Herbs as Adjuncts to Surgery

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Abstract

Herbs offer many ways to help make surgery safer. Case reports of herbs complicating surgery spur a false sense of concern, as the vast majority of controlled trials show benefits when certain herbs are used in conjunction with surgery. In this review, the effects of various herbs on aspects of surgery are discussed.

Agents that can decrease postsurgical nausea include *Zingiber officinale* (ginger), *Alpinia galangal* (galangal), *Mentha* x *piperita* (peppermint), and *Morinda citrifolia* (noni). Bromelain can reduce postsurgical swelling and *Centella asiatica* (gotu kola) can reduce postsurgical scarring and improve healing. Topical *Aloe vera* (aloe) is contraindicated in surgery as it delays healing. Herbs to possibly offset postsurgical pain include *Cannabis sativa* (marijuana), *Lavandula angustifolia* (lavender), and *L.* x *intermedia* (lavandin).

Agents that may decrease stress ulceration include *Panax ginseng* (Asian ginseng), deglycyrrhizinated licorice, and *Zanthoxylum rhoifolium* (*mamica de cadela*). Postoperative ileus is countered by a formula known as Major Construct the Middle Decoction (*Dà Jiàn Zhōng Tāng, dai-kenchu-tō*), particularly its component *Z. piperitum* (Sichuan pepper).

The article ends with a discussion about why evidence supports the safety of several herbs. These include *Allium sativum* (garlic), Asian ginseng, and *Ginkgo biloba* with respect to the risk of surgery-related bleeding.

Introduction

Major surgery entails many risks, including—but not limited to—problems with general anesthetics, infections, wound healing, scarring, stress ulcers, and pain. Herbs can potentially offset some of these risks and are frequently used by patients who undergo surgery; however this practice involves little direction by experts. A survey in Scotland showed that 60% of adult and pediatric surgical patients at an otolaryngologic clinic had taken supplements at some point, and 35% had done so in the prior year.[1] A Canadian survey of several hepatobiliary surgical practices showed that 16% of patients were taking herbs or supplements.[2]

Some surgeons view all herbs as potentially harmful and risky, and advise against taking anything before or right after major surgery. Some surgeons extrapolate from single extreme case reports to urge blanket caution, such as using the case of a woman who took large doses of garlic perioperatively and had bleeding complications to suggest that garlic at any dose should be avoided.[3] Other surgeons take a more reasonable approach of inquiring about dietary supplement use by surgical patients and educating them about potential problems.[4] Unfortunately, most nurses, surgeons, and anesthesiologists still do not ask their patients about supplement use,[5] and even fewer of these practitioners have the knowledge to educate their patients about such use. Uncritical lists of supposedly problematic herbs (usually based on animal studies or single human cases, some of which are highly dubious) create a perception of fear and suspicion about herbs and surgery.[6]

This article explores the many herbs that have been shown specifically to be beneficial for patients undergoing major surgery. The aim is to highlight the great potential for beneficial interactions and shift the current atmosphere of fear to one of focusing on ways to make surgery safer and more effective.

Of course, there is always some level of risk when combining any medical interventions, but the current authors' viewpoint (which is supported by the vast majority of published research) is that the risk is very low and well worth taking, given the much greater chance of benefit when using certain herbs for patients undergoing surgery.

Nausea and Vomiting Caused by Major Anesthesia

To perform major surgery, patients must generally be kept unconscious, with their pain mitigated, and, often, with their muscles paralyzed. The multiple agents that accomplish these changes are generally lumped together as major anesthetics

but quite a few different substances are used for different purposes. Most research on herbs has focused on mitigating the risk of nausea and vomiting caused by inhaled anesthetics.

Postoperative nausea and vomiting (PONV) comprise a common problem encountered with the use of inhaled anesthetics, with ~ 25% of patients experiencing this complication.[7] Various pharmaceutical methods for avoiding PONV exist, but come with additional risks and, in some cases, high costs. Various herbal medicines exist to mitigate this complication safely.

