REVIEW ARTICLE

Herbal medication: potential for adverse interactions with analgesic drugs

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SUMMARY

The use of herbal supplements in the US has increased dramatically in recent years. These products are not regulated by the Food and Drug Administration (FDA) with the same scrutiny as conventional drugs. Patients who use herbal supplements often do so in conjunction with conventional drugs. This article is a review of potential adverse interactions between some of the commonly used herbal supplements and analgesic drugs. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, have the potential to interact with herbal supplements that are known to possess antiplatelet activity (ginkgo, garlic, ginger, bilberry, dong quai, feverfew, ginseng, turmeric, Meadowsweet and willow), with those containing coumarin (chamomile, motherwort, horse chestnut, fenugreek and red clover) and with tamarind, enhancing the risk of bleeding. Acetaminophen may also interact with ginkgo and possibly with at least some of the above herbs to increase the risk of bleeding. Further, the incidences of hepatotoxicity and nephrotoxicity may be augmented by acetaminophen when concomitantly used with the potentially hepatotoxic herbs Echinacea and kava, and with herbs containing salicylate (willow, meadowsweet), respectively. The concomitant use of opioid analgesics with the sedative herbal supplements, valerian, kava and chamomile, may lead to increased central nervous system (CNS) depression. The analgesic effect of opioids may also be inhibited by ginseng. It is suggested that health-care professionals should be more aware of the potential adverse interactions between herbal supplements and analgesic drugs, and take appropriate precautionary measures to avoid their possible occurrences. However, as most of the interaction information available is based on individual case reports, animal studies and in vitro data, further research is needed to confirm and assess the clinical significance of these potential interactions.

Keywords: acetaminophen, adverse drug interactions, analgesic drugs, herbal supplements, NSAIDs, opioids

INTRODUCTION

The use of herbal supplements in the US has become increasingly popular in recent years. In a survey conducted in 1999, about 49% of adult Americans were estimated to have used herbal products during the previous year (1). Of these, about 24% had used these products on a regular basis. These medications fall into the category of alternative/complementary medicines and, as such, are not regulated by the Food and Drug Administration (FDA) with the same scrutiny as conventional drugs. Their regulation by the FDA is restricted as a result of the Dietary Supplement Health and Education Act (DSHEA) passed by US Congress in 1994. These products are available to consumers as over-the-counter (OTC) items in various forms of preparations or dosages. Several factors are believed to contribute to the increasing trend of herbal supplement utilization in this country: ease of accessibility, the desire for self-medication, and the perceptions that herbs are safer, gentler and less costly than conventional drugs, among others. These and related aspects of utilization of herbal
supplements have been reviewed in some details recently (2–4).

As the use of herbal supplements in the US continues to grow under the prevailing scenario, some concerns have become apparent regarding the safety of these products. Of particular safety concern is potential interactions of these products with conventional drugs. It has been documented that as many as 31% of the patients who use herbal supplements do so in conjunction with prescribed drugs and about 70% of these patients do not regularly report the use of these products to their health care providers (1). Another study also demonstrated that about 26% of presurgical patients who utilize herbal supplements take OTC drugs concurrently (5). In view of the ongoing trend, it is likely that health-care professionals will encounter more often than before patients who use herbal supplements and who may seek their help concerning herb–drug interactions. In order to appropriately tackle this problem and provide a more adequate health-care service to such patients, practitioners should be knowledgeable of at least the commonly occurring or anticipated interactions between herbal supplements and conventional drugs. These interactions may be additive or synergistic, whereby the herbal product increases or potentiates the action of the drug. By contrast, the herb may also be antagonistic to the action of the drug. While herb–drug interactions may involve pharmacodynamic and pharmacokinetic mechanisms, they may result in either beneficial or adverse effects.

In this paper, possible adverse interactions that may occur between some of the popular herbal supplements in the US market and analgesic drugs are reviewed briefly based on the available literature information. Some of the information provided is supported with documented data, whereas others have their basis on theoretical grounds. Along with this information, a brief description of the major therapeutic applications of each herb is provided.

