Review Article

The Impact of Complementary and Alternative Treatment Modalities on the Care of Orthopaedic Patients

David T. Rispler, MD
Julie Sara, MD

Abstract

The use of complementary and alternative medicine is widespread and popular with the lay public. Although prevalence of use varies among specific patient populations, complementary and alternative medicine, in particular herbal remedies, are widely marketed and used by orthopaedic patients. Herbal supplements can have a negative impact on the perioperative period and may interact with conventional medicines used to manage chronic conditions. Physician-patient communication often does not include the subject of alternative medicines, leading to underreporting of use. Orthopaedic surgeons should adopt methods to routinely elicit from their patients the use of complementary and alternative medicine and should monitor and counsel patients on potential side effects and drug-herb interactions. Preoperative instructions should include cessation of the use of herbal supplements.

From the Department of Orthopaedic Surgery, Michigan State University College of Human Medicine, Grand Rapids, MI.

Neither of the authors nor any immediate family member has received anything of value from or has stock in a commercial company or institution related directly or indirectly to the subject of this article.

J Am Acad Orthop Surg 2011;19: 634-643

The use of complementary and alternative medicine (CAM) in the United States is widespread. The prevalence of use increased exponentially from 1990 to 1997 but since then appears to have stabilized, at approximately one third of the US population.[1,2] Specific subpopulations of patients exhibit greater use. Older patients (≥65 years) and those with chronic pain or chronic conditions associated with pain have the greatest prevalence, ranging from 52% to 64%.[3,4] Among ambulatory surgical patients, prevalence of CAM use ranged from 27% to 43% within 2 weeks of surgery.[5,6] Among orthopaedic patients, trends are similar, with a prevalence ranging from 35% to as high as 70%.[7,8] The associated cost is large: an estimated $33.9 billion was spent on CAM products and services in 2007.[9]

Many forms of CAM exist, including herbal, nutritional, and megavitamin supplements; physical manipulation (eg, massage, chiropractic); and other modalities, (eg, aromatherapy, self-help organizations, folk and ayurvedic remedies, hypnosis, energy healing). Herbal supplementation is perhaps the most common: an estimated 38 million US adults use herbs.[2]

Unlike conventional medicines, herbal remedies are not regulated by governmental agencies such as the FDA. The Dietary and Supplement Health and Education Act of 1994 classified herbal remedies as dietary supplements, which rendered them exempt from the safety and efficacy regulations required of prescription and over-the-counter medications. As a result, the safety and efficacy of individual herbal remedies have not

been thoroughly evaluated in large clinical trials. Furthermore, limited information is available in the medical literature on drug-herb interactions. Compounding these issues, herbal remedies in particular are marketed to consumers with labels such as "natural" and "homeopathic," which consumers may interpret as being synonymous with "safe." This attitude may contribute to the widespread practice of taking prescription medications simultaneously with herbal medicines, which is practiced by approximately one in five prescription users (approximately 15 million adults).[2] In contrast to the assumption that these remedies are safe, a recent study reported the deaths of four children that resulted from the use of alternative medicine used in place of conventional medicines.[10]

Given the widespread use of CAM, orthopaedic physicians must educate themselves regarding the potential side effects, drug interactions, and perioperative complications of herbal remedy use. It is also necessary to develop standard techniques for eliciting from patients their history of alternative therapy use.

Eliciting CAM Use by Patients

Underreporting of CAM use is a well-documented phenomenon. In one study, 64% of patients with osteoarthritis (OA) in an orthopaedic clinic underreported CAM use, and a surgical population with OA underreported its use by 40.6%.[8] Nondisclosure of CAM use creates the potential for drug-herb interaction and risk.

One of the main reasons that patients do not disclose the use of CAM is that they may not believe it is important information to convey to the physician.[7] This attitude may be a reflection of marketing strategies, which tout supplements as natural remedies, in turn creating the perception that no side effects are associated with herbal supplement use.[7] However, at least one study has documented that physicians may choose not to record the use of CAM when patients report it.[3] Other reasons for nondisclosure include patient perception of prejudice against their use by physicians and physician ignorance of herbal medications.[11]

Because of the prevalence of the use of CAM, it is important that the use of these supplements be documented in all patients. However, routine patient histories often do not elicit CAM use.[3,8] Physicians must develop and implement techniques to monitor CAM use in their patients. Unbiased, specific questions regarding CAM use, with checklists, increases patient reporting of herbal supplement use.[7,8] Such lists may prompt patients to name nonprescription medications that they use even if the medications are not present on the list. Patients should be counseled to fully disclose all medications—prescription, over-the-counter, and herbal remedies. Finally, continual monitoring, in the form of an annual update of this information, helps in the assessment of new herbal medications that patients may begin taking.

Counseling Patients Perioperatively

The perioperative period presents a unique challenge in monitoring CAM use because of the physiologic alterations associated with surgery as well as with the drugs administered during and after surgery. CAM use may contribute to increased blood loss and the potential need for blood transfusions. As mentioned, the problem for surgeons is a pervasive one; the prevalence of herbal supplement use perioperatively was reported in one study to be 27%.[5] Because of the absence of regulatory oversight, no comprehensive research is available on the physiologic effects of many herbal remedies. Neither the half-lives of the active ingredient or ingredients of herbal remedies nor the pharmacokinetic and pharmacodynamic properties are well established. Adding to this uncertainty, formulations often are not standardized from product to product.

