Dietary Supplements and Current Available Evidence

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Summary: Dietary supplements are frequently used in surgical patients. Surgeons should be up to date with regard to the efficacies and potential complications related to these supplements. This article provides the most updated practices and evidence of commonly used supplements. (*Plast. Reconstr. Surg.* 146: 474e, 2020.)

Recent survey-based study of 30,899 U.S. adults demonstrated that dietary supplement users are generally white, female, nonsmoking, relatively older individuals (>50 years) with a healthy lifestyle; have an education level at college or above; and have higher socioeconomic status.[1] As this is precisely the same population that seeks elective aesthetic surgery,[2] plastic surgeons should be aware of the use, efficacy, and potential complications of these supplements.

A survey of surgical patients demonstrated that 40.5 percent admitted to taking herbal medications with coagulation effects; 32.7 percent, with blood pressure effects; 20 percent, with cardiovascular effects; and 8.9 percent, with electrolyte effects.[3] Among these, approximately one-fourth of these patients reported using herbs that are known to have adverse interactions with prescription medications.[3] Another study of surgical patients demonstrated taking supplements within 2 weeks leading up to surgery, including those that may inhibit coagulation.[4] As there is little regulation of herbal supplements, patients generally do not think of reporting them to health care professionals.[5] The actual percentage of this subset of the population taking supplementation is likely much higher than that reported.[1,5,6]

In 2007, the senior author (R.J.R.) published an extensive review of herbal and vitamin supplements.[2] From this study, he derived his current perioperative supplementation protocol to enhance healing. The goal of this study was to provide updated evidence on commonly used herbal and vitamin supplements that have potential wound healing benefits.

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HERBAL SUPPLEMENTS

Arnica (*Arnica montana*)

Arnica is native to mountainous regions of Europe and western North America. The reported effect of arnica is mainly when it is used as a topical analgesic, antiseptic, or antiinflammatory agent. It is a classic homeopathic remedy frequently used in the trauma and sports settings to alleviate bruising and muscle soreness. It has been proposed, based on in vitro studies, that arnica works by inhibiting histamine release from mast cells, and serotonin release during neutrophil migration and adhesion.[7] As with many other herbal supplements, there are other claimed but unproven applications, including alleviating cardiac insufficiency, arteriosclerosis, and myocarditis.

From a clinical standpoint, arnica has been one of the more commonly studied supplements in prevention of postoperative complications. There have been several randomized, prospective, placebo-controlled trials demonstrating a significant decrease in postoperative edema and bruising in liposuction and rhytidectomy patients.[8,9] One recent meta-analysis of 11 studies with 627 rhinoplasty patients[10] demonstrated, in collective

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analysis, a statistically significant decrease in postoperative eyelid edema and ecchymosis in the arnica group when compared to the control group, up to postoperative day 7. This same study showed that cold compression had positive effects only up to postoperative day 1, whereas nasal taping reduced edema and ecchymosis up to 21 days postoperatively.[10] A second systematic review looking at integrative medicine use in plastic surgery demonstrated a similar outcome for arnica and postrhinoplasty edema and ecchymosis, citing strong Level II evidence.[11]

Generally, topical formulation is well-tolerated, with very few reported adverse events.[12,13] Isolated cases of allergic reaction and sensitivity have been reported.[12–14] The oral formulation is safe at the homeopathic concentration.[15] A non-homeopathic concentration is more dangerous, and can lead to fatal poisoning, cardiotoxicity, severe hypertension, and paralysis.[16] As previously reported in our study, arnica demonstrates a paradoxical concentration-to-efficacy relationship. The more dilute forms of the supplement are more potent.[17,18] Unsupervised use of arnica should be terminated 2 weeks before surgery. Topical arnica should not be used on broken skin.

Bromelain

Bromelain, which is derived from pineapple stems and fruit,[19,20] has long been used for therapeutic purposes. The major active compound is a complex mixture of thiol proteases, peroxidases, cellulases, phosphatases, and glucosidases.[21] Clinical studies have demonstrated antiinflammatory, antithrombotic, and fibrinolytic effects, and some have shown cytotoxic and antitumoral activities,[22–24] by enhancing the immune-cytotoxic activity of monocytes. The mechanism of action involves interplay of these enzymes; unfortunately, the exact nature of this interplay remains unclear.