Zingiber officinale (ginger) rhizome has been studied in many clinical trials for addressing PONV. A meta-analysis of five clinical trials showed that 1 g of crude ginger powder was more effective than placebo for reducing PONV.[8] Generally, this dose is administered 1 hour before surgery with the patient having an otherwise empty stomach. In a double-blinded trial in 120 patients undergoing thyroidectomy, 500 mg of ginger did not produce any benefit, compared to placebo in patients who were given intravenous (IV) dexamethasone as PONV prophylaxis.[9] However, this trial used what appears to be a subtherapeutic dose, compared to what the meta-analysis found (with 1 g being the minimal effective dose).

At least two other positive double-blinded trials comparing 1 g of ginger to placebo have been published since the meta-analysis was published.[10,11] One of these trials showed that adding 1 g of ginger to 10 mg of the antinausea drug ondansetron was superior to ondansetron alone.[11] The most recent meta-analysis, thus, should be updated. One double-blinded trial showed that 2 g of ginger was not effective, compared to placebo, for reducing vomiting, though the ginger did reduce intraoperative nausea significantly, in patients receiving only epidural anesthesia during cesarean sections.[12]

Overall, ginger appears to be extremely safe and potentially effective for reducing PONV. At least 1 g should be administered 30–60 minutes before major anesthetics are introduced.

It is uncertain if ginger is effective for PONV after epidural anesthesia without inhaled anesthetics. *Alpinia galangal* (galangal) rhizome, a very close relative of ginger, is a therapeutic alternative. Although galangal has not yet been assessed in clinical trials, it is empirically effective at similar doses, particularly in patients who cannot tolerate or who do not like ginger.

Several other herbal medicines have been investigated in humans for preventing PONV; however, none of these herbs have been tested as comprehensively as ginger. Acupressure application of *Capsicum frutescens* (cayenne) plaster at various acupuncture points has been shown repeatedly to reduce PONV.[13–16] The K-D2 Korean hand acupuncture point (lateral edge of the distal index finger phalanx), Pericardium 6 (midwrist), and Liver 4 (lateral hand, midway along the border of the second metacarpal) points have all been used successfully in studies of various surgeries. Inhalation of *Mentha* x *piperita* (peppermint) spirits was more effective than green sterile water for rapidly reducing postoperative nausea that occurred despite the use of ondansetron or promethazine.[17] A concentrated aqueous extract of *Morinda citrifolia* (noni) fruit at a dose of 600 mg 1 hour before surgery was more effective than placebo or lower doses of noni for reducing PONV.[18]

Edema, Wound Healing, and Scarring

Bromelain is a complex mixture of enzymes found in pineapple stems. Bromelain has been assessed in many trials to help reduce postsurgical edema. One randomized trial compared oral bromelain to escin—a complex of saponins from *Aesculus hippocastanum* (horse chestnut) fruit—for reducing edema after surgical setting of fractured limbs.[19] Bromelain was superior to escin for reducing edema. In three clinical trials of bromelain after surgical removal of molars or after jaw surgery, edema was significantly reduced, compared to placebo.[20–22] Bromelain was also just as effective as diclofenac for reducing swelling and pain after removal of impacted molars in one double-blinded, randomized trial.[23]

A potency measure of bromelain is critical; this is something not generally necessary for or established with other herbal medicines. The two most common standards used in North America are the milk-clotting unit (MCU) and gelatin-dissolving unit (GDU). The usual dose (of 2400 MCU or 3200 GDU potency material per g) is 1–2 g three times per day. It is important that bromelain not be taken with food (30 minutes before or 2 hours after eating) to be effective for this purpose.

The whole plant of *Centella asiatica* (gotu kola) is a very effective agent for promoting wound healing and preventing and treating postsurgical scars. An early trial showed that gotu kola's triterpenoid asiaticoside helped speed healing of surgical wounds for cataract removal and retinal-detachment surgeries.[24] The ability of an aqueous extract of gotu kola to promote corneal healing has been verified further in vitro.[25]

A more-recent trial showed that a gotu kola extract providing 50 mg of asiaticoside per capsule, at a dose of two capsules three times per day, was significantly more effective than placebo for promoting surgical wound healing in patients with diabetes.[26] There was less scarring in the gotu kola group, and no significant adverse effects occurred.