As a result of this lack of data, no standardized timetables exist for cessation of herbal medications before surgery. This is in contrast with conventional medicines, use of which is stopped before surgery on a timetable that reflects the half-life of these drugs and their potential for perioperative complications. For example, the half-life of ibuprofen is 1.6 to 1.9 hours, and it is recommended that this drug be discontinued 1 to 2 days before surgery to reduce the risk of bleeding.[12] Likewise, naproxen, with a half-life of 15 hours, is discontinued 3 days before surgery. By contrast, aspirin, which irreversibly inhibits platelet activity, must be discontinued 7 to 10 days before surgery, thereby allowing sufficient time for platelet regeneration.

In general, given the lack of information on the metabolism of herbal remedies, it is prudent to counsel patients to cease taking herbal remedies at least 1 week before surgery because of the possibility of producing negative outcomes.[13] In regard to herbal remedies with long or unknown half-lives, cessation 2 weeks before surgery is warranted. Herbal supplementation should be avoided in the postsurgical period until the wound heals and the risk of hematoma and subsequent infection has subsided, usually 1 to 2 weeks, de-

pending on the magnitude of the surgery.

Conservatively, any herbal remedy with the potential to interact with anticoagulant therapy should not be taken within 2 weeks of surgery. Additionally, such herbs should not be used until anticoagulants are discontinued. Depending on the anticoagulant, this delay may be for 2 to 4 weeks. Finally, in patients whose CAM use stems from cultural beliefs or lifestyle, communication between the primary care physician, anesthesiologist and naturopath may be warranted.

Common Supplements and Potential Side Effects

The popularity of herbal supplements changes over time, but use of the herbs discussed here has been demonstrated as recently as 2009[14] (Table 1). Table 2 provides a summary of the marketed uses, the potential side effects and drug interactions, and the perioperative and postoperative recommendations for the 12 popular herbal supplements discussed below.

Table 1

The 20 Top-selling Herbal Supplements[a]

	Rank	
Supplement	**2009**	**2008**
Cranberry	1	1
Soy	2	2
Saw palmetto	3	4
Garlic	4	3
Echinacea	5	6
Ginkgo biloba	6	5
Milk thistle	7	7
St. John's wort	8	8
Ginseng	9	9
Black cohosh	10	10
Green tea	11	11
Evening primrose	12	12
Valerian	13	13
Horny goatweed	14	14
Bilberry	15	17
Elderberry	16	16
Grape seed	17	15
Ginger	18	18
Aloe vera	19	—
Horse chestnut	20	19

[a] Popular herbal supplements sold via food, drug, and mass market retailers in 2009.[14] Data do not include all retail markets (eg, Internet sales direct marketing, warehouse club sales). Rankings in 2008 are given as a comparison.[15]
— = not reported

The assessment of risks associated with herbal use is complicated by several factors, but the most important is the lack of data from large, well-designed placebo-controlled clinical trials. The incidence and severity of adverse events associated with herbal supplement use is not studied, and postmarketing surveillance information is not cohesively monitored by the FDA or any other governmental agency.[16,17] Adverse effects and drug-herb interaction have been reported in the literature, mainly as case reports.[18] Such case reports are helpful, but often they do not establish a cause-and-effect relationship between herbal remedy and side effect. In general, herbal remedies can potentiate the side effects or change the efficacy of conventional medicines by interfering with the metabolism or bioavailability of these medicines via cytochrome P450 (*CYP*) enzymes.[3,7,19,20] Further, herbs can act synergistically or additively to change the efficacy of a drug. The recommendations below are based on such resources and represent our current understanding of these herbs.

Cranberry (*Vaccinium macrocarpon*) is mainly used to treat or prevent urinary tract infections (UTIs) by preventing adherence of harmful bacteria to the urinary tract epithelium. Several clinical trials support the assertion that cranberry products reduce the number of UTIs in women with recurrent infections; however, the dropout rates in these trials were high, and no reliable evidence exists that cranberry can treat UTIs.[21] Anecdotal evidence that cranberry juice interacts with warfarin to potentiate anticoagulation was tested in a clinical trial of warfarin users; no pharmacokinetic effect on warfarin was observed.[22] Side effects include mild diarrhea. Cranberry can potentiate kidney stones in at-risk patients.

Echinacea (*Echinacea purpurea, E angustifolia, E pallida*) is used as prophylactic treatment for upper respiratory tract infections. Research shows that echinacea stimulates the immune system.[13,17,23] However, long-term use of echinacea may be immunosuppressive and increase the risk of perioperative opportunistic infec-

