyllium) seed is also a good addition to a treatment plan for IBS. One study shows that psyllium delays gastric emptying and reduces the acceleration of colon transit in patients with IBS.[28] This supports its use as an antidiarrheal component of treatment. It also has laxative properties that are discussed below in the section on aperients.

In many cases, the herbs used to treat diarrhea are astringent. Most of these are rich in tannins that bind up fluid in the colon, inhibiting the protective excretory function of diarrhea.[2] Mild astringents, such as *Morella cerifera* (bayberry) root bark and *Filipendula ulmaria* (meadowsweet) leaf, may be useful in a standardized IBS formula. However, because of the tendency of stool patterns to alternate in IBS, stronger astringent herbs such as *Geranium maculatum* (cranesbill) root may be best used in cases of IBS where psyllium, antimicrobials, and milder astringents fail to provide needed relief.

APERIENTS

Aperients are mild laxatives that are used to relieve constipation. A standard Chinese medicinal formula (see Table 19-3) included psyllium seed that is used as a bulk laxative in Western botanical medicine. The textbooks typically recommend soluble fiber (such as psyllium or flax) or mild aperients such as dandelion or *Rumex crispus* (yellow dock) root.[24,25] The Iberogast digestive tonic formula contains celandine and bitter candytuft, both of which have an aperient action.

In general, an appropriate fiber type should be recommended in IBS because it will prove useful both in diarrhea and constipation. A meta-analysis of fiber in IBS concluded that while convincing data was lacking, soluble fiber did appear to be beneficial to global symptom improvement whereas insoluble fiber was not.[29] In small, albeit not necessarily well-designed, studies, partially hydrolyzed guar gum, psyllium, and *Linum usitatissiumum* (flax) seed[29–31] have shown benefit in people with IBS. Of course, fiber use also requires an increase in water intake that also helps overcome constipation.

Cathartic laxatives are contraindicated in IBS because of the real possibility that their use may shift the disease into the diarrhea phase.[2]

NERVINES AND ADAPTOGENS

There is a consensus that there is a strong emotional component to IBS, though it is unclear if this is a cause or result of the disease. Thus, one reviewer comments, "It remains unclear whether IBS represents a normal perception of an abnormal function or an abnormal perception of a normal function, or if it is heterogeneous in this respect."[32] Psychiatric diagnosis and anxiety in particular are common in IBS. Panic disorder and agoraphobia also occur in excess proportions in patients with IBS compared to the general public.[32]

It follows that both nervines and adaptogens should be prescribed to these patients. We always include nervine herbs intended to help patients handle the emotional stress of the moment. Some, like the more sedative nervine *Valeriana officinalis* (valerian) root or its close cousin *V. sitchensis* (Pacific valerian) and the more mood-elevating nervine *Melissa officinalis* (lemon balm) also have a mild antispasmodic action that is helpful in IBS.[2] However, there are many nervine plants, each with subtle differences, and the individual patient will benefit from a personalized choice of nervine. For more information on nervine profiles, see chapter 5.

Adaptogenic herbs that help the individual cope with long-term physical and emotional stress are indicated in IBS patients but have received little to no attention in either textbooks or

Table 19–3. Standard Chinese Medicine Formula

Herb	*Amount (percent)*
Artemesia capillaris (capillary wormwood, yin chen) herb	13
Atractylodes macrocephala (bai zhu) rhizome	9
Codonopsis pilosula (codonopsis, dang shen) root	7
Schisandra chinensis (schisandra, wu wei zi) fruit	7
Coix lacryma-jobi (Job's tears, yi yi ren) seed	7
Agastaches rugosa (licorice mint, tu huo xiang) herb	4.5
Bupleurum chinensis (thorowax, chai hu) root	4.5
Magnolia officinalis (magnolia, huo po) bark	4.5
Wolfiporia cocos (hoelen, fu ling), sclerotium	4.5
Fraxinus spp. (ash, qin pi) bark	4.5
Zingiber officinalis (ginger, gan jiang) rhizome	4.5
Plantago spp. (water plantain, che qian zi) seed	4.5
Glycyrrhiza uralensis (gan cao) root	4.5
Phellodendron spp. (huang bai) bark	4.5
Citrus reticulata (tangerine, chen pi) aged peel	4.5
Saposhnikovia divericata (fang feng) root	3
Paeonia lactiflora (peony, bai shao) root	3
Saussurea spp. (mu xiang) root	3
Coptis spp. (gold thread, huang lian) root	3
Angelica dahurica (bai zhi) root	2

The study was well designed. One hundred sixteen patients were given 5 capsules of a standard formula, an individually prepared herbal formula or placebo, three times daily for 16 weeks. At the end of the trial, 76% of the patients on the standard formula, 64% on the individualized formula, and 33% on placebo had improved as assessed by the patients. Their gastroenterologists found improvement in 78% of those on the standard formula, 50% on the individualized formula, and 30% on placebo. Interestingly, in a follow-up assessment 14 weeks after the end of the trial, only the group that had taken individualized formulae maintained the improvement achieved during the trial, although 63% of those on the standard formula still felt an improvement compared to 32% of those on placebo.

Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine. *JAMA* 1998;280:1585–1589.

research studies. We strongly recommend the inclusion of an adaptogen in any IBS formula both because the stress of a chronic ailment is depleting and because there tends to be an exaggerated stress response in these patients. As with nervines, the patient will benefit most if the adaptogen is selected specifically to meet the individual needs of the client.

CONCLUSION

Botanicals have a great deal to offer patients with IBS. See Table 19-4. A combination formula that contains herbs from the various categories discussed in this article, selected for the individual

patient, will provide substantial benefit. An example of such a formula is set out in Table 19-4. It is noteworthy that the individual formulas tested in the TCM study provided longer lasting benefits to the patients even though the standardized formula appeared more useful during the study. (See Table 19-1.) Thus, whereas a standard formula may work well—both Iberogast and the Chinese medicine formula seemed to do so—an individual formula shaped to accentuate herbs with actions specifically needed by the patient may prove more useful in the long run. A substantial amount of dietary advice to remove food items that may cause or aggravate the symptoms is also recommended and although not discussed in this chapter is a very important component of providing complete relief to the patient.

Table 19–4. Dose Limits, Contraindications, and Safety Concerns

Name	*Dose Limits, Contraindications, and Safety Concerns*
Anise (*Pimpinella anisum*) fruit	Not for use in pregnancy.
Wormwood and related species (*Artemisias* spp.)	Emmenagogue and uterine stimulant, not for use in pregnancy; due to thujone content, not for use in pregnancy or for long-term use. Recommended not to exceed 1.5 g of herb as tea per day.
Artichoke (*Cynara scolymus*) leaf	
Bayberry (*Myrica cerifera*) root bark	Contains tannins but no known contraindications.
Belladonna (*Atropa belladonna*) root	To be used only under the supervision of an expert qualified in the appropriate use of this herb. Contains atropine.
Bitter candytuft (*Iberis amara*) herb	Not mentioned
Caraway (*Carum carvi*) fruit	None
Celandine (*Chelidonium majus*) leaf and flower	Not for use in pregnancy or in children.
Chamomile (*Matricaria recutita*)	None
Crampbark or blackhaw bark (*Viburnum* spp.)	*V. opulus*: none; *V. prunifolium*: individuals with a history of kidney stones should use cautiously as it contains oxalates.
Cranesbill (*Geranium maculatum*) root	None
Dandelion (*Taraxacum officinalis*) leaf	None
Dill (*Anetheum graveolens*) fruit	None
Fennel (*Foeniculum vulgare*) fruit	None
Flax (*Linum usitatissiumum*) seed	Contraindicated in bowel obstruction; take with at least 6 oz of liquid.

(*continued*)

Table 19–4. (*continued*)

Name	*Dose Limits, Contraindications, and Safety Concerns*
Fumitory (*Fumaria officinalis*) leaf	Not covered
Gentian (*Gentiana* spp.) root	Contraindicated in gastric and duodenal ulcers and when gastric irritation and inflammation are present.
Ginger (*Zingiber officinale*) rhizome	Dried root: Persons with gallstones should consult a practitioner prior to use.
Goldenseal (*Hydrastis canadensis*) root	Not for use in pregnancy; uterine stimulant and emmenagogue.
Lemon balm (*Melissa officinalis*)	None
Licorice (*Glycyrrhiza* spp.) root	Not for use in pregnancy; not for prolonged use or in high doses unless prescribed by a qualified practitioner; and contraindicated in diabetes, hypertension, liver disorders, severe kidney insufficiency, and hypokalemia. May potentiate potassium depletion of thiazide diuretics, stimulant laxatives, cardiac glycosides, and cortisol.
Meadowsweet (*Filipendula ulmaria*) leaf	None
Oregon grape (*Mahonia aquifolium*) root	Not for use in pregnancy.
Peppermint (*Mentha* x *piperita*) herb	None
Psyllium (*Plantago* spp.) seed	None
Slippery elm (*Ulmus rubra*) bark	None
Valerian (*Valeriana* spp.) root	Although reports of toxicity of valepotriates have been published, poor absorption and quick degradation into less toxic metabolites ensure no acute adverse reactions.
Wild yam (*Dioscorea villosa*) root	Large amounts may cause emesis.

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20

TREATING AND PREVENTING KIDNEY STONES

Acute kidney stone passage remains one of the most dreaded conditions due to the severe pain of ureteral colic. The formation of calcium oxalate, calcium phosphate, and uric acid kidney stones is strongly associated with deleterious dietary habits common in the western world. Though there are numerous high-technology solutions for relieving acute kidney stones (including lithotripsy and surgery), these are expensive and carry significant risks of adverse effects. Besides many known problems, a recent bombshell study revealed that patients who undergo lithoripsy suffered significant long-term increased risks of developing hypertension and diabetes mellitus.[1] Though treatment is obviously necessary if stones develop, excessive resources are being pulled into further treatment research instead of focusing on how to best prevent what is largely a preventable disease.

In this chapter we review holistic approaches to preventing as well as treating kidney stone patients. This discussion assumes that proper diagnosis and monitoring will take place to determine if, and when, referral for other therapies is indicated in cases of acute renal colic. Our analysis considers only the most common type of stones—calcium oxalate/calcium phosphate and uric acid. Other types of truly rare kidney stones, such as cystine stones, are not covered.

PREVENTING CHRONIC RECURRENCE

Long-term prevention of urolithiasis (also called nephrolithiasis) remains the most important goal. See Sidebar 20-1. This ultimately depends on changing lifestyle factors, particularly if one calculates in the costs of any other therapy. For some, botanical therapies are also indicated, and are safer and more affordable than drugs (though researchers have consistently failed to compare their efficacy). The lifestyle changes necessary to prevent kidney stones have multiple other beneficial effects, having been repeatedly associated with reduced risks of most other major chronic diseases of western society, notably cancer and atherosclerosis.[2] For unclear reasons, men are affected with stones about three or four times more frequently than women. It has been estimated that 12% of men and 5% of women in the West will develop a kidney stone by age 70.[3] Even though men should be particularly encouraged to follow these guidelines, they are still entirely applicable and important in women as well.

Simple sugars and sodium chloride both promote urinary calcium excretion and very consistently contribute to renal lithiasis.[4,5] Both are consumed in great excess in the United States and Western Europe. Another area of excess in the developed world is consumption of exorbitant quantities of animal products. This too has been fairly consistently linked to urolithiasis.[6] Ethanol, caffeine, and lack of dietary fiber are also potentially important in the etiology of kidney stones. It is a serious oversimplification to restrict calcium and oxalate intake and ignore the negative effects of meat, fat, salt, sucrose, caffeine, and insufficient fiber intake. In fact, the vast majority of stone formers should not restrict dietary calcium but should instead focus on avoiding these other foods.[7]

20–1. *Prevention Protocol for Urolithiasis*

Sufficient water each day to maintain clear or nearly clear urine (urinary-specific gravity < 1.025).
Lemonade without sucrose or artificial sweeteners and herbal teas can be substituted for some of the water, or added to it. Dandelion or goldenrod tea is particularly useful.
Pyridoxine 250 mg daily.
Magnesium citrate (providing around 150 mg elemental mg) 2 capsules two times daily.
Calcium citrate 500 mg three times daily with meals (assuming the patient does not have absorptive hypercalciuria).
Eat low on the food chain and moderate oxalate intake: few animal products (including fish and dairy products), high fiber, choose whole foods (avoid refined sugars in particular), low salt, plenty of fruits and vegetables (except spinach, beet greens, and strawberries), avoid nuts, avoid all caffeinated beverages and foods, and avoid alcohol.
Prevent Renal Calculi formula (Table 20-1), with or without *Phyllanthus niuri* leaf, 1 tsp three times daily away from food.

Some vegetables are urinary tract tonics and diuretics, and will therefore be helpful in the long run for preventing urolithiasis. These vegetables include celery, asparagus, parsley, and carrots. Vegetables, fruits, and grains with a high magnesium-to-calcium ratio are also highly recommended as a low ratio of these two minerals in the diet has been linked to increased risk of calculi formation.[8] Examples of foods with a good ratio are avocado, banana, potato, soy, barley, buckwheat, rye, oats, and rice. Aloe gel has also been studied as a food in Thai children and adults. Doses of 100 g per day improved citraturia and had other mild, beneficial effects suggesting this might help prevent stone formation.[9,10]

Table 20–1. Prevent Renal Calculi Formula

Latin Binomial	*Common Name(s)*	*Part Used*	*Parts**
Taraxacum officinale	Dandelion	Leaf	1.5
Rubia tinctoria	Madder	Root	1.5
Serenoa serrulata	Saw palmetto	Fruit	1.5
Aesculus hippocastanum	Horse chestnut	Fruit	1
Berberis vulgaris	Bayberry	Root	1
Agropyron repens	Couch grass	Root	1
Eupatorium purpureum	Gravel root	Root	0.5
Alchemilla arvensis	Parsley piert	Flowering Tops	0.5
Hydrangea arborescens	Hydrangea	Root	0.5
Equisetum arvense	Horsetail	Leaf	0.5 (syrup)
Parietaria diffusa	Pellitory of the wall	Flowering Tops	0.5

*All are ethanol extracts (tinctures) unless otherwise mentioned.
Formula developed by Silena Heron, ND.

WATER, HERBAL BEVERAGES, AND FREQUENT URINATION

Dietary factors are paramount in the pathogenesis of calcium-containing and uric acid stones, hence nutritional therapies are critical in prevention. The exact dietary problems are numerous and interconnect, creating a very complex picture. No single aspect of this approach can be said to be more vital than another due to the interlocking nature of the risk factors. Nevertheless, infrequent urination, resulting in stagnant urine with more time for crystallization to occur, is almost certainly one of the most problematic issues.[11,12] Long-term, increased frequency of urination related to increased hydration has been shown to be beneficial in preventing stone formation.[13] Rather than prescribing an arbitrary amount of water to drink, the goal should be for patients to modulate intake such that they urinate at most once every two waking hours, generally produce 2–3 qt (approximately 2–3 L) of urine per day, and that all but the early-morning urine be clear or at most pale yellow (associated with a specific gravity below 1.025). In a wet climate, intake of eight glasses of water a day usually suffices. In a dry climate, in patients who exercise frequently, and in some chronically underhydrated patients, additional water is usually needed. Mineral water may have additional benefits beyond plain water, though it appears to be problematic in patients with calcium phosphate stones.[14]

Patients who have trouble drinking enough water may do better drinking lemonade that has been used in studies to treat urolithiasis.[15] For treatment, 4 oz of reconstituted lemon juice was mixed with water to make 2 L (about 2 qt) of lemonade, the daily dose. Sweetener was added to taste, though ideally sucrose should be limited to the greatest extent possible as it contributes to stone formation.[16] In this study, the lemonade greatly increased citrituria, an anticipated result as lemon juice is extremely high in citrate, a strongly antilithogenic compound in the urine.[17] Lemonade has the advantage of being a tasty way to take in adequate fluids and it is much cheaper than citrate pills. Though potassium citrate is more citraturic than lemonade, only lemonade also increases urine volume.[18] Long-term open trials show the benefits of lemonade are durable for at least five years in many patients.[19] Lemonade will also help maintain a urinary pH between 6 and 7, which prevents uric acid (hence uric acid stones) and calcium phosphate from precipitating. Orange juice also appears to have similar benefits.[20] Acidic lemon juice can erode tooth enamel so it should generally be followed up with some water or by brushing the teeth. See Sidebar 20-2 for suggested herbal lemonade recipes.

20–2. *Herbal Diuretic Lemonade Recipes*

General lemon pointers:

A medium lemon generally yields 2–3 tbsp juice (1–1.5 oz or 30–45 ml). Therefore, 5–6 medium lemons will yield approximately 1 cup of juice. One tbsp concentrate is about the same as 1 tbsp fresh juice. Limes can be substituted for lemons. One fresh lime yields 2 tbsp juice, which is about equal in potency to 3 tbsp lemon juice (in other words, if substituting lime for lemon, use two thirds the amount of lemon juice in any recipe). Limes have slightly more citrate than lemons. Room temperature fruit yields more juice than refrigerated. Rolling the fruit with the palm a few times on the counter eases juice removal. If you have leftover fresh juice, it can be best preserved by freezing it in an ice

(*continued*)

20–2. *Herbal Diuretic Lemonade Recipes (continued)*

cube tray. Zest should only come from organic lemons because pesticides concentrate in the peel.

Note that strawberry lemonade should be avoided due to the relatively high oxalate content of strawberries.

LOW-SUGAR HIBISCUS DIURETIC LEMONADE

4 cups water
2 tbsp dried *Hibiscus* spp. flower
1 tbsp dried *Solidago canadensis* (goldenrod) flower
½ cup sugar (or less, to taste)
2–4 oz lemon juice (to taste)
Zest of 1–6 organic lemons (to taste)
Yield: approximately 1 quart

Hibiscus is discussed in chapter 18. It imparts a beautiful red color to the final product while simultaneously enhancing the diuretic nature of the lemonade.

Boil the water. Dissolve the sugar in the water. Turn the heat off and stir in the dried herbs. Allow to steep, covered, for 15 min. Strain out the herbal material and stir in the lemon juice and zest.

If the final product is not sufficiently sweet, stir in ½ tsp of stevia leaf extract to the final product. If the patient does not mind it even less sweet, the sugar can be further reduced. Note that most recipes call for three times the level of sugar used here, and so many patients will have to adapt to the stronger sour and astringent taste of this brew.

LOW-SUGAR GINGER LEMONADE

4 cups water
Two 1-inch pieces of fresh *Zingiber officinale* (ginger) rhizome, sliced (or more, to taste; the finer the chopping/slicing, the more potent the ginger flavor)
½ cup sugar (or less, to taste)
2–4 oz lemon juice (to taste)
Yield: approximately 1 quart

Heat the water and sugar to a boil. Turn the heat down to simmer and add the ginger slices. Cover and allow to decoct for 15 minutes. Remove from heat and add the lemon juice. Allow to chill, then strain out the ginger slices. This version is particularly applicable for patients with poor digestion, who have an acute infection or tendency to get them, or who just want a change of pace.

NO-SUGAR NETTLE LEMONADE

4 cups water
½ tsp stevia extract powder
1–2 tbsp *Urtica dioica* (nettle) dried leaf, or 2–4 tbsp fresh leaf (beware those stingers!) (to taste)
2–4 oz lemon juice (to taste)

(*continued*)

20–2. *Herbal Diuretic Lemonade Recipes (continued)*

Boil the water and then remove from heat. Immediately add the nettle leaves and allow to steep for 15 minutes. Strain out the leaves. Stir together the lemon juice and stevia extract, then add to the nettle infusion.

The final interesting herbal beverage that may modulate kidney stone risk is the juice of *Vaccinium macrocarpon* (cranberry) fruit. The oldest human trial on the topic seemed to find that cranberry juice could reduce calciuria.[21] A later, though still small, study found mixed effects of cranberry tablets on urine in human subjects, yet overall declared that cranberry might increase the risk of stones.[22] A similar small trial found that cranberry juice slightly acidified the urine and increased calciuria and oxaluria, while uric acid and ammonium levels fell, both in healthy men and recurrent stone formers.[23] Another small trial in healthy European men found increased oxaluria and slightly increased urinary acidification.[24] Contrary to these findings were increased citraturia and decreased oxaluria and phosphaturia in South African men drinking cranberry juice in a small trial.[25] Overall, the trials on cranberry juice are woefully inadequate, with none reporting on relevant clinical outcomes (rate of stone formation) and all being too small and short term to apply clinically. Future research is awaited to determine if cranberry plays any role related to kidney stones.

DIURETIC HERBS

Diuretic herbs can be added to any program for preventing kidney stone recurrence. They are safe and extremely cheap, even compared to the main drug diuretics recommended for stone prevention, thiazide diuretics. There is some evidence that these drugs may slightly increase the risk of diabetes and that approximately 20% of patients who take them become hypomagnesemic.[26,27] Unfortunately, the efficacy of diuretic herbs has barely been assessed in clinical trials. Their obvious effects empirically on urine volume and their historical use, coupled with some initial trials, supports their use.

Solidago canadensis (Goldenrod)

Solidago canadensis (goldenrod) and related species flowering tops have been used as inflammation-modulating, reliable, and potent diuretics.[28,29] This herb is particular popular in German phytotherapy, where it is considered a first-line agent with no adverse effects.[30] Goldenrod has a high content of flavonoids that aid in kidney repair and support blood vessels and connective tissues throughout the body. Goldenrod reduces edema by reducing capillary permeability.[31] Contrary to popular belief goldenrod is not a significant allergen (the myth appears to be because ragweed and goldenrod bloom simultaneously) and does not have windborne pollen, a prerequisite for any major allergenic pollen.

Figure 20–1. *Solidago canadensis* (goldenrod) flowers

Taraxacum officinale (Dandelion)

Taraxacum officinale (dandelion) leaf simultaneously holds the titles of much maligned weed and important medicine. Whereas the whole plant is useful for both liver and kidney tonification and detoxification, the leaf is most reliable as a diuretic—no doubt the source of its French common name "pee-in-bed" (pis en lit). It has been favorably compared with furosemide in animal studies,[32] and clinically is observed to have a similar effect if enough of the plant is used. Animal studies have also shown it to be beneficial in treating urolithiasis.[33] In contrast to most prescription diuretics that deplete potassium, dandelion leaf is a significant source of potassium—300 mg/100 g typically (for comparison, bananas contain around 360 mg/100 g).[34] It can be used for extensive periods of time because it enhances rather than interferes with physiological functioning in urinary, biliary, and rheumatic conditions.

Orthosiphon stamineus (Java Tea)

Orthosiphon stamineus (Java tea), a fantastically beautiful flower found in the tropics, is widely considered a diuretic in the traditional medicine of Indonesia. A clinical trial assessed the efficacy of herbal tea made from 6 g dried flowers of the related herb *O. grandiflorus* drunk as 2 cups (500 ml) per day with sodium potassium citrate in known stone formers.[35] The two were equally effective at reducing stone size on ultrasound over one year's time, with far fewer adverse effects in the Java tea group. Although not ecologically the best choice given the distance it has to travel to the U.S. market, this herb serves as an indication of the potential advantage of diuretic plants.

Zea mays (Corn Silk)

Zea mays (corn silk) reputedly increases urine flow and has a demulcent effect that decreases irritation from stones and facilitates their passage. One human study unfortunately did not confirm the diuretic action of corn silk.[36] Only very high doses (500 mg/kg body weight) have been shown to be diuretic in rats.[37] However, this is one herb that is best used fresh and carefully collected so as only green or yellowish stigmata are used. Those stigmata that have dried out and darkened—especially those from corn that have been sprayed to prevent worm infestations—are suspect. Most commercially available corn silk is of low quality and this may have affected the study results. Except for the occasional patient who is allergic to corn, this herb is very safe.

Hydrangea arborescens (Hydrangea)

Hydrangea arborescens (hydrangea) is a native U.S. plant that has been investigated only minimally by scientists. Its root is traditionally used primarily for all manner of urinary complaints including the passage of kidney and bladder stones and for their prophylaxis. Empiricially it is a mild diuretic. Hydrangea is also employed in helping patients with urinary tract infections and prostatic inflammation or enlargement. There are no known adverse effects.

Equisetum arvense (Horsetail)

Equisetum arvense (horsetail) is used for connective tissue repair, particularly in the lungs and the urinary passages. Horsetail also contains β-sitosterol[38] that tends to reduce prostatic hyperplasia.[39] Saw palmetto also contains a fair amount of β-sitosterol. Horsetail also causes some degree of diuresis, as was confirmed in humans using another, related species.[40] Several similar species had a similar magnitude of effect as spironolactone in animal studies.[41] Because it is a general urinary tract tonic and increases connective tissue resistance, it is useful in both acute and chronic calculi formulas. Horsetail is also very safe.

Elymus (Agropyron) repens (Couch Grass)

Elymus (*Agropyron*) *repens* (couch grass) leaf is a common and most unwelcome weed in moist climates. It is a saponin- and mannitol-based diuretic that also contains some silica[42] to repair irritated mucosal walls. Couch grass is useful to facilitate passage of stones and later to repair and assist in preventing recurrence. One rat study on couch grass did not find it to help prevent

urolithiasis.[43] As yet, human clinical trials have not been attempted to investigate its effects. Couch grass also contains mannose that may prove valuable for treating patients with urinary tract infection.

Herbal diuretics probably work better in combination than singly. One animal study that investigated this issue found a combination of several mild diuretic herbal extracts (corn silk combined with *Betula pubescens* [birch] leaf, *Crataegus laevigata* [hawthorn] fruit, *Fragaria vesca* [strawberry] leaf, *Matricaria recutita* [chamomile] flower, and horsetail herb) superior to either horsetail by itself or hydrochlorothiazide.[44]

OXALATE

Hyperoxaluria (elevated urine levels of oxalic acid) significantly contributes to calcium oxalate stone formation. Calcium oxalate saturates the urine far more rapidly in the presence of hyperoxaluria than in the presence of hypercalciuria, leading some to suspect that hyperoxaluria needs to be addressed more than calcium-related problems.[45,46] Regardless of which is more of a problem, oxalate and calcium are intimately interconnected.

Only about 10–20% of oxalates in the body come directly from diet. In addition, oxalic acid is very poorly absorbed with only around 5% of ingested oxalic acid actually getting into the body.[47] Other dietary sources of oxalate are vitamin C (roughly 40%), glycine (an amino acid encountered in many foods, roughly 40%), and other endogenous sources of oxalate (about 10%). Despite this, dietary oxalates seem to have a disproportionate effect on stone formation. Only eight foods, all of them plants, consistently increase urinary oxalate levels in people with oxalate absorption and secretion problems.[48] These are spinach, rhubarb, nuts, chocolate, black tea, wheat bran, beet greens, and strawberries. Patients can easily avoid many of these but often find the wheat, chocolate, and nuts difficult foods to avoid.

Restricting oxalates in the diet may not provide substantial relief from stone formation. In a study of 207 patients with recurrent oxalate stones, only about 20% had hyperoxaluria.[49] Of this subgroup, less than half (45%) improved when dietary oxalates were restricted. In other words, only 10% of the original group did better while avoiding high-oxalate foods. Additionally, this trial found that routine tests for oxaluria or urinary oxalate crystals are not especially productive as many stone formers will test false negative whereas many nonstone formers will test false positive.

More important than restricting oxalate in patients with calcium oxalate stones and hyperoxaluria is ensuring adequate calcium intake. This is because calcium taken with a meal containing oxalate reduces oxalate absorption dramatically.[50] Calcium is also used by the body to excrete oxalate and an increase in dietary calcium will reduce urinary calcium levels in many cases.[51] Supplemental calcium taken *with meals*, especially in the afternoon and evening (meals that tend to contain higher oxalate amounts), reduces stone formation as well according to this large-scale study.[52]

Ascorbic acid has been blamed for causing kidney stones because a breakdown product of this critical vitamin is oxalic acid. However, at doses under 6 g daily, ascorbic acid does not change urinary oxalate levels significantly in most people compared with those on a typical Western diet.[53] For the most part, it is not necessary to take more than 6 g of vitamin C. If an infection arises necessitating higher doses of vitamin C, an increase in citrate and water intake along with generally increasing protective measures will offset the relatively small increase of risk the high-dose vitamin C represents.

Table 20–2. Pass Stone Formula

Latin Binomial	*Common Name(s)*	*Part Used*	*Parts**
Lobelia inflata	Lobelia, Indian tobacco	Leaf, Flowers, Seed	2 (vinegar extract)
Rubia tinctoria	Madder	Root	2
Ammi visnaga	Khella	Seed	2
Eupatorium purpureum	Gravel root	Root	1.5
Aesculus hippocastanum	Horse chestnut	Fruit	1.5
Zea mays	Corn silk	Stigmata (silk)	1
Taraxacum officinale	Dandelion	Leaf	1
Solidago canadensis	Goldenrod	Leaf, Flower	1
Hydrangea arborescens	Hydrangea	Root	1
Equisetum arvense	Horsetail	Leaf	1 (syrup)
Agropyron repens	Couch grass	Root	1
Serenoa serrulata	Saw palmetto	Fruit	0.5

*All are ethanol extracts (tinctures) unless otherwise mentioned.
Formula developed by Silena Heron, ND.

A number of nutritional supplements are important as part of a plan to prevent kidney stones. Pyridoxine (vitamin B6) is necessary for oxalic acid catabolism and helps retard stone formation.[54] Pyridoxine works synergistically with the mineral magnesium that increases calcium oxalate solubility.[55] These two together with citrate (as supplement or lemonade) will very effectively help inhibit precipitation of stone-forming compounds, and provide a very effective approach. For patients taking citrate as a supplement, the use of magnesium citrate is a simple way to get both compounds in a single pill.

URINARY TRACT TONICS

The late Silena Heron, ND, developed a formula to help prevent stone formation, presented in Table 20-2. This formula combines a number of common urinary tract tonic herbs to prevent urolithiasis. Though generally poorly researched, they have a long history of use as tonics and deserve further scrutiny.

Serenoa repens (Saw Palmetto)

Serenoa repens (saw palmetto) contains a number of ethyl esters of fatty acids, enzymes, tannins, resins, terpenoids, and sitosterols. It is best known as a treatment for benign prostatic hyperplasia.[56] Saw palmetto has a spasmolytic effect, and thus is also used during acute stone passage and for patients with dysuria and tenesmus. It reduces the pressure on the neck of the bladder and has a sedative effect on an irritated detrusor, a common problem in many prostate and bladder problems. It is included as a central theme in the preventive formula because of its general tonic effects for the entire urinary tract and is equally indicated in male and female patients.[57]

Parietaria diffusa (Pellitory-of-the-Wall)

Parietaria diffusa (pellitory-of-the-wall), a relative of *Urtica dioica* (stinging nettles), contains flavonoids including quercetin. Unfortunately it has not received much scientific study. It was used traditionally as a diuretic and demulcent for cases of cystitis, pyelonephritis, and kidney stones and appears to relieve urinary tract-related edema. Pellitory appears to have nonspecific protective effects on nephrons, and thus may, if nothing else, protect functional tissue from harmful effects of gravel or stones.

Berberis vulgaris (Barberry)

Berberis vulgaris (barberry) and other berberine-containing herbs are primarily used for inflammation and infections in the intestinal tract (including the liver and gall bladder). They are also used in eye washes. Clearly berberine and other alkaloids in barberry are antimicrobial,[58] and therefore might be considered if there is an indication of presence of infected stones. Recurrent urinary tract infection without an obvious cause in someone known to be a stone former hints at the presence of infected stones.

Alchemilla arvensis (Parsley Piert)

Alchemilla arvensis (parsley piert), also referred to as *Aphanes arvensis*, is another poorly researched plant used widely by British herbalists. It is historically considered to have astringent, diuretic, and antilithic properties.

STONEBREAKER

Phyllanthus niuri is known as chanca piedra and quebra pedra, or stonebreaker, in South America. It is also found in Southeast Asia, along with the related species *P. urinaria* and *P. amarus*. Though *P. amarus* has been shown to have intriguing activity in patients with hepatitis B infection, these herbs are also relevant in kidney stone patients. The leaf is used medicinally of all these species. Chanca piedra or bhumyamlaki aqueous extracts have been shown to inhibit calcium oxalate crystallization in the test tube.[59] Though reportedly diuretic in a rodent and human study,[60,61] low-dose studies find that it is not significantly diuretic in rats, though it still significantly dissolves stones.[62] This occurred without affecting any known urine parameters associated with dissolution including calciuria or oxaluria.

In a moderately large trial involving chronic calcium stone-forming adults, ingestion of 450 mg freeze-dried, aqueous chanca piedra extract three times daily was associated with reduction of hypercalciuria in those patients who had this problem initially.[63] The difference was significant compared to placebo.

Finally, a large clinical trial found that intake of 2 g of an unclear phyllanthus extract per day after extracorporeal shockwave lithotripsy for stone removal was significantly more effective than no additional treatment at preventing stone recurrence.[64] This herb should be further investigated for its long-term abilities to prevent stone formation.

MANAGING THE ACUTE STAGE

Calming renal colic and assisting in the passage of a stone during the acute phase can be done effectively with botanicals. Obviously a great deal of clinical supervision is necessary to ensure the patient gets through the acute stage without complications. In addition, this condition is usually excruciatingly painful and may require narcotic analgesics or other pharmaceutical drugs. Nonetheless, some patients can be managed with medicinal plants alone. The diuretic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and narcotics often prescribed to treat acute urolithiasis have numerous side effects not seen with the botanical approach. For example, diuretics can cause dangerous mineral depletion and NSAIDs can negatively impact the kidneys, intestines, joints, and liver.

A dedicated patient with a typical calcium oxalate stone can often get through the passage of a stone without complications. Generally, 85% of patients with a stone under 4 mm (1/10 inch) in diameter will pass it spontaneously anyway,[65] and natural therapies can safely enhance the process. Patients with unusual types of stone (staghorn, cystine, and stones larger than 2 cm [3⁄4 inch] diameter) may require a different approach not discussed here. Serum creatinine levels should be checked if a stone has not passed after 10–14 days to ensure no renal damage is occurring.

In the acute stage, a hot bath is advised along with hot compresses directly over the kidney or ureter where the pain is felt. If the pain is not so acute as to warrant an emergency room visit to get major pain killers, botanical teas with diuretic, inflammation modulating, and spasmolytic effects directed at the urinary tract organs will often successfully move the calculus. Combination tinctures along with large volumes of dandelion leaf tea, or just hot water, are quite effective. If dandelion leaf cannot be obtained, goldenrod is one possible substitute. The botanical formula works by relieving edema in the ureteral mucosa, decreasing spasm due to irritation by the calculus, and promoting flow of urine. This enhances expulsion by pressure and volume of fluid, which is important when the normal movement imparted by urethral spasm is inhibited by the herbs.

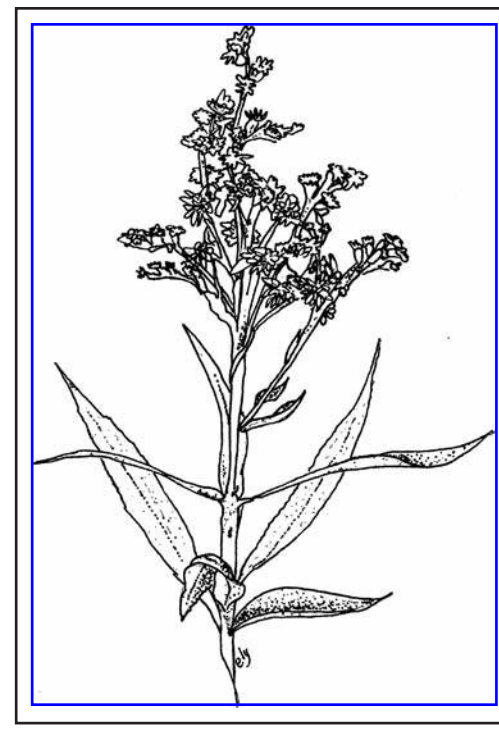

Figure 20–2. *Solidago canadensis* (goldenrod)

The Pass Stone Formula (see Table 20-2) can be dosed at 3–5 ml (5 ml is 1 tsp) every 30 minutes to 2 hours as needed, taken with as many cups of dandelion leaf or goldenrod tops tea as possible. Use 2 tsp (10 g) of dandelion or goldenrod per cup of boiling water and allow to steep for 15 minutes. An entire day's batch can be mixed in the morning and kept in the refrigerator, then heated up or drunk at room temperature when each cup is to be taken. Each component of this special formula is discussed below.

BOTANICALS FOR EASING PASSAGE OF ACUTE URINARY CALCULI

Lobelia inflata (Lobelia)

Lobelia inflata (lobelia) is used primarily as a respiratory stimulant and spasmolytic. However, its powerful relaxant and antispasmodic effects make it uniquely helpful in passing stones through the ureter. Lobeline and other alkaloids in lobelia are acetylcholine antagonists,[66] though other mechanisms may account for its broncho- and uretero-dilating effects. The nicotine-like lobeline can provoke emesis and the dose of lobelia is limited by this effect. Some patients do better if lobelia is taken separately and the individual's nonnauseating dose is determined gradually increasing the number of drops from 2–3 up to 15 drops per dose as frequently as needed.

Rubia tinctoria (Madder)

Rubia tinctoria (madder) root enjoys a long tradition of use in Europe including Russia.[67] While not well studied, its active principles appear to be anthraquinone glycosides such as alizarin. This is also the red pigment in madder and the source of its fame as a dye plant. It is important to remember to warn the patient that his or her urine may turn red while taking madder. The use of the small quantities suggested here will likely only cause a light pink coloration. Madder is traditionally considered a diuretic, though it is probably only mildly so. It appears to have a spasmolytic effect on the ureter, thus helping the stone to pass. Studies on a related plant, *Rubia cordifolia* (Chinese madder, chien tsao), have shown it to have calcium channel-antagonizing effects,[68] which might contribute to relaxing of smooth muscle. Madder is also used to prevent calcium and phosphate oxalate salts from forming stones. Other studies in mice have shown no toxicity from madder administration, even in very large doses.[69]

Ammi visnaga (Khella)

Ammi visnaga (khella) originates from North Africa where it is primarily used as a spasmolytic in asthma[70] and to treat angina.[71] This, similar to lobelia, highlights that antispasmodic plants used in the respiratory tract are frequently also of value in the urinary tract. Khellin, the main active compound in khella, as well as visnadin, may act as a mild calcium channel blocker, explaining its dilating effect on the ureter.[72] Visnagin, another furanocoumarin from khella, also has interesting smooth muscle relaxing effects related to nonstandard calcium channel activity.[73] Rodent studies have shown that khella is significantly diuretic and prevents the formation of calcium oxalate stones as well.[74]

In Egypt, khella is a popular medicine for kidney stones as it relieves ureteric spasms. Kidney, ureter, and bladder stones are quite common in Egypt due to the frequency of bilharziasis. Interestingly, *Ammi majus* (Bishop's weed), a relative of khella, has shown to kill *Schistosoma mansoni* (one of the organisms that causes bilharziasis).[75] Khella's active compounds are excellently absorbed and have low toxicity as evidenced by the almost total lack of side effects with long-term use in treating people with asthma. Its spasmolytic effects last approximately six hours, and thus more frequent dosing than this will potentiate the effect of previous doses still active in the body.

Eupatorium purpureum (Gravel Root)

Eupatorium purpureum (gravel root), as its name implies, has traditionally been used for treating urinary gravel. The Eclectics, physicians who employed natural therapies at the end of the 19th and beginning of the 20th centuries, considered it mildly astringent, stimulant, and tonic with a specific action on the urinary tract.[76] It was said to have the power to dissolve concretions.[30] Gravel root is also prescribed for patients with cystitis, urethritis, fluid retention, and cases of irritable bladder. More recently it has been determined that this Asteraceae family plant contains unsaturated pyrrolizidine alkaloids, which have been associated with hepatotoxicity in other plants. So far no accounts of harm from this plant have been reported, but concern is warranted until a definitive determination about its safety can be made.

Aesculus hippocastanum (Horse Chestnut)

Aesculus hippocastanum (horse chestnut) is used in a variety of conditions for the anti-edematous effects of escin. This compound dramatically decreases small-pore number and diameter in capillary endothelium, thereby reducing fluid seepage into the tissue space.[77,78] The late R.F. Weiss reports that escin is 600 times more effective than rutin and is most often used to improve the tone of the venous walls.[79] In the case of calculi caught in the ureter, horse chestnut's anti-edematous effects enlarge the internal diameter of the ureter. As a result the stone

Figure 20–3. *Eupatorium purpureum* (gravel root) stem and leaf

can move more easily, even in resistant cases. In preventing recurrences of urolithiasis, horse chestnut appears to help gravel pass smoothly.

In some cases this formula has helped to break up stones that are then passed in smaller pieces. It is important to remind the patient to urinate through a fine screen, or, if that is not available, to urinate into a jar. When the stone passes into the jar, it will often make an audible sound permitting a subsequent analysis of the stone.

CONCLUSION

Together, nutritional and botanical approaches provide very potent tools in controlling urolithiasis. Prevention can work well provided the patient is willing to follow a regular program. Acute nephrolithiasis can also sometimes be managed by entirely natural means in the hands of an experienced practitioner who knows when to refer patients who are progressing poorly for allopathic intervention.

We had one patient who was followed on this protocol for several years. His mother and maternal grandfather had a history of kidney stones, and his paternal grandfather also had some kidney problems. When he was first seen he had just given up taking hydrochlorothiazide (HCTZ) 100 mg a day. He had previously taken this for over five years during which time he passed two calcium oxalate stones. He was 46 years old at that time. The first renal lithiasis occurred when he was 20 years old. That calculus was removed by cystoscopy. The frequency of occurrences increased throughout his twenties and he experienced six episodes in his thirties. He passed a stone every month for the year before he started the HCTZ, requiring strong pain medication each time.

The patient took the supplements and botanicals faithfully but only sporadically adhered to the dietary recommendations. He passed one acute stone during an emotionally stressful period while on this regimen. He drank copious amounts of dandelion leaf infusion along with the Pass Stone Formula during this acute episode. After several days of alternating renal colic, which was milder than he remembered, and vague, lightheaded, toxic feelings, he decided to see a urologist who ordered an intravenous urogram (IVU). Shortly thereafter he passed some gravel in a bit of pink-tinged urine and the sharp pain subsided. The next day the IVU revealed no abnormalities. Over the next three days he gradually felt better on a modified botanical formula to soothe and heal the urinary tract, and resumed full activities a few days after that. Over the next two years, he experienced one recurrence, a stone that again passed easily, which he attributed to using the botanicals. He continues on the supplements and an individualized botanical formula. This case illustrates that natural medicine has a lot to offer, both preventively and therapeutically, for patients with recurrent urolithiasis.

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21

LUPUS ERYTHEMATOSUS AND HERBAL MEDICINE

Mainstream treatments for people with discoid or systemic lupus erythematosus (DLE and SLE, respectively) remain inadequate in terms of safety, efficacy, and cost-effectiveness. This chapter reviews herbal approaches with promise to improve this situation.

IMMUNOMODULATORS

Clearly immune dysfunction, particularly dysfunction in the complex regulatory network in the interconnected immune and neuroendocrine systems, plays a central role in SLE. In traditional herbal medicine, herbs with immunomodulating properties have been used for people with autoimmune diseases for a very long time. These herbs generally have minimal or no known adverse effects with excellent cost-to-benefit ratios.

A glycoprotein extract dubbed PSK derived from *Trametes versicolor* (cloud mushroom, yun zhi), formerly named *Coriolus versicolor*, has been studied in patients with SLE and shown to improve symptoms.[1] This medicinal mushroom has long been valued in traditional Asian medical systems for syndromes that, in the West, we would call cancer and autoimmune diseases. No other studies were located following-up on the promising preliminary trial. Large-scale trials of PSK and related extracts in patients with cancer show they are very safe.[2] The usual dose in these trials has been 1–3 g daily.

Cordyceps sinensis (cordyceps, duong chong xiao cao) is a fungus that in the wild grows exclusively on a very specific caterpillar species and has a remarkably complex life cycle. This herb has been used in traditional Chinese medicine for patients with syndromes that in the West we would call autoimmune diseases. Preliminary studies in patients with SLE in China found that among other herbs, cordyceps could improve abnormal IL-2 production.[3] A follow-up trial found that administration of decoction of cordyceps to NZB/NZW F1 female mice, a common animal model of SLE, prolonged life span and decreased anti-double-stranded (ds) DNA autoantibody production compared to untreated controls. A steroidal saponin isolated from cordyceps known as H1-A was administered orally to male and female MRL 1pr/1pr mice, another animal model of SLE, for eight weeks.[4] Treated animals lived longer, had less proteinuria and lymphadenopathy, less mesangial proliferation in the kidneys, and less anti-ds DNA autoantibody production compared to controls treated only with the same vehicle as H1-A. These results were confirmed in another study using a crude aqueous extract of cordyceps in MRL 1pr/1pr mice.[5] Clearly human trials are warranted on the effects of cordyceps extracts in human SLE patients.

Similar animal studies have been conducted using extracts of *Ganoderma lucidum* (reishi, ling zhi) mushroom or the closely related species *G. tsugae*. Extracts were shown to reduce anti-ds DNA autoantibody formation, prolong life span, reduce proteinuria, and reduce cellular infiltrates into internal organs in NZB/NZW F1 mice compared to those treated with prenisolone.[6] No human trials have been published on use of reishi in patients with SLE.

An open clinical trial was conducted using 60–120 mg daily of a standardized extract of triterpenoid glycosides from *Centella asiatica* (gotu kola) herb in patients with SLE in Germany.[7]

It found that the extract could cause symptomatic improvement. Gotu kola is considered an immunomodulating herb and is extremely safe.

A different approach was taken using a lectin isolated from *Urtica dioica* (stinging nettle) that eliminates a specific T-cell subset (V beta 8.3+) when administered to mice. In this case, the lectin was administered to MRL lpr/lpr mice and was shown to prevent development of any clinical signs of lupus or kidney damage.[8] Although this information may be important in understanding the immune pathology of lupus, it also suggests that ingestion of certain herbs may be able to prevent onset of the disease in people who are genetically susceptible or at risk. Whether nettles would be useful in patients with established SLE is unknown though they are traditionally used as inflammation modulators in such settings.

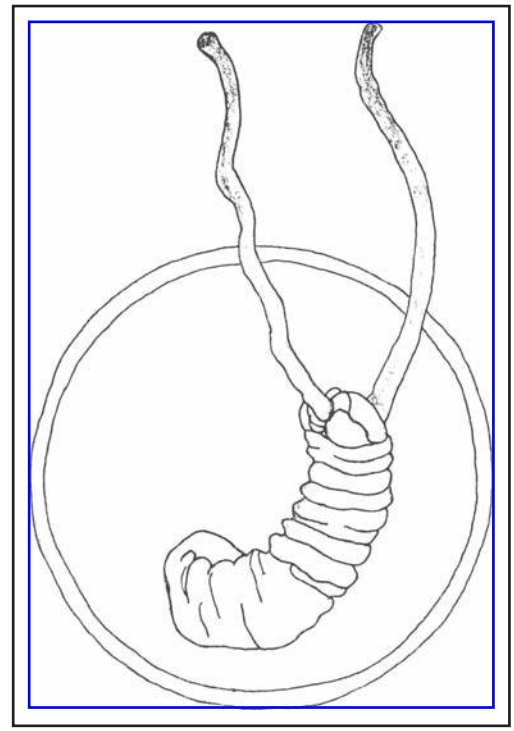

Figure 21–1. *Cordyceps sinensis* (cordyceps)
Drawing by Kathy Abascal, BS, JD.

IMMUNOSUPPRESSANTS

Tripterygium wilfordii (lei gong teng, "thundergod vine") is an Asian native plant whose roots have been determined to contain immunosuppressive glycosides. Only extracts of roots with bark removed should be used to avoid amenorrhea, male infertility, kidney damage, and leucopenia.[9] These effects are believed to be mediated by nontherapeutic alkaloids that may be further decreased by decoction. Another potential problem with long-term use of *Triterygium* is decreased bone mineral density, though the problem is not as severe as that seen in women who taken prednisone.[10] Any patient treated with this herb should have their serum creatinine, CBC, and reproductive health assessed monthly.

All indications are that lei gong teng works by immunosuppression and that the herb is not immunomodulating (that is, it does not occasionally work through immune activation).[11] It also has substantial inflammation-modulating activity.

Several clinical trials have been conducted on various extracts of the herb in patients with autoimmune diseases. In an open trial, use of tablets providing 5 g three times daily of the whole root and stem in 15 patients with SLE and 8 with discoid lupus was compared to prednisone in 19 patients.[12] Both treatments were equally effective in general, though the herb improved arthralgia and rash significantly better than prednisone. Some kidney damage and leukopenia was seen in patients treated with the herb. Another open trial followed SLE patients treated with 30–45 g of decorticated stems and roots daily.[13] Symptoms improved as did ANA and LE cell titers. Occasional, reversible amenorrhea and gastrointestinal upset occurred, mostly disappearing after a few days despite continued therapy.

A more recent trial looked at the effect of methylprednisolone (MP) followed by prednisone and *Tripterygium wilfordii* treatment on seven children with juvenile onset SLE without kidney or neurological involvement.[14] Comparison groups were treated with either MP and cyclophos-

phamide (if they had nephritis or CNS involvement, n = 18) or prednisone alone and no renal or CNS involvement (n = 5). Patients in the prednisone-only group fared far worse clinically (including four deaths) than the other two groups, which were otherwise fairly comparable, particularly after nine or more months of therapy. Two patients in each of the MP and cyclophosphamide and *Tripterygium* groups were asymptomatic 12 months after discontinuation of treatment. Frequent infections were not encountered in any of the groups.

Animal studies on artemisinin and its cogeners, antimalarial constituents of the plants *Artemisia annua* and *Artemisia apiacea* (sweet Annie, qing hao), have demonstrated they possess immunosuppressive properties.[15] Some preclinical research suggests it may actually be immunomodulatory.[16] Although not all studies agree, this fact coupled with the traditional use of these herbs for inflammatory conditions supports the clinical potential of sweet Annie in SLE patients. Indeed, one preliminary trial in China found that *Artemisia apiacea* was helpful, though full details of this study are not available in English.[17] Artemisinin, 200–600 mg daily, was used successfully in another study of 25 patients with SLE in China.[18] *Artemisia annua* was apparently also helpful in patients with discoid lupus in another open study.[19]

Studies in mice have shown that an alkaloid isolated from *Nelumbo nucifera* (lotus) rhizome, *S*-armepavine, could inhibit T lymphocyte proliferation in a mouse model of SLE.[20] Lotus rhizome extracts, especially into alcohol, have been shown to have strong antioxidant activity, which could help counteract some of the pathology of SLE.[21] Lotus rhizome is used primarily as an antihemorrhagic in traditional Chinese medicine. Clearly more research is warranted to determine the complete spectrum of action and utility of this intriguing herb for patients with lupus.

PHYTOESTROGENS

Estrogen or its metabolism has long been believed to play a role in SLE, in large part due to the preponderance of women who are affected. Given this fact and evidence that environmental endocrine disruptors (xenoestrogens) can induce SLE-like syndromes in mice,[22] phytoestrogens may play a useful role in patients with SLE.

One study found that administration of the phytoestrogen coumestrol was associated with decreased autoantibody production, reduced splenomegaly, and less severe proteinuria in NZB/NZW F1 mice.[23] Survival time did not differ from control groups fed diets without coumestrol. This preliminary evidence supports the need for studies of other phytoestrogens, different dose levels, and human trials to see if phytoestrogens will indeed be helpful. Studies of another phytoestrogen for lupus nephritis make such this research even more important to conduct.

One phytoestrogen that should be avoided is sprouted *Medicago sativa* (alfalfa). Alfalfa sprouts contain a substantial level of the arginine homolog canavanine, which has been shown in limited research to potentially trigger SLE.[24] Although not an apparently common phenomenon, alfalfa sprouts should be avoided by people with SLE to prevent any chance of worsening. Any form of alfalfa that excludes the seed is acceptable and does not contain canavanine.[25]

LUPUS NEPHRITIS

Glomerulonephritis is a common and serious complication of SLE. Botanical medicine also has much potential to help patients who develop lupus nephritis. *Linum usitatissimum* (flax) seed contains phytoestrogenic lignans and inflammation-modulating omega 3 essential fatty

acids. A single-blind, randomized clinical trial sought to have 26 23 patients with SLE on prednisone take 30 g flax seeds daily for one year, then cross over to a year of not taking the supplement.[26] Unfortunately, there were many dropouts and poor follow-through, with only nine patients clearly having taken the flax seeds as requested. Nonetheless, there were clear indications that the nine who did take the flax regularly had improved renal function.