Analgesics are one of the most frequently used drugs for medical as well as dental purposes in the US. These drugs are available as OTC and/or prescription items. The commonly used analgesic drugs include (i) aspirin and the non-salicylate non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen, flurbiprofen, diflunisal, naproxen, ketorolac, ketoprofen, meclofenamide and etdolac; (ii) acetaminophen and (iii) the opioids, codeine, oxycodone, dihydrocodeine, morphine, hydromorphone, oxymorphone, methadone, fentanyl, suphentany1, alfentanil, levorphanol, meperidine, pentazocine, nalbuphine, buprenorphine, butorphanol, hydrocodone, dihydrocodeine and propoxyphene (6–8). The widespread use of analgesics, both as OTC and prescription items, demands that health-care professionals should be aware of their possible interactions with herbal supplements. Such information has not yet been compiled systematically and this brief review is the first attempt towards that goal. For the purpose of this review, the analgesics are classified as described above and their possible interactions with herbal supplements are examined according to this classification.

**POTENTIAL INTERACTIONS OF ASPIRIN AND NON-SALICYLATE NSAIDS WITH HERBAL SUPPLEMENTS**

Aspirin and non-salicylate NSAIDs are commonly used for the management of mild-to-moderate pain. These drugs reduce the synthesis of prostaglandins and thromboxanes by inhibiting/inactivating the cyclooxygenase enzyme (6, 7). While the inhibitory effect of aspirin on cyclooxygenase is irreversible, that of the non-salicylate NSAIDs is reversible. Therefore, compared with the non-salicylate NSAIDs, aspirin has a greater potential for causing effects resulting from inhibition of cyclooxygenase. However, for both groups of drugs, interactions may occur with herbal supplements whose actions involve the production of prostaglandins and/or thromboxanes. In addition, both aspirin and the non-salicylate NSAIDs are highly plasma protein-bound and this may further predispose them to possible interactions with herbs that share this property, although such interactions have not yet been documented in the literature. Aspirin, at relatively high doses (e.g., >3 g/day), also causes a reduction in prothrombin, a plasma factor involved in blood clotting (8).

A survey of the literature indicates that a number of herbal supplements have antiplatelet and anticoagulant (i.e., those containing coumarin derivatives) properties, and tamarind can interact with aspirin and some of the other NSAIDs (9–16).
**Interactions with antiplatelet herbs**

One of the consequences of thromboxane synthesis inhibition by aspirin and the non-salicylate NSAIDs is a reduction in platelet aggregation. This process interferes with clotting mechanisms, prolonging bleeding time. High doses of aspirin by reducing prothrombin production can also contribute to bleeding problems, as noted above. Moreover, NSAIDs, particularly aspirin, by inhibiting prostaglandin generation in the gastric mucosa, eliminate cytoprotection with possible damaging effects on the mucosa, leading to gastric bleeding, specially in the elderly (17). Therefore, when NSAIDs are used by patients taking herbal supplements with antiplatelet activity, there clearly is an increased risk of bleeding in the stomach and elsewhere in the body. In fact, some antiplatelet herbs have been reported to cause bleeding on their own (i.e., in the absence of NSAIDs or any other drugs), strengthening this contention. The following are herbal supplements that have been documented or suspected to possess antiplatelet activity, thus having the potential to cause increased risk of bleeding with NSAIDs, particularly aspirin.

