Peter O'Neill. *Father's Day*. Oil on linen, 30″ × 40″.

Herbal supplements commonly used by cancer patients in the perioperative period can produce pharmacokinetic interactions that can complicate surgery.

Perioperative Herbal Supplement Use in Cancer Patients: Potential Implications and Recommendations for Presurgical Screening

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Background: *Products made from botanicals that are used to maintain or improve health are known as herbal supplements, botanicals, or phytomedicines. Many herbs have a long history of use and claimed health benefits. However, many herbal supplements and botanicals have potent pharmacologic activity that can contribute to adverse effects and drug interactions. The use of herbal supplements by cancer patients in the perioperative period is common and consistent with the substantial increase in the use of alternative medical therapies.*

Methods: *We reviewed the literature to examine the constituents, safety, pharmacokinetics, and pharmacodynamics of those herbal supplements that are predominantly used by cancer patients.*

Results: *Different supplements possess antiplatelet activity, adversely interact with corticosteroids and central nervous system depressant drugs, have gastrointestinal manifestations, produce hepatotoxicity and nephrotoxicity, and produce additive effects when used with opioid analgesics.*

Conclusions: *With the increasing use of herbal supplements by cancer patients, surgical staff need to screen patients presurgically for use of these supplements. Clinical practice guidelines are needed for screening and prevention of herbal supplement usage to prevent potential adverse events that may arise from herbal medications taken alone or combined with conventional therapies during the perioperative period.*

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Background

Herbal supplements are dietary supplements that contain herbs, either singly or in mixtures. An herb (also called a botanical) is a plant or plant part used for its scent, flavor, and/or therapeutic properties. Products made from botanicals that are used to maintain or improve health have been called herbal supplements, botanicals, or phytomedicines.[1] Currently, more than

20,000 herbal products are available as over-the-counter therapeutic agents in the United States.[2]

Many herbs have a long history of use and of claimed health benefits. However, herbal supplements and botanicals have potent pharmacologic activity and, consequently, contribute to potential adverse effects and drug interactions.[1] The 2002 National Health Interview Survey conducted by the Centers for Disease Control and Prevention indicated that 38.2 million American adults (approximately 19%) use nonvitamin, nonmineral natural products — primarily botanical supplements — despite a lack of evidence for most of these products regarding their safety and effectiveness. Herbal supplements are regulated by the Dietary Supplement Health and Education Act, which limits their regulation by the US Food and Drug Administration.[1]

The use of herbal supplements by cancer patients in the perioperative period is prevalent and consistent with the substantial increase in the use of alternative medical therapies by cancer patients.[3] Anywhere from 25% to 85% of cancer patients are seeking alternative and complementary nutritional therapies for prevention or during cancer treatment. The use of these therapies is highest among patients with breast cancer (80% to 85%),[4,5] pediatric cancer (46%),[6] prostate cancer (27% to 43%),[7-9] and head and neck cancer (25%).[10] In a study of 820 cancer patients receiving chemotherapy or radiation therapy, 29.1% reported using complementary/integrative nutritional therapies that were not prescribed by their physician.[3] Of the 820 patients, 50.8% were men and 49.2% were women. Caucasians and patients over 60 years of age were predominant users of complementary/integrative therapies during treatment. Over 63% of the patients had a college degree or higher, and 40% were employed at the time of treatment. Most of the patients (65.3%) had a family history of cancer. Of the 820 patients, 237 (29.1%) reported taking one or more nutritional supplements during treatment. Although 58.6% of this group consumed multivitamin/mineral preparations, several patients reported taking one or more vitamins, minerals, botanicals, and/or biologics in addition to the multivitamin/minerals. The most frequently used complementary/integrative nutritional therapies were modular vitamins (86.9% of the patients), followed by botanicals/biologics (43.8%) and mineral supplements (28.6%). Many biologics and botanical supplements used by these patients have no proven efficacy in cancer treatment and may even interfere in traditional treatment modalities such as chemotherapy and radiation therapy if taken perioperatively.[3]