From a clinical standpoint, there are recent publications in the oral and maxillofacial surgery literature indicating reduction of facial edema in the early and late stages after molar extraction.[25,26] A recent meta-analysis[25] of six previously published, randomized controlled trials demonstrated collective data indicating statistically significant postoperative reduction of facial swelling on quantified facial analysis (bromelain versus control group standardized mean difference, −0.24; $p = 0.03$). Dosing unfortunately varies significantly, ranging from 40 mg four times per day to 250 mg four times per day. This could be largely attributable to lack of standardization in manufacturing, as supplements are not scrutinized to the same level as medical pharmaceuticals in most countries. The plastic surgery literature recently demonstrated use of bromelain for enzymatic débridement of burn wounds.[27–29] Several placebo-controlled trials showed efficacy in resorption of hematomas and improved wound healing.[30,31] Our previously published, randomized, placebo-controlled, double-arm crossover study demonstrated that oral supplementation with bromelain, vitamin C, grape seed extract, calcium, and rutin resulted in a significant decrease in wound healing time, with less inflammation and without bleeding complications.[31] This finding is consistent with the current literature in other specialties.

Because of its antiinflammatory properties, there may be a theoretical risk of bleeding with bromelain; however, there remain no reported data to substantiate this concern. Nevertheless, caution is advised for those with a history of bleeding disorders or already taking anticoagulants. There have been reports of bromelain increasing serum levels of antibiotics, such as amoxicillin and tetracycline, when used concomitantly.[32] In addition, it may elevate heart rate at higher doses. Bromelain should be stopped 2 weeks before surgery in the select group of patients taking anticoagulants or with a history of bleeding disorder or liver disease.

Dong Quai (*Angelica sinensis*)

Dong quai, known as Chinese angelica, has been used in Asian traditional medicine for thousands of years. Known for its ability to regulate female health conditions, it has been called the "female ginseng." It has been used widely to treat various health conditions ranging from dysmenorrhea to postpartum weakness to general fatigue.

Organized studies in recent years have been focused on clarifying effects and understanding its mechanism. Several active ingredients have been identified, including organic acids, volatile oils, polysaccharides, and phthalates,[33] some of which have demonstrated antioxidative and antiinflammatory effects in animal myocardial infarction models and animal traumatic brain injury models.[34] However, there are no clear clinical correlations to these results.

Approximately 0.9 percent of patients use dong quai in the perioperative period.[35] As dong quai has anticoagulation effects, including prolonged prothrombin time and activated partial thromboplastin time,[36] it may interact with other anticoagulants.[37] Certain active chemicals within the supplement may induce sun sensitivity; therefore, sun protection is key. Certain preparations

may also contain a high level of sucrose; thus, it should be used with caution in diabetic patients.[2] Other adverse effects include diarrhea, dyspepsia, nausea, anorexia, and bloating. Given its anticoagulation effects, it is recommended that dong quai be stopped 2 weeks before any surgery.

Echinacea (*Echinacea purpurea*, *Echinacea pallida*, and *Echinacea angustifolia*)

Echinacea belongs to the daisy family, indigenous to North America. Specifically, the *Echinacea purpurea* species has long been used by Native American tribes for treatment of infections, wounds, and animal bites. It is one of the most commonly used herbal dietary supplements used by U.S. adults, most often for the prevention and treatment of the common cold and upper respiratory infections. However, its efficacy is not strongly favored by the literature when compared to placebo.[38]

Echinacea is used by approximately 12.7 percent of surgical patients.[39] There are three major active groups linked to its pharmacologic activities, including alkamides, caffeic acid, and polysaccharides,[40] each with significant in vivo and in vitro immunomodulatory activity by enhancing phagocytes and T cells.[41] Immunosuppression is associated with long-term use (>8 weeks).[41] As a result, it is usually contraindicated in patients with immune-related diseases. Although yet to be substantiated, its immune effects pose a theoretical risk toward infection and poor wound healing. There are also isolated reports linking echinacea to dry eye symptoms.[42] It may also affect efficacy of certain medications, including cyclosporine, steroids, and barbiturates, and may induce hepatotoxicity of certain medications by inhibition of cytochrome CYP3A4.[43] Because of the risk for significant drug interactions, patients should stop using echinacea 2 weeks before surgery.

