

Kava

Piper methysticum G. Forst.

[Fam. *Piperaceae*]

OVERVIEW

Kava is traditionally served as a beverage in social or ceremonial rituals in island communities of the South Pacific, where it is revered as the primary cultural and medicinal botanical. While kava use has been popular as a phytomedicine in Europe for decades, it only recently became a top-selling herbal dietary supplement in the U.S., used by consumers mainly for dealing with feelings of anxiety.

Recently, kava has been implicated in some cases of hepatotoxicity in Europe and subsequently in the U.S. As a result, its use has been either limited or banned in such countries as Switzerland, Germany, Canada, Australia, France, and the U.K.

Previous reviews of kava safety did not include evidence suggesting the potential for hepatotoxicity. A toxicological review of kava-associated hepatic adverse event reports (AERs) from Europe and the U.S. concluded that, based on the available data, “there is no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava.” A detailed review of the chronology of the events related to kava and its alleged association with hepatotoxicity, plus updates on recent developments, is available on the American Botanical Council website (www.herbalgram.org).

PRIMARY USE

Neurology

- Anxiety disorder

OTHER POTENTIAL USES

- Sleep disorder
- Stress and restlessness
- Muscle relaxant

PHARMACOLOGICAL ACTIONS

Anxiolytic; sedative; reduces hot flashes.

DOSAGE AND ADMINISTRATION

The German Commission E monograph published in 1990 recommends a maximum treatment duration of 3 months without medical supervision. This limitation was based not on concerns of potential toxicity of kava (no adverse side effects were noted in the monograph, based on observations at that time), but on the Commission E’s desire to ensure that patients using kava for anxiety-related conditions were receiving adequate professional supervision every 3 months. Because some of the recent reports of adverse liver effects are associated with the use of kava for 1 month or less (along with conventional medications or alcohol, in most cases), the American Botanical Council suggested in

December 2001 as a precautionary measure, based on the information available at that time, that use longer than 1 month be monitored by a qualified healthcare professional.

Crude preparations

Daily dosage for cut dried rhizome and other galenical preparations for oral use equivalent to 60–120 mg kavalactones (aka kavapyrones). 60–120 mg of kavapyrones is equivalent to 1.7–3.4g of dried rhizome (based on the *German Drug Codex* quantitative requirement of minimum 3.5% (35 mg/g) kavapyrones).

COLD MACERATE: The fresh or dried rhizome is ground to a powder (traditionally it is masticated to a pulp) and then macerated in cold water. The first filtrate is strained and drunk. The residue is then compressed and the second filtrate can either be mixed with the first or consumed separately. A standard bowl of the traditionally prepared cold macerate beverage contains about 250 mg of kavalactones.

DRIED RHIZOME: 1.5-3 g daily, divided throughout the day, chewed well.

FLUID EXTRACT: (1:2): 3-6 mL daily, divided throughout the day.

Standardized preparations

CAPSULES OR TABLETS: Powdered dry extract (not less than 30% kavalactones) or semisolid (paste) extract (not less than 50% kavalactones) in daily dosage equivalent to 70–280 mg kavalactones. Most controlled clinical trials are based on three 100 mg doses of a dried extract (acetone solvent), standardized to 70 mg (70%) kavalactones, or 210 mg kavalactones per day.

CONTRAINDICATIONS

The Commission E contraindicated the use of kava in cases of endogenous depression. Industry labeling guidelines suggest that it is not for use by persons under 18 years of age. In response to reports of hepatotoxicity that may be associated with use of kava preparations, the FDA, ABC, and various industry trade organizations have advised consumers of the rare but potential risk of severe liver injury associated with the use of kava-containing preparations: Persons who have or have had liver disease or liver problems, persons taking any medication with known or suspected hepatotoxic effects, and persons who frequently use alcoholic beverages should consult a healthcare practitioner before using kava-containing products. Persons who use a kava-containing product and who experience signs of illness associated with liver disease should discontinue use and consult their physician. Symptoms of serious liver disease include jaundice (yellowing of the skin or whites of the eyes) and brown urine. Non-specific symptoms of liver disease can include nausea, vomiting, light-colored stools, unusual tiredness, weakness, stomach or abdominal pain, and loss of appetite.

PREGNANCY AND LACTATION: Kava should not be used during pregnancy or while nursing.

ADVERSE EFFECTS

Adverse effects with recommended doses of kava are relatively rare. Large doses (400 mg kavalactones or more per day for longer than 3 months) may cause a scaly, yellowing skin condition (scaly ichthyosis), which resolves itself when use is discontinued. Kava preparations may be a contributing risk factor for the development of melioidosis, a tropical disease caused by *Burkholderia pseudomallei*. In 2 case reports necrotizing hepatitis occurred after ingestion of an herbal preparation containing kava extract and celandine (*Chelidonium majus*); however, the effects may have resulted from the celandine and/or the combination.

By early 2002, there had been approximately 30 cases of possible hepatotoxicity associated with ingestion of kava reported in international literature, with at least 28 cases reported in total (4 in Switzerland; 24 in Germany), prompting regulatory actions by authorities. The hepatic AERs in these cases include cholestatic hepatitis (inflamed liver with obstruction of bile flow), icterus (jaundice), increased liver enzymes, liver cell impairment, severe hepatitis with confluent necrosis, and irreversible liver damage (required transplant in four cases). Additionally, at least 5 cases of liver dysfunction purportedly associated with kava consumption have been reported in the U.S.

Although much of the data on the reported cases of hepatotoxicity is either incomplete or generally unavailable, relatively detailed information has been published for 5 of these cases, including one case of recurring necrotizing hepatitis that was reported in a 39-year old woman who may have consumed an ethanolic-based kava extract. In a 50-year old man a relation between ingestion of kava and fulminant hepatic failure was suggested by the chronology, histological findings, and exclusion of other causes of hepatitis. He reportedly took no other drugs, nor did he consume alcohol; yet his liver function tests showed a 60-fold and 70-fold increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, respectively.

Kava consumption is considered relatively risk free in its native regions in Polynesia. However, in a population of Australian aboriginal people known to be relatively heavy consumers of alcohol, heavy kava consumption has been associated with increased concentrations of glutamyltransferase, suggesting potential hepatotoxicity with alcohol.

