Preface

Sales of herbal products have increased dramatically over the past five years. Unfortunately, the knowledge base devoted to the adverse effects of these products has not grown in proportion to their increased usage. Data of questionable accuracy, often designed to sell products rather than to provide objective information, can be found in the print and electronic media, most notably on the Internet. Even in medical journals, misleading information about the beneficial and adverse effects of herbs can be found.

Toxicology and Clinical Pharmacology of Herbal Products is designed to provide medical examiners, toxicologists, and health care providers with an objective review of the available information on the pharmacology and toxicology of commonly used herbs. Clinical and pathological findings from case reports of herbal adverse effects are described in detail. Sections on the relevant pharmacokinetics, chemical analysis, and analysis of biofluids are unique to this volume, and will be of use to pathologists and forensic scientists, as well as to clinicians. Animal, human, and in vitro data are presented on the known pharmacologic and toxicologic effects of each herb, arranged by organ, organ system, or therapeutic/toxicologic effect. A good deal of pharmacology and therapeutics information is included in this section, not only because toxicology is an extension of pharmacology, but also to make the book useful for a wide variety of applications by professionals with various interests. Adverse effects noted in clinical trials are noted in this section as well. At the end of the book, a summary table lists herbal toxicities by affected organ, provides a list of herbs involved in drug interactions, and indicates the type of data supporting the reported toxicities.

Each herbal monograph begins with a discussion of the herb's uses, products, and the dosage forms available. This information, in conjuction with color photographs[1] of some of the most popular products, can be of assistance in those situations where the identity of an herbal product is in question.

A chapter on the legal aspects of herbal products provides an overview of the regulation of herbal products in the US and abroad. In addition, each herbal monograph reviews the herb's status internationally, including approved uses.

The incidence of adverse effects associated with the use of herbal products is unknown, and may be underreported. Without a foundation of knowledge upon which to inquire whether an herbal product might be the cause of a given finding, further exploration of the possibility of an herb-induced toxicity might not be undertaken. Even if an herbal product is suspected of causing an adverse outcome, without information about similar cases, toxicological analysis of biofluids, or the pharmacologic or toxicologic effects of the herb, further investigation might prove difficult or impossible. *Toxicology and Clinical Pharmacology of Herbal Products* is designed to provide the necessary knowledge base upon which such investigations may efficaciously proceed.

Melanie Johns Cupp

[1]I want to acknowledge Mark Branciaroli of Elkins, WV for producing the photographs of the herbal products.

Chapter 2

Kava

Shawn Reeder and Melanie Johns Cupp

Piper methysticum, kava-kava, awa, kew, tonga (Anonymous, 1996), kawa, yaqona, sakau (Norton and Ruze, 1994), ava, ava pepper, intoxicating pepper (Heiligenstein and Guenther, 1998)

2.1 History and Traditional Uses

Kava is a term used to describe both *Piper methysticum* and the preparation made from its dried rhizome and root (Anonymous, 1996). This South Pacific plant is a robust, branching, perennial shrub with heart-shaped, green, pointed leaves (Singh, 1992) that grow up to 28 cm long and flower spikes that grow up to 9 cm long (Anonymous, 1996). The shrub grows best in warm, humid conditions with lots of sunlight, at altitudes of 150–300 m above sea level (Singh, 1992), where it forms dense thickets (Norton and Ruze, 1994). Kava reproduces vegetatively, without fruit or seeds, usually under cultivation (Norton and Ruze, 1994). There are reports of up to 72 varieties of the kava plant which differ in appearance, and chemical analysis has shown differences in their composition as well which may lead to differences in physiologic activity (Singh, 1992). Kava has been described in the European literature since the early 1600s when it was taken there by the Dutch explorers LeMaire and Schouten, who had acquired it while seeking new passages across the Pacific (Norton and Ruze, 1994). Captain James Cook was the first to describe the use of kava during the religious and cultural ceremonies of the people of the South Sea Islands, where it was, and still is, prepared as a beverage and consumed for its intoxicating, calming effects that promote sociability (Norton and Ruze, 1994). Thus, kava is used for the purposes that Western society uses alcohol,