Table 2

Common Supplements

Supplement	Marketed Uses	Potential Side Effects	Drug-herb Interactions	Perioperative Cessation	Postoperative Resumption
Cranberry	Prevent/treat UTI	—	Potentially warfarin	2 wk	2 wk
Echinacea	Upper respiratory infections (prophylaxis)	Long-term use may lead to immunosuppression	Immunosuppressives	2 wk	2 wk
Feverfew	Prevention of migraine headaches	Rebound headaches	Warfarin, aspirin	1 wk	After AC therapy
Garlic	Hypercholesterolemia/ blood pressure reducer	Bad breath, body odor	Disrupts anticoagulants and cyclosporine, inhibits platelet aggregation	1 wk	After AC therapy
Ginger	Motion sickness, postoperative nausea, arthritis, bronchitis	Mild heartburn	Warfarin and aspirin	2 wk	After AC therapy
Ginkgo	Memory loss, vascular disease, tinnitus, macular degeneration	Rare; GI upset, headaches, dizziness	Aspirin, ibuprofen, rofecoxib, COX-2 inhibitors, cilostazol	36 h	After AC therapy
Ginseng	Bleeding disorders, stress, atherosclerosis, memory, headaches, cancer	Lower blood glucose; insomnia, headache	May antagonize warfarin, may act synergistically with MAOIs	1 wk	After AC therapy
Milk thistle	Liver cirrhosis, hepatitis	Mild GI upset	Halothane, clopidogrel, warfarin	2 wk	After AC therapy
Saw palmetto	Urinary dysfunction due to prostatic hyperplasia	Cardiac symptoms, hypoglycemia	May have additive effect with anticoagulant therapy	2 wk	After AC therapy
Soy	Menopause, osteoporosis, hypercholesterolemia, cancer	Mild GI upset	May antagonize tamoxifen	None	None
St. John's wort	Depression, anxiety	Mild nausea, bloating, constipation	Antifungals, statins, Ca^{2+} channel blockers, immunosuppressives, warfarin	1 wk	After AC therapy
Valerian	Sedative	Headache, drowsiness, rare hepatotoxicity	Anesthetic synergism	1 wk	2 wk

AC = anticoagulant, COX-2 = cyclooxygenase-2, GI = gastrointestinal, MAOI = monamine oxidase inhibitor, UTI = urinary tract infection, — = not reported

tion; thus, concomitant use with immunosuppressive medicines is discouraged.[17] For this reason, it is prudent for patients to stop taking echinacea 2 weeks before surgery and resume its use no earlier than 2 weeks after surgery.

Feverfew (*Tanacetum parthenium*), a popular herbal remedy used for the prevention of migraine headaches, functions by inhibiting serotonin release. Feverfew has shown some benefit in several clinical trials, although the largest trial to date did not show any benefit.[24] Feverfew inhibits collagen-induced platelet aggregation. Thus, persons taking blood thinners (eg, warfarin, enoxaparin, ticlopidine, clopidogrel, aspirin) should avoid taking feverfew. Acute withdrawal symptoms after cessation may occur, including rebound headaches. Postoperatively, feverfew should not be resumed until after anticoagulant therapy.

Garlic (*Allium sativum*) is used to reverse hypercholesterolemia and to decrease blood pressure. The mechanism of action is unknown. Data from clinical studies are inconclusive; garlic shows only very modest or no improvements in total cholesterol.[23] Research has shown that garlic inhibits thromboxane production and platelet aggregation in a dose-dependent manner. It also may potentiate postoperative bleeding by interaction with other platelet inhibitors (eg, prostacyclin, forskolin, in-

domethacin, dipyridamole).[13] Garlic has a short half-life; it should be stopped 1 week before surgery and should not be resumed postoperatively until anticoagulant therapy is stopped. Garlic reduces serum levels of cyclosporine and therefore should be avoided in persons taking this drug.[25]

Ginger (*Zingiber officinale*) is used to treat motion sickness, postoperative nausea, and inflammation resulting from arthritis and bronchitis. The mechanism of action is unknown but is thought to be increased gastrointestinal (GI) cell motility, mediated in part through 5-hydroxytryptamine receptor inhibition. Ginger may inhibit platelet aggregation and cause GI upset.[13,26] It has the potential to interact with antiplatelet therapies and increase the risk of bleeding.

Ginkgo (*Ginkgo biloba*) is marketed for several uses, including cognitive decline associated with Alzheimer disease, peripheral vascular disease, vertigo, macular degeneration, tinnitus, and erectile dysfunction. Among its effects, ginkgo appears to inhibit platelet-activating factor, and bleeding time may be prolonged when used with cilostazol: several case reports attribute spontaneous intracranial hemorrhage or postoperative bleeding to use of ginkgo.[13,25] Ginkgo increases the risk of stomach bleeding and should not be used concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 inhibitors.[18]

Ginseng (*Panax quinquefolius*) is used to prevent the effects of aging, decrease stress, improve energy levels, and treat bleeding disorders, atherosclerosis, appetite loss, memory loss, headaches, and cancer. Ginseng decreases postprandial blood glucose levels and inhibits platelet aggregation, leading to increased coagulation times in animal models.[27] However, ginseng use leading to a decrease in warfarin anticoagulation has been reported.[28] Concerns regarding its use include hypoglycemia in the perioperative period and bleeding.

Milk thistle (*Silybum marianum*) is marketed for the treatment of liver cirrhosis and hepatitis and for general liver health. It is thought to alter hepatic cell membrane structure and prevent its penetration by toxins.[29] More recently, it has been marketed as an agent to reduce insulin resistance in patients with type II diabetes mellitus and as an anticancer agent, based on reported antioxidant properties. Clinical research supporting a benefit to patients with cirrhosis resulting from alcohol use or hepatitis comes from trials that were not well designed, leaving open the question of any benefit to be derived from milk thistle.[29] Side effects are mild and can include stomach upset.

