Kava

Scientific Name(s): Piper methysticum Forst.f.
Common Name(s): Ava, Awa, Intoxicating pepper, Kava, Kava kava, Kava pepper, Kava root, Kava-kava, Kavain, Kawa, Kawain, Kew, Rauschpfeffer, Sakau, Tonga, Wurzelstock, Yangona

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Clinical Overview

Use

A number of meta-analyses and systematic reviews of kava use in anxiety have found in favor of kava over placebo, but results are not consistent. Kava has also been studied for effects on cognitive function and for potential cancer applications. However, concerns over hepatotoxicity have limited clinical studies.

Dosing

A maximum daily dose of kavalactones 250 mg is suggested to avoid potential hepatotoxicity. Studies in children are lacking, and use is not recommended.

Contraindications

Kava and kava-containing products are not recommended for use in children or in patients with hepatic disease. Kava should be used cautiously in patients with renal or liver disease, blood disorders, Parkinson disease, or depression.

Pregnancy/Lactation

Documented adverse effects. Avoid use.

Interactions

Kava extracts have been shown to interfere with cytochrome P450 (CYP-450) enzymes; however, specific reports on the metabolism of pharmaceuticals are sparse. Case reports exist on interactions with alprazolam, alcohol, barbiturates, and levodopa. Concomitant administration of kava with haloperidol, risperidone, and metoclopramide, among other drugs, may be associated with adverse reactions.

Adverse Reactions

Heavy kava use may cause a scaly skin rash. A variety of adverse reactions, including visual disturbances, urinary

retention, GI discomfort, exacerbation of Parkinson disease, extrapyramidal effects, and rhabdomyolysis, have been reported.

Toxicology

Rare cases of severe liver toxicity have been reported. Fatal intoxication with concomitant IV administration of kavalactones and ethanol has been reported.

Scientific Family

- Piperaceae (black pepper)

Botany

The dried rhizome and roots of P. methysticum, a large shrub widely cultivated on many Pacific islands, including Hawaii, Tahiti, and New Guinea, are consumed in various forms as kava. The plant can grow as tall as 3 m, has large, heart-shaped leaves, and is vegetatively propagated exclusively by root cuttings. It is thought to be derived from the wild species Piper wichmannii C. DC. Many cultivars of kava are recognized, and the rootstock color ranges from white to dark yellow, depending on the amount of kavalactones present. The comparative chemistry and ethnopharmacology have been studied in detail, and 121 named cultivars from 51 islands have been grouped into 6 chemotypes.[1, 2, 3, 4, 5]

History

The kava beverage is prepared from the plant's roots, which are chewed or pulverized and then steeped in water or coconut milk. The cloudy mixture is filtered and served at room temperature. Kava has been an important part of Pacific Island ceremonial cultures for many centuries, with elaborate rituals attending its consumption. Its main use has been to induce a relaxed state in ceremony participants by initially causing a numbing and astringent effect in the mouth, followed by anxiolytic and muscle relaxant effects. Eventually, a state of sleep is induced and no hangover effects are experienced. The kava beverage has been used to symbolize respect and hospitality for visiting dignitaries, with traces of kava extract identified on archaeological artifacts from the Fiji islands by mass spectrometry.

Research into the use of kava has been conducted since the late 19th century. In the early 1900s, kava was used as a diuretic and for gonorrhea and nervous disorders. It has been one of the top botanical sellers in the United States and Europe for anxiety and sleep disorders. However, many countries have regulated its sale because of reports of hepatotoxicity. In 2002, the US Food and Drug Administration issued a consumer advisory warning of the potential for liver injury.[5, 6, 7, 8]

Chemistry

Fresh kava root contains about 80% water. Dried kava root contains 12% water, 43% starch, and 20% fibers, with the balance being made up of protein, sugars, and minerals. The primary active constituents in the resin include kavalactones, chalcones and other flavanones, and conjugated diene ketones. At least 18 lipid-soluble kavalactones, the primary bioactive constituents, have been isolated from kava root extract, accounting for 3% to 20% of the dry weight. The 6 major kavalactones are kawain, 7,8-dihydrokawain, methysticin, 7,8-dihydromethysticin, yangonin, and demethoxyyangonin, which occur in varying proportions in different cultivars. Toxic alkaloids have been identified in the leaves and stem peelings. Many methods have been developed for the analysis of kavalactones, including thin layer chromatography, gas chromatography, high-performance liquid chromatography, gas chromatography–mass

spectrometry, and nuclear magnetic resonance. Proposals for standardization of constituents exist. 5, 9, 10, 11, 12, 13, 14

