

Herbal Medications Commonly Used in the Practice of Rheumatology: Mechanisms of Action, Efficacy, and Side Effects

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OBJECTIVE To review the literature on herbal preparations commonly utilized in the treatment of rheumatic indications.

METHODS Search of MEDLINE (PubMed) was performed using both the scientific and the common names of herbs. Relevant articles in English were collected from PubMed and reviewed.

RESULTS This review summarizes the efficacy and toxicities of herbal remedies used in complementary and alternative medical (CAM) therapies for rheumatologic conditions, by elucidating the immune pathways through which these preparations have antiinflammatory and/or immunomodulatory activity and providing a scientific basis for their efficacy. Gamma-linolenic acid suppresses inflammation by acting as a competitive inhibitor of prostaglandin E2 and leukotrienes (LTs) and by reducing the auto-induction of interleukin-1 α (IL-1 α)-induced pro-IL-1 β gene expression. It appears to be efficacious in rheumatoid arthritis (RA) but not for Sjogren's disease. The antiinflammatory actions of *Harpagophytum procumbens* is due to its action on eicosanoid biosynthesis and it may have a role in treating low back pain. While in vitro experiments with *Tanacetum parthenium* found inhibition of the expression of intercellular adhesion molecule-1, tumor necrosis factor alpha (TNF- α), interferon- γ , I κ B kinase, and a decrease in T-cell adhesion, to date human studies have not proven it useful in the treatment of RA. Current experience with *Tripterygium wilfordii* Hook F, *Uncaria tomentosa*, finds them to be efficacious in the treatment of RA, while *Urtica dioica* and willow bark extract are effective for osteoarthritis. *T. wilfordii* Hook F extract inhibits the production of cytokines and other mediators from mononuclear phagocytes by blocking the up-regulation of a number of proinflammatory genes, including TNF- α , cyclooxygenase 2 (COX-2), interferon- γ , IL-2, prostaglandin, and iNOS. *Uncaria tomentosa* and *Urtica dioica* both decrease the production of TNF- α . At present there are no human studies on *Ocimum spp.* in rheumatic diseases. The fixed oil appears to have antihistaminic, antiserotonin, and antiprostaglandin activity. *Zingiber officinale* inhibits TNF- α , prostaglandin, and leukotriene synthesis and at present has limited efficacy in the treatment of osteoarthritis.

CONCLUSIONS Investigation of the mechanism and potential uses of CAM therapies is still in its infancy and many studies done to date are scientifically flawed. Further systematic and scientific inquiry into this topic is necessary to validate or refute the clinical claims made for CAM therapies. An understanding of the mechanism of action of CAM therapies allows physicians to counsel effectively on their proper and improper use, prevent adverse drug-drug interactions, and anticipate or appreciate toxicities.

RELEVANCE The use of CAM therapies is widespread among patients, including those with rheumatic diseases. Herbal medications are often utilized with little to no physician guidance or knowledge. An appreciation of this information will help physicians to counsel

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patients concerning the utility and toxicities of CAM therapies. An understanding and elucidation of the mechanisms by which CAM therapies may be efficacious can be instrumental in discovering new molecular targets in the treatment of diseases.

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The use of complementary and alternative medical (CAM) therapies has been increasing among patients with rheumatologic diseases. Forty-seven percent of older adults with osteoarthritis use complementary medicine. Nonprescribed medications now account for 17%, while massage therapy and chiropractic services make up the remainder. Expenditures for alternative therapies averaged \$1127 per year per patient, compared with \$1148 for traditional therapies. (1) Within the category of CAM, herbal medications are commonly used for rheumatic conditions. Several of these medications are easily available and claim a long history of safety and efficacy.

While many physicians are somewhat skeptical of nontraditional therapies, patients appear to be satisfied with the complementary approach to their own care. A study involving 232 adult patients with established relationships with a rheumatologist in the university and outpatient setting evaluated for the usage of CAM therapy during a consecutive 6- and 12-month period. Approximately one-third of the responders reported using CAM at each survey period. Of the responders, 44% remained nonusers, while 12% started, 22% maintained, and 22% stopped CAM therapies. Of the participants 19% had fibromyalgia, 15% had osteoarthritis, and 39% had rheumatoid arthritis (RA). Seventy-four percent of these patients were receiving disease-modifying therapies or corticosteroids. (2)

The lay public believes herbals are safe; since they are found in nature, such remedies are assumed to be safer than allopathic prescription medications. Furthermore, the value of many of the herbs has been celebrated throughout the ages, without any mention of detrimental side effects. Due to the popularity of herbal medications, physicians frequently discover their patients are already using such therapies or are contemplating their use. Physicians often do not elicit a history of CAM therapies unless they directly question their patients about usage of herbal and dietary supplements. Patients rarely disclose using CAM therapies, as they do not view them to be drugs: CAM therapies are safe, natural supplements, not "drugs." Furthermore, many patients feel somewhat embarrassed to admit they use CAM or are concerned that their use of CAM will embarrass or annoy their allopathic doctors.

Since the passage of the Dietary Supplement and Health Education Act of 1994, which allowed for the sale of dietary supplements without the approval of the Food and Drug Administration, the availability and use of herbal supplements has soared despite limited knowledge as to modes of action or proof of efficacy or claims. Physicians need to focus

on obtaining a clinical history of their patient's use of CAM. Physicians also need to educate themselves to responsibly advise patients about CAM therapies and appreciate and anticipate CAM-associated side effects. This review summarizes the English language literature concerning herbal remedies commonly used in the treatment of rheumatologic diseases, discussing their efficacy, the immunological basis for the purported therapeutic effects, and their known toxicities (Table 1).

Methods

English-language literature from 1966 to 2004 was searched using PubMed as the database. Key words used include the scientific, common, and traditional names of herbs commonly used in the treatment of rheumatic conditions. Data extracted include indications for usage, mechanisms of action, therapeutic value, and side effects of these herbs.