Saw palmetto (*Serenoa repens*) is commonly used to alleviate urinary dysfunction associated with benign prostatic hyperplasia. Saw palmetto appears to decrease the uptake of testosterone and dihydroxytestosterone. Results from blinded clinical trials suggest that saw palmetto does not significantly decrease symptoms, prostate size, or peak urinary flow compared with placebo, although it causes few side effects.[17,30,31] Patients should stop taking saw palmetto at least 2 weeks before surgery because it may increase bleeding time.

Soy is used as a remedy for hypercholesterolemia, hot flashes associated with menopause, memory difficulty, elevated blood pressure measures, several forms of cancer, and osteoporosis. Little evidence exists to support the beneficial role of soy in these conditions, with the exception of a slight decrease in low-density lipoprotein associated with its use.[32] The isoflavones in soy are considered to be the active components, but the mechanism of action of soy is unknown.[32] Soy consumption has not been associated with negative side effects other than mild nausea, constipation, and bloating.

St. John's wort (*Hypericum perforatum*) is commonly used to treat mood disorders such as depression. Hypericin and hyperforin are thought to be the active ingredients; hypericin inhibits monoamine oxidase, and hyperforin inhibits the reuptake of serotonin, norepinephrine, dopamine, and γ-aminobutyric acid (GABA). A systematic review of clinical trial data suggests that St. John's wort is effective in the treatment of major depression, with fewer side effects than conventional medicines.[33] Side effects include nausea, headaches, confusion, fatigue, constipation, and photosensitivity. St. John's wort interacts with many other conventional medicines. It increases the metabolism of concomitantly administered drugs by inducing the metabolic liver enzymes *CYP3A4* and *CYP2C9*,[26] thereby reducing the efficacy of antifungal drugs, statins, and calcium channel blockers. St. John's wort may interact with immunosuppressive drugs and can potentially lead to transplant rejection. Finally, it reduces the effectiveness of warfarin. St. John's wort should be stopped at least 1 week before surgery or chemotherapy.

Valerian (*Valerian officinalis*) is commonly used as a sedative for insomnia. Clinical data on valerian are heterogeneous and suggest that it is of little benefit to insomnia. Valerian is reported to act on GABAergic pathways. Side effects include headache, drowsiness, and cardiac symptoms.[34] One case of cardiac symptoms and delirium following surgery has been reported and attributed to valerian withdrawal, suggesting that valerian may interact with perioperative anesthesia.[26] Valerian should be stopped at least 1 week before surgery to avoid such interaction.

Table 3

Supplements Marketed for Osteoarthritis

Supplement	Marketed Uses	Potential Side Effects	Drug-herb Interactions	Perioperative Cessation	Postoperative Resumption
Glucosamine	OA, inflammation	GI upset, headache, leg pain, itching, allergic reaction	Warfarin, hypoglycemia	2 wk	After AC therapy
Chondroitin	OA, inflammation	GI upset, heartburn	Blood thinners	2 wk	After AC therapy
SAM-e	OA, depression	Nausea, diarrhea on initiation of therapy	Serotonin syndrome	1 wk	2 wk
ASUs	OA, inflammation	Headache, GI upset	None characterized	1 wk	2 wk
Black cohosh	Menopause, OA	GI upset, rash, dizziness, hepatotoxicity	Tamoxifen, anticancer agents	1 wk	2 wk
Boswellia	OA, cough, asthma	Unknown	Mild nausea, diarrhea	1 wk	2 wk
Bromelain	Burn wounds, OA	GI upset	Warfarin, phenytoin, tetracycline	2 wk	After AC therapy
Cat's claw	Immunostimulant, OA	Hypotension, diarrhea	Antihypertensives, anticoagulants, cyclosporine	2 wk	After AC therapy
Flavocoxid	OA	Nausea, diarrhea, gas	Additive with antiplatelet drugs, statin interference	2 wk	After AC therapy
Thunder god vine	Immunostimulant, RA	GI upset, rash, headache, hair loss	Unknown	1 wk	2 wk
Turmeric	OA, RA, digestive aid	Indigestion, allergic dermatitis	Inhibits many cytochrome *P450* enzymes, warfarin	2 wk	After AC therapy

AC = anticoagulant, ASUs = avocado/soybean unsaponifiables, GI = gastrointestinal, OA = osteoarthritis, RA = rheumatoid arthritis, SAM-e = S-adenosylmethionine

Osteoarthritis

The treatment of painful musculoskeletal disease, in particular, OA, is a large proportion of any orthopaedic surgeon's practice. In this patient population, it is important to consider that conventional medicines prescribed for OA are prone to produce their own set of undesirable side effects. For instance, patients with OA are readily prescribed NSAIDs, which reduce inflammation, pain, and stiffness in arthritic joints. However, side effects can include GI ulcers and bleeding, renal failure, and worsening of the symptoms of preexisting congestive heart failure. An estimated 16,000 deaths annually are related to bleeding of peptic ulcers in patients taking NSAIDs.[35]