Much preclinical evidence also supports the vulnerary properties of gotu kola on skin.[27] Gotu kola is also helpful for preventing surgical adhesions and scarring. This is particularly important in major abdominal or pelvic surgeries, in which adhesion rates are as high as 90%–100% of patients.[28] While clinical trials are lacking to prove gotu kola's effectiveness for preventing surgical adhesions, it has been shown to be very helpful empirically, and research in corneal surgery shows reduction of risk of postsurgical adhesions.[24] In a study comparing gotu kola to white petrolatum applied topically after shave biopsy, there was significant reduction in scarring with gotu kola.[29] Asiaticoside has previously been shown to help prevent keloid formation after surgery.[30]

Numerous studies have also investigated the effects of topical *Allium cepa* (onion) bulb in a silicone gel base for preventing postsurgical scarring. Most of these products are composed

of a 10% onion gel. Starting 7 days after cesarean sections, 16 Thai women randomly applied onion gel three times daily to scars on one side of the body and placebo gel on the other side of the body.[31] After 12 weeks there was a reduction in scar height and symptoms with use of onion gel, compared to placebo, with no adverse effects.

In a trial of 44 adults of any skin tone, each of whom had two seborrheic keratoses removed, one on each side of the chest, onion gel or no treatment were compared starting 2 weeks after surgery.[32] After 8 weeks, the onion-gel treatment produced significantly improved scar appearance and pliability, compared to no treatment.

A double-blinded trial involving 60 adult patients after medial sternotomy found that topical onion gel was superior to placebo for preventing scar hypertrophy.[33] Treatment lasted 12 weeks. In a very similar study in 39 patients after medial sternotomy, in each patient, onion gel was applied to part of the wound and placebo gel to the rest of the wound.[34] Hypertrophic scars were prevented by onion gel, compared to placebo, but keloid formation did not differ between the groups.

Aloe vera (aloe) leaf gel is frequently used as a topical burn and wound healer in traditional medicine. In one study of 21 women who underwent cesarean section or gynecologic laparotomy, topical aloe gel delayed wound healing significantly, compared to usual care.[35] A meta-analysis concluded that there is no evidence for a wound healing effect of aloe and that there is reason to believe it may delay wound healing topically.[36] Whether oral aloe gel (that can be used in surgery inside the mouth) would be effective remains an open question; it is also confounding why clinical trials contradict aloe's strong historical indication as a vulnerary.

Reducing Pain and Anxiety

Opioids, originally isolated from *Papaver somniferum* (opium poppy) latex, comprise the mainstay for postoperative pain management. They frequently cause adverse effects, including constipation, itching, and dysphoria.

The female flower bud of *Cannabis sativa* (cannabis, marijuana) is a traditional analgesic herb that is increasingly being legalized around the world, particularly for medical use. There are few trials assessing cannabis use for postoperative analgesia. One standardized, whole-plant extract of cannabis was tested at single 5-mg, 10-mg, and 15 mg doses for rescue analgesia postoperatively.[37] The 10-mg and 15-mg doses reduced pain significantly, compared to the 5-mg dose (there was no other control group), although the trial was discontinued when there was a severe vasovagal reaction in one user who was taking the 15-mg dose. There were no other significant adverse effects.

A trial of pure oral δ-9-tetrahydrocannabinol (THC) at a dose of 5 mg was not superior to placebo for reducing postoperative pain in another double-blinded trial.[38] This strongly suggests that compounds other than THC in cannabis are active and partially explains why the complex extract noted above was effective, as it contains the whole range of compounds in cannabis, not just THC. More research is needed to determine the role, if any, of cannabis for relieving postoperative pain.

A prior prospective observation trial found that regular cannabis smokers in Jamaica required more opioid pain relievers postsurgically than nonusers required.[39] The observers assessing pain-medication use were blinded as to prior cannabis use by the study volunteers. Taking the scant information from these studies into account, it appears that patients who are already using cannabis regularly may not derive much benefit postoperatively from additional cannabis, while cannabis-naïve patients may derive some benefit.