Results

Gammalinolenic Acid

Gammalinolenic acid (GLA), an unsaturated fatty acid, is found in the oils of evening primrose (*Oenothera biennis*), borage seed (*Borago officinalis*), and black currant seed (*Ribes nigrum*). It is thought to be effective in decreasing joint inflammation in patients with rheumatoid arthritis (RA) and the sicca symptoms of Sjogren's syndrome. A diet rich in evening primrose oil has been found to elevate the serum concentration of GLA. GLA is metabolized to dihomogammalinolenic acid (DGLA), the immediate precursor of prostaglandin E₁ (PGE₁), an eicosanoid with known antiinflammatory and immunoregulatory properties. GLA itself cannot be converted to leukotrienes (LT) but it can form a 15-hydroxyl derivative that blocks the transformation of arachidonic acid to LTs. Increasing GLA intake may allow it to act as a competitive inhibitor of PGE₂ and LTs and thus suppress inflammation. (3)

Lipopolysaccharide (LPS)-induced interleukin-1 β (IL-1 β) release is followed by IL-1-induced IL-1 β release, a process termed "auto-induction." In vitro administration of GLA reduces LPS-induced pro-IL-1 β mRNA modestly, but markedly reduces the auto-induction of IL-1 α -induced pro-IL-1 β gene expression. While IL-1 β is important to host defenses, the amplification process may be excessive in genetically predisposed individuals and could predispose to inflammation. (4) When IL-1 receptor antagonist (IL-1Ra) was used to block auto-induction and IL-1 α -induced auto-induction, ap-

proximately 40% of IL-1 β released from LPS-stimulated cells was attributable to auto-induction. GLA reduces auto-induction of IL-1 β while leaving the initial IL-1 β response to LPS intact. GLA is thought to induce a protein that reduces pro-IL- β mRNA stability. Therefore, the reduction of IL-1 β auto-induction may be protective in patients with chronic inflammatory diseases. GLA also increases the amount of IL-1Ra secreted from LPS-stimulated human peripheral blood monocytes and mononuclear cells, increasing the serum IL-1Ra/IL- β ratio. (5)

Black currant seed oils (BCSO) are rich in GLA and alpha-linolenic acid (ALA). GLA and the eicosapentaenoic acid that is derived from ALA both suppress inflammation and joint tissue injury in RA. A 24-week double-blind, placebo-controlled randomized study of patients with active rheumatoid synovitis found that 1.4 g/day of BCSO resulted in reduction in signs and symptoms of disease activity. GLA reduced the number of tender joints by 36%, and the number of swollen joints by 28%, whereas the placebo did not cause significant improvement. GLA was well tolerated and effective in the treatment of RA. (6,7) Beneficial effects occur after 6 to 12 weeks of therapy. Smaller doses of GLA than used in this study have not been found to be beneficial. While no patients withdrew from the treatment group due to adverse reactions, patients did withdraw due to the large number of capsules administered (15). A review of studies gauging the effectiveness of GLA in RA has suggested that GLA is effective in RA but that further controlled studies are needed. (8)

The utility of omega-6 fatty acid GLA in primary Sjogren's syndrome was evaluated in a 6-month, double-blind, and placebo-controlled randomized trial of 90 patients. There was no statistically significant improvement in the primary endpoint of fatigue as assessed by the Visual Analog Scale (VAS) nor in the time needed for sleeping/resting during a 24-hour period. Similarly, the secondary endpoints of dry eyes, dry mouth, pain, changes in the Schirmer-I test, van Bijsterveld score, unstimulated whole sialometry, the use of artificial tears, or analgesics did not improve significantly. (9)

Side effects of GLA include headache, soft stools, constipation, flatulence, and belching. (10) Borage seeds contain small amounts of the liver-toxic pyrrolizidine alkaloids (PA). The consumption of 2 to 4 capsules of 500 mg of borage seeds can contain 5 to 10 μ g of PA. While there are no reports of adverse effects due to PA, its use during pregnancy and lactation is not recommended. (11) Evening primrose oil has been reported to exacerbate the symptoms of temporal lobe epilepsy and should not be used in patients with a history of epilepsy. (12) It may also cause seizures when taken with phenothiazines and increase the risk of seizure when used with anesthetics.

Harpagophytum Extracts

Harpagophytum procumbens is a perennial plant belonging to the family Pedaliaceae. It grows in the southern and eastern parts of Africa. The plant's common name, Devil's claw, is due to the fact that its fruit is covered with sharply curved, woody, thorny barbs; it is also called the wood spider and

grapple plant. Although the name of the plant comes from the appearance of its fruit, its medicinal properties are derived from use of its tuber. Devil's claw is used in traditional southern African medical therapies for arthritis, low back pain, neuralgia, headaches, as a digestive aid, and to reduce fever. (13)

The tubers contain a heterogeneous mixture of substances. Depending on the extraction process, the end product contains differing fractions of constituents with agonistic, antagonistic, synergistic, or complementary analgesic or anti-inflammatory properties. The leading compound, harpagoside, belongs to the iridoid glycoside family and accounts for much of the extract's effects. It has anti-inflammatory effects due to its action on eicosanoid biosynthesis. A study by Fiebich and coworkers on *Harpagophytum* extract SteiHap 69 (Steiner *Harpagophytum procumbens* extract 69) demonstrated its dose-dependent anti-inflammatory effects by preventing the LPS-induced synthesis of tumor necrosis factor alpha (TNF α) by human monocytes. However, harpagide and harpagoside had no effect on LPS-induced TNF- α release. (14)

In vitro studies have shown that biosynthesis of cysteinyl-leukotrienes (Cys-LT) and thromboxane after stimulation of cells with the Ca²⁺ ionophore A23187 can be inhibited by *Harpagophytum* extract. While this inhibition is a function of the harpagoside concentration, the activity of the extract is stronger than that of pure harpagoside. Therefore, other constituents may be responsible for the extract's activity or may synergize with harpagoside. It is hypothesized that plasma constituents may convert harpagoside into a more bioactive form. This is supported by the finding that harpagide, which is formed by the cleavage of harpagoside, does not display any activity. The additional removal of a glycoside moiety from harpagide creates harpagogenin, which can suppress A23187-induced eicosanoid biosynthesis. (15)

A study of different *Harpagophytum* extracts found that extract WS1531 has a stronger inhibitory effect on ionophore A23187-induced Cys-LT production than pure harpagoside or other extract fractions. As in previous studies, fractions without harpagoside did not have a pronounced inhibitory effect. There is also evidence that the extract reduces production of myeloperoxidase from stimulated neutrophils and may block the prostaglandin E2 inflammatory pathway by inhibiting cyclooxygenase-2 (COX-2) activity. Thus, harpagoside inhibits arachidonic acid metabolism and interacts with eicosanoid biosynthesis to produce anti-inflammatory effects. (16)