Immunomodulators may also be of benefit in patients who have progressed to lupus nephritis. One open trial lasting five years in lupus nephritis patients in China compared the effects of two different regimens.[27] The immunomodulator group received a combination of cordyceps (1 g three times daily) and artemisinin (200 mg three times daily). The control group received a combination of *Tripterygium wilfordii* and the combination formula baoshenkang. All 61 patients had previously shown no response to corticosteroids or cyclophosphamide. Kidney function was stable in the immunomodulator group whereas it declined in the control group. Clinically, patients in the immunomodulator group were rated significantly improved compared to the control group. Adverse effects were also reportedly fewer in the immunomodulator group.

CONCLUSION

Numerous herbal medicines show great promise for mitigating SLE and lupus nephritis. Though much more research is needed, preliminary indications are strong that various immunomodulators, immunosuppressives, and inflammation-modulating botanicals may be of great benefit for these patients.

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22

BOTANICAL TREATMENT AND PREVENTION OF MALARIA

Most practitioners today rarely consider malaria due to the triumphant, near total eradication of this disease from the developed world. Unfortunately, malaria remains a major scourge in the undeveloped world, and this has significant economic and political impacts on the developed world. The rise of multidrug-resistant malaria in various parts of the world also bodes poorly for global health and raises the specter of a new introduction of these virulent parasites to the southern United States and/or Europe. Though most natural medicine clinicians in the United States are primarily interested in preventing malaria infection in their patients traveling to malarious regions, the historical and modern situation related to treatment of malaria is also relevant, particularly because of how intertwined it is with botanical medicine.

This chapter looks at two topics. First, we discuss botanical mosquito repellents and research on their efficacy. This represents an indirect method of preventing not only malaria but other diseases carried by insects. Second, we review potential herbal treatments and prophylaxis for malaria. The history of treatment of malaria is intimately bound up with herbal medicine and this disease and botanicals will continue to remain related in many intriguing ways.

Throughout this chapter the standard definitions of cure and radical cure are used in relation to malaria. Cure, perhaps better termed *clinical cure*, is defined as absence of detectable parasites in the blood and no symptoms; it does not mean absolute removal of the parasite from the host. Radical cure means additionally the elimination of hepatic reservoirs of the parasite and thus the possibility that all malaria has been removed from the host. Recrudescence refers to return of symptoms and *Plasmodium* blood forms after a remission.

MOSQUITO REPELLENTS

Modern medicine tends to focus heavily on the use of drugs internally to prevent malaria infection. However, this approach can be expensive and exposes many otherwise healthy people to the risk of adverse effects. When the risk of infection in particular areas is very low, the risks can outweigh the potential benefits, as shown by a study of visitors to Kruger National Park in South Africa, which has a low rate of malaria infection.[1] Chemophylaxis is usually most relevant for those traveling to areas with high infection rates.

Another option exists and is fairly well studied—prevention of mosquito bites. The most convenient method for most people is use of topical mosquito repellents. Mosquito netting over one's bed will prevent night-biting mosquitoes from spreading malaria. Wearing long sleeves, long pants, and socks can also reduce mosquito bites. Staying inside at twilight when the majority of malarial mosquitoes are active is also important. Burning various mosquito repellents for group or home protection may give some benefit.

Numerous botanical medicines have shown promise as potential mosquito repellents. Although the synthetic agent N,N-diethyl-3-methylbenzamide, formerly known as N,N-diethyl-m-toluamide,

or DEET, is effective as a mosquito repellent, questions about its safety linger. For instance, one study found that application of normal doses of DEET to rats' skin led to no overt neurotoxicity but produced clear signs of behavioral deficits and cortical degeneration.[2] It is generally more neurotoxic in children, particularly girls, though the overall rate of clinical neurotoxicity is <0.5%.[3] DEET erodes plastic, making it somewhat inconvenient for those using binoculars, computers, and so on. Finally, DEET cannot be produced locally without industrial infrastructure and thus is not particularly available to poor people in the undeveloped world. A botanical alternative to this product that is just as effective and safer, and that can be produced in a sustainable fashion at the local level, would therefore be a boon.

Basil as a Mosquito Repellent

Various species of *Ocimum* (basil) have historically been used to repel and kill mosquitoes.[4] Basil has been employed in numerous ways to this end including application of basil oil to the skin, growing potted plants in houses, and burning basil leaves. Basil has also been shown to kill mosquito larvae, and thus may be useful as a botanical insecticide.[5]

In a preliminary study, *Ocimum selloi* (basil pepper) leaf volatile oil (diluted 90% in ethanol) was applied to forearm skin of volunteers in a field test to detect repellency against *Anopheles braziliensis* in Brazil.[6] The median repellency compared to the ethanol vehicle was 89% (range 75–100%). DEET applied to protect the face showed 100% repellency in all subjects. None of 30 other volunteers patch tested against the oil showed any negative reaction over 4 hours. Single intragastric doses of up to 1.25 mg/kg of the oil showed no toxicity in mice, whereas 1.5 mg/kg caused significant mortality. Further clinical trials of various basil oils are indicated to further quantify their efficacy and safety.

Liquid paraffin solutions of *Ocimum gratissimum* (wild basil) and *O. basilicum* (basil) oils at concentrations of 1% and higher exhibited 70% bite protection for two to three hours in one study in Nigeria.[7] Using higher concentrations (20% and 35%) resulted in 99% bite-free for two to three hours. This information, supported by the study on basil pepper above, suggests that higher concentrations (20%+) of basil oils should be used for optimal protection and that concentrations below 10% are insufficient.

Placing six potted plants of *Ocimum americanum* (hairy basil, which is actually native to Africa) inside of experimental huts in netted greenhouses decreased entry of mosquitoes by 40% compared to a nonfragrant native grass.[8] Although obviously not an enormous difference, this is significant and represents a totally nontoxic, sustainable, and simple way to reduce mosquito exposure. The oil of hairy basil has previously been shown in laboratory conditions to repel numerous species of malaria-carrying mosquitoes for up to eight hours, particularly when combined with 5% vanillin.[9]

In a similar vein, placing leaves of various species of basil in boiling water inside huts to drive away mosquitoes has been tested.[10] Leaves and seeds of *Ocimum suave* (smooth basil) and *O. kilimandscharicum* (camphor basil) repelled 53% and 52% of mosquitoes, respectively, compared to the control in screened greenhouse testing. Direct burning of smooth basil leaves repelled 28% of mosquitoes. This approach needs further real-life testing but represents another highly sustainable method of reducing malaria exposure.

Neem Oil Repels Mosquitoes

Azadirachta indica (neem) is a tree native to India and has been spread to many places in the tropics. Similar species are found in other tropical nations. This tree yields an insecticide that

may help control mosquitoes, but an oil extract of the leaves has also been investigated as a topical mosquito repellent. In numerous field trials in India, a 2% neem oil solution in coconut oil has been shown to be effective at repelling mosquitoes. One open trial showed 100% repellency against all species of *Anopheles* mosquitoes tested for 12 hours.[11] Similar efficacy was seen against *Anopheles* mosquitoes in another field trial, but protection against other mosquitoes and biting insects ranged from 37 to 94%.[12] An even more realistic field trial in a forested region of India found that 1–4% neem oil in coconut oil had an 81% or better repellency against *Anopheles* mosquitoes for 12 hours.[13] A cream formulation has also shown mosquito repellent activity.[14] Neem oil has also been shown to repulse other insect vectors such as sandfly.[15] None of these trials were double-blind or used DEET or any other control, leaving the question as to true efficacy somewhat open.

One trial has compared the repellent effect of neem oleoresin and other essential oils with DEET primarily against *Mansonia* mosquitoes. At a 50% concentration, neem repelled 87% whereas DEET repelled 97.9% of the mosquitoes.[16] Neem was less effective than the other repellent herbs tested (see below). However, the authors note that the neem results may have been reduced because it was in the form of an oleoresin and was tested against a different type of mosquito than in other more positive studies.

The choice of coconut oil as a base for neem oil mosquito repellent may not be optimal. Neem oil in a mustard oil base has been shown to provide longer-lasting protection than in a coconut base (445 vs. 404 minutes).[17] Mustard oil has also been shown to prolong the repellent activity of the volatile oils of *Zanthoxylum rhetsa* (mullilam) fruit, formerly known as *Z. limonella*, and *Citrus aurantifolia* (orange) leaf by approximately 25%.[18]

Burning a mixture of 1% neem oil and kerosene in lamps has been shown to reduce mosquito entry and biting inside houses in an experimental trial.[19] As with the basil-burning studies discussed above, this was not nearly as strongly repellent as topical application of the oil. The burned oil was generally more effective against *Anopheles* than other species of mosquitoes.

Other Botanical Mosquito Repellents

Cymbopogon nardus (citronella) and related species volatile oils are the best known botanical mosquito repellents for most people. In a small (n = 16) clinical trial, various products with differing concentrations of citronella were tested against various formulations of DEET.[20] A 10% citronella product gave protection against *Aedes aegypti* bite for only 20 minutes on average (range 7–60 minutes) compared to 301 minutes on average for a 23.8% DEET product (range 200–360 minutes), a significant difference. Lower-concentration citronella products were even less effective. This study was notable for being entirely independent of any manufacturer.

A major problem in this study, as in the basil studies above, was an insufficient concentration of oil being applied. A study of a related oil, that of *Cymbopogon martinii martinii* (palmarosa), was found to provide 99% protection indoors and 96.5% protection outdoors for 12 hours after application of 1 ml of 100% oil.[21] This study was conducted on the Nicobar Islands off the coast of India in a real-life setting, and thus may represent a more accurate result than greenhouse or laboratory studies.

The importance of concentration of oil used is further supported by a study on *Cymbopogon citratus* (lemongrass) volatile oil, a close relative of citronella. This trial found that 10–25% solution of the oil had a 94–96% repellency up to three hours after application in a Nigerian population against *Aedes aegypti* bites.[22] Concentrations below 10% were half as effective, as was application of 15% citral, a major ingredient in lemongrass volatile oil. This also shows that isolated constituents are not always superior to complex oil mixtures.

A product with the primary active component of 2% soy oil has been shown to provide protection against bites for 94 minutes on average (range 19–195 minutes) in the same study as the citronella study mentioned above.[23] Though significantly less effective than any DEET product tested, it was still within a clinically useful range.

Eucalyptus citriodora (lemon eucalyptus) leaf volatile oil is the source of p-methane-3,8-diol (PMD), which is considered a safe and effective mosquito repellant by the U.S. Environmental Protection Agency and the Centers for Disease Control and Prevention.[24,25] PMD was reported to be almost as effective as DEET at repelling a variety of mosquitoes.[26] The volatile oil with multiple constituents may also be effective. An unstated concentration of volatile oil protected against mosquito bites for an average of 120 minutes (range 60–217 minutes).[20] This product was included in the citronella study at the last moment and thus was not compared statistically to the other products tested. In a trial using DEET as a control, lemon eucalyptus (*Ecuaclyptus citrodora*) oil gave a percent protection equivalent to that of DEET at identical concentrations (40–75%).[16]

Chrysanthemum cinerariaefolium (pyrethrum) has known repellent properties but previously was reported to be unsuccessful in skin formulations. However, a pyrethrum oleoresin provided a percent protection of 87–96% protection at concentrations of 40–75%, indicating

Figure 22–1. *Eucalyptus* spp. (eucalyptus)
Drawing by Kathy Abascal, BS, JD.

that further research is needed on this herb.[16] The same study tested the repellent activity of *Ruta chalepensis* (rue) oil. Rue was more effective than neem in this study but not as effective as lemon eucalyptus or pyrethrum.

A hexane extract of *Foeniculum vulgare* (fennel) fruit had a 99% repellency in a laboratory test against *Aedes aegypti*, the mosquito vector for yellow fever.[27] The compound (+)–fenchone was isolated from this fraction and shown to have 100% repellency when applied at a concentration 0.02 mg/cm^2 on the skin. However, by 30 minutes efficacy had dropped to 76% repellency and to 51% by one hour, whereas DEET still provided 97% repellency at one hour. Further research is needed to find a longer-lasting repellent form of fennel and to extend work to look at malaria vectors, given the excellent safety profile and pleasant odor of this herb.

A highly preliminary trial found that *Mentha* x *piperita* (peppermint) oil had repellant activity against adult mosquitoes, though details of this study were not available.[28] The main focus of the study was another intriguing area, which is the use of botanicals to kill mosquito larvae in the wild and thus reduce mosquito prevention on a larger scale. In the study, 3 ml peppermint oil per cubic meter of water killed 85–100% of various mosquito larvae in the laboratory. Though DDT is highly efficient at destroying malaria-bearing mosquitoes, its environmental and possibly human toxicity as well as emergence of resistance mosquitoes have made it unacceptable for this purpose. The possibility of a botanical replacement is very exciting, but much more work is needed to determine if this is effective or practical. Further research is also clearly needed on botanical mosquito repellants, but the early promise suggests that an effective, safe, convenient DEET alternative may yet be possible. See Table 22-1.

Mosquitoes inject sporozoites into humans while feeding (see Figure 22-2). These are transported to the liver through the blood where they enter hepatocytes. These organisms can then multiply asexually, leading to formation of nonmotile merozoites that enter the circulatory system. Some *Plasmodium vivax* and *P. ovale* organisms delay entry into asexual reproduction, instead forming dormant hypnozoites that reanimate weeks to years later, causing relapsing infection. Merozoites enter erythrocytes and enlarge, consuming heme from hemoglobin, becoming known as trophozoites. Early trophozoites are called ring forms due to their shape. Ultimately the trophozoites begin to divide, forming schizonts. These can in turn form new merozoites that invade more erythrocytes cyclically. Each time merozoites emerge from erythrocytes, they do so in a synchronized format, and malarial fevers occur simultaneously every 48 or 72 hours. Erythrocytes containing schizonts or merozoites tend to stick to endothelium and can cause serious damage to the brain, heart, lungs, and kidneys.

Some merozoites develop into sexually reproducing gametocytes. When these are ingested by mosquitoes, motile microgametocytes fertilize macrogametocytes, forming zygotes that ultimate become motile ookinetes. These can penetrate into the mosquitoes' gut lining and form an oocyst, which undergoes asexual replication, forming sporozoites that rupture into the mosquito gut. The sporozoites travel to the mosquito salivary glands and can then spread to other hosts, starting the cycle over again.

CINCHONA: THE HERB THAT CHANGED THE WORLD

Few plants have had quite as dramatic and widespread an impact on the world as *Cinchona* spp. (Peruvian or Jesuit bark), family Rubiaceae. These trees are native to the Andean rainforests in what are today Colombia, Peru, Bolivia, and Ecuador. After their discovery in the 17th century, apparently by the Jesuits, as a long-revered native treatment for periodic fevers, bark started being shipped to Europe. In no small part, the availability of Jesuit bark made it

Table 22–1. Review of Botanical Mosquito Repellents

Latin Binomial	*Common Name*	*Part(s) Used*	*Clinical Trials*
Ocimum spp.	Basil	Leaf volatile oil, whole live plant, burned leaf	Uniformly positive but preliminary
Azadirachta indica	Neem	Leaf oil extract (topical or burned); oleoresin	Generally positive but preliminary
Cymbopogon nardus	Citronella	Leaf volatile oil	Mixed, short duration of activity, use at least 20% oil
Cymbopogon martinii martinii	Palmarosa	Leaf volatile oil	One small positive trial
Cymbopogon citrates	Lemongrass	Leaf volatile oil	One small positive trial
Eucalyptus citriodora	Lemon eucalyptus	Leaf volatile oil or PMD	Three positive trials
Glycine max	Soy	Seed fixed oil	One positive trial
Mentha x *piperita*	Peppermint	Leaf volatile oil	One small positive trial
Foeniculum vulgare	Fennel	Seed extracts	None located
Ruta chalapensis	Rue	Leaf volatile oil	One positive trial
Chrysanthemum cinerariaefolium	Pyrethrum	Leaf oleoresin	One positive trial

Note: All volatile oils can cause contact dermatitis in sensitive patients, though this is rare; otherwise, no adverse effects have been reported.

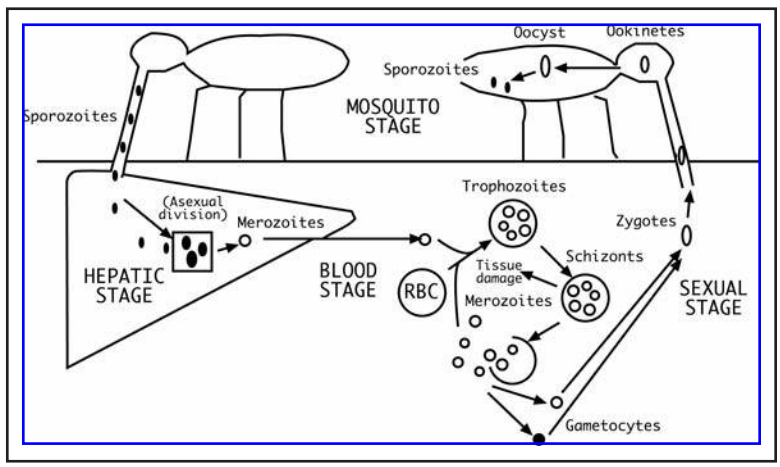

Figure 22–2. Review of Lifecycle of *Plasmodium* spp.

possible for European empires to expand in the tropics by reducing the threat of malaria. Nearly 200 years later, the British merchant Charles Ledger finally managed to sneak out viable seeds of the most esteemed species, eventually named *Cinchona ledgeriana* in his honor. Foolishly, the British refused the seeds, and thus Ledger sold them to the Dutch, who established plantations in Java and a global monopoly on quinine by the time of World War I. The antimalarial alkaloid quinine was first isolated from the bark in 1820 by the French scientists Joseph Pelletier and Joseph Caventou. Eventually the Japanese capture of Java in 1942 led to such a severe quinine shortage for the Allies that plantations were established in what is today the Democratic Republic of the Congo, formerly Zaire. During the attempt to synthesize quinine, the first antibiotics (sulphonamides, by Gerhard Domagk) were discovered as a result of the serendipitous finding of aniline dyes by William Perkin. Thus not only was quinine arguably the first important, global pharmaceutical drug, but it was also the catalyst for the rise of antibiotics.

Crude *Cinchona* is not used in mainstream medicine; instead, only its purified alkaloid quinine and various semisynthetic derivatives developed starting in World War II, the most famous being chloroquine and mefloquine. There are three lines of reasoning that support a return to either multicomponent *Cinchona* alkaloid use or whole-plant extracts—the development of resistance to single agents by *Plasmodium* spp., toxicity of high-dose single agents, and economic sustainability. See Figure 22-2.

The widespread use of chloroquine has resulted in widespread resistance among *Plasmodium* spp. to the drug, particularly in parts of Africa and Asia. Once the parasites become resistant to quinine, chloroquine, or mefloquine, they tend to develop cross-resistance to the other agents because they have similar mechanisms of action. Of particular concern in a study in Cameroon documenting this cross-resistance was the fact that some *Plasmodium* isolates in northern Cameroon showed resistance to mefloquine though this drug had not yet been used to any significant degree in that part of the country.[29] Cross-resistance secondary to quinine and chloroquine resistance was the apparent cause, and the outcome is that some malaria drugs are becoming ineffective even before they are used.

The medical community worldwide is finally starting to realize that using single antimicrobial agents, including against malaria, is ultimately a losing strategy. Single agents put enormous evolutionary pressure on a species and strongly encourage development of resistance. A growing chorus of those who treat patients with malaria are calling for use of multiple agents simultaneously, both for prevention and for treatment.[30] To some extent it is too late to combine existing drugs, as resistance has already emerged against many of them, though this may help curtail spread of resistance and reduce new resistant strains from evolving.

MULTIPLE ALKALOIDS VERSUS ISOLATED QUININE

This multidrug approach is remarkably similar to the logic behind the use of whole plants. In the case of *Cinchona*, it is very well established that quinine is not the only antimalarial agent in the bark. There are at least four known antimalarial alkaloids—quinine, quinidine, cinchonine, and cinchonidine. See Figure 22-3. All four alkaloids are equally effective at killing *Plasmodium* spp.[31] In vitro these four alkaloids show additive properties when combined, and a combination of quinine, quinidine, cinchonine, and cinchonidine was more effective than a total alkaloid extract of the bark.[32] The combination of quinine, quinidine, and cinchonine is dramatically more effective than quinine alone against drug-resistant malaria in vitro.[33] Thus, although these alkaloids likely act by similar mechanisms, they are still more effective

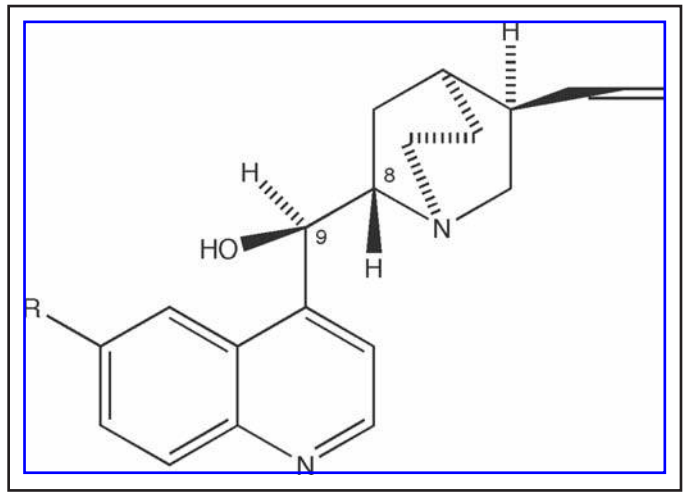

Figure 22–3. Chemical Structures of Quinine, Quinidine, Cinchonine, and Cinchonidine
Quinine: R = CH_3O; bonds are as shown at carbons 8 and 9
Quinidine: R = CH_3O; bonds are reversed at carbon 8 (hydrogen is down) 9 (hydroxyl group is down and hydrogen is up)
Cinchonine: R = H; bonds are as in quinidine
Cinchonidine: R = H; bonds are as shown at carbons 8 and 9 (like quinine)

combined than in isolation and thus cross-resistance may not be as big a problem. Researchers should also look at whether nonalkaloids in Peruvian bark may have indirect beneficial effects on the antimalarial alkaloids, such as improving absorption or reducing resistance.

Clinical trials have demonstrated that products containing equal parts quinine, quinidine, and cinchoinine at a dose of 200 mg each three times daily by intravenous administration, or one third the usual dose of quinine by itself, can effectively cure adults with malaria.[34] Intramuscular administration of 10 mg/kg of a combination of all four alkaloids for seven days led to 89% cure rates in children in Guinea-Bissau (measured 28 days after stopping therapy), whereas three days treatment led to only 21% being cured.[35] Intrarectal administration of all four alkaloids at a dose of 20 mg/kg in Nigerian children has been shown comparable to intramuscular administration of 12.5 mg/kg, though the IM administration acts moderately more rapidly.[36] Quinine and quinidine together showed a superior cure rate to quinine alone in children in Thailand with similar, clinically unimportant effects on heart rhythm.[37] In double-blind trials in Thailand, quinine alone was not superior to a combination of quinine, quinidine, and cinchonine in patients with known chloroquine-resistant disease.[38]

These trials provide strong though preliminary evidence that mixed alkaloid extracts of *Cinchona* spp. are viable options in treating patients with malaria. They should be studied for possible prophylactic use and larger studies performed to prove efficacy and safety and to investigate resistance formation, if any. Since quinine and most of its semisynthetic derivates are schizontocidal, they do not effect radical cures in malaria patients, and should generally be prescribed with drugs that kill hypnozoites in the liver, such as primaquine.

The total quantity of quinine in crude *Cinchona* bark is rarely more than 2%, with total alkaloid levels being 3–15% depending on the species. *C. ledgeriana*, as mentioned, tends to

have the highest alkaloid levels, followed by *C. succiruba*, *C. officinalis*, and then *C. calisaya*. To deliver a full 1 g of quinine daily would take 100 g of top-quality bark if quinine explained all the activity of Peruvian bark, which based on the multialkaloid studies above we know is false. Still, approximately 30–50 g of good quality bark is likely necessary to deliver a sufficient dose to prevent or treat malaria.

Isolated quinine has significant toxicity. At doses sometimes used clinically, (> 1.5 g daily in most people), and in cases of accidental or intentional overdose, a syndrome termed *cinchonism* occurs. This consists of nausea, vomiting, tinnitus, vasodilation, sweating, headache, arrhythmias with elongation of the QT interval on the electrocardiogram, ataxia, and delayed-onset bilateral vision loss that can be only partially reversible.[39] Thrombocytopenia and purpura may occur, as well an hemolytic anemia, and it is contraindicated in patients with myasthenia gravis and erythema multiforme.[40] It may also provoke pseudoallergic reactions in aspirin-sensitive patients. Photosensitivity can occur.

Generally it is quite difficult to give enough crude bark to deliver sufficient quinine to cause cinchonism, though it is possible and may occur more readily in some highly sensitive people. Whole *Cinchona* and bark extracts are quite bitter and have a tonifying and stimulating effect on the digestive tract. However, it also contains significant quantities of tannin, which can be quite irritating to the gut and cause nausea. It appears from the literature of the Eclectic physicians in the late 19th century that *Cinchona* extracts tended to cause more gastric upset in antimalarial doses than quinine but was less likely to cause cinchonism.[41] The comparative safety of multialkaloid and whole plant extracts of *Cinchona* should be carefully compared to that of isolated agents.

There are still very large *Cinchona* plantations in Africa. The sustainability of growing antimalarial plants and making extracts directly where they are needed is a big advantage over pharmaceuticals that require intensive manufacturing and often cannot be produced locally. Ultimately, given the extreme poverty in many malarious areas, if the local people are not empowered to deal with the problem, malaria will simply return once outside interest or money dries up, as occurred after the disastrous DDT spraying campaign in the 1970s.

Cinchona spp. gave the world the first effective treatment for malaria, and opened the doors to pharmacological medicine. Use of complex extracts of this still critical herb should be investigated as a way to help overcome the limitations of the isolated constituent/drug model. The more recent discovery of another antimalarial herb, *Artemisia annua*, shows that this approach does not apply only to *Cinchona*.

HUMBLE QINGHAO

To look upon *Artemisia annua* (sweet Annie, or qinghao in Chinese), one would not think it harbored potent antimalarial constituents. It is an inconspicuous green weed in the Asteraceae family that is generally low growing but in particularly wet areas may reach 2 m in height. It is primarily found in temperate areas with less than 50 cm rain per year.

Based on the traditional Chinese uses of qinghao for fevers, Chinese researchers in the 1960s and 1970s isolated the sesquiterpene lactone qinghaosu, dubbed artemisinin by westerners, as the apparent major antimalarial constituent in this herb. The total content of artemisinin in wild sweet Annie varies from 0.01 to 0.5%.[42] The compound has low water solubility. Oral bioavailability of pure artemisinin has been measured at 32%, but absorption from whole plant has not been reported.[43] Despite this, human trials comparing oral and intramuscular (IM) doses of artemisinin found that oral doses led to more rapid recrudescence and parasite clearance than IM.[44]

Figure 22–4. *Artemisia annua* (sweet Annie)
Photograph by Brian Hunter.

Multiple semisynthetic derivatives of artemisinin are now available as drugs to treat people with malaria, including artesunate, arteether, and artemether. They are almost always used in combination with other agents to help prevent the development of resistance to a completely new category of antimalarial drugs, though in areas where such rigor is not followed, resistance to artemisinin derivatives was documented as early as 2005.[45] All artemisinin-related compounds interact with heme to produce free radicals that appear to kill asexual blood forms and possibly gametocytes of *Plasmodium* spp. organisms.[46] They act more rapidly than any other antimalarial to clear the blood of parasites and may reduce transmission in areas where they are heavily used.

Unfortunately, the short half-lives of artemisinin and related agents leads to frequent recrudescence when they are used in isolation, as sufficient blood levels cannot be maintained to completely destroy all blood parasites. Thus either very frequent dosing is required, or coupling with other antimalarial agents. One study of combined artesunate with chloroquine in the Gambia, a nation with fairly high and growing chloroquine resistance, found that although there was a reduction in infectiousness related to reduced circulating gametocytes in children treated with both drugs compared to chloroquine alone, the benefits were lost after 28 days.[47] This suggests that short-duration artemisinin and derivative therapy (three days or fewer) does not lead to sustainable benefits clinically or in terms of preventing transmission.

A combination of artemether with grapefruit juice nearly doubled blood levels of the active metabolite dihydroartemisinin in a small clinical trial, probably because intestinal cytochrome 3A4 (CYP3A4) is responsible for breaking down the drug—grapefruit juice inhibits this enzyme.[48] The juice stopped working after two days, apparently due to induction of other enzymes that degrade artemether unrelated to CYP3A4. Using grapefruit juice simultaneously may allow for initial improvements in efficacy of sweet Annie, artemisinin, and derivatives. See Figure 22-5.

SWEET ANNIE FOR MALARIA

A special cultivar of *Artemisia annua* cv *Artemis* has been bred from Chinese and Vietnamese plants and contains 0.5–0.75% artemisinin in dried plant material. This cultivar has been studied as a sustainable way for people in Africa to combat malaria in an uncontrolled field trial in the Democratic Republic of the Congo.[49] The *Artemis* cultivar was raised locally, dried, then 5 g covered with 1 L boiling water and allowed to steep for 15 minutes, in accordance with the Chinese pharmacopoeia. The infusion was then filtered. Patients drank 250 ml of this preparation four times daily. Decocting the leaves greatly decreases artemisinin content and was abandoned. Extraction efficiency was found to be maximal using 5–10 g of leaves/L, yielding 12–24 mg artemisinin (~40% extraction compared to content in the dried plant). Thus, with five days treatment, most subjects in the study took in 60 mg artemisinin. By comparison, pure artemisinin is often administered orally at doses of 500–5,000 mg over the same time period, or roughly 1–100 times higher than the amount present in the infusion.

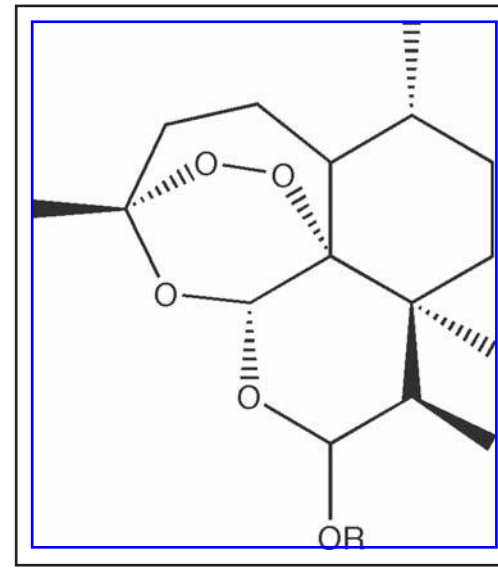

Figure 22–5. Structure of Artemisinin and Related Drugs

Artemisinin: R = double-bonded oxygen
Artemether: R = CH_3
Arteether: R = C_2H_5
Artesunate: R = $COCH_2CH_2CO_2^-$
The endoperoxide bridge in the upper left-hand ring is essential for antimalarial activity. All agents appear to act only when biotransformed in the body to dihydroartemisinin.

Despite the very low doses of artemisinin delivered by the tea, five volunteers infected with *P. falciparum* were all clinically cured and had complete clearance of trophozoites in their blood after five days. Synergy with other constituents in the herb is the most likely explanation for this phenomenon. In a larger study on 48 volunteers, 44 had total parasites clearance and 77% were asymptomatic after five days of treatment. One quarter of the patients had nausea during therapy that passed when use of sweet Annie tea was discontinued. In an unofficial control group of 12 patients seen at the same hospital for malaria who did not take sweet Annie tea, 25% were shown to become free of trophozoites spontaneously after four days. The total amount of artemisinin delivered is either sufficient to attain the 10 mcg/L blood concentration of dihydroartemisinin that appears necessary for parasite reduction, or else there are other constituents that act with the artemisinin.[50]

What this initial study did not determine was the long-term efficacy of treatment. In a follow-up open study, this same group using the same approach found that, although seven days treatment with the same dose of infusion led to 74% of patients being clinically cured and free of blood parasites, the recrudescence rate was very high.[51] This again supports the notion that this herb should be combined with other antimalarial treatments or used in very frequent doses throughout the day to maintain blood levels of active sesquiterpene lactones.

One of the most important things about *A. annua*, artemisinin, and its derivatives are the very low rates of adverse effects. Sweet Annie itself and artemisinin may occasionally cause

nausea. Some artemisinin semisynthetics may cause neuropathies, but this is rare. They are considered safe in the second and third trimesters of pregnancy.[52]

The open trials performed to date on crude sweet Annie were conducted in people with chronic malaria exposure. These results cannot be directly extrapolated to visitors from nonmalarious areas. Artemisinin has not yet been shown to be an effective prophylactic drug against malaria, and lingering concerns exist about the possibility of cumulative neurotoxicity.[53] Future studies should focus on combining sweet Annie extracts with other known antimalarial herbs, mosquito nets, botanical mosquito repellents, and pharmaceuticals. The possibility of people in areas affected by malaria growing their own medicine is too important not to continue this line of research.

THE POTENTIAL OF OTHER *ARTEMISIA* SPP.

Artemisia absinthium (wormwood) is a relative of *A. annua* with a very long history of use to treat intestinal parasites, as suggested by the common name. Though this herb very likely does not contain artemisinin, 95% ethanol extracts of it have shown significant antimalarial activity in mice.[54] In vitro, aqueous extracts of wormwood and a total sesquiterpene lactone fraction exhibited significant activity against *P. falciparum* in mice.[55] *A. vulgaris* (mugwort) aqueous extract had no effect. The fact that essentially no other reports have appeared since these studies came out in the early 1990s is highly unfortunate whether because efficacy was not maintained in humans or that funding was not available. Research on wormwood and non-artemisinin antimalarial constituents should be continued.

MISCELLANEOUS CLINICAL TRIALS ON ANTIMALARIAL PLANTS

The native African herbs *Cochlospermum planchonii* and *C. tinctorium* (n'dribala) and a formula known as AM-1 containing *Jatropha curcas* (purging nut; Euphorbiaceae), *Gossypium hirsutum* (cotton; Malvaceae), *Physalis angulata* (Solanaceae), and *Delonix regia* (royal Poinciana; Fabaceae) have been investigated in clinical trials for treatment of malaria patients. No other clinical trials have been located on use of herbal medicines alone for this purpose.

In the first trial, conducted in Burkino Faso, 50 g dried n'dribala root powder was decocted in 1,500 ml water for 10 minutes, then the final 600 ml volume was drunk in three divided doses each day for five days.[56] The control group was treated with chloroquine. All patients had *P. falciparum* malaria without severe complications. Symptom relief was comparable between the two groups. By the fifth day of the study, 52% of patients treated with n'dribala and 57% of those treated with chloroquine had no detectable parasites in the blood—a nonsignificant difference. Continuing the n'dribala for an additional five days in patients who still have detectable parasites led to six of seven developing lower-parasite burdens compared to only one additional patient being improved by continuing chloroquine. There were no adverse effects reported. This highly promising trial should be followed by further research on this herb, as well as its combination with *A. annua* and *Cinchona* spp. The value of this herb for preventing malaria is unknown.

In the second trial, five patients in Ghana with either *P. falciparum* or *P. malariae* infection were administered 125 ml decocted AM-1 formula six times daily for two days then three times daily for up to five more days.[57] Fever was abated, and total elimination of blood parasites

was achieved in all patients within 12 days of starting treatment. There was no sign of any toxicity in any patient. Urine tests confirmed no concomitant use of any antimalarial drugs. A concomitant rat study also showed no toxicity though there was sex-specific induction or suppression of various cytochrome P450 enzymes raising the theoretical possibility of interactions between the formula and antimalarial drugs. This formula represents a widely used phytotherapy for malaria in western Africa and its potential should continue to be assessed. Again, nothing is known about using the herbs for prevention of malaria.

OTHER HERBS AGAINST MALARIA

The list of herbs that have shown some antimalarial activity in vitro or in animals is very long. A brief survey of some of the more promising agents is discussed here, but readers should be aware that there is a rich trove of other studies in this area.

Khaya grandifolia (khaya) bark and seeds, a member of the Meliaceae family, are widely used in West Africa to treat fevers. A Khaya extract caused about 91% chemosuppression of *P. berghei berghei* in vivo and IC50 values comparable to the reference drug chloroquine diphospate against a multidrug-resistant clone and Nigerian *P. falciparum* isolates.[58] The crude extract of *K. grandifoliola* bark and seeds as well as a number of its liminoids were active against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains. One of its liminoid constituents, gedunin, had an additive effect when combined with chloroquine.[59]

Another traditional treatment for malaria is the shrub *Cryptolepsis sanguinolenta* that is reported to be clinically effective by local people. One of its constituents, cryptolepine, was highly active against a multidrug-resistant (K1) strain of *P falciparum*. In a four-day suppression test, there was, however, no significant reduction in parasitaemia in *P. berghei*–infected mice treated with cryptolepine.[60]

The traditional Amazonian malaria remedy *Tabebuia ochracea* ssp *neochrysantha* (pau d'arco), a relative of the popular antifungal tree *T. impetiginosa* (both in the Bignoniaceae family), has also been investigated in vitro against malaria. A chloroform extract was effective, and two furanonaphthoquinones were isolated from this extract that showed strong activity.[61] Further research is warranted on this entire genus for antimalarial activity.

A petroleum ether extract of *Carica papaya* (papaya) fruit rind and a petroleum ether and ethanol extracts of *Swertia chirayita* (chirata) root exhibited significant and moderate activity, respectively, in vitro against *P. falciparum*.[62] These herbs were chosen because they are traditional Ayurvedic herbs for malaria.

Azadiractha indica (neem) leaf and bark have also been shown to have moderate antiplasmodial activity in mice.[63] The leaf was more effective than the bark. Neither was as potent as the drug pyrimethamine. Extrapolating from the doses used, the researchers suggested that 48 g daily would be needed to treat an average adult with malaria. The potential for combining neem with other antimalarials should not be overlooked but it may not be sufficiently potent for use as a monotherapy.

Finally, one study looked at the ability of a traditional Nigerian formula to protect mice against malaria infection.[64] This formula was made up of *Cajanus cajan* (pigeon pea) leaf, *Euphorbia lateriflora* leaf, *Mangifera indica* leaf and bark, *Cassa alata* leaf, *Cymbopogon giganteas* leaf, *Nuclea latifolia* leaf, and *Uvaria chmae* bark. The herbs were decocted for three hours and then administered to the rats orally ad libitum (average intake was 12 ml daily). Compared to untreated controls, all of which were infected and died, none of the mice receiving Agbo-Iba formula were even infected. After infection was established in mice, all died

when given Agbo-Iba as treatment, whereas only five died (15%, most within one to three hours after administration of chloroquine suggesting they died of prior malaria infection) in mice treated with chloroquine. Thus, this formula appears to be useful for prevention but not treatment.

BOTANICALLY REVERSING ANTIMALARIAL DRUG RESISTANCE

Another area of great importance is the tantalizing possibility of reversing resistance to antimalarial drugs using herbs and herbal extracts. Many in vitro and animal studies suggest this might be possible, and human clinical trials to confirm this result are needed.

For instance, one set of in vitro studies found that methyoxylated flavonoids found in sweet Annie are synergistic with artemisinin against malaria parasites.[65] This mirrors some of the preliminary work done on herbs and antibiotic resistance or antibiotic synergy. There are a substantial number of primarily in vitro studies showing that plant compounds without any measurable antimicrobial activity (often flavonoids) enhance the activity of other plant compounds or overcome resistance by acting on cellular drug pumps. (see chapter 30 for more information on this topic). It appears that plants have developed these complex interactions to prevent pathogens from acquiring resistance to plant defenses. For the most part, scientists seem to have ignored the possibility of synergy among constituents in sweet Annie, instead sticking to the strict pharmacological model of single active constituents with defined actions. Similarly, the research on cinchona is limited to a group of active alkaloids without investigation of possible plant synergists that themselves are not especially active. More work is urgently needed to explore these findings, as they may have profound implications for the future efficacy of both pharmaceutical and botanical antimalarials.

There are already a few preliminary studies indicating that such research might be very fruitful. In one animal study, combination of the alkaloids febrifugine and isofebrifugine, isolated from the herb *Hydrangea macrophylla*, with chloroquine reversed chloroquine resistance in mice infected with *P. berghei*. Chloroquine or the alkaloids in isolation had no effect.[66] Various alkaloids found in several species of *Strychnos* (poison nut trees) native to Africa have been shown to reverse chloroquine resistance in vitro and in animal studies. Strychnobrasiline and malagashanine from *S. myrtoides* had this effect in vitro and in animals in one study.[67] The alkaloids icajine and isoretuline from *S. icaja* reversed chloroquine resistance in vitro along with strychnobrasiline, and icajine was also synergistic with mefloquine.[68]

The only clinical trial in the area of combining herbs with drugs involved berberine in combination with pyrimethamine to treat patients in Tanzania with chloroquine-resistant recrudescent malaria.[69] Control groups were treated with pyrimethamine and either tetracycline or sulfamethoxazole (SMP) and trimethoprim (TMP). Patients were randomly assigned to their groups but no mention was made of blinding. The berberine dose used was 500 mg three times daily from tablets. After three days of treatment, 74% of patients in the pyrimethamine/berberine group were asymptomatic and had no parasitemia compared to 67% of the pyrimethamine/tetracycline group and 48% of the pyrimethamine/SMP–TMP group. Prior research has shown that berberine is antimalarial in vitro, though one study found no activity in mice infected with malaria.[70,71] Major berberine-containing herbs are *Mahonia aquifolium* (Oregon grape), *Berberis* spp. (barberry), *Hydrastis canadensis* (goldenseal), and *Coptis* spp. (goldthread). Pharmacological data also suggest that combining berberine-containing herbs with other botanical synergists might prove even more effective. More information on herbs and drug resistance is provided in chapter 30.

CONCLUSION

Botanical medicines made it possible to reliably treat malaria for the first time (thanks to *Cinchona* spp.) and continue to provide exciting new antimalarial options (thanks to *Artemisia annua*). Numerous botanical mosquito repellants have shown promise in preliminary trials with minimal toxicity, and should be further researched. The availability of a wide range of other potentially active herbs and constituents, to either potentiate known antimalarial drugs or reduce their side effects, may have a leading role in the ongoing struggle against malaria. The enormous funds being spent to look for new drugs will not fundamentally alter the paradigm of the current methods of fighting malaria, though vaccine research might. Unfortunately, vaccine research has so far produced nothing useful. If even a fraction of this money went toward looking at the use of whole plants and whole plant extracts already shown in preliminary trials to have some efficacy, the benefits could be enormous.

For the time being, those who choose to rely on botanicals instead of prescription prophylactic medicines must do so on faith and empirical reports because no clinical trials proving efficacy exist. This is unfortunate given the number of intriguing possibilities. The combination of berberine-containing herbs, *Cinchona* spp. extracts, and *Artemisia annua* extracts may potentiate other prophylactic medicines, but again there are as yet no data in humans to confirm this.

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23

HERBS FOR SEASONAL INFLUENZA

Flu usually refers to viral infections of the upper respiratory tract that are common and usually seasonal. Flu can also refer to seasonal, infectious gastrointestinal upset but this chapter focuses on respiratory influenza. Influenza is technically caused by one of three types of influenza viruses (A, B, or C), but many other viruses cause various flu-like syndromes. The viruses spread between people by airborne respiratory droplets, commonly in the late fall and winter. Recently it has been shown that cool temperatures in the autumn and winter stabilize and protect viruses for longer, thus enhancing transmission.[1] Symptoms include runny nose, sore throat, nonproductive cough, fever, headache, muscle ache, and fatigue. In simple cases, the acute symptoms lessen within five days. Cough and fatigue, however, can persist. Viral pneumonia and secondary bacterial infections can be complications of flu; so ongoing fatigue and lung involvement are a red flag calling for medical evaluation, especially in the more vulnerable groups: young children, seniors, diabetics, the immune compromised (HIV, hepatitis, mononucleosis, etc.) and overworked, fatigued adults.

Influenza A is clinically the most important strain and its infection is characterized by fever and chills, often with cough, sore throat, headache, and myalgia.[2] The best predictors of a laboratory confirmed diagnosis of influenza A are cough and fever.[3] Other symptoms and complications may occur such as otitis media, conjunctivitis, and more severe respiratory tract symptoms. The most severe complication is viral pneumonia that can develop rapidly. Some patients also are at risk for developing secondary bacterial infections. The magnitude of viral replication, fever, respiratory and systemic symptoms directly correlate with levels of IL-6 and TNF-alpha in upper respiratory secretions.[4] In volunteers treated with antiviral drugs, the reduction of viral replication was associated with a reduction in the production of these cytokines along with improved symptoms indicating that moderating these cytokines is beneficial.[4]

Plant medicines offer a unique preventive and therapeutic approach. Herbs are often able to support physiological function in the human body so as to "boost" the body's own immune response. Because they are not isolated molecules (but a mix of multiple molecular structures in a complex soup of active and inert ingredients) their antibacterial and antiviral actions are not particularly susceptible to the development of microbial resistance, drug-resistant bacterial strains may be more effectively treated with select herbal remedies.[5]

PREVENTIVE BOTANICAL MEDICINES DURING FLU SEASON

The best treatment for seasonal influenza is prevention. In all the traditional medicine systems of Africa, Asia, the Middle East, and so on, the distinction between plants as foods and as medicines is vague and arbitrary. People intent on protecting themselves and their children from flu who stay up late, snack on sweet or refined treats, and skip balanced, nourishing meals while religiously taking doses of echinacea or other herbs are fighting a losing battle. In a nut-

shell, proper nutrition is the best method of avoiding coming down with the flu in the first place. A healthy diet, rich in fruits and vegetables as well as spicy, warming dishes prepared with cayenne or jalapeno peppers (*Capsicum* spp.), mustard (*Brassica nigra*) seed, ginger (*Zingiber officinale*) rhizome, horseradish (*Cochlearia armoracia*) root, and garlic (*Allium sativum*) bulbs, are the best preventative. Vitamin-rich herbs, as teas or juices, can also be added to the diet during flu season. These include rose hips (*Rosa canina*) and berries, as teas or food. Other key nutrients include selenium. Animal studies show that selenium-deficient mice are more susceptible to flu virus and also tended to develop pneumonia when infected with the flu. Interestingly, selenium deficiency altered both the animals' immune systems and the viral pathogen itself.[6]

The rapid replication of the virus induces oxidative stress in the host cells. Cellular glutathione content helps the host down-regulate viral replication, protects against viral production in airway epithelial cells, and has anti-influenza activity in vitro and in vivo.[6] N-acetyl-cysteine (NAC) is a precursor to reduced glutathione and appears to quiet production of pro-inflammtory cytokines in glutathione-depleted alveolar macrophages.[6]

Mice fed a vitamin E-supplemented diet had significantly lower pulmonary viral titers compared to mice on a regular diet and the vitamin appeared to decrease the production of pro-inflammatory cytokines in cells. Other antioxidants are also important: quercitin appeared to protect the lung from free radicals released during influenza virus infection. Curcumin, from turmeric, induced synthesis of glutathione in alveolar epithelial cells, and antioxidants generally suppressed the production of IL- in bronchial epithelial cells. Vitamins (vitamins A, C, B2, B5, folic acid, B12, and K1) and the mineral magnesium have also been shown to improve immune function in influenza.[6]

Thus, a combination of a diet rich in fruits, vegetables, herbs, and spices (to provide antioxidants, vitamins, and minerals) along with well-chosen supplements are important to avoid getting the flu and to ensure a milder case of the flu if one is contracted.

In addition, research is beginning to show that the prophylactic use of adaptogens helps reduce susceptibility to respiratory infections and influenza. In a study of 43 adults 65 and older, participants took 400 mg/day of American ginseng (*Panax quinquefolius*) extract or placebo for 4 months. In the last two months of the study, the frequency and duration of colds was reduced by nearly 50% and symptom duration by more than 50% in the active group.[7] In another study of 323 adults (ages 16–65), American ginseng again reduced the mean number of colds and severity of symptoms.[8] In two randomized trials of elderly individuals living in a long-term-care setting, patients given 400 mg/day of American ginseng suffered less laboratory-confirmed influenza than did the placebo groups even though the trials were relatively short (8 and 12 weeks).[9] A related species of ginseng has also shown benefit: In a randomized, placebo-controlled, double-blind trial, 227 volunteers were treated with an influenza vaccine and placebo or 100 mg of an Asian red ginseng (*Panax ginseng*) extract for 3 months. Colds and flu were highly reduced in the active group (15 vs. 42 cases).[10] Although clinical research on other adaptogens in influenza prevention are not available, it is likely they will have the same ability to strengthen the individual and increase resistance to infection, with California spikenard (*Aralia racemosa*, *A. californica*) having perhaps the greatest affinity for the lungs and patients with influenza among all the traditional adaptogens. See chapter 3 on adaptogens for more details.

Traditionally, tonic-digestive "alternatives" to help maintain optimum digestive function are considered useful preventatives as well. In most traditions, herbs are used to maintain good bowel function as a method of preventing infectious diseases. Although no known

studies exist on sluggish transit time and chronic constipation related to infectious disease incidence, the theoretical association is plausible. There may be an indirect relationship between the volume of resorbed bowel metabolites and the freedom of the body's immune system to respond to external infectious agents. Many herbal systems gave cathartic herbs or enemas to enhance resistance to infection. Our preference is to avoid such drastic measures, and we instead use mild alternatives such as dandelion root (*Taraxacum officinale*) that are more gentle liver stimulants along with adequate fluid and fiber intake for those prone to constipation.

TREATING EARLY SYMPTOMS

Diaphoretic (also known as sudorific) herbs are a traditional flu treatment in the very early stages of influenza, such as a scratchy throat or slight cough during flu season.[11] These herbs gently raise the body temperature and induce sweating, which appears to have a beneficial effect on the immune system.[12] Diaphoretic herbs have been shown to promote sweating when given cold or given hot, although the hot infusions were the most effective. Traditional herbal diaphoretics of Europe and North America include German chamomile (*Matricaria recutita*)[11] or Roman chamomilee (*Chamaemelum nobilis*) flower tea,[13] brittlebush or incienso (*Encelia farinosa*) herb,[14] añil de muerto (*Verbesina encelioides*) herb,[14] yarrow (*Achillea millefolium*) flowering tops,[15] and elder (*Sambucus nigra*) flower tea.[11] Chamomile tea can also be inhaled as a steam, and elder flowers can be used as a bath. These remedies are particularly useful in infants and children as they are palatable and simple. Patients who already have very high fevers generally do not need diaphoretics.

Mucilaginous (demulcent) plants can soothe the mucosal surfaces of the throat, bronchi, and sinuses as well as reduce inflammation and irritation.[11] Marsh mallow (*Althaea officinalis*) root, which is 5–35% mucilage when dried, is an excellent example. To extract the plant's mucilage in a palatable form, a cold infusion (*not* a hot one) is prepared by pouring 8 oz of cool distilled or spring water over approximately 8 g of finely chopped marsh mallow root, and allowing it to steep, covered, at room temperature for 30 minutes with frequent stirring—four to eight hours with less frequent stirring. The cold infusion is then strained and sipped in 1–2 oz doses throughout the day to soothe an irritable cough or scratchy throat. A fresh batch is prepared daily, to protect against bacteria growing in the rich medium. Marsh mallow syrup is another typical preparation of this herb and is taken in teaspoon doses throughout the day during acute flu and cough symptoms. Other demulcent herbs to consider preparing as cold infusions for patients with influenza include elecampane (*Inula helenium*) and globemallow (*Sphaeralcea* spp.).

