Expert Opinion

General

Safety review of kava (*Piper methysticum*) by the Natural Standard Research Collaboration

Catherine Ulbricht†, Ethan Basch, Heather Boon, Edzard Ernst, Paul Hammerness, David Sollars, Candy Tsourounis, Jen Woods & Stephen Bent
†*Natural Standard Research Collaboration, 1 Broadway, 14th Floor, Cambridge, MA 02142, USA*

This systematic review discusses the proposed uses, dosing parameters, adverse effects, toxicology, interactions and mechanism of action of kava. The widespread concern regarding the potential hepatotoxicity of kava is discussed. A recommendation is made to consolidate and analyse available reports and to continue postmarket surveillance in an international repository to prevent duplicates and promote collection of thorough details at the time of each report so that any association with kava is clearly defined.

Keywords: anxiolytic, dihydrokawain, dihydromethysticin, hepatotoxicity, herb, kava, kawain, methystici, Piper methysticum, safety, yangona

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1. Research methodology

1.1 Search strategy

To prepare each Natural Standard review, electronic searches are conducted in nine databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline and NAPRALERT. Search terms include the common name(s), scientific name(s), and all synonyms for each topic. Hand searches are conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions are placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) are consulted for access to additional references or ongoing research.

1.2 Selection criteria

All literature is collected pertaining to efficacy in humans (regardless of study design, quality or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays and mechanism of action (*in vitro*, animal research, human data). Standardised inclusion/exclusion criteria are utilised for selection.

1.3 Data analysis

Data extraction and analysis are performed by healthcare professionals conducting clinical work and/or research at academic centres, using standardised instruments that pertain to each review section (defining inclusion/exclusion criteria and analytical techniques, including validated measures of study quality). Data are verified by a second reviewer.

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1.4 Review process

Blinded peer review is conducted by multidisciplinary research-clinical faculty at major academic centres with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addresses conflicts and consults experts when applicable. Authors of studies are contacted when clarification is required.

2. Introduction

Kava beverages, made from dried roots of the perennial shrub *Piper methysticum*, have been used ceremonially and socially in the South Pacific for hundreds of years and in Europe since the 1700s [1-7]. The drink is reported to have pleasant mild psychoactive effects [8], similar to alcoholic beverages in western societies. Recreational use of kava has spread over the last 20 years to Aboriginal communities in Australia, where it is often heavily consumed in combination with alcohol [9]. In Fiji, kava is still used today during welcome ceremonies for local and international political and religious dignitaries.

Currently, pharmaceutical preparations of the herb are widely used in Europe and the US as anxiolytics, but they have recently been withdrawn in several European markets and Canada due to safety concerns (see **Table 1**) [1-5,7,10-13].

Several well-conducted human trials and meta-analyses [6,14,15] have demonstrated the efficacy of kava in the treatment of anxiety, with effects observed after as few as 1 – 2 doses, and progressive improvements over 1 – 4 weeks [16-18].

Oral preparations are widely recommended by European physicians and natural medicine practitioners. Reportedly, 350,000 prescriptions for kava are written in Germany each year. In the US, kava has gained popularity over the past 10 years among clinicians, with multi-million dollar sales and numerous books supporting its use. Self-medication with kava by patients in the US is prevalent. However, US physicians and pharmacists are more apt to recommend benzodiazepines to patients with anxiety due to lack of government-enforced safety or manufacturing standards for kava.

There is widespread concern regarding the potential hepatotoxicity of kava [10-13,19-26]. Many cases of liver damage have been reported in Europe, including hepatitis [27-29], cirrhosis, fulminant liver failure [30,31] and death [32,33], although some researchers have challenged these reports and maintained that kava is safe in most individuals at recommended doses [34,35]. The German BfArM (the German Federal Institute for Drugs and Medical Devices), a division of the Ministry of Health, reported a total of 82 case reports related to kava. Of these, one case of acute necrotic hepatitis was possibly related to kava intake with review conform dosage [19], one case of cholestatic hepatitis was possibly related to kava intake with overdosing [19], and one liver transplant due to hepatitis was also possibly related to kava intake with overdosing [19]. Of the 82 reports, several duplicate or triplicate patient reports were issued. For instance, from 1990 to 2002, 5 patients reported 11 case reports. Also, 20 case reports were unrelated to kava, 21 were probably connected to concomitant medication, 7 were doubtfully related to kava, and 31 reports did not have sufficient documentation to link kava to the reported adverse effects [36]. This remains an area of controversy, and it is unclear whether or not the safety profile of kava is comparable to other agents used in the management of anxiety (see **Table 1**).

The FDA issued a letter on 18 December, 2001, stating that it was investigating whether or not kava-containing products are a health concern. The FDA noted 26 cases of liver toxicity in Germany and Switzerland, including one fatality and one liver transplant that were reportedly associated with kava products. In 2002, the US Centres for Disease Control and Prevention (CDC) issued a report on hepatotoxicity associated with kava-containing products. On March 25, 2002, the FDA warned that kava may be linked to serious liver damage, including hepatitis, cirrhosis, and at least four urgent liver transplants. A letter was also issued urging healthcare professionals to review cases of liver toxicity to determine if they were associated with kava.