Fifty-four patients undergoing laparoscopic gastric-banding surgery were randomized to receive either inhaled *Lavandula angustifolia* (lavender) flower 2% volatile oil or unscented baby oil immediately after surgery via oxygen mask.[40] Analgesic and morphine use was significantly lower in the lavender group, compared to controls. No adverse effects were noted. This contradicts a prior study of 50 patients undergoing breast biopsies that showed no difference in pain-medication use when comparing lavender oil to no treatment, although satisfaction with pain control was rated significantly higher among the lavender-oil users.[41]

Sixty women who underwent cesarean sections were randomized to inhale either 10% lavender oil or a placebo volatile oil mixture without lavender after surgery.[42] Postoperative pain (4 hours after surgery) was rated significantly lower, satisfaction with analgesia was rated significantly higher, and diclofenac use was significantly lower in the lavender group, compared to the placebo group. A similar single-blinded, randomized trial comparing repeated inhalations of lavender oil or "clinically neutral aromatic material" placebo in 200 women after cesarean section showed that lavender reduced pain significantly compared to the control substance.[43]

Lavender, and its related species *L.* x *intermedia* (lavandin; often regarded as inferior to lavender), have the added benefit of being anxiolytic. One single-blinded randomized trial ($n = 150$) showed that inhaled and topical (1 drop on the wrist) lavandin volatile oil reduced anxiety significantly before surgery, compared to *Simmondsia chinensis* (jojoba) oil or standard treatment only.[44] In another study, 50 patients awaiting upper endoscopy were randomized to view a relaxing video while using a lavender oil vaporizer or no treatment.[45] The relaxation protocol reduced blood pressure and anxiety, compared to producing no benefits in the untreated group.

In a randomized, single-blinded trial, a (*Prunus* spp.) cherry scent was not found to have any effect on pain, compared to just oxygen.[46] Thus, the specific scent involved was responsible for the beneficial effect—not just a generic scent.

Stress-Ulcer Prevention

Acid-blocking drugs are routinely used for surgical patients to prevent stress-ulcer formation, and aspiration pneumonia in some cases. However, this practice has been criticized as

overused, with one analysis of 63 noncritical, general surgery patients showing that 79% of these patients had no clear indication for use of acid blockers.[47] Acid-blocking drugs are associated with many complications and problems that are increasingly documented to include increased risk of infectious pneumonia, gastroenteritis, osteoporosis, and malabsorption of many nutrients.[48] There is thus a great need to replace acid-blocking drugs for patients who need stress-ulcer prophylaxis in surgery.

Injection of ginsenosides from *Panax ginseng* (Asian ginseng) and alkaloids from *Aconitum carmichaeli* (*fu zi*), also referred to as *shen fu* injection, in Chinese children undergoing cardiac surgery to repair congenital defects reduced gastrointestinal damage, shortened intensive-care stay time, and improved cardiac function, compared to what occurred in patients who received a placebo injection, in a randomized trial.[49] While rates of actual stress ulcers were not reported, the changes seen in this trial support that this intervention has the potential to prevent these ulcers. Although this treatment is not available in North America, it is worth further study to determine the treatment's full effects and benefits, and to evaluate if oral Asian ginseng and/or *fu zi* could be useful in a similar way. *Shen fu* injection has also been shown to mitigate postoperative ileus in one trial involving 150 patients who underwent abdominal surgery.[50]

Deglycyrrhizinated licorice (DGL) is used to treat peptic ulcer and, given its safety and affordability, is a natural candidate for stress-ulcer prevention. However, in a double-blinded clinical trial, DGL was not shown to be effective for this purpose.[51] Unmodified *Glycyrrhiza glabra* (licorice) root extract was effective for stress-ulcer prevention in rodents, suggesting that a trial of whole licorice (as opposed to DGL) is warranted.[52] Other demulcent herbs are potential candidates for stress-ulcer prevention but tend to need to be used in such volumes that they could, theoretically, increase the risk of aspiration pneumonia.