Figure 23–1. *Encelia farinosa* (brittlebush) habit in flower

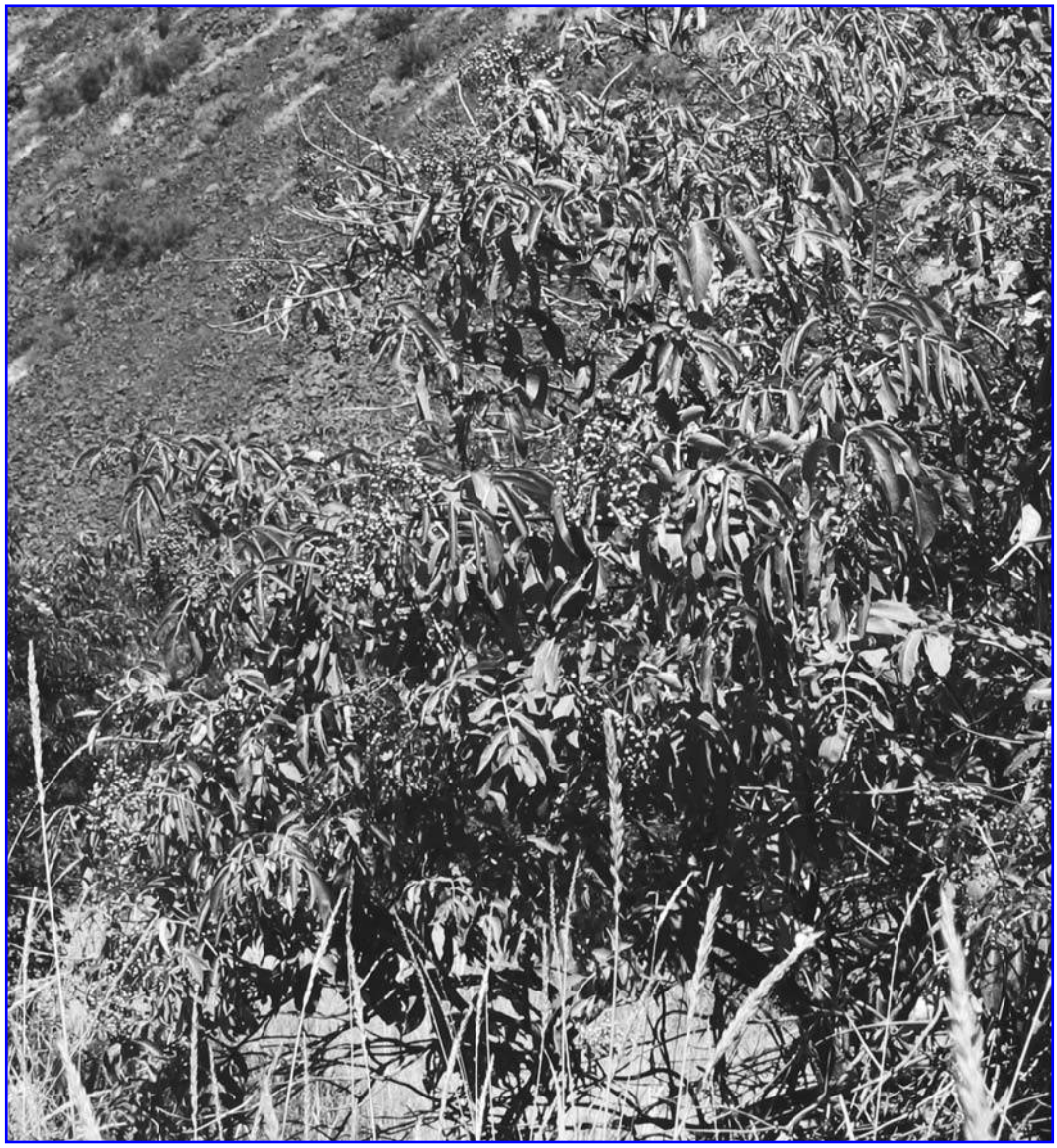

Figure 23–2. *Sambucus cerulea* (blue elder) habit in fruit

ANTIMICROBIAL PLANTS AND IMMUNOMODULATORS

Herbal tradition includes many infection-fighting plants. Many of these plants are now known to contain various immunomodulating fractions, particularly polysaccharides, as in licorice (*Glycyrrhiza glabra*) root and the popular echinacea (*Echinacea* spp.) roots or seed heads.[16] Both plants can be taken as decoctions of the roots, as herbal tinctures or in combination with other herbs in a formula. Licorice is an underutilized herb in viral infections in Western botanical practice especially in children who typically enjoy its taste. Licorice has not been well

studied in influenza but drew much attention in the deadly sudden acute respiratory syndrome (SARS) epidemic. An herbal formula containing licorice was dispensed to 3,160 at-risk hospital workers during the epidemic. None of those taking the formula contracted the disease compared to 0.4% among those who did not.[17] Another study looked at the antiviral potential of certain constituents against coronavirus from patients with SARS. Glycyrrhizin from licorice was the most active and successful at inhibiting replication of the virus.[18] Licorice, of course, has a long folk history of use to treat coughs and inflamed throats, providing needed symptom relief in influenza.[19]

Echinacea helps aid recovery from flu and colds in many people. In a mouse model of influenza A infection, an extract known as Esberitox (containing *Echinacea purpurea* and *E. pallida* root, *Baptisia tinctoria* root, and *Thuja occidentalis* leaf extracts) significantly prolonged survival compared to placebo.[20] Many of the clinical trials involving various Echinacea species and extracts have been in patients with poorly characterized upper-respiratory-tract infections; many of these easily could have been influenza infections. The latest meta-analysis of these clinical trials concludes that whereas Echinacea can reduce the incidence and duration of upper-respiratory-tract infections, no one extract has been conclusively proven to be the best.[21] Most of the trials assessed in this analysis did not include sufficient testing to rule out influenza infection, though influenza pneumonia was definitely not studied. Though valuable by itself, we add Echinacea to formulae containing other herbs with specific history of long use in influenza. Good choices include lomatium (*Lomatium dissectum*) root, elder (*Sambucus nigra*) fruit, boneset (*Eupatorium perfoliatum*) herb, pleurisy root (*Asclepias tuberosa*) or inmortál (*Aslcepias asperula*) root, and, perhaps, wild indigo (*Baptisia tinctoria*) root.

Figure 23–3. *Baptisia tinctoria* (wild indigo) flowering stalk

Elder fruit has long been used to treat influenza and clinical trials show that elderberry syrup, a highly palatable remedy, has the ability to reduce the duration and intensity of influenza.[22] Another classic flu remedy is boneset that, while poorly researched, is recommended by past and present herbalists as especially useful in alleviating the myalgia and pain of seasonal influenza. (See chapter 24 on pandemic influenza for a more detailed description.) Lomatium is also poorly researched but was widely used by both Native Americans and Mormon settlers in Utah and Oregon for lung problems, difficult fevers, and pneumonia. A Dr. Krebs reported that a decoction of the root was used successfully as a treatment in the 1918 pandemic.[23] However, Dr. Krebs also noted that a decoction would fail to extract the plant's oils that he considered to be the most active constituents. Lomatium contains many complex constituents and is known to occasionally cause a rash that is deemed not to be allergic in nature.[24] Michael Moore states that the skin reaction can be avoided if loma-

tium is combined with dandelion root.[25] Pleurisy root, as its name suggests, has a long history of use in various pulmonary afflictions. It was widely used by Eclectic physicians during the 1918 pandemic (see chapter 24). Pleurisy root continues to be used for the chest tightness or painful cough of influenza. The root has a diaphoretic action that is useful in fevers. See Tables 23-1 and 23-2.

Many practitioners also include baptisia as a treatment for influenza, usually as part of the Esberitox formula mentioned above. Interestingly, the use of baptisia in the acute phase of influenza runs counter to the Eclectic tradition in which the herb was saved for more "septic" or congested stages of influenza. Thus, it was used as a treatment for influenza-related pneumonia in the 1918 pandemic.[26] Small studies show that Esberitox safely and effectively reduced the duration of upper-respiratory infections in adults.[27] The formula combined with antibiotics in patients with severe bacterial bronchial infections (a condition that the Eclectics would have considered appropriate for treatment with baptisia) led to a faster recovery than antibiotics alone.[28]

Table 23–1. Doses of Anti-Influenza Herbs

Herb	*Part Used*	*Dose*
Panax quinquefolius (American ginseng)	Root	Tincture, 2–4 ml three times per day
Panax ginseng (Asian ginseng)	Root	Tincture 2–4 ml three times per day
Taraxacum officinale (dandelion)	Root	Tincture, 3–5 ml three times per day; tea, 1 tsp/cup water, sipped 10–15 minutes ac
Glycyrrhiza glabra (licorice)	Root	Tincture, 3–5 ml three times per day
Echinacea spp.	*E. purpurea*, seed head; *E. angustifolia*, root	Tincture, 5 ml every hour for first 48 hours, then 5 ml every 3–4 hours
Lomatium dissectum	Root	Tincture, 1–3 ml three times per day
Sambucus nigra (elder)	Fruit	Tincture, 2–5 ml three to four times per day; tea, 1 tsp/cup water, three to four times per day; syrup, 1 tsp four times per day
Eupatorium perfoliatum (boneset)	Flowering tops	Tincture, 1–3 ml three to four times per day
Asclepias tuberosa (pleurisy root)	Root	Tincture, 1–3 ml four times per day
Baptisia tinctoria (wild indigo)	Root	Tincture, 1–2 ml three times per day

Table 23–2. Specific Indications of Herbal Remedies According to Michael Moore and the Eclectics

Symptoms	*Herbal Remedies*
General remedies	*Aralia racemosa* (California spikenard) root, *Lomatium dissectum* root
Hot, dry patients who are not secreting (no sweating, dry cough)	*Aslcepias asperula* (inmortál) root, *A. tuberosa* (pleurisy) root, *Capsicum* spp. (cayenne) fruit with *Lobelia inflata* (lobelia) flowering tops
Malaise, body aches	*Actaea racemosa* (black cohosh) root, *Eupatorium perfoliatum* (boneset) flowering top
Pleurisy, hacking irritated cough, blood streaks in mucus	
With flushed face, sweating, headache	*Bryonia cretica* (bryony) root
With lymphadenopathy	*Phytolacca americana* (poke) root
Wet cough, perspiring, flushed face, acute onset, restless	*Gelsemium sempervirens* (gelsemium) root
Wet cough, dyspnea	*Grindelia* spp. (gumweed) flower bud, *Ligusticum porteri* (oshá) root, *Prunus virginiana* (wild cherry) bark, *Verbascum thapsus* (mullein) flower
Wet, persistent cough after influenza	*Eriodictyon angustifolia* (yerba santa) leaf

Based on Moore M, *Specific Indications for Herbs in General Use* 1994, www.swsbm.com/ManualsMM/SpecIndic3.txt.

CONCLUSION

Herbal medicines can play a useful role in treatment of patients with seasonal influenza infection. It is necessary for the clinician to choose the appropriate herbal remedies and not get caught in the trap of mindlessly prescribing the same treatments to every patient as though they were all identical. Rest and ample intake of water will generally serve all patients, but individualized herbal prescriptions chosen from those herbs discussed above will yield the best results. Patients should not expect perfect protection or an absolute cessation of symptoms, but instead reduced risk, symptom reduction, and quicker recovery than otherwise. The goal is to use herbs to provide a balance of improved health with minimal adverse effects. See Sidebars 23-1 and 23-2.

23–1. *Dr. Mitchell's Knockout Antiviral Tea*

The late Dr. William Mitchell, naturopathic physician and a cofounder of Bastyr University in Kenmore, Washington, recommended a flu tea discussed below. This is a diaphoretic, antimicrobial, astringent, demulcent tea to be taken three times daily or more.

(*continued*)

23–1. *Dr Mitchell's Knockout Antiviral Tea (continued)*

Cinnamon bark sticks (*Cinnamomum* spp.), 2–3
Ginger root slices (*Zingiber officinale*), 4–5
Cardamon seeds (*Elletaria cardamomum*), 1 tbsp (optional)

Add the above ingredients to 4 cups of water or more. Bring to a boil, then simmer for 20 minutes, covered. Remove from heat.
Add the juice of half of a fresh-squeezed lemon. Add honey to taste.
Drink 1 cup three times a day for a maximum of seven days during a bout of flu.

23–2. *A German Diaphoretic Tea*

Elder flowers (*Sambucus nigra*), 1 tsp
Lime flowers (*Tilia cordata*), 1 tsp
German chamomile flowers (*Matricaria recutita*), 1 tsp

Add the above ingredients to 1 pint of boiling water. Remove from heat. Cover and allow to steep 10 minutes. Drink immediately.
Drink 1 cup three to five times a day for up to 10 days during a bout of flu.

Recipe from Rudolf Fritz Weiss, MD, of Germany.

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24

HERBAL TREATMENTS FOR PANDEMIC INFLUENZA

Pandemic influenza looms on the horizon and society remains poorly equipped to deal with an outbreak despite many years advance warning. Mainstream medicine stockpiles vaccines and antiviral drugs for this coming crisis but will be both in short supply and ineffective in a pandemic. A dispassionate review of clinical trials on influenza vaccine by the esteemed Cochrane Clinical Trials group found little evidence that this intervention is effective, evidence far out of proportion to how aggressively it is recommended.[1] Viral resistance to influenza strains appear quickly, and patients have already died from avian influenza strains resistant to neuramidase inhibitor anti-influenza drugs.[2] Currently, life support in the form of respirators and intravenous fluids remains the primary treatment for patients with avian influenza. However, virtually all of the respirators available in this country are already in use, and we lack the facilities, drugs, and personnel to care for a sharp upsurge in patients needing intensive treatment. For most individuals, little to no conventional treatment will be available in a fast-moving epidemic. Thus, there is a great need for alternative ways to cope with severe influenza.

Given our concern about this threat, it is surprising that society continues to overlook that physicians successfully treated patients with herbs in earlier pandemics. Their treatments alleviated the painful symptoms of the 1918 influenza, and prevented pulmonary complications and death in many of the patients. Overall, the Eclectics reported a fatality rate of only 0.6% in an epidemic that typically claimed closer to 3% of its victims. They reported similar treatment successes in the 1889–1890 influenza pandemic during which some 40% of the population got the flu in a very short amount of time. Modern research on herbal medicines is overall fairly weak and has yet to have anything like the efficacy of the Eclectic treatments.[3]

This chapter introduces the Eclectic treatment of influenza. It does not cover all of the herbs used by them during the pandemic but it provides some essential tools to help health care practitioners cope with the next pandemic that appears likely to arrive in the not-too-distant future, as well as for treating patients with serious influenza in nonpandemic settings.

GENERAL ADVICE FOR INFLUENZA PATIENTS

The general Eclectic advice given pandemic influenza patients was much the same as that given anyone stricken with seasonal influenza: bed rest, warm baths, and plenty of fluids, including ginger tea, hot lemonade, or hot infusions of herbs. The Eclectics also used tepid sponge baths to bring down the fever, and considered it more useful than ice or cold water. A tepid sponge bath was given by constantly sponging the head with warm water, drawing the sponge back and forth, and at the same time fanning the person.

In the 1918 pandemic, Eclectics found it imperative that the patient rest, both mentally and physically, and many physicians commented that complications were more common in patients who got up and about too early. Then, as now, working people and those caring for sick family members had a hard time complying with this directive. The Eclectics also noted that sleep was necessary to allow recovery, and that sleeplessness often occurred in the feverish patients and

caused complications if not countered. In some hospitals, sleep was considered so vital to recovery that heroin was sometimes administered to ensure that the patient got a good night's sleep. Most physicians, however, relied on herbal sedatives such as *Passiflora incarnata* (passionflower) to help the patient rest.[4]

Most Eclectics were adamant that aspirin and other coal-tar remedies (synthetic medicines) were damaging to the influenza patient. Aspirin can, of course, have serious side effects in children with influenza, and is no longer administered to them. Eclectics felt aspirin weakened the already stressed hearts of adult influenza patients. They also tended to disapprove of pain medicines that depressed the system, such as codeine, especially where there were pulmonary complications. They instead used herbs to alleviate pain.

Experimental vaccines were available back in 1918. As the viral nature of the disease was not understood at the time, these vaccines were prepared against various bacteria from patients who died of lung complications. They were widely recommended by allopathic physicians but the Eclectics warned against the use of vaccines of unknown efficacy, and some reported that a patient vaccinated and infected with influenza at about the same time seemed to fare poorly. This can happen with some frequency in an epidemic as it usually takes a few weeks for the vaccine to effectively "teach" the immune system to respond to the virus. We may find ourselves urging similar cautions against the use of newly created vaccines in a fast moving or possibly mutating pandemic.

Except for these general warnings, the Eclectics did not have specific remedies or treatments for influenza as such. Instead, they selected herbs to match the symptom picture of the individual influenza patient. Given the many different symptom pictures in pandemic influenza, a wide variety of herbs were used. However, the following four herbs very often "fit" the symptom picture of patients in the 1918 pandemic and were widely used.

Gelsemium sempervirens (Gelsemium)

Along with *Aconitum* spp. and *Veratrum viride,* gelsemium or yellow Jessamine formed a triad of "chief sedatives" that were used to treat feverish conditions.[4] In both the 1889 and 1918 pandemics, gelsemium was praised for its ability to quickly reduce the high, hectic fever that so many patients experienced. The Eclectics considered it to be the specific remedy for the highly feverish state with tremulous, jerky muscles, nervous excitation, spasms, and pain. Gelsemium was described as a sedative because it diminished the velocity of blood delivery to the head and spinal tract, and prevented spasms. It was considered useful for all types of hyperemia but was contraindicated in congested conditions. Thus, it was considered highly useful in the early stages of acute meningeal inflammations but was not used beyond the sthenic stage; it was not given to patients with dull eyes, dilated pupils, and an expressionless face.

Physicians reporting on their influenza treatments commented, "With boneset and gelsemium almost the whole range of symptoms of influenza may safely be brought under control. Only when there is a known damaged heart need one be specially careful in the use of gelsemium . . . . Study these two drugs faithfully before an invasion comes and by thus being prepared, you will be doubly armed to battle the foe."[5] One physician, with many years of experience treating influenza, favored gelsemium in patients with a high fever, intense headache, and body aches along with extreme restlessness and sleeplessness.[6] Another wrote, "If the patient displays marked restlessness, flushed face, bright eyes, and evidences excited cerebral excitation, gelsemium should be used."[7]

Gelsemium became the standard influenza treatment at an allied military hospital in France after an investigation into the effectiveness of various remedies used to treat soldiers with influenza.[8] An American and British physician team administered 8 drugs to groups of 15 influenza patients with influenza and compared their progress. The groups were randomly selected based on the order in which the patients were admitted, and the treating physicians worked independently of each other. Three of the drugs were herbs (aconite, *Atropa belladonna* (belladonna), and gelsemium) whereas five were remedies more commonly used by allopathic physicians (aspirin, sodium salicylate, arsenic, quinine, and Dover's powder, a mixture of opium and ipecac).

"Those treated with gelsemium improved in a manner far exceeding those given any other treatment. After a few doses their headache and backache were much relieved, the temperature began to fall, and the general condition was observably improved." With the exception of belladonna, none of the other treatments appeared to have the slightest effect.[8]

Although treatment was randomized, the investigators still questioned their results. Because "we are well aware of the fallacies of judgment attending the action of remedies," they repeated the test. The second study results were so striking that the physician–investigators decided to use gelsemium to treat all of their influenza patients. Although far less helpful, belladonna also provided some benefit and was added to the gelsemium formula. (See Sidebar 24-1 for the full formula.) Using this formula, the physicians treated 937 influenza cases among soldiers sick enough to be hospitalized. Those who were treated with the formula had a mortality rate of 2.77%, a good result in that population group.[9] (In one sector of the Western front, one third of American soldiers hospitalized with influenza died of the disease.)[10] Except for rare cases of visual disturbances, there were no side effects.[8]

24–1.

GELSEMIUM FORMULA USED AT THE MILITARY HOSPITAL IN FRANCE

Gelsemium sempervirens tincture: 9 drops	Potassium citrate: 10 grains
Atropa belladonna tincture: 5 drops	Orange syrup: 1 dram
	Aqua chloroformi: 1 dram

One dram was given every 4 hours for the first 24 hours, and ½ dram every 4 hours thereafter until the patient's temperature returned to normal, at which point the formula was discontinued. One dram is approximately ⅛ of an ounce. The potassium citrate was added as a mild diuretic.

PROPHYLACTIC FORMULA

Eupatorium perfoliatum: ½ oz	Water: 4 oz
Aconitum napellus: 5 drops	

Dose: One tsp every two hours the first day, thereafter three times daily.

Gelsemium continues to be used by herbalists and naturopathic physicians to treat fevers associated with influenza, muscular weakness, myalgia, flowing pulse, apathy, deliriousness, and/or hysteria.[11] Michael Moore, director of the Southwest School of Botanical Medicine, teaches that gelsemium cools the brain and decreases wasteful fever in adults. He considers it useful in the person with red eyes, flushed face, overly acute hearing, skin hypersensitivity, and agitation with lots of blood to the surface.[12] French herbalists use gelsemium for neuralgic headaches using a dose of 15 drops three or four times a day.[13] German phytotherapists use it as a cardiac sedative for extrasystoles and functional heart disease.[14]

Gelsemium is a plant that should only be administered by an experienced practitioner. It is very safe in appropriate doses and the Eclectics reported that gelsemium poisoning was quite rare despite its extensive use.[4] Nonetheless, it is toxic in excess. The cardinal symptoms of poisoning are ptosis, diplopia, dropping of the lower jaw, and absolute muscular prostration. Death takes place from respiratory paralysis and almost simultaneous arrest of the heart.

The Eclectics preferred a gelsemium tincture made from the fresh root, and considered it to be vastly superior to that made from the dried plant. John Uri Lloyd wrote, "For thirty years or more, Eclectic physicians have insisted that the green drug [fresh herb] possesses qualities entirely absent in the dry. This we accept without reserve, and for decades have worked only the green drug, believing that the point as concerns its superiority is not debatable."[15]

The Eclectic dose was 0.1–10 drops of Specific Medicine of gelsemium, usually administered by mixing 10 drops to 1 dram in 4 oz of water, 1 tsp every one to three hours. Practitioners presently dose gelsemium tincture at 2–10 drops.

Eupatorium perfoliatum (Boneset)

The name boneset comes from this plant's successful use in influenza pandemics that caused such severe pain that the patient felt like his or her bones were breaking. Many Native American tribes used boneset for colds, fever, sore throat, chills, influenza, pneumonia, and pleurisy, and it is sometimes referred to as Indian sage.[16] Herbalists, naturopathic physicians, and other modern practitioners continue to use boneset similarly, especially for febrile diseases.

The Eclectics considered boneset a very valuable medicine. "In every epidemic of influenza it has been used with great advantage. During the severe pandemic of 1918–1919 it was one of the safest and most successful remedies employed and contributed much to the successful management of disease under Eclectic treatment."[17] They commented that boneset was used as a prophylactic but that this action was unproven. However, they also noted, "That cases were rendered milder, deep-seated pain promptly relieved, cough and respiratory irritation lessened, and recovery expedited under the liberal administration of eupatorium is a matter of record. It is especially valuable to relieve the intolerable backache and pain in the limbs."[17] They found that boneset consistently relieved deep-seated pain in febrile conditions. It was considered especially useful in coughs in the elderly and the weak who lacked the strength to cough up the abundance of mucus caused by the influenza.

In 1889, one physician commented that boneset was very valuable in allaying cough with high fever, free perspiration, and lack of power to expectorate.[18] In a review of influenza in 1915, a physician recommended boneset any time black cohosh failed to relieve pain.[19] Another physician commented that almost the whole range of influenza symptoms could be controlled with boneset and gelsemium. Boneset is "absolutely safe under all conditions. If too much is used, emesis is the only unpleasant result."[20] In 1918, it was reported that "recent experiences point to [boneset] as being one of the best agents to give quick results in epidemic influenza."[21]

Boneset gained popularity as part of a preventative formula after the following announcement was published in 1918: "In a well-known manufacturing establishment five employees were recently stricken in one day with 'Spanish influenza.' Immediately a prescription of this remedy was compounded and a bottle given to every member in the establishment, with directions to take 1 tsp every two hours the first day, afterward three times daily. Since that date not one member of the establishment has been afflicted. And yet strenuous business has kept them employed night and day. Possibly this result is exceptional, but it is no less a fact." (See Sidebar 24-1 for the prophylactic formula.)

In the 1918 pandemic, one physician noted that the choice of the "most important" remedy in influenza varied from patient to patient but that boneset fit more cases than any other remedy. Another physician used boneset "from start to finish," and sometimes gave it as a tonic after the acute stage of the disease was over. In the very early stages where the patient only complained of aches and pains, this physician immediately gave large doses of boneset *often*. He was convinced that many influenza cases were aborted by the early use of boneset.[4]

One physician who saw 10–35 influenza patients a day during the epidemic began treatment by mixing 2 tsp of boneset and 1 tsp of pleurisy root in a cup of hot water. This was given immediately with a second dose 15 minutes later, a third half an hour later, and a fourth dose an hour after the first dose. He reported that this treatment typically reduced a fever of 103–104°F by three to four degrees in a few hours. Yet another physician reported that boneset was always a significant remedy in influenza.[4]

The German physician Dr. Rudolf Weiss echoed the Eclectic view that boneset appears to enhance resistance to infection by influenza. He also acknowledged that there was no objective proof of its anti-infectious effect but commented that practical experience strongly indicated such an effect. Because it alleviated many symptoms of influenza and was quite safe, he used it extensively in influenza.[14]

Despite its long history of use, there is little research on boneset. An early study showed that the plant has antibacterial activity in vitro against *Staphyloccus aureus* and *Escherichia coli*. It contains eupatorin characterized both as a hydroxyflavone (antioxidant) and methoxyflavone (anti-inflammatory).[11] Some of its sesquiterpene lactones and polysaccharide fractions have immuno-stimulatory effects in vitro. Although safe for short-term use, the plant belongs to a plant family that often contains liver toxins, pyrrolizidine alkaloids, and boneset should not be used casually.[22] In large doses it can be emetic and cathartic.

The aboveground parts of the plant are used, and many practitioners think it works best as a fresh plant tincture. It is diaphoretic when taken as a hot tea, and the tincture is usually dispensed in hot water to capture this effect. The Eclectic dose was 5–60 drops of Specific Medicine Eupatorium or an infusion of 1–4 fluid drams. The dose for boneset tincture is 20–40 drops of tincture in hot water, three times a day.

Actaea racemosa (Black Cohosh)

Formerly known as *Cimicifuga racemosa* or macrotys, the root of this plant was historically used primarily as an analgesic. Native American tribes used it to relieve arthritic pain but also used it as a tonic and a remedy for colds, cough, and consumption.[16] Today, of course, black cohosh is best known for its ability to ease negative symptoms in perimenopause but botanical practitioners still consider it one of the better remedies for muscle, rheumatic, intercostals, and ovarian pain.[11,23] One clinical study shows that black cohosh, combined with other herbs, may provide some pain relief in arthritis.[24] The root contains salicylic acids.[25]

One of the first Eclectic uses for black cohosh, learned from the Native Americans, was for putrid sore throats. The plant soon came into general use and they reported, "Few of our remedies have acquired as great a reputation in the treatment of rheumatism and neuralgia."[26] It was used for any dull, tensive, intermittent pain, soreness in muscular tissue, and especially over the abdomen.

Black cohosh was described as promptly curative for the headache of influenza. In tuberculosis, it was used to lessen cough, soothe pain (especially aching under the scapulae), lessen secretions, and lessen nervous irritability. It was used to relieve a variety of fevers. The Eclectic physician Dr. Harvey Felter called it the most important remedy to relieve muscular discomfort, and when combined with boneset—both in liberal doses—was the best remedy for the intense muscular aching and "bone-breaking" pains at the onset of influenza.[17]

One physician successfully treated 200 cases of influenza during the 1918 pandemic using a combination of gelsemium, black cohosh, and *Euphrasia officinalis* (eyebright). He estimated that 75% of all influenza cases could be handled with these three herbs alone. After bringing down the fever with gelsemium, he would switch to 10 drops *each* of gelsemium and black cohosh in 4 oz of water, administering 1 tsp every two to three hours.[27] Another physician recommended black cohosh for all cases in which the patient stressed the symptom of muscular soreness; he also used it in the early stages of pneumonia to alleviate the aching.[28]

The Eclectics typically used low doses of black cohosh, often 10–20 drops of Specific Medicine Actaea by mixing 10–30 drops in 4 oz of water, dispensing 1 tsp every two hours. However, they also noted that fuller doses, short of producing headache, were very effective and the amount given to an adult could be increased to a dram or fluid ounce.[4] The current dose for black cohosh tincture is 10–25-drop doses of tincture three times a day.

Asclepias tuberosa (Pleurisy Root)

The root of this plant has a very long history of use for respiratory problems, hence its common name, pleurisy root. It is also called butterfly weed because of the monarch butterfly's fondness for it.

Native American tribes used pleurisy root for pleurisy, pneumonia, influenza, and other respiratory ailments. Contemporary herbalists and naturopathic physicians use it to treat respiratory infections, reduce inflammation, and promote expectoration.[23] Pleurisy root is often used today for influenza where there is a tight feeling in the chest or a painful cough. Michael Moore notes that pleurisy root is useful in pleurisy and mild pulmonary edema because it increases fluid circulation, cilia function, and lymphatic drainage.[29] Pleurisy root is diaphoretic, which makes it useful in fevers.[24] Its diuretic and diaphoretic effect may be due to constituents that strengthen the heart contraction and allow fluid removal as a result of improved circulatory force.[11]

The Eclectics considered pleurisy root to be a very safe remedy because, even if used without the proper indications, it did not cause harm. At worst, it simply did not produce the desired result. They reported that it worked well as a diaphoretic, no matter how high the fever and, because it normalized secretion through the skin, could be used even in a patient who was perspiring heavily. It was considered an excellent remedy for ordinary colds and was used as a cold remedy in infants. Although pleurisy root can reduce high fevers, the Eclectics thought it was best for moderate fevers where the skin is moist and where the pulse is vibratile but not too rapid. Combined with a properly chosen chief sedative, it was one of their preferred remedies in the early stages of pneumonia and pleuropneumonia. As a rule, they viewed pleurisy root as

an assistant to other herbs than as a simple in pneumonia. For instance, where there was a dry and constricted cough, they used small doses of pleurisy root with 1–2-drop doses of lobelia.[4] See Sidebar 24-2.

Physicians made the following comments on pleurisy root's usefulness in pandemic influenza: for pectoral pains, it was one of the best herbs. It controls inflammatory conditions within the lungs and is particularly valuable in allaying cough.[18] One physician who treated influenza for decades and who "failed only six times in a thousand cases" stated that pleurisy root can be used in "all pleuritic complaints."[30] Another Eclectic physician noted that, while gelsemium was the mainstay, he minimized bronchial complications by giving pleurisy root in small doses at the onset of symptoms.[31] In an article on treating influenza in the *Eclectic Medical Journal*, the author commented that pleurisy root was one of his favorites and he used it in all catarrhal affections, especially in children. He used it when the patient's skin was hot and dry and especially where there were pneumonia symptoms.[4] In a monograph, another physician reported that veratrum combined with pleurisy root will abort pneumonia in two to four days but the combination was most effective if given in the early stages.[32]

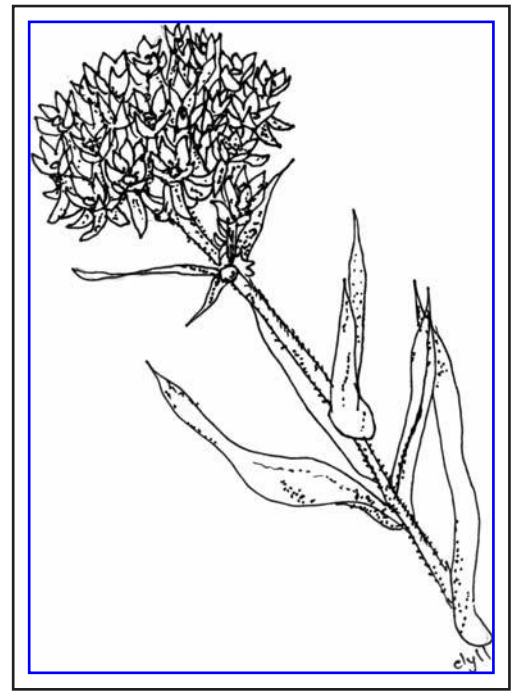

Figure 24–1. *Asclepias tuberosa* (pleurisy root)
Drawing © 2006 by Eric Yarnell, ND, RH.

24–2. *Chest Applications*

Most Eclectic physicians used some type of chest application, and considered them vital in preventing pulmonary complications. Historically, chest rubs and applications were widely used by physicians and layfolk alike. There is no explanation for when, or why, these practices were discontinued but they are not commonly used today. No research indicates that they lack benefit. In fact, animal research indicates that volatile oils (often found in chest rubs) penetrate the lung tissue and have a strong antimicrobial action. A recent study showed that Vicks salve applied to the chest enhanced lung clearance in patients with chronic airways obstruction.* Many types of applications were used in the 1918 pandemic, and one of the most popular was the Compound Powder of Lobelia consisting of: *Lobelia* spp. powder, 6 drams; *Sanguinaria canadensis*, powder 3 drams; *Symplocarpus foetidus*, 3 drams; *Cephaelis ipecacuanha* powder, 4 drams; *Capsicum annuum* powder, 1 dram. Mix and then sprinkle on a larded or oiled cloth and applied warm.

*Hasani A, Pavia D, Toms N, et al. Effect of aromatics on lung mucociliary clearance in patients with chronic airways obstruction. *J Alt Comp Med* 2003;9(2):243–249.

Figure 24–2. *Symplocarpus foetidus* (skunk cabbage)

Figure 24–3. *Capsicum annuum* (cayenne)

There is no clinical research on pleurisy root. It should be used cautiously in individuals taking cardiac glycoside drugs (such as digoxin) because it may possibly increase the risk of drug toxicity. However, some herbalists believe that it is such a feeble cardiac stimulant that it should not have a synergistic effect on heart and blood pressure medications but caution against combining it with anticholinergic drugs.[29] It is contraindicated in pregnancy, and may cause vomiting but this occurs only at rather high doses of the plant.

The Eclectic dose was 1–60 drops of Specific Medicine Asclepias typically administered by mixing 20 drops to 1 dram in 4 oz of water, giving 1 tsp every one or two hours.[4] Today, the tincture is dosed at 30–90 drops or the cold infusion of the dried root at 2–4 oz three times a day.

Figure 24–4. *Sanguinaria canadensis* (bloodroot)

HERBS AND CYTOKINE STORMS

Human influenza replicates primarily in respiratory epithelial cells. Experiments with a reconstituted strain of the 1918 influenza show that, in mice, the virus had close to a 200-fold replication rate compared to a milder seasonal influenza strain.[33] Thus, one feature of pandemic influenza is an ability to replicate at an unusually fast rate. Influenza damages the epithelial cells in this process, and there is evidence that bacteria are much more able to attach and move into the respiratory tract after the epithelial cells are damaged by the influenza virus. Secondary infections thus pose a much greater risk in pandemic influenza.

The human immune system uses cytokines and chemokines to communicate and muster an appropriate response to viruses, cancer, bacteria, and parasites. All influenza strains induce a disregulation of the cytokine and chemokine system resulting in increased levels of pro-inflammatory messengers, such as interleukin (IL)-6 and decreased concentration of anti-inflammatory cytokines such as IL-10.[34] An avian flu strain from a deceased patient dramatically increased the cytokine interleukin-6 and the chemokine interferon-10.[35] This severe disregulation has been referred to as a cytokine storm. It is the rapid production of pro-inflammatory cytokines that is responsible for the severe damage done to lung tissue in avian flu victims, and thus is a major cause of fatality.

The existence of a cytokine storm has many concerned about the appropriateness of the use of botanicals that in common parlance are viewed as immune stimulants. As we discuss in chapter 17 on immune modulators, herbs in fact act as inflammation and immune modulators rather than as stimulants or suppressors.[36] There is one interesting study that strongly supports our view, and shows that herbs may be capable of moderating the influenza "cytokine storm."[37]

The common cold, a rhinovirus, also disregulates the immune system in humans, although to a vastly lesser degree than pandemic influenza.[37] The rhinovirus does not replicate with any substantial speed, and does little damage to the respiratory epithelial system. However, it does change the profile of 31 different cytokines and chemokines. Like influenza, it sharply up-regulates IL-6 and interferon-gamma while down-regulating IL-10. This disregulation of the system causes the inflammation, fatigue, and other bothersome symptoms of the common cold. The researchers in this study puzzled over the fact that herbs like *Echinacea* spp. (echinacea) were used to ease these symptoms even though they also were commonly referred to as immune-stimulants. Echinacea should make cold symptoms worse if it in fact stimulated the already disregulated immune response to the rhinovirus. In the next experiment, the effect of echinacea on cytokine and chemokine production in healthy and infected respiratory cells was studied. Interestingly, echinacea down-regulated, or normalized, the cytokine production in infected cells and up-regulated cytokine production in healthy cells.[37]

Unfortunately, similar experiments have not yet been done on cells infected with influenza virus. However, we feel confident that herbs that historically have been used successfully to alleviate flu symptoms also work to normalize the cytokine balance. We know that pro-inflammatory cytokines produce influenza-like symptoms. We know that certain herbs reduce such symptoms in influenza. Although unproven, the clinical evidence of symptom reduction likely is the result of the herbs acting to quiet the cytokine storm.

CONCLUSION

Herbs have long been used to treat influenza, a disease that has afflicted humans for millennia. They are highly useful in seasonal influenza and will likely prove critical for influenza patients when the next pandemic arrives.

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25

HERBS IN PERIODONTAL DISEASE

Chronic inflammation of the gums that leads to loss of the connective tissue and alveolar bone holding the teeth in place characterizes periodontal disease. This condition leads to recession and bleeding of the gingiva, loose teeth, abscesses, caries of the exposed root, and, ultimately, loss of teeth. Research shows that even teeth severely compromised by periodontal disease can be saved with consistent, adequate management.[1] Saving those teeth is important. For many, dentures are uncomfortable and make proper chewing of food difficult. Improper mastication can compromise digestive function—a setup for all types of problems secondary to malnutrition. In addition, preliminary evidence suggests that the inability to chew properly due to missing or loose teeth may actually be a risk factor for senile impairment of spatial memory, a factor in Alzheimer's disease.[2] Fortunately, herbs can be used with the old standbys of regular brushing, flossing, and professional cleaning to hold periodontitis in check.

NATURE OF THE DISEASE

The exact cause and course of periodontal disease remain elusive. It tends to be episodic but relentless, and may affect certain areas of a person's mouth with great virulence while leaving nearby teeth practically unaffected. Research has focused on the oral bacteria known as periodontopathogens that have been isolated from the fluid in pockets around afflicted teeth. However, studies sometimes find the same microbes in healthy mouths, and a pathogen specifically responsible for periodontitis has not yet been identified. Nonetheless, research shows that both antimicrobial plants and antibiotics can curtail inflammation, bleeding, and bone loss in periodontal patients, and it is clear that the use of antimicrobial agents can be helpful in periodontal disease.[3] Unfortunately, although antibiotics reduce symptoms of periodontal disease, the use of antibiotics presents problems, and current research indicates that it is the host response to oral pathogens that is the real culprit in periodontal disease. As a result, changing the body's response to oral pathogens is a more promising approach than trying to kill the various pathogenic oral bacteria.[4]

CONVENTIONAL TREATMENT

Researchers were initially hopeful that low doses of tetracycline and other antibiotics would control oral pathogens. Tetracycline did reduce oral microbes and periodontal symptoms in patients, though there is doubt about the degree of clinical significance of the modest improvements seen according to meta-analysis of clinical trials.[5] Now, researchers increasingly warn that antibiotic use threatens to create antibiotic-resistant microbes that might lead to an overgrowth of pathogenic bacteria in the patient's body or might spread to other patients.[6,7] At the same time, some studies showed that professional cleaning could be as effective in reducing periodontitis as the antibiotics.[8,9] The current position is that "prudent use of effective antibiotics is ethically acceptable in appropriately selected patients," but they should be used conservatively so as not to fuel the emergence of antibiotic resistance.[10]

The research emphasis has instead shifted to moderating the host's immuno-inflammatory responses deemed responsible for much of the tissue damage.[11] A family of enzymes, matrix metalloproteinases (MMPs), implicated in the degradation of the periodontal ligament that connects teeth to the bone was one area intensely investigated.[12] MMPs have both positive functions (aiding in tooth eruption) and negative functions (periodontitis). MMPs have been studied for decades, and researchers today are confident that an imbalance between activated MMPs and the body's own inhibitors of MMPs (TIMPs or tissue inhibitors of MMPs) lead to a pathological breakdown of the matrix that helps hold teeth in place. Thus, for example, saliva of healthy individuals contains more of an inactive pro-collagenase whereas saliva in disease contains more activated collagenase that breaks down collagen.[13,14,15] The cause of this imbalance remains unknown. The levels of MMP and TIMP vary during healing, inflammation, and the normal turnover of healthy gum tissue. Cleaning or root planing is, in part, helpful in periodontal disease because it reduces the amount of activated collagenase in saliva.

Presently, research is focused on developing "chemically modified non-antimicrobial analogues (CMTs)." In the meantime, low "non-antimicrobial" doses of antibiotics like doxycycline are being tested in clinical trials, and are marketed for periodontal disease.[16] These drugs purportedly have an inhibitory effect on MMPs but are assumed not to induce antibiotic side

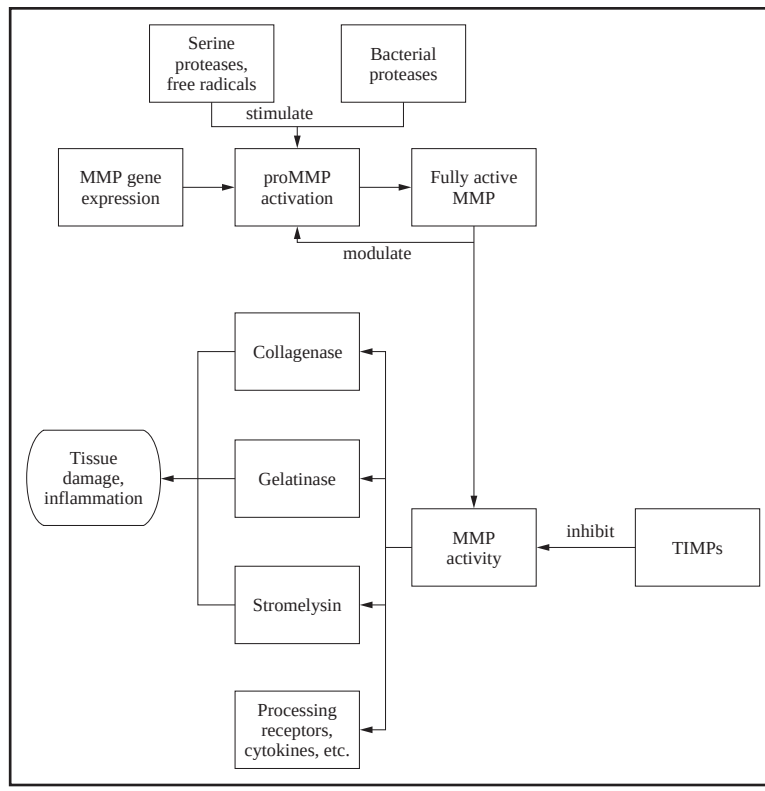

Figure 25–1. Regulation and Activity of Matrix Metalloproteinases

Basic overview of the complex factors that regulate expression and activity of MMPs, and the many possible actions of this enzyme family. MMP = matrix metalloproteinase, TIMP = tissue inhibitor of metalloproteinase

effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) and prostaglandin inhibitors are often added to lessen and control inflammation.[17] However, researchers caution that inhibition of MMPs is a two-edged sword—although MMPs are implicated in periodontal disease, they are also necessary to the healthful turnover of normal gum tissue.[4] NSAIDs and prostaglandin inhibitors have substantial adverse effects. And, of course, the long-term effect of low-dose antibiotics on antimicrobial resistance and intestinal flora balance in patients has not yet been studied in depth but is likely to be detrimental.

Given these problems, we find herbs to be a better choice in periodontitis. Many herbs are both antimicrobial and inflammation modulating but do not cause antibiotic resistance and do not pose the risk of serious adverse effects such as those caused by NSAIDs.

HOLISTIC TREATMENT

In selecting an herbal approach to periodontal disease, herbs should be selected for their ability to promote healing by stabilizing collagen and lessening inflammation in the mouth. Whereas a basic treatment should include some antimicrobial aspects, killing pathogenic bacteria should not be the main focus of the treatment. We recommend the topical application of inflammation-modulating, tissue-healing herbs using a Waterpik-type device. A formula we have used successfully is discussed below. Irrigation devices flush food debris out of gum pockets and help prevent plaque formation but can be more effective when combined with an appropriate topical formulation.[18] Irrigation should be done at least twice daily, using a mild to moderate stream of lukewarm water. The idea is to gently deliver the herbs to gum pockets allowing the herbs to improve the microenvironment around afflicted teeth. The object is not to sandblast the gums with a strong jet of water. Success will also require consistent brushing with a soft-bristled brush, flossing, and frequent professional cleanings. Toothbrushes should be changed every few months to avoid reintroducing pathogens into healing areas of the mouth, and the use of several toothbrushes is strongly recommended to allow drying of the bristles between brushings. See Sidebar 25-1.

25–1. *Why Brushing Does Not Get at Plaque Formation in Gingival Pockets*

A gum pocket of 4 mm is a transition point between healthy gums and disease, and a 5 mm pocket is definitely considered diseased. One online dental site, www.fitmouth.com, helps us visualize how deep these pockets are from the perspective of an oral bacteria: The average bacteria is about 1 micron in diameter, and a 3 mm pocket is 3,000 times its average height. If the bacteria were human size (e.g., 6 feet tall), the depth of the pocket would be about 18,000 feet (3.4 miles) or three times the deepest spot in the Grand Canyon.

Average toothbrushes and floss only clean about 1.5 mm deep into a pocket. The site gives the analogy of using a 9,000-foot fishing line but still being almost 4 miles short of the bottom-feeding fish you want to catch. Sonic toothbrushes claim to clean up to about 3.5–4.5 mm into pockets. Some dentists question this estimate but even assuming the claims are true, you remain a mile short of your prey if you have a 6 mm pocket—and pockets of that depth are not unusual in periodontal disease.

THE TOPICAL FORMULA

We suggest that 2–3 ml (0.5 tsp) of an herbal formula be added to the irrigation tank for each treatment. Initially this may require two treatments per day, though one per day may eventually be sufficient. Our formula consists of equal parts of tinctures of *Anemopsis californica* (yerba mansa) root, *Scutellaria lateriflora* (skullcap) herb, and *Centella asiatica* (gotu kola) whole plant. In our experience, all raw materials for these tinctures should be fresh at the time of processing for optimal outcomes. See Sidebar 25-2.

Yerba mansa is not a well-researched herb, although it has a long history of use among Native Americans and Hispanics in New Mexico, California, Arizona, and Mexico. Many practitioners report that yerba mansa is invaluable for severely inflamed gum tissue because it has a strong astringent action that pulls fluid out of inflamed tissue. Unlike many herbal astringents, yerba mansa does not thicken or close the skin over the inflammation. Instead it permits continued drainage from the infected area. We have used yerba mansa in dozens of cases of patients with teeth hovering on the brink of an abscess when drainage is critical and have found it to be highly effective. Yerba mansa also has a numbing effect that soothes and reduces the pain of inflamed gums. Its volatile constituents have been shown to be antimicrobial, both when extracted by steam distillation and in aqueous extracts.[19,20] In addition to use in irrigation, yerba mansa tincture can be applied directly to a developing abscess while also being taken internally with other immune-enhancing herbs, such as echinacea (*Echinacea angustifolia*) root, usually averting the abscess.

Chinese skullcap (*Scutellaria baicalensis*) root is primarily used for chronic inflammatory and allergic conditions in traditional Chinese medicine but also has a history of use as a mouthwash. It is rich in flavonoids (baicalein, baicalin, and wogonin) and most of the research on this herb has been done on its isolated flavonoids. Skullcap was nearly as effective as tetracycline in reducing oral periodontopathogens,[21] although it had to be used at a higher dose than the antibiotic. Chinese skullcap and its flavonoids had an effect similar to prednisolone on certain

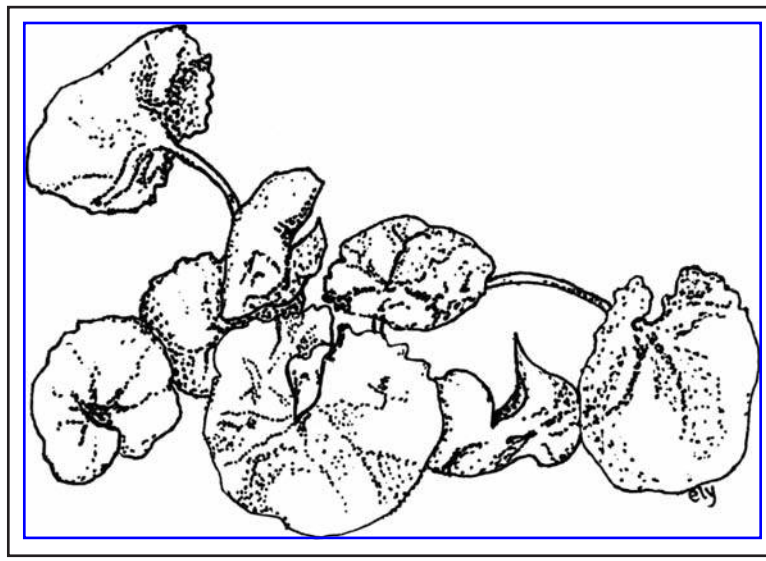

Figure 25–2. *Centella asiatica* (gotu kola)
Drawing by Eric Yarnell, ND, RH.

25–2. *Example of an Internal Formula*

This formula was designed for an essentially healthy woman with severe periodontal disease. She was a former smoker (1 pack per day for 12 years). She was in a period of substantial stress due to illnesses in her family, and was in the early stages of perimenopause. Her skin was dry, her hair was fine, and she had a tendency to gain weight easily. Her tongue had a fine white coating. Her teeth were cleaned every 3–4 months. At her first appointment, close to three months after following this protocol, her dental hygienist commented on the fact that her gums were greatly improved and her pockets had shrunk by around 3 mm in several areas. The patient reported that teeth that previously had felt very loose now seemed more firmly attached.

Oregon grape (*Mahonia aquifolium*) 20%
Skullcap (*Scutellaria lateriflora*) 20%
Gotu kola (*Centella asiatica*) 20%
Heal-all (*Prunella vulgaris*) 15%
American ginseng (*Panax quinquefolium*) 15%

6 ml (90 gtt) twice a day, 15 minutes before lunch and dinner.

TOPICAL FORMULA

Skullcap (*Scutellaria lateriflora*)
Gotu kola (*Centella asiatica*)
Yerba mansa (*Anemopsis californica*)

Equal parts. Add ½ tsp to irrigation tank, apply twice a day.

aspects of inflammation, and worked as well as tetracycline at inhibiting prostaglandins and collagen degradation while also strengthening collagen and protein in fibroblasts—cells vital in ensuring tooth attachment.[22] Baicalin, at a noncytotoxic dose, inhibited the release of matrix metalloproteinase-8 (MMP-8) from polymorphonuclear leukocytes and also indirectly inhibits cyclooxygenase-2.[23] The presence of MMP-8 correlates with the degradation of collagen in the periodontal tissue.[24] Due to its long history of use as an inflammation modulator combined with research studies that confirm its ability to quiet inflammation, Chinese skullcap is a good choice in a periodontal formula.

In Western herbalism, the aboveground parts of *Scutellaria lateriflora* are used medicinally, primarily as a nervine. However, all of the skullcap species (including *S. lateriflora*) appear to contain the same main flavonoids. We have used fresh skullcap herb tincture in our formula with good success, although it is possible that Chinese skullcap flavonoid profile might have a slightly stronger effect on inflammation. A preliminary thin-layer chromatographic analysis performed by us has shown that the Western and Chinese species of *Scutellaria* have similar flavonoid profiles.[25]

The final ingredient of the topical formula is gotu kola. Gotu kola and its constituents are beneficial in promoting wound healing and have been used to treat people with keloids,[26] phlebitis and venous hypertension,[27,28] leprosy,[29] stretch marks in pregnancy,[30] and a variety of other ailments. In wound studies, gotu kola increased antioxidants in newly formed tissue

while greatly reducing toxic lipid peroxide levels.[31] Gotu kola and its flavonoids increased tensile strength, collagen content, and epitheliazation in many types of wounds when used internally or topically.[32,33,34] Gotu kola had different actions at different stages of wound healing, and consistently increased collagen synthesis at the wound site.[35,36] Gotu kola has been used in plastic surgery because it helps the body produce a type of collagen that has a beneficial effect on scar formation while decreasing the inflammatory reaction around the wound.[37] Thus, it is an ideal herb to help gently heal the chronically inflamed tissue of the mouth. Most herbalists think that gotu kola should be tinctured fresh for optimal effectiveness. It has no known adverse effects.

Some additional herbs to consider adding to the formula if the results desired are not obtained are suggested in Table 25-1.

