

# Nutraceuticals: Potential Roles and Potential Risks for Pain Management

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■ **Abstract:** Over the past 2 decades, the world health market has been flooded with over the counter herbal products, also known as nutraceuticals. Although many of these products are neither recommended nor prescribed by conventional medical practitioners, an increasing number of people are taking these products on a daily basis. A recent survey at Texas Tech University School of Medicine in Lubbock, Texas concluded that 32% of patients scheduled for elective surgery or pain procedures were taking one or more herbal supplements; however, 70% did not disclose these during a routine anesthetic assessment.<sup>1</sup> Pain physicians are also increasingly needed in the care of these patients. As many of these agents carry a potential to cause bleeding problems, we have reviewed here briefly, the basic mechanisms of coagulation and correlated the role of commonly used herbs known to possess side effects, which can cause excessive bleeding. In addition, we have reviewed a number of potential useful herbal derived agents for pain management. ■

## THE HEMOSTATIC MECHANISM

The cessation of bleeding from a damaged blood vessel depends on 3 processes, primary hemostasis, coagulation, and fibrinolysis. Primary hemostasis is a local process and takes place within seconds of vascular injury and involves the interaction between platelets and in-

jured vascular intima. In a process called platelet activation, platelets spread along the surface of the denuded blood vessel and adhere to the subendothelial collagen layer via glycoprotein receptors and the von Willebrand factor.<sup>2</sup> The activation process causes the platelets to change shape and undergo a release reaction, extruding the contents of their granules, and releasing multiple compounds into the blood, including ADP, serotonin, clotting factors V, VIII, fibrinogen and many other chemical mediators, important to primary hemostasis and the subsequent coagulation process. With sufficient stimulus, the platelets synthesize thromboxane A<sub>2</sub> (TXA<sub>2</sub>), which stimulates further ADP release and also has potent vasoconstrictor actions. ADP increases platelet activation and leads to the aggregation of platelets to each other via fibrinogen strands. Finally, the platelets expose a new phospholipid on the surface called platelet factor 3, which changes the surface charge of the platelet and creates a “procoagulant” activity. The interaction of clotting factors will follow on the phospholipid surface of the activated platelet and result in the formation of fibrin, reinforcing the friable platelet plug.<sup>3</sup> Endothelial cells secrete prostacyclin (PGI<sub>2</sub>), which has actions opposite those of TXA<sub>2</sub>. PGI<sub>2</sub> inhibits platelet activation, secretion, and aggregation, and prostacyclin is a potent vasodilator. Any imbalance in the production of the 2 prostaglandins, thromboxane or prostacyclin, can lead to a defect in primary hemostasis or to abnormal coagulation. Besides prostacyclin, intact endothelial cells

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release ADPase, which degrades surplus ADP, decreasing platelet activation and platelet aggregation at the periphery of the platelet plug.

### BASIC PRINCIPLES OF THE COAGULATION MECHANISM

Coagulation involves the interaction of many plasma proteins, called clotting factors, which interact in various reaction sequences to produce insoluble fibrin clot.<sup>4</sup> Most of the clotting factors circulate in an inactive form, called a procoagulant molecules or zymogens. During the process of coagulation, a portion of this protein molecule is cleaved off and the remaining protein becomes an active cleavage enzyme, called a serine protease. The “activated clotting factor,” designated by a small “a” after the Roman numeral of the factor, cleaves off a portion of the next procoagulant clotting factor, which “activates” that factor in succession.

In a chain reaction-like fashion, one factor “activates” another, until fibrinogen (factor I) is cleaved to form fibrin. All of the plasma zymogens, except von Willebrand factor (vWF), are synthesized in the liver. The synthesis of factors II, VII, IX, and X is dependent on vitamin K. Factor VIII circulates as part of a factor VIII-vWF complex. The major role of vWF is to promote adhesion of platelets to subendothelial surfaces.<sup>5</sup>

Commonly used herbs known to potentially cause excessive bleeding by modulation of the coagulation pathway include garlic, ginger, ginkgo biloba, ginseng (see Table 1):

**Table 1. Commonly used herbs known to cause excessive bleeding**

Herb	Suggested Mechanism(s) of Coagulation Dysfunction	Clinical Implications
Garlic	Platelet Dysfunction	Concomitant use of drugs eg, NSAIDs, aspirin, and anticoagulants should be avoided.
Ginger	Inhibition of Thromboxane Synthetase	Concomitant use of drugs eg, NSAIDs, aspirin, and anticoagulants should be avoided.
Ginseng	Antiplatelet effect	Concomitant use of drugs eg, NSAIDs, aspirin, and anticoagulants should be avoided. Hypertension, hypoglycemia prolonged use.
Ginkgo biloba	Inhibition of Platelet Activating Factor (PAF)	Concomitant use of drugs eg, NSAIDs, aspirin, and anticoagulants should be avoided. May decrease effectiveness of drugs such as phenobarbital, phenytoin.