Goldenseal (*Hydrastis canadensis*)

Goldenseal is an herb indigenous to eastern North America. Native Americans used the roots to treat infections and gastrointestinal tract upsets.[44] Primary active compounds are beta-hydrastine and berberine,[45] which has antimicrobial activities, especially when combined with flavonoids. Leaf extract has shown efficacy against methicillin-resistant *Staphylococcus aureus* infections[46] and some *Mycobacterium* species.[47]

Goldenseal is used by 1.4 percent of surgical patients.[39] It is found to cause sodium depletion and may affect other diuretics.[48] In addition, it is known to inhibit cytochrome CYP3A4[43] in the in vitro setting, and may affect drugs metabolized by the same system. In addition, photosensitivity has been documented; thus, exposure to ultraviolet light and laser is contraindicated.[41] Other minor effects include gastrointestinal tract upset, nervousness, and respiratory failure. Because of inhibition of the cytochrome system, it is recommended that use of goldenseal be stopped 2 weeks before surgery.

Grape Seed

Grape seed is commonly extracted from red and purple grapes, and there are claims that its benefits include antioxidant activities. The active ingredient is proanthocyanidin, which is a bioflavonoid that scavenges free radicals. Other claims include reduction of inflammation, stabilization of collagen and elastin, antihistaminic effects, and chemopreventative effects in patients with cancer.[49,50] Research is currently ongoing to determine its effects and side effects.

There is currently no clinical evidence of any adverse effects from using grape seeds. In vitro studies have demonstrated potential anticoagulant effects.[51] Given in vitro findings regarding antiplatelet functions, it is prudent to stop grape seed supplements 2 weeks before surgery, although there are currently no surgical recommendations.

Licorice (*Glycyrrhiza glabra*)

Licorice root has long been used because of its antiinflammatory properties in both topical and oral formulations. Uses extend from skin emollient to treat eczema, infections, upper respiratory tract disease, and stomach ulcers. There have been in vitro studies demonstrating the efficacy of glycyrrhizin, licorice's active ingredient, against hepatitis B, influenza, and human immunodeficiency virus by modulation of T cells and activation of interferons.[32]

Licorice is used by 0.8 percent of surgical patients.[39] Known side effects include hypertension, arrhythmia, and electrolyte imbalance (hypernatremia and hypokalemia), which may be further potentiated by concomitant diuretic use.[52] In the in vitro setting, licorice is found to inhibit CYP3A4 and may affect the metabolism of drugs processed by the same system.[43] There have been isolated reports of contact dermatitis to licorice root extract.[53] Licorice supplementation for medicinal purposes should be discontinued 2 weeks before surgery, given possible drug interactions.

St. John's Wort (*Hypericum perforatum*)

St. John's wort is most commonly used to treat anxiety and mood-related disorders, but the claimed therapeutic effects range from alleviating aches and pains to treating asthma and sleep disorders. The active ingredient, hypericin, is found to inhibit monoamine oxidase in the in vitro setting,[54] and may interact with selective serotonin reuptake inhibitors, leading to serotonin syndrome.[41,54] A recent randomized, placebo-controlled, clinical trial demonstrated that St. John's wort may reduce postoperative pain in spinal surgery.[55] Several studies have reported phototoxicity induced by St. John's wort when exposed to ultraviolet light type A/B[56,57] and laser treatment.[58] In vitro studies of the extracts hypericin, pseudohypericin, and hyperforin have demonstrated marked production of reactive oxygen species with sun exposure.[56,57] In addition, St. John's wort has been shown to induce the cytochrome P450 pathway and affect drug metabolism.[59]

St. John's wort is taken by approximately 4.5 percent of surgical patients.[35] Some associated side effects include dry mouth, constipation, gastrointestinal tract discomfort, and fatigue. In addition, because of its mood modulation effects, prolonged postoperative sedation, particularly when combined with narcotics, is possible. Long-term use has been associated with cardiovascular insufficiency on anesthesia induction.[60] As mentioned previously, St. John's wort can induce photosensitivity and phototoxicity, and can interact with other medications by means of induction of the cytochrome P450 pathway.