Table 25–1. Modifications of Topical Peridontal Disease Formula

Situation	*Suggestion*	*Dose*	*Notes*
Early or severe infection	*Sanguinaria canadensis* (blood root) fresh root tincture*	5–10 drops per irrigation tank	Not for use for more than four weeks continuously. Very bitter taste. Avoid in pregnancy and lactation. This plant is endangered in the wild so only cultivated blood root should be used.
	Thymus vulgaris (thyme) volatile oil	1–5 drops per irrigation tank	May cause burning.
Antibiotic resistance	*Rosmarinus officinalis* (rosemary) fresh leaf tincture	1–2 ml per irrigation tank	
Insufficient healing	*Symphytum oficinale* (comfrey) fresh leaf glycerite	3–5 ml per irrigation tank	Not for use for more than four weeks continuously. Avoid in liver or kidney disease, pregnancy, and lactation.
	Echinacea angustifolia fresh root tincture	3–5 ml per irrigation tank	*Possibly* contraindicated in patients on immunosuppressive drugs or with autoimmune diseases. Also helps with infection and inflammation.
Excessive bleeding	*Rubus discolor* (Himalayan blackberry) fresh root tincture	2–3 ml per irrigation tank	May cause nausea. Invasive weed—important to use as medicine.
	Salvia officinalis (sage) fresh leaf tincture	2–3 ml per irrigation tank	Also antimicrobial.

*Cullinan MP, Powell RN, Faddy MJ, et al. Efficacy of a dentrifice and oral rinse containing sanguinaria extract in conjunction with initial periodontal therapy. *Aust Dent J* 1997;42(1):47–51.

INTERNAL HERBAL SUPPORT

In addition to the topical formula, herbs and lifestyle changes should be used to change conditions that create an environment that feeds and sustains an imbalance in the oral flora. Michael Moore, director of the Southwest School of Botanical Medicine in Bisbee, Arizona, suggests that inadequate flow and composition of saliva due to stress is a root cause of oral disease. He explains that adrenaline significantly inhibits the flow of the alkaline parotid saliva that contains cell proliferative factors, lysozymes that slow down flora growth, and amylase that begins digestion of starches. People who are chronically stressed and have poor coping mechanisms can produce excessive quantities of adrenaline, which can decrease or halt parotid secretion, changing the pH of the mouth. This altered environment may allow different bacteria to proliferate in the mouth. It also changes the way food is digested, and changes the food debris that is available to feed bacteria thereby favoring different bacterial strains. Scientific research at present does not correlate proper salivation with periodontal disease although the ability of the diet to affect salivation and gingival resistance to infections has been mentioned.[39] However, science has found a strong link between stress and periodontal disease.[40,41,42,43]

Thus, it is essential to introduce methods for coping with stress such as adaptogens, nervines, and stress reduction techniques like meditation or yoga. Increasing appropriate saliva excretion and healthy digestion at mealtimes through the use of bitter herbs may also promote more beneficial bacteria. These are discussed in more detail below. Other lifestyle changes are also recommended. Smoking is unequivocally correlated with periodontal disease because volatile components of cigarette smoke destroy the fibroblast cells necessary for healthy gum tissue.[44] Professional cleaning offsets some of the detriment of smoking, and more frequent cleanings are necessary for patients who are unable to quit the nicotine habit.[45] Sugar is a known cause of caries whereas fibrous and nonfibrous complex carbohydrates are beneficial to the oral flora.[46] Sugars should be eliminated and replaced with more healthful fruits and vegetables.

Camellia sinensis (green tea) makes an excellent substitute for sodas and other sweetened drinks because its catechins strongly inhibited collagenase in one study.[47] Green tea has inhibitory activity against oral pathogens, is antioxidant, and has other benefits, such as possibly reducing cavities, that recommend its use.[48,49] Implanting green tea–impregnated strips has been shown effective for reducing pocket depth and fighting Gram-negative bacteria in periodontal pockets in a clinical trial.[50] Chewing sugar-free green tea gum reduces gingival inflammation.[51] Studies show that if green tea is held in the mouth for 2–5 minutes, it provides prolonged exposure (over an hour) to the beneficial periodontal constitutents (primarily catechin-type flavonoids).[52]

Vaccinium macrocarpon (cranberry) has been investigated as a potentially healthy food for people with periodontal disease. Cranberry has been shown to inhibit MMPs, elastase, and inflammation induced by oral microflora in vitro.[53,54] Cranberry has shown microbe attachment inhibitory effects in the urinary tract and small intestines, and there is no reason to think it would not have similar benefits in the mouth. Cranberries and unsweetened cranberry juice (or its cousin, blueberry) should be considered as regular additions to the diet.

Periodontal disease is increasingly tied to impaired glucose tolerance. Patients with diabetes mellitus tend to have much more severe periodontal disease, with increased concentrations of MMP-8 and MMP-9 in their gingival tissue,[55] and the extent of alveolar bone loss was associated with impaired glucose tolerance in a study of Japanese men.[56] Dietary changes to improve glucose tolerance, including eliminating simple sugars, eating more vegetables, and eating cinnamon, should be part of any treatment of periodontal disease.

INTERNAL TONIC

We use a formula taken internally as well as the topical formula described above. Any internal formula should contain a bitter unless the patient has copious saliva and a red tongue. Bitters should definitely be added to the formula of patients with a persistent white coating of the tongue or other signs of poor digestion. The most familiar bitter is *Gentiana lutea* (gentian) root, and its purpose is to increase salivation and set the stage for a proper digestive sequence in the intestinal tract, improving assimilation of nutrients. Bitter formulae are taken 5–15 minutes before meals to properly assist digestion. Many other bitters can be substituted for the gentian, which is threatened due to overharvesting. These include *Rumex crispus* (yellow dock) root, *Taraxacum officinale* (dandelion) root, and *Berberis aquifolium* (Oregon grape) root. A digestive stimulant that does not taste bitter and also has anti-inflammatory properties is *Zingiber officinale* (ginger) root.

The formula should also contain appropriate calming herbs. As mentioned, skullcap is a nervine that is used to strengthen the nerves. It may reduce the anxiety that interferes with salivation in some patients, and, in addition, will help promote wound healing when taken internally. Skullcap also has a protective effect on the liver, and can be a valuable tonic herb in many patients. Other nervines used to reduce stress are *Avena sativa* (oat) seed, *Piper methysticum* (kava kava) root, and adaptogens like *Panax quinquefolium (*American ginseng) root.

Gotu kola increases skin healing when taken internally, and has other effects that make it a good tonic herb for many individuals. Many herbalists use gotu kola to boost thyroid metabolism in people with subclinical hypothyroidism, and it is of benefit in varicose veins and edema of the limbs, and is reported to show some benefit in chronic liver ailments[57] as well as some anticancer effects in vitro.[58]

The herbs in the internal formula should, of course, be selected to best suit the needs of the individual patient, and patients should be reminded, as the formula will contain herbs that also are beneficial topically in periodontal disease, to swish the liquid around in the mouth for 15–30 seconds or longer before swallowing it. This allows the herbs to have a local as well as systemic effect.

OTHER HELPFUL HERBS

Many herbs modulate inflammation, promote wound healing, and have a mild anti-microbial action. Both *Calendula officinalis* (calendula) flower and German chamomile (*Matricaria recutita*) flower increase wound healing,[59,60,61] and might be substituted for the gotu kola. More stimulating herbs, such as echinacea (*Echinacea* spp.), are a good choice if there is acute inflammation and a swift response to infection is desired. Echinacea also has been shown to quiet inflammation[62] and inhibits enzymes that could be promoting tissue breakdown, and is a common ingredient in many herbal periodontal formulas. Toothache plant (*Spilanthes* spp.) has the tongue-tingling constituents of echinacea, and is another herb that may be useful.

Symphytum officinale (comfrey) leaf has also been studied in periodontal disease[63] but there are concerns about the effect of its pyrrolizidine alkaloids. These liver-damaging alkaloids are not typically absorbed well through the skin[64] but absorption may be increased in inflamed tissue, especially when applied several times daily over a long period of time. Pyrrolizidine alkaloid-free products are becoming available and might be appropriate for long-term use.

Other herbs that may be very useful include the Lamiaceae (mint) family astringents such as *Stachys betonica* (wood betony) herb, *Salvia officinalis* (sage) leaf, and *Mentha* × *piperita* (peppermint) leaf. It is likely that any formula that combines herbs with substantial skin-healing properties and a gentle antimicrobial action will be useful in treating the gums.

CONCLUSION

Herbs can substantially reduce gum bleeding and the depth of tissue pockets, and significantly reduce the mobility (or looseness) of teeth. They can also help avert abscesses, allowing patients to avoid root canals and extractions, and help reduce caries, a common cause of tooth loss. Combined with a healthful diet and consistent, frequent professional monitoring and cleaning of the gums, botanical therapies offer a real solution to the common problems of periodontal disease.

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26

PROSTATE CANCER: GUIDELINES FOR TREATMENT AND PREVENTION

As with so many chronic, degenerative diseases seen in modern society, prostate cancer presents a daunting challenge to the clinician. The multifactorial nature of the disease makes effectively addressing it difficult. However, numerous risk factors and etiological contributors have been well delineated, and it is theoretically possible to prevent all but those cases of the disease caused entirely by genetic factors. Unfortunately, social structures currently lack the necessary organization to make preventive measures common in any widespread way. Natural medicine has much to offer in terms of prevention of prostate cancer, treatment of patients with early- and late-stage disease, and adjunct treatment of patients with advanced disease.

CLUES TO THE CAUSES OF PROSTATE CANCER FROM EPIDEMIOLOGY

Overall, prostate cancer is the most common cancer and the second most lethal cancer among men in western societies.[1] This highlights the fact that many men (approximately 160,000 per year in the United States alone) develop localized prostate cancer. Most men with localized disease will not die of the cancer; if it were not for prostate-specific antigen (PSA) testing, most would never have even known they had the problem. The other group of men with prostate cancer (approximately 40,000 per year in the United States) develop a progressive, much more serious form of the cancer and will die from it. These men have what is known as clinically apparent or aggressive prostate cancer.

The rate of aggressive prostate cancers in non-western societies is dramatically lower than in the West. For example, the rate of serious prostate cancer was 20 times lower in China than in the United States in one study.[2] However, the rates of localized prostate cancer found at autopsy in men who die in China versus those in the United States (from causes other than prostate cancer) are very similar.[3] Studies show that as men move from an area of low incidence to an area of high incidence, they develop an increased risk of developing aggressive prostate cancer based on where they end up residing. This has been most studied with Japanese and African men moving to the United States.[4,5] The studies on blacks in the United States versus Africa were conducted with the U.S. military health care system in an attempt to minimize the impact of racial prejudice on health care services, thereby obscuring the effect of other cultural elements on prostate cancer in African American men. Societies that are undergoing industrialization and adopting Western culture more and more show increasing levels of prostate cancer, such as Mexico.[6]

The sum of this evidence leads to the following difficult-to-refute conclusion: Western lifestyle promotes either transformation of generally nonlethal, localized prostate cancer to more lethal, progressive forms or causes more men to develop new, highly malignant prostate cancer. See Table 26-1.

Table 26–1. Watchful Waiting Plus: Integrated Protocol for Patients with Localized Prostate Cancer

Recommendation	*Dose*	*Rationale*
Exercise	Aerobic (walking, etc.) three times weekly (30–45 minutes per session) sufficient to elevate HR to 75% maximum. Do not do more than this (may immunosuppress)!	Immunopotentiating, antidepressant, antistress
	Anaerobic (weight lifting) on non-aerobic days	
Dietary recommendations	All the same items mentioned in the prevention protocol in Table 26-4 apply doubly here. Strict animal product avoidance is important.	Same as prevention protocol in Table 26-4
Soy foods and/or extracts*	Provide 100 mg isoflavones per day minimum	Phytoestrogen, antineoplastic, anti-angiogenesis
Individualized botanical formula	5 ml three times per day is the standard dose of a formula containing no toxic herbs	Antineoplastic, phytoestrogen, immunomodulating, tonifying, anti-metastatic
Selenium	1,000 mcg daily or more	Antineoplastic (may only be useful for prevention)
Vitamin D	800 IU daily	Antineoplastic
Modified or fractionated citrus pectin	1 tsp powder three times daily prepared in a glass of warm, filtered water each time	Anti-metastatic
Support group	Once weekly or more	Immunopotentiating, lengthens survival time

*Protein powders or encapsulated products made from soy.
Note: Therapy must be individualized for every patient; these are only general suggestions. This list is not exhaustive.

PROSTATE CANCER AND AFRICAN-AMERICAN MEN

African American men are disproportionately affected by aggressive prostate cancer—nearly twice as much according to some estimates. Probing the reasons for this provides insight into how prostate cancer comes to be a problem and what is to be done about it. Several features of the differences in prostate cancer among black and white men in the United States must first be considered, and have been discussed in greater detail elsewhere.[7] Black men have higher mortality rates from prostate cancer, particularly younger black men. At the time of diagnosis, prostate cancer is generally more advanced in black than at diagnosis in white men. This is much less so in groups where PSA screening is readily available. Racial bias leads to delayed diagnosis, hence more advanced cancers at time of diagnosis and therapy. Rates of localized, nonclinically apparent prostate cancer are the same among blacks and whites in the United States. Prostatic intraepithelial neoplasia, a precancerous form of prostate cancer likely to progress to invasive

disease, is more common in African Americans. Black men eat a diet higher in fat derived from nonfish animal sources. Androgen stimulation seems to be higher in black men.

Clearly these features suggest numerous important elements of the cause of prostate cancer. First, there may be genetic differences in the black and white population that make blacks more susceptible to prostate cancer. Because black Africans leading a traditional lifestyle are not at higher risk of prostate cancer, one could surmise that these genetic factors only make blacks more likely to be harmed by a western lifestyle. A more well-understood example of this phenomenon is the so-called thrifty genotype among Native Americans. Essentially, it is believed that Native Americans are better equipped genetically to handle starvation as a population than other racial groups. In particular, they appear to store fat more effectively. Unfortunately, when someone with a thrifty genotype is placed in a culture of plentiful calories derived primarily from animal products and refined carbohydrates, the person tends to gain weight, have severe problems with atherosclerosis, have higher rates of gall stones, have increased risks of developing diabetes, and so on. It may be that some protective mechanism in blacks in the context of native culture is protective against prostate cancer, but in the setting of Western society becomes counterproductive. The details of this situation remain to be elucidated. What is becoming increasingly clear is that eating traditional foods helps prevent a number of diseases of modern society in numerous populations.[8]

THE HORMONE LINK

Prostate cancer is one type of cancer that is strongly linked to a variety of hormones. Most practitioners are aware that androgens can stimulate prostate cancer cells. Though testosterone itself has this action, its conversion product dihydrotestosterone (DHT) is at least five times more stimulating. DHT is formed by the action of one of at least two subtypes of the enzyme 5-alpha-reductase. However, other hormones including estrogens and hormone-carrier molecules, particularly steroid hormone-binding globulin (SHBG), also play a role that is only just becoming apparent. For more on the complex role of hormones, signaling factors, proto-oncogenes and other metabolic factors that affect prostate cancer, see the comprehensive review by Griffiths, Morton, and Nicholson.[9]

For years, allopathic drug therapies for prostate cancer patients have focused on various ways of decreasing or eliminating testosterone. Initially this meant no drugs at all but rather bilateral orchidectomy (surgical castration) to remove most of the testosterone-synthesizing tissue in the body. This obviously leaves much to be desired cosmetically, creates all the adverse effects of testosterone deficiency, fails to remove nontesticular testosterone sources (primarily the adrenal glands), and remains a highly unpopular treatment option. Over time five classes of drugs have been developed that interfere with testosterone action in one way or another. These are summarized in Table 26-2. As will be seen, some natural products have similar though milder actions as these agents. It should be noted that as yet, direct comparative studies have not shown cyproterone or diethylstilbesterol to be superior to orchidectomy alone.[10] Therefore one must question whether these drugs represent much of an advance. It would seem that if a man prefers to avoid castration, the drugs will be at least as effective.

Anti-androgen drugs of all types have numerous adverse effects. They can induce a complex of symptoms that looks remarkably like menopause—hot flashes, night sweats, moodiness, reduced libido, osteopenia, and other problems. Atherosclerosis may be accelerated by some of the drugs, particularly diethylstilbestrol. Mastalgia and gynecomastia are common problems. Some drugs (such as flutamide and ketoconazole) have significant potential to cause hepatic

Table 26–2. Drugs Used to Treat Prostate Cancer Patients

Drug Class	*Specific Drugs*	*Action*
LHRH analogs	Leuprolide (Lupron), goserelin (Zoladex), nafarelin (Synarel)	Overstimulate LHRH production, leading eventually to feedback inhibition of LHRH production, hence removing the ultimate hypothalamic signal for testosterone synthesis
Estrogens	Diethylstilbesterol	Inhibit LHRH release from the hypothalamus
Direct synthesis inhibitors	Ketoconazole, aminoglutethimide	Inhibit synthesis of testosterone and other steroid hormones in the adrenals
Anti-androgens	Bicalutamide (Casodex), flutamide (Eulexin), cyproterone	Block binding of DHT to its receptor inside prostate cells
5AR inhibitor	Finasteride (Proscar)	Inhibits type I 5AR, preventing DHT synthesis in the testes

5AR: 5-alpha-reductase; LHRH: luteinizing hormone-releasing hormone.
Garnick MR. The dilemmas of prostate cancer. *Sci Amer* April 1994:72–81 [review].

damage. Impotence is a frequent concern. Another problem with some agents, particularly DHT receptor blockers and luteinizing hormone-releasing hormone (LHRH) analogs, is that testosterone levels are actually elevated in the blood either temporarily or consistently by these them. This may actually lead to worsening of the prostate cancer eventually. Using various drugs in combination can help reduce this problem, particularly by combining an anti-androgen with a DHT receptor blocker or an LHRH analog.

Another problem with continuous androgen blockade is androgen resistance. The longer prostate cancer cell populations are subjected to drug therapy depriving them of growth-driving androgen signal molecules, the more likely an androgen-independent strain is to come to dominance. As a result, androgen blockade will cease to be effective altogether and the patient is then at very high risk of dying of the prostate cancer. In fact, continuous androgen blockade almost always leads to androgen resistance and treatment failure.[11] One solution to this problem has been the supposition that androgen blockade should be administered intermittently. Several studies are starting to demonstrate the superiority of this approach.[12,13]

Natural products can generally be used safely and effectively in combination with drugs for men who choose this route. One area where this has been specifically studied is the combination of high-dose melatonin with LHRH analogs. A study in 14 men with metastatic prostate cancer progressing while taking triptorelin were given 20 mg melatonin in the evening.[14] LHRH resistance seemed to be reversed in 57% of the participants, and survival greater than 12 months was seen in 64%. Though this study requires replication, it supports many other studies suggesting that high-dose melatonin can benefit cancer patients, including in combination with drugs.[15] Other than morning grogginess, no significant side effects are seen at this dose of melatonin. It is generally recommended that other people not use such a high dose as long-term side effects cannot be ruled out. There is evidence from rat studies that daytime administration of melatonin may cause cancer, so it should be strictly avoided except at night.

BOTANICAL HORMONE MODIFIERS

The most well-known testosterone-modifying natural product is perhaps *Serenoa repens* (saw palmetto) fruit. Saw palmetto is a member of the Araceae (palm) family. Saw palmetto has not yet been studied in patients with prostate cancer, though in vitro it has been shown to induce apoptosis and necrosis in prostate cancer cells.[16] Its numerous actions suggest it might be a valuable treatment nevertheless. For example, it has mild 5-alpha-reductase-inhibiting, DHT-receptor-inhibiting, and estrogen antagonist effects in various model systems or in vivo.[17,18,19,20] Not all studies have confirmed these actions, notably one human study that failed to show that a saw palmetto standardized extract inhibited 5-alpha-reductase in humans compared to the drug finasteride (Proscar).[21] Unlike the drugs finasteride and dutasteride, saw palmetto does not artificially lower PSA levels and thus is unlikely to mask the presence of prostate cancer in patients with benign prostatic hyperplasia.[22]

Though saw palmetto is often thought of in the new terminology of technologized phytotherapy, it has long been used as an herbal medicine in simpler form. The Eclectic physician Harvey Wickes Felter, MD, said the following of saw palmetto:[23]

> Its most direct action appears to be upon the reproductive organs when undergoing waste of tissue; in some nutritional way it is asserted to enlarge the breasts, ovaries, and testicles, while the paradoxical claim is also made that it reduces hypertrophy of the prostate. This can only be explained, if, indeed, it has such opposite effects, by assuming that it tends toward the production of a normal condition, increasing parts when atrophied, and reducing them when unhealthily enlarged. . . . It has been observed also that it increases the sexual appetite and restores lost power from excess, in both man and woman.

Thus, it is believed by clinical practitioners who use botanical medicines regularly that saw palmetto is more than just an antihormonal agent. It has as yet unexplained tonifying effects on the prostate and all reproductive organs (male or female). It may help alleviate symptoms of impotence after prostate cancer surgery, and may work synergistically with drugs. Because saw palmetto is nutritive in nature, it is essentially without adverse effect. An occasional patient will develop mild nausea while taking it. Tinctures have been used for centuries to good effect—3–5 ml three times per day is a standard dose of this medicine used alone. Extracts standardized to 80–90% of the lipids of saw palmetto are taken at a dose of 160–320 mg daily. Often saw palmetto is used not alone but combined with other plants with complementary actions. When used this way, less of the tincture is required.

Two other botanicals worth mentioning as hormone modulators are *Prunus africanum* (pygeum) bark and *Urtica dioica* (stinging nettle) root. Pygeum is a member of the Rosaceae family whereas stinging nettle is in the Urticaceae family. The combination of these two has been shown in vitro to inhibit 5-alpha-reductase and aromatase.[24] Aromatase converts testosterone to potentially cancer-promoting estrogens in the prostate. Both have primarily been used to treat men with benign prostatic hyperplasia (BPH), an approach shown effective in numerous clinical trials. They have not yet been studied in men with prostate cancer. But as with saw palmetto, their physiological actions suggest they might be beneficial. Nettle roots have also been shown to block bindings of SHBG to prostate membranes and to block the activity of epidermal growth factor in vitro.[25,26] While these actions clearly apply to BPH patients, it is possible they might also help interfere with prostate cancer. Nettle leaves are traditionally used as a nutritive tonic similar to saw palmetto, though with no special tropism

Table 26–3. Hormone-Modulating Botanicals

Latin Name	*Common Name*	*Action(s)*	*Dose*	*Side Effects*
Serenoa repens fruit	Saw palmetto berry	Anti-testosterone, anti-estrogen, nutritive tonic	3–5 ml tincture three times per day;* 160–320 mg 85% sterol StE daily	Nausea (rare)
Prunus africanum bark	Pygeum bark	Anti-testosterone, aromatase-inhibitor	2–4 ml tincture three times per day;* 50–100 mg two times per day 13% sterol StE	Nausea (rare)
Urtica dioica root	Stinging nettle root	As pygeum, also acts on SHBG	4–5 ml tincture or glycerite three times per day;* 600 mg extract two times per day	None
Glycine max fruit	Soy bean	Phytoestrogen, antineoplastic	StE providing 100 mg isoflavones daily**	Flatulence
Vitex agnus castus fruit	Chaste tree berry	Pituitary hormone effects	1–2 ml tincture three times per day*	None

SHBG: sex hormone-binding globulin; StE: standardized extract.
*Lower amounts are necessary if the tincture is used in combinations with other herbs.
**Should definitely be a whole-bean extract as there other anticancer compounds in soy besides isoflavones.

for the prostate. The use of the roots has only been a modern development, so much less is known about it.

At this time, pygeum cannot be recommended for routine clinical use. Secure measures have yet to be taken to ensure this African plant will not be made extinct by overharvesting. Projects are underway to develop pygeum plantations in an attempt to ensure an ecologically safe supply of the medicine.[27] However, some local genetic variants within the species have already been exterminated. Fortunately, stinging nettle has none of the environmental problems posed by pygeum. Pygeum is a tree and requires a long time to grow. Harvesting the bark generally kills the tree although harvesting younger bark from branches may prove a more viable way to harvest without killing the tree. Although stinging nettle is a perennial, it grows as a weed in many wet places. It is something of a nuisance, stinging hikers as they pass by or giving trouble to children who stumble into nettle stands. Thus it would actually be a benefit to use this plant as medicine and it would be difficult to wipe out such a tenacious, easily cultivated herb. There is also presently no sign that saw palmetto is endangered or being unsustainably harvested. See Table 26-3.

THE IMPORTANCE OF SOY IN PROSTATE CANCER

The fourth major hormone-modulating plant is *Glycine max* (soy). The beans of this plant contain numerous constituents with antineoplastic activity: isoflavones, protease inhibitors (particularly Bowman-Birk inhibitor), saponins, and inositol hexaphosphate.[28] Of particular interest to the subject of prostate cancer are isoflavones. These flavonoid-like compounds bind to estrogen receptors but trigger a much weaker effect. Studies have generally concluded that the soy isoflavone genistein has approximately one thousandth the estrogenic activity of estradiol.[29]

Balancing this is the fact that genistein levels can be 1,000 times higher than estradiol levels by eating moderate levels of soy.[30] A meta-analysis of eight epidemiologic studies confirms that regular dietary intake of soy reduces the risk of developing prostate cancer in men.[31] It is believed that consumption of approximately 100 mg isoflavones per day will result in sufficiently high serum levels to interfere with the action of circulating estradiol.[32] To obtain this amount would require eating a lot of legumes—⅛ cup of tofu has 20–40 mg isoflavones, as does 1 cup of soy milk. Other beans actually appear to be greater sources of these compounds, as well as the root of *Pueraria montana* var *lobata* (kudzu).[33] The underlying expectation is that these compounds would block estradiol's stimulatory effects on prostate cancer cells.

Some human research suggests that soy or other phytoestrogens may have a beneficial impact on patients with prostate cancer. Intake of a high-soy and -flaxseed bread was correlated with lower total PSA and higher free PSA compared to wheat bread without phytoestrogens in one small randomized trial.[34] A one-year open clinical trial using an extract of *Trifolium pratense* (red clover) providing 60 mg of isoflavones daily found that it decreased total PSA by 30% compared to baseline.[35] A fermented soy drink called Ecogen 851 was shown in one uncontrolled trial funded by the product's maker to decrease PSA levels by an average 37% in 14 men with prostate cancer.[36] Such data are preliminary but suggest that controlled clinical trials on treatment of men with prostate cancer with isoflavones are urgently needed.

The effects of soy isoflavones do not stop at phytoestrogenicity. They have also shown an anti-angiogenic action[37] and have induced apoptosis in prostate cancer cells,[38] decreased androgen-receptor expression,[39] inhibited a number of cancer-promoting enzymes including various tyrosine kinases and topoisomerase II,[40] become antioxidant,[41] and many other effects.

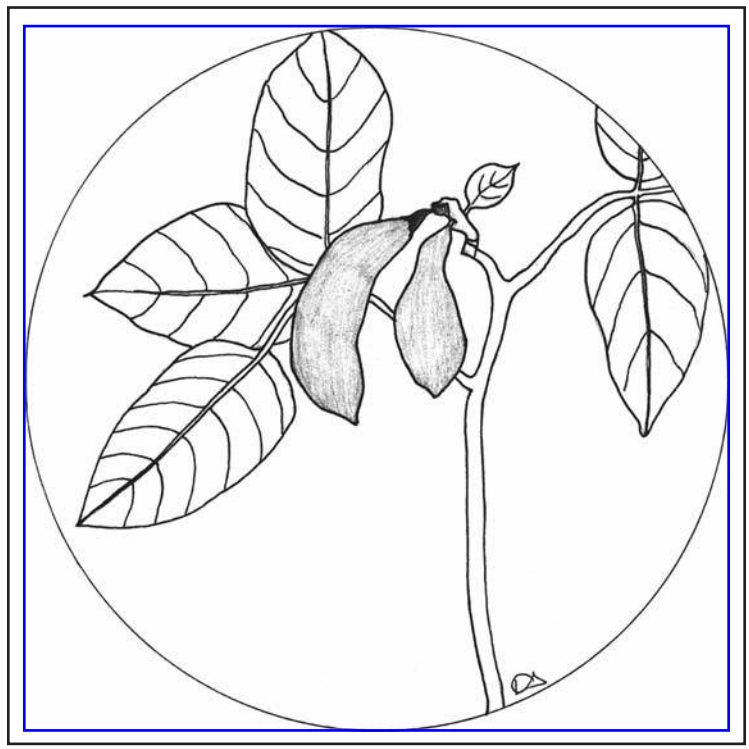

Figure 26–1. *Glycine max* (soy) bean
Drawing ©2008 by Kathy Abascal, BS, JD.

Figure 26–2. *Glycine max* (soy) bean

Additional constituents in soy may account for some of these actions as well. The bottom line is that for patients who are not allergic to soy, it is a crucial part of any protocol for prostate cancer prevention and treatment. Intake of soy foods greatly increases isoflavone levels in the prostatic fluid of most men.[42] See Table 26-4. Differences in gene expression has been shown in prostate tumors of native Japanese men versus Japanese American men, which directly correlate to dramatically lower intake of soy in Japanese American men.[43]

Soy supplements have also been studied in men with prostatic intraepithelial neoplasia (PIN), believed to be a precursor to prostate cancer. A combination supplement delivering 200 mcg selenium, 60 mg vitamin E (exact form not stated), and 100 mg soy isoflavones per day was given to 71 men with PIN for 6 months.[44] The average serum total PSA (tPSA) level was significantly decreased compared to baseline throughout the trial. In those men who had stable or reduced tPSA, the risk of progressing to prostate cancer on repeat biopsy was halved compared to men whose tPSA levels rose during the trial. Although the overall progression rate to prostate cancer (around 33%) was not different from historical published studies on men with PIN, those men who had an effect measured by tPSA also were clearly protected against cancer progression.

THE PC-SPES RIP-OFF

Several years ago studies started to appear about a formula dubbed PC-SPES, created by BotanicLab of California. This formula contained highly concentrated, proprietary extracts of *Isatis indigotica* (indigo), *Glycyrrhiza glabra* (licorice), *Scutellaria baicalensis* (Baical skullcap), *Ganoderma lucidum* (reishi mushroom), *Serenoa repens* (saw palmetto), *Panax ginseng*

Table 26–4. Integrated Protocol for Prevention of Prostate Cancer

Recommendation	*Dose*	*Rationale*
Exercise	Aerobic (walking, etc.) three times weekly (30–45 minutes per session) sufficient to elevate HR to 75% maximum or every day (10–15 minutes per session) without particularly elevated HR. Anaerobic (weight lifting) on non-aerobic days.	Immunopotentiating including by preventing depression and improving stress coping
Soy milk,[c] soy foods, and/or extracts*	Provide 100 mg isoflavones per day minimum.	Phytoestrogen, anti-neoplastic, anti-angiogenesis
Eat fish	Wild-caught ocean fish (salmon, tuna, etc.), at least one helping per week (more is better)	Anti-inflammatory, antineoplastic, immunomodulating
Eat fruits and vegetables	Any kind, all kinds (yes, even avocado), all the time, as much as possible. Choose organic as often as possible. Should form base of almost any diet. Include garlic and tomatoes frequently.	Profoundly antineoplastic,[a] anti-atherosclerotic, and generally promote all aspects of health. The pesticides and herbicides in nonorganic produce are carcinogenic and xenoestrogenic.
Camellia sinensis (green tea)[d]	Drink 3 or more cups per day, preferably 10 (preferably of water-process decaffeinated form).	Potent cancer preventive
Linum usitatissimum (flax) seeds	2–3 tsp freshly ground seeds per day. Can bake with this meal or whole seeds. Flax oil less helpful.	Antineoplastic and phytoestrogen. If not freshly ground, the powder goes rancid. Flax oil does not contain significant amounts of the phytoestrogen constituents desired.
Curcurbita pepo (pumpkin) seeds	1 handful per day or every other day (more is fine).	Traditional prostate tonic. Fatty acids are beneficial.
Avoid animal products[b,e]	Avoid as much as possible, including chicken and dairy products (other than live-culture yogurt). Organic eggs are fine. If animal products are eaten, use only organic products.	Fatty acids are immunosuppressive and pro-cancer. Hormones and antibiotics are pro-cancer including as xenoestrogens.
Limit ethanol ingestion[f]	No more than 1 glass of red wine per day; avoid beer and hard alcohol altogether.	May promote PrC, possibly by increased estrogen levels

(*continued*)

Table 26–4. (*continued*)

Recommendation	*Dose*	*Rationale*
Multinutrient supplement	Contains at least 400 IU vitamin E, 200 mcg selenium,** 1,000 mg vitamin C, 10,000 IU natural mixed carotenes, 400 IU vitamin D, 15 mg zinc.	Profoundly antineoplastic
Have fun; find and give love	Find personal balance	A positive attitude help prevents cancer and promote wellness.

DRE: digital rectal exam; HR: heart rate; PC: prostate cancer; PSA: prostate-specific antigen.
*Protein powders or encapsulated products made from soy.
**This is the most important element of any protocol and must be obtained in some form, either from the multinutrient or as a separate supplement.
***Younger if there is a family history of prostate cancer.

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(Asian ginseng), *Dendranthema morifolium* (chrysanthemum), and *Rabdosia rubescens*.[45] It was not based on any traditional herbal formula and was not a simple mixture of crude extracts. The first major, published clinical trial, in the *New England Journal of Medicine*, found that administration of 320 mg of the formula four times daily for at least two weeks to men with advanced prostate cancer led to decreased PSA levels, but also led to mastalgia, loss of libido, and even one case of venous thrombosis.[45] Although it was biologically plausible that the herbs in this formula could have caused some effects on men with prostate cancer, the effects were grossly out of alignment with most results of herbal clinical trials.

Eventually it was revealed that the formula had been spiked with diethylstilbestrol, and then later, anticoagulant drugs such as warfarin to attempt to reduce side effects, which accounted for the extreme results.[6] BotanicLab went out of business in 2002 and stopped selling the product due to failure to produce working extracts without adulterating drugs and due to mounting legal bills. The expense of PC-SPES (over $100/bottle), high rate of adverse effects, and failure to disclose its pharmaceutical ingredients have led to the filing of a class-action lawsuit against the makers of the formula. Whether the company knowingly sold an adulterated product or not is still unknown, but clearly, this formula is not an acceptable treatment.

In 2008, a new formula, known as PC-SPES2, appeared on the scene in a published, open trial.[47] The authors of this report claim that the new formula was carefully monitored to ensure it contained no drugs. Of 18 men with advanced prostate cancer who took the formula, 10 with-

Figure 26–3. Fresh *Panax ginseng* (Asian ginseng) from Seoul, Korea.
Photo ©2008 Eric Yarnell, ND, RH.

drew within one month due to severe diarrhea. Nevertheless, declines in PSA kinetics (doubling time and velocity) were detected within one month and were durable to six months in those patients who did not withdraw. Whether this represents a useful treatment or not is highly dubious based on these preliminary results, and the avoidance of a repeat of the original PC-SPES debacle is still entirely possible.

OTHER BOTANICAL MODULATORS OF HORMONES

Several other herbs may potentially be of benefit in patients with prostate cancer because of less well-understood hormonal actions. Many of these are now regarded as herbs useful only

for female reproductive problems, when in fact they have historically been used for men and women and the information we do have about their actions supports such a crossover.

Vitex agnus castus (Chaste Tree or Vitex)

Vitex agnus castus (chaste tree or vitex) berries have long been used for numerous hormonally related conditions in women. Vitex is a member of the Verbenaceae family. Research indicates that the constituents of vitex act in the pituitary and hypothalamus, mildly reducing follicle-stimulating hormone (FSH) production while stimulating luteinizing hormone (LH) production.[48] In women this shifts the balance of estrogen and progesterone in favor of progesterone. It is not yet known what effect this might have in men. Vitex also inhibits release of prolactin from the pituitary via dopamine-receptor agonism.[49] This prolactin-lowering effect has been corroborated in a clinical trial in healthy men.[50] The role of prolactin is unknown in prostate cancer, with some studies suggesting it inhibits 5-alpha-reductase and others showing it potentiates testosterone effect in prostate tissue.[51] A related tree from China, *Vitex negundo*, has been shown to have definite anti-testosterone effects in dogs.[52]

The complexity of action of vitex makes it difficult to decide if it would be useful in men with prostate cancer or if it might actually compound the problem. One of its other common names is monks' pepper, as it was used by monks to reduce their libido and tastes peppery. This would not seem helpful in men who are already having libido problems. It does suggest that vitex has an anti-testosterone effect, though other mechanisms could explain the anhedonic effect of vitex. On the other hand, the Eclectics used drop doses of vitex to actually treat impotence and "sexual melancholia."[53] In clinical practice it frequently seems that vitex acts as an hormonal normalizer—if hormone balance is incorrect, vitex brings it back toward homeostasis. It can thus be considered in small doses as part of a complex approach to prostate cancer patients, particularly because its actions work in a different way from any other hormonally active herb.

CHOLECALCIFEROL (VITAMIN D)

The fat-soluble molecule known as vitamin D has shown increasingly strong relations to prostate cancer in the past decade. Vitamin D is truly a hormone like other fat-soluble vitamins, and one should keep this in mind when thinking about its activities and use. For this reason, vitamin D is referred to as calciferol in the generic for the rest of this chapter. Like all hormones, calciferol has great potential for benefit as well as harm.

Calciferol has numerous forms. The basic form in plants is known as ergocalciferol whereas the basic form in animals, including humans, is cholecalciferol. Either form can be consumed in the diet, though cholecalciferol can be synthesized to some extent in humans from cholesterol and then undergo ultraviolet irradiation in the skin; ergocalciferol appears to be at best marginally active in humans. Ergocalciferol or cholecalciferol are transported by vitamin D-binding protein to the liver and then the kidney, each carrying out a hydroxylation step to activate the molecule. It is also known that many peripheral tissues including neurons and leukocytes can accomplish the final hydroxylation step previously believed to occur only in the kidney. The final, active form of calciferol is 1,25-dihydroxycalciferol or calcitriol. It is calcitriol that is ultimately responsible for the antineoplastic and all actions of vitamin D.

Low serum levels of various forms of vitamin D have been linked to an increased risk of developing prostate cancer.[54] Though not all studies agree on the effect or its magnitude, the

balance of evidence supports this association. A diet high in dairy products and non-fish meat may lead to calcium overload and thus reduced calcitriol synthesis—this may partially explain why non-fish animal products are associated with increased risk of prostate cancer.[55] Men with low sunlight exposure (particularly comparing northern and southern latitudes of the United States) have increased rates of prostate cancer.[56] Finally, the previously explored link between African American race and prostate cancer could also potentially be explained by the fact that darker skin pigmentation in blacks reduces the amount of vitamin D that is synthesized. Interestingly, all of these factors are also known to be risks for breast cancer, possibly with the exception of African American race. See Sidebar 26-1.

Calcitriol binds to vitamin D receptors. Prostate cancer cells express vitamin D receptors, and vitamin D appears to inhibit growth of these cells regardless of the testosterone or DHT levels present.[57]Almost all in vitro work suggests that calcitriol, particularly higher concentrations thereof, inhibits prostate cancer cell growth in the test tube independent of vitamin D receptor concentration.[54] The exact mechanisms of calcitriol in relationship to cancer are still being explored. One theory is that mutations in the vitamin D receptor gene could explain why some men develop lethal prostate cancer and others never do. Studies are mixed on whether this hypothesis is valid.[58,59] For the time being, the action of calcitriol remains unknown.

Clinical studies have shown some promise from therapeutic administration of calcitriol. One uncontrolled study found that it could significantly slow the rate of PSA concentration in patients with recurrent prostate cancer after either prostatectomy or radiation therapy.[60] This study used up to 2.5 mcg calcitriol orally per day. A prior study used a maximum of 1.5 mcg calcitriol per day and did not show any significant benefits.[60] Calcitriol causes hypercalciuria almost universally. It is a prescription drug and is dosed by starting at 0.5 mcg per day by mouth and slowly working up by increasing the dose 0.25 mcg at a time over one week's time. Serum and urinary calcium levels must be monitored during this process. It has been suggested that the maximum tolerable serum calcium level should be 11 mg/dl—if a patient goes higher than this, decrease the dose and do not elevate it again. Kidney stones are highly likely to form in such a calcium-rich urine. For this reason, it is crucial that the patient supplement magnesium citrate 500 mg twice per day at the very least during calcitriol therapy (see chapter 20 for more information). Further measures for preventing kidney stones are discussed in chapter 20.

26–1. *Links Between Vitamin D and Prostate Cancer*

- High sunlight exposure correlated to low rates of prostate cancer. This includes the observation that prostate cancer is more common in northern than southern latitudes in the United States.
- Japanese who consume large quantities of vitamin D–rich fish have low prostate cancer risks.
- Elderly men with greater tendency to vitamin D deficiency are at greatest risk of prostate cancer.
- Administration of activated vitamin D (calcitriol) improves men with prostate cancer.
- Consumption of meat and dairy products, believed linked to prostate cancer due to high saturated fatty acid content, may lower vitamin D levels in circulation.
- African Americans, at highest risk of prostate cancer, have lower vitamin D levels compared to races with lighter-colored skin.

Studies are underway with calcitriol analogs that do not cause hypercalcemia but still have anticancer activity. It should also be noted that calcitriol acts synergistically with platinum chemotherapy drugs in the test tube,[61] raising the possibility of using it during chemotherapy treatment to enhance efficacy.

Regular sun or full-spectrum light exposure, or supplementation with 2,000–10,000 IU vitamin D3 daily (sufficient to raise serum 25-hydroxyvitmain D3 levels to 60–90 ng/ml) are now advocated to both prevent and treat localized prostate cancer. Clinical trials are urgently needed to determine the efficacy of this approach. What is clear is that these doses of vitamin D3, once thought highly dangerous, are in fact quite safe and do not approach the approximately 20,000 IU of calciferol the body synthesizes when exposed to adequate sunlight.[62]

DEHYDROEPIANDROSTERONE (DHEA)

Dehydroepiandrosterone (DHEA) is a precursor molecule to testosterone and other steroid hormones and has achieved something of fad status in natural health circles. It would logically seem that DHEA would be strictly contraindicated in prostate cancer patients, as driving testosterone levels higher is the last thing one wants. Androstenedione, another precursor made popular by baseball star Mark McGwire, is in a similar class. One case study has been published showing that intake of high levels of DHEA (400–700 mg daily) in a patient with prostate cancer led to severe worsening of the disease.[63] Therefore, these agents should be strictly avoided by prostate cancer patients. Seven-oxo DHEA and 7-hydroxy DHEA are exceptions to this rule as they do not serve as androgen precursors.

BOTANICAL IMMUNOSTIMULANTS AND IMMUNOMODULATORS

Optimizing immune function is a unique way to prevent and treat all types of cancer, including prostate cancer. Natural immunomodulators offer an important crossover point between standard cancer therapy and natural approaches, because they can be used to reduce adverse effects of chemotherapy and radiation therapy. This provides an excellent example of how mainstream and natural medicine are actually complementary and not antagonistic.

We discuss two categories of medicinal plants with activity in the immune system. The first is used to elevate immune function in healthy and prostate cancer patients. The classic examples are *Echinacea angustifolia*, *E. purpurea*, and *E. pallida* (purple coneflower) root or flowering tops. The second category is used to regulate the immune system, increasing its activity where appropriate and reducing it when there is pathologic overactivity. A class example is *Panax ginseng* (Asian ginseng) root.

Various species of *Echinacea* have significant potential as treatments for prostate cancer patients. Oral administration of extracts of echinacea has shown a fairly consistent ability in controlled clinical trials to enhance human immune function.[64] The quality of these studies has generally been low, and thus more carefully controlled studies are warranted. Specific to cancer, two studies have shown that intramuscular injection of a preparation of expressed juice of *E. purpurea* flowering top, low-dose cyclophosphamide, and thymostimulin could have some beneficial effects on patients with advanced, metastatic colon or liver cancer.[65,65] Improvement in immune function was demonstrated in these groups even when standard cancer therapies were continued. Survival time was not dramatically enhanced but in some cases was more than eight months after initiation of therapy, a clinically relevant finding. Prostate cancer patients

have not specifically been studied in this context, but given the safety of echinacea, there is little to lose from a therapeutic trial. Table 26-5 reviews several other possible immunostimulants to consider in treating patients with prostate cancer.

The field of immunomodulators is large. One example is *Eleutherococcus senticosus* (eleuthero or Siberian ginseng), the root of which has been investigated as an adjunct to chemotherapy and radiation therapy for various forms of cancer. Russian researchers found that 0.5, 1. and 2 ml per day of fluid extract of eleuthero allowed patients with melanoma to tolerate standard therapy better, and had significant increases in various measures of immune function compared to prior to therapy after just one month.[66] In metastatic breast cancer, eleuthero allowed women to tolerate two courses of chemotherapy with little change in leukocyte counts.[67] Other studies suggest eleuthero lowers toxicity of chemotherapy.[68,69] These studies have not looked at prostate cancer, but the nonspecific immune effects seen with eleuthero administration are likely to benefit all types of cancer patients.

Table 26–5. Immunostimulating Botanicals of Potential Benefit for Prostate Cancer Patients

Latin Binomial	*Common Name*	*Part Used*	*Notes*
Echinacea purpurea, *E. angustifolia*, *E. pallida*	Purple coneflower	Root, herb	Multiple active constituents including alkylamides, caffeic acid compounds, and polysaccharides
Eupatorium perfoliatum	Boneset	Root	Also diaphoretic; polysaccharides implicated[a]
Eupatorium cannabinum	Hemp agrimony	Root	Polysaccharides implicated[a]
Viscum album	European mistletoe	Herb	Given by subcutaneous injection one to two times per week[b]
Ligusticum porteri	Oshá	Root	Also antiviral; "southwestern echinacea"
Baptisia tinctoria	Wild indigo	Root	Found to counter leukopenia combined with *Echinacea* in cancer patients undergoing chemotherapy[c]
Dionaea muscipula	Venus flytrap	Herb	Suspected immunostimulator;[d] endangered, poorly studied
Symphytum officinale	Comfrey	Leaf, root	Polysaccharides implicated;[a] poorly studied; use of root for more than three months not recommended due to possible liver-damaging effects of pyrrolizidine alkaloids

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Some concern has been raised about eleuthero and *Panax ginseng* (Asian ginseng) root because both have hormonal activity beyond their immunomodulatory activity. Because prostate cancer is a hormone-dependent cancer, particularly early in its course, this concern is theoretically justifiable but has not been seen in practice.

It is surprising that despite reams of in vitro and animal research on Asian ginseng, there is very little available in the way of clinical trials, particularly for cancer patients. Immunomodulation has been shown in double-blind, randomized human studies using standardized extracts of Asian ginseng.[70] Asian ginseng intake has been correlated with prevention of all types of cancer including prostate cancer in China and Korea.[71–73] The evidence for this preventive effect is strong and consistent. Contrary to traditional Chinese medicine, which holds that roots aged at least six years are superior medicine, consumption of four-year-old or younger roots was correlated with the greatest level of protection in one study.[73] A clinical trial should be started immediately to determine if Asian ginseng can truly prevent cancer.

The list of immunomodulators is long. Table 26-6 mentions several promising agents, none of which have been specifically studied in prostate cancer patients but should be as soon as possible.

Table 26–6. Immunomodulating Botanicals of Potential Benefit for Prostate Cancer Patients

Latin Binomial	*Common Name*	*Part Used*
Panax ginseng	Asian ginseng	Root
Eleutherococcus senticosus	Siberian ginseng, eleuthero	Root
Withania somnifera	Ashwagandha	Root
Ocimum sanctum	Holy basil	Leaf
Rhodiola rosea	Rhodiola	Root
Codonopsis pilosula	Dang shen	Root
Aralia manshurica	Manchurian spikenard	Root
Lentinus edodes	Shiitake	Mycelium
Coriolus versicolor	Yun zhi, cloud mushroom	Mycelium
Astragalus membranaceus	Huang qi	Root
Ganoderma lucidum	Reishi, ling zhi	Mycelium
Ligustrum lucidum	Nu zhen zi, privet	Fruit
Cordyceps sinensis	Dong chong xia cao	Mycelium
Panax quinquefolium	American ginseng	Root
Picrorhiza kurroa	Picrorhiza, kutki	Root

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THE IMPORTANT ROLE OF ZINC

Several nutritional supplements have known modulating effects on the immune system. Zinc and selenium are discussed in depth below. Zinc is necessary for normal T lymphocyte and macrophage activity.[74] Zinc deficiency, even if borderline, can cause an imbalance between T-helper lymphocyte subpopulations.[75] Although it is more likely this imbalance would allow for viral infection more readily, it could potentially contribute to the pathogenesis of prostate cancer. One study in children with acute leukemia found that 150 mg zinc aspartate per day and a fermented extract of *Carica papaya* (papaya) as immunomodulators and antioxidants significantly reduced side effects of radiation therapy.[76] While not directly applicable to prostate cancer patients, this study suggests a role for zinc as an adjunct to radiation therapy for all cancers.

The large majority of human studies have shown a profoundly lower level of zinc in prostate cancer cells compared to normal prostate cells or benign prostatic hyperplasia (BPH) cells.[77] In contrast, BPH cells accumulate enormous quantities of zinc relative to normal cells. It is believed that normal prostate cells accumulate high levels of zinc to inhibit the activity of mitochondrial aconitase, thereby blocking oxidation of citrate. This limits energy production in the prostate cell and prevents uncontrolled growth. By failing to accumulate as much zinc, prostate cancer cells are able to oxidize more citrate and produce energy to support rapid growth, division, and spread. Metastatic prostate cancer cells do not uptake zinc, but zinc and zinc citrate in solution around them still have profound effects on their growth.[78]

Figure 26–4. *Panax quinquefolium* (American ginseng)

Testosterone and prolactin exert controlling influences on zinc accumulation by prostate cells normally by unknown mechanisms. This mechanism implicates a nonimmunological role for zinc in prostate cancer. The implications of these findings are far-reaching and urgently need to be delved into further to see if new therapies aimed at raising zinc levels or inhibiting citrate metabolism in prostate cancer cells can be developed. It should be noted that not every study has found a correlation between prostate zinc levels and prostate cancer. For example, no clear correlation between prostatic zinc levels and prostate cancer incidence was shown in a study comparing African Americans and Africans.[79]

Oral zinc supplementation generally has minimal impact on intraprostatic zinc levels, and there was no link between zinc consumption level and prostate cancer in an epidemiological study.[80] At least one study has shown that intraprostatic injection of zinc for BPH can raise these levels.[81] Given the already high levels of zinc in the prostatic tissue of men with BPH, it is difficult to understand how more zinc would be helpful. Nevertheless, this study suggests a novel if invasive delivery form for zinc to help combat prostate cancer.

Zinc is also a cofactor for superoxide dismutase and is required for normal smell and taste. Therefore, it may have adjunctive uses as an antioxidant and to correct taste and small abnormalities during the course of chemotherapy in prostate cancer patients.

SELENIUM AND ANTIOXIDANTS AGAINST PROSTATE CANCER

In one of the most profound and startling clinical trials ever conducted relating to prostate cancer, intake of 200 mcg per day of selenium from a selenium-rich yeast product has been shown to dramatically reduce the risk of developing prostate cancer.[82,83] Prostate cancer was diagnosed in one third as many men who took 200 mcg selenium per day as those who took placebo. In other words, the selenium supplement reduced the risk of prostate cancer 63%. The huge Selenium and Vitamin E Cancer Prevention trial (SELECT) (over 35,000 men participated), designed to specifically test whether 200 mcg selenomethionine, 400 IU alpha-tocopherol, or both had any effect on prostate cancer incidence compared to placebo was stopped in October 2008 after it was determined neither supplement affected the incidence of prostate cancer.[84] There was a worrying trend, which does not prove causation, toward higher prostate cancer in men taking vitamin E alone and higher diabetes in men taking selenium alone. Publication of full details of the trial are awaiting to try to make sense of the results.

Previous epidemiological research has found that those men with the lowest serum selenium levels are twice as likely to develop prostate cancer as those with the highest levels.[85] The mechanism of action is very likely enhancement of function of antineoplastic elements of the immune system.[86] Clinical trials are presently underway to determine if extremely high doses of selenium (up to 3,200 mcg per day) can actually destroy prostate cancer cells in humans after they have established themselves.[87] This high-dose selenium approximates levels of selenium found to kill prostate cancer cells in vitro. Though it is unknown how effective selenium will be as treatment, clearly it ranks as the single most important thing a man can do to prevent it from getting to that point.

The results of several large double-blind trials have found not only that supplementation of synthetic vitamin E and synthetic beta-carotene fails to prevent heart disease and lung cancer in male smokers, but also that beta-carotene may even promote lung cancer.[88] However, there was a 33% reduction in prostate cancer incidence associated with supplementation of 50 IU of vitamin E daily compared to men who received no vitamin E. This finding was confirmed in a reanalysis of the data from this study.[89] Interestingly, vitamin E did not reduce the incidence of

latent prostate cancer, only cases of clinically evident prostate cancer with serious likelihood of local or distant spread. Vitamin E at much higher doses (400–1,600 IU daily) or when combined with mixed natural tocopherols (as vitamin E is found in nature) might have a superior effect. High-dose vitamin E has also been used in an attempt to mitigate hot flashes in men undergoing androgen ablation therapy. This has met with limited success but offers a safe first option to try in reducing this uncomfortable side effect.