### GARLIC (ALLIUM SATIVUM)

Garlic has been used for therapeutic purposes, for centuries. The most active ingredient of garlic is allicin, which contains sulfur, and when combined with breakdown products, gives garlic its characteristic smell. Crushing the garlic clove activates the enzyme allinase, which converts alliin to allicin.<sup>6</sup> Garlic derivatives are frequently used for antiplatelet, antioxidant and fibrinolytic effects.<sup>7,8</sup> There is a reported case of spontaneous spinal/epidural hematoma in an 87-year-old male, with associated platelet dysfunction related to excessive garlic ingestion.<sup>9</sup> In this regard, garlic-induced decreased platelet aggregation has been described in the literature.<sup>10</sup>

#### Clinical Aspects

The clinician should be aware that garlic may augment the effects of warfarin, heparin, NSAIDs, and aspirin and may result in an abnormal bleeding time, which can lead to an increased risk of bleeding during or after an invasive pain procedure.<sup>11</sup>

### GINGER (ZINGIBER OFFICINALE)

Ginger has been described as an effective therapy for nausea, vomiting, motion sickness, and vertigo. Antivertigo effects of ginger have been observed in a study with no study subject experiencing nausea, when compared to placebo.<sup>12</sup> Ginger has been shown to exert a superior antimotion sickness response as compared to dimenhydrinate. These studies concluded that ginger exerts a gastric mechanism unlike dimenhydrinate, which has a centrally mediated mode of action.<sup>13</sup> Ginger has been found to be effective in controlling the symptoms in hyperemesis gravidarum.<sup>14</sup> However, results from two recent clinical trials, revealed that ginger was ineffective in reducing the incidence of postoperative nausea and vomiting in patients undergoing gynecologic laproscopic surgery.<sup>15,16</sup> Ginger is a potent inhibitor of thromboxane synthetase enzyme,<sup>17</sup> thereby limiting the capability of platelets to synthesize TXA2 and decreased ADP release with subsequent decreased platelet aggregation. This cascade of reactions can hence cause a prolonged bleeding time.

#### Clinical Aspects

Use of ginger may alter bleeding time; therefore, it is suggested that it should be discontinued at least 2 to 3 weeks prior to any invasive pain procedure. Use of ginger in patients on anticoagulants such as warfarin, and heparin and drugs such as NSAIDs or aspirin is not recommended.<sup>11</sup>

## PANAX GINSENG

There is a wide variation in the components of this herb. Depending upon its geographic origin, ginseng can be classified as American ginseng (*Panax quinquefolius* grows in the United States), Chinese ginseng, or Korean ginseng. Ginseng has been reported to have significantly decreased international normalized ratios (INR) suggesting clinically relevant coagulation modulation albeit in an isolated case.<sup>18</sup> In this regard a study suggested that there might be some antiplatelet components in ginseng.<sup>19</sup> Adverse effects associated with a prolonged use of this herb include hypertension, headache, vomiting, and epistaxis. Steven-Johnson syndrome, abnormal vaginal bleeding has been reported with the use of panax ginseng.<sup>11</sup>

### Clinical Aspects

Ginseng should be avoided in patients on drugs like warfarin, heparin, NSAIDs and aspirin. Since prolonged use of ginseng can cause hypertension, the clinician should be focused on perioperative hemodynamic variation as these patients are often volume depleted due to long-standing hypertension and since many anesthetic agents can cause generalized vasodilatory effects causing profound intraoperative hypotension. Concomitant use of ginseng with monoamine oxidase inhibitors (eg, phenelzine sulphate), should be avoided as manic episodes have been reported with routine use of ginseng.<sup>20,21</sup> Ginseng, with potential hypoglycemic effects, should be cautiously used in diabetic patients on insulin or oral hypoglycemic medications. It would, therefore, follow that the clinician would need to have appropriate evaluation of blood glucose levels perioperatively for applicable patients.<sup>11</sup>

