

**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 regards to the efficacies and potential complications related to these supplements. This manuscript provides the most updated practices and evidence of commonly used supplements.

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## INTRODUCTION

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

A survey of surgical patients demonstrated that 40.5% admitted to taking herbal medications with coagulation effects, 32.7% with blood pressure effects, 20% with cardiovascular effects and 8.9% with electrolyte effects.<sup>3</sup> Amongst these, approximately  $\frac{1}{4}$  of these patients reported using herbs that are known to have adverse interactions with prescription medications.<sup>3</sup> Another study of surgical patients demonstrated taking supplements within 2 weeks leading up to surgery, including those that may inhibit coagulation.<sup>4</sup> As there is little regulation of herbal supplements, patients generally do not think of reporting them to healthcare professionals,<sup>5</sup> the actual percentage of this subset of the population taking supplementation is likely much higher than the reported.<sup>1,5,6</sup>

In 2007, the senior author (RJR) previously published an extensive review of herbal and vitamin supplements.<sup>2</sup> From this study derived his current perioperative supplementation protocol to enhance healing. The goal of this study is to provide updated evidence on commonly used herbal and vitamin supplements that have potential wound healing benefits.

## HERBAL SUPPLEMENTS

### **Arnica (*Arnica montana*)**

Arnica is native to mountainous regions of Europe and western North America. Reported effect of Arnica is mainly when used as topical analgesic, antiseptic or anti-inflammatory agent. It is a classic homeopathic remedy frequently used in the trauma and sports setting to alleviate bruising and muscle soreness. The proposed mechanism of action based upon in vitro studies suggest that arnica works by inhibiting histamine release from mast cells, and serotonin release during neutrophil migration and adhesion.<sup>7</sup> Like 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 significant decrease in postoperative edema and bruising in liposuction and rhytidectomy patients.<sup>8,9</sup> One recent meta-analysis of 11 studies with 627 rhinoplasty patients<sup>10</sup> demonstrated, in collective 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 cold compression had positive effects only up to postoperative 1, while nasal taping reduced edema and ecchymosis up to 21 days postoperatively.<sup>10</sup> A second systematic review looking at integrative medicine use in plastic surgery demonstrated a similar outcome for arnica and post-rhinoplasty edema and ecchymosis, citing strong level II evidence.<sup>11</sup>

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

### **Bromelain**

Bromelain, which derives from the pineapple stems and fruits,<sup>19,20</sup> has long been used for therapeutic purposes in human history. The major active compound is a complex mixture of thiol proteases, peroxidases, cellulases, phosphatases and glucosidases.<sup>21</sup> Clinical studies have demonstrated anti-inflammatory, anti-thrombotic and fibrinolytic effects, and some showed cytotoxic and anti-tumoral activities,<sup>22-24</sup> 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 extractions.<sup>25,26</sup> A recent meta-analysis,<sup>25</sup> of six previously published randomized controlled trials, demonstrated collective data indicating statistically significant postoperative reduction of facial swelling on quantified facial analysis (bromelain vs. control group SMD -0.24, P=0.03). Dosing unfortunately varies significantly, ranging from 40mg QID to 250mg QID. 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 debridement of burn wounds.<sup>27-</sup>

<sup>29</sup> Several placebo-controlled trials showed efficacy in resorption of hematomas and improved wound healing.<sup>30,31</sup> Our previously published randomized, placebo-controlled, double-arm crossover study demonstrated oral supplementation with bromelain, vitamin C, grape seed extract, calcium and rutin resulted in significant decrease in wound-healing time, with less inflammation, without bleeding complications.<sup>31</sup> This finding is consistent with the current literature in other specialties.

Because of its anti-inflammatory properties, there may be theoretical risk of bleeding with bromelain; however, there remains no reported data to substantiate this concern. Nevertheless, caution is advised for those with 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.<sup>32</sup> In addition, it may elevate heart rate at higher doses. Bromelain should be stopped 2 weeks prior to surgery in select group of patients taking anticoagulants or with 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 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 phthalides,<sup>33</sup> some of which have demonstrated

antioxidative and anti-inflammatory effects in animal myocardial infarction models, and animal traumatic brain injury models.<sup>34</sup> However, there are no clear clinical correlations to these results.

Approximately 0.9% of patients use Dong Quai in the perioperative period.<sup>35</sup> As Dong Quai has anticoagulation effects, including prolonged prothrombin time and activated partial thromboplastin time,<sup>36</sup> it may interact with other anticoagulants.<sup>37</sup> Certain active chemicals within the supplement may induce sun sensitivity, therefore sun protection is key. Certain preparation may also contain high level of sucrose so should be used with caution for diabetic patients.<sup>2</sup> Other adverse effects include diarrhea, dyspepsia, nausea, anorexia and bloating. Given its anticoagulation effects, it is recommended to stop taking Dong Quai 2 weeks prior to any surgery.