The newest yet oldest antioxidant on the block is *Punica granatum* (pomegranate) fruit juice. A double-blind clinical trial found that 8 oz of pomegranate juice could significantly slow PSA rises in men after prostate cancer surgery or radiation compared to baseline.[90] There were minimal side effects other than occasional nausea. Despite concerns based on in vitro and animal studies, pomegranate juice has not shown any herb–drug interactions in human studies.[91]

POTENTIAL ANTIMETASTATIC AGENTS

Modified citrus pectin consists of polysaccharides with many galactosyl terminal groups. These are believed to bind galactoside-binding lectins or galectins. Metastatic cells normally utilize galectins to bind to epithelial cells, particularly in the endothelium. This enhances their ability to spread. One rat study found that oral administration of modified citrus pectin could significantly reduce lung and colon metastases of prostate cancer cells.[92] An uncontrolled pilot trial using 15 g modified citrus pectin daily has been conducted in 18 patients with metastatic and nonmetastatic prostate cancer.[93] PSA doubling times were slowed in most patients. It has been suggested that modified citrus pectin is best taken if first soaked in hot water to maximize their absorption and antimetastatic activity.[94] Products available as powder are easily mixed with water; otherwise capsules should be opened up and their contents placed into water.

Camellia sinensis (green tea) leaves contain high levels of tannins and flavonoids that inhibit the enzyme urokinase.[95] When produced by cancer cells, urokinase allows them to degrade basement membrane compounds, promoting metastatic spread. Green tea tannins are also antioxidant, may interfere with testosterone conversion to dihydrotestosterone by inhibiting 5-alpha-reductase, impairs ornithine decarboxylase (an enzyme highly active in prostate cancer tissue), and have many other actions that might inhibit or prevent prostate cancer.[96] This may partially explain the extremely low incidence of prostate cancer in Asian populations where green tea is drunk in large quantities.[96] Of additional interest is the possibility of using green tea as an adjunct to chemotherapy based on animal trials showing they can have synergistic anticancer activity.[97] In men with metastatic, androgen-independent prostate cancer, 1 g of green tea six times per day was not clinically effective in one clinical trial.[98] The trial seemed almost doomed to fail, having basically started with the sickest possible patients and expecting to see dramatic results. This trial in no one speaks to the potential use of green tea in men with the much more common localized form of prostate cancer. See Table 26-7.

VITAMIN A

Vitamin A and other retinoids are intimately linked with androgens in regulating cell growth and division in the prostate gland. Vitamin A is necessary to prevent abnormal prostate epithelial cell differentiation.[99] Vitamin A deficiency provokes squamous metaplasia of prostate tissues.[100] Vitamin A inhibits 5-alpha-reductase as much as 25% in prostate cancer cells, more

Figure 26–5. *Camellia sinensis* (green tea) flower
Photo ©2008 Eric Yarnell, ND, RH.

in benign prostatic hyperplasia cells.[101] Retinol partially (15–20% in test tubes) competes with testosterone for binding to testosterone-binding protein. Vitamin A and its analogues have successfully been used to treat other androgen-dependent diseases, such as acne vulgaris, raising an intriguing role for retinoids as supplements in prostate cancer patients. No studies are yet available showing vitamin A has any therapeutic benefit in such men. In light of the previous discussion of zinc and prostate cancer, one should also note that vitamin A and zinc work interdependently in many tissues, and a significant correlation between serum zinc and vitamin A levels has been shown in prostate cancer patients compared to men with BPH.[102] Vitamin A and zinc may thus be most active when given simultaneously.

PSYCHONEUROIMMUNOLOGY

The role of the mind in cancer should never be overlooked. Just as support groups have been shown to significantly prolong life in women with advanced breast cancer, so too are they helpful in men with prostate cancer. Learning how to cope with stress, express emotions healthily, and lead a joyful life are important to preventing prostate cancer. Once the disease has established itself, thoroughly discussing it, one's reactions to it, and fears and hopes are almost uniformly beneficial. It is also clear from a number of studies that patients who ask difficult

Table 26–7. Integrated Protocol for Patients with Severe or Metastatic Cancer

Therapy	*Dose and Notes*
Vitamin C	50 g intravenous once or twice weekly; maintain high oral intake (several grams a day)
Melatonin	20 mg at bedtime, particularly as adjunct to LHRH superagonist drugs
Calcitriol	1.5–2.5 mg po; must monitor urinary or serum calcium levels
Antioxidants	1,200 IU vitamin E, 50,000 IU vitamin A, and so on, particularly as adjunct to chemotherapy or radiotherapy
Modified citrus pectin	1 tsp powder three times daily prepared in a glass of warm, filtered water each time to prevent further metastasis
Zinc	50 mg po with 1 mg copper, or consider 100 mg intraprostatic injections weekly
Botanical immunomodulators	See Table 26-6 for suggestions.
Essential fatty acids	6+ g fish oil per day, immunomodulator and antineoplastic
Botanical antineoplastic agents	Numerous herbs have a reputation for fighting cancer, though few have been studied in humans. The Hoxsey formula (administered at a clinic in Mexico of the same name) has a relatively good track record. Consult with a naturopathic physician or other professional herbal prescriber for information.
Vitamin E and progesterone	400–1,200 IU vitamin E or 4–10 drops sublingual natural progesterone (1 mg/drop) three times per day for hot flashes due to hormonal blockade

Note: Therapy must be individualized for every patient; these are only general suggestions. This list is not exhaustive.

questions, seek complete answers, do not settle for the status quo, and fight for the best treatment available have the best outcomes in general. The mere fact that it is so difficult for men in western society to open up suggests just how powerful and important this aspect of prevention and treatment is in terms of not only prostate cancer but also all illness.

TREATMENT OF ADVANCED CANCER

Once prostate cancer has metastasized to distant tissues, the chances of survival decrease dramatically. Therefore it is urgent to use all available therapies, allopathic, naturopathic, and otherwise, in an attempt to help the patient recover or survive as long as possible with as little loss of quality of life as possible. The following suggestions are fully intended as safe and often synergistic adjuncts to allopathic therapies.

High-dose melatonin (i.e., 20 mg or more) taken at bedtime has shown promise in treating many types of metastatic cancer. These extreme doses of melatonin should never be taken in the daytime and are contraindicated except in cancer patients. Though side effects other than sleepiness have not been noted, long-term use of high doses of this potent hormone could be potentially severe. One interesting study looked at patients who had stopped responding to the

luteinizing hormone superagonist drug triptorelin, and gave them high-dose melatonin.[14] Many of the patients started to respond based on declines in PSA levels more than 50%, improvement in thrombocytopenia in three of five patients who had the problem prior to melatonin administration, and survival time greater than one year in 64% of study patients. This exciting study needs to be replicated but offers a safe way to bolster efficacy of hormonal therapy. It is particularly handy for patients with insomnia and cachexia.[103]

There has been a lot of enthusiasm for use of high-dose coenzyme Q10 in cancer patients after a handful of cases were published on the benefit of this therapy in women with advanced breast cancer. These cases involved use of up to 600 mg per day of CoQ10, an extremely expensive therapy. It is simply too early to know if CoQ10 is helpful for men with advanced prostate cancer, and given the extreme expense, should be regarded as highly experimental.

There has been little other research documenting the benefit of natural therapies in men with advanced prostate cancer. It is our belief and experience that therapies used nonspecifically for most cancer patients are just as relevant here. For example, large amounts of immunomodulators and antioxidants are recommended, particularly as adjuncts to chemotherapy and radiation therapy. Intravenous vitamin C, dilute (1:500) hydrochloric acid, artemisinin, and other immunomodulators are also potentially of great benefit. Phytoestrogens offer a new hormonal therapy and the issues discussed above in connection with this apply at this stage as well. The anti-metastatic treatments discussed above should be continued to prevent any further spread. Innumerable other options are available, and should be individualized to meet the patient's specific needs. A variety of resources are available for other natural approaches to advanced cancer.[104] Cancer patients need to be wary of believing in every cancer treatment they hear of, as many are supported only by marketing hype and have no track record of benefit. It is imperative for the patient to establish a relationship with an impartial doctor of natural medicine so an objective opinion is always available. Otherwise a lot of money and time stand to be wasted. It is hoped that if all these things are used in conjunction, the patient's quality of life will not deteriorate too much and life span can be lengthened.

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27

BOTANICAL MEDICINE FOR THYROID REGULATION

Thyroid dysfunctions of various types plague the health of Western society. Most authoritative sources agree that the annual incidence of hyperthyroidism is 1 in 1,000 women (and about one tenth that many men) in the Western world, whereas the incidence of hypothyroidism is at least 10 times as great. The problem is only accelerating, in part due to environmental pollution that damages the thyroid, some of it intentional (particularly the infamous 1949 Green Run experiment that deliberately exposed a wide swath of the Pacific Northwest United States to radiation released from the Hanford Nuclear Reservation).[1] Though little research has been done, there are many herbal medicines available that offer options to patients with thyroid disorders.

BUGLEWEED, A THYROSUPPRESSIVE

In most areas of medicines, herbs are primarily used to support normal function. This is not the case with the thyroid, where it turns out that the herbs that suppress thyroid function are the most effective. In most other areas of medicine, herbal tonics that support normal function stand out.

Lycopus virginicus (bugleweed) is a native to North America, found east of the Mississippi. At least three other mint species are used similarly to bugleweed in different parts of the world—*Lycopus europaeus* (gypsywort) from Europe, *L. lucidus* (water horehound) from Asia, and *L. americanus* (water horehound) from North America. At least one in vitro study has found extracts of bugleweed and gypsywort to be equally effective.[2] These plants are members of the Lamiaceae (mint) family. It appears, at least in preliminary studies, that many other members of this family also have thyrosuppressive activities, suggesting that there is a common set of constituents present in the Lamiaceae with this action. These constituents, based on work with bugleweed and other herbs, are most likely various hydroxycinnamic acid–derived simple plant acids, such as lithospermic, rosmarinic, caffeic, and chlorogenic acids.

Historically, the effects of bugleweed have mostly applied to the heart and lungs. For instance, the noted Eclectic physician Harvey Wickes Felter, MD, wrote in 1922 that bugleweed was primarily used for "vascular excitement, with rapid, tumultuous action of the heart, but lacking power."[3] He also discussed this herb as a remedy for bleeding in various organs, cough, and diabetes, all when a rapid heartbeat was present. Bugleweed was, however, also used by the Eclectics for insomnia in acute and chronic diseases, and to treat exophthalmic goiter.[4] One of the main symptom pictures for its use was wakefulness and morbid vigilance with an inordinately active circulation and rapid pulse. This picture coincides with the fact that patients with hyperthyroidism often experience insomnia, palpitations, and tachycardia.

In Germany, bugleweed or gypsywort have been studied for their effects on the thyroid since at least the 1950s.[5] Bugleweed and extracts of it or its cousins have been shown to have many beneficial effects that might explain its efficacy at reducing the symptoms of hyperthyroidism. These include inhibiting binding of the stimulating antibodies of Graves disease to the thyroid cells, blocking thyroid-stimulating hormone (TSH) production, decreasing peripheral

T4 deiodination, and possibly inhibiting iodine metabolism.[6,7,8] In a prospective, two-armed open study, bugleweed significantly increased urinary excretion of T4 and diminished symptoms such as increased heart rate in the morning.[9] Another trial of 34 patients did not document the efficacy of bugleweed for hyperthyroidism but reported that bugleweed improved cardiac symptoms such as extrasystolia, palpitations, or arrhythmias.[10] Twenty-one of the patients suffered from latent hyperthyroidism. Interestingly, while bugleweed improved cardiac symptoms in these patients it did not change any thyroid levels significantly.[11] Another study of hyperthyroid rats looked at bugleweed using atenolol as a reference standard. Even low doses of bugleweed effectively reduced body temperature and at higher doses reduced the increased heart rate and blood pressure, and alleviated cardiac hypertrophy as well as atenolol. However, bugleweed again did not affect any significant changes in thyroid hormone concentrations or TSH levels.[12]

Bugleweed and its cousins have other documented effects. Extracts have been shown to decrease prolactin levels (and to inhibit secretion of luteinizing (LH) and follicle-stimulating hormones (FSH).[13] One case study has been published confirming that 5–13 g of a freeze-dried extract taken daily for one month decreased LH secretion in one woman.[14] Gypsywort has been demonstrated to enhance the efficacy of various antibiotic drugs against drug-resistance microbes in vitro.[15] More recently, water horehound has been studied more extensively in Asia and has shown some very interesting properties, including having antioxidant activity, decreasing blood viscosity, and having antiallergic properties.[16,17,18] Given all this potential, clearly bugleweed and related herbs deserve more research, and should be investigated in clinical trials.

Aqueous extracts have been the most traditional form of delivering bugleweed and its cousins although the Eclectics often used alcoholic extracts. At least one study found that tinctures prepared using 70% ethanol had much higher levels of the critical hydroxycinnamic acid derivatives than did aqueous extracts.[19] A typical dose of tincture is 2–4 ml three times per day for an average-sized adult. An increased amount may be required initially for more severe hyperthyroid symptoms. To prepare a tea, infuse 2–3 tsp (5–10 g) of air-dried herb in a cup (250 ml) of hot water, covered, for 15–20 minutes. Drink one such cup three times per day. This dose may be able to be decreased over time. Few if any adverse effects have been observed with bugleweed in practice, though it should not theoretically be given to people with hypothyroidism or during pregnancy.

OTHER MINTY POTENTIAL THYROSUPPRESSIVES

Melissa officinalis (lemon balm) is a gentle herb found in the Lamiaceae family. It has long been a favorite for treating infant colic and viral infections even in newborns, attesting to its gentleness. Old European herbals report its memory-improving properties, the German Commission E has approved its use for nervous sleeping disorders, and the European Scientific Cooperative for Phytotherapy Symposium (ESCOP) lists its use for restlessness, irritability, digestive disorders, and cold sores.[20] It has no history of use for hyperthyroid conditions but clinicians are increasingly including it as a component of herbal formulas for hyperthyroidism based on constituent research. It is widely used as a nervine and an antiviral, and there are no reports of anyone becoming hypothyroid while taking lemon balm for other conditions, nor are there any suggestions that persons who are hypothyroid should not use lemon balm. This clinical experience suggests (but does not prove) that it may only inhibit an overactive thyroid

and not one that is functioning normally. Of course, it is also possible that there are other constituents in lemon balm that counteract its thyrosuppressive action.

As mentioned, the current use of lemon balm in hyperthyroidism is based in large measure on pharmacological studies. In vitro, lemon balm has been shown to inhibit the binding of TSH to thyroid follicles, to block peripheral deiodination of T4, and to block stimulating autoantibodies of Graves disease.[21,22] In addition, lemon balm was historically considered useful for calming the heart. However, lemon balm was not considered a primary herb for the heart in the manner of bugleweed.

In contrast to bugleweed, lemon balm contains higher levels of low-molecular-weight terpenoids such as citral and citronellal and this at least in part contributes to effects not generally seen in bugleweed. Lemon balm is antiviral, most notably against herpes simplex, and also as a smooth muscle spasmolytic and nervine.[23,24,25] Add to this a recent double-blind clinical trial documenting benefits in patients with Alzheimer's disease, and lemon balm starts to look pretty distinctive.[26]

We have not used lemon balm on its own as a treatment for hyperthyroidism, but in our clinical practice, lemon balm has been added to enhance the action of bugleweed. Lemon balm's effect on the thyroid is both deserving of research and long overdue. A usual dose of lemon balm tincture (60%+ ethanol) is 3–5 ml three times per day for an average-sized adult. There are no known contraindications. Lemon balm resembles several other Lamiaceae family plants in its non-thyroid actions, particularly *Rosmarinus officinalis* (rosemary) and *Salvia officinalis* (sage). Both of these herbs are antiviral, antioxidant, nervine, and spasmolytic, and contain both hydroxycinnamic acid derivatives and low-molecular-weight terpenoids. Although neither rosemary nor sage is considered thyrosuppressive, it is possible they may have such actions and should be investigated for such. The same holds true of other members of this family with similar constituent profiles.

Figure 27–1. *Rosmarinus officinalis* (rosemary)

Figure 27–2. *Salvia officinalis* (sage)

GROMWELL: A DIFFERENT STORY

Two herbs with actions very similar to bugleweed, and somewhat stronger, are *Lithospermum ruderale* (gromwell) from North America and *L. officinale* (European gromwell) from Europe. These herbs are in the Boraginaceae family. They also contain hydroxycinnamic acid derivatives similar to those seen in Lamiaceae thyrosuppressives, such as lithospermic acid. However, these herbs also contain naphthoquinone compounds and unsaturated pyrrolizidine alkaloids that distinguish them from bugleweed.

Nonetheless, gromwell has basically been shown to act similarly to bugleweed. For instance, it blocks binding of TSH to thyroid follicles, inhibits iodide transport into thyroid follicles, decreases peripheral deiodinization of T4, and blocks thyroid hormone secretion.[27,28] It is also clear that gromwell blocks the secretion of LH and FSH, with minimal to no effects on the direct binding of estrogen, progesterone, or testosterone to their receptors.[29,30,31] In general, gromwell seems to be more potent at all of these actions than bugleweed. As a result, it can also be more dangerous.

The unsaturated pyrrolizidine alkaloids in gromwell are also of concern. Other plants with these compounds have caused severe liver and kidney damage when ingested. As yet, there are no reports of gromwell's alkaloids causing any harm to humans. This is rather surprising, given the apparently toxicity of these alkaloids and the fact that this herb has been used for millennia and usually for long periods of time. It is possible that the relatively low levels of alkaloids in these plants, and/or the fact that they were traditionally prepared as teas, which would not be as effective at extracting alkaloids, could explain this. Additionally, liver disease actually caused by gromwell may not have been attributed to a distant herbal ingestion. Most experts caution against long-term use of gromwell to avoid any risk of pyrrolizidine alkaloid toxicity. See Sidebar 27-1.

To minimize alkaloid content in the herb (and they are not known to contribute any benefits in terms of the thyroid, so excluding them should only make the herb safer), a low-ethanol tincture is utilized with an acidic menstruum. Typically no more than 40% ethanol is used. The usual dose is 1–2 ml three times per day for an average-sized adult. This herb should definitely not be used in lactation or pregnancy due to increased sensitivity of fetuses to unsaturated pyrrolizidine alkaloids.

On a final note, the Chinese herb *Lithospermum erythrorhizon* (zicao) root has been shown to contain various naphthoquinones, notably a compound dubbed shikonin. Numerous studies have documented a range of effects of this herb and shikonin, including inhibition of HIV, suppression of angiogenesis, inhibition of *Helicobacter pylori* and decreasing resistance of this organism to antibiotics, inducing apoptosis in cancer cells, and many other effects.[32,33,34,35] In one highly preliminary case series from China, shikonin significantly improved clinical status of inoperable lung cancer patients and appeared to lengthen life span in some patients.[36]

27–1. *Dr. Heron's ThyroNix Formula*

The late Silena Heron, ND, (Dr. Yarnell's mentor), and Dr. Yarnell utilized a formula known as Dr. Heron's ThyroNix successfully in several patients with hyperthryoidism, primarily Graves disease, often for months or years continuously. Additionally, other clinicians who used the formula reported that it was efficacious and no adverse effects were encountered during long-term use. This formula is described in the table below, and was often adjusted to fit the exact situation with any particular patient. None of the patients using this formula experienced liver toxicity or gonadotropin suppression.

Latin Name	*Extract Used*	*Percent in Formula*
Lithospermum ruderale	Tincture of fresh root	10–15
Fucus vesiculosus	Tincture of dried thallus	10–20
Leonurus cardiaca	Tincture of fresh herb	10–20
Lycopus virginicus	Tincture of fresh herb	10–20
Melissa officinalis	Tincture of fresh herb	10–20
Rorippa nast.-aquat.	Glycerite of fresh herb	5–10
Verbascum thapsus	Glycerite of fresh leaf	5–10
Armoracia pusticana	Tincture of fresh root	5–10

Dose: 1 tsp (5 ml) three times per day for average-sized adult.

Whether gromwell has any of these effects is unknown. Equally unknown is whether zicao has any effect on the thyroid or gonadotropins.

THE DUAL NATURE OF BLADDERWRACK

Fucus vesiculosus (bladderwrack) and closely related brown algae in the family Fucaceae, particularly *F. serratus* (blackwrack), are not plants at all, but photosynthetic protists. Unlike plants they do not have specialized protective structures around their gametes and do not undergo embryonic development. Unlike fungi they do not have chitin in cell walls. Thus, seaweed such as bladderwrack are in their own separate kingdom, Prostista. The part used is known as the thallus, the undifferentiated frond often seen lying on beaches.

Bladderwrack has historically been used to regulate and protect the thyroid, regardless of whether it is hyperactive, normal, or underactive.[37] Despite this, there is very little information available about the effects of this seaweed on the thyroid. Bladderwrack and all seaweeds contain substantial but variable quantities of iodine. One study of commercially available seaweeds in the United States found a range of 16 to over 8,000 mcg/g iodine.[38] Dried bladderwrack gen-

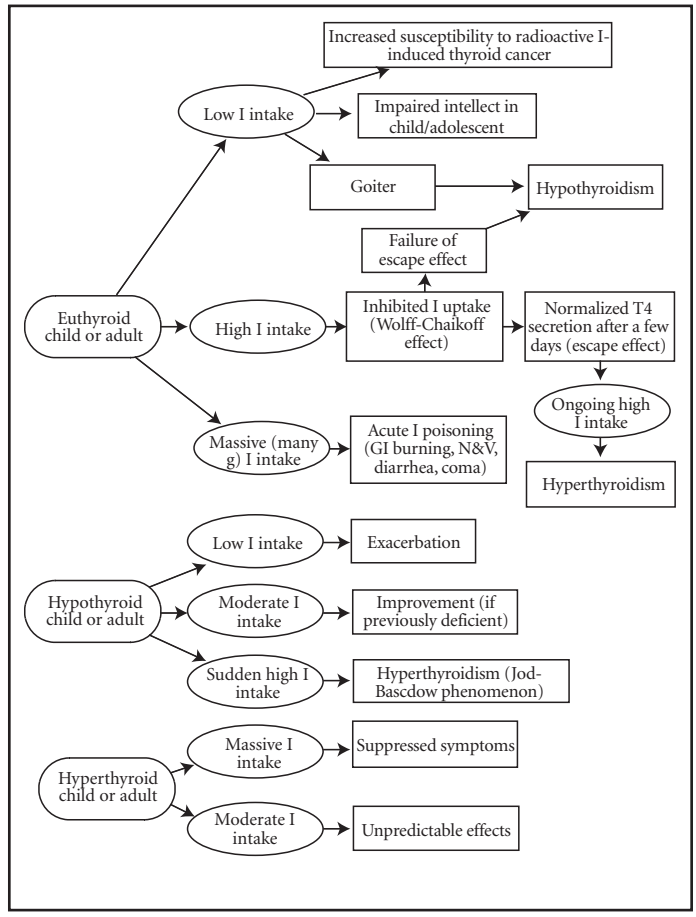

Figure 27–3. Iodine and the Thyroid

erally contains approximately 0.05% iodine, or 50 mcg/g. The effects of iodine on the thyroid are very complex, and may help explain both the ability of bladderwrack to help some people with hypothyroidism and some with hyperthyroidism. See Figure 27-3.

The German Commission E states that daily ingestion of more than 150 mcg iodine from bladderwrack could induce or exacerbate hyperthyroidism. Total daily iodine intake should generally not exceed 1,000 mcg, though there is wide individual variability in sensitivity.[39] Healthy subjects given two or four kelp (probably *Laminaria*) capsules per day had significant elevations in TSH levels and decreased T3 levels compared to baseline whereas patients taking alfalfa capsules had no such changes.[40] Though Hashimoto's thyroiditis is common in Japan where dietary seaweed and thus iodine intake is very high, studies disagree as to whether differences in iodine levels between affected and unaffected patients explain the incidence of this condition.[41,42]

The bottom line is that how bladderwrack acts in thyroid patients is unknown, but that low levels of supplementation are probably safe in most patients. Patients who are clearly iodine deficient can obtain reasonable amounts of iodine by eating 1–2 g dried bladderwrack per day. Anyone who is already consuming more than 1,000 mcg iodine per day probably will not benefit and may be harmed from bladderwrack supplementation.

OTHER HERBS FOR HYPOTHYROIDISM

Hypothyroidism, both diagnosed and self-diagnosed, is rampant in our culture where obesity is common. As might be expected, the Internet is filled with remedies for this ailment. Unfortunately, there is little evidence documenting the efficacy of herbs in hypothyroid patients. The sole exceptions are a number of open clinical trials conducted on a variety of herbal formulas in China for what they call kidney yang deficiency that have shown benefit.[43] Otherwise, clinical information on herbal treatments for hypothyroidism is entirely lacking.

One of the most promising herbs is the adaptogen *Withania somnifera* (ashwagandha). Ashwagandha administered daily to female mice increased serum thyroxine (T4) concentrations.[44] Fish exposed to organochlorine pesticides had elevated TSH levels that were normalized by treatment with the aqueous root extract of ashwagandha and *Convolvulus pleuricaulis*.[45] Finally, there is a Dutch case report of a healthy woman who developed thyrotoxicosis while taking ashwagandha capsules for fatigue. Her symptoms resolved after discontinuing the capsules.[46] As the article was in Dutch we were unable to review it to determine whether the capsules contained other herbs and whether its conclusion that ashwagandha was responsible for elevating her thyroid levels was sound. It does nonetheless support the animal studies suggesting that ashwagandha can stimulate thyroid function.

Another herb frequently recommended for hypothyroidism is *Centella asiatica* (gotu kola) leaf. The noted Southwestern herbalist Michael Moore has written that this herb stimulates T4 synthesis in patients with subclinical hypothyroidism.[47] We have not located any data pertaining to gotu kola's effect on the thyroid and have not observed any remarkable clinical effects in hypothyroid patients taking gotu kola in our practice.

Other herbs that have a potential place in the treatment of hypothyroidism are *Bauhinia purpurea* (bauhinia) bark, *Plectranthus barbatus* (forskholii, coleus) leaf, and *Commiphora mukul* (guggul) gum resin. Bauhinia administered orally to mice increased both T3 and T4 levels in one study, and combined with ashwagandha and guggul again increased both levels.[48] In another study, bauhinia increased T4 concentration by 41% while decreasing hepatic lipid peroxidation, suggesting a potential as a thyroid-stimulating herb.[49] Guggul, 200 mg/kg daily, has

been shown to counteract drug-induced hypothyroidism in female mice in one study.[50] Another found that it elevated triiodothyronine production in mice.[51] However, one case series in humans found that 750 mg guggulsterone daily from guggul had no effect on thyroid function in obese patients.[52]

Plectranthus barbatus (forskohlii, coleus) leaf is sometimes recommended based on its mechanism of action (stimulates adenylate cyclase). There is a theoretical argument that it could mimic the effect of TSH, which also activates adenylate cyclase when it binds to the TSH receptor. In vitro, the compound forskolin from this herb has in fact been shown to increase T4 synthesis by thyroid follicles.[53] No clinical data could be located. Finally, in Turkish folk medicine, the leaves and fruits of *Juglans regia* L. (walnut) are used for thyroid dysfunction. In mice, walnut extract enhanced thyroid hormone levels.[54]

Further research on the ability of these herbs to stimulate thyroid function is needed as hypothyroidism is a common condition that is inadequately treated.

CONCLUSION

Given the promising preclinical research and supportive empirical results from clinical practice, bugleweed, gromwell, and other Lamiaceae family plants, like lemon balm, should be studied in clinical trials for patients with hyperthyroidism as relatively safe and inexpensive alternatives to thyrosuppressive drugs. Much less information is available supporting the use of herbs for hypothyroid patients, though there is still an urgent need for research in this area given the large degree to which people are likely taking various herbs in an attempt to remediate this common condition.

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28

TAKING THE WHOOP OUT OF WHOOPING COUGH

Whooping cough (pertussis) is on the rise in the United States, with the number of reported cases topping 25,000 in 2004 and the incidence continuing to rise into 2007.[1] Presently, however, there are no effective treatments for the symptoms of pertussis. Antibiotics are prescribed to limit the spread of the disease, but the evidence supporting this approach is very weak. This chapter covers botanical treatments used by physicians to treat pertussis before the advent of vaccines and antibiotics and should work today as well. Many of these treatments have been approved by the German Commission E and should be studied in clinical trials to determine if they not only provide effective symptom relief but also possibly limit the spread of the virus as well. Herbs of interest include *Thymus vulgaris* (thyme), *Drosera rotundifolia* (sundew), *Hedera helix* (English ivy), *Matricaria recutita* (chamomile), *Lobelia inflata* (lobelia), *Trifolium praetense* (red clover) blossoms, *Passiflora incarnata* (passionflower), and *Eucalyptus* spp. (eucalyptus).

THE BACTERIUM BEHIND THE COUGH

Pertussis is an old disease; its first recorded epidemic occurred in 1578.[2] The primary agent of pertussis is *Bordetella pertussis,* although a related organism, *B. parapertussis,* is capable of causing a form of the disease that usually runs a milder course.[3] A pertussis vaccine was approved in 1944 and its use has substantially changed the prevalence and nature of the disease in the western world. From 1922 to 1931, there were 1.7 million cases of pertussis in the United States, with 73,000 related deaths.[2] In comparison, there were some 34,325 reported cases and 56 deaths between 1983 and 1992.[2] However, in recent years the number of cases has started to rise. In 2004, the number of whooping cough cases spiked past 25,000, the highest level since 1959.[4] Although infants have the highest incidence of pertussis of any age group, adolescents and adults account for the majority of reported cases.

B. pertussis is transmitted by close contact with aerosolized droplets; its incubation period is typically 7–10 days, although it can be as long as 6 weeks. The incubation period is followed by the catarral phase, which usually lasts one to two weeks. This phase is clinically indistinguishable from a mild respiratory infection, and pertussis is very contagious in this stage. With time, a cough develops, increasing in frequency and severity. This paroxysmal phase is characterized by spells of coughing (often with the characteristic whoop), vomiting, cyanosis, and apnea. The phase typically lasts two to six weeks, at which point the patient enters a convalescent phase that can last up to several months.[5] Complications that include pneumonia, seizures, encephalopathy, syncope, rib fractures, and hernia typically occur only in infants and the elderly. Almost 90% of the deaths associated with whooping cough occur in unvaccinated infants who are less than one year old. These children have a case-fatality rate of 0.6%.[5]

Whooping cough is diagnosed based on clinical symptoms combined with a mild increase in leucocyte count and marked lymphocytosis, although this may not be present in adults with previous pertussis exposure.[2] Laboratory methods for diagnosis include identification of

B. pertussis through culture of nasopharyngeal secretions and serologic testing for evidence of seroconversion of specific antibodies. The positive predictive value of nasopharyngeal secretion cultures is very high but is most reliable in the early stage of infection, in severe cases, in unvaccinated patients, and in infants. Positive results may be diminished by antibiotic treatment.[5]

Vaccination status, age, and sex strongly influence the clinical presentation of the disease. In one study, vaccinated individuals ages 5–30 did not display the three typical stages of pertussis. Instead, the clinical course was characterized by a cough that persisted for a median of three weeks, and only 6% of these patients developed the classic whoop.[5] Recent studies indicate that a significant percentage of teenagers and adults with a persistent cough have a pertussis infection despite the fact that they do not display the classic paroxysmal cough. In a French study, 30% of adults with a persistent cough (n = 217) were infected with *B. pertussis*. Recent studies also found that 17–25% of unvaccinated children have cases that are of relatively short duration (e.g., less than three weeks).[2] Thus, cases of pertussis may easily go undiagnosed, which allows the continued spread of the disease within the community and to more vulnerable children and infants. (See discussion of fatality rates among infants above.)

THE PROBLEM WITH ANTIBIOTICS

The recommended allopathic treatment for pertussis is the administration of a macrolide antibiotic. This treatment does not significantly affect the clinical course of the illness but is instead intended to help prevent its further spread. While macrolide antibiotics rather quickly clear the bacteria from the airway, there is little evidence supporting the concept that this clearance actually slows the spread of pertussis.[6]

Antibiotics are also usually administered to all persons in close physical contact with the patient. This use is controversial, with at least one researcher pointing out that erythromycin may have more effect on eradicating the bacteria from the nasopharynx than in preventing infection.[7] A recent Cochrane review found insufficient evidence of benefit from antibiotic use in close contacts but, due to the high risk of infant morbidity and mortality, recommended prophylaxis for families with an infant under six months of age.[6] Another systematic review concluded that "erythromycin appears to be modestly efficacious in preventing secondary cases of pertussis although the effect appears to increase with decreasing vigor of the study design." It ultimately recommended that prophylactic antibiotic prescriptions be restricted to vulnerable close household contacts (e.g., nonimmunized children or partially immunized infants as well as adults in close household contact with such children).[7] All reviewers commented that the research on the use of antibiotics in pertussis is minimal and antiquated. Macrolide antibiotics typically cause substantial side effects,[8] and although limiting the spread of pertussis is important, avoiding the use of antibiotics—especially if they are not actually helpful—is also important.

The patient's symptoms are often treated with antihistamines, usually diphenhydramine, corticosteroids, and salbutamol. None of these treatments show any benefit on coughs compared to placebo.[9] These drugs are associated with a variety of side effects, and a recent systematic review concluded that their use in the treatment of whooping cough was not justified.[8]

THE BENEFITS OF BOTANICALS

Physicians treated pertussis with botanicals prior to the advent of vaccinations and antibiotics. Many of their preferred treatments are gentle and were considered highly useful for symptom

relief. As mentioned, there is very little clinical research on treatments for whooping cough, and, as might be expected, published research on the botanical remedies for pertussis are lacking. Nonetheless, these treatments offer both a good way to treat the disturbing cough of pertussis and a rich source for future research on their effectiveness for pertussis symptoms. In addition, most of the remedies are antimicrobial and may diminish the presence of *B. pertussis* in the nasopharynx of patients, perhaps limiting the spread of the disease.

Thymus spp. (Thyme)

Dr. Rudolf Fritz Weiss noted that pertussis presents a challenge but that some of the "old-established remedies for it" could be very useful. Foremost among these was *Thymus vulgaris* (thyme). Dr. Weiss strongly recommended the wild growing thyme harvested in a Mediterranean climate. He reported that the essential oils contained in thyme were eliminated through the alveoli of the lungs, concentrating it at the site where it was most needed. He characterized the plant as an expectorant with antispasmodic properties as well as a plant that, because of its gentle action, could be unhesitatingly used in high doses. Dr. Weiss concluded that thyme is to the trachea and bronchi what peppermint is to the stomach and intestines.[10] The German Commission E, which reviewed proprietary evidence of efficacy, has approved thyme as a remedy for whooping cough based on its bronchial spasmolytic, expectorant, and antibacterial activities.[11,12] Thyme was used as a traditional folk remedy among many populations, including the Basque and the Palestinians, specifically as a treatment for whooping cough.[13,14]

Thyme contains thymol and carvacrol, both of which are deemed to have spasmolytic and antitussive properties, though its flavonoids also relax tracheal smooth muscles in animal models and in vitro.[15] Thyme, in combination with other herbs, has shown positive effects on acute bronchitis in a multicenter post-marketing survey (n=7,783).[15] Two double-blind, randomized trials have shown thyme, paired with either *Primula veris* (primrose), an astringent herb, or *Hedera helix* (ivy), an immunomodulating expectorant, was more effective than placebo for patients with acute bronchitis.[16]

Thyme has shown strong antimicrobial actions in vitro, and was valued for those (and other) properties by the ancient Sumerians, Egyptians, and Romans.[13]

Drosera rotundifolia (Sundew)

In most cases, Dr. Weiss found that whooping cough would respond to thyme used alone as a simple, and that children could benefit from taking thyme syrup by the teaspoonful.[10] However, thyme combined with a small amount of *Drosera rotundifolia* (sundew)—a small, insect-eating plant—was, on occasion, shown to be a more effective remedy. The German Commission E has approved the use of sundew as a bronchial antispasmodic and antitussive for coughing fits and dry cough.[17] The Eclectic physicians in the United States also recommended sundew for whooping cough patients, and it is a commonly used remedy in many folk traditions.[19] For example, the Irish boiled its leaves in milk and gave it to their children when they had whooping cough.[20] Research indicates that it has anti-inflammatory, antimicrobial, and antispasmodic actions. [21,22]

However, while sundew may be a highly useful plant, it is also a slow-growing and endangered plant, and its use for symptom relief is unacceptable today unless it comes from sustainably cultivated stocks. This is especially true given the fact that the other recommended pertussis remedies are abundant. See Sidebar 28-1. It is also likely that other species of *Drosera* are effective, though none are particularly abundant and should be utilized only if cultivated.

Figure 28–1. *Drosera* spp. (sundew)

28–1. *Other Interesting Ethnobotanical Pertussis Remedies*

- The Basque use a tincture of violet leaves and flowers (1:5, 70% alcohol) in whooping cough, administered in doses of 1–2 tsps in a little water two times per day.[11]
- In Argentina, rutabaga is valued not only as a food but also as a useful medicinal. Rutabaga syrup is recommended in pertussis, chronic bronchitis, asthma, and any paroxysmal cough. The rutabagas are cooked and then pressed; the liquid is mixed 1:2 with honey, and cooked until a proper syrupy consistency is obtained.

Hedera helix (English Ivy)

Another remedy recommended by Dr. Weiss is not only abundant but also often considered a noxious weed. *Hedera helix* (English ivy) is a vining plant with a very long history of use. Dr. Weiss characterized the plant as having a predominantly spasmolytic action but also a secretolytic and sedative effect that acts to reduce the number of attacks and the paroxysmal nature of the cough.[10] English ivy contains some 6% saponins, and it is postulated that its saponins are responsible for the plant's expectorant actions. Saponins trigger responses in the gastric mucosa, which in turn activate mucous glands in the bronchi through parasympathetic signaling to aid in the removal of mucus.[10] It also contains falcarinol, which has been shown to have antibacterial, analgesic, and sedative effects. The German Commission E has approved the use of English ivy as a treatment for respiratory catarrhs and chronic inflammatory bronchial conditions.[10] There are some published studies on the use of English ivy leaves to treat coughs that suggest it has a very positive effect on coughs. These were open, uncontrolled studies but did include a significant number of participants (e.g., n=5,850; n=52,479).[22–24]

Figure 28–2. *Hedera helix* (English ivy)
Drawing © 2006 by Kathy Abascal, BS, JD.

RESTORATIVE RUBS

Dr. Weiss recommended adding inhalation therapy and topical applications of chest rubs to the internal use of the botanical medicines discussed above. See Sidebar 28-2. For children, he favored a simple but reportedly highly effective inhalation treatment consisting of placing equal parts *Matricaria recutita* (chamomile) flowers and thyme in a bowl. Boiling water is poured over the herbs, and the patient inhales the rising vapors through a stiff paper funnel or by draping a towel over his or her head for 5–10 minutes at a time.[10]

To support his recommendation for chest rubs, Dr. Weiss referred to animal studies showing that topical applications of essential oils can penetrate through the skin, with a significant amount reaching the lungs. He applied a volatile rub containing eucalyptus, rosemary, thyme, and camphor oil to a child's chest and back, covered the rub with a thick layer of cotton wool, and held it in place with a flannel binder. This was to be done once a day, although it might be repeated a second time in difficult cases.[10] Many chest rubs on the market today, ranging from the over-the-counter product Vick's Vaporub® to a variety of similar products made without a petroleum base, contain these ingredients.

28–2. *Dr. Weiss' Chest Rub*

2 parts thyme oil	2 parts eucalyptus oil
2 parts rosemary oil	44 parts camphorated oil or ointment

Dr. Weiss recommends applying the chest rub both on the chest and the back of the neck before going to bed at night and another time during the day, if needed.

THE ECLECTICS DO BATTLE WITH PERTUSSIS

The Eclectic physicians tended to use a different assortment of plants than the Germans for pertussis. Their plant remedies often are not part of the European tradition, and for the most part have not been presented for approval by the German Commission E. This does not mean that they lack efficacy. On the contrary, these remedies were recommended by highly skilled physicians because they were quite effective and locally available. The Eclectic physicians favored *Lobelia inflata* (lobelia), *Trifolium praetense* (red clover) blossoms, *Passiflora incarnata* (passionflower), and sundew in pertussis. Although *B. pertussis* had yet to be identified, they knew that this highly infectious disease was transmitted through aerosol droplets. They also realized that the disease was most amenable to treatment in the catarrhal stage and that it was a grave disease for children under the age of two.[18]

Eucalyptus Inhalation Therapy

The Eclectics strongly advocated the use of antiseptic vapors both to limit the spread of pertussis and to treat the patient. Maintaining the warmth and moisture content of the air in the sickroom, accomplished by dropping a hot brick or red-hot iron into a pot of boiling water along with a few drops of eucalyptus, helped reduce paroxysms and helped the patient breathe more easily. It was also considered antiseptic and, indeed, eucalyptus oil is a strong antimicrobial agent. A recent case report detailed how inhalation therapy using eucalyptus oil in primary tuberculosis rendered a patient tuberculosis-negative and without clinical symptoms.[25] In vitro studies show that it has a spasmolytic effect on smooth muscles.[26] Eucalyptus is considered an effective pertussis remedy in many folk traditions, including Argentinian botanical medicine.[27]

Red Clover

Red clover has been described as "one of the few remedies which favorably influences pertussis."[18] Apparently, red clover could suspend a spasmodic cough in two or three days if a strong infusion was administered in half-ounce doses every hour or two throughout the day. Red clover was also dispensed as a simple syrup. The Eclectics viewed red clover as antispasmodic and alterative, meaning that it was essentially restorative and used to help the body function more appropriately and regain a more healthful balance. Most of the current research on red clover has focused on its ability to supply phytoestrogens, primarily in menopause. There is no research on red clover's action as an antispasmodic or antitussive. However, red clover makes a pleasant and safe tea, and is worthy of further study in pertussis based on the Eclectics' strong recommendations for its use.

Figure 28–3. *Trifolium pratense* (red clover)

Lobelia

Lobelia in small doses stimulates the respiratory centers and the vagal terminals and ganglia in the lungs. Large doses depress these areas, can cause asphyxiation, and are powerfully emetic. The Eclectics rarely used lobelia in doses large enough to cause emesis, and never used it as an emetic in children. Instead, they considered lobelia in small doses "a certain remedy" for the relief of spasmodic croup in children. In pertussis, they found it especially helpful where "abundant secretions of a stringy character almost strangle the sufferer."[28] Its sedative effects were helpful in certain types of convulsions in children and were a side benefit in whooping cough. The Eclectics usually mixed 5–30 drops of lobelia tincture in 4 oz of water and dispensed 1 tsp (5 ml) every one to three hours.

Today, lobelia continues to be widely used by clinicians because of its antispasmodic and sedative effects in respiratory ailments.

Passionflower

The Eclectics used passionflower in many different spasmodic ailments and to produce rest, especially in young children and the elderly. They used it as a calmative in influenza and to limit convulsions. As for its use in pertussis, they simply state, "Whooping cough is often mitigated by passiflora."[18] The German Commission E has approved passionflower's use for nervous restlessness but has not investigated its potential in pertussis. It is, however, used as a remedy for pertussis in South America.[26] Passionflower tincture was shown to have

antiasthmatic effects in an animal asthma model, and in mice it suppressed SO_2–induced cough in mice.[29,30]

Passionflower is generally a very safe medicine, although the Eclectics commented that, on occasion, it could cause vomiting and should be discontinued in such cases.[29]

CONCLUSION

Pertussis has coexisted with human beings for centuries, if not millennia. Despite historic decreases in its prevalence, it remains endemic in the United States, with increasing numbers of cases being diagnosed each year. There are no allopathic treatments for its symptoms, and the drugs used to limit its spread are of questionable effectiveness and are associated with significant side effects. There are many botanical remedies that physicians historically have used to relieve pertussis symptoms; these can be administered as teas or syrups to children along with soothing, antimicrobial inhalation therapies. See Table 28-1. These remedies have not been investigated and many are no longer widely used in clinical practice. However, given the high safety profile of many of these botanicals, clinicians would be well advised to explore their use in pertussis.

Table 28–1. Botanical Remedies for Pertussis Doses

Plant	*Form*	*Recommended Dose*
Thymus spp. herb	Infusion	1–2 g/8 oz water, several times daily as needed
	Fluid extract	1–2 ml, 3–5 times per day
Drosera spp. herb and root	Crude herb	3 g per day in divided doses
	Syrup (50 g 1:5, 60% tincture in 500 ml simple syrup)	Children: 1 tsp, 3–6 times per day Adults: 1 tbsp, 3–5 times per day
Hedera helix leaves	Infusion	300–1,000 mg/150 ml hot water steeped 15 minutes, drink 1 cup every 2–3 hours
	Tincture 1:5, 30% alcohol	1–3 ml, 3–5 times per day
Lobelia inflata seeds or herb	Tincture 1:5, 45% alcohol	5–30 drops in 4 oz of water, 1 tsp every 1–3 hours
Trifolium pratense blossoms	Infusion	3–5 g/250 ml hot water steeped 15 minutes, drink 1 cup every 2–3 hours
Passiflora incarnata herb	Infusion	2 g/150 ml hot water steeped 15 minutes, drink 1 cup every 2–3 hours

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29

INTERACTION OF HERBAL CONSTITUENTS WITH CYTOCHROME P450 ENZYMES

The cytochrome P450 (CYP450) enzymes play a critical role in the metabolism of endogenous and exogenous compounds both in the intestinal lining and in the liver. Drugs are commonly metabolized by these major enzyme systems as are many herbal constituents. This is a cause for concern as constituents using the same pathway may alter the absorption, metabolism, toxicity, and excretion of each other. Typically, research focuses on drug–herb interactions that may be detrimental to the proper delivery of the drug. However, knowledge of herb–CYP450 interactions are also important in terms of understanding the pharmacokinetics of herbs and may shed light on their mechanisms of action and how to enhance their effectiveness, as well as clarify any potential toxicity. In this chapter, we review what is known about clinically relevant herbal interactions with CYP450 and discuss where these interactions may be problematic or useful to the clinician.

CYP450 are iron-containing molecules that act by oxidizing various chemicals (particularly lipophilic ones). The oxidation causes the molecule to become more polar, hence more water soluble. This process is generally energy dependent, in the form of reducing equivalents or NADPH. When coupled with various phase 2 enzyme reactions (which act to attach yet more polar groups to the hydroxyl group added by CYP450), the result is improved excretion of unwanted compounds (usually potential toxins) by the kidney. CYP450 are also vital to numerous physiochemical processes inherent to the body including metabolism of endogenous steroid hormones and formation of cholesterol eicosanoids. Many CYP450 genes are polymorphic, meaning there are multiple forms of the gene that can give rise to slightly different variations or alleles. This can lead to distinct individual metabolic differences and help account for variability in patient response to many herbal constituents.

The P450 name comes from the pigment that absorbs the 450 nm wavelength of light. These are designated by a common three-symbol system: a letter designating the enzyme family, a second letter designating the subfamily, and a third letter designating the individual enzyme and its gene. We consider each of the major CYP450 enzymes and their relationships to herbs (see Figure 29-1).

CYP3A4, ST. JOHN'S WORT, AND GRAPEFRUIT

More than half of all drugs and chemicals are metabolized by this enzyme, making it by many accounts the most important CYP450.[1] Therefore, the greatest concern has been raised about herbal compounds that interact with it and the potential for drug–herb interactions. Polymorphisms of 3A4 occur but are of unknown relevance. Two of the best-documented herbs that interact with drugs are *Hypericum perforatum* (St. John's wort), a CYP3A4 inducer, and *Citrus* x *paradisi* (grapefruit), a CYP3A4 inhibitor. St. John's wort is a native Eurasian perennial plant that has become a weedy invader in North America and is used as an effective treatment for people with depression. Grapefruit is a tree that is a hybrid cross, perhaps accidental, believed to have occurred in Barbados (though all its ancestors are native to China) prior to 1750. It has

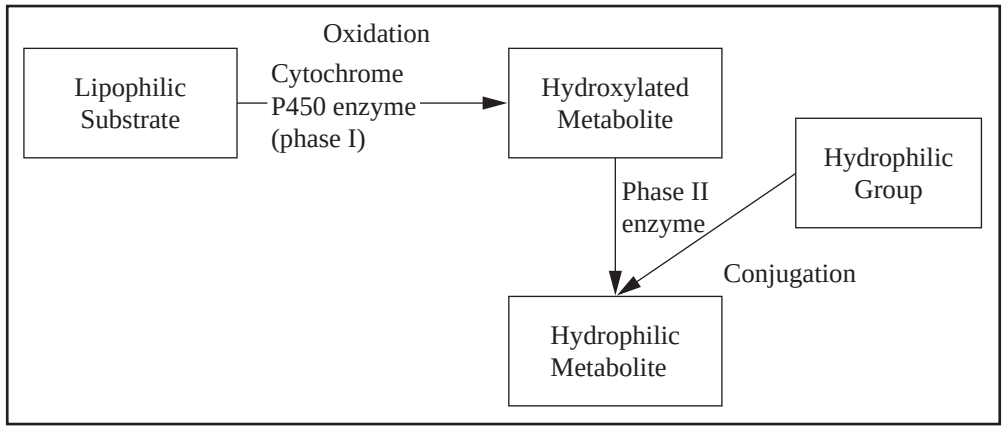

Figure 29–1. Overview of Mechanism of Action of CYP450

become a major fruit crop centered in Florida and is widely consumed as part of a healthy diet in the United States and elsewhere.

The major constituent of concern in St. John's wort is hyperforin as recent trials show that low-hyperforin extracts of St. John's wort have a minor or no effect on CYP3A4 in humans.[2,3,4] The major constituents of concern in grapefruit are furanocoumarins such as bergamottin, polymers of furanocoumarins, and flavonoids such as quercetin and naringen.[5] Grapefruit inhibits CYP3A4, as well as P-glycoprotein, in the intestines but not in the liver.[6,7,8,9] Thus, oral grapefruit extracts have no effect on drugs administered intravenously.[10] St. John's wort acts primarily on CYP3A4 in the intestines though it may have some effects in the liver as some studies (though not all) show it to affect the metabolism of intravenously administered drugs in humans.[11,12]

Numerous trials confirm that St. John's wort and grapefruit have clinically significant effects on drug metabolism in humans. Tables 29-1 and 29-2 summarize the major interactions of these two herbs in clinical trials or multiple cases studies. The list is limited to interactions likely to be clinically relevant. Because of its broad effects on CYP450, St. John's wort should not be administered simultaneously with any drug that is metabolized to a large extent by CYP3A4. It is important to point out that many of these clinical trials were conducted in healthy volunteers, and demonstration of changes in pharmacokinetics does not always translate into changes in efficacy or toxicity. For instance, although St. John's wort was shown to decrease absorption of quazepam, it had no effect on the pharmacodynamics of the drug.[13]

In the case of grapefruit and related bitter citrus, its use with CYP3A4 drugs should not be considered absolutely contraindicated, at least when there is close clinical supervision. However, its effects are somewhat unpredictable, in part because it may affect other drug transport proteins and CYP450 enzymes that offset its effects on CYP3A4.[14,15] Grapefruit shows significant potential as a dose-sparing agent, allowing expensive or toxic drugs to be given at smaller doses than usual with no loss of activity. This has been most thoroughly studied with cyclosporine, a drug that is both toxic and expensive.[16] However, even this research is incomplete, making it difficult to control the interactions and keep the drug dose correct and safe.[17] Case studies have been published of other instances in which grapefruit juice beneficially augmented the effects of CYP3A4 substrate drugs, such as felodipine.[18] Clinicians need to be aware that any patient who takes grapefruit or other bitter citrus but does not reduce the doses of CYP3A4 substrate drugs risks serious harm, as has been shown in case studies. While the intentional use of grapefruit as a dose-sparing agent is intriguing, it is also tricky at best with drugs that have

Figure 29–2. *Citrus decumana* (grapefruit)

narrow therapeutic windows and should only be attempted by those highly experienced with the drug in question and only in very diligent, reliable patients.

An in vitro and one rat study have suggested that *Punica granatum* (pomegranate) juice might inhibit CYP3A4, similar to grapefruit.[19] A human clinical trial using healthy volunteers found no such effect related to the drug midazolam, a CYP3A4 substrate.[20] Along similar lines, *Schisandra chinensis* (wu wei zi) fruit, commonly used as a liver tonic in Chinese medicine, had CYP3A4-inhibiting effects in vitro but not in rats.[21] No human studies on Schisandra related to drug interactions were located. These cases highlight the folly of basing decisions for humans solely on test tube or animal studies.