Uses and Pharmacology

Chewing kava causes numbness in the mouth because of the local anesthetic action of kavalactones, which is similar to that produced by cocaine and longer lasting than that of benzocaine. In addition, kava produces a mild euphoria characterized by feelings of contentment and fluent, lively speech. Sight, smell, and sound are also reported to be heightened. Higher doses may lead to muscle weakness, especially in the legs, although some observers relate this to sitting for long periods during the kava ceremony rather than to kava itself. Very high doses may induce a deep sleep.15, 16

Anxiety

Animal data

There is no animal data regarding the use of kava for anxiety, aside from studies attempting to elucidate the mechanism of action. Suggested mechanisms include enhanced ligand binding activity at gamma-aminobutyric acid (GABA) receptors, reversible inhibition of monoamine oxidase (MAO)-B, and reduced uptake of norepinephrine and dopamine. Kavalactones, however, do not appear to bind directly to the GABA receptors.17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28

Clinical data

A number of meta-analyses and systematic reviews of kava use for anxiety have been conducted, with findings favoring kava over placebo (5 point reduction in Hamilton Anxiety Scale [HAM-A] score [confidence interval (CI), 1.1 to 8.8]).28, 29, 30 Efficacy has been shown to be similar to that of oxazepam, opipramol (a tricyclic antidepressent available in Europe), and buspirone.28, 29, 30, 31, 32 Studies included in these reviews tested older preparations of kava, while trials evaluating water-derived preparations using accepted dosages are limited.28, 30 The Kava Anxiety Depression Spectrum Study evaluated aqueous kava extract 250 mg per day over 3 weeks in 60 adults with generalized anxiety disorder (GAD) and found reductions in HAM-A measurements (reduction of 9.9 points [CI, 7.1 to 12.7]) versus placebo (reduction of 0.8 points [CI, −2.7 to 4.3]).33 Some of the same investigators conducted a 6-week, placebo-controlled trial in GAD that included determination of pharmacogenetic profiles. Response, defined as at leaset 50% reduction in HAM-A score, occurred in 37% with kava and 23% of placebo patients ($P = 0.046$). Remission (HAM-A up to 7) was seen in 26% and 6% with kava and placebo, respectively ($P = 0.04$). Two of five alleles of GABA transporter were associated with kava response.89 Limited studies suggest efficacy in menopausal-related anxiety.30, 34, 35, 36, 37 Studies with negative findings for kava in generalized anxiety disorder have been published, including a single-dose study for acute management of anxiety.38, 39, 40 Head-to-head trials evaluating efficacy against selective serotonin reuptake inhibitors have not been conducted.28, 31

Cancer

Animal data

Rats fed kava for 14 weeks showed a reduction in colon cancer risk markers.41 Constituents of kava extracts, including the flavokawains, yangonin, and methysticin, have been studied for anticancer effects. Apoptosis and reduced proliferation have been demonstrated in lung, liver, pancreatic, prostate, uterine, and squamous cell lines. Chalcone analogs have also been studied.42, 43, 44, 45, 46, 47

Clinical data

Epidemiological data suggest a correlation between kava consumption and a low incidence of cancer.[48], [49] In vitro data from a study of flavokawain B (FKB), a kava extract, found it arrested the cell cycle and induced apoptosis in human sarcoma cells, and was less toxic to bone marrow and intestinal epithelial cells than doxorubicin.[90]

Cognition

Animal data

No animal data exist on the effect of kava on cognition, aside from studies attempting to elucidate the mechanism of action. Suggested mechanisms include enhanced ligand binding activity at GABA receptors, reversible inhibition of MAO-B, and reduced uptake of norepinephrine and dopamine. Kavalactones, however, do not appear to bind directly to the GABA receptors.[17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28]