Recent observations[3] and a growing body of literature have increased our understanding of the composition and function of these herbal supplements. As a result, serious concerns have been raised on the widespread use of herbal supplements among the presurgical population, which may have a negative impact on preoperative patient care. More specifically, several botanicals, based on their chemical structure, may produce adverse effects for perioperative use. These herbal supplements have been demonstrated to have adverse effects, possess antiplatelet activity, adversely interact with corticosteroids and the central nervous system depressant drugs, have gastrointestinal manifestations, produce hepatotoxicity and nephrotoxicity, and produce additive effects when used concomitantly with opioid analgesics. In addition to known consequences based on the biochemical composition of herbal supplements, adulteration and product quality issues are particular concerns. Currently, as there are no legal standards for packaging or processing. The content of the supplements varies significantly from batch to batch as well as from the content statements and claims made on the label.[10] Some of the products tested may have less than half the potency listed on the label.[11] In one analysis, some botanicals tested had unsafe levels of mercury and other toxic metals, and prescription drug compounds were discovered in more than a third of products tested.[12]

Despite the rise in herbal medicine consumption, explicitly eliciting and documenting herbal medicine usage among surgical patients by surgical healthcare staff (eg, anesthesiologists, dentists, and surgeons) is poor.[13,14] Few surgeons question patients regarding their use of herbal medicines, and 70% of patients do not reveal their use of herbal medicines to their physicians, clinical pharmacists, or dietitians. In a recent study of 2,186 survey respondents undergoing elective surgery,[13] 57% admitted to using herbal medicine at some point in their life and 38% within the past 2 years. One in 6 respondents continued the use of herbal medicine during the month of surgery. In a study by Leung et al[14] in the California hospital systems, 39.2% of 2,560 survey respondents admitted to using some form of alternative medicine supplements, the most common type being herbal medicine (67.6%). Of those who admitted to taking alternative medicine supplements, 44.4% did not consult with their primary physicians, and 56.4% did not inform the anesthesiologists before surgery regarding their use of these products. Only 53% of the patients ceased using these products before surgery. Although the use of supplements in cancer patients is well documented,[3] there are no randomized clinical trials that have examined the effects of these supplements in the perioperative period.

The objectives of this report are (1) to review the constituents, safety, pharmacokinetics, and pharmacodynamics of those herbal supplements predominantly used by cancer patients, as observed by our group,[3] that may contribute to potential adverse consequences during and following surgery and (2) to provide recommendations for developing and implementing surgical/clinical practice guidelines for screening and prevention of use of herbal supplements perioperatively. As most of these herbal supplements have multiple constituents with specific properties, we focus on the predominant property of

the herbal supplement, with implications specific to its use in the preoperative period. The Figure presents several examples of the botanical supplements are pictured in plant form, and their potential adverse effects in cancer therapy are noted in the Table. Although we selected the herbal supplements used by cancer patients, these are also the most commonly used herbal supplements in other patient populations. Thus, the recommendations and discussions are applicable to other preoperative patient populations.