From Forensic Science: *Toxicology and Clinical Pharmacology of Herbal Products*
Edited by: M. J. Cupp © Humana Press Inc., Totowa, New Jersey

the Native American populations use peyote, and the people of the Middle or Far East use opium (Singh, 1992). Events typically accompanied by kava ceremonies included weddings, funerals, births, religious occasions, seasonal feasts, reconciliations, welcoming of royalty or other guests, and the exchange of gifts (Norton and Ruze, 1994). Women and commoners seldom participated in these ceremonies because that was viewed as unacceptable; however, some cultures did permit use by commoners to relax after a hard day's work (Norton and Ruze, 1994). The beverage was traditionally made by mixing grated, crushed, or chewed fresh or dried root with cool water or coconut milk and then straining the mixture through plant fibers to isolate the liquid, which was consumed (Norton and Ruze, 1994). Today the beverage is most often prepared by crushing dried roots with a large mortar and pestle, then straining the mixture in the traditional way or through cotton cloth (Norton and Ruze, 1994). Other folk uses of kava have included treatment of headaches, colds, rheumatism, sexually transmitted diseases, and inflammation of the uterus (Anonymous, 1996). It has also been used as a sedative, aphrodisiac, urinary antiseptic (Heiligenstein and Guenther, 1998), wound healing agent, and a treatment for asthma (Anonymous, 1996). Several substances extracted from the roots were also used briefly in Europe as diuretics (Norton and Ruze, 1994).

2.2 Current Promoted Uses

Kava is currently promoted for relief of anxiety and stress.

2.3 Products Available

Kava is available from a variety of manufacturers in most health food stores under a variety of names. Kavatrol® is a popular brand found in retail outlets in the United States. Kava is marketed in Europe under a variety of names including Laitan® or Kavasporal® in Germany, Potter's antigian tablets in the United Kingdom, Viocava® in Switzerland, and Mosaro® in Austria (Schelosky et al., 1995).

2.4 Pharmacologic/Toxicologic Effects

2.4.1 Neurologic Effects

The neurologic effects of kava are attributed to a group of substituted dihydropyrones called kava lactones (Anonymous, 1996). The main bioactive constituents include yangonin, desmethoxyyangonin, 11-methoxyyangonin, kavain (kawain), dihydrokavain, methysticin, dihydromethysticin, and 5,6-dehydromethysticin (Keller and Klohs, 1963). It is believed that the components present in the lipid-soluble kava extract, or kava resin, are responsible for

the central nervous system (CNS) activities of kava including sedation, hypnosis, analgesia, and muscle relaxation (Jamieson et al., 1989). Aqueous kava extract was not active orally in mice or rats.

A randomized 25-wk placebo-controlled study by Volz and Kieser showed a significant benefit from the use of kava-kava extract WS 1490 over placebo in treating anxiety disorders of nonpsychotic origin. One hundred one patients suffering from agoraphobia, specific phobia, generalized anxiety disorder, or adjustment disorder with anxiety—as per the Diagnostic and Statistical Manual of Mental Disorders, Third edition, revised (DSM-III-R)—were randomized to placebo or WS 1490 containing 90–100 mg dry extract per capsule three times daily. The main outcome criterion, the patients' score on the Hamilton Anxiety Scale (HAMA), was significantly better ($p<0.001$) for the WS 1490 patients compared to placebo at 24 wk. Few adverse effects were judged to be related or possibly related to kava administration. Two patients in the WS 1490 group experienced stomach upset, two experienced vertigo, and one experienced vertigo and palpitations. These results support use of kava as an alternative to antidepressants and benzodiazepines (Volz and Kieser, 1997). Another study compared the cognitive effects of this same kava extract at a dose of 200 mg three times daily for 5 d to oxazepam 15 mg, followed by 75 mg on the experimental day (Heinze et al., 1994). The results suggest that kava is less likely to affect cognitive function than oxazepam, but the oxazepam dosing regimen used was not typical of that seen in practice. Nevertheless, kava is purported to promote relaxation and sleep without dampening alertness, causing heavy sedation, or causing a "hangover" effect the morning after consumption (Anonymous, 1998). The limbic structures of the brain might represent the site of action of kava, explaining its ability to promote relaxation and sleep without cognitive effects (Jussofie et al., 1994).