**Ginkgo** (Ginkgo biloba L.). Ginkgo is one of the most popular herbal products available in the US. An extract of ginkgo leaves is commonly used for conditions associated with cerebral and peripheral ischaemia (e.g. dementia, impotency, claudication) in various dosage forms including capsules, tablets and tinctures. Among several other effects, ginkgo is reputed to have vasorelaxant, anti-oxidant and anti-inflammatory properties. Ginkgo extract is composed of several compounds including the flavone glycosides, kaempferole and quercetin, diterpenes (ginkgolides A, B, C and M) and sesquiterpenes (9, 11, 13–15, 18, 19). Of these, ginkgolides (particularly ginkgolide B) have also been shown to inhibit the binding of platelet activating factor (PAF) to its receptors on platelet membranes, resulting in reduced platelet aggregation. In this regard, a study in human volunteers found marked inhibition of platelet aggregation after single doses of mixed ginkgolides (9, 18, 20, 21). Consistent with this, bleeding has been reported in patients taking ginkgo with and without concomitant administration of NSAIDs. A case report suggested spontaneous bleeding in the eyes of a 70-year-old man who was given aspirin while taking ginkgo extracts (21, 22). Therefore, the concurrent administration of aspirin or other NSAIDs with ginkgo may present an additional risk of bleeding. Appropriate precautions are recommended for avoiding such herb–drug interactions.

**Garlic** (Allium sativum). Garlic is one of the largest selling and most extensively researched herbs. It is popularly believed to provide several cardiovascular benefits including the lowering of blood pressure, prevention of age-related changes in the vasculature and a reduction of serum lipids (9, 11, 13–15, 18, 19). Garlic is available as cloves, minced bulb, oil-filled capsules and tablets. Among other ingredients, it contains alliin/alllicin and its degradation products, and sulphur-containing essential oils. Dosage forms are standardized for alliin content as well as garlic oil. These constituents of garlic, particularly allin/alllicin, have been demonstrated to possess antioxidant properties, and to inhibit the production and/or release of mediators such as PAF, adenosine, prostaglandins and thromboxanes (9, 13, 19). The inhibitory effect of garlic on the production and/or release of one or more of these mediators decreases platelet function. In support of this, there is a report indicating that platelet aggregation could be reduced by garlic oil in blood samples from healthy adults (23). In addition, in an elderly man, the development of a spontaneous epidural haematoma was observed after ingestion of garlic (24). Also, in a male patient who underwent transurethral resection of the prostate, haemorrhage occurred for a period of 4 h after surgery as a result of prior ingestion of garlic tablets (25). However, there have been no reports that directly relate the occurrence of adverse interactions between NSAIDs and garlic in humans. It is, nevertheless, prudent that patients should be appropriately instructed or closely observed if garlic consumption occurs concomitantly with the use of these analgesics.

**Ginger** (Gingiber officinale). Ginger has been used primarily as a prophylaxis in nausea and vomiting. It is also promoted for use in anorexia, certain cardiovascular problems, bronchitis and arthritis (9, 15, 18, 21). The herb is available as fresh or dried root, powder, liquid extract, tablets, capsules, or
tea. The volatile oil of ginger is composed of zingiberene, bisabolene, shogaol and gingerols (9, 15, 21). Ginger has also been reported to reduce platelet aggregation through inhibition of thromboxane synthase (26). It is therefore suspected that the use of aspirin or other NSAIDs may enhance bleeding tendency when simultaneously taken with ginger supplements, particularly in amounts of ginger greater than regularly found in food products.

*Bilberry* (Vaccinium myrtillus). This herb has been variously used for the treatment of diarrhoea, circulatory diseases, eye conditions, inflammation and diabetes (9, 15, 18, 21). It is supplied as tinctures, fluid extracts, dried leaves and berries. Bilberry contains anthocyanins and flavonoid glycosides. It is believed that bilberry’s medicinal properties stem primarily from the anthocyanins, which also exert antagonism of platelet aggregation (9, 15, 21). Although no drug-herb interactions have been documented to date, it would be prudent to avoid concomitant use of aspirin and other NSAIDs with bilberry, which may elicit additive or synergistic antiplatelet effect and possibly haemorrhage (9, 15, 21). There is also the possibility that other berries (e.g. blackberry, blueberry, cranberry, red raspberry, grape, wild cherry) may have similar adverse interactions with these analgesics.