A double-blind, randomized 4-week study compared 2 daily doses of oral *Harpagophytum* extract WS 1531, 600 and 1200 mg/day, with placebo in 197 patients who were prone to chronic lower back pain with exacerbations. The study explored relief of pain in exacerbations worse than 5 on a 0 to 10 visual analog pain scale. Tramadol, up to 400 mg/day, was allowed as the rescue medication. Of the 183 patients who completed the study, 10 patients in the high-dose group were pain free, as were 6 in the low-dose group and 3 in the placebo group ($P = 0.027$). (17)

Doleteffin, an extract of *Harpagophytum*, was compared

Table 1 Profile of Common Herbal Medications Used in Rheumatic Diseases

Scientific Name	Common Name	Common Indications
<i>Oenothera biennis</i>	Evening primrose	RA, Sjogren's syndrome
<i>Borago officinalis</i>	Borage seed	
<i>Ribes nigrum</i>	Black currant seed	
<i>Harpagophytum procumbens</i>	Devil's claw	Osteoarthritis, low back pain, neuralgia, headaches, fever
<i>Ocimum americanum</i>	American basil	Fever, headache
<i>Ocimum basilicum</i>	Common basil	
<i>Ocimum sanctum</i>	Tulsi/ Holy basil	
<i>Salix alba</i>	White willow	Low back pain, osteoarthritis
<i>Salix fragilis</i>	Crack willow	
<i>Salix purpurea</i>	Purple willow	
<i>Salix daphnoides</i>	Violet willow	
<i>Tanacetum parthenium</i>	Feverfew	Fever, RA, migraines
<i>Tripterygium wilfordii</i>	Lei gong teng	RA, SLE, ankylosing spondylitis, psoriasis, nephropathy
Hook. F. (TwFH)	Thunder god vine	
<i>Uncaria tomentosa</i>	Cat's claw	SLE, chronic fatigue syndrome, osteoarthritis, bursitis
<i>Uncaria guianensis</i>		
<i>Urtica dioica</i>	Stinging nettle	Alopecia, eczema, gout, urticaria, allergic rhinitis, RA, BPH
<i>Zingiber officinale</i>	Ginger	Osteoarthritis, antiemetic, motion sickness, dizziness
<i>Alpinia officinarum</i>		

RA, rheumatoid arthritis; GLA, gammalinolenic acid; ALA, alpha-linolenic acid; DGLA, dihomogammalinolenic acid; SLE, systemic lupus erythematosus; BPH, Benign prostatic hypertrophy.

*These are some of the most common side effects; not all side effects are shown.

**Caution is recommended with use of all of these herbs as they have not been studied rigorously.

with rofecoxib in a randomized double-blind pilot study for the treatment of low back pain. Two groups of 44 participated in this study, 1 group receiving Doleteffin containing 60 mg of harpagoside for 6 weeks, the other receiving rofecoxib 12.5 mg/day. Both groups were allowed to use Tramadol up to 400 mg/day as rescue medication. There were no intergroup differences: studies with larger numbers of patients will be needed to show equivalence. (18)

Side effects reported due to *Harpagophytum* extracts include mild gastrointestinal disturbance. Traditionally patients with gastric or duodenal ulcers, gallstones, or diabetes are advised not to use these extracts. No long-term toxicities or drug interactions are known. (13)

Ocimum spp.

Species of *Ocimum* or basil have been used for centuries in Ayurvedic medicine. *Ocimum sanctum* is popularly known as the "Tulsi" or holy basil in India and has been used in the prevention and cure of the common cold, headache, and various forms of poisoning. It is also said to have antimalarial,

analgesic, antiinflammatory, and antipyretic properties. The oil contains at least 5 fatty acids: palmitic, stearic, oleic, linoleic, and linolenic. The linolenic acid in *O. sanctum* may be responsible for its antiinflammatory activity. (19) *O. sanctum*, *O. basilicum* (common basil, *Kali tulsi*), and *O. americanum* (American basil) contain various amounts of linolenic acid and show inhibition of carrageenan-, prostaglandin E₂ (PGE₂)-, leukotriene-, and arachidonic acid-induced paw edema. (20) The fixed oil, a nonvolatile oil, of *O. basilicum* has the highest percentage of linolenic acid and is the most efficacious. (20)

When compared with control, intraperitoneal administration of the fixed oil of *O. basilicum* at 3.0 mL/kg reduced rat paw edema induced by histamine by 69%, serotonin-induced edema by 50%, edema induced by prostaglandin by 44%, bradykinin-induced edema by 54%, and hyaluronidase-induced swelling by 55%. This suggests that the fixed oil possesses potential antihistaminic, antiserotonin, and antiprostaglandin activity. The same study demonstrated that *O. basilicum*-fixed oil inhibited arachidonic acid-induced

Table 1 (continued)

Active Constituents	Side Effects*	Cautions/Contraindications**
GLA ALA DGLA Harpagoside Harpagide Linolenic acid	Soft stools, constipation, flatulence, belching, seizures Gastrointestinal upset Harpagogenin	Temporal lobe epilepsy; use during pregnancy and lactation; concomitant use of anesthetics or phenothiazines Gastric or duodenal ulcers, gallstones, diabetes Use during pregnancy and lactation
Salicylic acid, tannins, flavonoids, salicin esters		Peptic ulcer disease, diabetes, hepatic or renal disorders, known allergy to aspirin; use in children
Parthenolide	Oral ulcers, nausea, vomiting, diarrhea, flatulence, emmenagogue, may alter bleeding time	Use in pregnant women; concomitant use of anticoagulants; ragweed allergy
Canin Triptolide	Diarrhea, nausea, vomiting, alopecia, dry mouth, headache, rash, skin pigmentation, angular stomatitis, oral ulcers, gastritis, weight gain/loss, diastolic hypertension, vaginal spotting, amenorrhea, osteoperosis	Peptic ulcer disease; premature menopause
Tripdiolide		
Alkaloids, polyphenols, quinovic acid glycosides	Nephrotoxic Urticarial rash, upset stomach	Underlying renal disease Use with sedatives, diabetic medications, antihypertensive medications
Gingeroles, caffeic acid, circumin	Dyspepsia, nausea	Possible effect on bleeding time

paw edema in rats in a dose-dependent mechanism, while neither indomethacin nor aspirin blocked the edema. When inflammation was induced by leukotriene B₄, *O. basilicum* and caffeic acid, a simple phenolic acid, reduced inflammation by 54 and 58%, respectively; this effect may be due to the oil's lipoxygenase inhibitory effect. *O. sanctum* (3 mg/kg) reduced arachidonic acid-induced paw edema in rats by 63%, whereas 10 mg/kg of indomethacin and 100 mg/kg of caffeic acid produced a 10 and 50% reduction, respectively. (21) These experiments illustrate that *O. sanctum* may inhibit both the cyclooxygenase and the lipoxygenase pathways of arachidonic acid metabolism. Further studies will have to be performed to elucidate the exact mechanism.