The mechanism of the anxiolytic effect of kava is unclear. Studies of kava's effects in vitro, in vivo, and ex vivo show conflicting results in regard to kava's effects on benzodiazepine or γ-aminobutyric acid (GABA) receptors (Davies et al., 1992; Jussofie et al., 1994; Heiligenstein and Guenther, 1998). This disparity may be explained by differences in GABA receptor subtypes among the different regions of the brain studied (Jussofie et al., 1994). It is thought that kavapyrones elicit a tranquilizing effect by enhancing GABA binding in the amygdala, but do not act directly as agonists at GABA receptors (Jussofie et al., 1994).

One study has suggested that a nonstereoselective inhibition of [^{3}H]noradrenaline uptake may be responsible for, or at least contribute to, kava's anxiolytic effect (Seitz et al., 1997). This study tested the effects of naturally occurring (+)-kavain, (+)-methysticin, and a synthetic racemic mixture of kavain on synaptosomes from the cerebral cortex and hippocampus of

rat brain. Both forms of kavain inhibited [^{3}H]noradrenaline uptake more than methysticin, but the concentrations necessary to achieve this effect were about 10 times higher than those in mouse brains after a dose of kavain high enough to cause significant sedation. This indicates that inhibition of noradrenaline uptake is probably only part of the psychotropic effects of kava. No effects were seen on the uptake of [^{3}H]serotonin. A subsequent study (Baum et al., 1998) in rats showed that (+)-kavain and other kavapyrones affect serotonin levels in the mesolimbic area. The authors postulated that this effect could explain kava's hypnotic action. Dopamine levels in the nucleus accumbens were decreased by yangonin and low-dose (+)-kavain, but were increased by higher doses of (+)-kavain and desmethoxyyangonin. The investigators attributed kava's anxiolytic and euphoric effects to its action on mesolimbic dopaminergic pathways.

A study conducted in Germany indicates that kava may have neuroprotective properties primarily due to its constituents methysticum and dihydromethysticum (Backhauβ and Krieglstein, 1992). The investigators studied the effects of kava extract WS 1490 and the individual pyrones kavain, dihydrokavain, methysticin, dihydromethysticin, and yangonin on the size of infarction in mouse brains. The extract as well as the individual pyrones methysticin and dihydromethysticin showed significant reductions in infarct area similar to those produced by memantine, an anticonvulsive agent known to have neuroprotective qualities (Backhauβ and Krieglstein, 1992).

Kava lactones are also centrally acting skeletal muscle relaxants (Tyler et al., 1981). A study by Kretzschmar et al. compared the antagonistic effects of kavain, dihydrokavain, methysticin, and dihydromethysticin to those of mephenesin and phenobarbital in preventing convulsions and death caused by strychnine. All the kava pyrones showed an antagonistic effect, with methysticin being the most potent; however, kavain and dihydrokavain doses required to produce an effect approached the toxic range (Kretzschmar et al., 1970). In contrast to mephenesin and phenobarbital, all the pyrones tested protected against strychnine at doses up to 5 mg/kg without causing impairment of motor function.

Kava also produces analgesic effects that appear to be mediated through a nonopiate pathway. A study conducted by Jamieson and Duffield compared the activity of an aqueous and a lipid extract of kava as well as eight purified pyrones on two tests for antinociception in mice. Both the aqueous and lipid extracts were effective analgesics, as were four of the eight purified pyrones (lactones): methysticin, dihydromethysticin, kavain, and dihydrokavain (Jamieson and Duffield 1990a). In hopes of discovering the mechanism of analgesia, the investigators attempted to antagonize the effects of kava with naloxone, a known inhibitor

of opiate-mediated pathways of analgesia. Naloxone failed to inhibit kava's effects at doses high enough to inhibit the action of morphine, indicating that kava works through a nonopiate pathway to produce analgesia.

In humans, kava is reported to produce a mild euphoria characterized by happiness, fluent and lively speech, and increased sensibility to sounds (Anonymous, 1996). It has also been reported to cause visual changes such as reduced near-point accommodation and convergence, increase in pupil diameter, and oculomotor balance disturbances (Garner and Klinger, 1985). It might even have an antipyretic effect (Tyler et al., 1981). Although kava is a centrally acting agent, it is unclear if tolerance and physical dependence occur with usual oral doses of commercially available kava products (Duffield and Jamieson, 1991). Its effects on the peripheral nervous system are limited to a local anesthetic effect, resulting in numbness in the mouth if kava is chewed (Anonymous, 1996). Lipid-soluble kava extract, or resin, is also capable of causing anesthesia of the oral mucosa, while the water-soluble fraction is not (Jamieson et al., 1989).