*Dong quai* (Angelica sinensis). Dong quai is a Chinese medicine promoted in the US for the treatment of several gynaecological complaints. It is also claimed to have mild sedative, analgesic, antispasmodic, anti-inflammatory and antiplatelet properties (9, 15, 27). Preparations used include tablets, teas and alcohol extracts. Phytochemical analysis found that don quai consists of ferulic acid, and several natural coumarin derivatives such as oxypeucedan, osthole, psoralen, bergapten and furocoumarin derivatives (9, 15, 21, 27). In vivo and *in vitro* studies have shown that ferulic acid and osthole have antithrombotic activity (27–30). These chemicals exert this effect by interfering with two pathways responsible for platelet activation. Ferulic acid interrupts platelet aggregation by inhibiting the release of serotonin and adenosine diphosphate from platelets and by reducing the production of thromboxane A2. Osthole interferes with platelet activation and aggregation through direct inhibition of arachidonic acid metabolism (27–30). Therefore, although not reported in the literature, these data suggest that dong quai may potentiate the risk of bleeding if combined with NSAIDs.

*Feverfew* (Tanacetum parthenium). Common use of feverfew is for prophylaxis and treatment of migraine headaches. Other uses include the treatment of arthritis, gastrointestinal disorders and fever (9, 15, 18). The herb is available as dry bulk, pills, capsules and tinctures. It is believed that the above effects of the herb are produced primarily because of its constituent parthenolide, which blocks the synthesis and/or release of various inflammatory mediators (e.g. prostaglandins, thromboxanes, leukotriens, histamine, serotonin) from platelets and polymorphonuclear leucocytes (31, 32). As a result, feverfew has a significant inhibitory effect on platelet aggregation (9, 15, 18). Although there are no documented reports of feverfew interacting with NSAIDs, the pharmacological data suggest at least the potential for additive antiplatelet effect in the presence of these analgesics.

*Ginseng*. At least three varieties of ginseng are available on the American market: American ginseng (*Panax quinquefolius*), Asian ginseng (*Panax ginseng*) and Siberian ginseng/eleuthero (*Eleutherococcus senticosus*). Asian ginseng is considered to be the most potent (33). All three varieties are used for the purposes of boosting the immune system, and enhancing stamina and physical capacity. Such ‘adaptogenic’ properties of ginseng are believed to be more useful for the elderly and those recovering from illness (9, 15, 18, 33). Ginseng roots are available as fresh or dried root, powder, capsules, tablets, tea and candy. American ginseng has been shown to contain panaxosides and Siberian ginseng, eleutherosides (9, 15, 33). Although the mechanisms remain unclear, these ingredients produce effects on the central nervous system (CNS), cardiovascular system, neuro-endocrine function, carbohydrate metabolism and lipid metabolism, and immune function (9, 15, 33). Regarding effects on platelets, *in vitro* studies have shown that several components of *P. ginseng* inhibit thromboxane A2 formation and thus platelet aggregation (9, 15, 33). In rats fed *P. ginseng* for 3 weeks, platelet aggregation was found to be
impaired, as measured by thrombin time and activated partial thromboplastin time (34). Moreover, in a 72-year-old woman, vaginal bleeding was observed to occur after ingestion of a tablet containing ginseng (35). Uterine bleeding was also reported in a 44-year-old woman after applying a ginseng-containing cream to her face (36). Although there are no supporting clinical data of interactions, as a result of the antiplatelet effects, ginseng is expected to interact with NSAIDs and increase the risk of bleeding. Hence, concomitant use of NSAIDs with ginseng is ill-advised or should be closely monitored.

**Turmeric** (Curcuma longa). Turmeric has been used medicinally for various conditions including indigestion, pain, arthritis and infections (externally). Preparations available are powdered root, capsules and liquid extracts. Turmeric contains the volatile oils zingiberen and turmerone that have antispasmodic and antibiotic activities, and curcumin with anti-inflammatory and antiplatelet properties (9, 15, 18). Most of these effects of turmeric/curcumin (including antiplatelet) have been reported to be due to inhibition of synthesis of prostaglandins and thromboxanes, and stimulation of hydrocortisone release (9, 15, 18). It is thus possible that NSAIDs additively interact with turmeric in certain aspects of their pharmacology, and concomitant therapy with these substances may lead to clotting disorders and enhanced risk of bleeding.