Special precautions should be used when managing patients taking St. John's wort. Because of induction of the cytochrome P450 pathway, metabolisms of common surgical drugs, such as midazolam and lidocaine, can be altered. In addition, in patients taking other photosensitizing medications, such as retinoids, use of St. John's wort should be noted and carefully discussed given likely synergistic effects, which may lead to toxicity. It should be stopped 2 weeks before surgery.

VITAMINS

Vitamin A (Retinoic Acid)

Vitamin A is known to enhance wound healing. When administered either topically or orally, it has been shown to reverse the effects of corticosteroids.[61,62] Doses as high as 25,000 IU/day have been advocated for reversal of steroids without significant side effects. Vitamin A enhances lysosomal membrane lability, increases macrophage influx, and activates collagen synthesis.

The recommended dietary dose is 900 μg/day for men and 700 μg/day for women,[32] and is generally nontoxic. Excess dosing may lead to toxicity, including liver damage, hemorrhage, and coma. There is no need to stop taking this supplement before surgery.

Vitamin B_{12} (Cyanocobalamin)

Vitamin B_{12} is commonly derived from food, such as fish, shellfish, meat, and dairy products. It is most commonly used in combination with other B vitamins as a complex formulation. Nutritional deficiency of vitamin B_{12} is very rare because the body is capable of storing the vitamin for several years. The elderly are most at risk if deficiency occurs. Deficiency is seen with pernicious anemia. The recommended dose is 2.4 mg/day for adults.

Side effects include itching and rash. Vitamin B_{12} and B_6 are both associated with rosacea fulminans.[63] Some severe cases may require treatment with corticosteroids. There is no need to discontinue vitamin B_{12} before surgery.

Vitamin C (Ascorbic Acid)

Vitamin C has historical significance, as it was found to be the key element to collagen synthesis and cross-linking, as reflected by symptoms of scurvy. Ascorbic acid is a cosubstrate for 4-prolyl hydroxylase and lysyl hydroxylase, and a reducing agent needed to convert proline and lysine to hydroxyproline and hydroxylysine, both critical to collagen crosslinking.[64] Vitamin C deficiency impairs wound healing by the same process. Wound infection in the setting of vitamin C deficiency is expectedly more severe as well. Dosing varies depending on treatment goal, but in general for healthy adults, typically 1000 to 2000 mg/day is used.[65]

Vitamin E (Tocopherol)

Vitamin E stabilizes cellular membrane integrity by protection against oxidation. As an antioxidant, it has been proposed that the reduction of free radicals leads to reduction of the inflammatory response needed for wound healing and thereby may result in chronic wounds. Reported effects of vitamin E vary depending on the user. For patients with normal platelets, vitamin E does not affect platelet aggregation but inhibits platelet adherence. However, for patients with abnormal platelets, such as those with diabetes, both aggregation and adherence are affected.[41] In addition,

Table 1. Supplements, Proven Efficacy (Level of Evidence), and Side Effects

Supplement	Efficacy	Level of Evidence	Side Effects
Arnica	Decreases early postoperative edema and ecchymosis	II	Cardiotoxicity, hypertension, paralysis
Bromelain	Decreases postoperative edema	III	Increased serum level of certain antibiotics
Echinacea	No significant data proving successful treatment of common infections	—	Negative CYP3A4; may delay wound healing
Dong quai	No significant data proving antiinflammatory results	—	Prolonged PT, aPTT; photosensitivity
Goldenseal	Antimicrobial	VI	Negative CYP3A4, photosensitivity
Grape seed	No significant data proving antiinflammatory results	—	None
Licorice	No significant data proving antiinflammatory results	—	Negative CYP3A4, hypernatremia, hypokalemia
St. John's wort	Reduce postoperative pain	II	Positive CYP3A4, photosensitivity

PT, prothrombin time; aPTT, activated partial thromboplastin time.

vitamin E is inhibitory to collagen synthesis and thereby may negatively affect wound healing.[66,67] Because of this, it is recommended that vitamin E supplementation be discontinued 2 to 3 weeks before surgery.[41]