Kava is still available in the US, although the FDA has issued warnings to consumers and physicians [37-39]. It is not clear what dose or duration of use is correlated with the risk of liver damage. The quality of these case reports has been variable; several are vague, describe use of products that do not actually list kava as an ingredient, or include patients who also ingest large quantities of alcohol. Nonetheless, caution is warranted.

In May 2004, the Scientific Advisery Panel on Heptatoxicity in Canada made draft recommendations concerning the 'Recommendations from the Scientific Advisery Panel subgroups on Hepatotoxicity: Hepatotoxicity of Health Products'. This group was prompted and established after concerns were raised about four Canadian cases of liver toxicity associated with kava. The cases were reported in February 2002 to the Health Product Safety Information Division. Health Canada banned preparations containing kava-kava in August 2002 (see **Table 1**).

Sales of products and preparations containing kava have been suspended in Germany, Switzerland, Australia and France, and such products have been withdrawn in Spain. In Japan, no new drug products containing kava-kava have been approved. In New Zealand, authorities recommend that labels should warn against the possibility of liver damage. Recently, the Medicine's and Healthcare Products Regulatory Agency (MHRA) in the UK launched a 12-week public consultation process for interested parties to submit evidence and representations as to whether or not the prohibition of kava should continue.

Chronic or heavy use of kava has also been associated with cases of neurotoxicity, pulmonary hypertension and dermatological changes. Most human trials have been shorter than two months, with the longest study being six months in duration [40]. Studies evaluating the effect of Kava on cognitive performance and mood were also recently conducted [32].

2.1 Historical or theoretical indications which lack sufficient evidence

Analgesic, anaesthesia [41], anorexia, anticonvulsant [42,43], antifungal, antipsychotic [41,44], aphrodisiac, arthritis, asthma, brain damage, bust enhancement, cancer [45], cerebral ischaemia, contraception, colds, depression, diuretic, dizziness, filariasis, gastrointestinal (GI) disorders, genitourinary disorders, gonorrhoea, haemorrhoids, infections, jet lag, kidney disorders, leprosy, menopausal/menstrual disorders [46], rheumatism, sleep disturbances, migraine, muscle relaxant [47], neuroprotective effects against ischaemia, otitis, pain, spasm, syphilis, toothache, tuberculosis, venereal disease, weight reduction and wound healing have all had historical or theoretical indications linking them with kava-containing products, but these have not been supported with sufficient evidence.

3. Dosing/toxicology

3.1 General

Recommended doses are based on those most commonly used in available trials, and/or on historical practice. However, with natural products the optimal dose to balance efficacy and safety is often not established. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active components of a product are, standardisation may not be possible, and the clinical effects of different brands may not be comparable.

3.2 Standardisation

Multiple formulations are available, including dried rhizome, cold macerate, fluid extract, dry extract and soft native extract. Kava extract is typically standardised to 30% kava lactones. The actual lactone content of the root varies between 3 – 20%. Many brands use the standardised preparation WS 1490.

A review published in 2000 by www.consumerreports.org of standardised kava brands in the US, found actual (measured) and labelled amounts of kava lactones to be approximately equivalent in 13 products that listed amounts of constituents. Kava lactones per tablet/capsule ranged from 50 to 110 mg. Two brands that did not label amounts of constituents contained 10 – 15 mg lactones per tablet/capsule.

In Australia, the Therapeutic Goods Administration has placed a limit on the amount of kava permitted per dosage form (i.e., 125 mg kavalactones per tablet/capsule, a 3g limit of dried rhizome in tea bags) and all kava products were to comply with a maximum daily dose of not more than 250 mg of kavalactone.

3.3 Adult dosing (≥ 18 years of age)

Safety concerns should be carefully reviewed prior to considering therapy with this agent.

The 300 mg/day of kava extract (standardised to WS 1490) in three divided doses is a regimen reported as efficacious and well-tolerated in multiple clinical trials [48-52]. Typical usage ranges from 70 to 280 mg kava lactones/day as a single bedtime dose or divided doses (60 – 120 mg of kavapyrones/day) has also been recommended. Many practitioners start at a lower dose and titrate up as needed. Doses as high as 800 mg/day of kava extract have been tolerated for short periods, but have not been extensively studied. A daily dosage of up to 250 mg kavapyrone is also common.

3.3.1 Anxiety disorder (associated sleep disorder)

Kava special extract WS 1490 has been studied in sleep disturbances associated with nonpsychotic anxiety disorders at daily doses of 200 mg [53]. Some experts have suggested a dose of 120 – 210 mg kavapyrone daily for a maximum of 2 months.