**Meadowsweet** (Filipendula ulmaria). Meadowsweet is commonly used for muscle aches, headaches, colds and flu, digestive upsets, menstrual cramps, arthritis and congestive heart failure (9, 12, 15, 18). It is available as tincture and dried bulk. The herb contains salicylates and phenolic glycosides, which are thought to contribute to its medicinal properties (9, 15, 18, 37). Because of the presence of salicylates, meadowsweet demonstrates antiplatelet activity. However, no interaction has been reported between meadowsweet and NSAIDs, and concerns about prescribing NSAIDs to patients taking this herb remain theoretical.

**Willow** (Salix spp.). Willow has been used for fever, flu, inflammation, pain and rheumatism. It comes as dried bark, capsules and liquid extracts. The active components of willow are salicylates, which are similar to aspirin (11, 12, 15, 18, 21). As with meadowsweet, there are no documented reports on the interactions between salicylates of willow and NSAIDs. Therefore, concerns about concurrently using willow and NSAIDs remain theoretical.

**Interactions with coumarin-containing (anticoagulant) herbs**

There are also herbal supplements that contain coumarin derivatives possessing anticoagulant activity (9, 11–15, 18, 19). These herbs provide additive blood thinning effects to the antiplatelet or hypoprothrombinaemic actions of aspirin and/or other NSAIDs when used concomitantly. They act as vitamin K antagonists by interfering with the coagulation processes (38). Consequently, these anticoagulant herbal supplements increase clotting time. The following is a list of such herbs.

**Motherworth** (Leonurus cardiaca). Motherworth is commonly used for treatment of menstrual disorders, menopause, and heart diseases (9, 11, 15, 18). It has also been reported to produce anticoagulant, anti-inflammatory, antispasmodic, anti-anxiety and anticancer effects. Among several other chemicals, motherworth contains alkaloids, leonurine, diterpenes, prehispanolone, flavonoids and caffeic acid, and the herb is available as tincture, extract and in bulk (11, 15, 39). The anticoagulant effect of motherworth was confirmed in a study of 105 participants who demonstrated a decrease in fibrinogen and blood viscosity (39). Prehispanolone is one of the chemical components reported to be responsible for this effect of the herb. It is therefore possible that the administration of NSAIDs while taking motherworth may increase the risk of bleeding. Appropriate precautionary measures need to be provided in order to avoid the possibility of such herb–drug interactions.

**Chamomile** (Matricaria recutita, Chamaemelum mobile). Chamomile is popularly used for its sedative and antispasmodic effects (9, 15, 18). It has also antiseptic and anti-inflammatory activity, for which it is applied as a vulnerary agent. The supplement is available as capsules, fluid extracts and in the form of topical preparations. Chamomile consists of several ingredients including coumarin,
glycoside, heniarin, flavonoid, farnesol, nerolidol
and germacranolide (9, 15, 18, 40). Despite the
presence of coumarin, as chamomile’s effect on the
coagulation system has not yet been studied, it is
unknown if a clinically significant drug–herb inter-
action exists with antiplatelet/anticoagulant drugs,
such as aspirin or non-salicylate NSAIDs. However,
until more information is available, it is not
recommended to use these substances concurrently.

Horse chestnut (Aesculus hippocastanum). Horse
chestnut has been traditionally consumed to treat
varicose veins and haemorrhoids (9, 15, 18). The
herb is available as standardized extracts of the
leaves, bark and/or seeds for oral administration,
and as tea and poultice for external use. As a
principal active ingredient, horse chestnut contains
the anti-inflammatory compound aescin, which
helps to strengthen blood vessel walls and reduce
fluid leakage (9, 15, 18). In addition, horse chestnut
contains the coumarin, aesculin, which can addi-
tively interact with blood thinners such as NSAIDs,
potentially leading to increased bleeding tendency
(9, 15, 18). Patients taking horse chestnut supple-
ment and NSAIDs simultaneously should therefore
be advised to watch for symptoms of bleeding.