Use of *Ocimum* has not been reported to cause any known side effects. Dermatologic evaluation for contact dermatitis via patch testing for basil revealed 0 responders at concentrations of 10 and 25%. (22) However, there is concern about the presence of estragole, a compound found in variable amounts in basil volatile oil. While present in small amounts, it may be a carcinogen and may cause uterine contractions. Therefore, caution is indicated in the usage of this oil, especially in pregnant and lactating women. (23) No references to clinical trials could be found in the literature.

Salix spp.

Salix spp., willow tree, is regarded as one of the first examples of a modern drug developed from an herbal remedy. The analgesic and antipyretic properties of willow bark have been known since the ancient Egyptian, Greek, Indian, and Roman civilizations. The first record of its use is found in the Ebers' papyrus, an Egyptian treatise on medicine dating to over 3500 years. Hippocrates, Dioscorides, and Pliny the Elder all recommended decoctions, or hot water extracts, of willow bark for rheumatic pain. Hippocrates even recommended chewing on the leaves to relieve the pain of childbirth. (24) In 1763 Rev. Edmund Stone ground up willow bark to treat 50 parishioners with fever and ague (possibly malaria). He reported his findings to the Royal Society of London and stated "I have no other motives for publishing this valuable specific, than that it may have a fair and full trial in all its variety of circumstances and situations, and that the world may reap the benefits accruing from it." (25)

The oxidation of salicin, a constituent of willow bark, yields salicylic acid. It was produced by the mid 1800s, but its use was limited by the severe gastric irritation it caused. By 1853 Charles Gerhardt, a French chemist, neutralized salicylic acid by buffering it with sodium and acetyl chloride,

creating acetylsalicylic acid. The product worked, but he had no interest in marketing it and abandoned his discovery. It was rediscovered by Felix Hoffmann, a Bayer chemist, in 1897, who was looking for a more palatable medicine to treat his father's RA. By 1899, acetylsalicylic acid was marketed by Bayer under the tradename of Aspirin, one of the most successful drugs in history. (26)

There is a resurgence of interest in willow bark as a treatment for chronic pain syndromes. While white willow (*Salix alba*) is the willow species most commonly used for medicinal purposes, crack willow (*Salix fragilis*), purple willow (*Salix purpurea*), and violet willow (*Salix daphnoides*) are all salicin-rich and may be sold under the label of willow bark.

A 4-week randomized double-blind study evaluated the efficacy of willow bark extract in 210 patients with current exacerbations of chronic lower back pain that was at least 5 of 10 on the visual analog scale. Patients in the study received a total of 120 or 240 mg of salicin per day or placebo as twice a day dosing. Up to 400 mg a day of tramadol was allowed as the rescue medication. Those in the low-dose group received 1 pill of 393 mg of dry willow bark extract (equivalent to 120 mg salicin) and a placebo pill, while the high-dose group received 2 pills containing 393 mg of dry willow bark extract. The principal outcome measure was the number of patients who were pain-free and did not use any tramadol for at least 5 days in the last week of the study. In the last week of treatment 39% of those in the high-dose group, 21% in the low-dose group, and 6% of those receiving placebo achieved this endpoint ($P < 0.001$). Patients in the placebo group also required more tramadol for each week of the study ($P < 0.001$) than the treatment groups. (27)

Another double-blind, placebo-controlled study included 78 patients with osteoarthritis of the hip or knee randomized to receive 2 tablets a day of willow bark corresponding to 240 mg salicin/day or placebo for 2 weeks after a washout period of 4 to 6 days with placebo. Additional nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and analgesics were not allowed at any point of the study. A moderate analgesic effect was found: the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score was reduced by 14% after 2 weeks of active treatment, compared with an increase of 2% in the placebo group. The patient diary visual analog scale confirmed salicin's efficacy (investigator's assessment, $P = 0.0073$; patients' assessment, $P = 0.0002$). (28)

A 4-week open, randomized trial of 228 patients compared 12.5 mg/day of rofecoxib, a cyclo-oxygenase-2 inhibitor, with 240 mg/day of salicin in patients 18 to 80 years of age with acute exacerbations of low back pain. At the end of the 4 weeks 60% of patients in each group responded well to the treatment, as determined by an improvement of $\geq 30\%$ of the Arhus total pain index from its baseline. There was no difference in effectiveness between the 2 treatment groups and there was a similar incidence of adverse effects, with rofecoxib being 40% more expensive than willow bark extract. (29)

The major metabolites of salicin are gentisic acid, salicylic acid, and salicyuric acid, with salicylic acid being the major

component in the serum. After oral ingestion of willow bark, peak levels of salicylic acid were found in less than 2 hours. A salicin content of 240 mg corresponds to approximately 87 mg of acetylsalicylate, which is more cardioprotective than analgesic. This study also found that the bioavailability of the salicin in the formulation being evaluated was greater than that found in other studies. (30) This suggests that different formulations of willow bark extract result in different bioavailabilities, a concept that may be applicable to all herbal medications. Oral consumption of 240 mg of extract was found have a lesser effect on platelet aggregation than did acetylsalicylate ($P = 0.001$). (31) While salicin is thought to be the main analgesic in willow bark, other components such as tannins, flavonoids, and salicin esters may contribute to its overall effect. (28)

Willow bark has been criticized for its higher cost compared with NSAIDs and a lack of proof of safety. Osteoarthritis is a chronic condition; therefore, trials longer than 4 weeks must be performed before declaring salicin's safety and efficacy. The compound must be thoroughly evaluated for renal, hematologic, and hepatic function, as well as interaction with other drugs before its safety is established. (32) It would be prudent to avoid willow bark in children to avoid the risk of Reye's syndrome, and in patients with peptic ulcer disease, diabetes, or hepatic or renal disorders and those known to be allergic to aspirin.