## GINGKO BILOBA

The extracts from the leaves of the Gingko biloba tree have been used in traditional Chinese medicine for centuries.<sup>8</sup> Asian civilizations have used this herb since 3000 BC to cure many ailments.<sup>22</sup> The use of gingko biloba is on the rise worldwide. The most important components of gingko are flavinoids, terpenoids, and organic acids. Metabolic pathways vary with different compounds.<sup>6</sup> Four preparations of gingko have been used in clinical trials so far, namely tebonin, tanakan, rokan, and kaveri. This herb is used as an antioxidant and a circulatory stimulant. Gingko is also used for the treatment of intermittent claudication, tinnitus, vertigo, memory enhancement, and sexual dysfunction.<sup>22</sup> The herb has a potential to inhibit platelet-activating-factor, modulate nitric oxide, and possesses a significant anti-

inflammatory effect.<sup>23-28</sup> The inhibition of the platelet-activating-factor (PAF) can cause a decreased platelet aggregation at the site of intimal injury thereby impeding the process of clot formation. Gingko biloba is considered to be relatively safe with few side effects limited to mild gastrointestinal upset and headache. However, a few disturbing case reports have been mentioned in the literature. Gingko biloba-induced spontaneous hyphema (bleeding from iris), subarachnoid hemorrhage, and spontaneous bilateral subdural hematomas have been described.<sup>29-32</sup> Of additional concern is the gingko toxin in both the gingko leaf and seed, which is considered to be potentially neurotoxic.<sup>33</sup>

### Clinical Aspects

Concomitant use of gingko biloba with aspirin, or any NSAIDs and anticoagulants such as warfarin and heparin, is not recommended as gingko may increase the potential of bleeding in these patients. It would also be appropriate to avoid its concomitant use with anticonvulsant drugs (eg, carbamazepine, phenytoin, phenobarbital) as gingko may decrease the effectiveness of these drugs.<sup>34</sup> In addition, it has been recommended that gingko should be avoided in patients taking tricyclic antidepressant agents, as it might increase the seizure threshold-lowering potential of these drugs.<sup>34</sup>

Commonly used herbs known to possess analgesic properties include AGA, belladonna, black pepper, capsicum, willow bark, wintergreen, clove, and cajuput oil (see Table 2):

## AGA

AGA is a mushroom with a red cap spotted with white. Putative compounds include: ibotenic acid, muscimol, muscarine, and betalains. The illusions that occur with AGA are a misinterpretation of sensory stimuli and are due to the ibotanic acid. This derivative of AGA mimics the neurotransmitter glutamic acid in the brain.

**Table 2. Herbals (scientific name, left; common name, right) with analgesic properties currently being evaluated for clinical practice**

<i>Amanita muscaria</i>	Aga
<i>Atropa belladonna</i>	Belladonna
<i>Piper nigrum</i>	Black pepper
<i>Capsicum annuum</i>	Cayenne
<i>Syzygium aromaticum</i>	Clove
<i>Melaleuca leucadendra</i>	Cajuput
<i>Salix species</i>	White Willow
<i>Gaultheria procumbens</i>	Wintergreen

### Clinical Aspects

It is used for nerve and joint pain. In addition, it is used for fever, anxiety, alcohol poisoning and as a hallucinogen.<sup>35</sup> The illusions with AGA are a misinterpretation of sensory stimuli and are due to the ibotanic acid,<sup>36</sup> which mimics the neurotransmitter glutamic acid in the brain and is converted rapidly to muscimol, which imitates the action on the neurotransmitter GABA. Side effects develop within 30 to 90 minutes and peak at 2 to 3 hours and include initially drowsiness, later confusion, ataxia, dizziness, euphoria, muscles jerks, and spasms.<sup>36</sup> A deep sleep or coma can result after large doses. In general, greater than 10 gm of fresh mushroom can lead to coordination disorder, confusion, illusions, and manic attacks; while doses greater than 100 gm can lead to unconsciousness, asphyxiation, coma and death.<sup>36</sup>

### ATROPA BELLADONA

Historically, belladonna was used by Italian women to dilate their pupils (belladonna means beautiful lady).<sup>37</sup> Leaves and roots derive the putative compounds, which include the alkaloid hyoscyamine, transformed to atropine; apoatropine, and scopolomine.