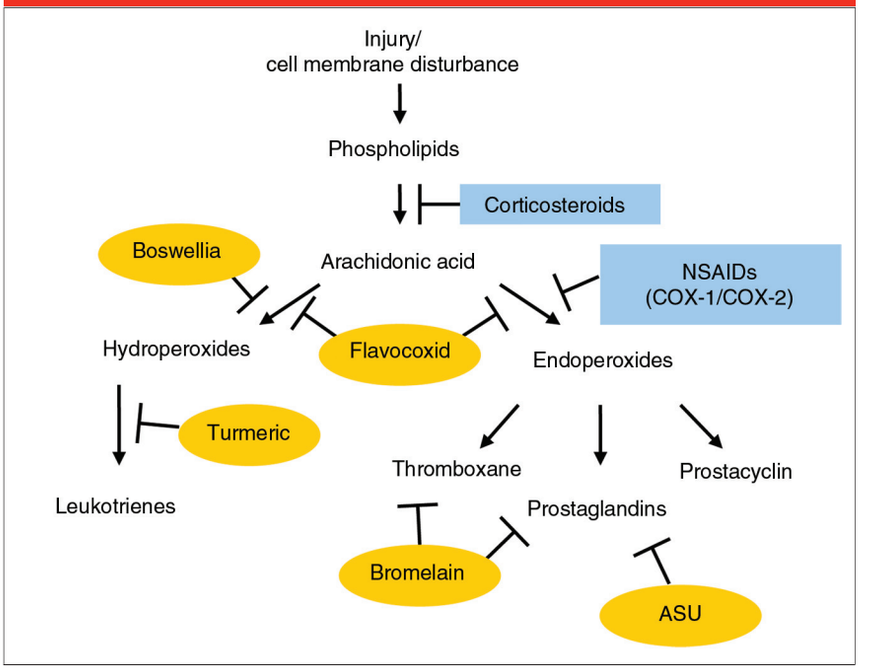
Another example is the injection of natural hyaluronic acid (ie, viscosupplementation) from rooster comb. Side effects range from mild allergic reaction to anaphylaxis in persons with chicken or egg allergies. Currently, five FDA viscosupplements are approved for use in the United States. Synvisc (Genzyme, Cambridge, MA), Hyalgan (Sanofi-aventis, Bridgewater, NJ), and Supartz (Smith & Nephew, Memphis, TN) have the potential for allergic reaction and carry black box warnings against their use in allergic persons. The bioengineered viscosupplements Orthovisc (DePuy, Warsaw, IN) and Euflexxa (Ferring Pharmaceuticals, Parsippany, NJ) can be used to avoid such reactions.

A large number of CAM supplements are marketed to patients with OA. Because of the high probability of unwanted side effects from conventional medicines, monitoring the use of herbal medicines is critical to the successful management of symptoms and side effects in these patients (Table 3). Careful history taking and thoughtful prescribing are critical.

Several herbal remedies show some promise in reducing inflammation without the side effects produced by conventional medicines. However, there may be more to the function of these herbs than we are aware of. Figure 1 illustrates the arachidonic acid pathway in inflammation, with the reported activities of herbal medicines highlighted.

Glucosamine sulfate and chondroitin are the most common supplements marketed to those with OA. Glucosamine is an aminosaccharide that is a substrate for the biosynthesis of chondroitin sulfate, hyaluronic acid, and other cartilage molecules. Chondroitin is a constituent of the

Figure 1



The arachidonic acid pathway, an important mechanism for producing pain and inflammation. Shown are the reported mechanisms of action of several herbal remedies (orange) and conventional medicines (blue). ASU = avocado/soybean unsaponifiables, COX = cyclooxygenase

extracellular matrix, increasing the load-bearing properties of cartilage by increasing its water content. These supplements have been heavily marketed to arthritis pain sufferers. However, the benefit of using these supplements for the treatment of OA is debatable. Several early studies have shown a benefit of using either glucosamine or chondroitin, although these studies were small.[36] A large, 6-month randomized controlled trial sponsored by the National Institutes of Health, the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), compared the use of glucosamine, chondroitin, or a combination of the two to celecoxib and placebo in the treatment of knee OA. The trial failed to show significant benefit with respect to pain or joint space width using either supplement alone or in combination. However, a subgroup of patients with moderate to severe pain taking the combination of both glucosamine and chondroitin showed a trend towards a measurable improvement.[36,37]

Glucosamine and chondroitin appear to be safe, with mild side effects that include headache, edema, leg pain, and GI upset. However, glucosamine, which is isolated from the exoskeleton of shellfish, has the potential to produce an allergic reaction in sensitive individuals, although this potential is not great because the protein that causes the allergy, tropomyosin, is found only in the muscle of shellfish. Nevertheless, patients with shellfish allergies should consult their physicians before taking glucosamine. Whether glucosamine affects blood glucose levels in patients with type II diabetes is unclear, but caution should be exercised regarding these patients. Glucosamine sulfate does not present concerns for patients with sulfa drug allergies because such allergies involve drugs with sulfonamide groups and not sulfate chemicals (eg, glucosamine, chondroitin). Several case reports have shown that glucosamine increased the international normalized ratio or bruising/bleeding in patients taking warfarin.[38] Chondroitin may cause bleeding in persons with bleeding disorders or in those using blood thinners. Glucosamine and chondroitin should be stopped 2 weeks before surgery and not resumed until anticoagulant therapy is completed.