Tanacetum parthenium

The aromatic herb feverfew, *T. parthenium*, has been used as a folk remedy for fever, RA, and migraines. The ancient Greeks called it *Parthenium* because legend has it that it was used to save the life of a worker who had fallen from the Parthenon during its construction. Pandonius Dioscorides, a first-century Greek physician, recommended it over 1900 years ago for "St. Anthonies fire, to all hot inflammations and hot swellings." (33)

The fresh leaves can be chewed and tablets made from the dried leaves are readily available in Europe and America. The active component, parthenolide, produces a dose-dependent inhibition in the production of thromboxane B₂ and leukotriene B₄ by rat peritoneal leukocytes and human polymorphonuclear leukocytes. (34) Feverfew also inhibits secretion of TNF- α and IL-1.

Studies of fractionated feverfew extracts have resulted in the identification of several sesquiterpene methylene butrolactoses, such as parthenolide and canin. These fractions mediate many of the properties attributed to the crude extracts. Both crude feverfew extracts and purified parthenolide can modulate adhesion molecule expression in human synovial fibroblasts. An elevation of adhesion-related molecules is found in the inflamed synovium of patients with rheumatoid arthritis. Pretreatment of synovial fibroblasts with either crude feverfew extract or purified parthenolide resulted in inhibition of the expression of intercellular adhesion molecule-1 (ICAM-1) induced by IL-1 (up to 95%), TNF- α (up to 93%), and interferon- γ (up to 39%) and a decrease in T-cell adhesion. (35)

An additional mechanism of feverfew is through the inhibition of I κ B kinase. Nuclear factor- κ B (NF- κ B) is a major transcription factor in the expression of multiple genes involved in the inflammatory process. NF- κ B is bound to I κ B, its inhibitor, in the cytoplasm of unstimulated cells. The phosphorylation of I κ B by I κ B kinase complex (IKK) leads to the degradation I κ B and the liberation of NF- κ B with its subsequent entry into the nucleus, where it activates several cytokine genes involved in the inflammatory process. IKK is composed of 2 active subunits, IKK α and IKK β . Parthenolide specifically binds to and inhibits IKK β . This results in maintenance of the I κ B-NF- κ B linkage and no NF- κ B activation or entry into the nucleus. (36)

IL-12 exerts multiple biological activities mainly through T cells and natural killer cells, by inducing their production of interferon- γ . Parthenolide significantly inhibited IL-12 production in LPS-activated mouse macrophages in a dose-dependent manner. This may be in part due to the down-regulation of NF- κ B binding to the p40- κ B sequence, a p40 promoter that contains the binding site for NF- κ B. (37)

NF- κ B plays a role in the generation of inducible nitric oxide synthase (iNOS) and dictates the transcription of acute phase proteins, cytokines, adhesion molecules, and antioxidant enzymes. Nitric oxide (NO), which can be generated from iNOS, has been implicated as a cause for migraines. Glyceryl trinitrate (GNT) is a NO donor that causes delayed migraines when infused into subjects susceptible to migraines. The latency for the onset of the headache may be due to the time needed to up-regulate the genes responsible for inducing the headache. A study by Reuter and colleagues found that parthenolide (3 mg/kg IP) inhibited GNT-induced NF- κ B activation, iNOS expression, and NO production by rat *dura mater*. (38) Therefore, blockade of NF- κ B may be an important target in the prevention and treatment of migraines.

An *in vivo* study of oral *T. parthenium* against acetic acid induced writhing in mice and carrageenan induced paw edema in rats revealed a dose-dependent antiinflammatory response. Feverfew exerted antinociceptive and antiinflammatory effects without altering the natural behavior of the animals. Administration of naloxone, an opiate antagonist, did not reverse the observed beneficial effects. (39) However, a double-blind, placebo-controlled study of feverfew (70 to 86 mg) in 41 women with active RA found no difference in stiffness, pain, grip strength, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or functional capacity at the end of the 6-week study. (40)

A systematic review of the efficacy of feverfew versus placebo for migraine by the Cochrane database found 4 trials that met inclusion criteria. The majority of the trials suggested a beneficial effect of feverfew compared with placebo. However, the largest trial, which was also the trial with the highest methodological quality, found no significant benefit of feverfew. (41) Since then, a randomized, double-blind, multicenter, controlled trial, with an adaptive design, evaluated the clinical efficacy and safety of MIG-99, an extract of feverfew, in 147 patients. Patients received MIG-99 at 2.08, 6.25, or 18.75 mg 3 times per day or placebo for 12 weeks

after a 4-week baseline period. Efficacy was gauged by comparing the number of migraine attacks during the last 28 days of the treatment period compared with baseline. MIG-99 was effective in only a small predefined subgroup of patients with at least 4 attacks during the 28-day baseline period. (42)

Feverfew may alter bleeding time and should not be used concomitantly with warfarin. (43) Other side effects include oral ulcers, nausea, vomiting, diarrhea, and flatulence. It should not be used in pregnant women as it is an emmenagogue, a substance that hastens and enhances menstrual flow, and may result in spontaneous abortions. Additionally, it is from the same family as ragweed and can elicit allergies due to its cross-reactivity.

***Tripterygium wilfordii* Hook F**

Tripterygium wilfordii Hook F (TwHF), a member of the *Celastraceae* family, is a perennial vine found in southern China. The herb is also called Lei Gong Teng, the Thunder God Vine. Derived from the root, not the flower or the vine, TwHF is a Chinese traditional remedy that has been used to treat a number of autoimmune and inflammatory diseases such as RA, systemic lupus erythematosus, ankylosing spondylitis, psoriasis, inflammatory lesions of leprosy, and nephropathy. TwHF extract inhibits the production of cytokines and other mediators from mononuclear phagocytes by blocking the up-regulation of a number of proinflammatory genes, including TNF α , COX2, interferon- γ , IL-2, prostaglandin, and iNOS. (44,45) The therapeutic and adverse effects of the preparation are thought to be due to triptolide and triptodioid. Both are diterpenoid compounds with epoxide groups and have immunosuppressive and antiinflammatory effects of similar efficacy *in vivo* and *in vitro*. (46)