2.4.2 Dermatological Effects

There have been many reports of skin disturbances associated with the use of kava that date as far back as the 1700s (Norton and Ruze, 1994). Chronic ingestion of kava may cause a temporary yellowing of the skin, hair, and nails (Blumenthal, 1997). Two yellow pigments, flavokawains A and B, have been isolated from the kava plant (Keller and Klohs, 1963) and may be responsible for this discoloration (Anonymous, 1996). Chronic ingestion may also lead to a temporary condition known as kava dermopathy (Norton and Ruze, 1994) or kawaism, characterized by dry, flaking, discolored skin and reddened eyes which is reversible with discontinuation (Jappe et al., 1998). In the early 19th century, Peter Corney, a lieutenant on a fur-trading vessel, described this phenomenon in great detail as it applied to the use of this side effect in treating other skin disturbances. "When a man first commences taking it, he begins to break out in scales about the head, and it makes the eyes very sore and red, then the neck and breasts, working downwards, till it approaches the feet, when the dose is reduced. At this time the body is covered all over with white scruff, or scale, resembling the dry scurvy. These scales drop off in the order of their formation, from the head, neck, and body, and finally leave a beautiful, smooth, clear skin, and the frame clear of all disease" (Norton and Ruze, 1996). The exact mechanism for this dermopathy is unknown but it has been speculated that kava may interfere with cholesterol metabolism, leading to a reversible, acquired ichthyosis similar to that seen with the use of lipid lowering agents such as triparanol (Norton and Ruze, 1996). Skin biopsies of two recent cases associated with use of the com-

mercially available product have revealed lymphocytic attacks on sebaceous glands, with subsequent destruction and necrosis caused by CD8+ cells (*see* Section 2.5) (Jappe et al., 1998). Yet another theory involves interference with B vitamin metabolism or action (Mathews et al., 1988).

2.4.3 Musculoskeletal Effects

As mentioned in Section 2.4.1, kava is a centrally acting skeletal muscle relaxant. The kava lactones kavain, dihydrokavain, methysticin, and dihydromethysticin isolated from kava rootstock were shown to antagonize strychnine-induced convulsions in mice (Kretzschmar et al., 1970).

2.4.4 Antimicrobial Activity

Kava has been used traditionally as an antibacterial in the treatment of urinary tract infections (Locher et al., 1995); however, no clinical trials have established that it is truly effective. Kava extracts were not able to inhibit growth of *Candida*, *Pseudomonas*, *E. coli*, *Streptococcus pyogenes*, or *Staphylococcus aureus* (Locher et al., 1995).

2.4.5 Hepatotoxicity

See Section 2.6.

2.4.6 Antiplatelet Effects

Racemic kavain, a component of kava, has been shown to have antiplatelet effects, presumably due to inhibition of cyclooxygenase, and thus inhibition of thromboxane synthesis (Gleitz et al., 1997). Antiplatelet effects have not been observed in vivo.

2.5 Case Reports of Toxicity Due to Commercially Available Products

Kava dermatopathy in association with traditional use of kava is well described in the literature (Norton and Ruze, 1994). In addition, two cases of dermopathy have recently been associated with commercially available kava products (Jappe et al., 1998). A 70-yr-old man who had been using kava as an antidepressant for 2–3 wk experienced itching, and later erythematous, infiltrated plaques on his chest, back, and face after several hours of sun exposure. Skin biopsy revealed CD8 lymphocytic infiltration with destruction of the sebaceous glands and lower infundibula. A 52-yr-old woman presented with papules and plaques on her face, chest, back, and arms after taking a kava extract for 3 wk. Skin biopsy revealed an infiltrate in the reticular dermis with disruption and necrosis of the sebaceous gland lobules. A kava extract patch test was strongly positive after 24 h.