### Clinical Aspects

Belladonna derivatives are used as sedatives, antispasmodics, for intestinal and biliary colic, motion sickness, and in hemorrhoid suppositories.<sup>37,38</sup> Side effects include dry mouth, decreased perspiration, dilation of pupils, blurred vision, red dry skin, tachycardia, hyperthermia, acute psychosis, convulsion, and coma.<sup>37-40</sup> It is contraindicated in congestive heart failure (can cause increase cardiac work from increased heart rate), constipation, esophageal reflux, gastric ulcer, gastrointestinal infections, hiatal hernia, narrow angle glaucoma, tachyarrhythmias and urinary retention.<sup>39</sup> It is contraindicated in lactation as it can reduce milk production and it is secreted into the milk.<sup>39</sup> Belladonna can increase anticholinergic effects and side effects of antihistaminics, phenothiazines, procainamide, quinidine, and tricyclic antidepressants.<sup>38</sup>

### BLACK PEPPER

*Piper nigrum* (black pepper) has an important role in a number of pain related states. The berries from which it is derived have volatile oils (sabinene, limonene, caryophyllene,  $\beta$ -pinene,  $\alpha$ -pinene), acid amines (eg, piperines), and fatty oils. Black pepper stimulates thermal receptors, which increases secretion of saliva and gastric mucosa as a taste bud reflex mediated effect.<sup>35</sup>

### Clinical Effects

Black pepper can be used externally as an irritant ointment for treating neuralgias and scabies and as a counterirritant for pain in general.<sup>38-41</sup> It increases oral absorptions of drugs, eg, phenytoin, propranolol, theophylline, possibly by modulating intestinal membrane dynamics.<sup>42-44</sup> Black pepper orally can be used for upset stomach, bronchitis, and cancer. *Piper nigrum* possesses anti-flatulent, antimicrobial, and diuretic properties.<sup>35,38</sup> Side effects include burning aftertaste, redness of eyes, and swelling of eyelids.<sup>45</sup> Death has been reported with aspiration of a large amount of pepper.<sup>45-46</sup>

### CAPSICUM

Also known as African pepper, bird pepper, red pepper, and sport pepper. Putative compounds involved in the modulation of pain include capsaicinoids, carotinoids, flavonoids, and steroid saponins.<sup>47-51</sup> A local effect including warmth occurs which reflects a series of biochemical responses. The mechanism of action when applied topically is by releasing substance P in the nerves. This initially causes pain, but after repeated applications substance P is depleted.<sup>52</sup> This reduces the ability of the nerves to transmit sensations and therefore reduces pain. Capsaicin also stimulates unmyelinated slow C fibers, which can induce cough, dyspnea, nasal congestion, and eye irritation.<sup>53</sup>

### Clinical Aspects

Capsaicin is used in muscular tensions/spasms and rheumatic and arthritic conditions. Its use should be limited to 2 days, longer usage can cause festering dermatitis, blistering, and ulceration. It is used topically for pain of shingles, postherpetic, trigeminal, diabetic, postmastectomy and postsurgical neuralgias, HIV associated peripheral neuropathy and fibromyalgia.<sup>47-49</sup> Also, capsaicin is used as a counterirritant to desensitize nerves and to create a feeling of warmth.<sup>37,50</sup> Orally it is used for stomach upset, colics, diarrhea, improvement of peripheral circulation, reduction of blood clotting tendencies, seasickness, malaria and yellow fever.<sup>35,50</sup> Side effects, if used topically, include burning, urticaria and contact dermatitis.<sup>38,47,54</sup> Orally it can cause mucosal irritation, sweating and flushing of the head and neck, lacrimation and rhinorrhea.<sup>55</sup> Excessive amounts of capsicum can lead to gastroenteritis and hepatic or renal damage. Theoretically, concomitant use with coca might increase the effects and risk of adverse effects of cocaine in coca.<sup>56</sup>

## WILLOW BARK

Orally used for mild feverish colds, influenza, headache, and pain caused by inflammation, muscle and joint pain, gouty arthritis, ankylosing spondylitis, rheumatoid arthritis, and others systemic connective tissue disorders characterized by inflammatory changes.<sup>57,58</sup> Willow constituents include flavonoids, tannins, and salicylates, which are attributed to the anti-inflammatory, antipyretic, uricosuric/antiuricosuric activities, increase in blood clotting time, and plasma-albumin binding.<sup>58</sup> The typical dose is 1 to 3 grams dried bark 3 to 4 times daily.<sup>59</sup>