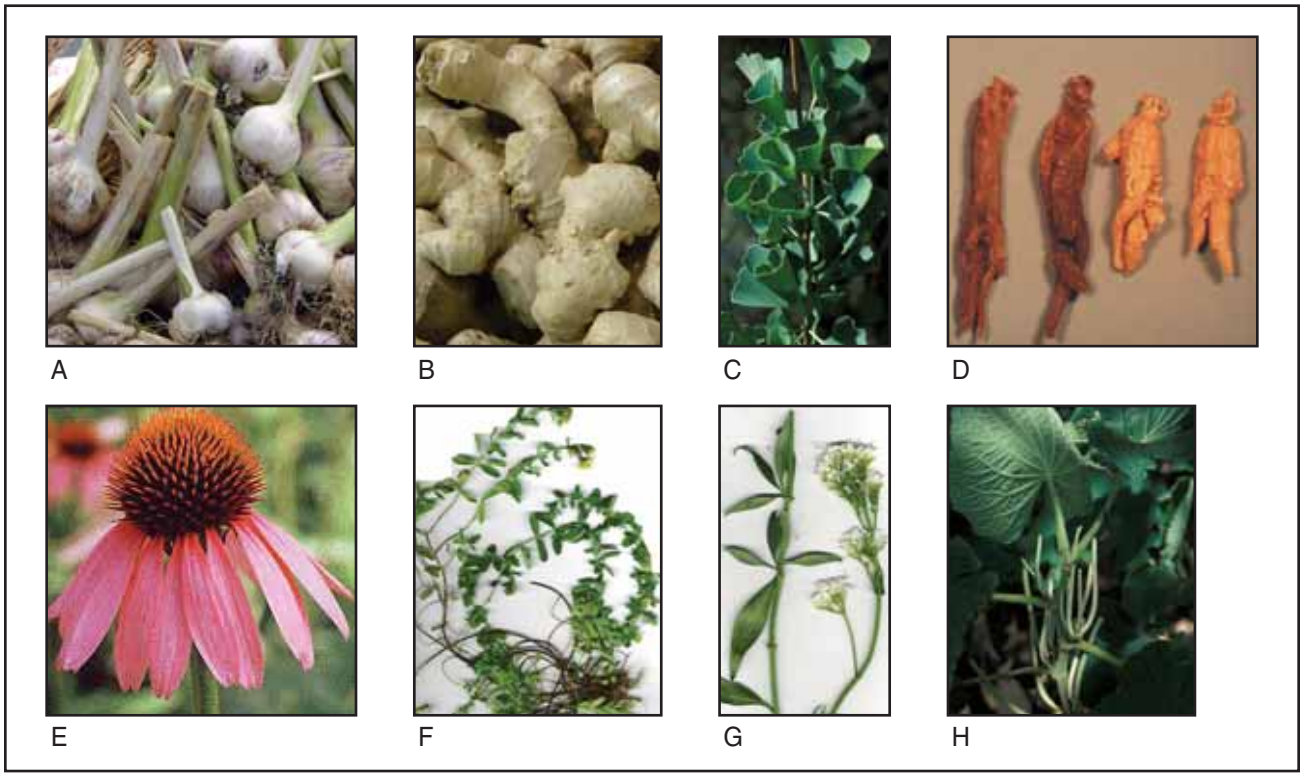
Herbal Supplements That Modulate Coagulation in Cancer Patients

Garlic, ginger, ginkgo, and ginseng, known as the "4 Gs," are the most popular herbal supplements used by cancer patients that modulate coagulation. Other herbal supplements that have been demonstrated to interact with aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are bromelain, cayenne, chamomile, feverfew, dong quai, eleuthero/Siberian, licorice, bilberry, turmeric, meadowsweet, and willow. Those containing coumarin (chamomile, motherwort, horse chestnut, fenugreek, and red clover) and tamarind enhance the risk of bleeding.

Garlic

Garlic is the most extensively researched herbal remedy in the United States and elsewhere, although there is considerable variation in the nature of the research. The major putative active constituents of garlic contain sulfur. Intact cloves contain alliin, which is stable. When a clove is cut, the enzyme alliinase (a C-S lyase)[1] reacts with alliin to form various strong-odored compounds associated with garlic, including the thiosulfinate allicin. Thiosulfinates are highly reactive, consisting of two linked sulfur atoms with an oxygen molecule attached to one. They transform relatively quickly to other substances. Alliin is short-lived and can launch many derivatives, including a large number of related thiosulfinates. Three of the more widely studied stable metabolites are diallyl sulfide, diallyl disulfide, and S-allyl cysteine. Other stable metabolites include ajoene, methyl ajoene, vinyldithiins, diallyl trisulfide, and S-allyl mercaptocysteine. Additional sulfides include methyl allyl trisulfide, allyl propyl disulfide, and allyl mercaptan. In addition, garlic contains fructosans and saponins as potentially active substances.[15]

Garlic has been reported to have antithrombotic properties.[16,17] It contains inhibitors of adenosine deaminase and cyclic AMP phosphodiesterase, which could account for antithrombotic and vasodilatory actions. Ajoene, an antithrombotic substance, is present in small quantities in some forms of macerated garlic.[18] Ajoene [(E,Z)-4,5,9-trithiadodeca-1,6,11-triene 9-oxide) is a potent antiplatelet compound isolated from alcoholic extracts of garlic (*Allium sativum*). Ajoene reversibly inhibits in vitro platelet aggregation as well as release reaction induced by all known agonists, suggesting that



Botanical images of garlic (A), ginger (B), ginkgo (C), ginseng (D), echinacea (E), St John's wort (F), valerian (G), and kava (H).