3.3.2 Enhanced mood

Preliminary evidence suggests that a single oral dose of 300 mg of kava extract may lead to an increase in cheerfulness [32].

3.3.3 Generalised anxiety disorder

400 mg of kava-kava LI150 daily has been shown to be well-tolerated and as effective as both buspirone and opipramol in the acute treatment of out-patients with generalised anxiety disorder [17].

3.3.4 Neurotoxic anxiety

A dose of 50 mg daily of kava special extract WS 1490 has been shown to be well-tolerated in patients with neurotoxic anxiety, with no influence on liver function [54]. The only adverse effect reported in this study was tiredness.

3.3.5 Nonpsychotic anxiety

A dose of 50 mg of kava special extract WS 1490, administered three-times daily has been used to treat patients with nonpsychotic anxiety without adverse effects [16].

3.4 Pregnancy and lactation

Kava has not been systematically studied during pregnancy or lactation. Use is discouraged during pregnancy due to possible decreases in uterine tone and during lactation due to the possibility of pyrone transport into milk (with unknown effects) [8].

3.5 Paediatric dosing (< 18 years of age)

There is insufficient available safety or efficacy data.

4. Adverse effects/precautions/contraindications

4.1 Allergy

Allergic skin reactions have been reported, including systemic/contact-type dermatitis, sebotropic reactions, and generalised erythema with papules following 2 – 3 weeks of use [55-57].

4.2 Adverse effects

4.2.1 General

In recommended doses over short periods of time (< 1 – 2 months), kava has traditionally been regarded as safe and well-tolerated. A poorly designed drug monitoring study of 4049 patients taking 105 mg/day of a 75% kavalactone extract for 7 weeks found side effects in 1.5% of cases, primarily GI complaints or allergic rashes (no serological measurements were done) [58]. A 4-week study of 3029 patients given 800 mg/day of 30% kavalactone extract reported side effects in 2.3% of subjects, including GI distress, allergic rash and mild headache. Severe adverse effects have been observed with chronic and/or heavy use. In one comparison study, intoxicated kava drinkers (who consumed 205g of kava powder (~ 140-times clinical doses) were compared with a control group. The intoxicated subjects showed ataxia, tremors, sedation, blepharospasm and elevated liver enzymes (γ-glutamyl transferase [GGT] and alkaline phosphatase), together with saccadic dysmetria, saccadic slowing, and reduced accuracy performing a visual search task [59-61]. The LD_{50} of kavalactones is ~ 300 – 400 mg/kg, according to animal studies [62]. The safety of kava use remains unclear; clinicians and patients should understand the risks involved prior to considering the use of this agent.

4.2.2 Cardiovascular

Tachycardia and electrocardiogram abnormalities (tall P waves) have been reported in heavy kava users [63]. It has been theorised that these P wave abnormalities reflect pulmonary hypertension, although study is lacking in this area. Chronic kava consumption has been associated with sudden death in Aboriginal Australians in Arnhem Land, an area where poor diets and coronary heart disease are common among community members [64,65].

4.2.3 Dermatological

Chronic use of kava in large quantities may cause dry, scaly skin or yellow skin discoloration, commonly referred to as 'kava dermopathy' (or called *kani* in Fiji) [66]. This type of dermopathy appears to be reversible upon discontinuation of kava. Because kava dermopathy may mimic the signs and symptoms of liver disease (also a concern with kava use), a thorough clinical assessment is warranted. Although thought to be related to reduced B vitamin uptake or assimilation, improvement has not been found after niacin supplementation [67]. Cases have been reported of systemic/contact-type dermatitis, sebotropic reactions and generalised erythema with papules following short-term use (2 – 3 weeks) [55-57]. Kava dermopathy is believed to result from large doses [68].

4.2.4 Gastrointestinal (hepatotoxicity)

There is growing concern regarding the potential hepatotoxicity of kava [19]. One study found that herbal and dietary supplements were potential hepatotoxins in a high proportion of patients with fulminant hepatic failure at the Division of Liver/Pancreas Transplantation, Oregon Health & Science University. More than 30 cases of liver damage have been reported, including hepatitis [27-29,69], cirrhosis, fulminant liver failure [30,31] and reports of death [32,33] The FDA issued warnings to consumers and physicians [37-39], and requested that US physicians report cases of hepatotoxicity that may be related to kava use. It is not clear what dose or duration of use is correlated with the risk of liver damage. The quality of these case reports has been variable; several are vague, describe use of products that do not actually list kava as an ingredient, or include patients who also ingest large quantities of alcohol. Nonetheless, caution is warranted. Published case reports include a 39 year-old woman taking kava, who developed acute hepatitis with confluent necrosis [70]. The product was not analysed for contaminants, and other causes of hepatitis were not ruled out. A 60 year-old woman required liver transplant due to fulminant hepatic failure, attributed to kava use (via process-of-elimination) [31]. In heavy Aboriginal kava users (mean 440g/week), GGT levels have been found to be significantly increased [63], although causality is not clear [9]. Two cases reported from Switzerland involved one specific brand (Leitan®, Schwabe). In November 2001, the BfArM announced that based on 24 cases of kava-associated hepatotoxicity (one death, three transplants) it is considering regulation of available kava dosing, to allow only low, 'proven-safe' doses [1]. Another study found that pipermethystine, found mostly in leaves and stem peelings, and kavalactones may contribute to rare, but severe hepatotoxic reactions to kava [71].