Grapefruit acts for two to four hours after ingestion in many people, though there is wide interindividual difference with some people having minimal or no inhibition.[22] Generally the increase in absorption does not exceed 50%, though this varies from drug to drug and person to person. Taking grapefruit simultaneously with a drug can affect absorption as it takes some time for the grapefruit to start working.

Table 29–1. Documented Drugs Whose Absorption Is Decreased by St. John's Wort

Drug Category	*Specific Drugs*
Immunosuppressives[a,f,i,n]	Cyclosporine, azathioprine, tacrolimus
Oral birth control pills[k]	Estrogen analogs
Chemotherapy drugs[b,g]	Imatinib, irinotecan
Positive inotropes[d]	Digoxin
Anticoagulants[c]	Warfarin
Protease inhibitors[l]	Indinavir
Antiasthmatic[h]	Theophylline
Tricyclic antidepressants[d]	Amitriptyline
Anti-anginal[m]	Ivabradine
Benzodiazepine anxiolytics[e,j]	Midazolam, quazepam

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CYP450 AND ACTIVATION OF PLANT TOXINS

CYP450 enzymes can on occasion convert harmless plant compounds into dangerous toxins. Members of the Boraginaceae and Asteraceae families, principally, contain potentially hepatotoxic, nephrotoxic, and carcinogenic alkaloids known as unsaturated pyrrolizidine alkaloids

Table 29–2. Documented Drugs Whose Absorption Is Increased by Grapefruit

Drug Category	*Specific Drug(s)*
Immunosuppressive[g]	Cyclosporin, tacrolimus, sirolimus
Benzodiazepine anxiolytics[d]	Triazolam (probably not clinically significant)
Nonsedating antihistamine[b,c]	Terfenadine*
Antimalarial[e]	Primaquine
Calcium channel blockers[i]	Felodipine
Statin cholesterol lowering[a,h]	Atorvastatin, simvastatin
Antiseizure[f]	Carbamazepine

* Though unlikely, this interaction could be lethal. Terfenadine is off the market due to this interaction and similar interactions with 3A4-inhibiting drugs such as ketaconazole.

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(uPA).[23] These alkaloids are not inherently toxic, but become harmful after undergoing phase I hepatic metabolism. Studies in multiple animal models as well as human liver microsomes confirm that CYP3A enzymes are principally responsible for activating uPA to their toxic intermediates, either as *N*-oxides or related molecules.[24,25]

Clinicians have observed that not everyone exposed to uPA-containing medicinal plants, such as *Symphytum officinale* (comfrey), develops toxicity.[26] The fact that CYP3A enzymes may be critical in activating comfrey uPA to a harmful state, and that these enzymes can vary in activity from person to person, could help explain this variable tendency to develop toxicity. It is also possible that administering CYP3A4 inhibitors such as grapefruit juice might reduce the toxicity of uPA, though this has not been investigated.

Compounds known as alkenylbenzenes are another group that can be activated by CYP450 to toxic intermediates. Safrole and estragole are probably the two best-known alkenylbenzene toxins. Safrole is found in *Sassafras* spp. as well as the *Areca catechu* (areca or betel) nut, chewed as a stimulant in north Africa, the Middle East, and parts of Asia. Estragole is found in small quantities in common medicinal spices including *Foeniculum vulgare* (fennel), *Pimpinella anisum* (anise), *Ocimum basilicum* (basil), and *Artemisia dracunculus* (tarragon). Safrole and

Figure 29–3. *Ocimum basilicum* (basil)

Figure 29–4. *Foeniculum vulgare* (fennel)

estragole are both metabolized by multiple CYP450 to carcinogenic 1'-hydroxy metabolites, including CYP2A6 (most notably), 2C9, 2D6, and 2E1.[27,28] The presence of 1'-hydroxysafrole correlates somewhat with development of esophageal cancer in chronic areca nut chewers in Taiwan.[29] This line of research also suggests that people who are poor 2A6 metabolizers may have relative resistance to the carcinogenicity of betel nut.

Thus, while CYP3A4 may play a role in drug–herb interactions, they also play a role in potentially dangerous toxicity reactions. This is an area in need of greater study and understanding so that potential plant hazards can be better understood, treated, or avoided.

PIPERINE AND CURRY

Piperine is an alkaloid found in various species of *Piper* including *P. nigrum* (black pepper) and *P. longum* (long pepper) fruit. It inhibits CYP3A4, though it may have other effects on

CYP450.[30] Piperine has been shown to increase absorption of the CYP3A4-substrate drugs phenytoin, propranolol, and theophylline in humans.[31,32] Thus, piperine shows some of the same potential as grapefruit to act as a dose-sparing agent for some medications.

Piperine-containing herbs have long been added in small amounts to herbal formulas in Asia to make the formulas work better.[33] The fact that piperine and possibly other compounds in peppers enhance absorption of other compounds gives a firm footing to this traditional belief. In fact, piperine has specifically been shown to greatly (by 2,000% in one pilot study) enhance absorption of curcumin, a key antioxidant component of *Curcuma longa* (turmeric).[34] Both black or long pepper and turmeric are key ingredients of curries, as well as herbal formulas used for people with arthritis and a host of other inflammatory diseases. Although it is not known for certain how piperine causes such a profound increase in curcumin absorption, it is at least partially related to CYP450. Some clinical trials have exploited this potential by combining the isolated constituents, curcumin and piperine. Of course, this approach ignores other potential but unknown beneficial interactions with other constituents present in the whole plants.[35]

Curcumin itself has now been shown to have inhibit several CYP450, including 1A1, 3A4, and 2B6 in vitro.[36] Surprisingly, curcumin was reported to decrease blood levels of the beta-blocker talinolol by about 33% on average in one clinical trial.[37] The authors speculate this could be due to inhibition of Pgp by curcumin, though again this should theoretically increase absorption. A direct chelation of curcumin and the drug cannot be ruled out either. In any case, more research is needed to determine if turmeric or curcumin may pose a risk of drug–herb interactions, especially as turmeric, like grapefruit, is widely consumed in the diet.

CRUCIFERS, CYP450, TOXINS, AND ESTROGEN METABOLISM

Cruciferous vegetables and medicinal plants such as broccoli contain isothiocyanates. These compounds or their metabolites have been shown to inhibit CYP2E1 while stimulating 1A1 and 1A2.[38,39] Sulforaphane, phenylethyl isothiocyanate (PEITC), and indole-3-carbinole are three compounds in this group that have received extensive scrutiny. Many studies have confirmed the general anticarcinogenic nature of foods that contain these compounds, though the protection is imperfect.[40] Much of the protection is believed to derive from an enhancement of the body's ability to eliminate carcinogenic toxins, in part by speeding up their breakdown by inducing CYP1A1/2.[41] The true mechanisms of action are almost certainly more complex than this and involve mechanisms unrelated to CYP450 or carcinogen metabolism.[42]

Charred or well-done meats contain elevated levels of carcinogenic heterocyclic amines (HA). Studies have looked at whether eating broccoli with such meats can reduce the harm from the HA, and it appears that it can.[43,44] HA are CYP1A1/2 substrates, and their hastened removal by concomitant consumption of CYP1A-inducing cruciferous vegetables appears to be protective. Much more work remains to be done to completely prove this hypothesis.

Complicating the picture is the fact that isothiocyanates are removed from the body in large part by the action of glutathione *S*-transferase mu-1 (GSTM1). Some people lack the gene for this enzyme (called the null genotype) and do not produce GSTM1. This means that less efficient, alternate metabolic pathways are responsible for excreting isothiocyanates, resulting in increased blood and body and, at least according to some studies, enhancing the effects of cruciferous vegetables against cancer.[45] GSTM1 activity appears to directly inhibit the ability of crucifers to induce 1A2.

Nasturtium officinale (watercress) is another Brassicaceae family plant rich in isothiocyanates, particularly PEITC, that inhibit CYP2E1. In one trial of healthy adults, 50 g watercress

effectively halved the activity of 2E1. It had twice the effect of isoniazid, an antitubercular drug well known to inhibit 2E1.[46] The effects of watercress inhibition of 2E1 last at least 10–12 hours according to a study on its effect on the pharmacokinetics of acetaminophen, a 2E1 substrate, in healthy adult volunteers.[47]

Estradiol catabolism critically involves CYP450 enzymes (see Figure 29-6). Of particular importance are CYP1A1 and CYP1A2, because these enzymes are highly inducible. CYP1B1, also involved in estradiol catabolism, is highly constitutively expressed, meaning it is very difficult to inhibit. There is mounting evidence that CYP1B1 metabolites of estradiol, notably 16--alpha-hydroxyestrone, are responsible for many of the negative effects attributed to estrogen.[48] This metabolite also stimulates human papilloma virus (HPV). CYP1A2 catabolizes formation of 2- and 4-hydroxyestrones, which are less or noncarcinogenic and do not stimulate HPV. Since CYP1B1 (which generates 16-alpha-hydroxyestrone) is so difficult to inhibit, much research has gone into using isothiocyanates to induce CPY1A2 instead. This forces the estrogen substrate down a more beneficial pathway, an interesting approach compared to the traditional method of suppressing undesired or harmful pathways.[49]

Indole-3-carbinol (I3C) is the major isothiocyanate studied as a beneficial estrogen inducer. I3C has been the subject of many clinical trials for helping people with estrogen-related diseases. Cabbage juice has been studied to a lesser extent even though about one third to half a head of cabbage contains as much indole-3-carbinol as used in most trials. One clinical trial found that 400 mg of I3C by mouth daily was able to completely cure cervical intraepithelial dysplasia, a significantly greater number than were helped by placebo.[50] A more recent trial showed that 200 or 400 mg I3C by mouth improved symptoms and shrunk lesions without altering their grade in women with vulvar intraepithelial neoplasia.[51] I3C at a dose of 200 mg twice daily was also extremely effective at preventing the need for surgery in adults with the HPV-mediated disease recurrent laryngeal papillomatosis.[52] These doses clearly shift the me-

Figure 29–5. *Nasturtium officinale* (watercress)

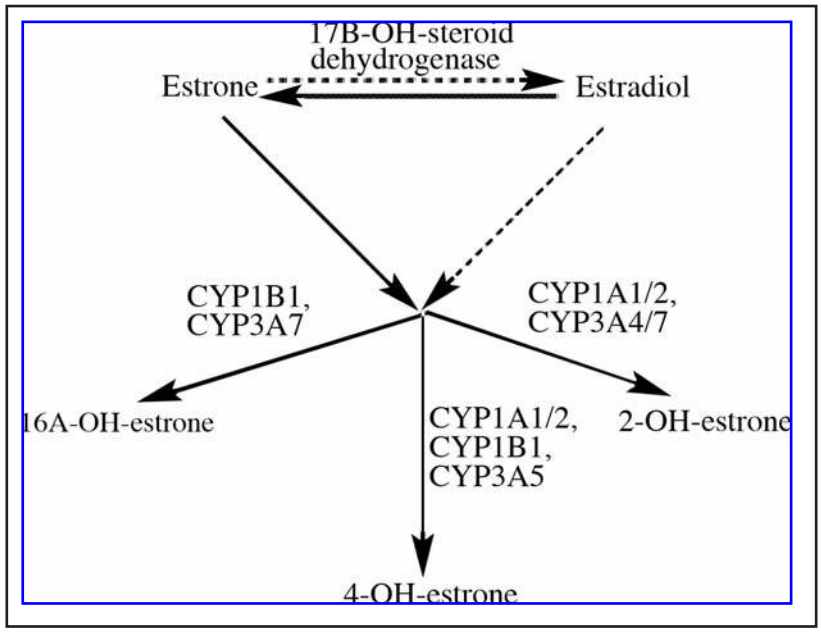

Figure 29–6. Catabolism of Human Estrogens

tabolism of estradiol away from 16-alpha- and toward 2-hydroxyestrone.[53] Side effects at these doses of I3C have been minimal.

Artemisia Annua and CYP450

Artemisia annua (sweet Annie) is a weedy herb in the Asteraceae family found around the world. It contains artemisinin and other compounds that are potent destroyers of the schizont, the major blood form of malaria. One small clinical trial has shown that purified artemisinin at a dose of 500 mg can significantly inhibit CYP1A2 in healthy human volunteers by 66% on average.[54]

The metabolism of artemisinin has been extensively studied both as an isolated drug and from tea of the crude herb. Artemisinin is primarily metabolized by CYP2B6, and it autoinduces higher levels of this very enzyme.[55] It is also metabolized by CYP2A6 and 3A4 to a less significant extent (the latter being more important in patients with poor 2B6 activity). Repeated administration of artemisinin over a period of days clearly leads to reduced absorption because of the 2B6 autoinduction problem.[56,57] Women tend to have higher baseline clearance of artemisinin, and thus it does not work for as long in women.[58] Absorption of artemisinin from an infusion of the crude leaf has also been studied and shown to have similar pharmacokinetics.[59]

The clinical implication is that sweet Annie or artemisinin should not be prescribed continuously as a treatment for malaria or cancer, but instead should be pulse dosed (roughly five to seven days on, then five to seven days off), as it will not be absorbed in useful amounts after about a week of continuous use. This also suggests that sweet Annie or artemisinin should be coupled with other agents that do not have this problem to achieve optimal efficacy. Further-

Figure 29–7. *Artemisia annua* (sweet Annie)

more, sweet Annie or artemisinin are unlikely to be useful for prevention, both because they cannot be effectively taken continuously and because they do not attack the portion of the life cycle of the malaria parasite that is injected by mosquitoes (known as sporozoites).

Grapefruit and CYP2A6

Grapefruit was discussed above primarily as a CYP3A4 inhibitor. Grapefruit and other bitter citrus may improve absorption of some natural compounds that are CYP2A6 substrates by blocking this enzyme as well. Two studies have shown that grapefruit juice increases bioavailability of coumarin, a very common plant constituent with venoprotective and inflammation-modulating effects normally broken down by 2A6.[60,61] A similar result has been seen with nicotine, which is also catabolized by 2A6. In a trial involving healthy volunteers, grapefruit juice significantly reduced nicotine conversion to its metabolite cotinine.[62] Thus, grapefruit may be a useful dose-sparing agent in nicotine replacement treatment.

Activation of Resveratrol

Resveratrol is an antioxidant stilbene compound found in grapes, peanuts, and other foods. There are varying reports about which CYP450 are involved, but they clearly play a role in hydroxylation of resveratrol to its more active metabolite piceatannol. One report suggested CYP1B1 was responsible, while others have found that CYP1A2 was.[63,64] Though resveratrol itself appears to have anticancer and cardioprotective activity, its metabolites may be even more potent or may have synergistic benefits.[65] Piceatannol has been shown to inhibit multidrug resistance protein-1, an important cause of multidrug resistant cancer, while resveratrol does not.[66] This is but one example of what are sure to be many where precursor chemicals in medicinal plants are activated by CYP450 to more potent healing metabolites.

Gingko, Artemisinin, and CYP2C19

CYP2C19 is a minor metabolizing enzyme in humans, but there are still a few drugs that are affected by it. One small clinical trial in Chinese people found that an extract of the leaf of *Ginkgo biloba* at 140 mg twice daily decreased serum omeprazole levels. Since omeprazole is a CYP2C19 substrate and there were no other clear reasons for this interaction, it is possible that ginkgo is a 2C19 inducer.[67] Artemisinin has also been reported in one trial to increase elimination of omeprazole, consistent with a CYP2C19-inducing effect.[68] Whether either may pose a problem in clinical medicine is not yet known.

Coffee, CYP1A2, and Biochemical Individuality

Coffea arabica, widely consumed as a beverage, is a stimulating bitter digestive herb that originated in northeastern Africa. Though simultaneously reviled and lauded in various circles around the globe, coffee is practically a fact of life in most parts of the world. Rather than prohibiting or recommending coffee to all people, discriminating healers seek to find those people for whom it will provide the most benefit with the least risk and recommend it to them, while avoiding it in those for whom risk is highest. This concept of individualized medicine is foreign to statistical averages–driven medicine, yet has significant potential for benefit for patients. As an example, one large case-control trial of coffee drinkers found that only people who were slow metabolizers of caffeine, related to possessing the CYP1A2*1F "slow" allele, had an increased risk of nonfatal myocardial infarction.[69] Coffee may also increase the risk of ovarian cancer, but only in women with any C allele of CYP1A2.[70] Women who ate cruciferous vegetables, which may affect CYP1A2 expression, had further modified risks for ovarian cancer if they drank coffee.

CONCLUSION

Botanical medicines interact with CYP450 in many ways. Most of the focus has been on the potential for interference with drugs metabolized by the same enzymes. This represents a biased view and has completely overshadowed the fact that drugs have the potential to adversely affect the healing potential of herbal treatments. For instance, *Ruscus aculeatus* (butcher's broom) has shown the ability to offset the side effect of edema in patients taking a calcium channel blocker without apparently diminishing the effect of the drug.[71] On the other hand,

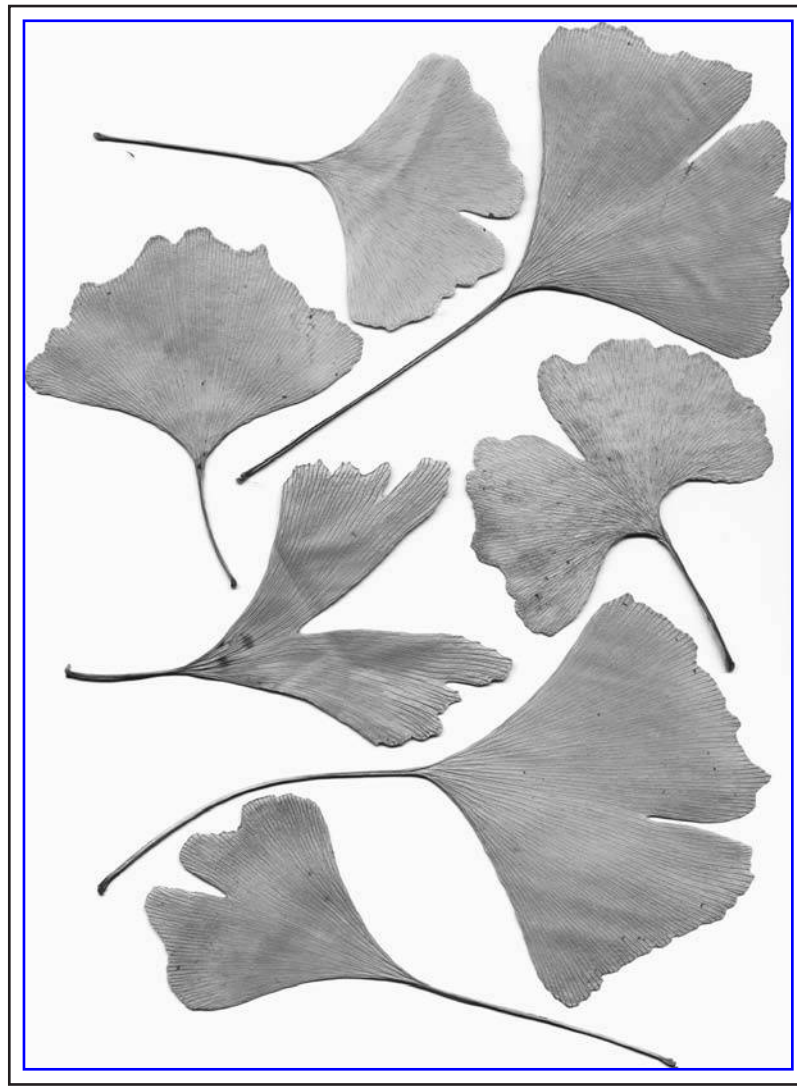

Figure 29–8. *Ginkgo biloba* (ginkgo)

in animal models, calcium channel blockers were shown to diminish the venoconstrictive effect of butcher's broom.[72] There is virtually no research on this topic but it is critical that botanical researchers begin to investigate the degree to which drugs are interfering with natural products.

Botanicals can also interact with one another via CYP450 enzymes. This includes changes in absorption and possibly changes in clinical actions, though the latter has not been formally documented. Herbal constituents can be activated to more potent healing agents, as well as more toxic metabolites. Individual differences between patients in their CYP450 makeup may change how they react to botanical medicines, both favorably or negatively. Thus more research and wider knowledge of botanical–CYP450 relationships are definitely warranted. See Tables 29-3 and 29-4.

Table 29–3. Critical Natural Product–CYP450 Interactions

Agent	*Induces*	*Inhibits*
Isothiocyanates (I3C, DIM, PEITC)	CYP1A1, 1A2	CYP2E1
Hypericum perforatum	CYP3A4 (intestinal)	
Piperine (*Piper longum*)		CYP3A4 (intestinal)
Ginkgo biloba	CYP2C19 (negative trial on 3A4 and 2D6)[b]	

* Much less potent than grapefruit.

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Table 29–4. Herbs Shown to NOT Interact with CYP450 in Clinical Trials

Actaea racemosa (black cohosh)[g]

Camellia sinensis (green tea)[a,b]

Echinacea purpurea[f]

Eleutherococcocus senticosus (eleuthero)[c]

Serenoa repens (saw palmetto) standardized extract[f,i]

Silybum marianum (milk thistle) silymarin extract[g,j]

Vaccinium macrocarpon (cranberry) juice[e,h]

Valeriana officinalis (valerian)[d]

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30

HERBS AND DRUG RESISTANCE

This chapter explores herbs and drug resistance. We begin with a discussion of the general phenomenon of antibiotic resistance and a review of studies showing that herbs may positively affect microbial resistance to antibiotics. Next we evaluate this research and discuss its clinical implications. Thereafter, we discuss herbs and chemotherapy resistance in cancer cells followed by more detailed information about the mechanisms of drug resistance and how herbs affect them. This topic is also discussed somewhat in regard to malaria.

Microbial resistance to drugs has grown remarkably, and each passing decade turns up new resistance. The sulfonamide antibiotics were initially effective against group A streptococci and pneumococci, but within 10 years developed modes of resistance. The pandemic of multidrug-resistant *Staphylococcus aureus* (MDRSA) in the 1950s, outbreaks of resistant Gram-negative enteric bacilli in the 1960s, beta-lactamase-producing *H. influenzae* and *Moraxella catarrhalis* in the 1970s, and the worldwide spread of multidrug-resistant (MDR) pneumococci beginning in the 1980s and continuing to the present are signs of ever-increasing drug resistance among bacteria globally.[1] Most recently, methicillin-resistant *S. aureus* (MRSA) organisms found in patients in the United States show reduced sensitivity to vancomycin, the only remaining drug that effectively kills MRSA.[2] The era of microbes resistant to all known antibiotics has arrived.

We first explore some causes of resistance, possible ways to use botanicals to slow this plague, and some interesting research showing that herbs may reduce or eliminate microbial resistance to antibiotics.

THE ROOT CAUSES

Inappropriate prescription is the best understood cause of resistance, though many other factors contribute significantly. Antibiotics were—and continue to be—prescribed for viral infections even though they are ineffective against viruses.[3] Many practitioners fail to test whether the organism(s) infecting a patient are sensitive to the antibiotics being prescribed. Broad-spectrum agents are often used where narrow-spectrum drugs would be more appropriate. Drugs are often prescribed without carefully evaluating the pharmacokinetic and pharmacodynamic factors essential for effective killing and result in the selection of resistant pathogens.[4] Other medical contributions to antibiotic resistance include insufficient hand washing and other hospital hygiene problems that spread nosocomial MDR microbes. Antibiotics are used prophylactically, especially in surgery, rather than demanding greater improvement of hygiene and sterility in the hospital or surgical arena. There are also many studies questioning the efficacy of chronic antimicrobial use in patients with quadriplegia or recurrent urinary tract infections, and the specter that MDR organisms are being promoted in such situations looms large.[5]

Patients and society also play a pivotal role in the evolution of MDR. Patients often quit taking their antibiotics when their symptoms improve. The more resistant bacteria are not killed and profit from an inadvertent selection over their more susceptible cousins. In many countries, antibiotics are sold over the counter, inviting uneducated and often inappropriate use by consumers.

Another source of resistance is the prophylactic use of antibiotics in animal factory farming, where they are used to prevent illnesses caused by poor feed, overcrowding, and generally disease-promoting environments. They are also used to hasten growth. In fact, the antibiotics used to increase growth exceed the amounts used therapeutically.[6] And much of the therapeutic use could be avoided by sound and humane treatment of the animals. Drug-resistant *Salmonella* infections have been transmitted from animals fed sublethal doses of antibiotics to humans, sometimes with fatal outcomes.[7]

Another lesser-known cause of resistance is the widespread use of aerially sprayed antibiotics to treat and prevent primarily cosmetic plant diseases. Between 40,000 and 50,000 pounds of tetracycline, streptomycin, and other antibiotics are sprayed annually on fruit trees in the United States.[8] Drift exposes many organisms to sublethal doses of the antibiotics, a perfect setting for inducing microbial resistance.

ANTIMICROBIAL BOTANICALS VERSUS DRUGS

Plant medicines are often the best first-choice medicine for many ailments instead of antibiotics. By using botanicals appropriately, particularly for mild and some chronic infections, we can save antibiotics for serious infection, reducing microbial contact with antibiotics. In Finland, a national health care policy was issued calling for reduced and more careful use (particularly using culture and sensitivity studies to ensure each organism being treated was sensitive) of macrolides to help combat erythromycin resistance. The approach proved quite successful, cutting erythromycin-resistance rates almost in half over five years.[9] Other applications of herbs include their use in animals, and there is also some interesting research on the use of herbs to combat plant diseases.

Most available drugs are not antiviral and do not stimulate the immune system. In contrast, many herbs combine antiviral properties with immune-modulating action. Botanicals should be used in viral infections where they provide an economical and effective approach in most cases. Herbs are also useful in bacterial infections, and many, many plants have demonstrated in vitro antibacterial activity. Classic clinical applications include herbs in cystitis and intestinal infections, and the use of herbal oils for ear infections in children. Some herbs commonly used as food show antimicrobial activity worthy of special note: *Momordica charantia*, a common medicinal food in the Chinese diet, showed broader and higher levels of activity against most of the organisms than did standard antibiotics.[10] *Allium sativum* (garlic) also has an antimicrobial action claimed to be comparable to that of standard antibiotics.[9]

HERBAL MEDICINES TO REDUCE ANTIBIOTIC RESISTANCE

The main focus here, however, is a use that is seldom applied in clinical practice: combining herbs with antibiotics to overcome resistance. A number of studies show that many herbs overcome microbial resistance in vitro, and act synergistically with antibiotics. The following herbs have demonstrated such properties in initial in vitro trials. Further research is warranted on all these botanicals to determine the full extent and complete details of their clinical use in cases of microbial resistance. Figure 30-1 illustrates the three basic mechanisms at play in the many herbal examples below.

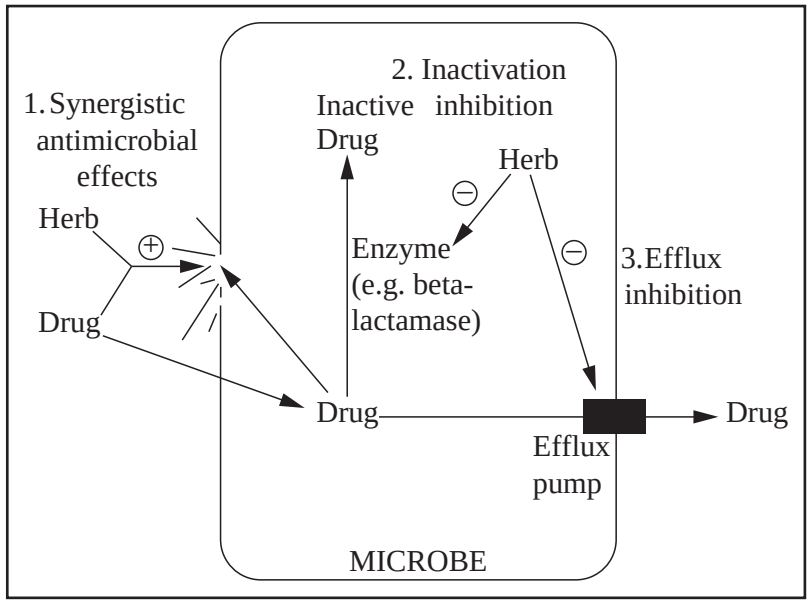

Figure 30–1. Mechanisms of Botanical Potential of Antibiotics
The three main areas where botanical medicines can enhance the efficacy of antimicrobial drugs: (1) Herbs can act additively or synergistically with drugs in the killing of microbes. An example would be using *Allium sativum* (garlic) with vancomycin. Not illustrated but definitely related are herbs that interfere with microbial adhesion (e.g., *Vaccinium macrocarpon* [cranberry]), which could lead to synergistic effects with antibiotic drugs. (2) Some antibiotics are degraded by bacterial enzymes (e.g., penicillin by beta-lactamase), enzymes that can be inhibited by herbs such as *Camellia sinensis* (tea). (3) Drug-resistant microbes often have pumps for removing antibiotics from their cells. Some herbs (*Silybum marianum* [milk thistle] and *Mahonia aquifolium* [Oregon grape]) inhibit these pumps, allowing the drugs to stay around long enough to kill the microbe.

HERBS AND ANTIBIOTIC RESISTANCE: CURRENT RESEARCH

The potential synergism between botanicals and antibiotics is very exciting from a clinical perspective. Many, but by no means all, of the herbs described are used as antimicrobials. We now explore the traditional uses and the clinical applications of these plants along with their potential role in patients taking antibiotics.

Table 30-1 summarizes the in vitro studies identifying herbs that may be useful in dealing with microbial drug resistance. Unfortunately, in vitro data do not necessarily reflect how herbs actually work in the human body, particularly where only single constituents are studied. Moreover, in vitro data do not provide reliable information on dosing, bioavailability, and other relevant clinical issues. As a result, although the data are very exciting, we cannot pronounce with any certainty that herbs will help us solve the predicament of antibiotic resistance.

Table 30–1. Summary of Herbs That Affect Antibiotic Resistance

Herb	*Effect on Drug Resistance*
Camellia sinensis	Reversed resistance in MRSA, and to some extent, penicillin resistance in beta lactamase producing *S. aureus*; epicatechin gallate lowered MIC of oxacillin and other beta-lactams in MRSA; epicatchin gallate became bacteriocidal when combined with oxacillin
Allium sativa	Fresh garlic and its constituent allicin reduced the MIC of vancomycin for vancomycin-resistant enterococci
Silybum marianum	Silybin inhibits the efflux pump in multidrug-resistant bacteria
Mahonia aquifolium, *Berberis* spp., *Coptis* spp.	Flavonoid from the leaf disabled the bacterial-resistance mechanism, increasing the effectiveness of the antimicrobial berbarine; when flavonoid, a prophyrin constituent and berberine are combined; subinhibitory concentrations of berberine are effective against MRSA
Hydnocarpus aureus	Appeared to contain a flavonoid that disabled the efflux pump but does not
Lonicera japonica	Contains a flavonoid shown to disable the efflux pump
Scutellaria spp.	Baicalin reduced dramatically MIC of benzylpenicillin against MRSA and PRSA; potentiated bacteriocidal effects of ampicillin, amoxycillin, benzylpenicillin, methicillin, and cefotaxime
Arctostaphylos uva ursi	Reduced MICs of beta-lactam antibiotics (oxacillin, cemetazole); corlagin reduced MICs of various beta-lactams 100- to 2,000-fold; had a synergistic effect with oxacillin and became bacteriocidal when combined with oxacillin
Acorus calamus	Acorenone strongly inhibited MRSA; inhibited an enzyme used to overcome chloramphenicol when combined with chloramphenicol
Atractylodes lancea	Sucroses modifed MDR in vitro as strongly as verapamil
Stephania japonica	MDR-reversing activity
Khaya grandifoliola	Herb and its liminoids active against chlorquine resistant and c-sensitive Plasmodium falciparum; gedunin had an additive effect when combined with chloroquine
Swertia chirayita	Improved antileprotic activity of dapsone
Herb	*Effect on Resistant Bacteria*
Nepeta cataria	Inhibits enzyme activities associated with the virulence of MRSA and MSSA strains; at sub-MIC doses, catnip reduces the adherence of *S. aureus.*
Hypericum perforatum	MRSA and PRSA were sensitive to hyperforin.
Nigella sativa	Oil showed prominent in vitro activity against eight MDR strains of *Shigella flexneri.*
Cryptolepsis sanginolenta	Cryptolepine active against MDR *P. falciparium*, but no in vivo reduction in parasitaemia in infected mice

(*continued*)

Table 30–1. (*continued*)

Herb	*Effect on Drug Resistance*
Camellia sinensis epigallocatechin	Epigallocatechin inhibited MRSA
Scutellaria spp., *Plantago* spp.	Baicalin inhibited MRSA
Arctostaphylos uva ursi, Camellia sinensis, Hammamelis virginiana	Myrecitin inhibited MRSA

Table 30–2. Prescription Guidelines

Herb	*Recommended Synergistic Uses*	*Dose*
Camellia sinensis (green tea) leaf	Infections, especially dermal or intestinal	At least 1 cup per day
Allium sativum (garlic) bulb	Intestinal and respiratory infections; vancomycin prescription	At least 1 raw clove garlic per day
Grifola frondosa (maitake) mushrooms	No recommendation; if patient cooks with maitake or is taking maitake as an immune enhancer, encourage continued use with antibiotics, particularly vancomycin	Not applicable
Silybum marianum (milk thistle) seed	Take with botanical antimicrobials, especially if containing berberine; take with antibiotics, especially if hepatotoxic	3–15 g seed; 1⁄2–1 tsp tincture both per day
Mahonia spp. and *Berberis* spp. (berberine-containing plants) roots	Synergistic principal is found in leaf; do not recommend using leaf internally	Not applicable
Lonicera japonica (honeysuckle) stem and flowers	Combine with berberine-containing plants in sinus infections and respiratory ailments; continue use if antibiotics prescribed for these conditions	9–15 g flowers; 9–30 g stems both per day
Scutellaria spp. (skullcap) herb	Combine with botanical formulas for viral and bacterial respiratory ailments; take with antibiotics prescribed for bacterial ailments	20–60 drops tincture up to three times per day
Arctostaphylos uva ursi (uva ursi) leaf	Supportive adjunct for patients prescribed antibiotics for urinary tract infections	30–60 drops tincture; 2–4 oz infusion both three times per day
Hypericum perforatum (St. John's wort) herb	Supportive adjunct for patients prescribed antibiotics for infected wounds	20–30 drops up to three times per day
Atractylodes lancea	Often combined with Chinese goldthread (contains berberine) for gastrointestinal ailments; continue where antibiotics prescribed	See a practitioner experienced in its use.

(*continued*)

Table 30–2. (*continued*)

Herb	*Recommended Synergistic Uses*	*Dose*
Stephania japonica	Historically used to treat fever and diarrhea; continue use where antibiotics prescribed	See a practitioner experienced in its use.
Acorus calamus (calamus)	Apply topically to indolent ulcers, blistered surfaces; take tincture internally	Strong root infusion

Because antibiotic resistance poses an ever-increasing threat to life and health, we should consider whether these herbs ought to be used in patients taking antibiotics. This question is best answered by trying to integrate historical use and available scientific data to determine the types of infections the plants may help the most. Our conclusions are summarized in Table 30-2. These conclusions are obviously only educated guesses, but we hope our discussion stimulates clinical research and insight on this very important topic.

A number of the plants with the potential ability to diminish antibiotic resistance are foods that include tea, garlic, and maitake mushrooms. Milk thistle could be, and perhaps should be, a food. Each of the aforementioned has a high safety profile, there is no known detriment associated with their use, and they may be helpful to patients taking antibiotics. We discuss these safest of resistant modifiers first before moving into the use of other types of herbs.

Camellia sinensis (Green Tea)

Tea in its dried, unfermented form is known as green tea. In its fermented form, it is known as black tea. Green tea is the second most commonly consumed beverage in the world (water being number one). Tea (in its green and black forms) is known to have antimicrobial properties.[11,12,13] Some preliminary controlled human trials have shown that various extracts of tea can have preventive or therapeutic effects in humans with various diseases caused at least in part by microbial infection including dental caries, gut dysbiosis, and chronic gastritis.[14,15,16] Animal studies have confirmed that tea retains its activity in vivo.[17] Tea showed a relatively high antimicrobial activity against pathogenic dermal fungi in vitro.[18] Constituents of green tea showed significant bactericidal action against the lethal *Escherichia coli* 0157:H7 in vitro, and had a synergistic effect when combined with *Mentha* x *piperata* (peppermint) leaf volatile oil.[11] Extracts of black tea appear to protect against *V. cholerae*.[12] Tea compounds were effective agents against *Shigella* spp. in vitro,[13] and the aqueous extract of black tea cured guinea pigs infected with experimental shigellosis

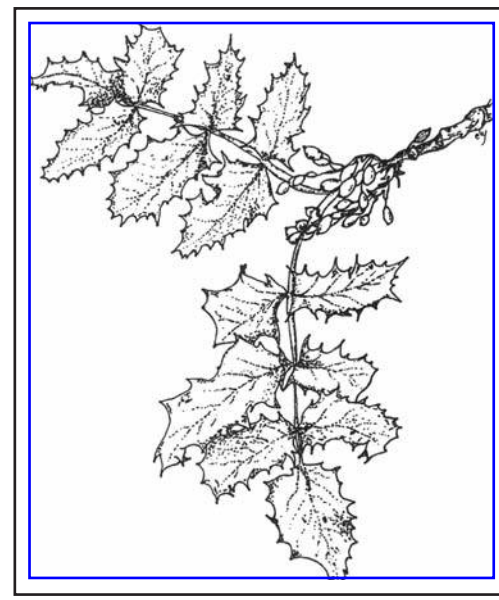

Figure 30–2. *Mahonia aquifolium* (Oregon grape)
Drawing by Eric Yarnell, ND, RH.

within three days. In the untreated group, the guinea pigs died within 24 hours.[17] Note that tea extracts have been shown to be bactericidal against *Staphylococcus* and *Yersinia* at well below standard "cup of tea" concentrations.[19] This data strongly suggest tea may be useful in a variety of infections, particularly in dermal and intestinal ailments.

Aqueous extracts of a variety of types of *Camellia sinensis* (tea) leaf inhibited a wide range of pathogenic bacteria, including methicillin resistant *S. aureus* (MRSA). Synergy between beta-lactam antibiotics and tea extracts were demonstrated by a number of techniques.[20] Green tea extracts reversed resistance in MRSA and also, to some extent, penicillin resistance in beta-lactamase-producing *S. aureus*.[10] Epicatechin gallate, from green tea, markedly lowered the minimum inhibitory concentration (MIC) of oxacillin and other beta-lactams in MRSA. When combined with oxacillin, it had gained a bactericidal action.[21]

Given the antimicrobial properties of tea, its high safety profile, and its potential ability to strengthen the effectiveness of antibiotics, patients should be advised to drink at least a cup (and preferably more) of green tea daily as part of a treatment plan for dermal and intestinal infections, and in instances where beta-lactam antibiotics are prescribed.

Allium sativum (Garlic)

An inhibitory synergism was observed when garlic was combined with vancomycin. Both freeze-dried, freshly mashed Spanish *Allium sativum* (garlic) bulb and its constituent allicin substantially reduced the MIC of vancomycin for vancomycin-resistant enterococci (VRE) with a synergistic effect on all but three of the VRE tested. The inhibitory concentration of garlic corresponded to a single clove of fresh garlic taken on an empty stomach.[22]

Garlic has been used medicinally for thousands of years. It was fed to Egyptian slaves to maintain their health, and the Romans used garlic for gastriointestinal (GI) disorders, asthma, and consumption, and as a vermifuge. It had a reputation of value against the plague. Raw garlic is a common home remedy for upper respiratory-tract infections.[22] In a Russian study, garlic removed symptoms from all patients with giardia in 24 hours, and removed any indication of giardia in stool within 72 hours at a dose of 1 mg/ml twice daily of the aqueous extract or 0.6 mg/ml commercially prepared garlic capsules.[22]

Although other human trials of its antimicrobial action are lacking (at least in English), researchers claim that its antimicrobial action is comparable to that of standard antibiotics based on pharmacological studies.[10] Garlic was effective against a plethora of Gram-positive, Gram-negative, and acid-fast bacteria including *Pseudomonas*, *Proteus*, *S. aureus*, *E. coli*, *Salmonella*, *Klebsiella*, *Micrococcus*, *Bacillus subtilis*, and *Clostridium* in vitro.[23] It was antifungal against many fungi including *Candida*, *Torulopsis*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, *Trichosporon*, and *Rhodotorula* in vitro. Studies with aged garlic (which has no allicin or allicin-derived constituents) lacked in vitro activity but when given to infected mice, the number of pathogens was reduced up to 80%.[24] In vitro studies show activity against influenza A and B, cytomegalovirus, rhinovirus, HIV, herpes simplex virus 1 and 2, viral pneumonia, and rotavirus.[22]

Figure 30–3. *Allium sativum* (garlic)

An interesting aspect of garlic is that it preferentially inhibits enterobacteria and has a much-reduced inhibitory effect on the benefi-

cial intestinal microflora. Thus at the same dose, garlic had 10 times the inhibitory effect on *E. coli* than on *Lactobacillus casei*.

The antibacterial effect of garlic is widely attributed to allicin, and garlic extracts kept at room temperature have a greatly reduced antibacterial effect.[22] Freshly mashed garlic potentiated vancomycin at a dose equivalent (assuming a 1:1 activity) to a single clove taken on an empty stomach. We strongly recommend that fresh garlic routinely be added to treatment protocols for intestinal and respiratory infections, especially in patients taking vancomycin. Where possible, patients should take several cloves of pressed garlic daily, raw or added just before the food is removed from heat to preserve its potency (cooking garlic has repeatedly been shown to eliminate its antimicrobial activity).[25] For some patients, garlic capsules standardized to allicin content may be the most efficient mode of administration.

Grifola frondosa (Maitake)

Maitake is a tasty food that is widely available dried, and increasingly available fresh in health food stores. It has a long history of medicinal use, primarily in Asia, to improve spleen and stomach ailments.[26] There are no human studies on maitake's antimicrobial effects, and most maitake research has been on various fractions of the mushroom typically administered intravenously. Studies show that some of its constituents are antimicrobial, and maitake D-fraction significantly boosted the effectiveness of vancomycin in mice inoculated with *Listeria monocytogenes* compared to both vancomycin alone and to controls. Mice administered the combination showed a 60% survival at day 10 compared with a 100% mortality in untreated mice at day 3.[27] Grifolin, another constituent, demonstrated strong in vitro activity against acid-fast bacteria as well as two species of mycobacterium but was inactive against Gram-negative bacteria such as *Bacillus anthracis*, *B. dysenteriae*, and *Salmonella typhimurium* at comparable dilutions.[28]

Maitake was not widely used as a botanical antimicrobial in traditional medicine, and it has an unclear scientific picture as an orally administered antimicrobial. As a result, we would not at this point recommend it to increase the effectiveness of antibiotics. However, a patient who is already taking a maitake preparation as an immune modulator, or who cooks with maitake, should definitely be encouraged to continue his or her maitake intake during a course of antibiotics.

Silybum marianum (Milk Thistle)

Silybin, one of *Silybum marianum* (milk thistle) seed's constituents, is a bacterial multidrug resistance pump inhibitor.[29] The antimicrobial aspects of milk thistle have not been studied, and its historical use was primarily as a bitter and a hepatoprotectant. However, milk thistle is extremely safe and may also reduce the hepatotoxicity of antimicrobials, though its ability to ameliorate side effects of drugs has only been established for antipsychotics and to some extent with tacrine.[30,31]

Silybinin, one of milk thistle's active constituents, was shown to inactivate one of the efflux pumps responsible for antibiotic resistance. In the test model, it enhanced the antimicrobial effect of berberine. We think patients should be encouraged to take milk thistle both while taking herbal antibiotic formulas and while taking prescription antibiotics, particularly when these drugs have a history of being hepatotoxic.

Mahonia spp. and *Berberis* spp. (Berberine-Containing Plants)

Hydrastis canadensis (goldenseal), *Mahonia aquifolium* (Oregon grape), *Berberis* spp. (barberry), and *Coptis* spp. (goldthread) contain berberine in their roots and stem bark. These berberine-containing plants have a long, worldwide history of use in a wide range of infections.

The leaves of these plants contain flavonoids that, tested alone, do not have antimicrobial action but strongly potentiate the action of berberine against MRSA cells. In one experiment, the flavonoid (5'-methoxyhydnocarpin) strongly increased the levels of berberine in the bacterial cells indicating that the compound effectively disabled the bacterial resistance mechanism against the berberine antimicrobial.[32] This flavonoid combined with a porphyrin constituent form potent synergistic couples with subinhibitory concentrations of berberine against MRSA.[13] Berberine also has an anti-adhesive effect.[33,34] Berberine-containing plants are highly complex, and research confirms that the whole plant is superior to the isolated berberine constituent at inhibiting microbes.[35]

Traditionally, aboveground parts of most berberine-containing plants were rarely used internally, except perhaps as ceremonial emetics and topically in ointments. We have no historical knowledge of any other internal use. Thus, while we often use berberine-containing plants in various infections, we would not consider adding leaf preparations to formulae until there is significantly more information on the benefits and detriments of the leaf. In contrast, we would definitely consider combining berberine-containing plants with herbs that have a compatible traditional history of use *and* indications of an ability to inhibit efflux pumps and potentiate the antimicrobial action of berberine. These combinations may aid in overcoming microbial resistance while benefiting from the wisdom contained in the traditional uses of the plants. We mentioned milk thistle above, and additional possible beneficial combinations might include *Scutellaria* spp., *Lonicera japonica*, and others discussed below.

Lonicera japonica (Honeysuckle)

Honeysuckle has a long history of use in Chinese formulas for cold and flu. It is not usually paired with berberine-containing plants in their patent formulae, but many Western herbal formulae use berberine-containing plants for sinus infections and respiratory ailments. Honeysuckle appears to contain the same flavolignan that potentiated berberine by disabling the drug efflux pump.[36] Thus, Western berberine-containing formulae might be improved by the addition of honeysuckle. Additional benefits might accrue if these formulae are continued where antibiotics are prescribed to address sinus infections and respiratory ailments.

Hydnocarpus aureus (chaulmoogra) seed oil, an Indian plant medicine historically used to treat leprosy and other chronic infections, also contains methoxyhydnocarpin.[15] Both chaul-

Figure 30–4. *Lonicera japonica* (honeysuckle) may disable one of the mechanisms of antibiotic resistance
Photo by Brian Hunter, www.huntergrafx.net

moogra and *Lonicera japonica* (honeysuckle) contain hydnocarpin that inhibits the drug efflux pump.[37]

Scutellaria spp. (Skullcap)

Baicalin, a *Scutellaria* spp. (skullcap) flavonoid, reduced dramatically the MICs of benzylpenicillin against MRSA and penicillin-resistant *S. aureus* (PRSA) (125 to 4 and 250 to 16 mcg/ml, respectively). It also potentiated the bacteriocidal effect of ampicillin, amoxycillin, benzylpenicillin, methicillin, and cefotaxime.[38]

Skullcap is another poorly researched plant. There are no clinical studies on its medicinal effects, and there are few studies of the whole plant. Instead, most research is on its isolated constituents. The plant has a worldwide history of traditional use, however. Various Chinese patent formulae combine *S. baicalensis* (Chinese skullcap) with *Coptis chinensis* (containing berberine), *Atractylodes* spp., or honeysuckle. Western herbal practitioners use the aboveground portions of *S. lateriflora* and other Western species, primarily as a nervine. Native Americans used the herb as a febrifuge, for diarrhea, and to prevent smallpox.[39]

Methoxyflavones from the leaf of Chinese skullcap showed significant in vivo anti-influenza activity in mice, and administered orally, one flavone reduced lung virus titers of influenza virus to a degree comparable to amantadine.[40] Another skullcap leaf flavone (F36) had the most potent in vitro activity against influenza virus sialidase compared with flavonoids isolated from 103 plant species. It significantly inhibited the virus's ability to infect cells and inhibited viral replication completely.[41] Chinese skullcap root decoction has significant antibacterial activity.[42–44] Chinese skullcap root enhances the bacteriostatic effect of goldthread and licorice, though its effect was concentration dependent.[45]

Both skullcap herb and Chinese skullcap root contain baicalin that dramatically potentiated benzylpenicillin's effect on MRSA and PRSA and potentiated the action of ampicillin, amoxycillin, benzylpenicillin, methicillin, and cefotaxime. It is likely that all species of skullcap herb also contain the antiviral methoxyflavones found in the leaf of Chinese skullcap.

Based on its long history of use, we think skullcap herb or root is an appropriate component of formulas for viral and bacterial respiratory infections, and should be used as a potential support during the administration of antibiotics for those types of ailments.

Arctostaphylos uva-ursi (Uva Ursi)

An extract of *Arctostaphylos uva-ursi* (uva ursi) leaf markedly reduced the MICs of beta-lactam antibiotics, such as oxacillin and cemetazole against MRSA. Corilagin, one of uva ursi's constituents, reduced MICs of various beta-lactams by 100- to 2,000-fold although it did not affect all of the antimicrobial agents tested. Corilagin had a synergistic effect with oxacillin, and showed a bactericidal action when added to the growth medium with oxacillin.[46]

Uva ursi has a long and well-supported history of use in cystitis. In a double-blind trial of women with recurrent cystitis, those taking uva ursi extract for one month had no further cystitis episodes in the following year.[47] In contrast, 23% of women in the placebo had at least one cystitis episode in the following year. Arbutoside in uva ursi is metabolized and excreted in the urine as the antimicrobial compound hydroquinone.[48]

In vitro, uva ursi enhanced cell aggregation of various *H. pylori* strains and showed a remarkable bacteriostatic effect.[49] A decoction of uva ursi increased remarkably the hydrophobicity of 40 strains of *E. coli* and 20 *Acinetobacter baumannii* strains, although its bacteriocidal action was relatively low. Thus, uva ursi appears to have the ability to change the surface

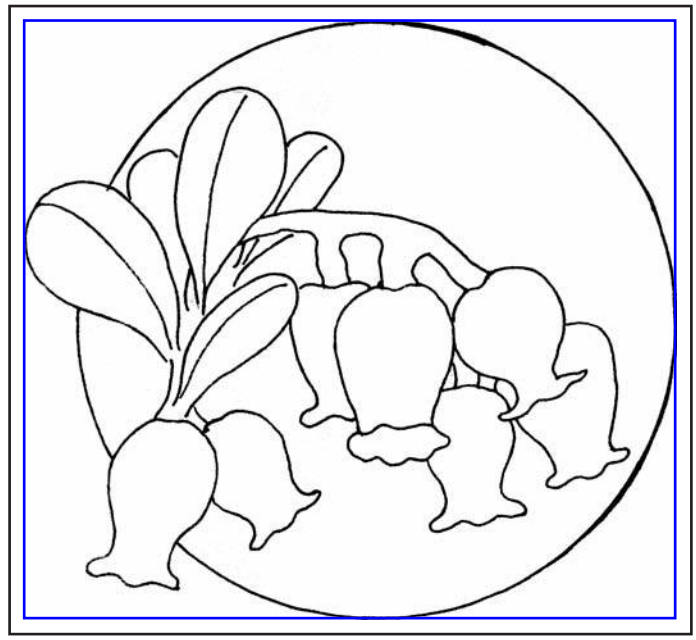

Figure 30–5. *Arctostaphylos uva-ursi* (uva ursi)
Drawing by Kathy Abascal, BS, JD.

properties of Gram-negative bacteria, perhaps allowing for easier aggregation and excretion of the bacteria in, for instance, the urine.[50] Uva ursi potentiated beta-lactam antibiotics in vitro, and its constituent corilagin[51] reduced the minimum inhibitory concentrations of various beta-lactams 100- to 2,000-fold. Corilagin was synergistic with oxacillin, and became bacteriocidal in its presence. We suggest that patients under treatment with antibiotics for urinary tract infections take uva ursi as a supportive adjunct.

Hypericum perforatum (St. John's Wort)

Hyperforin, a St. John's wort (*Hypericum perforatum)* constituent, showed strong bacteriocidal effects on Gram-positive bacteria, and both MRSA and PRSA were susceptible to hyperforin. The MDRSA was resistant to several penicillins, cephalosporins, erythromycin, clindamycin, ofloxacin, gentamicin, and piperacillin/tazobactam.