No other clinical trials were found regarding the effect of herbs for stress-ulcer prevention. However, many herbs have been studied in preclinical settings for this purpose (see Table 1). Most of these herbs have been shown to improve the quantity and/or quality of gastric mucus and not to act as antisecretory agents. A good example of this is *Zanthoxylum rhoifolium* (Brazilian prickly ash, *mamica de cadela*) bark, a Brazilian native tree studied in mice and rats for its ability to prevent ulcers caused by cold restraint.[53]

North American species of prickly ash such as *Z. clava-herculis* (southern prickly ash) and *Z. americanum* (northern prickly ash) are routinely used very similarly to the way *mamica de cadela* is used. The Brazilian species was shown to prevent decreases and actually increase production of sulfhydryl-rich mucus in the rodents' stomachs. There was no diminution of gastric acidity. This novel approach to stress-ulcer prevention could be much safer and more effective than the current antiacid-drug approach but needs to be studied first in humans. Note that several other bitter herbs, such as prickly ash, have been shown to have similar effects, including *Arctium lappa* (burdock) leaf, *Cynara scolymus* (artichoke) leaf, and *Quassia amara* (Surinam quassia) bark.[54–56]

Postoperative Ileus

Major Construct the Middle Decoction (*Dà Jiàn Zhōng Tāng* in Chinese and *dai-kenchu-tō* in Japanese) is a formula first described in the *Essentials of the Golden Cabinet* (*Jīn Guì Yào Lüè*) by Zhāng Zhòng-Jǐng written in ~ 220 AD. The formula was used historically to alleviate pain and warm and tonify the middle *Jiao*. This relatively simple formula is detailed in Table 2. It has been studied rather extensively for its ability to counteract postoperative ileus, a very common complication of surgery.[57] The key ingredient in this formula

Table 1. Preclinical Evidence for Herbal Prevention of Stress Ulcers

Herb (common name) & part(s) used	Animal models	References
Trigonella foenum-graecum (fenugreek) seed	Rats (gastric and duodenal ulcers)	a
Cenostigma macrophyllum (caneleiro) leaf	Mice (gastric ulcers)	b
Ficus religiosa (sacred fig) leaf	Mice (gastric ulcers)	c
Potentilla fulgens (Himalayan cinquefoil, bajradanti) root	Rats (gastric ulcers)	d
Cleome viscoa (Asian spiderflower) flowering tops	Rats (gastric ulcers)	e
Cinnamomum spp. (cinnamon) bark; *C. tamala* (Indian cassia) leaf	Mice and rats (gastric ulcers)	f,g
Zingiber officinale (ginger) rhizome mixed with calcium carbonate & sodium alginate	Rats (gastric ulcers)	h

[a]Khil'ko TD, Iakubtsova IV, Preobrazhens'ka TD, Ostapchenko LI. Glycoproteins of mucus of gastric and duodenal wall surface during ulcerogenesis and the impact of fenugreek [in Ukrainian]. Fiziol Zh 2013;59:74–79; [b]Viana AF, Fernandes HB, Silva FV, et al. Gastroprotective activity of *Cenostigma macrophyllum* Tul var *acuminata* Teles Freire leaves on experimental ulcer models. J Ethnopharmacol 2013;150:316–323; [c]Gregory M, Divya B, Mary RA, et al. Anti-ulcer activity of *Ficus religiosa* leaf ethanolic extract. Asian Pac J Trop Biomed 2013;3:554–556; [d]Laloo D, Prasad SK, Krishnamurthy S, Hemalatha S. Gastroprotective activity of ethanolic root extract of *Potentilla fulgens* Wall ex Hook. J Ethnopharmacol 2013;146:505–514; [e]Gupta PC, Rao CV, Sharma N. Protective effect of standardized extract of *Cleome viscosa* against experimentally induced gastric lesions in the rat. Pharm Biol 2013;51:595–600; [f]Tankam JM, Sawada Y, Ito M. Regular ingestion of *Cinnamomi cortex pulveratus* offers gastroprotective activity in mice. J Nat Med 2013;67:289–295; [g]Eswaran MB, Surendran S, Vijayakumar M, et al. Gastroprotective activity of *Cinnamomum tamala* leaves on experimental gastric ulcers in rats. J Ethnopharmacol. 2010;128:537–540; [h]Kumar Singh P, Pal Kaur I. Development and evaluation of a gastro-retentive delivery system for improved antiulcer activity of ginger extract (*Zingiber officinale*). J Drug Target 2011;19:741–751.