4.2.5 Gastrointestinal (GI discomfort)

Gastrointestinal upset, including epigastric pain and nausea, have been reported as an infrequent adverse event in trials [50-52,72].

4.2.6 Haematological

Chronic and heavy use has been associated with increased red blood cell volume, reduced platelet volume, reduced lymphocyte counts and reduced serum albumin [61,63]. Haematuria has also been reported anecdotally, with unclear association to haematological parameters [63]. Racemic kavain, present in kava preparations, has been shown to have antiplatelet effects due to cyclooxygenase inhibition and inhibition of thromboxane synthesis in animals [73].

4.2.7 Musculoskeletal

A case of rhabdomyolysis has been reported in a 29 year-old man after self-administration of an herbal combination of ginkgo, guarana and kava [74]. The causal role of kava in this case is unclear.

4.2.8 Neurological/CNS (sedation)

It remains unclear to what extent clinically relevant sedation occurs at recommended doses, and it has been theorised that kava selectively acts on limbic structures, promoting anxiolysis without clinically relevant sedation [75]. Sedation

has been occasionally reported anecdotally, in case reports, and in trials, although preliminary evidence from three small human studies suggests lack of neurological-psychological impairment [76-78]. No effect of kava on motor vehicle driving performance was found in two double-blind, placebo-controlled trials [79,80]. In California, there were two cases of drivers arrested for 'driving under the influence' after ingesting kava tea; neither case resulted in successful prosecution. In a case report, a 54 year-old man experienced lethargy and disorientation for several hours after taking recommended doses of kava for three days, in addition to alprazolam, cimetidine and terazosin. However, the independent contribution of kava is unclear [81]. In one study, tracking tasks (maintaining a pointer between parallel lines) and reaction time tasks (response by pressing correct key) were measured as indicators of cognitive performance and physiological function [82]. Results showed no statistically significant differences between kava and placebo. Another randomised controlled trial found no conclusive evidence that kava interferes with normal cognitive processes [59,60]. In a small, double-blind, placebo-controlled comparison trial with the European benzodiazepine clobazam, synthetic kavain was found to improve intellectual performance, attention, concentration, reaction time and motor speed reaction time, whereas clobazam produced the opposite results [83]. Similar results were seen in a small trial comparing kava extract standardised to 30% kavalactones versus diazepam and placebo [77]. Kava may also cause adverse neurological effects and cause excessive perioperative sedation. Such a reaction may be due to benzodiazepine and antidepressant activities on noradrenergic and/or serotoninergic pathways that may potentiate benzodiazepine and induction anesthetic potency [84]. A recent review suggests possible effects of kava upon electroconvulsive therapy outcome [85].

4.2.9 Neurological/CNS (extrapyramidal)

Several cases of extrapyramidal side effects (central dopamine antagonism) [44] have been reported after short-term use (1 – 4 days), including torticollis, oculogyric crisis and oral dyskinesias in young to middle-aged people, serious exacerbations of Parkinsonian symptoms [86,87] and three episodes of generalised choreoathetosis (abnormal body movements) following ingestion of high-dose kava in a 27 year-old Aboriginal man [88]. Tremor and malcoordination, as well as headache, drowsiness and fatigue have been reported as infrequent events in clinical trials and surveys, particularly in association with large oral doses of kava [52,63]. Neurological manifestations seem uncommon after kava consumption. A 2002 case report cited three cases of meningismus, two of them with focal neurological manifestations after kava absorption [89].

4.2.10 Ocular

Anecdotally, accommodative (ocular) disturbances have rarely been associated with continuous kava use. There is one case report of impaired accommodation and convergence, increased pupil diameter and oculomotor disturbance following one-time use [90]. Eye irritation has been reported with heavy consumption [67].

4.2.11 Psychiatric

Apathy has been associated with traditional heavy kava use [41].

4.2.12 Pulmonary/respiratory

In one study, shortness of breath was reported in 72% of heavy Aboriginal kava users versus 39% of non-users. Pulmonary hypertension has been proposed as a possible aetiology, based on tall P waves on the electrocardiograms of kava users [63].

4.2.13 Renal/genitourinary

There has been a single case report of rhabdomyolysis in a 29 year-old man after self-administration of an herbal combination of ginkgo, guarana and kava [74]. It is not clear if renal failure occurred. The causal role of kava in this case is unclear. Acute urinary retention secondary to kava ingestion has also been reported [91].