There have also been four cases of extrapyramidal effects associated with kava use (Schelosky et al., 1995). A 28-yr-old man with a history of antipsychotic-induced extrapyramidal effects experienced torticollis and oculogyric crisis 90 min after a single 100-mg dose of Laitan® (kava extract). These effects resolved spontaneously after 40 min. A 22-yr-old woman experienced oral and lingual dyskinesia, painful twisting movements of the trunk, and torticollis 4 h after a 100 mg dose of the same product taken by the previously described male. The symptoms did not resolve spontaneously, so after 45 min, a 2.5 mg intravenous dose of beperiden was given, with immediate relief. A third patient, a 63-yr-old female, also presented with oral and lingual dyskinesia after taking Kavasporal Forte® (150 mg of kava extract) three times a day for 4 d. A single 5 mg intravenous dose of beperiden was immediately effective. Finally, a 76-yr-old woman experienced worsening of Parkinson's disease symptoms after taking Kavasporal Forte® for 10 d. Improvement was noted 2 d after discontinuation of the product. These extrapyramidal side effects suggest cautious use of kava in the elderly, in patients with Parkinson's disease, and in patients taking antipsychotics.

2.6 Toxicity Associated with Traditional Use by Native Populations

Chronic use of the kava beverage has been associated with a wide range of abnormalities. A study (Mathews et al., 1988) of an Australian Aboriginal community revealed malnutrition and weight loss associated with kava use. Red blood cell volume increased in proportion to kava use, while bilirubin, plasma protein, platelet volume, B-lymphocyte count, and plasma urea were inversely proportional to kava consumption. Although these values were not outside the normal range, it was hypothesized that malnutrition and/or reduced hemoglobin turnover might explain these observations. Other findings included hematuria and difficulty acidifying and concentrating the urine, suggesting an effect on the renal tubules; and increased serum transaminases and increased high-density lipoprotein (HDL) cholesterol, suggesting some effect on the liver. Transaminase elevations were greater in the kava-using Aboriginal community compared to those in a community where alcohol, but not kava, was consumed. This suggests that kava might be more hepatotoxic than alcohol. Shortness of breath and EKG abnormalities (tall P waves) consistent with pulmonary hypertension were seen and are interesting in that like kava, the prescription anorexiants fenfluramine and dexfenfluramine withdrawn from the US market in 1998 were associated with pulmonary hypertension. It was also noted by the authors of this observational study that sudden death in relatively young

men is more common in kava-using Aboriginal communities than in non-using communities.

2.7 Drug Interactions

Alcohol appears to at least add to the hypnotic effect of kava in mice, and was also observed to increase the lethality of kava (Jamieson and Duffield, 1990b). These findings may be of importance because some Australian Aboriginal populations now frequently consume kava with alcohol. Concomitant use of barbiturates, melatonin, and other psychopharmacological agents might potentiate the effects of kava as well (Thorndyke and Rhyne, 1998). The hepatotoxic potential of kava (Mathews et al., 1988) also raises concerns about concomitant alcohol use.

Although a Web site (Anonymous, 1998) promoting a kava product states that it is safe to use kava in combination with benzodiazepines, a case report (Almeida and Grimsley, 1996) suggests otherwise. The combination of kava and alprazolam was believed to be responsible for hospitalizing a 54-yr-old man. The patient's semicomatose (lethargic and disoriented) state improved after several hours. He had been taking an undisclosed brand of kava purchased in a health food store in combination with alprazolam for 3 d. Other medications taken included cimetidine and terazocin.

2.8 Pharmacokinetics/Toxicokinetics

2.8.1 Absorption

In mice and rats, the aqueous kava extract is inactive when administered orally (Jamieson et al., 1989).

2.8.2 Metabolism/Elimination

Several kava lactones have been identified in human urine samples after ingestion of a kava beverage prepared from a commercial 450-g sample of *Piper methysticin* extracted with 3 L of room temperature water (Duffield et al., 1989). Observed metabolic transformations include reduction of the 3,4 double bond and/or demethylation of the 4-methoxyl group on the α-pyrone ring system. Demethylation of the 12-methoxy substituent in yangonin and hydroxylation at carbon 12 of desmethoxyyangonin have also been observed. Chemical structures for these kava components and metabolites can be seen in the cited reference.

2.9 Analysis of Biofluids

Methane chemical ionization (CI) gas chromatography–mass spectrometry (GC–MS) and high-performance liquid chromatography (HPLC) (diode

array detector) have been utilized to identify kava metabolites in human urine (Duffield et al., 1989). A detailed description of these analyses can be found in the cited reference.