***Echinacea (Echinacea purpurea, Echinacea pallida, 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 US 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.<sup>38</sup>

Echinacea is used by approximately 12.7% of surgical patients.<sup>39</sup> There are three major active groups linked to its pharmacological activities, including alkamides, caffeic acid and polysaccharides,<sup>40</sup> each with significant in vivo and in vitro immunomodulatory activity by enhancing phagocytes and T-cells.<sup>41</sup> Immunosuppression is associated with long-term use (>8wks).<sup>41</sup> 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.<sup>42</sup> 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.<sup>43</sup> Because of 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 upsets.<sup>44</sup> Primary active compounds are beta-hydrastine and berberine,<sup>45</sup> which has antimicrobial activities especially when combined with flavonoids. Leaf extract has shown efficacy against Methicillin-resistant *Staphylococcus aureus* infections,<sup>46</sup> and some *Mycobacterium* species.<sup>47</sup>

Goldenseal is used by 1.4% of surgical patients.<sup>39</sup> It is found to cause sodium depletion and may affect other diuretics.<sup>48</sup> In addition, it is known to inhibit cytochrome CYP3A4<sup>43</sup> in the in vitro setting, and may affect drugs metabolized by the same system. In addition, photosensitivity has been documented, so exposure to UV light, and laser is contraindicated.<sup>41</sup> Other minor effects include gastrointestinal upset, nervousness and respiratory failure. Due to inhibition of cytochrome system, it is recommended to stop using Goldenseal 2 weeks prior to surgery.

### **Grape Seed**

Grape seed is commonly extracted from red and purple grapes, and claims to have benefits from its antioxidant activities. Active ingredient is proanthocyanidin, which is a bioflavonoid that scavenges free radicals. Other claims included reduction of inflammation,



stabilization of collagen and elastin, anti-histamine and chemopreventative effects in patients with cancer.<sup>49,50</sup> Research is currently ongoing in determination of its effects and side-effects.

There is currently no clinical evidence of any adverse effects from using grape seeds. In vitro studies demonstrated potential anticoagulant effects.<sup>51</sup> Given in vitro findings regarding anti-platelet functions, it is prudent to stop grape seed supplements 2 weeks prior to surgery, although there are currently no surgical recommendations.

### **Licorice (*Glycyrrhiza glabra*)**

Licorice root has long been used for its anti-inflammatory properties, both as topical and oral formulations. Uses extended from skin emollient to treat eczema, infections to upper respiratory disease and stomach ulcers. There have been in vitro studies demonstrating efficacy of glycyrrhizin, licorice's active ingredient, against hepatitis B, influenza, and human immunodeficiency virus by modulation of T-cells and activation of interferons.<sup>32</sup>

Licorice is used by 0.8% of surgical patients.<sup>39</sup> Known side effects include hypertension, arrhythmia and electrolyte imbalance (hypernatremia and hypokalemia), which may be further potentiated by concomitant diuretic use.<sup>52</sup> In the in vitro setting, licorice is found to inhibit CYP3A4 and may affect metabolism of drugs processed by the same system.<sup>43</sup> There have been isolated reports of contact dermatitis to licorice root extract.<sup>53</sup> Licorice supplementation for medicinal purposes should be discontinued 2 weeks prior to 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. Active ingredient, hypericin, is found to inhibit monoamine oxidase in the in

vitro setting,<sup>54</sup> and may interact with selective serotonin reuptake inhibitors leading to serotonin syndrome.<sup>41,54</sup> Recent randomized placebo-controlled clinical trial demonstrated that St. John's Wort may reduce postoperative pain in spinal surgery.<sup>55</sup> Several studies have reported phototoxicity induced by St. John's Wort when exposed to UVA/B<sup>56,57</sup> and laser treatment.<sup>58</sup> In vitro studies of extracts, hypericin, pseudohypericin and hyperforin, demonstrated marked production of reactive oxygen species with sun exposure.<sup>56,57</sup> In addition, St. John's Wort has been shown to induce cytochrome P450 pathway and affect drug metabolism.<sup>59</sup>

St. John's Wort is taken by approximately 4.5% of surgical patients.<sup>35</sup> Some associated side effects include dry mouth, constipation, gastrointestinal 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.<sup>60</sup> As previously mentioned, St. John's Wort can induce photosensitivity and phototoxicity, and interact with other medications via induction of cytochrome P450 pathway.

Special precautions should be utilized 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, usage 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 prior to 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 effects of corticosteroid.<sup>61,62</sup> Doses as high as 25,000 IU/day has been advocated for reversal of steroids without significant side effects. Vitamin A enhances lysosomal membrane lability, increases macrophage influx and activates collagen synthesis.

Recommended dietary dose is 900 ug/day for men and 700 ug/day for women,<sup>32</sup> 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 prior to surgery.

### Vitamin B<sub>12</sub> (Cyanocobalamin)

Vitamin B12 commonly derives 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 B12 is very rare because the body is capable of storing several years of vitamin. The elderly is most at risk if deficiency occurs. Deficiency is seen with pernicious anemia. The recommended dose is 2.4mg/day for adults.