Adverse Effects of Herbal Supplements Most Commonly Used By Cancer Patients

Barberry (*Berberis vulgaris*)	Coagulant herb. May inhibit effects of anticoagulant medications such as warfarin.
Bilberry *(Piccinium myrtillus)*	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Bromelain, from pineapple stem *(Ananas comosus)*	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Buckthorn bark and berry (*Rhamnus frangula, Frangula alnus*)	Laxative herbs speed digestion, which reduces absorption time of drugs. Chronic use results in a loss of potassium, thereby strengthening effects of cardiac glycosides and antiarrhythmic agents. Simultaneous use of thiazide diuretics, corticosteroids, or licorice root may increase potassium loss.
Cayenne (*Capsicurn annuum*)	Exhibits anticoagulant activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Chamomile (*Chamaemelum nobile*)	Exhibits anticoagulant activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Coleus, or forskolin *(Coleus forskohlii)*	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Dong quai *(Angelica sinensis*)	Exhibits anticoagulant activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Feverfew *(Tanacetum parthenium*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Flaxseed oil *(Linum usitatissimum*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Garlic *(Allium sativum)*	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Ginger *(Zingiber officinale)*	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Ginkgo (*Ginkgo biloba)*	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Ginseng, American *(Panax quinquefolium)*	May increase side effects of stimulants. Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Green tea (*Camelia sinensis*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Horse chestnut (*Aesculus hippocastanum*)	Exhibits anticoagulant activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Kava (*Piper methysticum*)	May cause drowsiness, dizziness, and intoxication. May enhance effects of sedatives or hypnotics.
Licorice (*Glycyrrhiza glabra*)	May impair action of drugs that cause potassium loss. May enhance action of corticosteroids. May counteract effectiveness of drugs used to treat hypertension. Licorice contains a substance known as glycyrrhizic acid, which can affect the hormone aldosterone that helps regulate blood pressure. For people with high blood pressure, edema, or electrolyte imbalance, use of licorice root or its products can lead to sodium retention, excessive potassium excretion, and water retention. Some licorice products have the glycyrrhizic acid removed, and are sold sometimes as DGL (deglycyrrhizinated licorice).
Meadowsweet (*Filipendula ulmaria*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Motherwort (*Leonurus cardiaca*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Oregon grape root (*Berberis aquifolium*, *Mahonia aquifolium*)	Coagulant herb. May inhibit effects of anticoagulant medications such as warfarin and potentiate bleeding.
Poplar (*Populus spp.*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Senna leaf and fruit (*Cassia senna*)	Laxative herbs speed digestion, which reduces absorption time of drugs. Chronic use results in a loss of potassium, thereby strengthening effects of cardiac glycosides and antiarrhythmic agents. Simultaneous use of thiazide diuretics, corticosteroids, or licorice root increases potassium loss.
Shepherd's purse (*Capsella buisa-pastoris*)	Coagulant herb. May inhibit effects of anticoagulant medications such as warfarin and potentiate bleeding.
St John's wort *(Hypericum perforatum)*	May enhance effects of narcotics and selective serotonin reuptake inhibitors (SSRIs). Increases side effects of photosensitizing drugs, alcohol, and melatonin. Laboratory reports have suggested but not confirmed that the mechanism of action for St John's wort may involve monoamine oxidase (MAO) inhibition, SSRI reuptake inhibition, increased melatonin production and others. This herb has been shown to induce the drug metabolizing enzyme cytochrome p4503A4 and has the potential to interact with many medications.
Turmeric (*Curcuma longa*)	Exhibits antiplatelet activity. May enhance effects of anticoagulant medications such as warfarin and potentiate bleeding.
Valerian (*Valeriana officinalis*)	Enhances the effects of sedatives, and hypnotic drugs.