Clinical data

Reviews of at least 10 studies on the effects of kava on cognition have been published.[28], [50], [51]

Heterogeneity of dosages/potency and preparations used precludes meta-analysis. Seven studies evaluated the short-term effects of kava on cognition, while 3 evaluated long-term effects. Despite the heterogeneity, kava appears to have little or no overall effect on cognition. At higher dosages, reaction time may be impaired.[28], [50], [51] Kava has been promoted for use in attention deficit hyperactivity disorder and as an alternative to methylphenidate; however, clinical trials are lacking and until safety concerns are resolved, such use is not recommended.[5], [51]

Other uses

Kawain showed an antithrombotic effect on platelets, dose-dependently blocking platelet aggregation, adenosine 5′-triphosphate release, and synthesis of prostaglandins at high micromolar concentrations.[52]

Despite a reputation as an antimicrobial agent in urinary tract infections, kava extracts demonstrated minimal antifungal activity and no antimicrobial or antiviral activity.[53] Antitrypanosomal activity has been demonstrated.[54]

The Veteran’s Administration and Department of Defense (VA/DoD) clinical practice guideline for the management of chronic insomnia disorder and obstructive sleep apnea (2019) recommend against the use of kava for the treatment of chronic insomnia disorder (Strong).Mysliwiec 2020

Dosing

The Australian Therapeutic Goods Administration requires the maximum strength of tablet or capsule preparations to be kavalactone 125 mg, with a recommended maximum daily dose of kavalactone 250 mg. No adverse reactions have been reported at this dosage, which is less than the traditional consumption.[14]

Kava does not appear to be addictive at therapeutic dosages.[55]

Studies in children are lacking, and use is not recommended.[51], [56]

Pregnancy / Lactation

Documented adverse effects. Avoid use.[57], [58], [59]

Interactions

Anti-Parkinson agents (dopamine agonist): Kava may enhance the adverse/toxic effect of anti-Parkinson agents (dopamine agonist). Kava may diminish the therapeutic effect of anti-Parkinson agents (dopamine agonist). Monitor therapy.(66, 94)

CNS depressants: Kava may enhance the CNS depressant effect of CNS depressants. Monitor therapy.(28, 67, 94, 95, 96, 100)

Paroxetine: Kava may enhance the adverse/toxic effect of paroxetine. Monitor therapy.(97)

Kava extracts have been shown to interfere with CYP-450 enzymes; however, reports on specific effects on the metabolism of pharmaceuticals are limited.(60, 61, 62, 63) Case reports exist on interactions with alprazolam, alcohol, barbiturates, and levodopa. Studies in healthy volunteers have demonstrated a lack of interactions with midazolam and digoxin.(15, 63, 64, 65, 66, 67, 68) Interactions with MAO inhibitors, antiplatelets, and hepatotoxic agents may exist. Drugs affecting dopamine, such as haloperidol, risperidone, and metoclopramide, among others, are associated with increased adverse reactions, especially Parkinson-like symptoms, when given concomitantly with kava-containing products.(69, 70)

Kava drug interactions (more detail)

Adverse Reactions

Acute adverse reactions of kava consumption may include oral anesthetic effects (especially of the tongue), sedation, euphoria, tremors, and ataxia.15, 16 Visual impairment (near-point accommodation, enlargement of the pupils, and disturbances in oculomotor equilibrium) has also been described.10, 15 One study saw a significantly higher incidence of headache compared with placebo in patients with GAD, but the investigators did not believe headache was related to study treatment.89 There was a significant increase in libido in female patients receiving kava in this same GAD study.91

Heavy consumption of kava has long been known to produce a scaly skin rash similar to pellagra and known as "kava dermopathy" on the palms of the hands, soles of the feet, and back. Supplementation with niacin did not reverse the condition,15, 71 but cessation of kava use resulted in its reduction or disappearance. Because flavokawain pigments are suspected to be responsible for this toxicity,72 they are commonly removed in the production of commercial extracts despite the lack of scientific proof.73

Urinary retention, exacerbation of Parkinson disease, extrapyramidal effects, myoglobinuria, severe rhabdomyolysis, and GI discomfort, among other effects, have been reported.10, 15, 74, 75, 76