S-adenosylmethionine (SAM-e) is often used by patients with OA to alleviate pain and to increase function in arthritic joints. It is also marketed as an antidepressant, particularly for patients who do not respond to serotonin reuptake inhibitors. Authors of a recent meta-analysis found that there may be some benefit with its use, although clinical trials to date have been small.[39] Side effects of SAM-e are mild and include headaches, flatulence, nausea, and vomiting; the SAM-e dose should be titrated over 1 to 2 weeks to avoid these side effects. Serotonin syndrome (ie, altered mental and neuromuscular status resulting from high levels of serotonin) can occur when SAM-e is administered concomitantly with prescription antidepressants, including serotonin reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors.

Avocado/soybean unsaponifiables (ASUs), a nutritional supplement heavily marketed to patients with OA, are composed of the oily fractions isolated from the parent compounds after hydrolysis, predominantly phytosterols. In vitro, ASUs demonstrate anti-inflammatory activity, and clinical trials suggest short-term symptomatic but not long-term benefit from its use.[40] Effects of ASU include increased collagen synthesis and inhibition of collagenase as well as reduction of

prostaglandin E_2.[40] Side effects are mild and include headache and stomach upset.

Black cohosh (*Actaea racemosa, Cimicifuga racemosa*) root has traditionally been used as a remedy for menstrual discomfort and the symptoms of menopause. It is also used to relieve inflammation associated with OA and to reduce bone loss in osteoporosis. Black cohosh is thought to have estrogenic effects, but data are conflicting. Preliminary studies suggest that it reduces inflammation and influences markers of bone turnover, but more research is needed.[41] Side effects include GI upset, rash, dizziness, headache, nausea, and vomiting, especially when higher-than-recommended doses are taken. Critical analysis of several case reports of hepatotoxicity associated with black cohosh uncovered confounding variables, thus preventing the establishment of a causal relationship.[42] Further study is required.

Boswellia serrata (ie, frankincense, salai guggal) is an ayurvedic remedy used to treat arthritis and musculoskeletal pain. It has been shown to have anti-inflammatory properties, and clinical trials have demonstrated that it is effective in the treatment of OA pain, although these trials had small sample sizes.[43] Boswellia is well tolerated; side effects include nausea and diarrhea.

Bromelain is a sulfhydryl proteolytic enzyme extract of pineapple used to débride burn wounds and as an anti-inflammation remedy for OA. Its anti-inflammatory properties result from the reduction of prostaglandin E_2 and thromboxane A_2, and inhibition of bradykinin by depletion of in kallikrein system.[44] To date, however, research results are unconvincing. A small double-blind placebo-controlled study did not find bromelain to be effective in relieving symptoms or enhancing quality of life in patients with diagnosed knee OA.[40,45] Bromelain is an antithrombotic, and it may cause bleeding if used in conjunction with warfarin and enoxaparin by increasing the activity of these drugs. Patients should stop taking bromelain 2 weeks before surgery. If postoperative anticoagulant therapy is necessary, bromelain should not be taken until anticoagulant therapy has been stopped. Bromelain is metabolized by and inhibits the enzyme *CYP2C9*; thus, it may decrease the metabolism of its substrates (eg, tetracycline).

Cat's claw (*Uncaria tomentosa, U guianensis*) is used to enhance immunity and as an anti-inflammatory to treat OA. Several studies suggest its use is beneficial, alone or in combination, in the treatment of OA; however, these studies were small, and further research is required.[40,46] Cat's claw is generally regarded as safe, although its use should be avoided by pregnant women. Side effects include hypotension and GI symptoms. Cat's claw also could have an additive effect when taken with hypotensive or anticoagulant medications. It inhibits *CYP3A4* and should not be taken with its substrates (eg, cyclosporine, some benzodiazepines).

Flavocoxid is a prescription medical food isolated from Chinese scullcap (*Scutellaria baicalensis*) and *Acacia catechu* bark. Flavocoxid is used to treat OA and is thought to inhibit cyclooxygenase and 5-lipoxygenase eznymes.[47] One study has shown that flavocoxid significantly reduces knee OA ($P \leq 0.001$) and is safe.[48] Because of its purported mechanism of action, its use should be avoided in those with ulcers or GI bleeding. Side effects are mild and include nausea.

Thunder god vine (*Tripterygium wilfordii*) is a Chinese herb used to treat inflammation and conditions involving overactivity of the immune system. It is marketed as an oral and/or topical remedy for rheumatoid arthritis. Several small clinical trials have demonstrated a benefit of its use in the symptomatic treatment of rheumatoid arthritis.[49] This herb is extracted from the root of the plant, but the skin of the root and the plant leaves and flowers are poisonous and can cause death. Other side effects include diarrhea, headache, rash, nausea, hair loss, and changes in menstrual cycle. Drug-herb interactions are uncharacterized.