ajoene may be useful for the acute prevention of thrombus formation induced by vascular damage.[19] Garlic has antiplatelet aggregation properties in a dose-dependent manner. Aqueous extract of garlic inhibited aggregation induced by adenosine diphosphate, collagen, arachidonate, epinephrine, and calcium ionophore A23187 in a dose-dependent manner. Garlic appears to contain components that might exert their effects at various stages involved in the process of platelet aggregation.[20] In addition, serious hematologic side effects have been reported when garlic has been taken in conjunction with blood-thinning prescription drugs such as warfarin.[21] Garlic changes pharmacokinetic variables of paracetamol, decreases blood concentrations of warfarin, and produces hypoglycemia when taken with chlorpropamide.[21]

Although there have been no randomized, controlled clinical trials on the use of garlic supplements in the preoperative period to examine their effect on bleeding risk, the properties of the constituents and metabolites of garlic to potentially inhibit platelet aggregation and antithrombotic action warrant discontinuation of this herbal supplement prior to surgery. Since the half-life of elimination of garlic is 10 to 30 hours, the patient should discontinue supplementation for a minimum of 2 to 3 days prior to surgery to avoid bleeding and poor surgical wound healing in this potentially nutritionally compromised patient population.

Ginger

Ginger is the rhizome part of the plant whose botanical name is *Zingiber officinale*. Its Chinese name is *sheng jiang* or *shen jing*. The plant is also known as Jamaica ginger, ingwer, gengibre, palu, shokyo, shoga, and other names in various cultures. Powdered ginger is the dried rhizome that contains 1% to 4% essential oil, but its composition varies considerably depending on the region where it is grown. Sesquiterpene hydrocarbons cause the characteristic ginger aroma. These compounds include (–)-zingiberene, (+)-*ar*-curcumene, (–)β-sesquiphellandrene, and β-bisabolene. The active constituents in ginger are thought to be chemicals known as gingerols [1-(3′-methoxy-4′-hydroxyphenyl)-5-hydroxyalkan-3-ones] and shogaols, their dehydration products, which are responsible for the sharp taste of ginger.[22]

Ginger has been shown to act as a potent inhibitor of thromboxane synthetase, raising levels of prostacyclin without a concomitant rise in prostaglandin E2 or prostaglandin F2 alpha having implications in bleeding times.[23] Patients who are taking anticoagulant drugs or those who have blood coagulation disorders may be at risk if they are also taking ginger supplementation. On the other hand, ginger has been known for its antiemetic properties and has been demonstrated to be as effective as the drug droperidol in the prevention of postoperative nausea and vomiting after outpatient gynecologic surgery.[24] The effect of ginger on postoperative nausea and vomiting was reported to be equal to or better than that of metoclopramide,[25] with significantly fewer cases of postoperative nausea and vomiting in 60 patients taking ginger compared with those taking placebo.[26] However, a double-blind, randomized study[27] found that ginger did not prevent postsurgical nausea and vomiting. In examining the mechanism of action, it is likely that ginger's antinausea and antimotion sickness effects derive from its influence on gastric activity and do not involve the central nervous system.[22]

Since no pharmacokinetics (PK) trials on ginger supplementation have been completed yet, the elimination half-life of ginger is unavailable to make a recommendation for its discontinuation a specific number of days prior to surgery based on empirical evidence. However, with the known implications of ginger on coagulation, it would be prudent to discontinue supplements a minimum of 5 to 7 days prior to surgery.