Kava should be used cautiously in patients with renal or liver disease, blood disorders, Parkinson disease, or depression. Regular liver function tests may be warranted.7, 15, 77

Data collected between 2004 and 2013 from 8 US centers in the Drug-induced Liver Injury Network revealed that 15.5% (130) of hepatotoxicity cases were caused by herbals and dietary supplements, whereas 85% (709) of cases were related to prescription medications. Of the 130 cases of liver injury related to supplements, 65% were from non-bodybuilding supplements and occurred most often in Hispanics/Latinos compared with non-Hispanic whites and non-Hispanic blacks. Liver transplant was also more frequent with toxicity from non-bodybuilding supplements (13%) than with conventional medications (3%) (P<0.001). Overall, the proportion of severe liver injury cases was significantly higher for supplements than for conventional medications (P=0.02). Of the 217 supplement products implicated in liver injury, 175 had identifiable ingredients, of which kava kava was among the 32 (18%) single-ingredient products.93 The European Association for the Study of the Liver (EASL) clinical practice guideline for drug-induced liver injury (2019) recommends

physicians consider herbal and dietary supplements as potential causative agents associated with liver injury (Level 4; Grade C), including kava, which has some of the highest levels of evidence supporting hepatotoxicity.99

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Toxicology

Kava has been implicated in several reports of fulminant hepatic failure in Europe and the United States. The FDA as well as the Australian and Canadian authorities have issued warnings to consumers and health care providers on the potential for liver damage from kava products.5, 30, 78, 79 Reviews of kava safety issues have been published. Although the incidence of hepatotoxicity in clinical trials has been too low to show causality, patients with any predisposition to hepatic dysfunction should avoid kava use.5, 12, 30, 80, 81, 82 Rats fed kava for 14 weeks showed no hepatic lesions on histology.41

Several theories have been suggested as to why kava may cause hepatotoxicity and to account for its apparent safe use among South Pacific populations for centuries. One theory is that because heavy demand for kava products led to the addition of kava leaves and stems to root products, the alkaloid pipermethystine, which is found in the leaves and stems but not in roots, may be responsible. Cytotoxicity of pipermethystine (50 to 100 mcM) to HepG2 cells has been demonstrated in support of this theory. Another theory, known as the "glutathione theory," suggests that aqueous extracts traditionally used in the South Pacific contain glutathione with the potential to react with kavalactones, providing hepatoprotection, as opposed to products that are chemically derived and appear on the market. Additionally, several studies have indicated that kavalactones are inhibitors of CYP-450 isoenzymes, increasing the risk for drug-herbal interactions, especially with kava formulations containing high concentrations of methysticin and dihydromethysticin. Hepatotoxicity may also result with coadministration of alcohol because kava decreases the conversion of ethanol to acetaldehyde; alcohol may also reduce detoxification of kavalactones. A fatal case of intentional suicide using

kavalactones injected intravenously with ethanol was reported in 36-year-old man with a history of depression.92 Another theory postulates that the hepatotoxicity of kava is due to the increased risk of liver damage in patients with deficiencies in CYP2D6, a major metabolic pathway for kavalactones. This phenomenon is seen in approximately 10% of white patients but rarely in Polynesian patients, which may explain the higher incidence of liver toxicity in European patients compared with those in the Pacific Islands. Specifically, kavalactones appear to inhibit cyclooxygenase enzymes COX-1 and COX-2. The mediators derived from the production of COX-2 have been shown to be hepatoprotective, the inhibition of which may contribute to kava hepatotoxicity. Immunological and/or toxicological reactions may also be implicated in hepatotoxicity from kava.8, 83, 84, 85, 86, 87, 88

Concerns over potential toxicity to the kidneys, brain, and hematopoietic system also exist.5 Data are insufficient to clarify the safe cosmetic use of kava products.13

References

Disclaimer

Frequently asked questions

- Does Kava interact with any drugs?
- Does Kava interact with any drugs?

More about kava

- Check interactions
- Compare alternatives
- Reviews (14)
- Drug class: herbal products

Related treatment guides

- Herbal Supplementation
- Anxiety
- Anxiety and Stress

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