Table 2. Major Construct the Middle Decoction

Herb (Chinese and/or common name)	Part used	Amount in formula
Zanthoxylum piperitum (*chuān jiāo*, Sichuan pepper)	Fruit (pericarp)	6% (3 g)
Zingiber officinale (*gān jiāng*, dry ginger)	Cooked, dried rhizome	24% (12 g)
Panax ginseng (*rén shēn*, Asian ginseng)	Steamed, dried root (Red ginseng)	12% (6 g)
Hordeum vulgare (barley) malt sugar, *yí tang*	Maltose	58% (30 g)

has been shown to be another spicy prickly ash, *Z. piperitum* (Sichuan pepper) fruit, along with maltose sugar.[58] Ginger has also been shown to stimulate gastric motility as part of this formula, while Asian ginseng has no such direct effect but, instead, serves as the synergizer in the formula, making all the components work together.[59]

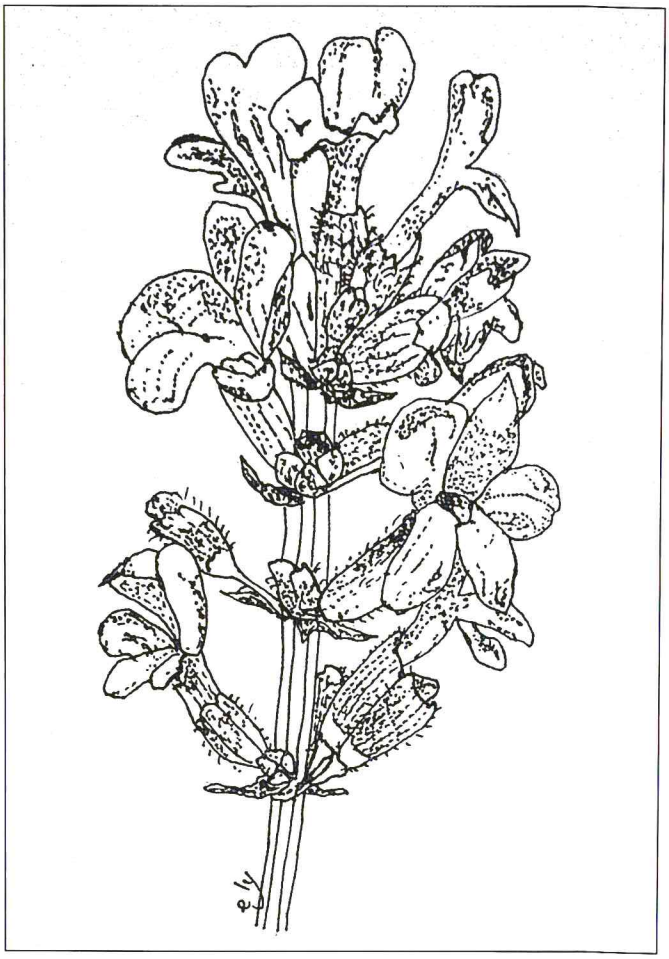
In a randomized trial (blinding was not described), 24 Japanese patients with postoperative ileus after major abdominal surgery received either 5 g tid of Major Construct the Middle granules or placebo for 14 days.[60] The need for repeat operations to correct the ileus was significantly lower in the herbal group, compared to the placebo group. Recurrence of ileus was not significantly different between the groups, but Major Construct the Middle granules approached statistical significance closely with respect to ileus recurrence. There were no adverse effects.