Red clover (Trifolium pratense). This herb has been
promoted for the treatment of skin conditions,
menopause, cough and other respiratory problems
(9, 15, 18). Some of these effects could be due to the
antispasmodic and expectorant properties of its
ingredients. Red clover is available as tablets, cap-
sules, tea, liquid preparations and raw spouts. The
supplement contains several volatile oils such as
benzyl alcohol, methyl salicylate and methyl
anthranilate; isoflavonoids; cyanogenic glycosides and
coumarins (9, 15, 18). Because of the presence of cou-
marins, red clover is suspected to have anticoagulant
activity and thus may interact with such blood thin-
ers as NSAIDs to augment the risk of bleeding.

Fenugreek (Trigonella foenum-graecum). Fenug-
reek is commonly indicated for diabetes mellitus,
gout, inflammation, gastrointestinal problems,
muscle pain and tuberculosis (9, 15, 18). It is sup-
plied as unprocessed seeds, extracts, capsules and
poultice. Some of these actions are associated with
its anti-inflammatory and anti-oxidant properties.
The herb is composed of various saponins, alka-

POTENTIAL INTERACTIONS OF ACETAMINOPHEN WITH HERBAL SUPPLEMENTS

Like the NSAIDs, acetaminophen is also indicated
for mild-to-moderate levels of pain. Although its
mechanism of action is poorly understood, it is
believed to involve inhibition of prostaglandin and
thromboxane synthesis (7). However, acetamin-
ophen may exert a varying degree of inhibition of
mediator synthesis at different sites, contributing to
its unique pharmacological properties. Acetamin-
ophen has the advantage of providing analgesia
without most of the side-effects associated with
aspirin, other NSAIDs or opioids (see below). It is
generally considered to be safe when taken in
recommended doses for a short duration. How-
ever, with prolonged or habitual usage, more seri-
ous adverse reactions such as nephropathy may
occur (38). Further, the ingestion of high doses of
acetaminophen (>10 mg) may result in severe
hepatic necrosis because of formation of a highly
reactive metabolite which depletes glutathione (38).
Although herb–acetaminophen interactions are not
common, the possibility for such interactions have
been mentioned under certain conditions. Below
are listed potential herb–acetaminophen adverse
interactions that need to be noted by patients and health-care professionals.

**Interactions with ginkgo (Ginkgo biloba L.) and possibly with other antiplatelet herbs**

The medicinal properties of gingko and its possible interactions with NSAIDs are discussed above. Although acetaminophen has relatively less drug interactions in the usually recommended doses, a recent report demonstrates that ginkgo can also interact with this analgesic. This effect is believed to be linked to the inhibitory effect of acetaminophen on thromboxane synthesis (and hence platelet aggregation). In a 33-year-old woman taking ginkgo, the administration of acetaminophen was found to induce spontaneous bilateral subdural haematomas (41). This condition is attributed to the presence of ginkgolide B in ginkgo, which leads to the inhibition platelet aggregation. However, it is not known whether similar interactions with acetaminophen occur with the other antiplatelet herbs listed above. Until further information is available, health-care professionals should be cautious of potential interactions of these herbs not only with NSAIDs but also with acetaminophen.

**Interactions with coumarin-containing (anticoagulant) herbs**

Coumarin-containing anticoagulant herbal supplements possibly interacting with NSAIDs are noted above. In view of the recently reported increased anticoagulation by acetaminophen in patients taking warfarin (42), it is suspected that the analgesic can also interact with supplements containing coumarin derivatives to elicit augmented bleeding. As pointed out earlier, the inhibitory effect of acetaminophen on thromboxane production may contribute to this adverse reaction. Therefore, precautions are in order in taking acetaminophen with such herbs as chamomile, horse chestnut, motherwort, red clover and fenugreek.