Several reviews of these reports emphasize that in many of these cases other known or suspected liver-toxic medications had been administered concurrently; in most of the other cases the possibility of virus infections or concurrently ingested medications or alcohol could not be ruled out as possible causes. Thus, only a few cases can be conclusively linked to the use of kava. An analysis of the approximately 30 hepatic AERs from Europe and 5 submitted to the U.S. FDA from May 1998 through September 2001 by an American toxicologist concluded that there is “no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava” and that those cases in which there is a possible association between the use of a kava extract and liver dysfunction “appear to have been hypersensitivity or

idiosyncratic base responses.” However, the report’s author acknowledged that he did not have adequate medical information on all the case reports to adequately assess them. Two U.S. case reports suggest relative safety of kava. In one case in which 4 prescription drugs plus relatively high levels of kava were used (300 pills or 45,000 mg per day) there was no liver damage observed; in another case, a 13-year old girl consumed 8–10, 500 mg tablets in a suicide attempt, but recovered the following morning. “From a toxicologist perspective, these 2 cases provide some evidence that kava itself is not a direct hepatotoxin even in extremely high concentrations.”

DRUG INTERACTIONS

Simultaneous consumption of kava with alcohol, barbiturates, psychopharmacological drugs, or other substances acting on the central nervous system (CNS) may potentiate inebriation or the CNS depressant effect. Kava may potentiate effects of other anxiolytics, and can increase Parkinson symptoms by reducing the effect of levodopa, according to one human case report. There is one case report of “coma” associated with the combined use of kava and the benzodiazepine, alprazolam (Xanax®), cimetidine (Tagamet®), and terazosin (Hytrin®).

CLINICAL REVIEW

Fifteen studies (669 participants) are outlined in the monograph table, “Clinical Studies on Kava.” These studies demonstrated kava’s positive effects for indications including anxiety, mental function, reaction time, sleep quality, and peri-menopausal symptoms, while 1 study focused on the safety of kava. Six randomized, double-blind, placebo-controlled (R, DB, PC) studies (357 participants) concluded that kava significantly reduced anxiety in several different populations. One R, DB, case-controlled study (172 participants) found a significant reduction in anxiety. Two DB, crossover (CO) trials showed that mental clarity remains intact with kava use. Kava demonstrated a favorable influence on sleep in one PC, CO study. One PC, CO comparison trial showed that kava did not affect reaction time or impair safety, compared to bromazepam and bromazepam combined with kava. A highly significant improvement in peri-menopausal symptoms was demonstrated in a R, DB, PC study. A meta-analysis of seven R, DB, PC trials conducted on various doses of kava confirmed an anxiolytic effect and demonstrated it was significantly superior to placebo as a symptomatic treatment for anxiety. In one PC pilot study (n=13), the preliminary findings suggest that kava might exert a positive effect on reflex vagal control of heart rate in generalized anxiety disorder patients. Another R, DB, PC study by some of these same researchers reviewed the safety profile of kava in 35 subjects. No significant adverse effects were measured between kava and placebo patients on any of the parameters evaluated.



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OVERVIEW

Kava is traditionally served as a beverage in social or ceremonial rituals in the South Pacific islands, where it is revered as the primary cultural and medicinal botanical. While kava use has been popular in Europe for decades, it only recently became a top-selling herbal dietary supplement in the U.S., used by consumers mainly for dealing with feelings of anxiety.

Recently, kava has been implicated in some cases of hepatotoxicity in Europe and subsequently in the U.S. A detailed review of the chronology of the events related to kava and its alleged association with hepatotoxicity, plus updates on recent developments, is available on the American Botanical Council website (www.herbalgram.org).

USES

Anxiety disorder; sleep disorders; stress and restlessness; muscle relaxant.

DOSAGE

Do not use kava for more than one month without medical supervision.

FLUID EXTRACT (1:2): 3–6 mL daily, divided throughout the day.

CAPSULES OR TABLETS: Powdered dry extract (not less than 30% kavalactones) or semisolid (paste) extract (not less than 50% kavalactones) in daily dosage equivalent to 60–120 mg kavalactones.

CONTRAINDICATIONS

Consult with a healthcare practitioner prior to using kava in cases of depression. Not for use by persons under 18 years of age. Persons who have or have had liver disease or liver problems, persons taking any medication with known or suspected hepatotoxic effects, and persons who frequently use alcoholic beverages should consult a healthcare practitioner before using kava-containing products. Persons who use a kava-containing product and experience signs of illness associated with liver disease should discontinue use and consult their physician. Symptoms of serious liver disease include jaundice (yellowing of the skin or whites of the eyes) and brown urine. Non-specific symptoms of liver disease can include

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.



nausea, vomiting, light-colored stools, unusual tiredness, weakness, stomach or abdominal pain, and loss of appetite.

PREGNANCY AND LACTATION: Kava should not be used during pregnancy or while nursing.

ADVERSE EFFECTS

Adverse effects with recommended doses of kava are relatively rare. Large doses (400 mg kavalactones or more per day for longer than 3 months) may cause a scaly, yellowing skin condition (scaly ichthyosis), which resolves itself when use is discontinued. In 2 case reports liver inflammation occurred after ingestion of an herbal preparation containing kava extract and celandine (*Chelidonium majus*); however, the effects may have resulted from the celandine and/or the combination. Current research does not provide clear evidence of any scientific rationale that kava use is associated with liver damage; nevertheless, consumers and patients are advised to heed the above cautions.

DRUG INTERACTIONS

Taking kava along with alcohol, barbiturates, drugs affecting mental activity, or other substances acting on the central nervous system may increase inebriation or the effect of the drug. Kava may also increase the effect of other relaxation-promoting drugs.



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Kava

Piper methysticum G. Forst.

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OVERVIEW

Kava is traditionally served as a beverage in social or ceremonial rituals in island communities of the South Pacific (e.g., Fiji, Vanuatu, Samoa, Tonga), where it is revered as the primary cultural and medicinal botanical (Lebot *et al.*, 1992; Singh, 1992; Singh and Blumenthal, 1997). Its uses were first described in detail by botanist J.G. Forster on the voyage of Captain James Cook in the late 1700s (Forster, 1777). Kava beverage is used as a symbol of welcome and respect to visiting heads of state and other dignitaries (Singh and Blumenthal, 1997).