In a randomized trial (blinding not described), 54 Japanese patients recovering from colectomy were given either 2.5 g tid of Major Construct the Middle granules or 1 g tid of *Lactobacillus* spp.[61] The time to first bowel movement after surgery was significantly shorter and colonic transit time was significantly faster in the herb group, compared to the probiotic group. There were no adverse reactions. Similar benefits have been noted in randomized trials in patients after hepatic resection, colon resection (in a double-blinded trial), and total gastrectomy.[62–64]

These studies support the use of Major Construct the Middle Decoction or granules to treat postoperative ileus. A convenient, typical, adult dose of granules is 2.5 g tid in warm water. These studies also suggest that other bitter and pungent herbs should be tested for their potential to overcome postoperative ileus.

Bleeding Concerns

One of the biggest concerns about combining herbs and surgery is the potential of herbs to cause bleeding. Several case studies have been published about various herbs being associated with excessive bleeding after surgery (see Table 3). Of course, bleeding can occur after surgery in any circumstance, and a case study cannot, by itself, definitively prove a causative role between exposure to an herb and bleeding. In addition, note that some of the cases cited (notably those involving garlic) involved extremely high doses often taken for prolonged periods that are not typically recommended or used.



Lavandula officinalis **(lavender). Drawing © Eric Yarnell, ND, RH, AHG.**

Controlled trials have routinely failed to confirm these case studies. In one trial involving 10 healthy adults, *Ginkgo biloba* (ginkgo) leaf, Asian ginseng, *Hypericum perforatum* (St. John's wort) flowering top, and *Serenoa repens* (saw palmetto) fruit extracts all failed to have any effect on platelet function after 2 weeks of use at the manufacturer's recommended maximum daily dose.[65] The positive control, aspirin, did inhibit platelet function significantly in this cohort. The equivalent of a single clove of fresh garlic did not affect platelet function in 18 healthy adults.[66]

Ginkgo extracts probably have the highest number of case reports indicating spontaneous hemorrhage or bleeding associated with surgery, but clinical trials do not support that it is a clinically relevant platelet inhibitor. A meta-analysis of 18 randomized controlled trials found no evidence of ginkgo in-

Table 3. Selected Case Studies of Herbs and Hemorrhage

Herb (common name	Patient & outcome	Dose	Reference
Allium sativum (garlic)	54-yo woman, DM2; hemorrhage during strabismus surgery	5 tablets daily (~ 5 g of fresh garlic equivalent) for unknown period	a
	37-yo woman w/ 20 year hx of menorrhagia; hemorrhage after vaginal hysterectomy requiring transfusions	~ 8 fresh cloves daily for 6 months	b
Panax ginseng (Asian ginseng)	39-yo woman, smoker, w/ 5 month hx of menometrorrhagia that stopped w/ ginseng discontinuation	Unknown quantities of oral & topical ginseng	c
Ginkgo biloba (ginkgo)	77-yo woman with blood oozing from hip-replacement wound	120 mg extract qd for unknown period; bleeding stopped 10 weeks after stopping supplement	d
	53-yo woman with bleeding during & after blepharoplasty & rhytidoplasty	160 mg extract qd, "chronic user"	e
	51-yo woman with bleeding during and after blepharoplasty	160 mg extract qd, "chronic user"	e
	65-yo woman with retrobulbar hemorrhage after anesthetic injection before cataract surgery	40 mg extract tid for 2 years	f

[a]Carden SM, Good WV, Carden PA, Good RM. Garlic and the strabismus surgeon. Clin Experiment Ophthalmol 2002;30:303–304; [b]Ref. 3; [c]Kabalak AA, Soyal OB, Urfalioglu A, et al. Menometrorrhagia and tachyarrhythmia after using oral and topical ginseng. J Womens Health (Larchmt) 2004;13:830–833; [d]Bebbington A, Kulkarni R, Roberts P. *Ginkgo biloba*: Persistent bleeding after total hip arthroplasty caused by herbal self-medication. J Arthroplasty 2005;20:125–126; [e]Destro MW, Speranzini MB, Cavalheiro Filho C, et al. Bilateral haematoma after rhytidoplasty and blepharoplasty following chronic use of *Ginkgo biloba*. Br J Plast Surg 2005;58:100–101; [f]Fong KC, Kinnear PE. Retrobulbar haemorrhage associated with chronic *Gingko biloba* ingestion. Postgrad Med J 2003;79:531–532.