Turmeric (*Curcuma longa*) has been used to treat inflammatory disease, in addition to other applications. Its anti-inflammatory properties are thought to derive from leukotriene inhibition; however, no large clinical trials have been undertaken to support its use in relieving symptoms of OA.[50] Although turmeric is safe, it may cause indigestion or exacerbate symptoms of gallbladder disease. Turmeric inhibits many of the *CYP* enzymes and by this mechanism can potentially interact with many drugs.[51]

Summary

Orthopaedic use of CAM is evolving. Lack of safety and efficacy data for herbal remedies is compounded by the lack of communication regarding their use by patients and physicians. Although the use of herbal medicines should be monitored by the patient's primary care physician to prevent or treat possible drug-herb interactions or side effects, orthopaedic surgeons must have an understanding of the most common remedies used by their patients. This knowledge may help in counseling patients about the possible interactions between conventional medicines and herbal supplements. In addition, providing instructions to help patients stop taking herbal supplements perioperatively may lead to reduced postoperative blood loss, thereby decreasing

the incidence of hematoma formation, infection, and need for transfusion. Specific questionnaires to elicit such information from patients, particularly in the presurgical interview, should be developed.

References

Evidence-based Medicine: References 22-24, 27, 31, 36, and 37 are level I studies. References 3, 5, 6, 18, 25, 29, 33, 34, 40, 43-45, 47-49, and 51 are level II studies. References 1, 2, 4, 7, 8, 26, 39, 41, and 46 are level III studies. References 10, 11, and 42 are level IV studies. References 12-17, 19, 21, 28, 30, 32, 35, 38, and 50 are level V expert opinion.

References printed in **bold type** are those published within the past 5 years.

1. Eisenberg DM, Davis RB, Ettner SL, et al: Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. *JAMA* 1998;280(18):1569-1575.
2. Tindle HA, Davis RB, Phillips RS, Eisenberg DM: Trends in use of complementary and alternative medicine by US adults: 1997-2002. *Altern Ther Health Med* 2005;11(1):42-49.
3. Cohen RJ, Ek K, Pan CX: Complementary and alternative medicine (CAM) use by older adults: A comparison of self-report and physician chart documentation. *J Gerontol A Biol Sci Med Sci* 2002;57(4):M223-M227.
4. **Rosenberg EI, Genao I, Chen I, et al: Complementary and alternative medicine use by primary care patients with chronic pain. *Pain Med* 2008;9(8):1065-1072.**
5. Norred CL: Complementary and alternative medicine use by surgical patients. *AORN J* 2002;76(6):1013-1021.
6. Wren KR, Kimbrall S, Norred CL: Use of complementary and alternative medications by surgical patients. *J Perianesth Nurs* 2002;17(3):170-177.
7. **Marsh J, Hager C, Havey T, Sprague S, Bhandari M, Bryant D: Use of alternative medicines by patients with OA that adversely interact with commonly prescribed medications. *Clin Orthop Relat Res* 2009;467(10):2705-2722.**
8. **Rispler D, Sara J, Davenport L, Mills B, Iskra C: Underreporting of complementary and alternative medicine use among arthritis patients in an orthopedic clinic. *Am J Orthop (Belle Mead NJ)* 2011;40(5):E92-E95.**
9. **Nahin RL, Barnes PM, Stussman BJ, Bloom B: Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. *Natl Health Stat Report* 2009;(18):1-14.**
10. **Lim A, Cranswick N, South M: Adverse events associated with the use of complementary and alternative medicine in children. *Arch Dis Child* 2011;96(3):297-300.**
11. Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altman DE: Americans' views on the use and regulation of dietary supplements. *Arch Intern Med* 2001;161(6):805-810.
12. **Howe CR, Gardner GC, Kadel NJ: Perioperative medication management for the patient with rheumatoid arthritis. *J Am Acad Orthop Surg* 2006;14(9):544-551.**
13. Trapskin P, Smith KM: Herbal medications in the perioperative orthopedic surgery patient. *Orthopedics* 2004;27(8):819-822.
14. **Cavaliere C, Rea P, Lynch M, Blumenthal M: Herbal supplement sales experience slight increase in 2008. *Herbal Gram* 2009;82:58-61.**
15. **Cavaliere C, Rea P, Lynch M, Blumenthal M: Herbal supplement sales rise in all channels in 2009. *Herbal Gram* 2010;86:62-65.**
16. Ko R: Adverse reactions to watch for in patients using herbal remedies. *West J Med* 1999;171(3):181-186.
17. O'Hara M, Kiefer D, Farrell K, Kemper K: A review of 12 commonly used medicinal herbs. *Arch Fam Med* 1998;7(6):523-536.
18. **Izzo AA, Ernst E: Interactions between herbal medicines and prescribed drugs: An updated systematic review. *Drugs* 2009;69(13):1777-1798.**
19. Abebe W: Herbal medication: Potential for adverse interactions with analgesic drugs. *J Clin Pharm Ther* 2002;27(6):391-401.
20. Brazier NC, Levine MA: Drug-herb interaction among commonly used conventional medicines: A compendium for health care professionals. *Am J Ther* 2003;10(3):163-169.
21. **Guay DR: Cranberry and urinary tract infections. *Drugs* 2009;69(7):775-807.**
22. **Ansell J, McDonough M, Zhao Y, Harmatz JS, Greenblatt DJ: The absence of an interaction between warfarin and cranberry juice: A randomized, double-blind trial. *J Clin Pharmacol* 2009;49(7):824-830.**
23. See DM, Broumand N, Sahl L, Tilles JG: In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacology* 1997;35(3):229-235.
24. Pittler MH, Ernst E: Kava extract for treating anxiety. *Cochrane Database Syst Rev* 2002;2:CD003383.
25. **Reinhart KM, Talati R, White CM, Coleman CI: The impact of garlic on lipid parameters: A systematic review and meta-analysis. *Nutr Res Rev* 2009;22(1):39-48.**
26. Ang-Lee MK, Moss J, Yuan CS: Herbal medicines and perioperative care. *JAMA* 2001;286(2):208-216.
27. Park HJ, Lee JH, Song YB, Park KH: Effects of dietary supplementation of lipophilic fraction from Panax ginseng on cGMP and cAMP in rat platelets and on blood coagulation. *Biol Pharm Bull* 1996;19(11):1434-1439.
28. Janetzky K, Morreale AP: Probable interaction between warfarin and ginseng. *Am J Health Syst Pharm* 1997;54(6):692-693.
29. **Rambaldi A, Jacobs BP, Gluud C: Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. *Cochrane Database Syst Rev* 2007;4:CD003620.**
30. **Suzuki M, Ito Y, Fujino T, et al: Pharmacological effects of saw palmetto extract in the lower urinary tract. *Acta Pharmacol Sin* 2009;30(3):227-281.**
31. **Tacklind J, MacDonald R, Rutks I, Wilt TJ: Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2009;2:CD001423.**
32. **Blachier F, Lancha AH Jr, Boutry C, Tomé D: Alimentary proteins, amino acids and cholesterolemia. *Amino Acids* 2010;38(1):15-22.**
33. **Linde K, Berner MM, Kriston L: St John's wort for major depression. *Cochrane Database Syst Rev* 2008;4:CD000448.**
34. **Taibi DM, Landis CA, Petry H, Vitiello MV: A systematic review of valerian as a sleep aid: Safe but not effective. *Sleep Med Rev* 2007;11(3):209-230.**
35. Berger RG: Nonsteroidal anti-inflammatory drugs: Making the right choices. *J Am Acad Orthop Surg* 1994;2(5):255-260.
36. **Clegg DO, Reda DJ, Harris CL, et al: Glucosamine, chondroitin sulfate, and**