Kava use has been popular as a phytomedicine in Europe for decades; it was approved in 1990 as a nonprescription drug by the German Commission E for treatment of symptoms of anxiety, stress, and nervous restlessness (Blumenthal *et al.*, 1998). Kava only recently became a top-selling herbal dietary supplement in the U.S., used by consumers mainly for dealing with feelings of anxiety (Singh and Blumenthal, 1997). The herb ranked ninth in retail sales in mainstream markets (e.g., grocery



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stores, drugstores, and mass market retailers) in the U.S. in 2000, with annual sales in this channel totaling about \$15 million. (Blumenthal, 2001). Additional sales in health food stores, multilevel marketing organizations, mail order houses, through health professionals, and miscellaneous channels would probably constitute a total estimated market sales of over \$40 million.

Recently, kava has been implicated in some cases of hepatotoxicity in Europe (Stoller 2000; Hagemann, 2001) and subsequently in the U.S. (Taylor, 2001; Waller, 2002). The German and Swiss governments have taken regulatory actions based on this preliminary information (Hagemann, 2001; Stoller, 2000), with the Swiss banning the sale of the leading acetone-based kava extract and requiring additional safety data for ethanolic extracts in 2000 (IKS, 2001), and the Germans withdrawing product licenses in 2002 (BfArM, 2002). The French government has banned its sale (Anon., 2002b) and the British government and

the dietary supplement industry voluntarily suspended its sale pending resolution of the question of hepatotoxicity (Woodfield, 2001); in early 2003, Kava sales were banned in the UK (MCA, 2002).

Previous reviews of kava safety did not include evidence suggesting the potential for hepatotoxicity. A peer-reviewed assessment of the safety of kava concluded that “when used in normal therapeutic doses, kava appears to offer safe and effective anti-anxiety and muscle relaxant actions without depressing centers of higher thought. The safe use of kava as a dietary supplement in cultures that do not have historical experiences with its use depends on responsible manufacturing, marketing, individual consumption patterns, and education” (Dentali, 1997). One recent meta-analysis of controlled clinical trials found kava to be safe and effective compared to placebo in the treatment of anxiety (Pittler and Ernst, 2002; 2000), and a small clinical study on its adverse effects profile concluded that the herb is relatively safe, not finding significant concerns of hepatotoxicity (Connor *et al.*, 2001). A toxicological review of kava-associated hepatic adverse event reports (AERs) from Europe and the U.S. concluded that based on the available data “there is no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava” (Waller, 2002) (see more below at Adverse Effects). A detailed review of the chronology of the events related to kava and its alleged association with hepatotoxicity, plus updates on recent developments, is available on the American Botanical Council website (ABC, 2001; Blumenthal, 2002b).

DESCRIPTION

German pharmacopeial-grade kava consists of the mostly peeled, chopped and dried rhizomes of *Piper methysticum* G. Forst. [Fam. *Piperaceae*], usually freed from the roots, containing not less than 3.5% kavalactones, calculated as kavain (DAC, 1998). There is a U.S. *Pharmacopeia-National Formulary* (USP-NF) kava monograph in development, requiring the dried rhizome, usually peeled and cut in pieces with the roots removed, containing not less than 4.5% of kavalactones (USPC, 2002). Because the peeled skin contains a greater concentration of kavalactones, many extractors use this non-official plant source and/or the unpeeled root and rhizome and occasionally the stems. Commercial kava extracts are commonly standardized to 30–40% kavalactones for dried powdered extracts, and 55–70% for concentrated extracts and pastes.

NOTE: Monographs for two kava preparations are also in process to become official in the USP-NF: (1) Powdered Kava Extract (drug-to-extract ratio 6–20:1, contains not less than 30% kavalactones) and (2) Semisolid Kava Extract (drug-to-extract ratio 13–20:1, contains not less than 50% kavalactones) (USPC, 2000).

PRIMARY USE

Neurology

- Anxiety disorder (Pittler and Ernst, 2002, 2000; Blumenthal *et al.*, 1998; Singh *et al.*, 1998; Volz and Kieser, 1997; Lehmann *et al.*, 1996; Woelk *et al.*, 1993; Warnecke, 1991; Kinzler *et al.*, 1991; Lindenberg and Pitule-Schödel, 1990)

OTHER POTENTIAL USES

- Sleep disorder (Emser and Bartylla, 1991)
- Stress and restlessness (Blumenthal *et al.*, 1998)
- Muscle relaxant (Dentali, 1997)

DOSAGE

Daily dosage for cut dried rhizome and other galenical preparations for oral use equivalent to 60–120 mg kavalactones (aka kavapyrones) (Blumenthal *et al.*, 1998; DAC, 1998). 60–120 mg of kavapyrones (kavalactones) is equivalent to 1.7–3.4 g of dried rhizome based on the DAC quantitative requirement of minimum 3.5% (35 mg/g) kavapyrones (kavalactones) (DAC, 1998).

Crude preparations

COLD MACERATE: The fresh or dried rhizome is ground to a powder (traditionally it is masticated to a pulp) and then macerated in cold water. The first filtrate is strained and drunk. The residue is then compressed and the second filtrate can either be mixed with the first or consumed separately (Lebot and Cabalion, 1988). A standard bowl of the traditionally prepared cold macerate beverage contains about 250 mg of kavalactones (Bone, 1993/94).

DRIED RHIZOME: 1.5–3 g daily, divided throughout the day, chewed well (Bone, 1993/94; Burgess, 1998).

FLUID EXTRACT: (1:2): 3–6 mL daily, divided throughout the day (Bone 1993/94; Burgess, 1998).

Standardized preparations

CAPSULES OR TABLETS: Powdered dry extract (not less than 30% kavalactones) or semisolid (paste) extract (not less than 50% kavalactones) in daily dosage equivalent to 70–280 mg kavalactones. Most controlled clinical trials are based on three 100 mg doses of a dried extract (acetone solvent), standardized to 70 mg (70%) kavalactones, or 210 mg kavalactones per day (Pittler and Ernst, 2002, 2000).