5. Interactions

- **Alcohol**: Animal studies have demonstrated marked increases in the hypnosedative effects of alcohol when taken with kava [92,93]. However, this effect has not been confirmed in healthy human volunteers [80];
- **Anaesthetics**: Kava may prolong the sedative action of anaesthesia due to presumed monoamine oxidase inhibitor-like action. Although numerous anecdotal reports have circulated, no clinical research has confirmed this interaction [94]. Anaesthesiologists may recommend patients to stop taking kava 2 – 3 weeks prior to surgery. Kava may effect electroconvulsive therapy outcome [85];
- **Anticancer agents**: Kava, and other herbs that have the potential to modulate the activity of drug-metabolising enzymes, such as garlic, gingko, Echinacea and St John's Wort, may participate in pharmacokinetic interactions with anticancer drugs [95];
- **Antiplatelet agents**: Racemic kavain, present in kava preparations, has been shown to have antiplatelet effects due to cyclooxygenase inhibition and inhibition of thromboxane synthesis [73]. Kavalactones may interact with antiplatelet agents [96]. Effects on platelets have not been reported in humans, and clinical relevance is not clear;
- **Benzodiazepines**: Kava may cause adverse neurological effects and excessive perioperative sedation. Such a reaction may be due to benzodiazepine and antidepressant activities on noradrenergic and/or serotonergic pathways that may potentiate benzodiazepine and induction anaesthetic potency [84];
- **Buspirone and opipramol**: Kava-kava LI150 has been used in the acute treatment of out-patients suffering from generalised anxiety disorder [17]. Therefore, kava may cause additive effects when taken concomitantly with these or other agents with similar effects;

- **Cytochrome P450 (1A2, 2C9, 2C19, 2D69, 3A4, 4A9/11) substrates:** Preliminary evidence suggests that kava may significantly inhibit multiple cytochrome P450 enzymes [97-102];
- **Diuretics:** Kava may increase effects of diuretic drugs such as acetazolamide, amiloride, furosemide or ACE inhibitors such as benazepril, captopril, lisinopril, quinapril and ramipril;
- **Dopamine, dopamine antagonists, dopamine agonists:** Kava has been reported to antagonise the effect of dopamine and elicit extrapyramidal effects [44,86,88]. Therefore, it may interfere with the effects of dopamine or dopamine agonists and exacerbate the extrapyramidal effects of dopaminergic antagonists such as droperidol, haloperidol, risperidol and metoclopramide. Avoid in patients with Parkinson's disease or in patients with a history of medication-induced extrapyramidal effects because kava may cause additive effects;
- **Hepatotoxic drugs:** Concomitant use with other potentially hepatotoxic drugs such as anabolic steroids, amiodarone, methotrexate, acetaminophen and antifungal medications such as ketoconazole is generally not advised;
- **Opioids:** Kava may add to drowsiness caused by opioid analgesics like oxycodone and propoxyphene;
- **Melatonin:** Theoretically, kava and melatonin taken concomitantly may have additive sedative effects;
- **Monoamine oxidase inhibitors:** The pyrone constituents of kava have been found to have weak monoamine oxidase (MAO) inhibitory properties *in vitro* [96]. Therefore, there may be an additive effect when used concomitantly with MAO inhibitory agents, including phenelzine, tranylcypromine, chromium, ephedra, evening primrose oil, fenugreek, *Ginkgo biloba,* hops, St. John's Wort, tyrosine, valerian, yohimbe, 5-hydroxytryptophan, DHEA (dehydroepiandrosterone), DLPA (DL phenylalanine), SAMe (S-adenosylmethionine), vitamin B6, and homeopathic remedies including aurum metcallicum, Kali bromatum, and sepia. Tyramine or tryptophan-containing foods may pose a risk of hypertensive crisis if eaten while taking kava, due to the monoamine oxidase inhibitory activity of kava found *in vitro* [96], although this interaction has not been reported in humans;
- **Neuroleptics:** The extrapyramidal side effects caused by neuroleptic agents may be reduced by Kava special extract WS 1490 [103];
- **Sedatives/CNS depressants:** Kava has been reported to occasionally cause sedation or lethargy [52,63] and it may act synergistically with benzodiazepines [81], although animal studies have revealed no interactions with benzodiazepine/GABA receptor binding [104,105]. Lethargy and disorientation were reported in a 54 year-old man taking kava in combination with alprazolam [81]. It is unclear to what extent kava might act additively or synergistically with other purported sedative herbs, such as calamus, calendula, California poppy, catnip, capsicum, celery, couch grass, elecampane, ginseng (Siberian), gotu kola, German chamomile, goldenseal, hops, dogwood, kava, lemon balm, sage, St. John's Wort, sassafras, scullcap, shepherd's purse, stinging nettle, valerian, wild carrot, wild lettuce, withania root, or yerba mansa. Kava may cause excessive drowsiness when taken with selective serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, paroxetine, sertraline. Use cautiously in patients with endogenous depression due to purported sedative activity of kava resin and the pyrones dihydrokawain and dihydromethysticin [8,106]. Kavalactones have been shown to potentiate the effects of CNS depressants such as ethanol and barbiturates, in animals with concurrent use being potentially toxic [93];
- **Valerian/St. John's Wort:** In a telephone survey, one woman reported nausea, diaphoresis, muscle cramping, weakness and elevated pulse and blood pressure after a single dose of combination St. John's Wort, (*Hypericum perforatum*), kava and valerian (*Valeriana officinalis*) [107].