the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; 354(8):795-808.

37. Sawitzke AD, Shi H, Finco MF, et al: The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: A report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum* 2008; 58(10):3183-3191.

38. Knudsen JF, Sokol GH: Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: Case report and review of the literature and MedWatch database. *Pharmacotherapy* 2008;28(4): 540-548.

39. Rutjes AW, Nüesch E, Reichenbach S, Jüni P: S-adenosylmethionine for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev* 2009;4: CD007321.

40. Ameye LG, Chee WS: Osteoarthritis and nutrition: From nutraceuticals to functional foods. A systematic review of the scientific evidence. *Arthritis Res Ther* 2006;8(4):R127.

41. Yang CL, Chik SC, Li JC, Cheung BK, Lau AS: Identification of the bioactive constituent and its mechanisms of action in mediating the anti-inflammatory effects of black cohosh and related Cimicifuga species on human primary blood macrophages. *J Med Chem* 2009; 52(21):6707-6715.

42. Teschke R, Schwarzenboeck A, Hennermann KH: Kava hepatotoxicity: A clinical survey and critical analysis of 26 suspected cases. *Eur J Gastroenterol Hepatol* 2008;20(12):1182-1193.

43. Ernst E: Frankincense: Systematic review. *BMJ* 2008;337:a2813.

44. Kumakura S, Yamashita M, Tsurufuji S: Effect of bromelain on kaolin-induced inflammation in rats. *Eur J Pharmacol* 1988;150(3):295-301.

45. Brien S, Lewith G, Walker AF, Middleton R, Prescott P, Bundy R: Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: A randomized placebo-controlled pilot study. *QJM* 2006;99(12):841-850.

46. Rosenbaum CC, O'Mathúna DP, Chavez M, Shields K: Antioxidants and antiinflammatory dietary supplements for osteoarthritis and rheumatoid arthritis. *Altern Ther Health Med* 2010; 16(2):32-40.

47. Altavilla D, Squadrito F, Bitto A, et al: Flavocoxid, a dual inhibitor of cyclooxygenase and 5-lipoxygenase, blunts pro-inflammatory phenotype activation in endotoxin-stimulated macrophages. *Br J Pharmacol* 2009; 157(8):1410-1418.

48. Levy RM, Saikovsky R, Shmidt E, Khokhlov A, Burnett BP: Flavocoxid is as effective as naproxen for managing the signs and symptoms of osteoarthritis of the knee in humans: A short-term randomized, double-blind pilot study. *Nutr Res* 2009;29(5):298-304.

49. Canter PH, Lee HS, Ernst E: A systematic review of randomised clinical trials of Tripterygium wilfordii for rheumatoid arthritis. *Phytomedicine* 2006;13(5):371-377.

50. Gregory PJ, Sperry M, Wilson AF: Dietary supplements for osteoarthritis. *Am Fam Physician* 2008;77(2):177-184.

51. Sun DX, Fang ZZ, Zhang YY, Cao YF, Yang L, Yin J: Inhibitory effects of curcumenol on human liver cytochrome P450 enzymes. *Phytother Res* 2010; 24(8):1213-1216.