DISCUSSION

A recent survey[68] demonstrated that as many as 80 percent of patients presenting for elective surgery used supplemental natural products within 1 year of surgery. As more research effort has been placed into clarifying the claimed efficacy of these products, physicians in many specialties have begun to recognize both the beneficial and adverse effects, and some have begun to integrate some into practice. As early as 2006, our senior author (R.J.R.) published an expansive review study[2] detailing efficacy, available evidence, and practice recommendations for 22 common herbal and vitamin supplements. In addition, our prior randomized placebo-controlled trial[31] demonstrated decreased wound healing time when supplemented with a mixture of bromelain, vitamin C, and grape seed extract. Since the study, the senior author has successfully implemented herbal supplements into his practice with good anecdotal perioperative results without complications, with the exception of frequent flushing, which is most likely attributable to B-complex (niacin component). Our current study is designed to provide updated evidence regarding commonly used herbal and vitamin supplement with claimed healing or antiinflammatory effects.

Which Supplements Favorably Affect Surgical Outcome?

Among the top eight herbal supplements, Level II evidence is available for arnica in treatment of postoperative edema and ecchymosis in rhinoplasty patients,[10] and St. John's wort for treatment of postoperative pain in spinal surgery patients[55] (Table 1). Level III evidence is available for bromelain in management of postoperative facial edema in dental extractions.[25,26] Level VI evidence is available for goldenseal for antimicrobial properties.[47] As previously discussed, vitamin A is useful for reversal of the long-term effect of corticosteroids in oral formulations,[61,62] and topical formulations are particularly useful as an adjunct

Table 2. Supplements Associated with Bleeding Complications

Supplement	Mechanism	Evidence
Bromelain	Unclear	Theoretical
Dong quai	Prolonged PT, aPTT	In vitro
Feverfew	Unclear	Level IV
Garlic	Antiplatelet, antithrombotic	Level III
Ginger	Negative thromboxane synthetase	Level IV
Ginkgo	Unclear	Level V
Ginseng	Inhibit platelet adhesion, platelet-activating factors	Level IV
Grape seed	Antiplatelet	In vitro
Kava kava	Platelet dysfunction	In vitro
Omega-3 fatty acids	Competition with arachidonic acid, decreased production of prothrombotic metabolites	Level II against

PT, prothrombin time; aPTT, activated partial thromboplastin time.

to improve facial skin quality before facial rejuvenation.[69] Vitamin C is essential for normal production of collagen. Both are beneficial for healing; however, given the possible toxicity of vitamin A, it should be used under strict care by providers.

Which Supplements Unfavorably Affect Surgical Outcome?

Among commonly used herbal and vitamin supplements, echinacea and vitamin E have isolated reports of delayed wound healing. Echinacea has immunomodulation effects, which may affect the inflammatory response needed for appropriate healing. Vitamin E may inhibit collagen synthesis, which in turn may delay wound healing. Both risks are not well-substantiated by clinical data.

There are three herbal supplements associated with photosensitivity: dong quai, goldenseal, and St. John's wort. In addition, retinoids (vitamin A derivatives) are also photosensitizing. Special care should be used when assessing patients taking these supplements for laser procedures, and when prescribing other photosensitive medications.

Perioperative Bleeding and the Five Gs

Expectedly, perioperative bleeding is the most common concern for surgeons. Table 2 details the evidence available for 10 supplements with bleeding concerns. Among these, only garlic has Level III evidence[70] linking therapeutic use to perioperative bleeding. Supplements such as feverfew,[71] ginger,[72] ginkgo,[73] and ginseng[74] demonstrated only Level IV/V/VI evidence. Grape seed[51] has only a theoretically proposed risk. Omega-3 fatty acids, in particular, have Level II evidence against bleeding risk.[75,76] In addition, vitamin E has been shown to affect platelet function.

One recent systematic review[11] showed that more than 90 percent of clinical studies available on supplements were published before 2000. This finding is consistent with our literature search as well. There are numerous in vitro and animal studies available. This most likely signals both caution among the medical community and eventual translation into the clinical realm once stronger understanding is obtained.

CONCLUSIONS

Herbal and vitamin supplementation is becoming increasingly prevalent as we obtain more understanding of their efficacies. Arnica and bromelain showed improved postoperative edema and ecchymosis in elective facial procedures. Neither is associated with major perioperative bleeding risks. Unfortunately, data are still limited in the clinical use of many herbal supplements, and better studies in the future are needed.

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