St. John's wort is presently used to treat skin injuries, burns, and neuralgia as well as depression. These uses stem from traditional Greek medicine.[52] Only its use in depression has been the subject of clinical studies. However, hyperforin, one of its constituents, inhibited all Gram-positive bacteria tested at concentrations as low as 0.2 mcg/ml in vitro but did not inhibit Gram-negative bacteria or *Candida albicans.* Oral administration of typical doses of St. John's wort results in serum levels of up to 500 ng/ml of hyperforin, enough to support its use as an internal antimicrobial, and researchers suggest that there is a sound basis for the use of St. John's wort in infected wounds and eczematous skin lesions.[53] In vitro studies do not show that hyperforin affects drug efflux pumps; however, they do show that methicillin- and penicillin-resistant *S. aureus* were sensitive to hyperforin. St. John's wort may as a result be very useful in accomplishing a complete healing of infected wounds.

Figure 30–6. *Hypericum perforatum* (St. John's wort)

Atractylodes lancea and *Stephania japonica*

Atractylodes lancea (cang-zhu atractylodes) contains sucroses that modulated MDR in vitro as strongly as the standard drug verapamil, whereas an alkaloidal extract of the vines of *Stephania japonica* (stephania) showed MDR-reversing activity.[54,55]

Both of these herbs have a long history of use in traditional Chinese medicine, and both have shown an ability to reverse microbial multidrug resistance. Atractylodes is combined with *Coptis* spp. (Chinese goldthread) in some Chinese patent medicines, and is used to treat diarrhea, fatigue, and vomiting. Stephania is diuretic and is used in fever and diarrhea. However, we do not have much clinical experience with these herbs. We suggest that it would be appropriate to use them in accordance with their historical use to help overcome drug resistance and resistant microbes.

Acorus calamus (Calamus)

A constituent of *Acorus calamus* (calamus) rhizome, acorenone, strongly inhibited a strain of *S. aureus* that had a resistance to 10 common antibiotics. Acorenone combined with chloramphenicol strongly inhibited the enzyme the bacteria uses to overcome the antibiotic.[56]

At present, calamus is most often used for digestive disorders. The Eclectic physicians,[57] however, used it topically to treat indolent ulcers.[58] Research shows that calamus inhibits a variety of fungi and is nematocidal. Calamus potentiated chloramphenicol in vitro, and strongly inhibited MRSA. Calamus may prove helpful in indolent ulcers not responding to treatment. *Note:* When taken internally, only preparations made from the North American variety of calamus should be used as other varieties contain a carcinogenic compound, asarone.

MISCELLANEOUS REPORTS

Nepeta cataria (catnip) herb inhibited the enzymatic activities associated with the virulence of methicillin-resistant and methicillin-sensitive strains of *S. aureus* equally. Slime production has been associated with *S. aureus* drug resistance. Catnip at sub-MIC doses also significantly reduced the adherence of *S. aureus*.[59]

The volatile oil of *Nigella sativa* (nigella) seed showed prominent in vitro activity against eight MDR strains of *Shigella flexneri*.[60] *Swertia chirayita* (chirata), used as an anti-leprotic, was tested against nine selected pathogens having characteristics common to *Mycobacterium leprae*. Dapsone in combinations with *S. chirata* improved anti-leprotic activity.[61]

Eleven plant flavonoids exerted an inhibitory effect against MRSA. Of these, baicalein, myricetin, quercetagetin epigallocatechin, and epigallocatechin gallate showed potent bactericidal activity.[62] Baicalein is found in skullcap but in even higher concentrations in *Plantago major* (plantain), an herb with many therapeutic applications. Myrecitin is found in uva ursi, tea, witch hazel (*Hamamelis virginiana*), and many other plants. Quercetagetin is found in at least one species of acacia, *A. catechu*. Epigallocatechin is found in *Camellia* spp., *Acacica nilotica* (acacia), and *Vaccinium myrtillus* (bilberry).[63]

MALARIA, DRUG RESISTANCE, AND HERBS

A number of herbs appear to moderate malarial drug resistance. Various species of *Artemisia* have a long history of effective use as antimalarial agents. *Artemisia annua* (sweet wormwood; qinghao

in Chinese) leaf has a long history of use as an effective antifebrile agent and possibly for treating malaria, though this disease category is not clearly delineated in traditional Chinese medicine. Therefore, it is somewhat difficult to determine to what extent it was used to treat this ailment. Artemisinin from qinghao yields dihydroartemisinin in vivo, which has a potent antimalarial effect. Qinghao's constituents completely eliminated *Toxoplasma gondii* in tissue culture.[64] *A. absinthium* (wormwood) herb is used primarily to treat chronic fevers, swellings, and inflammation of the liver.[65] It has also been shown to kill malaria and various amoebas in vitro.[65,66]

Another herb that is quite useful in malaria is *Khaya grandifolia*, an herb widely used in West Africa to treat fevers. The bark and seeds of Khaya were active in vitro against *Plasmodium falciparum*. Both the crude extract and a number of its liminoids were active against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains. One of its liminoid consituents, gedunin, had an additive effect when combined with chloroquine.[67] A hexane extract caused about 91% chemosuppression of *P. berghei berghei* in vivo and IC50 values comparable to the reference drug chloroquine diphospate against a multidrug-resistant clone and Nigerian *P. falciparum* isolates.[68]

Another traditional treatment for malaria is the shrub *Cryptolepsis sanguinolenta*, which is reported to be clinically effective. One of its constituents, cryptolepine, was highly active against a multidrug resistant (K1) strain of *P. falciparum*. In a four-day suppression test, there was, however, no significant reduction in parasitaemia in *P. berghei*–infected mice treated with cryptolepine.[69]

Note that this discussion of herbs and malaria only scratches the surface of the information regarding herbs and the prevention and/or treatment of malaria; see chapter 22 on malaria treatment. The discussion here is intended simply to pique your interest in the topic, and to underscore research showing that herbs can help overcome many types of drug resistance in microbes.

SAFETY OF DRUG–HERB COMBINATION

As a rule, herbs seem to combine safely and effectively with antibiotics. None of the research shows any tendency for the herbs to increase the toxicity or the side effects of antibiotics. Only two cautionary notes need be made: there is an indication that dandelion, because of its high potassium content, may reduce the effectiveness of quinolone antibiotics, such as ciprofloxacin.[70] The findings on this were somewhat equivocal as dandelion did not change relative bioavailability of the drug. Second, in one clinical trial, tetracycline and berberine appeared to interfere with one another when given simultaneously (probably due to complexing in the gut)—so patients should be warned not to take these compounds at the same time.[71]

HERBS AND ANTIBIOTICS: A PRELIMINARY SUMMARY

The foregoing analysis leads us to draw several conclusions regarding herbs and antibiotic resistance. First, it has strengthened our belief that herbs, used in accordance with traditional wisdom, can be of great value in treating infections ranging from the simple cold to malaria. An appropriate use of herbs in early stages of more benign infections can save antibiotics for cases where they alone will effect a cure, thereby reducing the exposure that may cause antibiotic resistance. Second, where herbal treatments fail to cure and antibiotics are prescribed, the herbs should not automatically, or even usually, be abandoned. Third, where antibiotics have been the first treatment but are failing, herbs should be considered as a possible synergist to help the antibiotic to accomplish its work.

DRUG RESISTANCE AND CHEMOTHERAPY

Drug resistance is a complex issue that affects more than antibiotics. Throughout the living world, cells have developed a number of variations on a theme to protect themselves from toxic chemicals. The central concept is a simple pump that moves toxins out of cells. Everything from bacterial to human cells contains such transmembrane pumps. The most classic example in humans is known as P-glycoprotein (P-gp). When human cells become neoplastic, they continue to use these pumps, which can be used to move multiple kinds of chemotherapy drugs out of the cancer cells. This is a major way that cancer cells become resistant to multiple drugs all at once, and there is also a growing need for natural products to counter resistance to drug therapies in the most serious cases.

We now review preclinical data suggesting that herbs might be able to mitigate the chemotherapy resistance problem. Clinical data are still not available to support application of these data to humans in a rigorous fashion, but some clinicians are beginning to see interesting results when combining natural products of many types with chemotherapy regimens. There are many other reasons to believe that chemotherapy might still not be the solution to cancer, as discussed in *Questioning Chemotherapy* by Ralph Moss.[72] Thus we can provide only an introductory, logical framework here around which later clinical data may be draped as the potentially beneficial interactions of certain herbs and chemotherapy are more fully investigated.

PLUGGING P-GLYCOPROTEIN

Many normal human cells, if not all, contain a variety of pumps that remove unwanted toxins and metabolic byproducts from the cells. As mentioned, one of the best known and studied of these is P-gp, coded for by a gene located on chromosome 7 in humans.[73] This pump is composed of two glycoprotein components and requires ATP to function. P-gp is able to remove a large variety of toxins from healthy cells to help protect them from damage.

P-gp is particularly important in helping maintain the blood–brain barrier and also occurs widely in the small intestines, where it prevents absorption of toxins in the first place. P-gp inhibitors can have a dark side because they may also interfere with absorption of beneficial agents. A great deal of research is focusing on botanicals such as St. John's wort and grapefruit juice that can decrease levels of pharmaceutical drugs, at least partially as a result of decreased absorption of these agents due to intestinal P-gp stimulation.[74] Theoretically, these herbs might also potentiate multidrug resistance, though this has never been shown to occur, in vitro or in vivo. We focus here primarily on P-gp inhibitors that may increase therapeutic levels of various drugs by decreasing their efflux from intestinal cells back into the gut lumen. This has yet to be shown for any P-gp inhibiting herb, but caution is warranted.

Neoplastic cells generally retain their ability to express P-gp, though the levels are frequently low. Most investigated cancer cell lines that overexpress P-gp develop resistance to multiple chemotherapeutic agents.[75] In other words, the cells start producing more and more pumps to help remove toxins, particularly chemotherapy drugs. Mounting evidence directly implicates exposure to chemotherapy drugs in causing this amplification of expression.[76] Basically the killing effect of the chemotherapy acts as a selective pressure, and those cells able to amplify P-gp expression are more likely to survive and spread, leading to increasing multidrug resistance.

Because P-gp is fairly well characterized and understood, and because multidrug resistance due to P-gp expression is common in cancer cell lines, most research on botanical agents that

might reverse chemotherapy resistance has focused on P-gp. The fact that various plant compounds can inhibit P-gp and thus reduce or reverse resistance is an evolutionarily logical concept. P-gp will remove various plant compounds just like other types of molecules. The plants then evolve various compounds that interfere with P-gp function in an attempt to counteract the pumping effect, particularly when the pump is removing a plant toxin that helps reduce browsing on the plant. The plant compounds normally pumped by P-gp may act as competitive inhibitors of the pump as they "fight" with the drugs for removal, allowing chemotherapy agents to remain in the cell longer. Additionally, the plant inhibitors of P-gp may slow the pumps so that chemotherapy drugs stay present longer.

No clinical trials could be located on the use of herbs to decrease or reverse multidrug resistance related to P-gp in cancer patients. This is unfortunate given the high incidence and devastating consequences of multidrug resistance in cancer and the large potential for benefit from a botanical approach.

CURCUMIN: MULTIFACETED BOTANICAL P-GP BLOCKER

The spice and medicinal plant *Curcuma longa* (turmeric) contains the compound curcumin. See Figure 30-7. Curcumin has anti-inflammatory and antineoplastic activity, and has been demonstrated to inhibit P-gp in vitro.[77] Curcumin's antineoplastic activity was not inhibited by the presence of P-gp in one in vitro study, whereas another suggested high P-gp expression decreased the cytotoxicity of curcumin toward normal hepatic cells.[78,79] Further study is warranted to determine if curcumin has synergistic effects with chemotherapy drugs in patients with normal and multidrug-resistant cancer.

It is possible that curcumin works through another mechanism unrelated to P-gp. Some tumors produce high levels of glutathione S-transferase (GST), an antioxidant enzyme that might protect the cells from oxidative injury by chemotherapy agents. Curcumin appears to inhibit this enzyme in vitro in cancer cells, potentiating the effects of the chemotherapy drug doxorubicin, even when P-gp levels are high.[80] When compared to several other GST inhibitors in vitro in neoplastic cells, curcumin was by far the strongest.[81] Resistance to chemotherapy drugs is commonly associated with elevations in cellular levels of the inflammatory mediator nuclear factor kappa B (NFkB), a process that is inhibited by curcumin, reducing drug resistance in cancer cells.[82] It is very typical for herbal compounds to have multiple mechanisms of action.

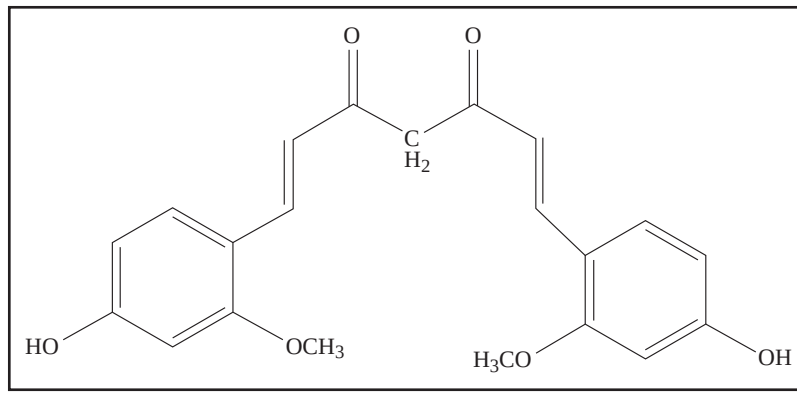

Figure 30–7. Curcumin

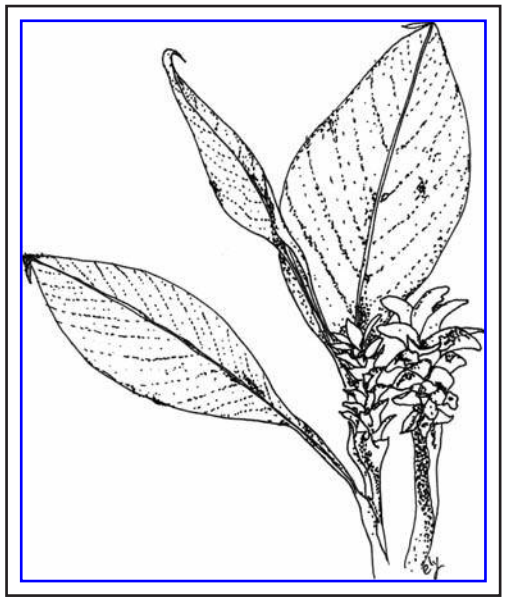

Figure 30–8. *Curcuma longa* (turmeric)
Drawing ©2002 by Eric Yarnell, ND, RH.

Clinical trials on curcumin specifically related to cancer are sparse. One uncontrolled clinical trial conducted in Taiwan involved patients with one of five types of premalignant lesions with a strong tendency to become cancerous.[83] Each patient took up to 8 g of curcumin per day for three months and showed no signs of toxicity. Doses higher than 8 g were not possible because the doses became too bulky to be acceptable to the patients. Lesions were reversed in a few patients, though two patients progressed to develop full-blown cancer. Preliminary data from human trials also suggest that topical application of curcumin can have a beneficial effect on skin cancers.[84] No trials were located showing that curcumin could modulate the effects of chemotherapy drugs in humans.

WHOLE PLANTS VERSUS ISOLATED CONSTITUENTS AND CHEMOTHERAPY RESISTANCE

Several berberine-containing plants, including barberry (Oregon grape), goldthread, and *Xanthorrhiza simplicissima* (gold root), have been shown to inhibit drug-resistance pumps in microbes, as discussed above. Not surprisingly, berberine itself has also been shown in some research to interfere with chemotherapy-resistance pumps, including P-gp.[85] One possible benefit may be that berberine-containing herbs might increase penetration of various chemotherapy drugs through the blood–brain barrier, thereby enhancing chemotherapy's effects against intracranial tumors. However, in one study, berberine failed to show any modifying effect on camptothecin levels in the brains of rats.[86]

At least one study has found that isolated berberine actually enhances expression of P-gp in rat hepatoma cells.[87] These results have been contradicted by other studies as mentioned above. It is possible that isolated berberine may have different effects than whole herbs or whole herb extracts, as discussed previously and in important ongoing research into whole barberry or Oregon grape root.[32] Various trials suggest berberine has direct anticancer properties, making it and the herbs that contain it good targets for research not only to treat cancer but also to potentiate chemotherapy.[88]

Another example of the synergistic effects of constituents within a plant relevant to reducing chemotherapy resistance is *Taxus brevifolia* (Pacific yew) and *T. baccata* (English yew). These trees are the original source of important chemotherapy drugs including paclitaxel (Taxol®) and docetaxel (Taxotere®). However, other constituents in these trees that lack antineoplastic activity are strong P-gp blockers and have been shown to increase the efficacy of paclitaxel against human MDR breast cancer cells in vitro.[89] In essence, the whole plant appears to have built-in mechanisms to decrease or prevent the development of MDR in cancer cells. This calls into question the entire concept of using single-plant compounds or semisynthetic derivatives

as chemotherapy and puts great urgency into the need to look at more complex plant-derived approaches to cancer.

An additional aspect of the paclitaxel example is that the oral bioavailability of this and similar compounds is very low, requiring administration by injection. However, a synthetic P-gp inhibitor, MS-209, has been shown to greatly increase oral absorption of paclitaxel in mice.[90] Oral paclitaxel was without activity when given orally by itself to mice with melanoma, but had strong activity when combined with MS-209. This provides a further basis for considering the use of whole plants or whole plant extracts to fight cancer. Clinical trials are urgently needed investigating the effect of natural P-gp inhibitors on absorption and activity of paclitaxel and docetaxel, as well as the effects of whole yew extracts, in cancer patients.

CRUCIFEROUS VEGETABLES

The isothiocyanate known as indole-3-carbinol (I3C) is a potent phytochemical found in cabbage and other cruciferous vegetables. This compound stands at the crossroads between nutrition and botanical medicine. I3C breaks down in the gastric juices to various metabolites including diindolylmethane (DIM) and many other compounds. Initial testing shows that some of these metabolites can reverse multidrug resistance in murine melanoma cells in vitro.[91] Mice with MDR melanoma showed greater response to chemotherapy when simultaneously given I3C compared to those given only chemotherapy, though there was no clear effect on survival times.

Cruciferous vegetables have repeatedly been shown to reduce the risk of cancer in epidemiologic research, particularly for GI cancers. It is possible that regular intake of these vegetables may have other benefits in patients with multidrug-resistant cancer. Future research is clearly warranted.

OTHER MDR MODULATORS

The list of preclinical research studies on botanical inhibitors of MDR is large and rapidly growing. Table 30-3 summarizes a few of the more intriguing recent studies in this realm. Clearly there are numerous phytochemicals that may prove to be useful in reducing drug resistance in neoplastic cells.

There are numerous other mechanisms of reducing chemotherapy resistance. For example, some breast cancer cells hyperexpress NF-kappa-B, a key inflammatory mediator, which appears to reduce their sensitivity to paclitaxel. Compounds in *Tanacetum parthenium* (feverfew) leaf have been shown to block NF-kappa-B and thereby partially or totally restore paclitaxel sensitivity.[92] Compounds in garlic bulb, particularly ajoene, have been shown to potentiate cytarabine and fludarabine in human acute myeloid leukemia cells previously resistant to these drugs in vitro.[93] These compounds actually enhance the apoptosis-inducing effects of the drugs, and do not apparently act through efflux pump inhibition. Saponin extracts from *Panax ginseng* (Asian ginseng) root were shown to drive acute myeloid leukemia cells to replicate, thereby making them more susceptible to various chemotherapy agents.[94]

This plurality of effects of many herbs on chemotherapy resistance suggests the possibility that complex formulae combined with cancer therapy may prove fruitful. This approach is often undertaken in Asia today, though the documentation of the outcomes of studies in this vein is only just beginning to become available in English and usually in abstract form only.

Table 30–3. Miscellaneous Natural P-gp Inhibitors

Latin Name (Common Name), Part Used, Family	*Cell or Animal Model*	*Notes*
Erythroxylon perveilli, *E. rotundifolium* (coca) leaf, Erythroxylaceae[a]	Cervical cancer cells in vitro	Reduced P-gp-mediated multidrug-resistance; tropane alkaloids appeared to be most active.
Quercetin, a ubiquitous flavonoid[b]	Doxorubicin-resistant human breast cancer cells	Reversed drug resistance dose dependently in vitro
Ficus citrifolia (Guadalupe ficus) leaf, Moraceae[c]	MDR human leukemia and sarcoma cells	Reversed drug resistance and enhanced killing effect of vinblastine
Euphorbia serrulata (upright spurge) and related spp., Euphorbiaceae[d]	MDR mouse lymphoma cells	Jatrophane diterpene polyesters reversed MDR in vitro
Camellia sinensis (tea) leaf, Theaceae[e]	Human MDR colorectal cancer cells	Polyphenols reduced P-gp-mediated MDR and potentiated effects of vinblastine.

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c. Simon PN, Chaboud A, Darbour N, et al. Modulation of cancer cell multidrug resistance by an extract of Ficus citrifolia. *Anticancer Res* 2001;21(2A):1023–1027.

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A wealth of preclinical research supports the concept that herbs can reduce resistance of cancer cells to chemotherapy drugs. Now clinical trials are required. Many of the herbs showing benefit in the test tube also have direct antineoplastic activity of their own, or have minimal adverse effects. Thus, there is support for the approach of combining these herbs with chemotherapy regimens even before research data have accumulated. Some clinicians will prefer a more conservative approach, awaiting trial data.

For those already prescribing herbs to their patients when a patient's life is threatened by MDR cancer, we suggest that turmeric and cruciferous vegetables be included in the patient's diet on a regular basis. Capsules providing curcumin might also be suggested at a dose of 500 mg three times per day, usually combined with bromelain to enhance absorption and taken away from meals. A tincture of Oregon grape root taken at a dose of 3–5 ml three times per day away from food is also likely to have some benefit. A more complex formula for expert herbal practitioners is suggested in Table 30-4, and includes some herbs not discussed in depth here but for which supportive preclinical data exist. We eagerly anticipate the day when oncologists

and natural medicine professionals work together to develop the most effective program for patients, and when cancer resistance is considered a problem that can be readily handled.

TOXINS CAN CAUSE DRUG RESISTANCE

In this last section, we provide a brief summary of the mechanisms of drug resistance. The research on cellular drug pumps is proceeding at a rapid pace, and involves highly technical information. These studies contain interesting data but are not reviewed in detail here. Instead, we create a "working picture" to help clinicians steer clients away from using compounds that tend to increase resistance, and instead steer them toward compounds that might reduce drug resistance.

It is evident that cells can activate a variety of drug pumps to protect them from hostile chemical attacks.[95–99] These pumps are at work in drug resistance, and are used to minimize the damage caused by toxin exposure. Once activated, a pump can usually remove a wide variety of apparently unrelated chemicals from the cell. Bacteria exposed to pesticides, disinfectants, and household cleaners, for example, turn on pumps that also pump out antibiotics and chemotherapy agents. This activation is passed on to future generations, and bacteria also communicate this information to each other with surprising ease and speed.[1]

Studies of aquatic organisms show that very low doses of pesticides can turn on drug pumps, and pump activation is now being used to more accurately assess pesticide effects in the environment.[100] Research indicates that exposure to minute amounts of toxins increases drug resistance in bacteria that colonize the intestine in primates.[101] The study found that mercury leaching from dental fillings increased the antibiotic resistance of oral and intestinal bacteria compared to controls.[101]

There is sufficient information on toxin-induced resistance to indicate that we should exercise extreme caution in our use of poisons because their effects range far beyond the simple problem at hand. Spraying a house plant with an insecticide to kill mites may create colonies of antibiotic resistance in a variety of organisms in that home. Casual use of disinfectants like triclosan—incorporated in a wide variety of products today, from soap to cutting boards to toys—appears to have the same effect. We consistently ask our patients to choose organic foods to minimize their exposure to toxins. Given our new knowledge, we should more strongly advocate that patients on antibiotics or chemotherapy avoid pesticides and other toxins because they may impede healing by causing drug resistance.

PHARMACEUTICALS INDUCE RESISTANCE

Toxins and chemicals used for nonmedicinal purposes that induce resistance to a variety of drugs are certainly a problem. Another troublesome prospect is that some medications may induce multidrug resistance. In one study, the prescription drugs clofibrate, used to treat dyslipidemia, and ethacrynic acid, a diuretic (both patterned on the structure of the herbicide 2-4-D and excreted unaltered through the kidneys), led to drug resistance in uropathogenic *Escherichia coli* strains in vitro.[102] These drugs induced antibiotic resistance at concentrations equivalent to those found in the urinary tract of experimental animals. The study cautions that prescription drugs may undermine the success of ongoing antibacterial treatments, and should be used cautiously as we tend to underestimate and do not know the full collateral effects of these drugs.

The methods used in this study conformed to current scientific standards and confirmed prior knowledge of how the activation of a particular DNA locus in *E. coli* led to antibiotic resistance according to Dr. Kim Lewis, PhD, professor of microbiology at Northeastern University, Boston).[103] He found the study credible and accurate in its design and conclusions. More research is needed to determine the magnitude of the problem of drugs inducing resistance. But it appears that there could be a serious problem of immense proportions looming, and it suggests that drugs should not be lightly prescribed but reserved for more serious situations that demand their use.

SYNERGISTIC ASPECTS OF WHOLE PLANTS MAY REDUCE RESISTANCE

Herbs show promise in helping overcome resistance. Plants are complex, their compounds interact synergistically, and many practitioners postulate that the whole plant is more than the sum of its parts. Whole plants in formulas enhance further these synergistic forces. It is wonderful to see glimmerings of scientific validation of this holistic view. Dr. Stermitz, Dr. Lewis, and their colleagues most eloquently explained this fact in one of their studies: " 'Synergy' is a popular concept in the field of herbal medicine, suggesting that plant extracts contain compounds potentiating each other's action. Possible synergy would explain many failed attempts to isolate single, active compounds from medicinal plants." The article points out that hydnocarpic acid, extracted from chaulmoogra oil (a traditional treatment for leprosy), was once considered the plant's principle active ingredient. It now appears that hydnocarpic acid is likely made more effective by at least one other seemingly impotent compound in the plant. "By extracting the 'active ingredient' from the oil, Western medicine might have missed the second essential component of the synergistic couple."[32]

Insightful research like this may mark the beginning of an era of more meaningful research into botanicals. At present, most botanical research consists primarily of quests to isolate active ingredients with an eye toward drug development, research that often proceeds even in the face of evidence that the whole plant has greater efficacy. Given the specter of drug resistance, future research may be more inclined to study traditional plant formulas and the synergistic effects of whole plants.

CAN HERBS INDUCE RESISTANCE?

A study has been published claiming that several natural products, including *Hydrastis canadensis* (goldenseal), *Echinacea* spp., *Hypericum perforatum* (St. John's wort), *Aloe vera* (aloe), and zinc, rapidly lost any antimicrobial properties and significantly increased drug resistance in microbes in vitro.[104]

Dr. Lewis pointed out three serious problems with this study's conclusions. First, currently accepted standards of testing were not followed in this study, making it virtually impossible to analyze the data. Second, though the study in particular suggested that ampicillin efficacy was being lost, the activity of ampicillin in *E. coli* depends on the growth rate, and testing a lower than minimum inhibitory concentration of the antibiotic likely caused a false result. Third, Dr. Lewis noted that the results strongly suggested the presence of persisters (or tolerant bacteria) rather than resistant bacteria.[105]

Persisters represent an unusual and elegant bacterial defense mechanism. Persisters survive exposure to toxins *without* mutating, and give rise to subsequent generations of toxin-sensitive

bacteria.[106] In contrast, resistant bacteria undergo a genetic change, and their offspring continue to display a toxin-*insensitive* trait. Persisters are found in biofilms, colonies that provide protection from toxins through the creation of slimy layers, or films, of bacteria.

Biofilms are commonly encountered clinically, and are difficult to eradicate.[13] Examples of biofilms include periodontal disease, *Helicobacter pylori* bacteria in the stomach, and bacteria-colonizing catheters. These bacteria in effect form a larger, multicellular organism to enhance survival. When an antibiotic does sufficient damage to bacteria in the film, a 'suicidal' gene is turned on that leads to cell death via apoptosis. These cells are not actually killed by the antibiotic, and they do not develop drug resistance. However, a subset of the bacteria fails to turn on the suicide gene. Instead, hidden away in the biofilm, they survive.

To the untrained eye, these bacteria might be assumed resistant because they survive the antibiotics. However, when cultured and retested, they again give rise to a colony of drug-sensitive bacteria. There is no genetic mutation that passes drug resistance from generation to generation. In Dr. Lewis's opinion, persisters were at play in the herbal study. The researchers were unaware of the phenomenon, and failed to take the necessary follow-up step of testing whether a mutation had occurred. He was quite confident that resistance had not been induced by the herbs.

We were not able to locate any other evidence that herbs or herbal extracts induce resistance. However, one study found that high concentrations of volatile oil of *Melaleuca leucodendron* (tea tree) could induce resistance in *Staphylococcus aureus* in vitro.[107] The drug mupirocin has a similar pattern of stepwise, low-level resistance induction, and that has not proved clinically relevant. However, the author noted that tea tree oil is often used in concentrations low enough to potentially fail to kill off resistant strains, and suggested that whereas tea tree oil had clinical value as a topical to eradicate multidrug resistant *S. aureus* strains, resistance was likely to arise if the essential oil were more widely used in a hospital setting.[107] Further research is needed to determine whether whole plant extracts and formula combinations are less likely to induce resistance than more refined products, like an essential oil or an isolated plant constituent.

SORTING OUT BOTANICALS AND RESISTANCE

In Mediterranean countries larger amounts of garlic, in the form of aioli and other delicacies, have been consumed on a near daily basis for millennia. At the same time, the traditional wisdom that garlic is a potent antimicrobial persists.[108] Studies conclude that garlic is strongly antimicrobial, and overcame vancomycin resistance at a dose equivalent to a human dose of a clove of raw garlic.[10,15,23,109] If garlic so rapidly lost its antimicrobial properties and so rapidly induced antibiotic resistance as suggested by the Ward study reviewed above, this effect would have been observed early in the history of antibiotics. Epidemiologists would have noted that antibiotic resistance was higher in countries where garlic is consumed regularly. Instead, other properly conducted studies show that garlic overcomes drug resistance in bacteria. And resistance is far more common in countries where environmental toxins and antibiotics are used more frequently than garlic.

The dynamic relationship between plants and microbes also speaks against the Ward study results. When we use plants as antimicrobials, we essentially borrow mechanisms the plant has developed to thwart its own bacterial and viral infections. If these defenses were so quickly overcome by microbes, the plants themselves would succumb—much as elms succumb to Dutch elm disease. The synergy that Dr. Stermitz and Dr. Lewis so elegantly prove in their studies is an important component of plant survival.[10, 29,110–112] Although bacteria may develop methods of countering an isolated compound like berberine, they have not found effective ways of dealing with

Figure 30–9. *Rosmarinus officinalis* (rosemary)

the synergistic defenses of berberine-containing plants: These plants combine the weakly antimicrobial berberine with other non-antimicrobial compounds that turn off bacterial defenses and potentiate berberine. In fact, these strategies are so well designed that some *Berberis* species are not susceptible to bacterial pathogens.[10] This, in and of itself, puts in question a study that shows that the berberine-containing goldenseal is rapidly rendered impotent by mutating bacteria.

CONCLUSION

Many herbs display a remarkable ability to overcome drug resistance in numerous, methodologically proper in vitro studies. Much research is needed to establish that these effects also occur in the human body. Nonetheless, we are convinced that herbs, used properly in accordance with traditional wisdom, will help overcome resistant bacteria. A practitioner should with confidence urge clients to avoid toxins that might induce resistance. And, a practitioner should with equal confidence use herbs judiciously as potential allies in the treatment of a wide variety of infections.

Table 30–4. Dr. Yarnell's Resistance Corrective Tincture Formula

Latin Name	*Common Name*	*Part Used*	*Percent in Formula*
Curcuma longa	Turmeric	Rhizome	20
Rosmarinus officinalis	Rosemary	Leaf	20
Berberis haematocarpa	Desert barberry	Root	20
Mahonia aquifolium	Oregon grape	Root	15
Scutellaria baicalensis	Asian skullcap	Herb and root	15
Camellia sinensis	Tea	Leaf	10
Gossypium herbaceum	Cotton root	Root	5
Panax ginseng	Asian ginseng	Root	5

Adult dose: 5 ml (1 tsp) three times per day.

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31

MODULATION OF INFLAMMATION BY BOTANICAL MEDICINES

Quieting inflammation is increasingly viewed as critical to health as research firmly establishes that virtually every chronic ailment (from Alzheimer's disease to hypertension to irritable bowel syndrome to diabetes to periodontal disease) has an aspect of chronic inflammation at its core. Though widely demonized as a result, inflammation also plays a critical role in healing. Some inflammatory processes lead to symptoms such as swelling, pain, and redness, but these are, at least initially, completely normal and protective. However, when inflammation settles in as a permanent feature, it rapidly becomes part of the problem. Often patients are given anti-inflammatory drugs for acute or chronic inflammation in an attempt to ease the suffering rampant inflammation can cause. There is a widespread belief in natural medicine that such suppressive intervention often runs counter to the healing processes of nature. Evidence that anti-inflammatory drugs actually worsen the disease processes in patients with osteoarthritis and rheumatoid arthritis support this belief.[1,2,3] Add to this the significant number of people harmed by these drugs and their enormous costs, and the necessity of utilizing alternatives becomes apparent.[4,5]

Herbal medicines offer one appealing way to reduce the use of anti-inflammatory drugs. The factors in favor of their use include a long history of use, extensive research on a number of agents, relative ease of administration, relatively low cost, and excellent safety records. It is unfortunate that some herbs have been given the moniker "anti-inflammatories," because almost none of them act like drug anti-inflammatories, either pharmacodynamically or clinically. Therefore, we propose that these agents should be referred to by a more correct descriptive phrase—inflammation modulators.

HERBS AND DRUGS ARE DIFFERENT

Herbal inflammation modulators and anti-inflammatory drugs work differently. Nonsteroidal anti-inflammatory (NSAID) drugs, one of the most common categories of such drugs, work primarily (if not exclusively) by inhibiting both isoforms of cyclooxygenase (COX-1 and COX-2). See Figure 31-1 for a review of the eicosanoid inflammatory cascade and COX's role in it. Herbal medicines, however, have never been demonstrated to act on a single enzyme or receptor. Instead, they have multiple constituents that act on multiple targets, and generally to a lesser extent than pharmaceuticals. The result is a gentler, slower onset of action coupled with vastly reduced or absent adverse effects compared to fast-acting, powerful, more toxic drugs and ultimately with long-lasting effects.

For example, *Boswellia serrata* (boswellia) was compared with valdecoxib (an NSAID) in a randomized, prospective, open-label study of osteoarthritis of the knee.[6] Boswellia improved symptoms (i.e., pain, stiffness, and mobility) after two months of treatment, a benefit that persisted one month after treatment ceased. Valdecoxib statistically improved all parameters within a month but the effect lasted only as long as the drug was taken. Numerous examples are discussed below to illustrate these critical differences and to show how herbal inflammation modulators

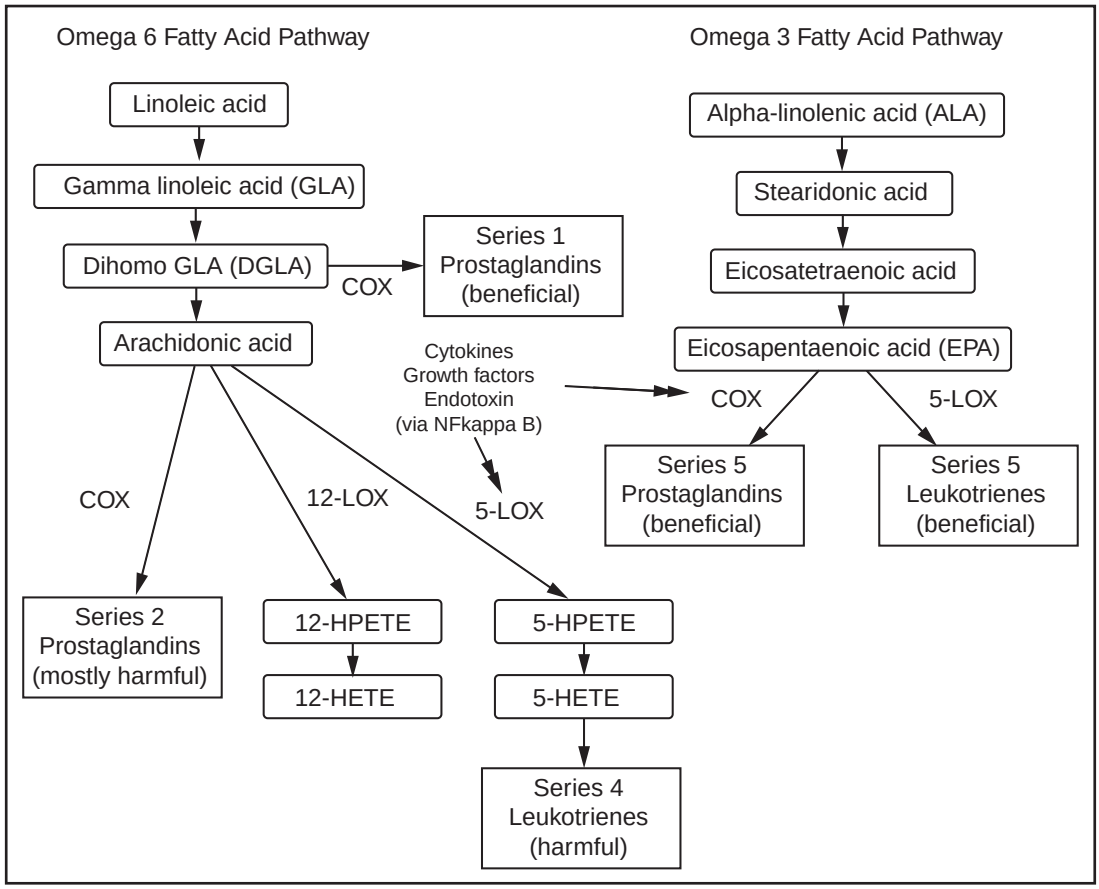

Figure 31–1. The Eicosanoid Cascade and Inflammation
COX: cyclooxygenase; HETE: hydroxyeicosatetraenoic acid: HPETE: hydroperoxyeicosatetraenoic acid; LOX: lipoxygenase
This figure gives an overview of the essential fatty acid–eicosanoid cascade and its many components. Double-headed arrows indicate induction of enzyme synthesis.

can be used effectively. Many other examples exist beyond those chosen for this chapter. Such herbs are typically discussed as an aspect of treatment in other chapters in this book.

Ginger: Inflammation Modulator

Zingiber officinale (ginger) is a tropical plant in the Zingiberaceae family and is esteemed in natural medicine around the world. The rhizome is used medicinally for many conditions characterized by excessive inflammation. Numerous studies have documented that many constituents of ginger, particularly [6]-gingerol and related molecules, inhibit 5-lipoxygenase (5-LOX), COX-1, COX-2, NF-kappa-B signaling pathway, and thromboxane synthetase, at a minimum (see Table 31-1). This wide pattern of activity is distinctly different than what is seen with NSAIDs or COX-2 inhibitors.

Ginger's action is deeper and broader than simply having multiple effects on inflammation-related eicosanoid and cytokine pathways. Indeed, a central theme in most historical descriptions

Table 31–1. A Sample of Ginger's Inflammation-Modulating Actions

What Was Studied	*What It Did*
Decoction of ginger rhizome[a]	Inhibited COX in vitro
Tincture of ginger rhizome[b]	Inhibited lipopolysaccharide-induced PGE_2 and TXA_2 release
Gingerols, diarylhepatonoids from ginger rhizome[c]	Inhibited COX and LOX in vitro
Various ginger extracts and compounds[d]	Inhibited thromboxane synthetase in vitro
Freeze-dried 70% ethanol extract of fresh ginger rhizome[e]	Inhibited serotonin-receptor-mediated inflammation in rats
Gingerol[f]	Inhibited NF-kappa-B translocation
Gingerol[g]	Inhibited NF-kappa-B-signaling pathway
Gingerol-rich aromatic extract of ginger rhizome[h]	Inhibited chemokine expression in vitro
[8]-paradol and [8]-shogaol from ginger rhizome[i]	COX-2 inhibition in vitro
Zerumbone from related plant *Zingiber zerumbet* rhizome[j]	Inhibited COX-2, iNOS, and TNF-alpha expression in vitro
[6]-gingerol and [6]-paradol from ginger rhizome[k]	Inhibited TNF-alpha production, antioxidant, in mice

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Figure 31–2. *Zingiber officinale* (ginger) root

of the herb is that it is a digestive stimulant, antiemetic, spasmolytic, antimicrobial, and diaphoretic.[7] Unlike NSAIDs, ginger actually combats gastric ulceration in animal studies.[8] Therefore, in natural medicine ginger is used not to stop inflammation but to moderate it and in some ways to potentiate it, while simultaneously addressing multiple other factors involved in the patient's healing.

Unfortunately, the available research on ginger has tended to reduce it to a far more simplistic, pharmaceutical-type agent. Besides the many trials on ginger for reducing nausea, the main area of study in humans has been on its effect in people with osteoarthritis. Both double-blind trials in this area used quite low doses for very short periods of time (a few weeks), with one

trial showing no improvement compared to placebo and significantly less symptom reduction than ibuprofen, while the other (using a slightly higher dose) showed a modest benefit over placebo.[9,10] The second trial combined a ginger extract and *Alpinia galanga* (galangal) rhizome, a close cousin of ginger. There were no serious adverse effects attributable to ginger in either trial.

A more typical approach in the actual practice of natural medicine would be to give ginger to someone with osteoarthritis who also has digestive problems, and combine it with herbs traditionally used to strengthen connective tissue such as *Equisetum arvense* (horsetail) herb or *Centella asiatica* (gotu kola) herb and root, glycosaminoglycan supplements to encourage tissue regrowth, and contrast hydrotherapy to stimulate normal healing processes, and of course remove any obvious factors that were promoting disease, such as cigarette smoking.

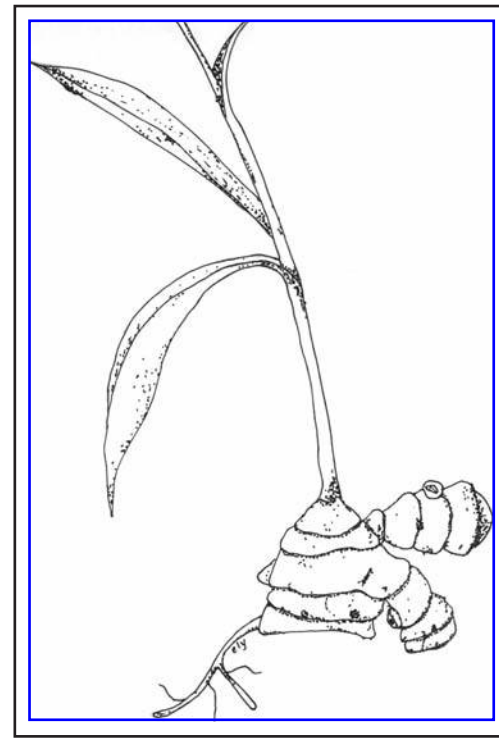

Figure 31–3. *Zingiber officinale* (ginger)
Drawing © 2006 by Eric Yarnell, ND, RH.

Ginger can also have a pronounced effect in acute or more serious chronic inflammatory conditions. A case series of people with osteoarthritis, rheumatoid arthritis, or myalgia were treated with several grams of ginger powder daily, often for years.[11] The majority had marked or moderate clinical improvement in symptoms. A double-blind clinical trial on a formula containing ginger along with an immunomodulator, *Withania somnifera* (ashwagandha) root, and two other inflammation modulators, *Boswellia serrata* (frankincense) resin and *Curcuma longa* (turmeric) rhizome, was effective compared to placebo in people with rheumatoid arthritis.[12]

To get more immediate results, which should be reserved for patients in great pain or who need some acute relief before they can focus on treating the causes, doses need to be more in the range of 2–4 g of rhizome every one to two hours or equivalent amounts in extracts (in the case of a tincture, 1–2 ml every one to two hours). For chronic problems or as a digestive tonic, doses are usually 1–3 g three times per day (or 0.5–1 ml of tincture three times per day).

Turmeric: The Golden Inflammation Modulator

Curcuma longa (turmeric) rhizome is another inflammation modulator from the Zingiberaceae family, and also native to the tropics of Central and Southeastern Asia like its cousin ginger. Much work has investigated the inflammation-modulating aspects of its diarylheptanoid constituents known as curcuminoids. A thorough review of research through 2002 found evidence that curcuminoids inhibit phospholipases, LOX, COX, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF), and interleukin-12 (IL-12).[13] Although many studies have focused specifically on diferuloyl methane (curcumin), other curcminoids and noncurcuminoid constituents of turmeric are also active inhibitors of LOX and COX.[14]

Like other herbal inflammation modulators, and unlike anti-inflammatory drugs, turmeric is not sufficiently powerful to suppress inflammatory pathways to the point that adverse effects occur. In fact, it has been used to treat people with gastric ulcers, and while it was not as effective as antacids, it did have some therapeutic effect.[15] In patients with *H. pylori* infection and functional dyspepsia, curcumin combined with pantoprazole did not eradicate the bacteria but significantly reduced dyspeptic symptoms and serologic signs of gastric inflammation that persisted two months after the seven-day treatment ended.[16] In rodents, curcumin has been shown to protect against the hepatotoxic effects of acetaminophen.[17]

Human trials have demonstrated that 400 mg curcumin three times daily can reduce postoperative inflammation as effectively as phenylbutazone and significantly better than placebo.[18] Turmeric, in varying combinations of *Withania somnifera* (ashwagandha), *Boswellia carteri*

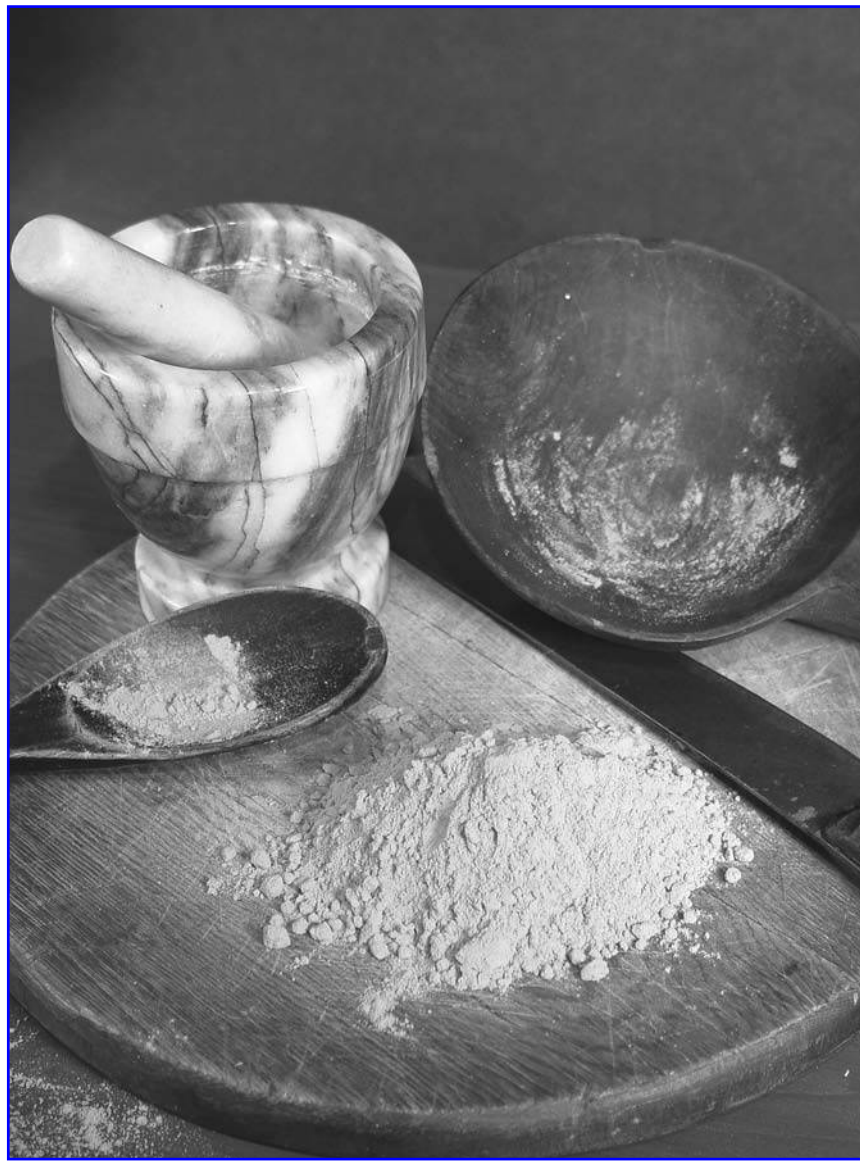

Figure 31–4. *Curcuma longa* (turmeric) powdered

(olibanum, frankincense), and ginger, has also been shown in double-blind trials to improve symptoms of osteoarthritis and rheumatoid arthritis.[19,20,21,22] In one trial curcumin 400 mg three times daily relieved symptoms of rheumatoid arthritis, though not as extensively as phenylbutazone.[23] Turmeric taken daily for 8 weeks improved symptomology in patients with irritable bowel syndrome according to a partially blinded pilot study of 207 participants.[24] Using isolated curcuminoids at a dose of 2 g daily failed to improve oral lichen planus compared to placebo in one blinded trial, though it is unknown if a whole-rhizome extract or higher dose would have worked.[25]

Turmeric, usually taken in doses of 5–30 g daily for acute problems or 3–10 g daily for chronic problems, is a useful therapy for inflammatory diseases. Because it is also a hepatoprotective herb and has antioxidant and antineoplastic activity, it can be targeted to patients with problems in these particular areas. Curcumin, which is more like a drug as its synergistic and supportive nutrients have been eliminated, should be reserved for cases where turmeric does not work or where a very rapid effect is desired. Turmeric and curcumin should not be viewed as "natural anti-inflammatories" that can be substituted for drugs that suppress inflammation in an unnatural way, but instead as very different agents with a broader range of activities, far lower toxicity (if any at all), and differences in how they affect inflammation.

Chaparral: Inflammation Modulator from the Desert

Larrea tridentata (chaparral) is a powerful native of the desert Southwest of the United States and northern Mexico. It is a member of the Zygophyllaceae family and the leaves, flowers, and seeds are utilized as medicine. It is also called creosote bush because of the sticky, aromatic resin that exudes from the plant.

Chaparral resin contains numerous inflammation-modulating constituents, including nordihydroguaiaretic acid (NDGA), a substance often used as a comparison compound in scientific studies of anti-inflammatory drugs because of its well-established 5-LOX inhibiting effects.[26] NDGA also inhibits COX and the NFkappaB transcription factor that induces inflammatory enzyme production and triggers much of the inflammatory cascade.[27,28] A methanol extract of chaparral herb has been shown to be very potent at inhibiting inflammation induced by carageenan injection into rodents.[29] A methanol extract of a related species, *L. divaricata* Cav., prevented gastric ulcers induced by necrotizing agents in rats.[30]

There have been isolated reports of hepatotoxicity in people taking chaparral extracts, particular encapsulated products and with very large doses. Given the frequency of use yet few cases reported, lack of historical reports of such problems, and an inability to induce hepatotoxicity in vitro and in animals with any consistency, we have argued that the problems with chaparral are idiosyncratic and demonstrated that, at least in some patients, reasonable doses can be taken safely.[31] Reasonable doses are 0.5–1 ml of tincture three times per day. We consider chaparral to be a useful antioxidant, antimicrobial, and inflammation-modulating herb that can be used to moderate excessive inflammation in the short term, and, with careful monitoring, help some patients with chronic inflammatory conditions to heal.

Inflammation and Chamomile

Though gentle, the flowers of *Matricaria recutita* (chamomile) do significantly modulate inflammation. Like the other inflammation-modulating herbs discussed above, chamomile is generally milder in its effects than drugs, yet affects multiple pathways involved in inflammation and has numerous other beneficial actions beyond the realm of inflammation.