DURATION OF ADMINISTRATION

The Commission E monographs published in 1990 recommended that kava not be used for more than three months without medical supervision (Blumenthal *et al.*, 1998). The purpose for this limitation was based not on concerns of potential toxicity of kava (no adverse side effects were noted in the monograph, based on observations at that time), but on the Commission E's desire to ensure that patients using kava for anxiety-related conditions were not doing so on a self-medication basis and were receiving adequate professional supervision every three months, especially since kava was seen as a drug lacking a clear European tradition. Thus, it was considered prudent to monitor the patient after three months (Busse, 2002a).

Because some of the recent reports of adverse liver effects are associated with the use of kava for one month or less (along with conventional medications or alcohol, in some cases), the American Botanical Council suggested in December 2001 as a precautionary measure, based on the information available at that time, that

use longer than one month be monitored by a qualified health-care professional (ABC, 2001; Blumenthal, 2002a, b).

CHEMISTRY

Kava root/rhizome contains 3.5–15% kavalactones (kavapyrones); these include kavain; 5,6-dihydrokavain; methysticin; dihydromethysticin; yangonin; and desmethoxyyangonin or 5,6-dehydrokavain). Kava also contains chalcones (flavokavins A, B, and C); 3.2% minerals (potassium, calcium, magnesium, sodium, aluminum, and iron) and 3.5% amino acids (Pizzorno and Murray, 1999; He *et al.*, 1997; Haberlein *et al.*, 1997; Singh and Blumenthal, 1997; Leung and Foster, 1996; Mack, 1994).

NOTE: There are numerous cultivars of kava containing varying proportions of these compounds. Research by Lebot *et al.* (1992) into the relative proportions of the various lactones in kava has revealed data on the origin of kava and its chemistry which has been modified through native selection of individual plants, where the chemical makeup of the kava, not its morphology, correlated with its ethnobotanical use. Thus, pharmacologically driven selection appears to have created chemical variations of kava far removed from its wild ancestor (Singh and Blumenthal, 1997).

PHARMACOLOGICAL ACTIONS

Human

- Anxiolytic (Pittler and Ernst, 2002, 2000; Boerner, 2001; Malsch and Kieser, 2001; Scherer, 1998; Volz and Kieser, 1997; Lehmann *et al.*, 1996; Woelk *et al.*, 1993; Johnson *et al.*, 1991; Kinzler *et al.*, 1991; Warnecke, 1991; Lindenberg and Pitule-Schödel, 1990);
- sedative (Emser and Bartylla, 1991);
- reduces hot flashes (Warnecke, 1991);
- locally mildly anesthetic (Singh and Blumenthal, 1997);
- improves sleep disorder (Holm *et al.*, 1991; Wheatley, 2001);
- can produce altered vision (Garner and Klinger, 1985).

Animal

- Analgesic (Bruggemann and Meyer, 1963; Hänsel, 1968; Jamieson and Duffield, 1990a);
- antispasmodic (Meyer, 1979);
- anticonvulsant (Klohs *et al.*, 1959; Kretzschmar *et al.*, 1970);
- sedative (Kretzschmar *et al.*, 1970; Gleitz *et al.*, 1996b);
- neuroprotection (Backhauss and Kriegelstein, 1992a,b; Gleitz *et al.*, 1996c).

In vitro

- Muscle-relaxant (without depressing CNS) (Singh, 1983);
- antispasmodic (natural kavain, Martin *et al.*, 2000), (synthetic kavain, Seitz *et al.*, 1997a);
- antithrombotic (Gleitz *et al.*, 1997);
- inhibitor (reversible) of MAO-B in human platelets (Uebelhack *et al.*, 1998).

MECHANISMS OF ACTION

The following mechanisms have been proposed for kava extract and/or specific kavalactones:

- Decreases levels of the excitatory neurotransmitter, glutamate (Meldrum, 1985; Ferger *et al.*, 1998);

- Activation of mesolimbic dopaminergic neuron, causing relaxation and slight euphoria (Baum *et al.*, 1998)
- Binds to GABA receptors in some regions of the brain (Davies *et al.*, 1992; Jussofie, 1993; Jussofie *et al.*, 1994; Boonen and Haberlein, 1998; Boonen *et al.*, 2000)
- Relaxes muscles through direct action on muscle contractility; not by inhibition of neuromuscular transmission (Singh, 1983)
- Increases delta, theta (daydreaming), and slow alpha brain wave activity, and decreases fast alpha and beta (concentrating) activity in a dose-dependent manner (Saletu *et al.*, 1989)
- Interacts with voltage-operated Na⁺ channels (Gleitz *et al.*, 1996a; Friese and Gleitz, 1998; Magura *et al.*, 1997; Schirmacher *et al.*, 1999)
- Inhibits [3H]-noradrenaline (norepinephrine) uptake (pyrone-specific), contributing to psychotropic properties (Seitz *et al.*, 1997b)
- Blockade of monoamine uptake resulting in elevation of dopamine and serotonin levels (Seitz *et al.*, 1997a; Boonen *et al.*, 1998; Baum *et al.*, 1998)
- Increases the β/α index in quantitative electroencephalograms, primarily in the β_2 -region (in dosages up to 600 mg, administered orally to humans); thereby exhibiting anxiolytic action without sedative or hypnotic effects (Johnson *et al.*, 1991)
- Kavalactones demonstrate a profile of cellular actions showing similarity with mood stabilizers (animal) (Grunze *et al.*, 2001)

CONTRAINDICATIONS

The Commission E contraindicated the use of kava in cases of endogenous depression (Blumenthal *et al.*, 1998). Not for use by persons under 18 years of age (AHPA, 2002; CRN, 2002). In response to reports of hepatotoxicity that may be associated with use of kava preparations, the FDA, ABC, and various industry trade organizations have advised consumers of the rare but potential risk of severe liver injury associated with the use of kava-containing preparations: Persons who have or have had liver disease or liver problems, persons taking any medication with known or suspected hepatotoxic effects, and persons who frequently use alcoholic beverages should consult a healthcare practitioner before using kava-containing products. Persons who use a kava-containing product and who experience signs of illness associated with liver disease should discontinue use and consult their physician. Symptoms of serious liver disease include jaundice (yellowing of the skin or whites of the eyes) and brown urine. Non-specific symptoms of liver disease can include nausea, vomiting, light-colored stools, unusual tiredness, weakness, stomach or abdominal pain, and loss of appetite (ABC, 2001; AHPA, 2002; Blumenthal, 2002a, b; CRN, 2002; FDA, 2002).