Ginkgo Biloba

Ginkgo biloba has been used for thousands of years in China and is widely used in Europe for the treatment of blood circulation disorders. It was the third best-selling herbal product in the US health food market in 1997.[28] The extract is obtained from the leaves of the *Ginkgo biloba* tree, also known as the maidenhair or kew tree, the oldest known living tree species. The active ingredients in *Ginkgo biloba* are believed to be two compounds — flavone glycosides and terpene lactones — found in the extracts of the whole leaf. Flavone glycosides include three separate bioflavonoids: quercetin (also present in certain vegetables such as red and yellow onion), kaempferol, and isorhamnetin. Terpene lactones are unique to ginkgo and have not been found in any other plant. The flavones act as antioxidants, and the terpene lactones (ginkgolides) inhibit blood clotting.[29]

Ginkgo contains compounds that act as anticoagulants, inhibiting platelet aggregation.[30,31] Long-term use has been associated with increased bleeding time and spontaneous hemorrhage and thus is contraindicated in patients taking prescription anticoagulants such as warfarin. The use of aspirin and NSAIDs combined with *Ginkgo biloba* extracts has been reported to cause bleeding into the brain and eyes.[32,33] Although the bleeding resolves after discontinuing the ginkgo usage, the combination of ginkgo with aspirin or any drug with anticoagulant action should be avoided during the perioperative period. Other ginkgo interactions include raised blood pressure when combined with a thiazide diuretic and coma when combined with trazodone.[21] Since no trials on the elimination half-life of ginkgo have been conducted, a recommendation to discontinue ginger supplementation prior to surgery lacks empirical evidence. However, with the known implications of ginkgo on coagulation, it would be prudent to discontinue supplements a minimum of 5 to 7 days prior to surgery.

Ginseng

Ginseng has been used for centuries in traditional Chinese medicine for diabetes and many conditions associated with aging, including reduced stamina and cognitive decline. The most commonly available and most popular varieties in the United States are the Chinese/Korean variety (*Panax ginseng*) and the American variety (*Panax quinquefolium*). The chief constituents responsible for the activity of ginseng are the ginsenosides or panaxocides. Chemical analysis indicates that there are at least four active compounds — saponin glycoside, panaxin, panacene, and panaxic acid.[34,35]

Ginsenosides have been shown to inhibit platelet aggregation in vitro.[36,37] Animal studies have demonstrated that ginsenocides prolong coagulation times of thrombin and activated partial thromboplastin.[38] A few case reports suggest that ginseng increases bleeding time in subjects taking warfarin, but subsequent animal studies show no significant impact of ginseng on the pharmacokinetics/pharmacodynamics of warfarin when the two are concomitantly administered.[39] Yuan et al[40] recently reported that American ginseng administered to 20 patients for a 4-week period reduced the anticoagulant effects of warfarin. Ginseng has also been shown to raise blood pressure, and its use is contraindicated with estrogens or corticosteroids due to possible additive effects.[41] Ginseng has also been reported to cause headache, tremulousness, and manic episodes in patients treated with phenelzine sulfate.[21,41] Pharmacokinetics studies are currently limited to animal models, with elimination half-lives in rabbits ranging between 0.8 and 7.4 hours.[42] Therefore, recommendations to discontinue supplement use 24 hours prior to surgery are warranted.

In summary, the effect of herbal supplements taken perioperatively in wound healing has not been established in clinical trials. However, there is sufficient data that poor platelet aggregation can affect wound healing, as demonstrated in prospective studies in patients using anticoagulant therapies.[43,44] Currently, there are no studies examining the adverse effect of specific herbal supplements on wound healing. With the current knowledge of the pharmacokinetic properties of herbal supplements — specifically, adverse effects such as inhibition of platelet aggregation — these herbal supplements may modulate surgical wound healing. To avoid endangering this patient population, this issue would be better addressed in retrospective observations rather than prospective randomized trials.