Figure 31–5. *Matricaria recutita* (chamomile)

In a mouse study, an extract of chamomile flowers significantly inhibited itch in response to the pro-inflammatory compound 48/80.[32] Apigenin-7-glucoside, a flavonoid glycoside found in significant amounts in chamomile, was an effective inflammation modulator in rat skin.[33] Apigenin from chamomile was also the most potent inhibitor of transcriptional activation of inducible COX-2 and nitric oxide synthase out of several flavonoids studied, with the mechanism clarified to be inhibition of NFkappaB.[34] Triterpnoids from *Matricaria matricarioides*, a close cousin of chamomile, showed inflammation-modulating effects in vitro.[35]

Besides its inflammation-modulating properties, chamomile is also antioxidant, anxiolytic, mildly antimicrobial, and spasmolytic.[36] In contrast to NSAIDs, it has been shown to protect against experimental ulcers.[37] It is also extremely safe, with no adverse effects other than occasionally causing allergic reactions in some sensitive people. It is safe for using in pregnancy and lactation as well as in any age group including newborns. A typical dose of chamomile tincture is 5–10 ml three times per day. Tea can also be made, using 5 g (roughly 2–3 tsp) flowers per cup, 1 cup three times per day.

Preliminary human clinical trials have confirmed that chamomile extracts can be as potent as low-dose corticosteroids at relieving chronic atopic dermatitis.[38,39] Such applications have also been shown to be more effective than placebo at relieving post-dermabrasion surgical wounds.[40] Trials have been mixed on the effect of chamomile for oral mucositis secondary to chemotherapy, but the fact that such a gentle, multifaceted herb could have any effect in any study flies in the face of current pharmacological theory.[41,42,43] It should also be noted that the negative double-blind trial used chamomile only to try and prevent mucositis—its use was discontinued when chemotherapy began though the positive trial used chamomile during chemotherapy and found it effective.

Table 31–2. Selected Other Inflammation-Modulating Botanicals

Latin Name (Common Name)	*Part Used*	*Traditional Use*	*Notes*	*Reference*
Ocimum tenuifolium (holy basil)[f], leaf.	For kidney problems, for gum ulcers, and as a hemostyptic in childbirth in China; for earaches, rheumatoid arthritis, anorexia, skin conditions, menstrual irregularities, and malaria in India; also antioxidant and insulin sensitizing			
Scutellaria baicalensis (Baikal skullcap)[c], root	Diarrhea, dysentery; urinary infections with bleeding; boils; jaundice, high fever; cough; bleeding due to heat syndromes	Also antioxidant; inhibits transcription of COX-2 gene		
Angelica dahurica (danggui)[b], root	Eliminate pus from sores, reduce swelling, alleviate pain, clear nasal passages	Furanocoumarins inhibited expression of COX-2 and microsomal prostaglandin E synthase in vitro		
Angelica pubescentis (danggui)[j,k], root	Eliminate pus from sores, reduce swelling, alleviate pain, clear nasal passages	Inhibited COX-1 and 5-lipoxygenase in vitro		
Harpagophytum procumbens (devil's claw)[d,I,m]		Pain management, inflammation	Inhibited COX-2 expression in vitro and in vivo in mice skin; topical application of methanolic extract inhibited TPA-induced COX-2 expression in mice skin in vivo; a proprietary preparation (60 mg harpagoside) showed equivalence to rofecoxib in a randomized, double-dummy, double-blind pilot study (n=88) of patients with acutely exacerbated low back pain	
Dioscorea tokoro (wild yam)[h], root	Arthritis, muscular pain, urinary diseases	Down-regulated COX-2 expression in vitro		
D. nipponica (wild yam)[l], root	Arthritis, muscular pain	Inhibited COX-2, 5-LO in vitro		

(*continued*)

Table 31–2. (*continued*)

Latin Name (Common Name)	*Part Used*	*Traditional Use*	*Notes*	*Reference*
Hypericum spp. (St. John's wort)[a,n], herb	Burns, HSV, depression	Hypericum orally administered to mice inhibited COX-2 expression in their peritoneal macrophages at a dose of 100 mg/kg; a lower dose did not have a significant effect; hyperforin in vitro suppressed COX-1 formation about 3–18 times more strongly than aspirin; suppressed 5-LO but did not interfere with COX-2 levels		
Actea racemosa (*Cimicifuga racemosa*) (black cohosh)[g], root	Dull, achy pain, arthritis, perimenopausal symptoms	Several fractions of an Actaea extract had dramatic analgesic action in mice and had an anti-inflammatory effect by inhibiting bradykinin/histamine-mediated actions		

a. Albert D, Zundorf I, Dingermann T, et al. Hyperforin is a dual inhibitor of cyclooxygenase-1 and 5-lipoxygenase. *Biochem Pharmacol* 2002;64(12):1767–1775.

b. Ban HS, Lim SS, Suzuki K, et al. Inhibitory effects of furanocoumarins isolated from the roots of *Angelica dahurica* on prostaglandin E2 production. *Planta Med* 2003;69:408–412.

c. Chi YS, Kim HP. Suppression of cyclooxygenase-2 expression of skin fibroblasts by wogonin, a plant flavone from *Scutellaria* radix. *Prostaglandins Leukot Essent Fatty Acids* 2005;72(1):59–66.

d. Chrubasik S, Model A, Black A, et al. A randomized, double-blind pilot study comparing Doloteffin and Vioxx in the treatment of low back pain. *Rheumatol* 2003;42:141–148.

e. Fiebich BL, Chrubasik S. Effects of an ethanolic salix extract on the release of selected inflammatory mediators in vitro. *Phytomedicine* 2004;11:135–138.

f. Kelm MA, Nair MG, Strasburg GM, et al. Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. *Phytomedicine* 2000;7(1):7–13.

g. Kim SJ, Kim MS. Inhibitory effects of cimicifugae rhizome extracts on histamine, bradykinin, and COX-2-mediated inflammatory actions. *Phytother Res* 2000;14:596-600.

h. Kim MJ, Kim HN, Kang KS, et al. Methanol extracts of dioscoreae rhizome inhibits pro-inflammatory cytokines and mediators in the synoviocytes of rheumatoid arthritis. *Int Immunopharmacol* 2004;4:1489–1497.

i. Kundu JK, Mossanda KS, Na HK, et al. Inhibitory effects of the extracts of Sutherlandia frutescens (L.) R. Br. and Harpagophytum procumens DC on phorbol ester-induced COX-2 expression in mouse skin: AP-1 and CREB as potential upstream targets. *Cancer Lett* 2005;218:21–31.

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k. Liu JH, Zschocke S, Reininger E, et al. Inhibitory effects of Angelica pubescens f. biserrata on 5-lipoxygenase and cyclooxygenase. *Planta Med* 1998;64:525–529.

l. Moon TC, Jung H, Lee E, et al. Screening of arachidonic acid cascade-related enzymes inhibitors from Korean indigenous plants (1). *Korean J Pharmaco* 2003;34:109–117.

m. Na HK, Mossanda KS, Lee JY, et al. Inhibition of phorbol ester-induced COX-2 expression by some edible African plants. *Biofactors* 2004;21:149–153.

n. Raso GM, Pacilio M, Di Carlo G, et al. In vivo and in vitro anti-inflammatory effect of Echinacea purpurea and Hypericum perforatum. *J Pharm Pharmacol* 2002;54:1379–1383.

CONCLUSION

We have reviewed just a small sample of the inflammation-modulating herbs available for clinical use to demonstrate that they have significant differences from all inflammation-suppressing drugs, both in terms of activity and safety, and to give a sense of their clinical use. Not explored in this chapter but of utmost importance is the inclusion of increased amounts of plants in the diet, that is, fruits, vegetables, whole grains, nuts, herbs, and spices will provide inflammation-modulating compounds in abundance that go far in quieting an excessive inflammatory condition. Herbs such as those described in this chapter would then be used to supplement diet in specific conditions that require greater modulation.

The existing research is insufficient, but generally supports our hypothesis that inflammation-modulating herbs work differently than anti-inflammatory drugs. A more expansive list of inflammation-modulating herbs is reviewed in Table 31-2. Pharmaceutical researchers are starting to realize that single-enzyme anti-inflammatory drugs are not safe or optimally effective. As a result, there is a growing move to find drugs that inhibit both COX and LOX.[44,45] Although this tacitly acknowledges the power of herbs and their prolific array of actions, it is still driven by a model that emphasizes suppressing inflammation instead of modulating and enhancing its beneficial aspects while minimizing the negative ones.

It is our belief that the continual search to partially mimic herbal actions using drugs that can be patented and produce enormous profits, regardless of their actual utility or safety, is misguided. We already have the tools necessary to help most people in whom inflammation has run amok. What we lack are the social, political, and economic structures that support people in obtaining and utilizing these tools, or even more modestly to simply study whether the natural medicine approach is actually more effective than drugs. As one review article noted, "Hopefully, federal agencies will provide the financial backing to support such studies. Thus, natural products serve as a gold mine for the treatment of arthritis."[46]

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32

ANTI-ADHESION HERBS

Some herbal medicines block adhesion of pathogenic microbes to epithelial cells. This mechanism of action demonstrates the diversity of antimicrobial activity in medicinal herbs and provides a therapeutic approach not available in antibiotic drugs. The continued failure of most of conventional medicine to appreciate the value of anti-adhesive botanicals, even if they are not as potent or immediate in their actions as drugs, does a disservice to patients. Some studies have shown that common antibiotics such as trimethoprim-sulfamethoxazole do not inhibit bacterial adhesion directly, and actually seemed to increase levels of more virulent uropathogens after cessation of treatment.[1]

There is some evidence that the anti-adhesive properties of botanicals also affect movements of cancer cells and may provide protection against local invasion and metastasis.

Vaccinium spp. and UTI

Vaccinium macrocarpon (cranberry) fruit is one of the best-studied and most well-known anti-adhesion herbs. This Ericaceae family herb contains proanthocyanidins that have been shown to block the adhesion of *Escherichia coli* to human urothelium in vitro and in clinical trials.[2] This same effect has been demonstrated by other members of the same genus, notably blueberry (*Vaccinium angustifolium*, *V. corymbosum*).[3,4,5] *Vaccinium myrtillus* (bilberry) and various huckleberries (*V. ovalifolium, V. ovatum*, *V. parvifolium*) contain similar constituents and are presumed to have anti-adhesive activity. Table 32-1 presents clinical trials that have given some degree of quantification of how effectively cranberry reduces *E. coli* adhesion.

Cranberry clearly does not deliver the same immediate results as antibiotics in most patients with uncomplicated urinary tract infections (UTI). As a monotherapy, cranberry juice or various encapsulated products have not been rigorously proven effective for treating urinary tract infections.[6] This is not surprising as cranberries do not have potent, direct toxicity to bacterial cells and anti-adhesive effects are less likely to be helpful in an already-established infection. See Sidebar 32-1.

Trials on prevention of UTI, however, at least in women with recurrent UTIs, show that cranberry products (juice and various powdered extracts) can, over 12 months' time, effectively reduce the incidence of UTI.[7,8] They achieve this effect with minimal toxicity, though long-term studies have fairly high levels of dropouts, mainly because patients stop taking cranberry juice due to time and taste issues.

Cranberry has also been assessed for cost effectiveness. In a 12-month trial, 150 sexually active women were randomly assigned to drink cranberry juice and take placebo tablets, take cranberry tablets and drink cranberry-flavored juice, or drink a placebo drink (cranberry-flavored juice) and take placebo tablets.[9] Juice doses were 250 ml three times per day; tablets containing a dried extract of juice (30:1) were taken twice per day. Participants taking either form of cranberry had significantly fewer UTIs compared with the placebo group. Due to reduced antibiotic use and less time off work, the cranberry-treated groups spent less money on treatment than the placebo group. Tablets proved to be twice as cost effective as juice in this

Table 32–1. A Sample of Studies Quantifying *E. Coli* Anti-Adhesive Effects of Cranberry

Trial (type)	*Daily Dose*	*Results*
Open, n=22[c]	15 oz juice	15 of 22 had significantly decreased adhesion one to three hours after drinking juice
Controlled, n=65[d]	400 or 1,200 mg dried juice	1,200 mg only reduced adhesion significantly compared with placebo
Controlled, n=5[b]	42.5 g dried fruit	3 of 5 subjects showed reduced adhesion after cranberries, none after raisins or baseline
Randomized, double-blind, n=20[a]	8.5 or 25 oz cranberry juice	8.5 oz cranberry reduced adhesion 45% and 25 oz, 62% compared with placebo drink

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d. Valentova K, Stejskal D, Bednar P, et al. Biosafety, antioxidant status, and metabolites in urine after consumption of dried cranberry juice in healthy women: A pilot double-blind, placebo-controlled trial. *J Agric Food Chem* 2007;55(8):3217–3224.

Figure 32–1. *Vaccinium macrocarpon* (cranberry)

Figure 32–2. *Vaccinium corymbosum* (blueberry)

Figure 32–3. *Vaccinium* spp. (huckleberry)

32–1. *Organisms Against Which Cranberry Has Shown Anti-Adhesive Activity*

Escherichia coli
Helicobacter pylori
Influenza
Proteus mirabilus
Pseudomonoas aeruginosa
Streptococcus mutans

[a] Burger O, Ofek I, Tabak M, et al. A high molecular-mass constituent of cranberry juice inhibits *Helicobacter pylori* adhesion to human gastric mucus. *FEMS Immunol Med Microbiol* 2000;29:295–301.
[b] Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and non-urinary bacterial isolates. *Microbios* 1988;55:173–181.
[c] Weiss EI, Houri-Haddad Y, Greenbaum E, et al. Cranberry juice constituents affect influenza virus adhesion and infectivity. *Antiviral Res* 2005;66:9–12.

trial. Though these results need to be independently replicated, they provide strong evidence that ongoing use of cranberry products can provide a significant benefit in women with recurrent UTIs.

Vaccinium spp. and *Helicobacter pylori*

Adhesion of *Helicobacter pylori* to stomach epithelium and possibly mucus is important to its ability to stay in the body and create disease.[10] In vitro, cranberry extract has been shown to reduce *H. pylori* adhesion to human gastric mucus.[11] Cranberry extracts also blocked adhesion directly to gastric epithelium in vitro.[12] Cranberry extracts showed additive inhibitory effects on *H. pylori* in vitro when combined with *Origanum vulgare* (oregano) extracts.[13] The mechanisms of action shown in this study included inhibition of urease and disruption of energy production by blocking proline dehydrogenase.

In a double-blind, randomized clinical trial, 225 adults in Linqu County, China, took either 250 ml cranberry juice twice daily or an artificially cranberry-flavored juice.[14] This area of China has one of the highest stomach cancer rates in the world. Only 189 subjects completed the trial with full compliance. All participants had positive[13] C-urea breath tests documenting *H. pylori* infection at the outset of the trial. By the end of the 90-day trial, significantly more subjects who drank real cranberry juice had negative breath tests compared with the placebo group (14.4% vs. 5.4% were negative in each group, respectively). Although clearly much less effective than antibiotics, the lack of side effects and ability to incorporate the treatment regularly suggest cranberry could, if the results of this trial are durable, represent a potentially huge reduction in gastric cancer rates in an endemic area. It is not known if these results would apply to Western populations, particularly because the Chinese villagers in this study had no prior exposure to antibiotics, not to mention the enormous dietary and cultural differences between China and the West.

In a double-blind clinical trial in Israel, 177 adults with breath test–confirmed *H. pylori* infection drank 250 ml twice daily of either cranberry juice or cranberry-flavored placebo drink (during drug treatment and for two weeks after).[15] All subjects took a combination of clarithromycin, amoxicillin, and omeprazole for seven days. An additional unblinded control group of 712

adults took the drugs without placebo or cranberry. Overall, cranberry was no more effective than placebo or no additional treatment in eradicating *H. pylori* as assessed by breath testing. However, when looking at just women in the trial, cranberry was associated with a nonsignificant, 8% higher rate of eradication compared with placebo, and a significant 15% higher rate of eradication compared with the antibiotic-only group. Women had higher levels of *H. pylori* growth than men in this trial.[15] More work is needed, and higher doses likely need to be used, but this trial provides evidence that women undergoing *H. pylori* eradication treatment may benefit from adding cranberry to their regimen.

Vaccinium spp. and Oral Flora

Various extracts and constituents from cranberry have been studied for their effect on oral microbes that can play a role in gingivitis, cavity formation, periodontal disease, and other problems. Flavonoids and proanthocyanidins from fresh cranberry fruit were found to moderately block glycosyltransferases and acid production by *Steptococcus mutans*.[16] Glycosyltransferases are critical enzymes for this microbe to form compounds that let it adhere to tooth surfaces. A combination of quercetin-3-arabinofuranoside, myricetin, and procyanidin A2 was more effective than any one component in isolation. A similar study found the same constituents active also at inhibiting biofilm development by *S. mutans* in vitro.[17] Crude cranberry juice has also been shown to block glycosyltransferases, inhibit binding to teeth, and reduce acidogenicity of *S. mutans*.[18] High-molecular-weight compounds in cranberry reduce the hydrophobicity of streptococci, which has been shown to be directly related to inhibiting biofilm formation.[19] Cranberry does not directly kill *S. mutans*.[20]

Another question is whether cranberry can break up a biofilm. In vitro, high-molecular-weight materials from cranberry, presumed to be high in proanthocyanidins, have been shown to promote *Streptococcus sobrinus* actually breaking out of biofilms ("desorption").[21] This same extract has previously been shown to help prevent biofilm formation in the first place.[22]

Only one human trial was located on the effect of cranberry on oral health. A mouthwash with high-molecular-weight cranberry compounds added was compared with placebo mouthwash in 59 healthy volunteers for 6 weeks.[23] The count of *S. mutans* was significantly lower in the cranberry group compared with placebo, whereas no differences in plaque or gingival indices were noted. This provides preliminary evidence for the value of cranberry in helping with various dental diseases.

Highly sweetened cranberry juices should be avoided, as sugar is simply not healthy although most studies used sweetened cranberry cocktail. Some patients tolerate unsweetened juice, but most will not. Rather than using synthetic sweeteners with unknown long-term consequences and scant evidence of reduced weight gain,[24,25] we suggest that patients either try mixing blueberry and cranberry juice in equal parts or diluting cranberry juice with water and the lowest amount of grape juice possible. For patients who cannot or will not tolerate juice or find it too expensive, then encapsulated products should be used (combinations of juice and capsules are of course possible). We generally recommend 2–4 oz of juice twice per day for prevention, increasing the dose to four times per day or more for acute problems. For capsules, 1,000 mg twice per day for prevention and 2,000 mg four or more times per day for acute problems are recommended.

Camellia sinensis

Camellia sinensis (tea) is a subshrub native to China now widespread there and in India, Sri Lanka, Indonesia, and many other parts of the world. The popularity of its leaves (in various

forms) as a beverage globally is rivaled only by water, coffee, and now soft drinks. Of these, only tea and water offer major health benefits with minimal risks at reasonable doses.[26] This is not to say that black tea is not bioactive, but that it has more potential for increasing the risk of gastrointestinal cancers with long-term regular use. Among the most overlooked of green tea's effects are its anti-adhesive properties.

An acidic polysaccharide from green tea inhibited *H. pylori* adhesion to gastric cells at very low concentrations (0.01 mg/ml).[27] It was also highly active in this study against adhesion of *Staphylococcus aureus* and *Propionibacterium acnes*, but did not interfere with adhesion of normal gut microbes.[27] Ethanol (50% or 95%) extracts of black tea were very effective, even at 0.5% dilution, at inhibiting *S. mutans* adhesion in vitro.[28] The tea extracts clearly inhibited glycosyltransferases of this microbe as well. Epigallocatechin gallate and other polyphenols from green tea potently blocked in vitro adhesion of *Porphyromonas gingivalis*, which plays a role in dental disease.[29] Oolong tea, which contains partially fermented tea leaves, has been shown to reduce caries formation in rats infected with *S. mutans*.[30]

Anti-adhesive effects of *Camellia sinensis* may extend beyond their utility against microbes. Theaflavins, polyphenolic compounds related to flavonoids, from black tea have shown the interesting ability in vitro to block adhesion of monocytes to vascular endothelium.[31] Blocking this oxidized low-density lipoprotein-stimulated process could be key to preventing formation or worsening of arteriosclerotic lesions. A green tea extract has been shown to induce annexin-I expression in lung cancer cells in vitro.[32] This compound is believed to play a role in normal cell–cell adhesion, and to help prevent cancer cells from spreading locally and/or distantly. Further study is clearly warranted in these areas.

Human research on tea as a preventive against dental caries is fairly extensive. A review of several clinical trials involving several thousand subjects on the issue found that various forms of tea did have a preventive effect against caries.[33] Typically 3–5 g of green, oolong, or black tea leaf or powder are mixed with 1 cup of water and 3–5 cups are drunk per day. For oral disease prevention or treatment, the tea should be swished around in the mouth before being swallowed for optimal efficacy.

MISCELLANEOUS ANTI-ADHESIVE HERBS

Panax ginseng (Asian ginseng) root carbohydrates have shown some ability to interfere with *H. pylori* binding to human cells based on a qualitative in vitro assay.[34] A quantitative assay as well as scanning electron microscopy have confirmed that concentrations as low as 0.2 mg/ml of Asian ginseng carbohydrates can significantly reduce *H. pylori* adhesion.[35] The immune- and inflammation-modulating actions of Asian ginseng may also have some relevance in mitigating the effects of *H. pylori* infection.[36,37] Humans trials should be undertaken.

Artemisia capillaris (yin-chen wormwood, capillary mugwort), a bitter herb used primarily in traditional Asian medicine, contains polysaccharides that block *H. pylori* adhesion to erythrocytes in a quantitative in vitro assay.[38] Yin-chen wormwood polysaccharides were approximately one third as potent as Asian ginseng polysaccharides at blocking *H. pylori* adhesion in vitro.[35] Yin-chen wormwood, like its European cousin *Artemisia absinthium* (wormwood), contains terpenoids that are also antimicrobial with some potential to directly attack *H. pylori*.[39] Its bitter qualities improve digestive function that creates a less hospitable environment for this microbe.[40,41]

Humulus lupulus (hops) bracts yield polyphenolic compounds that were significantly more potent than green or Oolong tea leaves at blocking adhesion of *S. mutans* and *S. sorbinus* in vitro.[42]

Other compounds in hops have been shown to be directly antimicrobial against *S. mutans*.[43] An extract of these compounds at a 0.1% concentrated was formulated into a mouthwash and tested in 29 healthy male volunteers.[44] After total plaque removal, they refrained from any oral hygiene for three days except for using the hops mouthwash or a placebo. New plaque formation was significantly lower in the hops group compared with the placebo group at the end of this period.

Propolis, which is a bee-harvested mixture of plant and tree resins, is a well-known and often-used herbal antimicrobial. It is simultaneously quite active at inhibiting adhesion of a wide range of microbes, including *Candida albicans*, streptococci, staphylococci, and enterococci, in vitro and at killing these organisms outright.[45]

Asarum sieboldii (xi xin) root finds use in traditional Asian medicine for respiratory tract infections. Ethanolic and aqueous extracts of this medicinal plant have been shown to inhibit glycosyltransferases, acid production, growth, and adhesion of *S. mutans* in vitro.[46] There are similar species of this genus native to the United States (*Asarum canadense*) and Europe (*A. europaeum*), generally known as wild ginger due to their spicy taste (though they have no relationship to *Zingiber officinale* or true ginger). These herbs should be used with caution as they contain the carcinogenic and nephrotoxic compound aristolochic acid.

Numerous medicinal algae have also shown potential as anti-adhesive agents. Fucosylated Lewis b antigen is one receptor to which *H. pylori* strains can bind.[47] Numerous algae contain fucoidans, glycosaminoglycans that may interfere with *H. pylori* adhesion, including *Cladosi-*

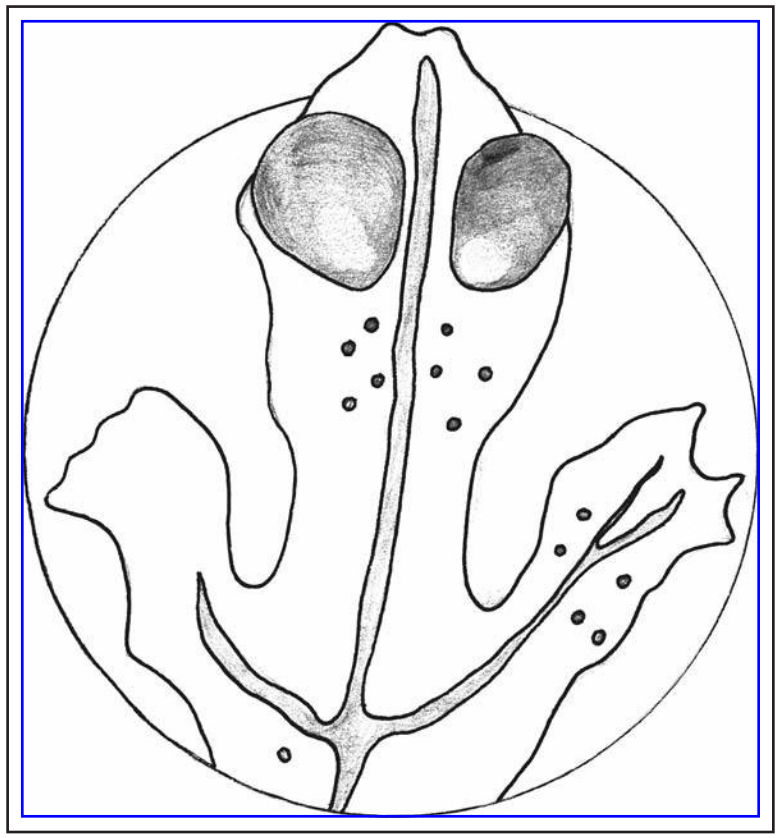

Figure 32–4. *Fucus vesiculosus* (bladderwrack)
Drawing © Kathy Abascal, BS, JD.

phon okmuranus (mozuku) and *Fucus vesiculosus* (bladderwrack). In vitro, fucoidans from these algae blocked *H. pylori* adhesion to human gastric cells.[48] Presumably the fucoidans are acting as "false receptors," looking like what *H. pylori* wants to bind to but not actually being attached to anything, so the microbe just drifts away down the gastrointestinal tract. Though unproven in human trials, fucoidans from *Cladosiphon* and *Fucus* have been shown to protect Mongolian gerbils from infection and those that were infected from developing gastritis.[49]

Fucoidan from *Fucus evanescens*, native to the Sea of Okhotsk, has been shown to moderately inhibit metastasis of lung cancer cells in mice.[50] Though it had some direct antineoplastic activity, it also has anti-adhesive activity. This was true of fucoidans from a range of algae in a separate study looking at breast cancer adhesion.[51]

CONCLUSION

Anti-adhesive herbal medicines represent an intriguing and unique approach to helping patients with a range of infections and cancer. Because these agents do not necessarily directly kill the microbes or cancer cells, they may be less likely to promote evolution of resistance. They may also represent a significantly useful synergistic addition to treatment with direct antimicrobial and antineoplastic agents, because they act through such distinctive mechanisms. Much research remains to be done, but some anti-adhesive herbs (cranberry and tea) are already in widespread use, have been validated clinically to varying degrees, and can realistically be prescribed now for clinical benefit with minimal risk.

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APPENDIX
RECOMMENDED DOSAGES OF BOTANICAL MEDICINES

DOSE CODES

FS (fresh, safe): This means a concentrated (1:2–1:3 weight:volume ratio), fresh-herb tincture; we recommend 3–5 ml three times per day for average-sized adults with chronic conditions. For acute conditions, when appropriate, this same dose is administered but more frequently (4–6 times per day). Generally all liquid extracts are mixed with water or good-tasting herb teas (especially ginger) to deliver the dose more palatably, though they can also be taken straight in the mouth if tolerated.

SP (special): See dose information given in the details column.

LD (low-dose): Individualized dosing is stated.

DS (dry, safe): As FS but using dry-herb tincture.

*: Indicates herbs that can also be prepared as glycerites and that work effectively as such, using the same doses as FS above.

LATIN ABBREVIATIONS AND ACRONYMS

ø: tincture
FE: fluid extract
cap: capsule
VO: volatile oil

qd: once daily
bid: twice per day
tid: three times per day
qid: four times per day

gtt: drops
ac: before food
cc: with food
ic: away from food (30 minutes before or two hours after)

hs: bedtime
prn: as needed
ppm: parts per million

Medicinal herbs are prepared in many ways. Doses used vary greatly depending on how the herb was prepared and whether it is used as a simple (alone) or is blended with other herbs in a formula. This dose table reflects how we commonly dose these plants. It is not intended to encompass all of the variety of ways these botanicals are dosed, only our beliefs about real-world

dosing. In particular, the doses given are for chronic situations. For acute situations, it is almost always best to increase the frequency of dose, and sometimes the amount.

Doses must always be adjusted for body size, age, and complicating conditions (such as liver or kidney failure). This is the art of clinical medicine, and such adjustments cannot realistically be separately denoted for every individual agent.

When used in formulae, it is not necessary to achieve these dose levels for efficacy. This is presumably due to synergy with other herbs.

Some herbs (those marked LD) must be used in very small doses, and either by or in consultation with experienced practitioners. Some are not appropriate in pregnancy or lactation or have specific use requirements. This important information is set out in full in the text and is *not* included here for the sake of clarity and simplicity. Therefore, it is critical that the text be reviewed *before* a dose for a particular patient is selected.

Not every herb mentioned in the book is included in this table; some were cited due only to research studies and we do not have access to these herbs. This is not to say these herbs are not valuable, only that for practitioners based in North America, these herbs are neither ecologically rational to use, nor are they likely to be available.

Herb	*Dose*	*Details (Chronic Dosing)*
Achillea millefolium (yarrow) flowering tops	FS*	
Aconitum spp. (aconite) herb	LD	ø: (fresh, 1:4) 1–5 gtt tid
Actaea racemosa (black cohosh) root	FS	
Aesculus hippocastanum (horse chestnut) seed	FS	Cap: 250 mg (w/100 mg escin), bid cc Cream: topically tid
Agathosma (formerly *Barosma*) *betulina* (buchu) leaf	FS, FD	
Agropyron repens (couch grass) rhizome	FS*	Cold infusion: 1 tbsp/cup water steeped overnight, 1 cup tid
Alcea rosea (hollyhock) leaf and root	SP	Cold infusion: 1 tbsp herb/cup water, steeped overnight, at least 1 cup tid
Alchemilla arvensis (lady's mantle) herb	FS*	Tea: 1–3 tsp/cup water, 1 cup tid
Allium sativum (garlic) bulb	FS*	Fresh cloves: eat 1–10 qd Cream: topically prn
Aloe vera (aloe vera) leaf exudate or mucilage	SP	2–4 oz qd (po or topically)
Althaea officinalis (marshmallow) leaf and root	SP	Cold infusion: 1 tbsp/cup of water steeped overnight, at least 1 cup tid
Ammi visnaga (khella) seed	LD	ø: (dry, 1:3–1:5) 1–3 ml tid
Anemopsis californica (yerba mansa)	FS*	
Anethum graveolens (dill) herb	FS	
Angelica archangelica (angelica) root	FS*	
Angelica sinensis (dang gui) root	FS*	
Apium graveolens (celery) seed	FS	
Aralia californica (California spikenard) root	FS	
Arctium lappa (burdock) root	FS*	
Arctostaphylos uva-ursi (uva ursi) leaf	FS*	Cold infusion: 4–5 tbsp/quart of water, steeped overnight, strained and consumed in divided doses throughout the next day

Herb	*Dose*	*Details (Chronic Dosing)*
Armoaracia rusticana (horseradish) root	FS	Grated root: eat 0.5–1.5 tsp
Artemisia absinthium (wormwood) herb	LD	ø: (fresh, 1:2–1:3) 0.25–1 ml tid
Artemisia annua (sweet Annie) herb	FS	Capsule: 1–3 g tid
Artemisia vulgaris (mugwort) herb	SP	ø: (dry, 1:5) 0.5–1 ml tid
Asclepias asperula (inmortal) root	LD	ø: (fresh, 1:2–1:3) 0.5–2 ml tid
Asclepias tuberosa (pleurisy root) root	LD	ø: (fresh, 1:2) 1–3 ml tid
Astragalus membranaceus (astragalus) root	DS*	Crude herb: 3–5 g tid
Atractylodes macrocephala (bai-zhu atractylodes)	FS	
Atropa belladonna (belladonna) leaf or root	LD	ø: (fresh, 1:3–1:5) 5–15 gtt tid
Avena sativa (oat) milky seed	FS*	
Azadiracta indica (neem) leaf	FS, DS	Oil: 1 ml tid or topically prn
Baptisia tinctoria (wild indigo) root	LD	ø: (fresh, 1:2) 1–3 ml tid up to six times per day
Berberis haematocarpa (desert barberry) root	FS*	Tincture: (fresh 1:2) 5 ml tid Cap:
Berberis vulgaris (barberry) root	DS*	Cap: 5–10% berberine: 250–500 mg tid
Betula spp. (birch) bark or leaf	FS	
Brickellia grandiflora (hamula, prodigiosa, bricklebush) herb	SP	Tea: 1–3 tsp herb/cup, 1 cup bid ø: (fresh 1:2) 1–3 ml tid cc
Cacalia decomposita (matarique) root	SP	ø: (fresh 1:2) 1–2 ml tid cc
Calendula officinalis (calendula) flower	FS*	
Camellia sinensis (green tea) leaf	FS	Tea: 1–2 tsp/cup, 1 cup tid
Capsicum spp. (cayenne) fruit or capsaicin	SP	ø: (fresh, 1:5) 1–15 gtt tid
Carum carvi (caraway) seed	DS	
Centella asiatica (gotu kola) leaf and root	FS*	
Cephalis ipecachuanaha (ipecac) root	LD	ø: (dry, 1:5): 1–10 gtt tid
Chamaelirium luteum (false unicorn) root	FS	
Chamaemelum nobilis (Roman chamomile) flower	FS	
Chelidonium majus (chelidonium) whole plant	LD	ø: (fresh, 1:2) 0.5–2 ml tid
Chimaphila umbellata (pipsissewa) leaf	FS	
Cinchona spp. (Peruvian bark) bark	LD	Cold infusion: 2–4 oz to tid ø: (dry, 1:5) 0.5–1 ml tid
Cinnamomum cassia (cassia) bark	SP	Crude powder: 0.5 tsp tid (modify based on blood sugar readings) ø: (dry, 1:5) 1–3 ml tid
Cinnamomum zeylanicum (cinnamon) bark	DS	Crude powder: 1 tsp tid (modify based on blood sugar readings) ø: (dry, 1:3) 1–3 ml tid
Codonopsis pilosula (codonopsis) fruiting body	DS	Herb powder: 1–3 g tid
Coix lacryma-jobi (Job's tears)		Herb powder: 3–5 g tid
Collinsonia canadensis (stone root) whole plant	FS	

Herb	*Dose*	*Details (Chronic Dosing)*
Commiphora molmol (myrrh) resin	SP	ø: (dry, 1:3–1:5) 1–3 ml tid
Commiphora mukul (guggul) resin	SP	Powder: 1 g tid
Convallaria majalis (lily-of-the-valley) herb	LD	ø: (fresh, 1:2) 0.5–2 ml tid
Coptis chinensis (goldthread) root	DS	Cap: 1–2 g tid
Cordyceps chinensis (cordyceps, Chinese caterpillar fungus) mycelium or fruiting body	SP	Cap: 1–3 g tid
Coriandrum sativum (cilantro) herb	FS*	
Craetagus spp. (hawthorn) leaf, flower, and/or fruit	FS*	Cap:
Crocus sativus (saffron)	SP	ø: (dry, 1:3–1:5) 5–20 gtt tid
Curcuma longa (turmeric) rhizome	DS, FS	Cap: 1–5 g tid
Cytisus (formerly *Sarothamnus*) *scoparius* (Scotch broom) leaf, flower, and seed	LD	ø: (fresh, 1:5) 0.5–1 ml tid
Dendranthema x *morifolium* (chrysanthemum) flower	FS	Crude powder: 3–5 g tid
Dionaea muscipula (Venus fly trap) herb	SP	ø: (fresh, 1:2) 5–10 gtt tid
Dioscorea villosa (wild yam) root	FS	
Echinacea spp. (echinacea) herb and/or root	FS*	Critical to dose frequently in acutes
Eleutherococcus senticosus (eleuthero) root	FS	FE: 3–5 ml bid–tid
Elletaria cardamomum (cardamom) seed	DS	
Emblica officinalis (amla) fruit	SP	Cap: 1–3 g tid
Encelia farinosa (brittlebush) leaf	FS	
Ephedra nevadensis (Mormon tea) stem	DS	
Ephedra sinica (ephedra) stem	LD	ø: (dry, 1:3–1:5) 0.5–1 ml tid
Equisetum arvense, E. hymenale, E. telamateia (horsetail) herb	FS*	
Eryngium yuccifolium (rattlesnake master) and *E. maritimum* (eryngo) root	SP	ø: (fresh, 1:2) 1–2 ml tid
Eschscholzia californica (California poppy) herb	FS	
Eucalyptus spp. (eucalyptus) leaf	SP	ø: (fresh, 1:3) 1–2 ml tid Volatile oil: 1–3 gtt tid
Eugenia jambolana (also known as *Syzygium jambolanum* and *Syzygium cumini*) or jambul, seeds		Juice: 2.5–10 ml (0.5–2 tsp) bid–tid
Eupatorium perfoliatum (boneset) herb	FS	Tea: 1–2 tsp/cup, 1 cup tid
Eupatorium purpureum (Joe Pye) herb	FS	
Filipendula ulmaria (meadowsweet) herb	FS	
Foeniculum vulgare (fennel) seed	FS	Volatile oil: 2–5 gtt tid
Fouquieria splendens (ocotillo) bark	SP	ø: (fresh, 1:2) 0.5–1 ml tid
Fragaria vesca (strawberry) leaf	FS	Tea: 1 tbsp/cup, 1 cup tid

Herb	*Dose*	*Details (Chronic Dosing)*
Frangula (formerly *Rhamnus*) *purshiana* (cascara sagrada) bark	SP	ø: (dry, 1:5) 5 ml hs Cap: 1–2 g hs
Fucus spp. (fucus) thallus	FS*	Cap: 500–1,000 mg tid
Fumaria officinalis (fumitory) herb	FS,* DS	
Ganoderma lucidum (reishi) fruiting body	DS	Crude powder: 3–5 g tid
Gelsemium sempervirens (yellow jasmine) root	LD	ø: (fresh, 1:2) 2–10 gtt tid
Gentiana lutea (gentian) root	SP	ø: (dry, 1:5) 2–4 ml in water sipped 10–15 minutes ac
Geranium maculatum (cranesbill) herb	FS, DS	
Geranium thunbergii (Thunberg's cranesbill) root	FS, DS	
Ginkgo biloba (ginkgo) leaf	FS*	Cap: 60–120 mg bid–tid, standardized to contain 24% ginkgo flavonoid glycosides, 6% terpene lactones, and <5 ppm ginkgolic acids
Glycine max (soybean) fruit	SP	Eat as food Cap: sufficient to provide 90+ mg isoflavones daily
Glycyrrhiza glabra (licorice) and *G. uralensis* (Chinese licorice, gancao) root	SP	FE: 1–5 ml tid Cap: 500–3,000 mg tid DGL: 500–1,000 mg chewed cc
Gossypium hirsutum (cotton) root	SP	ø: (fresh, 1:2) 1–2 ml tid
Gymnema sylvestre (gymnema) vine	SP	FE: 1–2 ml tid
Hamamelis virginiana (witch hazel) leaf or bark	FS, DS	
Hedera helix (English ivy) leaves	SP	ø: (dry, 1:5) 5-15 gtt tid
Hibiscus spp. (hibiscus) flower	SP	Tea: 2–3 tsp/cup, 1 cup tid
Houttuynia cordata (yu xing cao) leaf and flower	SP	Crude powder: 2–5 g tid
Huperzia serrata (toothed clubmoss) thallus	LD	ø: (dry, 1:5) 1–5 gtt tid
Hydrangea arborescens (hydrangea) root	FS	
Hydrastis canadensis (goldenseal) root	FS*	Cap: 250–500 mg tid, usually containing 5–10% berberine
Hylocereus undatus (night-blooming cereus) stem	LD	ø: (fresh ,1:2) 5–15 gtt tid
Hypericum perforatum (St. John's wort) flowering tops	FS*	Oil or ointment: topically prn
Iberis amara (bitter candytuft) herb	SP	ø: (dry, 1:5) 1–3 ml in water sipped 10–15 minutes ac
Inula helenium (elecampane) root	FS*	
Isatis tinctoria and *I. indigotica* (isatis) root	SP	ø: (dry, 1:2–1:3) 1–3 ml tid
Juniperus communis (juniper) fruit	LD	ø: (fresh, 1:3) 0.5–2 ml tid
Laminaria spp. (kelp)	SP	Eat 1–3 g bid–tid.
Larrea tridentata (chaparral) leaf, flower, and seed	LD	ø: (fresh, 1:3) 0.25–1 ml tid

Herb	*Dose*	*Details (Chronic Dosing)*
Lentinula edodes (shiitake) mushroom	DS	Crude powder: 1–5 g tid
Leonurus cardiaca (motherwort) herb	FS*	
Lespedeza capitata (round-headed lespdeza) flowering tops	FS	
Levisticum officinale (lovage) root	FS	Tea: 2–3 tsp/cup, 1 cup tid
Ligustrum lucidum (privet) fruit	DS	Crude powder: 3–5 g tid
Linum usitatissimum (flax) seed	SP	Crude powder: 3–5 g bid–tid cc
Lithospermum spp. (gromwell) herb	LD	ø: (fresh, 1:3) 1–2 ml tid
Lobelia inflata (lobelia) herb and/or seed	LD	ø: or acetract (fresh, 1:3) 0.5–2 ml tid
Lomatium dissectum (lomatium) root	SP	ø: (fresh, 1:3) 1–3 ml tid
Lycopus spp. (bugleweed) herb	FS	
Lysichiton americanum (western skunk cabbage) rhizome	LD	ø: (fresh, 1:3–1:5) 0.5–2 ml tid
Magnolia spp. (magnolia) stem bark	DS	Crude powder: 3–5 g tid
Mahonia aquifolium (Oregon grape) root	FS*	
Marrubium vulgare (horehound) herb	FS	
Matricaria recutita (chamomile) flower	FS	Tea: 1 tbsp/cup, 1 cup tid cc
Medicago sativa (alfalfa) herb	FS*	Tea: 1 tbsp/cup, 1 cup tid cc
Melaleuca alternifolis (cajuput) oil	SP	Volatile oil: 1–5 gtt tid
Melia azedarach (melia) bark of root	LD	ø: (dry, 1:3) 0.5–2 ml tid
Melissa officinalis (lemon balm) leaf	FS*	
Mentha spicata (spearmint) herb	SP	Tea: 1 tbsp/cup, 1 cup tid
Mentha x *piperita* (peppermint) herb	FS	Tea: 1 tbsp/cup, 1 cup tid
Mitchella repens (partridge berry) berry	FS*	
Momordica charantia (bitter melon) fruit, seeds	SP	Fresh glycerite: 1:1: 3–5 ml tid Succus: 5–15 ml tid Fresh melon: 1–5 slices cc
Morella cerifera (bayberry) bark	FS	
Nelumbo nucifera (sacred lotus) rhizome	SP	Crude powder: 3–5 g tid
Nepeta cataria (catnip) herb	FS*	
Ocimum spp. (basil) herb	SP	ø: (fresh, 1:3) 1–3 ml tid
Olea europaea (olive) leaves	FS*	
Oplopanax horridum (devil's club) root, rhizome	FS*	
Opuntia spp. (prickly pear) pads	FS	Eat 1 pad cc
Origanum vulgare (oregano) herb	SP	Volatile oil: 1–5 gtt tid ø: (fresh, 1:3) 1–3 ml tid
Orthosiphon stamineus (Java tea) flower	SP	Tea: 1 tbsp/cup, 1 cup tid
Panax ginseng (Asian ginseng) root	SP	Decocted crude root: 1–2 g/cup, 1 cup bid–tid ø: (dry, 1:5) 2–3 ml tid Cap: 200 mg tid standardized to 4% ginsenosides
Panax quinquefolius (American ginseng) root	FS	Cap: 1–3 g tid
Parietaria judaica (pellitory-of-the-wall) herb	FS	
Passiflora incarnata (passionflower) leaf	FS*	Include hs dose

Herb	*Dose*	*Details (Chronic Dosing)*
Pausinystalia yohimbe (yohimbe) bark	LD	ø: (dry, 1:3–1:5) 3–10 gtt tid
Peganum harmala (Syrian rue) seed and root	LD	ø: (fresh 1:2) 0.5–1 ml tid
Pelargonium sideroides (citrosa) root	SP	Cap: 1 g tid
Petasites hybridus (butterbur) root	SP	Fresh glycerite: 1:2: 3–5 ml tid
Phoradendron spp. (American mistletoe) herb	LD	ø: (fresh, 1:5) 0.5–2 ml tid
Phyllanthus urinarina or *P. niuri* (chanca piedra) leaf	FS, DS	
Physostigma venenosum (Calabar bean) seed	LD	ø: (dry, 1:10) 1–5 drops bid–tid
Picrorhiza kurroa (picrorhiza) root	SP	FE: 1–3 ml tid
Pilocarpus jaborandi (Pernambuco jaborandi) leaves	LD	Tea: 1 tsp/cup prn for diaphoresis ø: (dry, 1:5) 15–30 gtt bid–tid
Pimpinella anisum (anise) seed	DS	Volatile oil: 1–5 gtt tid
Piper methysticum (kava) root	FS	
Piscidia piscipula (Jamaica dogwood) bark	LD	ø: (dry, 1:3) 0.5–3 ml tid
Plantago ovata (Indian plantain) seed	SP	Cap: 1–3 g tid with water
Plecanthus barbatus (formerly *Coleus forskohlii*) leaf	SP	FE: 1–3 ml tid
Populus tremuloides (quaking aspen) bark	FS	Decoction: 2–4 oz qd–qid
Propolis	SP	ø: (dry, 1:2–1:3), 1–3 ml tid
Prunella vulgaris (heal all) herb	FS*	
Prunus africana (pygeum) bark	SP	Not recommended for ecological reasons
Psacalium decompositum (psacalium, matarique, maturín), rhizome, root	SP	ø: (fresh 1:2) 15–30 gtt tid cc (short-term use)
Pueraria montana var *lobata* (kudzu) root	SP	Fresh glycerite: 1:2, 3–5 ml tid Crude powder (brown, not white): 3–5 g tid
Pulsatilla (formerly *Anemone*) vulgaris (pasque flower, pulsatilla) herb	LD	ø: (fresh, 1:2) 3–10 drops tid
Punica granatum (pomegranate) fruit	SP	Juice: 4–8 oz qd cc
Rauvolfia serpentina (rauwolfia, Indian snakeroot) root	LD	FE, standardized to 0.1–0.125 mg reserpine/4 gtt: 2–4 gtt qd–bid
Rheum palmatum (Chinese rhubarb, Turkey rhubarb) root	SP	Crude herb: 300–3,000 mg tid ø: (dry, decocted, 1:2) 1–3 ml tid ø: (dry, not decocted, 1:2) 5–10 ml hs as cathartic
Rhodiola rosea (rhodiola) root	DS	Cap: 170–300 mg qd
Ribes nigrum (black currant) oil	SP	1–3 tsp qd cc
Rorippa nasturium-aquaticum (watercress) herb	FS*	
Rosmarinus officinalis (rosemary) leaf	FS	Volatile oil: 1–5 gtt tid
Rubia tinctoria (madder) root	DS	

Herb	*Dose*	*Details (Chronic Dosing)*
Rubus discolor (Himalayan blackberry) root	FS*	
Rumex crispus (yellow dock) root	FS*	
Ruscus aculeatus (butcher's broom) root	SP	Cap: 150 mg tid
Ruta graveolens (rue) herb	LD	ø: (fresh, 1:3) 0.5–2 ml tid
Salix spp. (willow) bark	FS	
Salvia lavandulaefolia (Spanish sage) herb	FS	Volatile oil: 1–5 gtt tid
Salvia miltiorrhiza (Chinese salvia) herb	DS	Crude powder: 3–5 g tid
Salvia officinalis (sage) herb	FS*	Volatile oil: 1–5 gtt tid
Sambuccus spp. (elderberry) fruit and/or flower	FS*	Syrup (fruit): 3–5 ml tid Tea (flower): 1 tbsp/cup, taken with hot bath
Schisandra chinensis (schisandra) fruit	DS*	
Scutellaria baicalensis (Asian skullcap, scute) root	FS, DS	
Scutellaria lateriflora (skullcap) leaf and flower	FS*	Include hs dose
Secale cereale (rye flower) pollen	SP	Cap: 500–1,000 mg tid
Selenicereus grandiflorus (night-blooming cereus) stem	LD	ø: (fresh 1:2) 5–15 gtt tid
Senna alexandrina (senna) fruit	SP	ø: (dry, 1:5) 5–10 ml hs
Serenoa repens (saw palmetto) fruit	FS	Cap: 320 mg qd standardized to 75% liposterolic compounds
Silybum marianum (milk thistle) seed	SP	Crude powder: 5 g tid FE: 3–5 ml tid Cap: 140 mg tid, standardized to 80% silymarin
Solidago canadensis (American goldenrod) and *S. virgaurea* (European goldenrod) flowering tops	FS	Tea: 1 tbsp/cup, 1 cup tid
Sphaeralacea spp. (globemallow) leaf	SP	Cold infusion: 1 tbsp/cup, steeped overnight, 1 cup tid
Stachys betonica (wood betony) herb	FS	
Swertia chirata (king of bitters) root	SP	Tea: 1 tsp/cup, 1 cup sipped 10–15 minutes ac ø: (dry, 1:3–1:5) 2–4 ml 10–15 minutes ac
Symphytum officinale (comfrey) herb and/or root	FS*	Cold infusion: 1 tbsp/cup, steeped overnight, 1 cup tid
Symplocarpus foetidum (Eastern skunk cabbage) rhizome	LD	ø: (fresh, 1:3–1:5) 0.5–2 ml tid
Syzygium (formerly *Eugenia*) *cumini* (formerly *jambolanum*) (jambul) fruit	SP	Succus: 2.5–10 ml (0.5–2 tsp) juice bid–qid Crude powder: 1 g tid
Tabebuia spp. (pau d'arco) bark	SP	Not recommended for ecological reasons

Herb	*Dose*	*Details (Chronic Dosing)*
Tanacetum parthenium (feverfew) leaf	FS, DS	
Taraxacum officinale (dandelion) root	FS*	FE: 1–3 ml tid
Taraxacum officinalis (dandelion) leaf	FS*	Tea: 1 tsp/cup, sipped 10–15 minutes ac
Thuja occidentalis (thuja) or *T. plicata* (red cedar) leaf	SP	ø: (fresh, 1:3–1:5) 0.5–2 ml tid
Thymus serpyllum (wild thyme) herb	FS	Volatile oil: 1–3 gtt tid
Thymus vulgaris (thyme) herb	FS	Volatile oil: 1–3 gtt tid
Tilia cordata (linden) flower	FS*	
Trametes versicolor (yun zhi, cloud mushroom) mushroom	DS	Cap: 1–3 g tid
Trifolium pratens (red clover) herb	FS*	
Tropaeolum major (nasturium) leaf	FS*	
Ulmus rubra (slippery elm) bark	SP	Cold infusion: 1 tbsp/cup, steeped overnight, 1 cup tid
Urtica dioica (nettle) leaf	FS*	Tea: 1 tbsp/cup, 1 cup tid
Urtica dioica (nettle) root	FS	Cap: 1–2 g tid
Urtica dioica (nettle) seed	FS	
Vaccinium macrocarpon (cranberry) fruit	SP	Cap: 400+ mg bid–tid Juice: 4–16 oz qd
Valeriana officinalis (valerian) or *V. sitchensis* (Pacific valerian) root	FS*	Include hs dose
Veratrum viride (false hellebore) herb and/or root	LD	ø: (fresh, 1:10) 1–10 gtt tid
Verbena spp. (vervain) herb	FS*	
Verbesina encelioides (añíl de muerto)	FS	
Viburnum opulus (cramp bark) bark	FS*	
Viscum album (European mistletoe) herb	SP	ø: (fresh or dry, 1:3–1:5) 1–2 ml tid Cold infusion: 1–2 tsp/cup, steep overnight, 1 cup tid SubQ injection: 1–three times per week
Vitex agnus-castus (chaste tree) fruit	DS*	Some give a single morning dose
Withania somnifera (ashwagandha) root	FS	
Xanthorrhiza simplicissima (yellowroot) root	FS	
Zanthoxylum americanum (prickly ash) bark	SP	ø: (fresh, 1:3–1:5) 0.5–2 ml tid
Zea mays (corn) silk	FS*	Tea: 1 tbsp/cup, 1 cup tid
Zingiber officinale (ginger) rhizome	SP	Tea: 1 tsp/cup, 1 cup sipped 10–15 minutes ac ø: (fresh or dry, 1:3–1:5) 0.5–1 ml tid
Zizyphus jujuba (jujube) fruit	DS	

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