PREGNANCY AND LACTATION: Kava should not be used during pregnancy or while nursing (Blumenthal *et al.*, 1998; McGuffin *et al.*, 1997).

ADVERSE EFFECTS

Until recently, reports of adverse effects with recommended doses of kava have been relatively rare. Extended consumption of large doses (400 mg kavalactones or more per day for longer than three months) may cause a scaly, yellowing skin condition (scaly

ichthyosis), which resolves itself when use is discontinued (Mathews *et al.*, 1988; Ruze, 1990; McGuffin *et al.*, 1997; Blumenthal *et al.*, 1998). Kava preparations have been reported to be contributing risk factors for the development of melioidosis, a tropical disease caused by *Burkholderia pseudomallei* (BP) and associated with high mortality. In a prospective study, 252 cases of BP were found in Australia over a 10-year period. Consumption of kava was a risk factor in 8% of those cases (Currie *et al.*, 2000). There are two case reports of necrotizing hepatitis after ingestion of an herbal preparation containing kava extract and celandine (*Chelidonium majus*). Glutamic acid pyruvate transaminase (GPT) levels dropped to normal in both cases when the herbs were discontinued, suggesting a possible causal connection. Due to the combination of herbs and lack of confirmed toxicological data on kava and the liver, and direct cause and effect, it is possible that these results are due to the celandine and/or the combination (Strahl *et al.*, 1998).

By early 2002, there had been approximately 30 cases of possible hepatotoxicity associated with ingestion of kava reported in international literature, with at least 28 cases reported in total (Switzerland—4; Germany—24), prompting regulatory actions by authorities (Hagemann, 2001). The hepatic AERs in these cases include cholestatic hepatitis (inflamed liver with obstruction of bile flow), icterus (jaundice), increased liver enzymes (a sign of liver dysfunction), liver cell impairment, severe hepatitis with confluent necrosis, irreversible liver damage (required transplant in four cases), etc. Additionally, at least 5 cases of liver dysfunction purportedly associated with kava consumption have been reported in the U.S. (Waller, 2002).

Although much of the data on the reported cases of hepatotoxicity is either incomplete or generally unavailable, relatively detailed information has been published for 5 of these cases (Kraft *et al.*, 2001; Russmann *et al.*, 2001; Brauer *et al.*, 2000; Escher *et al.*, 2001; Sass *et al.*, 2001; Strahl *et al.*, 1998). In all of these 5 well-documented cases, notes one review, “severe liver damage or liver failure developed within days. This indicates a sudden, strong insult to the organ and contrasts with an often long kava intake....” (Schulze and Siegers, 2002). In the most detailed report, a case of recurring necrotizing hepatitis was reported in a 39-year old woman who may have consumed an ethanolic-based kava extract (Strahl *et al.*, 1998). In a 50-year old man a relation between ingestion of kava and fulminant hepatic failure was suggested by the chronology, histological findings, and exclusion of other causes of hepatitis. He reportedly took no other drugs nor did he consume alcohol, yet his liver function tests showed a 60-fold and 70-fold increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, respectively (Escher *et al.*, 2001).

Although kava consumption is considered relatively risk free in its native regions in Polynesia, heavy kava consumption has been associated with increased concentrations of glutamyltransferase, suggesting potential hepatotoxicity (in a population known to be relatively heavy consumers of alcohol), according to a report of its use in Australian aboriginal people (Mathews *et al.*, 1988).

In response to the potential for hepatotoxicity, the German Federal Institute for Drugs and Medical Devices (BfArM) called for labeling of such potential risk on package inserts in kava products (BfArM, 2000). Swiss authorities have taken similar measures after four cases were reported (Stoller, 2000). Seen in perspective to total estimated consumption of kava doses, these cases would constitute one case per 10 million daily doses (Busse, 2000).

Several reviews of these reports emphasize that many of these cases noted other known or suspected liver-toxic medications (e.g., diclofenac and others in Europe; docusate, Ogen®, Percocet®, Celexa®, Oxycontin®, Coumadin®, Celebrex®, and others) had been administered concurrently; in most of the other cases the possibility that concurrently ingested medications, alcohol or virus infections could not be ruled out as possible causes (Schmidt, 2001, 2002; Schulz and Siegers, 2002; Waller 2002). Thus, only a few cases can be conclusively linked to the use of kava (e.g., a case in which liver enzyme values were elevated upon re-exposure to kava after an initial presentation of necrotizing hepatitis [Strahl *et al.*, 1998]). One review suggests that the elucidation of possible mechanisms would add evidence of a causal relationship but that the current animal safety data are scarce and indicate a low hepatotoxic potential (Schulze and Siegers, 2002). An analysis of the approximately 30 hepatic AERs from Europe and 5 submitted to the U.S. FDA from May 1998 through September 2001 by an American toxicologist concluded that there is “no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava” and that those cases in which there is a possible association between the use of a kava extract and liver dysfunction “appear to have been hypersensitivity or idiosyncratic base responses.” (Waller, 2002). However, the report’s author acknowledged that he did not have adequate medical information on all the case reports to adequately assess them. Two U.S. case reports suggest relative safety of kava. In one case in which four prescription drugs plus relatively high levels of kava were used (300 pills or 45,000 mg per day) there was no liver damage observed; in another case a 13-year old girl consumed 8–10, 500 mg tablets in a suicide attempt, but recovered the following morning. “From a toxicologist perspective, these two cases provide some evidence that kava itself is not a direct hepatotoxin even in extremely high concentrations.” (Waller, 2002).