When compared with control, 0.1 mg/kg/day of Triptolide via daily gavage feedings for 28 days significantly delayed onset of arthritis in rats immunized with bovine type II collagen ($P = 0.039$). Triptolide also significantly decreased the incidence of arthritis ($P = 0.024$), clinical arthritis severity score ($P < 0.0001$), histopathological arthritis severity score ($P < 0.0001$), and *in vivo* cell-mediated immunity to collagen ($P = 0.0004$). (47) Treatment of MRL-lpr/lpr mice with TwHF from age 7 to 21 weeks decreased the mortality rate and severity of glomerulonephritis and arthritis in MRL-lpr/lpr mice. (48) Clinical observations of the efficacy of 1 mg/kg/day of TwHF in 13 children with idiopathic nephrotic syndrome appeared promising. Eight of the children, 4 of whom were steroid-resistant, went into remission. In 4 subjects, remission was maintained for 3 years after withdrawal of treatment. In 3 children the proteinuria decreased and plasma protein concentrations normalized, and in 1 child the improvement was maintained for 4 years after treatment ceased. (49)

An additional antiinflammatory mechanism by which TwHF may work is its effect on the expression of cellular adhesion molecules. When incubated with TwHF, the amount of soluble E-selectin, ICAM-1, and vascular cellular adhesion molecule-1 expressed by human neutrophils, synovial fibroblasts, and endothelial cells was decreased. TwHF at

high concentrations (50 ng/mL) has a significant ($P < 0.05$) inhibitory effect on both secretion and expression of cellular adhesion molecules. (50) Cellular adhesion molecules of the endothelium and leukocytes can be targeted for the development of new therapies. (50) The extracts of TwHF have an immunosuppressive as well as direct antiinflammatory effect.

A prospective, double-blind, placebo-controlled study in patients with long-standing RA in whom conventional therapy had failed evaluated the efficacy of TwHF. Patients were randomly assigned to placebo, low-dose (180 mg/day), or high-dose (360 mg/day) TwHF. The study involved 35 subjects, 21 of whom completed the 20-week study. The number of patients withdrawing from the study due to adverse side effects was similar in the treatment and placebo groups. A therapeutic benefit, as defined by American College of Rheumatology (ACR) 20, was noted in the group receiving 360 mg/day of the ethyl acetate (EA) extract when compared with placebo ($P = 0.0001$). The effectiveness of the low-dose group was less than that of the high-dose group ($P = 0.027$), but greater than that of placebo ($P = 0.0287$). (45)

A phase I study of the EA extract of TwHF on 13 patients with RA found it to be safe in dosages of 570 mg/day with clinical improvement evident at dosages greater than 360 mg/day. Three patients withdrew during the first 16 weeks of dose escalation as they did not experience any improvement. Nine of the 10 remaining patients tolerated the EA extract at a dosage of 570 mg/day. Six of the 10 patients treated with 180 mg/day of EA showed disease improvement; 8 of the 9 patients who received EA extract at doses greater than 360 mg/day experienced both clinical and laboratory improvement. Improvement was defined by the ACR 20, in the number of tender joints, swollen joints, morning stiffness, physician global assessment, as well as a change in the ESR and CRP. One patient met ACR criteria for remission. (51)

Amenorrhea is a side effect reversible on withdrawal of the drug if it occurs in patients younger than 40 years of age and if the amenorrhea is present for less than 2 years. However, in perimenopausal patients it has been irreversible. (44,52) Osteoporosis may be an important problem in women who have had long-term administration of TwHF as it has been shown to significantly decrease bone mineral density in systemic lupus erythematosus patients. The degree of decrease is less severe than that induced by prednisone and was found to be more significant when TwHF was used for more than 5 years. (53)

The most common side effects of TwHF are diarrhea, nausea, vomiting, hair loss, dryness of mouth, headaches, leukopenia, thrombocytopenia, rash, skin pigmentation, angular stomatitis, oral ulcers, gastritis, abdominal pain, weight gain, weight loss, diastolic hypertension, and vaginal spotting. (44,45,52) This herb is not readily available in the United States. However, due to its long history of use in Chinese medicine, the ease with which it can be obtained in China, and recent studies demonstrating its efficacy, it is likely that there are patients who will obtain the extract and who are using it. Large-scale studies of TwHF in RA are currently being organized.

Uncaria spp.

Uncaria tomentosa (UT) and *Uncaria guianensis* (UG) are Peruvian herbs commonly known as "cat's claw." Small, claw-like thorns at the base of the leaf allow it to climb to heights of up to 100 feet. Traditionally, the bark of cat's claw is prepared as a decoction, said to be beneficial in the treatment of arthritis, bursitis, lupus, chronic fatigue syndrome, and disorders of the stomach and intestines. (54) Cat's claw bark contains oxindole alkaloids and polyphenols (flavonoids, proanthocyanidins, and tannins) and quinovic acid glycosides, pentacyclic alkaloids, and sterols. (55,56)

Utilizing the carrageenan-induced mice paw edema model, the in vivo antiinflammatory properties of a freeze-dried aqueous UT extract were compared with a spray-dried hydroalcoholic UT extract. While both extracts had antiinflammatory actions, the latter was shown to have significantly ($P < 0.05$) greater activity. Hydroalcoholic extract (50 mg/kg) produced an antiinflammatory effect similar to 7 mg/kg of indomethacin. The aqueous freeze-dried extract produced an equivalent effect but only at a higher dosage, 200 mg/kg. When Jurkat T-cells were pretreated with 500 $\mu\text{g/mL}$ of the hydroalcoholic extract, the activation of NF- κB was nearly completely reduced, while the aqueous extract only slightly prevented NF- κB binding at the same concentration. Both extracts had moderate-to-weak activity against cyclooxygenase (COX)-1 and -2. (55)

Decoctions of both freeze-dried and micropulverized UT have also been shown to inhibit TNF α production. LPS-induced TNF α production by murine macrophages (RAW 264.7) was significantly suppressed by pretreatment for 2 hours with UT ($P < 0.001$). This response was found at all the UT doses studied. The cytotoxicity of the free-radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) was determined by exposing RAW 264.7 to DPPH for 1 hour. DPPH decreased ($P < 0.001$) cell viability at all concentrations tested. When cells treated with DPPH were incubated with UT for 16 hours, there was an increase in cell viability ($P < 0.01$). Similar results were found when the cells were exposed to UV irradiation for 1 hour: ultraviolet (UV) irradiation significantly induced necrotic cell death ($P < 0.001$) and apoptosis ($P < 0.01$), but cells pretreated with cat's claw were protected against cell death ($P < 0.01$). In this series of experiments it was shown that cat's claw suppresses TNF α production by 65 to 85% ($P < 0.01$) and that this inhibition is approximately 1.5×10^4 more potent than its antioxidant activity. (56) Therefore, the primary mechanism of action of UT may be through its inhibition of TNF α production.