Side effects include itching and rash. Vitamin B12 and B6 are both associated with rosacea fulminans.<sup>63</sup> Some severe cases may require treatment with corticosteroids. There is no need to discontinue vitamin B12 prior to 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 co-substrate 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.<sup>64</sup> 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 1000-2000mg/day is used.<sup>65</sup>

#### Vitamin E (Tocopherol)

Vitamin E stabilizes cellular membrane integrity by protection against oxidation. As an antioxidant, it's been proposed that the reduction of free radicals lead to reduction of the inflammatory response needed for wound healing, and thereby may result in chronic wounds. Reported effects of vitamin E varies depending on the user. For patients with normal platelets, vitamin E does not affect platelet aggregation but inhibits platelet adherence. But for patients with abnormal platelets, such as those with diabetes, both aggregation and adherence are affected.<sup>41</sup> In addition, vitamin E is inhibitory to collagen synthesis, and thereby may negative affect wound healing.<sup>66,67</sup> Because of this, it is recommended to discontinue vitamin E supplementation 2 to 3 weeks before surgery.<sup>41</sup>

#### DISCUSSION

Recent survey<sup>68</sup> demonstrated that as high as 80% of patients presenting for elective surgery used supplemental natural products within a year of surgery. As more research effort has been placed into clarifying the claimed efficacy of these products, physicians in many specialties begin to recognize both the beneficial and adverse effects, and some begin to integrate some into practice. As early as 2006, our senior author (RJR) published an expansive review study<sup>2</sup> detailing efficacy, available evidence and practice recommendations for 22 common herbal and vitamin supplement. In addition, our prior randomized placebo-controlled trial<sup>31</sup> demonstrated decreased wound healing time when supplemented with mixture of bromelain, vitamin C, and grape seed extract. Since the study, the senior author 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 anti-inflammatory effects.

***Which supplements favorably affect surgical outcome?***

Among the top 8 herbal supplement, level II evidence is available for Arnica in treatment of postoperative edema and ecchymosis in rhinoplasty patients,<sup>10</sup> and St. John's Wort for treatment of postoperative pain in spinal surgery patients.<sup>55</sup> [Table 1] Level III evidence is available for Bromelain in management of postoperative facial edema in dental extractions.<sup>25,26</sup> Level VI evidence is available for goldenseal for antimicrobial properties.<sup>47</sup> As previously discussed, vitamin A is useful for reversal of long-term effect of corticosteroids in oral formulations,<sup>61,62</sup> and topical formulations are particularly useful as adjunct to improve facial skin quality prior to facial rejuvenation.<sup>69</sup> Vitamin C is essential to normal production of collagen. Both are beneficial to healing; however, given 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, St. John's Wort. In addition, retinoids, vitamin A derivative, are also photo-sensitizing. Special care should be used when assessing patients taking these supplements for laser procedures, and when prescribing other photo-sensitive medications.

### ***Perioperative bleeding and the Five G's***

Expectedly, perioperative bleeding is the most common concern for surgeons. Table 2 details the evidence available for 10 supplements with bleeding concerns. Amongst these, only garlic has level III evidence<sup>70</sup> linking therapeutic use to perioperative bleeding. Supplements, such as Feverfew,<sup>71</sup> Ginger,<sup>72</sup> Ginkgo<sup>73</sup> and Ginseng,<sup>74</sup> only demonstrated IV/V/VI evidence. Grape seed<sup>51</sup> has only theoretically proposed risk. Omega-3 fatty acids, in particular, have level II evidence against bleeding risk.<sup>75,76</sup> In addition, vitamin E has been shown to affect platelet function.

One recent systematic review<sup>11</sup> showed that more than 90% 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.

### **CONCLUSION**

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

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Table 1. Supplements, Proven efficacy (Level of Evidence), Side-effects

Supplement	Efficacy	Level of Evidence	Side-Effects
Arnica	Decrease early postoperative edema and ecchymosis	II	cardiotoxicity, hypertension, paralysis
Bromelain	Decrease postoperative edema	III	Increased serum level of certain antibiotics
Echinacea	No significant data in prove for treatment of common infections	--	(-) CYP3A4 May delay wound healing
Dong Quai	No significant data in prove for anti-inflammatory results	--	Prolonged PT, aPTT Photosensitivity
Goldenseal	Antimicrobial	VI	(-) CYP3A4, photosensitivity
Grape Seed	No significant data in prove for anti-inflammatory results	--	None
Licorice	No significant data in prove for anti-inflammatory results	--	(-) CYP3A4, hypernatremia, hypokalemia
St. John's Wort	Reduce postoperative pain	II	(+) CYP3A4, photosensitivity



Table 2. Supplements associated with bleeding complications

<b>Supplement</b>	<b>Mechanism</b>	<b>Evidence</b>
Bromelain	Unclear	Theoretical
Dong Quai	Prolonged PT, aPTT	In-vitro
Feverfew	Unclear	IV
Garlic	Anti-platelet, Antithrombotic	III
Ginger	(-) thromboxane synthetase	IV
Ginkgo	Unclear	V
Ginseng	Inhibit platelet adhesion, platelet-activating factors	IV
Grape Seed	Anti-platelet	In-vitro
Kava Kava	Platelet dysfunction	In-vitro
Omega-3 Fatty Acids	Competition with arachidonic acid, decreased production of pro-thrombotic metabolites	II against