**Other possible interactions with salicylate-containing herbs**

It has been reported that acetaminophen is associated with nephrotoxicity, when used in combination with aspirin (38). Although no data of direct relevance is available, it is reasonable to assume that the combined use of acetaminophen and herbs containing salicylate can also result in nephrotoxicity, particularly over long-term and at high doses. Appropriate precautions need to be taken by patients and health practitioners in order to avoid or minimize such possible interactions. Salicylate-containing herbs with the potential for causing interactions with acetaminophen include meadowsweet and willow (12, 18, 21). It should also be noted that the concomitant use of acetaminophen and salicylates can induce additive inhibitory effect on platelet function as stated earlier.

**Interactions with echinacea (various species, including Echinacea angustifolia, Echinacea pallida, Echinacea purpurea)**

Echinacea is promoted for treating abscesses, burns, colon cancer, eczema, liver cancer, upper respiratory tract infection, urinary tract infection, skin wounds and varicose leg ulcers (9, 15, 18, 40). The herb has been found to possess antiviral, antibacterial, antifungal and anti-inflammatory activities and to stimulate the immune system. Echinacea is available as tablets, capsules, lozenges, liquid extracts and tinctures. Among other natural ingredients, it contains several essential oils, phenylpropenoids, alkaloids, flavonoids and alkylamides (9, 18, 21, 40). An important concern about echinacea is that certain species of the herb contain pyrrolizidine alkaloids, which can cause liver toxicity by depleting glutathione (14, 18, 40). Although it has not yet been shown experimentally/clinically, this effect of the supplement has the potential to enhance the chance of hepatotoxicity when acetaminophen is co-administered. Health-care providers as well as patients should therefore be cautious when acetaminophen is administered together with echinacea.

**Interactions with kava (Piper methysticum)**

Kava is popularly used for anxiety, asthma, depression, insomnia, muscle spasms, pain, psychosis, rheumatism, seizures and wounds (9, 11, 18). Products of kava are available as tablets, capsules, beverages, extracts and tinctures. The herb consists of a number of ingredients including kava lactones, which are also known as kava pyrones. Recently,
the FDA has issued a warning concerning liver toxicity of kava. About 25 reports of serious liver toxicity in Germany and Switzerland, including cases of cirrhosis, hepatitis and liver failure have been reported (43). There is also documentation of a case in the US of a previously healthy young women who required a liver transplant after using a kava-containing supplement. The mechanism(s) for the hepatotoxic effect of kava has not yet been delineated. As a precautionary step, it is advisable not to use acetaminophen in conjunction with kava, particularly in high doses for prolonged periods, as this combination may have the potential to enhance the risk of hepatotoxicity.

**POTENTIAL INTERACTIONS OF OPIOIDS WITH HERBAL SUPPLEMENTS**

Opioid analgesics are used primarily for the management of moderate-to-severe pain, either alone or in combination with NSAIDs or acetaminophen. The use of these analgesics is associated with a number of side-effects, including sedation and respiratory depression (7). These effects become more severe in the elderly, pregnant women, young children and the foetus. While there are a few documented herb–opioid interactions, most of the interactions are theoretical. These interactions may occur at the CNS level with herbal supplements having sedative properties (i.e., valerian, kava, chamomile) and with ginseng eliciting inhibitory effect on opioid-induced analgesia. As described below, the sedative herbs are expected to enhance the CNS depression/sedation caused by opioids, and vice versa.