In vitro UT may also exert antiinflammatory effects by inhibiting LPS-induced iNOS gene expression, nitrite formation, cell death, and activation of NF- κB . Chronic intestinal inflammation was induced in rats by orally administering indomethacin (7.5 mg/kg) in drinking water (5mg/mL). UT (100 $\mu\text{g/mL}$) attenuated ($P < 0.05$) peroxynitrite (an oxidative agent) production and induced apoptosis in epithelial cells (HT29) and murine macrophage cells (RAW 264.7). (57) This inhibition of NF- κB activation may be an additional explanation of UT's ability to suppress chronic inflammation.

A 52-week, double-blind, placebo-controlled study of 40 patients with active RA who were receiving sulfasalazine or hydroxychloroquine evaluated the efficacy of UT. During the first phase of 24 weeks, patients received either UT extract or placebo and in the second phase of 28 weeks, all patients received the extract. Patients who received *Uncaria* during phase I experienced a 53% reduction in the number of painful joints compared with 24% seen in placebo ($P = 0.044$). Those who received *Uncaria* only during the phase II had a reduction in the number of painful ($P = 0.003$) and swollen joints ($P = 0.007$) and the Ritchie Index ($P = 0.004$) when compared with the values after 24 weeks of placebo. (58) Cat's claw can be nephrotoxic and there is a case report of acute renal failure in a patient with lupus. (59,60)

Urtica dioica

The stinging nettle, *Urtica dioica*, is a perennial plant found worldwide. The word urticaria is derived from the Latin term for nettle, which is "urtica." The root word "urere" in Latin means to burn and signifies the inflammatory, type I hypersensitivity reaction, which results from disruption of the sharp hairs that cover the leaves and the stem. Trichomes, the hollow hairs that cover the plant, contain histamine, acetylcholine, and 5-hydroxytryptamine among other compounds that are released when the structure is disrupted. The leaf has been used to treat alopecia, eczema, gout, urticaria, allergic rhinitis, and rheumatoid arthritis, while the root is used to treat benign prostatic hypertrophy. (61,62,63)

The pathogenesis of RA is not fully understood, but certainly involves T-cell activation. Dendritic cells are potent antigen-presenting cells (APC) that almost certainly play a role in T-cell-mediated diseases such as RA. (64) Immature dendritic cells express large amounts of CD36, a receptor important in the uptake of antigen, and receptors for inflammatory chemokines, such as chemokine receptor 1 (CCR 1), CCR 2, and CCR 5. (65) Dendritic cells mature to a form that presents antigens to T-cells, leading to a clonal expansion of T-cells and the production of proinflammatory cytokines. Mature dendritic cells express low amounts of CD36 and CCR 5. (66) CCR 5 is thought to contribute to the recruitment of Th1 cells and the development of RA. (67)

Human dendritic cells were evaluated for their ability to activate naive autologous T-cells in the presence of IDS 30, an extract of *U. dioica*. Cytokine production was measured by enzyme-linked immunosorbent assay (ELISA). Mature dendritic cells were generated using keyhole limpet hemocyanin (KLH). IDS 30 prevented the maturation of dendritic cells, as was measured by a dose-dependent down-regulation in the number of cells expressing CD83, a protein associated with mature dendritic cells. IDS 30 also decreased the expression of the costimulatory molecules CD80 and, to a lesser extent, CD86, while increasing the expression of CCR 5 and CD36 in a dose-dependent manner. CD80 and CD86 are important costimulatory molecules on dendritic cells and macrophages that provide the second signal required for the antigenic stimulation of T-cells. (68) Secretion of TNF- α was also reduced. This in vitro study shows that the therapeutic effect of

IDS 30 may be mediated through its suppression on the maturation of human myeloid dendritic cells leading to a reduction of T-cell induction. (69)

CD36 is found on platelets, adipocytes, monocyte/macrophages, endothelial cells, and red blood cells (RBC)s and serves as a receptor for oxidized LDL. It may be involved in the clearance of apoptotic polymorphonuclear neutrophils (PMNs) in the first step of a process leading to cell clearance. (70) CD36 is abundantly expressed in the rheumatoid synovium and has an important role in regulating T-cell function. It has been implicated in decreasing the threshold for T-cell activation when present as the trimolecular complex CD47-TSP-1 (Thrombospondin-1)-CD36. TSP-1, a transiently expressed matricellular protein known to promote chemotaxis to inflammatory sites and the receptor for CD36, is abundantly expressed in inflamed tissues. CD47 binds to the C-terminus of TSP and is a T-cell membrane glycoprotein indicated to be comitogenic with the TCR/CD3 complex. (71)

Up-regulation of matrix metalloproteinase (MMP) expression leads to enhanced degradation of extracellular matrix, characteristic of inflammatory joint diseases. Hox alpha, a stinging needle extract acid, was found to significantly suppress in vitro IL-1 β -induced expression of MMP-1 (interstitial collagenase), MMP-3 (stromelysin 1), and MMP-9 (gelatinase B) by human chondrocytes. (72) This may be one of the mechanisms by which *Urtica* is efficacious in RA.

IDS 23, another standardized preparation of *Urtica*, was studied by Riehemann and coworkers for its inhibition of NF- κ B activation. The study suggests that *Urtica* extracts inhibit the proteolytic degradation of I κ B by either inhibiting I κ B kinases or signaling molecules further upstream, thus inhibiting activation of NF- κ B pathway. (73) An additional target may be the transcription factor AP-1, a complex of the Fos and Jun proto-oncogene products, implicated in the hyperplasia of synovial tissues. AP-1 targets MMP-1 and MMP-3, which play a major role in the degradation of cartilage matrix molecules. (73) Previous studies have shown that inhibition of AP-1 may prevent collagen-induced arthritis in animal models. (74)

A study of 20 healthy subjects who received 2 capsules bid of IDS 23 for 21 days revealed that after 7 and 21 days of ingestion there was a decrease of LPS-stimulated TNF- α release by 15 and 24%, respectively, while IL-1 β was reduced by 19 and 39%, respectively. When IDS 23 was added in vitro to whole blood, there was an inhibition of LPS-stimulated TNF- α and IL-1 β secretion which correlated with the duration of drug ingestion. (75)

A randomized, double-blind crossover study in 27 patients with osteoarthritis pain at the base of the thumb or index finger, in which patients applied stinging nettle leaf extract daily for 1 week to the area of pain, revealed reductions in both the VAS and the health assessment (disability) questionnaire that were significantly higher than with placebo ($P = 0.026$ and $P = 0.0027$). (76) The effect of *U. dioica* in RA has not been studied.