6. Pharmacology

Kava contains pyrones, lactones (methysticin, dihydromethysticin (DMH), yangonin, dihydrokawain (DHK), kawain), flavonoids and alkaloids [108-114]. Kavalactones or kavapyrones may alter central GABA transmission, blocking voltage-gated ion channels (Na^+ and Ca^{2+}), and by means of monoamine mechanisms.

Pyrones have been noted for their anticonvulsive, spasmolytic and antimycotic effects, as well as synergistic hypnotic (barbiturate), analgesic and local anesthetic effects [115-123]. Pyrones exhibit neuroprotective [124] and 'recovery-supporting' effects on neurological deficits after cerebral infarction in animals [125]. These effects have been attributed to calcium channel agonism [126,127] sodium channel blocking [42,128,129] inhibition of monoamine oxidase [96] and inhibition of noradrenaline uptake [130]. In the rat, kava does not appear to interact with benzodiazepine/GABA receptors [104,105], although other sources suggest that kava may facilitate GABA transmission [78,131].

Kava may selectively act on limbic structures, promoting anxiolysis without sedation [75]. Neurophysiological studies with EEG have demonstrated similar activity of kava to GABA agonists [78,131].

Interactions with glutamate [129], dopamine [44], noradrenaline [130], serotonin [44,126,127] and their respective receptors may mediate the anxiolytic effect of kava. Neither high single doses nor chronic administration of kavain, from the lipophilic fraction of kava, alter dopaminergic or serotonergic tissue levels in rats [132]. Therefore, dopaminergic or serotonergic effects may reside in the water-soluble fraction of kava [133,134].

The analgesic effect of kava is not antagonised by naloxone [93,106], suggesting a mechanism unrelated to opiate receptors. In an animal model, tolerance and dependence formation have not been demonstrated [135].

Kava use has been associated with elevations of liver function tests in animals and humans [24,25,61,63]. Chronic heavy use has been paradoxically associated with decreased bilirubin [63]. Chronic heavy use of kava has been associated with decreased albumin and total protein [63]. Causality is unclear and may be due to poor nutrition in chronic kava users or hepatic damage. Chronic heavy use has been associated with decreased lymphocyte counts [61,63]. Chronic heavy use has also been associated with increased red blood corpuscle volume and reduced platelet size [63]. It is not clear if poor nutrition or iron deficiency coincides with chronic kava use, thus confounding these findings.

Haematuria of unclear aetiology has been reported anecdotally with kava use, although scientific data are scant [63].

7. Pharmacodynamics/kinetics

A psychophysiological study of kavain (Klinge Pharma, Munich, Germany) found pharmacodynamic peaks at 1 – 2 and 8 hours, suggesting active metabolites. Peak levels occurred at 1.8 hours, with an elimination half-life of ~ 9 hours and a distribution half-life of 50 minutes [63].

Absorption of kava root extracts may be faster than absorption of isolated lactones.

Metabolites and unchanged lactones of kava are excreted in human urine and faeces [136,137].

8. Expert opinion

Multiple studies suggest that kava lessens anxiety. However, scientific evidence does not support the use of kava for any other conditions. The safety of kava use remains unclear. Clinicians and patients should understand the risks involved prior to considering use of this agent. There have been recent reports of serious liver damage or death in people using kava. It is not clear if these problems occurred at high doses or after long-term use. Therefore, kava should only be used under the supervision of a qualified healthcare provider. Kava should never be taken at doses higher than recommended, or for longer than two months. Kava should be avoided in people with liver disease, Parkinson's disease, or lung disease, in pregnant or breastfeeding women, and in children. It should not be used in people taking monoamine oxidase inhibitors or drugs that may damage the liver or cause drowsiness.

Where the cases of liver damage connected to administration of preparations containing kava-kava are concerned, results of systematic studies of adverse effect frequency lack validation. In clinical trials up to the year 2002, they are listed as nonexistent or negligible. There have not been any well-designed case-controlled studies for relative risk determination.

Currently, the kava ban exists in Germany, the UK and France. The German Minister for Health in Berlin announced that the ban will be lifted once scientific evidence of the safety of kava is available. Following the announcement, the International Kava Executive Council in Berlin met with German health authorities to discuss the issue. In May 2005, the kava ban of German products was lifted by the German BfArM. The revokal of the German drug registrations is lifted, but the drugs themselves can still not be marketed as the registrations are temporarily suspended. There is still the chance that the BfArM will now cancel the registrations one by one, based on flaws in the registration dossiers so there is still considerable work that would need to be done before kava would be back on the market. Even if they will not allow the formally existing products back on the market, the companies can now theoretically apply for new registrations.