*Interactions with valerian* (*Valeriana officinalis*)

Valerian is a widely recognized herbal sedative used primarily for sleep disorders and restlessness. It is also promoted for nervous excitability, hysterical states, cramps, rheumatic pains and dysmenorrheal (9, 15, 18, 40). The action of the herb is related to a group of compounds that include the sesquiterpenes (e.g., valepotrites, valeric acids). Commercially available preparations are standardized to valerenic acid and are formulated as infusions, solid extracts, tinctures and fluid extracts. Valerian has been demonstrated to induce sedation and hypnosis through modulation of gamma-aminobutyric acid (GABA) neurotransmission and receptor function (9–11, 18). In experimental animals, valerian has been shown to cause increased barbiturate-induced sleeping time (10, 12). Further, in a human patient, valerian withdrawal appeared to mimic the withdrawal syndrome of benzodiazepines after the patient presented with delirium and cardiac complications following surgery (9, 12, 14, 18). The patient’s symptoms were attenuated by benzodiazepine administration. Based on these findings, valerian would be expected to potentiate the sedative effects of opioids, and thus caution is advised if these are used in combination.

*Interactions with kava* (*Piper methysticum*)

Kava is briefly discussed above in connection to its possible hepatotoxic effect. Kava is used at least partly because of its CNS depressant action. Among other ingredients, the herb is composed of kava lactones which are believed to provide at least its anxiolytic, analgesic and muscle relaxant effects, by potentiating GABA neurotransmission (9, 18). Accordingly, the kava lactones have been observed to increase barbiturate-induced sleeping time in laboratory animals and anticonvulsant effects in humans (44). Kava has also been shown in mice to have antinociceptive effects that are not antagonized by the opioid antagonist naloxone (45). It is therefore likely that the administration of opioid analgesics in patients taking kava may cause increased CNS depression/sedation, and vice versa. Caution is thus needed if these substances are used together.

*Interactions with chamomile* (*Matricaria recutita, Chamaemelum mobile*)

Chamomile is discussed above in relation to its anticoagulant property. The herb also has a sedative effect (9–11, 18) believed to be due to the presence of the flavonoid, apigenin (40). Therefore, chamomile has the potential to increase the CNS depressant effects of drugs such as opioid analgesics.

*Interactions with ginseng* (*Panax ginseng, Panax quinquefolius*)

In animal studies, ginseng has also been shown to cause a reduction in the analgesic effect of opioids...
The mechanism(s) for this interaction between ginseng and opioids is unknown, although it has been hypothesized to involve a non-opioid phenomenon in the CNS. Therefore, it is worth noting that the possibility of reduced opioid-induced analgesia exists in patients taking ginseng concomitantly.

**LIMITATIONS OF THE REVIEW**

It is clear that most of the reported data on the potential interactions between herbal supplements and analgesic drugs are based on *in vitro* experiments, animal studies, or individual clinical case reports. Clinical case reports may be confounded by patient-specific variables, such as age, sex, disease, genetic and lifestyle factors and data from animal and *in vitro* studies may not always predict responses in humans. A number of the herb–drug interactions suggested are on the basis of theoretical knowledge. These uncertainties make difficult informed decision-making by health-care professionals.

A complicating factor is the lack of appropriate regulations governing the purity and potency of herbal products during manufacture and the lack of sufficient information about safety and therapeutic efficacy of most of the products. Unlike conventional drugs, there is no premarketing review and post-marketing surveillance requirements for herbal supplements in the US. In addition, as the pharmacodynamic and pharmacokinetic properties of most herbal supplements are poorly understood, potential interactions with analgesics and other drugs cannot be predicted with any certainty. Therefore, the information presented in this review cannot be claimed to be definitive. There is an obvious need for further research and documentation in this area. However, until definitive interaction information becomes available, it is prudent for health practitioners as well as patients to take account of the available to avoid possible adverse interactions particularly by patients who are more vulnerable to such effects (e.g. geriatric patients, infants, pregnant women).

**CONCLUDING REMARKS**

The increased use of herbal supplements in the US in recent years has made information about potential herb and drug interactions more relevant. This is particularly important for drugs that are frequently prescribed or used by patients, such as analgesics. There is documented and theoretical evidence in the biomedical literature for herbal product–drug interactions. Health professionals should question all patients about the use of herbs and report documented or suspected interactions to appropriate agencies such as the FDA under its MedWatch Programme (800-FDA-1088). Consistent reporting should improve knowledge and awareness of potential interactions and improve the quality of patient care.

**REFERENCES**