Herbal Supplements That Interact With Corticosteroids

Echinacea

Among the herbal supplements that potentially interact with corticosteroids, echinacea (purple coneflower) is used commonly by cancer patients, mainly due to "immune boosting" claims. All varieties of echinacea contain four main constituents: glycoproteins, polysaccharides, pigment anthocyanins, and caffeic acid.[34,41] In vitro studies show that echinacea appears to be a nonspecific immunostimulant. It increases phagocytosis and lymphocyte activity, including natural killer cell activity. Macrophages cultured in concentrations of echinacea as low as 0.012 µg/mL produced significantly higher levels of interleukin 1 (IL-1), IL-6, IL-10, and tumor necrosis factor alpha (TNF-α) ($P<.05$) vs unstimulated cells.[45] Roesler et al[46] found that polysaccharides from *Echinacea purpurea* enhanced spontaneous motility of immune cells from human donors. Monocytes were activated to secrete TNF-α, IL-6, and IL-1, whereas class II MHC expression was unaffected. The acute-phase C-reactive protein was also induced, leading the investigators to suggest that echinacea polysaccharides could induce acute-phase reactions and activation of phagocytes in humans.

Melchart and colleagues[47] reviewed five placebo-controlled, randomized studies investigating extracts of echinacea in healthy volunteers. Two of the studies revealed that phagocytic activity was significantly enhanced compared with placebo (maximal stimulation 22.7% [95% confidence interval (CI) 17.5% to 27.9%) and 54.0% [95% CI 8.4% to 99.6%], respectively). The remaining studies reported no significant effect. Leukocyte number was not influenced significantly in any of the investigations. Because echinacea is believed to be immunostimulatory, it is contraindicated in individuals using immunosuppressants such as corticosteroids and cyclosporine.[21] In addition, if used continuously for more than 8 weeks, echinacea may cause hepatotoxicity. It is also contraindicated in individuals taking drugs that affect liver function such as anabolic steroids, amiodarone, methotrexate, and ketoconazole. Currently, pharmacokinetics studies of elimination half-life are unavailable for this herbal supplement, warranting the recommendation that patients discontinue supplements 1 week or more prior to surgery. Due to potentially toxic interactions, echinacea should also be avoided with cyclophosphamides, epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors, taxanes, and vinca alkaloids.

Herbal Supplements That Interact With the Central Nervous System

St John's Wort

St John's wort (*Hypericum perforatum*) contains active compounds such as naphthodihydrodianthrones (particularly hypericin and pseudohypericin) and flavonoids (including quercitrin, rutin, and hyperin).[48] Cancer patients often take St John's wort to reduce anxiety or depression. Situational depression is common among

patients with cancer and may lead to increased use of the herb. Although it has shown some improvement of mild depression, effectiveness with long-term use has not been observed. St John's wort is metabolized in the liver and increases the production of cytochrome P450 3A4 enzyme and the active efflux pump P-glycoprotein, both leading to decreased plasma blood levels of medications metabolized by the same enzyme.[49] Perioperative medications metabolized by the enzyme include benzodiazepines, anesthetics, and natural and synthetic opioids. Natural and synthetic opioids are first-line agents in palliating severe pain in cancer patients. Other medications metabolized by P450 3A4 include serotonin receptor antagonists, antiarrhythmics, anesthetics, anticoagulants, barbiturates, irinotecan, and beta-blockers. In addition, St John's wort has been reported to cause organ transplant rejection by decreasing blood cyclosporine levels by 49%,[48] which may be applicable to bone marrow transplant recipients. The half lives of the active ingredients hypericin and hyperforin are 43.1 hours and 9.0 hours, respectively. Discontinuation of the herb is recommended at least 5 days prior to surgery.[50]

Valerian

The root of the valerian herb *(Valeriana officinalis)* is often used for treatment of insomnia and fatigue both common symptoms reported by cancer patients. Valerian includes multiple compounds such as isovalerianic, formic, and acetic acids, and pinene. The sedative and hypnotic properties are mediated through modulation of gamma-aminobutyric acid (GABA) neurotransmission and receptor function.[51] Theoretically, valerian could modulate sedative effects of anesthetics, depending on the nature of the binding. When taken with barbiturates and benzodiazepine, it has the potential to increase a sedative effect and also may increase the anesthetic requirements with long-term use.[50] The pharmacokinetics of valerian is currently unknown, but it is thought to be prudent to taper use several weeks before surgery.