After evaluating the available literature on kava in all languages, including the WHO reports and reviews published on kava, duplicate reports exist under numerous publication titles partially due to multiple reporting mechanisms and multiple language translations. Natural Standard Research Collaboration is working with the WHO Advisery Committee on Safety of Medicinal Products on a new official report on kava and hepatotoxicity. Results will be published in 2005. In order to study kava adequately in the future, a central reporting mechanism, data collection and multidisciplinary review of postmarket surveillance data to prevent bias is recommended. When a signal is detected, suggesting that a safety problem exists with a marketed health product, a number of factors must be taken into consideration. These include: the seriousness of the disease state/condition for which the product is indicated, the seriousness of the adverse reaction, the estimated incidence of the reaction, and the available alternative therapies. Consideration of these factors will influence the product's new benefit-risk profile, which will, in turn, influence the choice of risk-mitigation strategy. The major difficulty in postmarket assessment when comparing the benefit/risk ratios between alternative therapies is the lack of accurate data regarding the numerator (number of reported reactions) and the denominator (number of patients exposed to the product).

Because kava is not available in many areas of the world, individuals can instead turn to alternative therapies for anxiety treatment. In addition to other herbs or supplements such as lavender, a variety of modalities, including aromatherapy, relaxation therapy and yoga may help reduce anxiety without hepatic effects.

Table 1a. Example restrictions on kava-containing products (US, Canada, Germany, Australia, France and UK)

Year	US	Canada	Germany	Australia	France	UK
2000			Small number of cases of liver damage reported to the German regulatory authority (BfArM) [201,202].			
2001	In a letter issued by the FDA on 18 December, the agency stated it is investigating whether or not kava-containing products are a health concern. The FDA noted 26 cases of liver toxicity in Germany and Switzerland, including one fatality and one liver transplant that were reportedly associated with kava products [38].		Kava is banned by BfArM due to suspected hepatotoxic risks [201].		Two nonserious liver case reports were filed with regulatory authorities. However, no kava product was registered for sale in France because it is traded as a food supplement. On 8 January, 2001, the French Agency for the Safety of Health Products halts Kava sales for one year based on German and Swiss reports [203].	The CSM first considers safety of kava. The MCA and CSM call for a voluntary suspension of kava-containing products [201].
2002	US Centres for Disease Control and Prevention issued a report on hepatotoxicity associated with kava-containing products. On 25 March, the FDA warned that kava is linked to serious liver damage, including hepatitis, cirrhosis and at least four urgent liver transplants in other countries. A letter was also issued urging healthcare professionals to review cases of liver toxicity to determine if they were associated with kava.	On 16 January, Health Canada begins safety assessment of kava and advises consumers not to use kava-containing products. The investigation found that as of 21 August, three cases of liver toxicity associated with kava were reported. A stop-sale order was issued for all kava-containing products [201,204].	Forty cases of severe liver damage were reported to BfArM from 1999 to 2002. Of the 40 cases, 3 were fatal and 6 patients required transplants [205].	On 15 August, kava-containing products were recalled by the TGA. The recall was sparked after a reported death of a woman from complications of fulminant hepatic failure associated with the use of a kava-containing medicine [201,206].		Three reports of liver toxicity (none fatal) were reported to the MCA up to June. On 18 July, the MCA considers proposal that prohibits the supply of kava in unlicensed medicinal products [207].

CSM: Committee on Safety of Medicines; FDA: Food and Drug Administration; MCA: The Medicines Control Agency; MHRA: Medicines and Healthcare products Regulatory Agency; TGA: Therapeutic Goods Administration.

Table 1a. Example restrictions on kava-containing products (US, Canada, Germany, Australia, France and UK) (continued)

Year	US	Canada	Germany	Australia	France	UK
2003	As of March 2003, the FDA reported that of the 21 case reports filed in the US, 5 stated some type of liver disorder [201].			In January, the TGA established a committee, called the Kava Evaluation Group to review the safety of kava products [206].		The CSM and the Medicines Commission found evidence linking kava to cases of liver toxicity. The MCA noted 70 worldwide reports of adverse liver reactions, In January, the MHRA bans kava-containing products [207].
2005	Kava products remain available for purchase.		May 2005: BfArM sends notice in written form to the individual companies producing registered kava products stating that the decision taken on 14 June, 2002 is revoked for reasons of appropriateness. Instead, the inactivation of the registrations is ordered as of now. The decision in 2002 was a complete cancellation of the registrations, which means a total stop of all activities. Nobody would have been able to submit a new registration for kava. Now, the products can still not be marketed, but anyone willing to go through a new application process could do so. Clinical studies are not possible with cancelled drug registration, but are possible with inactive registrations. Companies are given until June 2007 to deliver new data on efficacy, the main concern for the BfArM. They say the risk–benefit ratio is negative because there is no proof of efficacy – at least none they would accept for the individual preparations, in the individual dosages. The problem is that most clinical studies were made with higher dosages than recommended, mostly for technical reasons. Toxicity is also discussed [138].			MHRA is reviewing the ban on kava (If the regulatory agency can find evidence that kava is safe, the herb may enter the UK market once again) [208].