The report concludes:

...kava when taken in appropriate doses for reasonable periods of time has no scientifically established potential for causing liver damage. However as with any pharmacologically active agent, there is always the possibility of drug interactions, preexisting disease conditions and idiosyncratic or hypersensitivity reactions, which can exacerbate the toxicity of such an agent. Increased surveillance or reports of adverse effects and judicious use of kava-derived products under the conditions recommended by the natural products industry would be a most prudent approach to confirm its safety and minimize any risk of liver damage. The medical community and the general public should be made aware that concomitant intake of prescription drugs associated with liver damage, excessive alcohol consumption and preexisting liver disease or hepatitis with compromised liver function are conditions which may preclude any kava consumption (Waller, 2002).

A recent pilot study on an American kava extract (KavaPure®, PureWorld, South Hackensack, NJ) assessed the potential adverse effects profile of kava (Connor *et al.*, 2001). The study concluded that there were no significant differences between kava and placebo on any of the parameters evaluated, including withdrawal symptoms, heart rate, blood pressure, laboratory assessments, and sexual function; there were slightly elevated liver enzymes in 3 kava patients (one at baseline) which was not deemed clinically significant by the authors.

DRUG INTERACTIONS

Simultaneous consumption of kava with alcohol, barbiturates, psychopharmacological drugs, or other substances acting on the central nervous system (CNS) may potentiate inebriation or the CNS depressant effect, according to Commission E, based on a variety of evidence, including speculation (Blumenthal *et al.*, 1998). Regarding interactions with alcohol, subjective measures of sedation, cognition, coordination and intoxication were increased in a clinical trial (n=20) in doses of 1gm/kg kava with alcohol (Foo & Lemon, 1997). Despite kava’s producing an increase in the hypnotic effect of ethanol in rats (Jamieson and Duffield, 1990b), an 8-day human trial (n=20) using Laitan® (W. Schwabe, Germany) at 300 mg per day did not produce negative additive effects; the kava group even showed increased scores on the concentration test on the 4th day (Herberg, 1993).

Kava may potentiate effects of other anxiolytics, and may increase Parkinson symptoms by reducing the effect of levodopa, possibly due to dopamine antagonism, according to one human case report (Ernst, 2000; Brinker, 2001). There is one case report of “coma” associated with the combined use of kava and the benzodiazepine, alprazolam (Xanax®), cimetidine (Tagamet®), and terazosin (Hytrin®) (Almeida and Grimsley, 1996). There are reports of interactions, some profound, between alprazolam and cimetidine since 1983 (Abernathy *et al.*, 1983). Cimetidine can reduce the hepatic clearance of alprazolam; thus, the simultaneous use of the two drugs increases levels of alprazolam. Terazosin, a hypotensive drug used for benign prostatic hyperplasia, is usually not noted for interactions with other drugs; however, a commonly reported side effect is “dizziness” and “somnolence” (Abbott Labs, 2002), which might help explain the disorientation of the patient. Since this disorientation (despite the title of the report there was no loss of consciousness (in the article the authors refer to a “semicomatose state”), began 3 days after the first use of kava, it is possible that kava may have triggered the adverse event, but the extent that a possible chronic overdose of alprazolam, plus the possible side effect of terazosin, or a combination of both, may have contributed to the “lethargic” state of the patient is not clear (Bergner, 1999).

AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

CLASS 2B: Not to be used during pregnancy.

CLASS 2C: Not to be used while nursing.

CLASS 2D: Caution is required when driving or operating other equipment, and simultaneous consumption of kava and alcohol or barbiturates may potentiate inebriation (McGuffin *et al.*, 1997).

REGULATORY STATUS

AUSTRALIA: Schedule 4 to the Customs (Prohibited Imports) Regulations and is listed on Appendix B-“Substances Subject to Import Controls” with annual license and permit required. Importation of kava into the Northern Territory not permitted, and clearance from the State Health authorities required for importation into Western Australia (TGA, 2000a, 2000b). The Australian Therapeutic Goods Administration (TGA) reviewed kava’s legal status and invited submissions for consideration (Burgess, 1998). In 2002, the TGA ordered a voluntary recall on the sale of kava based on the prevailing international concerns over potential association with hepatotoxicity (Worth, 2002).

CANADA: Kava is not acceptable as a nonmedicinal ingredient in oral-use products (HPB, 1993; Health Canada 1995a). When identified as a Traditional Herbal Medicine (THM) or a homeopathic drug, kava was formerly regulated as a schedule OTC drug requiring premarket authorization and assignment of a Drug Identification Number (DIN) (Health Canada, 1995b, 2001; WHO, 1998). Health Canada reviewed the safety of kava in light of the recent hepatotoxicity reports (Anon, 2002a) and banned the sale of kava, and issued a product recall in August 2002 (Health Canada, 2002).

FRANCE: No monograph in the *French Pharmacopoeia*. Kava products banned by Ministry of Health in January 2002 due to concerns over potential hepatotoxicity (Anon., 2002b).

GERMANY: Product licenses withdrawn (BfArM, 2002).

SWEDEN: Approved for use as a drug (De Smet *et al.*, 1993).

SWITZERLAND: Dry native extract 10–23:1 (*w/w*) available in solid dosage form (capsule or tablet) is classified by the *Interkantonale Kontrollstelle für Heilmittel* (IKS) as a List D medicinal product, requiring premarketing authorization and product license, with sales limited to pharmacies and drugstores, without prescription (AKS, 2001; Ruppner and Schaefer, 2001; WHO, 1998). In 2000 the IKS withdrew the license for the acetonic kava product standardized to 70% kavalactones, owing to concerns of possible hepatotoxicity, based on AERs (see Adverse Effects above), despite the fact that most of the serious kava AERs implicated ethanolic extracts. The acetone extract dominates about 80% of the Swiss market, and was thus the first extract to produce AERs. Manufacturers of ethanolic extracts are allowed to maintain their products on the market for three years, during which time they must produce toxicology, pharmacology, and clinical studies on their respective extracts (Busse, 2002b).

U.K.: Kava was formerly an herbal medicine on the *General Sale List*, Schedule I (requiring full Product License), Table A (internal or external use) with maximum single-dose of 625 mg (GSL, 1994). In December 2001 the British Medicines Control Agency (MCA) and the dietary supplement trade organizations agreed to voluntarily suspend the sales of kava until such time as the issue of potential hepatotoxicity was adequately resolved (Woodfield, 2001). In December 2002, MCA announced a ban on Kava effective January 2003 (MCA, 2002).