### Clinical Aspects

Very few side effects are reported with the use of Willow bark. Theoretically, gastrointestinal disturbances as well as kidney and liver damage are possible due to the tannin content.<sup>60</sup> Salicylate content theoretically could cause gastric and renal irritation, hypersensitivity, gastrointestinal bleeding, tinnitus, nausea, and vomiting.<sup>58</sup> Theoretically, concomitant use with salicylate containing herbs such as wintergreen, poplar, sweet birch, black cohosh, and aspen bark may enhance salicylate effects and side effects.<sup>54</sup> Also, concomitant use with agents possessing antiplatelet/anticoagulant effects such as angelica, anise, arnica, celery, chamomile, clove, garlic, ginkgo, ginseng, horseradish, and licorice could increase the risk of bleeding.<sup>54-58,61,62</sup>

## WINTERGREEN

Used orally for headache, stomach discomfort, flatulence, neuralgia particularly sciatica, pleurisy pain, ovarian pain, gouty arthritis, dysmenorrhea, fever, and kidney disorders.<sup>35</sup> Topically, it is used as a wash for rheumatism, sore muscles, and lumbago.<sup>37</sup> The plant contains galutherin that changes into methyl salicylate as the plant is dried.<sup>35</sup> It is usually prepared as a tea with a teaspoon of dried leaves added to a cup of boiling water.

### Clinical Aspects

Wintergreen oil is used topically as a counterirritant for musculoskeletal pain. The plant should be used cautiously with patients with a history of salicylate allergy, asthma, or nasal polyps.<sup>63</sup> It is contraindicated in patients with gastrointestinal inflammation.<sup>54</sup> Concomitant use of topical wintergreen oil and warfarin can increase INR and bleeding risk due to systemic absorption of methyl salicylate contained in wintergreen.<sup>64-65</sup>

## CLOVE

Topically, is used for toothache, as a counterirritant for pain, for mouth and throat inflammation and as a part of multi-ingredient preparation for premature ejaculation.<sup>38,42,57,58</sup> Orally, it is used for stomach upset and as an expectorant.<sup>37,58</sup> The active ingredient is eugenol, which depresses sensory receptors involved in pain perception by inhibiting prostaglandin biosynthesis.<sup>66</sup>

### Clinical Aspects

Eugenol also has an antiplatelet activity and therefore can potentiate the effects of other antiplatelet or anticoagulant drugs increasing risk of bleeding.<sup>54,58</sup> Side effects include local tissue irritation damage to dental pulp when used topically on the oral mucosa.<sup>38,47,58,67</sup> Orally, the clove may cause hemoptysis, bronchospasm, pleural effusion and respiratory insufficiency.<sup>38,47,58,67</sup> Fifteen percent clove tincture is used in treating athlete's foot.<sup>67</sup>

## CAJUPUT OIL

Topically, is used to treat rheumatic, neuralgic discomforts and arthritis.<sup>38</sup> Cajuput oil acts as a counterirritant by producing mild inflammation of the skin for the purpose of relieving a deep-seated inflammatory process.<sup>50</sup>

### Clinical aspects

Orally or by inhalational route, it is used as an expectorant or tonic.<sup>4</sup> Also, cajuput oil is used to treat headache, colds, toothache, and indolent tumors.<sup>38</sup> Topical use can potentially produce allergic reactions, hypersensitivity and irritation of mucus membranes. Orally cajuput oil may cause dyspepsia.<sup>50</sup>

It is critical to understand that derivatives of herbal medicines represent roughly one-third of conventional medicines presently utilized. Some of the drugs, of importance in pain practice and anesthesia, derived from plants are listed below in Table 3.

**Table 3. Many conventional drugs commonly used in pain practice and anesthesiology are derived from herbs**

Plant	Drug
Atropa Belladonna	Atropine
Digitalis Purpurea	Digitalis
Papaver somniferum	Codeine
Cephaelis ipecacuanha	Ipecac
Physostigma venunosum	Physostigmine
Ephedra sinica	Ephedrine
Erythroxylon coca	Cocaine
Datura fastuosa	Scopolamine

## CONCLUSION

The pain clinician should have a detailed knowledge and understanding of the potential risks and purported benefits of herbal medicines and should thoroughly inquire about patient's use of herbal products. In addition, the education of each patient regarding the serious, potential drug-herb interactions should be a routine component of preoperative assessment. The American Society of Anesthesiologists (ASA) suggests that all herbal medications might be discontinued 2 to 3 weeks prior to elective surgical/pain procedures. If the patient is not sure of the contents of the herbal medicine, he/she should be urged to bring the container so that the pain clinician or anesthesiologist can attempt to review the contents of the herb/preparation. More scientific studies in this regard would be prudent to label nutraceuticals as risk factors for bleeding during invasive pain procedures and more precisely understand potential benefits of herbal agents for acute and chronic pain relief.

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