Side effects attributed to *Urtica* include urticarial rash and upset stomach. Caution should be used when used with sed-

atives, diabetic medications, and antihypertensive medications.

Zingiber officinale

Z. officinale belongs to the Zingiberaceae family, commonly referred to as “gingers.” Ginger has been used in Auyurvedic and Sino-Japanese medicine for thousands of years for inflammation and rheumatism. Other uses include the dizziness, nausea, and vomiting of motion sickness; postoperative vomiting; and vomiting of pregnancy. (77)

Z. officinale contains hundreds of known constituents, including gingeroles, beta-carotene, capsaicin, caffeic acid, and curcumin. (78) The rhizomes of *Z. officinale* are potent inhibitors of prostaglandin and LT synthesis. (79) Ginger extract has also been shown to inhibit the production of TNF α via the inhibition of gene expression in human osteoarthritis synoviocytes and chondrocytes. (80) Ginger extract also decreases carrageenan-induced rat-paw edema. (81)

A randomized, double-blind, placebo-controlled trial studied the effects of ginger in the treatment of knee osteoarthritis in 261 patients. During the treatment period patients ingested 255 mg of EV.EXT 77, a patented ginger and galangal, a spice that is closely related to ginger and is of the ginger species. The extract contained 500 to 4000 mg of dried ginger rhizomes and 500 to 1500 mg of dried galangal rhizomes and was given twice daily. The primary endpoint of the study was pain in standing after 6 weeks of treatment with improvement defined as ≥ 15 mm on the VAS pain scale. In the ginger extract group 63% versus 50% in the placebo group showed improvement ($P = 0.048$). The study failed to show improvement in quality of life, decrease in the consumption of the rescue analgesic (acetaminophen), or statistical improvement in the WOMAC score. The dosage of medications used in this study was based empirically on what is typically consumed in Europe. Patients in this study had an average body mass index of 30 and might have benefited from a higher dosage. Those receiving the ginger extract experienced more gastrointestinal side effects (116 events in 59 patients, 45%) than did those who received placebo (28 events in 21 patients, 16%). (82) While a significant number of patients experienced side effects, they were mild and mostly gastrointestinal, dyspepsia, and nausea.

Another randomized, placebo-controlled, crossover study of ginger extracts and ibuprofen in patients with osteoarthritis of the hip or knee found efficacy was ibuprofen > ginger extract > placebo for VAS scores on pain and the Lequesne index. A statistically significant effect of ginger extract could only be demonstrated by explorative statistical methods in the first period of treatment before crossover. (83) At present, ginger appears to be of limited efficacy for osteoarthritis.

Discussion

Herbal medications, a major component of CAM therapy, are becoming increasingly popular and are of much interest to the public and health care providers. Many patients use CAM therapy thinking that natural remedies with a long history of

use are safe, without any knowledge of their true clinical efficacy or side effects. Guidance to inquiring patients by their health care providers is often limited by a lack of familiarity of the practitioner with these compounds. Even if the practitioner has knowledge of the literature, it is lacking in scientifically verified information on the topic. Much of CAM therapy has not been well studied and there is no central source for information about the many commonly used herbal remedies. The action of many of the herb-derived preparations can be affected by the extraction procedure utilized, dosage, duration of treatment, and route of administration. There is a lack of uniformity of preparations, within and between manufacturers. Furthermore, the efficacy of the botanical may be due to synergistic action of multiple compounds or a balance of synergist and antagonist actions, so that testing of single compounds may not be a fair estimation of the efficacy of the “crude” extracts used by patients. Therefore, lack of efficacy of CAM therapy may be multifactorial and these preparations will have to be studied further before efficacy can be determined.

In the United States, herbal medications are not subject to the rigorous testing and high standards to which allopathic medications are held. There is no assurance that the customer is receiving the advertised product at the claimed dose or with an acceptable purity. An analysis of the content of parthenolide in commercially available feverfew products demonstrated wide variation. Consumption of the daily dose of dried feverfew leaf as recommended by the label revealed a 10-fold variation, while the intake of parthenolide varied by 160-fold. (84) The problem is further complicated by the sale of combinations of several herbs and the possibility of adulteration with contaminants. Many products contain heavy metals, undisclosed prescription or over-the-counter medications such as glyburide, sildenafil, colchicine, ephedrine, phenacetin, or phenylbutazone. (85,86) Standardization and monitoring for adulteration is necessary to ensure quality and to ensure toxic substances are not present. Physicians should play an active role in obtaining federal oversight of these preparations to assure the safety of our patients. Only by controlled studies and surveillance can we learn the true depth and breadth of adverse effects of these preparations.

The concomitant use of CAM therapy with prescription or over-the-counter medications may lead to adverse herb-drug interactions, especially in the elderly who are more likely to be using multiple drugs. Borage seed oil, feverfew, ginger, garlic, and willow bark have all been implicated in bleeding or in potentiating the effects of warfarin therapy. (43) Therefore, CAM therapy is not without its risks, some of them potentially fatal. Rigorous testing evaluating the mechanisms of action, side effects, tolerability, and potential drug interactions have to be performed before recommending usage of CAM therapy. Certainly further insights into mechanisms may allow us to better predict some toxicities, eg, effects on prostaglandin production relating to gastrointestinal side effects.

Elucidation of the mechanisms of various CAM therapies may also be instrumental in discovering new molecular targets for the treatment of diseases. Such knowledge will help

educate practitioners, allowing them to better counsel their patients and aid in the development of new pharmaceuticals via the rediscovery of age-old compounds.

Thus, for a number of reasons, it is crucial that we determine from our patients what nonprescription therapies they are using. Herbal remedies are often used, but their use is often not volunteered to the clinician. Specific questioning is warranted, even if we may be skeptical of the efficacy of the therapy being used.

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