U.S.: Dietary supplement (USC, 1994). Kava Rhizome, Powdered Kava, Powdered Kava Extract, Semisolid Kava Extract and Kava Tablets are subjects of botanical monographs in development for *United States Pharmacopeia-National Formulary*. Previews of the standards development were published in the *Pharmacopeial Forum* (USPC, 2000; 2002). In March 2001, the FDA issued a public warning on kava in response to concerns about potential hepatotoxicity (FDA, 2002).

CLINICAL REVIEW

Fifteen studies are outlined in the following table, “Clinical Studies on Kava”, including 669 participants. These studies demonstrated kava’s positive effects for indications including anxiety, mental function, reaction time, sleep quality, and perimenopausal symptoms, while one study (Connor *et al.*, 2001) focused on the safety of kava. Six randomized, double-blind, placebo-controlled (R, DB, PC) studies have been performed on 357 participants, concluding that kava significantly reduced anxiety in several different populations (Malsch and Kieser, 2001; Singh *et al.*, 1998; Volz and Kieser, 1997; Lehmann *et al.*, 1996; Warnecke *et al.*, 1991; Kinzler *et al.*, 1991). One R, DB,

case-controlled study of 172 participants found a significant reduction in anxiety (Woelk *et al.*, 1993). Two DB, crossover (CO) trials showed that mental clarity remains intact with kava use (Heinze *et al.*, 1994; Munte *et al.*, 1993). Kava demonstrated a favorable influence on sleep in one PC, CO study (Emser and Bartylla, 1991). One PC, CO, comparison trial showed that kava did not affect reaction time or impair safety, compared to bromazepam and bromazepam combined with kava (Herberg, 1996). A highly significant improvement in peri-menopausal symptoms was demonstrated in a R, DB, PC study (Warnecke *et al.*, 1990). A meta-analysis of seven R, DB, PC trials conducted on various doses of kava, confirmed an anxiolytic effect and demonstrated it was significantly superior to placebo as a symptomatic treatment for anxiety (Pittler and Ernst, 2002, 2000). The Cochrane Review has designed a protocol for evaluating R, DB, PC trials of Kava for anxiety, but has not concluded their evaluation (Bent *et al.*, 2001). In one PC pilot study (n=13), the preliminary findings suggest that kava might exert a positive effect on reflex vagal control of heart rate in generalized anxiety disorder patients (Watkins *et al.*, 2001). Another R, DB, PC study by some of these same authors reviewed the safety profile of kava in 35 subjects. No significant differences were found between kava and placebo on any of the parameters evaluated, including withdrawal symptoms, heart rate, blood pressure, laboratory assessments, and sexual function, with slightly elevated liver enzymes in 3 kava patients (one was elevated at baseline) which was not deemed clinically significant (Connor *et al.*, 2001).

BRANDED PRODUCTS*

GITLY kava extract: Produced as 400 mg tablets containing 120 mg kavalactone. Product manufacturer and distributor not identified.

KavaPure®: PureWorld Botanicals Inc. / 375 Huyler St. / South Hackensack, NJ 07606 / U.S.A. / Tel: (201) 440-5000 / Fax: (201) 342-8000 / www.pureworld.com. Powdered extract of kava rhizome standardized to 30% kavalactones.

Kavatro!®: Natrol Inc. / 21411 Prairie Street / Chatsworth, CA 91311 / U.S.A. / Tel: (800) 326-1520 / www.natrol.com. Produced from dried kava roots in a multistage process. Packaged in 200 mg capsules, containing 60 mg kavalactones in each capsule.

Kavosporal®: Polcopharma F Polley & Co. / P.O. Box 100 / Epping / NSW 1710 / Australia / Tel: +61-02-98-7664 / Fax: +61-02-98-6822-6 / Email: sales@polcopharma.com / http://polcopharma.com.au.

Laitan®: Dr. Willmar Schwabe Pharmaceuticals / International Division / Willmar Schwabe Str. 4 / D-76227, Karlsruhe / Germany / Tel: +49-721-4005 ext. 294 / Email: melville-eaves@schwabe.de / www.schwabepharma.com. Standardized to 70% kavalactones.

Laitan® 100: Dr. Willmar Schwabe Pharmaceuticals. Packaged in 100 mg capsules, each standardized to contain 70 mg kavalactones.

WS 1490: Dr. Willmar Schwabe Pharmaceuticals. Standardized to 70% kavalactones.

*American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Kava (*Piper methysticum* G. Forst.)