DM2, type 2 diabetes mellitus; hx, history; w/, with; yo, years-old.

terfering with platelet function according to many measures.[67] A review of clinical trials also showed that ginkgo did not interact with warfarin or aspirin.[68] These are averages of large populations and suggest that the overall risk of bleeding with ginkgo is very low. This does not rule out possible problems in individuals who may be idiosyncratically susceptible to the effects of ginkgo, but precisely who these individuals might be has not been determined.

Caution is of course warranted in anyone undergoing major surgery. However, prohibiting the use of any herb reported in a case study to be associated with bleeding seems to be an unfortunate overreaction.

Cytochrome 3A4-Related Concerns

Two herbs that should be considered very carefully before being used in surgery are St. John's wort and grapefruit (*Citrus* x *paradisi*).[69] St. John's wort contains a constituent, hyperforin, which is a pregnane X receptor agonist, which then leads to induction of CYP3A4 and P-glycoprotein in the gut.[70] Because so many drugs are substrates for these two compounds, St. John's wort has been reported to reduce absorption of many drugs, thus lowering their efficacy. However, no commonly used major anesthetics are substrates of concern. Some macrolide antibiotics (clarithromycin, erythromycin, and telithromycin) that are occasionally used perioperatively—as well as the opioid drug fentanyl and the antinausea drug ondansetron—which are commonly used perioperatively, could all be impaired by concomitant St. John's wort use. None of these drugs have been tested or reported to cause problems in combination with St. John's wort, but, for safety, they still should not be combined until research is conducted.

St. John's wort should not necessarily be excluded from use by all surgical patients in all forms, however. Topical St. John's wort preparations have been shown to accelerate wound healing safely after cesarean section operations and scalp operations, and are highly unlikely to be absorbed sufficiently to cause drug interactions.[71,72] St. John's wort has also been used successfully after coronary artery surgery to promote efficacy of the antiplatelet prodrug clopidogrel, which is partially converted to its active form by CYP3A4.[73]

Grapefruit pulp contains furanocoumarins and related compounds that inhibit intestinal CYP3A4. This has the potential to increase absorption of CYP3A4 substrates, which could lead to toxicity if the dose of the substrate drug is not lowered. This also has the potential to be dose-sparing, allowing lower doses of the substrates to be used without altering efficacy. Fentanyl is often administered by a transmucosal route (as a lollipop essentially), and one human trial showed minimal effects of grapefruit juice on the pharmacokinetics of this dose form.[74]

One human trial showed no significant effect of grapefruit juice on alfentanil (a closely-related drug) pharmacokinetics.[75] No research of grapefruit juice's effects on any other commonly used preoperative drug was found. Patients taking any

CYP3A4 substrate drugs, whether they are undergoing surgery or not, should be evaluated carefully to determine if St. John's wort or grapefruit juice would be appropriate.

Conclusion

There is considerable evidence demonstrating the ability of various herbs to offset various adverse effects of surgery. This varies from reducing nausea caused by major anesthetics, decreasing swelling, improving wound healing, lessening scarring and adhesion formation, decreasing pain, reducing stress ulceration, and lessening postoperative ileus.

While there is the one case of aloe gel in which there is relatively good evidence that it is harmful because it delays wound healing after surgery, there is little other evidence from clinical trials that the herbs that have been studied are harmful in any respect. In particular, despite case studies of concern, there is no evidence from randomized trials that garlic, Asian ginseng, or ginkgo increase bleeding during or after surgery. St. John's wort and grapefruit juice should be used cautiously in patients exposed to ondansetron, fentanyl, or any other CYP3A4 substrate drugs used perioperatively.

Additional research is clearly needed to investigate further what benefits herbs might bring to the surgical arena. Meanwhile, there is sufficient evidence to warrant introducing some of the approaches outlined herein more routinely. ■

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