CSM: Committee on Safety of Medicines; FDA: Food and Drug Administration; MCA: The Medicines Control Agency; MHRA: Medicines and Healthcare products Regulatory Agency; TGA: Therapeutic Goods Administration.

Table 1b. Example restrictions on kava-containing products (Portugal, Switzerland, Singapore, Austria, Ireland and New Zealand).

Year	Portugal	Switzerland	Singapore	Austria	Ireland	New Zealand
2000		In September 2000, the government warned marketers of safety concerns related to kava, based on four case reports [201].				
2001		Health authorities, (SWISSMEDIC) issued a safety protocol [201,203].				
2002	Although no reports of liver damage were reported in the country, Portugal followed France and suspended all kava-containing products for one year [201,203].		In January, the country's HSA warned consumers of the potential adverse effects of kava. On 25 July, kava was banned. Although no adverse effects associated with kava were reported in Singapore, HSA prohibited the importation and sale of kava products in the country, based on German and Swiss case reports [201].	Following the German ban of kava, Austria banned kava. The recall of all kava products followed a single case of liver failure associated with kava consumption [201].	In February 2002, the Irish Medicines Board initiated a voluntary withdrawal of all kava-containing products. Unable to find any case reports.	On 16 January, 2002, the New Zealand Ministry of Health announced that it was investigating overseas concerns about kava and liver damage. The ministry noted that available evidence is poor because of additional liver-effecting factors, such as alcohol consumption. On 16 August, 2002, the New Zealand Food Safety Authority (FSANZ) issued a warning to consumers about the safety of kava-containing products. The Medicines Adverse Reactions Committee recommended to the New Zealand Food Safety Authority that labels, warning against the possibility of serious liver damage, should be required for kava-containing products. No case reports of hepatotoxicity [201,203,209].
2003		In February, the In February 2003, the SWISSMEDIC banned the sale of kava-containing products [201].				

HSA: Health Sciences Authority.

Table 1c. Example restrictions on kava-containing products (New Caledonia, South Africa, Wales, South America and Asia).

Year	New Caledonia	South Africa	Wales	South America	Asia
2002	Although no case reports of liver damage were recorded in the country, on 11 January, 2002, the Health and Social Department announced a ban on the sale of kava-containing products sold in pharmacies. Traditional kava preparations and kava products sold in supermarkets were exempt from the ban [201].	In November 2002, the South African (MCC) issued a drug alert, stating that kava may cause irreversible liver damage. No cases of liver damage were reported to the MCC [201,210].	The National Assembly for Wales bans all kava-containing products [211].		
2003			The National Assembly for Wales reversed a two-year ban on the sale of kava-containing products. The decision went into effect in October 2003 [212].	In Brazil, one woman died from renal failure associated with kava consumption. The case report documented that a 30 year-old woman experienced fulminant hepatitis possibly associated with kava. The woman suffered from renal failure and needed haemodialisis, noradrenaline and ventilatory support. The patient died after going into sepsis.	
2004				In Brazil, one case report was documented in a 44 year-old woman who experienced fulminant hepatitis associated with kava consumption. The patient had a liver transplant in the end of February 2004. A biopsy found that the liver showed a high probability of toxic hepatitis.	

MCC: Medicines Control Council.

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- **[201-212] are regulatory publications.**

Affiliation

Catherine Ulbricht[†1] PharmD,
Ethan Basch[2] MD, Heather Boon[3] BScPhm, PhD, Edzard Ernst[4] MD, PhD,
Paul Hammerness[5] MD,
David Sollars[6] MAc, HMC,
Candy Tsourounis[7] PharmD,
Jen Woods[8] BSc & Stephen Bent[7] MD
[†]Author for correspondence
[1]Natural Standard Research Collaboration, 1 Broadway, 14th Floor, Cambridge, MA 02142, USA
Tel: +1 617 758 4270; Fax: +1 617 758 4274; E-mail: Info@naturalstandard.com
[2]Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA
[3]University of Toronto, Toronto, Ontario, M5S 1A1, Canada
[4]University of Exeter, The Queen's Drive, Exeter, Devon, EX4 4QJ, UK
[5]Harvard Medical School, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
[6]New England School of Acupuncture, 40 Belmont Street, Watertown, MA 02472, USA
[7]University of California, San Francisco, San Francisco, CA 94143, USA
[8]Northeastern University, 360 Huntington Avenue, Boston, MA 02115, USA