Herbal Supplements That Cause Gastrointestinal Disturbances and Hepatotoxicity

Kava

Kava is derived from the pepper plant (*Piper methysticum*). Kavalactones appear to be responsible for the pharmacologic activity of kava. These include psychomotor effects, antiepileptic properties, neuroprotection, and a local anesthetic effect. In patients with Parkinson's disease, kava may interfere with the effects of levodopa and can cause a semicomatose state when given concomitantly with alprazolam.[21] This may be due to the sedative-hypnotic effect potentiated by GABA neurotransmitter inhibition. Animal studies have shown an increase in barbiturate-induced sleep time when kava is used.[52] Peak plasma levels for kava occur 1.8 hours after an oral dose. The elimination half-life for kavalactones is 9 hours.[53] Due to the possibility that kava may potentiate the sedative effects of anesthesia, it is recommended that patients should not take kava for at least 24 hours prior to surgery.

Kava has also been reported to cause serious liver toxicity, including several deaths, which has prompted the US food and Drug Administration Center for Food Safety and Applied Nutrition to notify healthcare professionals and consumers of this potential risk in March 2002. This toxicity is particularly relevant in patients with a history of pre-existing liver disease or those receiving drugs known to have potential hepatotoxicity such as camptothecins, cyclophosphamide, EGFR-TK inhibitors, taxanes, and vinca alkaloids.[54]

Herbal supplements such as feverfew, *Ginkgo biloba*, echinacea, and St John's wort have been associated with oral manifestations such as aphthous ulcers, lip and tongue irritation and swelling, gingival bleeding tongue numbness, and xerostomia.[55] Essiac tea contains a combination of four herbs: burdock root (*Arctium lappa*), Indian rhubarb root (*Rheum palmatum*), sheep sorrel (*Rumex acetosella*), and the inner bark of slippery elm (*Ulmus fulva* or *Ulmus rubra*). Although Essiac is promoted as having other immune-enhancing and disease-fighting properties, the only documented effect is that of a laxative.[55] It has also been found to have strong emetogenic potential. The strong laxative effect and the variation in concentration of active ingredients that is dependent on preparation may lead to dehydration and electrolyte disturbances with potassium losses. Essiac should not be consumed prior to or after surgery. Belladonna herb and its preparations have been used for their antimuscarinic actions in a wide range of conditions, including the relief of gastrointestinal and urinary tract disorders associated with smooth muscle spasm, but they generally are regarded as an outmoded form of treatment. The anticholinergic effects of belladonna are xerostomia, abdominal distention, and urinary retention. This should be avoided in all patients who will undergo surgery.

Conclusions and Recommendations

Herbal supplements possess significant pharmacologic activity and, consequently, potential adverse effects and drug interactions. Awareness and documentation of the use of herbal medicines by surgical healthcare staff are critical in identifying, preventing, and treating potential problems that may arise from herbal supplements taken either alone or combined with conventional medications during the perioperative period. For presurgical patients, it is ideal to incorporate specific screening criteria during the preoperative visit screening completed by the anesthesiologist or nursing assessment. Surgical staff must

include an open-ended question regarding use of herbal or other nutritional supplements during this visit. Once these are identified, patients must be directed to stop taking these supplements and schedule the surgical date accordingly. Current data suggest that all herbal medicines should be ceased 2 weeks before surgery.[56] The American Society of Anesthesiologists suggests that all herbal medications should be discontinued 2 to 3 weeks before an elective surgical procedure.[57] When patients are unsure of the contents of the herbal medicine, they should be urged to bring the container so that the healthcare team can review the contents of the herb or preparation. Although this recommendation is promising and feasible in elective-care settings, anesthetic care in emergency settings should be based on a thorough supplement and drug-intake history from the patient or a relative.

Many herbal supplements have the potential to cause serious health problems and drug-herb interactions, specifically in vulnerable and compromised cancer patients. Since the use of herbal supplements is well documented in cancer patients, current clinical practice guidelines must address these complementary and alternative supplements, specifically in the perioperative and treated patient populations.

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