Anxiety

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Malsch and Kieser, 2001	Nonpsychotic nervous anxiety, tension, restlessness	R, DB, PC n=40	5 weeks	50 mg/day (week 1) 300 mg/day (after week 1)	WVS 1490 (Laitan® 100)	Pretreatment of patients with benzodiazepines was tapered off over 2 weeks. Kava was superior to placebo on HAMA (p=0.01) and subjective well-being scale (p=0.002). Study confirms anxiolytic effects and good tolerance of kava, and shows that further symptom reduction is possible after changeover from benzodiazepine treatment.
Singh <i>et al.</i> , 1998	Nonclinical levels of daily stress and anxiety	R, DB, PC, PG n=60	4 weeks	400 mg/day (200 mg 2x/day)	Kavatrof®	Significantly (p<0.0001) decreased daily stress due to interpersonal problems, personal competency, cognitive stressors, environmental hassles, and the sum of these varied stressors. Significantly (p<0.0001) decreased anxiety due to environmental, psychological, and personal circumstances. Significance occurred after one week of treatment with continual decline for subsequent weeks of trial, with no side effects reported.
Volz and Kieser, 1997	Anxiety and agitation caused by unspecified mental disorder	R, DB, PC, MC n=101	25 weeks	100 mg 3x/day (3 x 70 mg of kavalactones per day)	WVS 1490 (Laitan® 100)	Significantly (p=0.02) reduced somatic and mental anxiety from eighth week on. Long-term treatment showed greater efficacy (p< 0.001 at week 24) than short-term treatment. Kava was well tolerated; adverse effects were rare; there were no withdrawal symptoms.
Lehmann <i>et al.</i> , 1996	Anxiety, tension, and excitedness of nonmental origin	R, DB, PC n=58	4 weeks	100 mg 3x/day (3 x 70 mg of kavalactones per day)	WVS 1490 (Laitan® 100)	Showed anxiolytic efficacy and significantly (p< 0.02) reduced total anxiety after one week of treatment. Efficacy increased over subsequent weeks. Did not produce any adverse reactions.
Woelk <i>et al.</i> , 1993	Anxiety, tension, agitation of nonpsychotic origin	R, DB, MC, CC n=172	6 weeks	100 mg 3x/day (3 x 70 mg of kavalactones per day)	WVS 1490 (Laitan® 100)	Showed equal anxiolytic efficacy as the benzodiazepines (oxazepam and bromazepam). Authors concluded WVS 1490 should be included in the therapeutic possibilities to consider in conditions of anxiety, tension, and agitation of nonpsychotic origin.
Warnecke, 1991	Anxiety and depression associated with menopause and post-menopause	R, DB, PC n=40	8 weeks	100 mg 3x/day (3 x 70 mg of kavalactones per day)	WVS 1490 (Laitan® 100)	Significantly reduced HAMA overall score of anxiety by an average of 50% by first week, with a continual reduction through week 4 (p<0.001). Therapeutic index for use-risk evaluation was comparable to placebo.
Kinzler <i>et al.</i> , 1991	Anxiety syndrome of nonpsychotic origin	R, DB, PC n=58	4 weeks	100 mg 3x/day (3 x 70 mg of kavalactones per day)	WVS 1490 (Laitan® 100)	Significantly reduced anxiety symptoms after one week of treatment, and difference between groups increased over course of study. At each checkpoint (7, 14, and 28 days) the treatment group vs. placebo had significantly lowered HAMA scores (p<0.01). Kava caused no adverse experiences.

Mental Function

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Herberg, 1996	Reaction time and safety performance	PC, CO, Cm n=18	14 days	400 mg (120 kavalactone) tablet 2x daily of kava extract alone; bromazepam alone (2 x 4.5 mg/day); kava and bromazepam combined	GITLY kava extract or bromazepam	Performance was impaired after treatment with bromazepam and the combination, but remained at the baseline level after treatment with the kava extract. The least impairment of well-being occurred with kava and the greatest with the combination.

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.

Clinical Studies on Kava (*Piper methysticum* G. Forst.) (cont.)

Mental Function (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Heinze <i>et al.</i> , 1994	Behavior, mental performance	DB, R, CO, Cm n=12 young healthy males, 24–37 years	5 days	200 mg 3x/day (6 x 70 mg kavalactones per day)	WS 1490 (Laitan® 100) vs. oxazepam	Kava did not alter behavior in psychometric tests, as did oxazepam. May slightly enhance mental performance associated with focal attention and processing capacity.
Munte <i>et al.</i> , 1993	Behavior, mental performance	DB, CO, Cm n=35 healthy volunteers 24–37 years	5 days	600 mg/day (200 mg 3x/day); oxazepam (10 mg/day before testing and 75 mg on morning of study); or placebo	WS 1490 (Laitan® 100) vs. oxazepam vs. placebo	Study showed nonsignificant trend toward improved cognitive function with kava. Suggests enhanced memory performance under kava. No adverse effects reported. Oxazepam produced significant decrease in quality and speed of response.
Russell <i>et al.</i> , 1987	Reaction time	Cm n=18	6 days	250 ml/day or 500 ml/day	Cold macerate of 30 g root powder	No effect on reaction time or errors with traditional or excess dosages. Consumption did not alter speed of activation of verbal information in long-term memory or reaction to warning signal.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Connor <i>et al.</i> , 2001	Safety profile	R, DB, PC n=35 adults with a 1+ month history of generalized anxiety disorder and HAMA score >16 (31–75 years of age)	6 weeks: Week 1: placebo only; Weeks 2–5: kava or placebo Week 6: No treatment, no placebo	Week 2: 140 mg kavalactones/day or placebo Weeks 3–5: 280 mg kavalactones/day or placebo	KavaPure® (standardized to 70 mg kavalactones)	No statistically significant differences were seen between kava and placebo groups for blood or urine studies, ECG assessments, blood pressure, heart rate, sexual function, or incidence of adverse events. No withdrawal symptoms were observed 1 week after abrupt cessation of treatment. Authors conclude kava was well-tolerated even though dosage used was higher than used in most other studies, but further studies of long term kava use are needed.
Watkins <i>et al.</i> , 2001	Vagal cardiac control measured by baroreflex control of heart rate (BRC) and respiratory sinus arrhythmia (RSA)	P, DB, PC n=13 adults with a 1+ month history of generalized anxiety disorder and HAMA score >16 (35–74 years of age)	4 weeks, with assessment 1 day prior to and 4 weeks after beginning treatment	280 mg kava/day or placebo	KavaPure® (standardized to 30% kavalactones)	Kava group showed statistically significantly improved BRC vs placebo group (p<0.05). Degree of BRC improvement correlated significantly with clinical improvement (p<0.05). No change in RSA was observed in either group.
Emser and Bartylla, 1991	Sleep	PC, CO n=12 healthy people 20–31 years	4 days	150 mg/day, 50 mg 3x/day; 300mg/day, 100 mg 3x/day; or placebo	WS 1490 (Laitan®)	Kava favorably influenced sleep. Increased sleep spindle densities and duration of slow wave (deep) sleep. No effects on duration of REM sleep. Tended to decrease sleep stage 1 (falling asleep) and sleep latency (waking stage).
Warnecke <i>et al.</i> , 1990	Peri-menopausal symptoms	R, DB, PC n=20	12 weeks	One 150 mg tablet kava extract (30 mg kavalactones) 2x daily for 4 weeks, followed by 1 tablet, 1x daily starting week 5	Kavosporal®	After 4 weeks, the kava group demonstrated a highly significant (p=0.001) reduction in peri-menopausal symptoms. At 12 weeks, statistical sampling was not possible due to a dropout in the number of placebo-group patients.

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.