2.10 Chemical Analysis

Duffield and colleagues performed methane CI GC–MS on three kava extracts obtained from a Samoan root piece, a dry powdered sample from Sydney, and ground plant from the United States. Similar results were obtained from all samples with the major components kavain, dihydrokavain, dihydromethysticin, yangonin, and desmethoxyyangonin being easily identifiable (Duffield et al., 1986). Several trace components were also identified. A detailed description of these analyses can be found in the cited reference. Additional information pertaining to GC–MS analysis of kava is available (Duve, 1981; Duffield and Lidgard 1986; Duffield et al., 1986; Cheng et al., 1988).

2.11 Regulatory Status

Kava is currently sold as a dietary supplement in the United States (Blumenthal, 1997). It has been approved as a nonprescription drug in Germany and is classified as a drug in Sweden.

References

Almedia JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. Ann Intern Med 1996;125:940–1.

Anonymous. Kava-kava. In: The review of natural products. St. Louis, MO: Facts and Comparisons, 1996.

Anonymous. Topic of the month. Available from: URL: www.ownhealth.com/Topic.html. Accessed 1998 Oct. 29.

Backhauβ C, Krieglstein J. Extract of kava (*Piper methysticum*) and its methysticin constituents protect brain tissue against ischemic damage in rodents. Eur J Pharmacol 1992;215:265–9.

Baum SS, Hill R, Rommelspacher H. Effect of kava extract and individual kavapyrones on neurotransmitter levels in the nucleus accumbens of rats. Prog Neuropsychopharmacol Biol Psychiatry 1998;22:1105–20.

Blumenthal M. Popular Herbs in the U.S. Market. Kava-kava rhizome. American Botanical Council. Austin, TX, 1997.

Cheng D, Lidgard RO, Duffield PH, Duffield AM, Brophy JJ. Identification by methane chemical ionization gas chromatography/ mass spectrometry of the products obtained by steam distillation and aqueous acid extraction of commercial *Piper methysticum*. Biomed Environ Mass Spectrom 1988;17:371–6.

Davies LP, Drew CA, Duffield P, Johnston GAR, Jamieson DD. Kava pyrones and resin: studies on $GABA_A$, $GABA_B$, and benzodiazepine binding sites in rodent brain. Pharmacol Toxicol 1992;71:120–6.

Duffield AM, Jamieson DD, Lidgard RO, Duffield PH, Bourne DJ. Identification of some human urinary metabolites of the intoxicating beverage kava. J Chromatogr 1989;475:273–81.

Duffield PH, Jamieson D. Development of tolerance to kava in mice. Clin Exp Pharmacol Physiol 1991;18:571–78.

Duffield AM, Lidgard RO. Analysis of kava resin by gas chromatography and electron impact and methane negative ion chemical ionization mass spectrometry. Biomed Environ Mass Spectrometry 1986;13:621–6.

Duffield AM, Lidgard RO, Low GKC. Analysis of the constituents of Piper methysticum by gas chromatography methane chemical ionization mass spectrometry. Biomed Environ Mass Spectrometry 1986;13:305–13.

Duve RN. Gas–liquid chromatographic determination of major contituents of *Piper methysticum*. Analyst 1981;106:160–5.

Garner LF, Klinger JD. Some visual effects caused by the beverage kava. J Ethnopharamacol 1985;13:307–11.

Gleitz J, Beile A, Wilkens P, Ameri A, Peters T. Antithrombotic action of kava pyrone (+)-kavain prepared from *Piper methysticum* on human platelets. Planta Med 1997;63:27–30.

Heiligenstein E, Guenther G. Over-the counter psychotropics: a review of melatonin, St. John's wort, valerian, and kava-kava. J Am Coll Health 1998;46:271–6.

Heinze HJ, Munthe TF, Steitz J, Matzke M. Pharmacopsychological effects of oxazepam and kava-extract in a visual search paradigm assessed with event-related potentials. Pharmacopsychiatry 1994;27:224–30.

Jamieson DD, Duffield PH. The antinociceptive actions of kava components in mice. Clin Exp Pharmacol Physiol 1990a;17:495–508.

Jamieson DD, Duffield PH. Positive interaction of ethanol and kava resin in mice. Clin Exp Pharmacol Physiol 1990b;17:509–14.

Jamieson DD, Duffield PH, Cheng D, Duffield AM. Comparison of the central nervous system activity of the aqueous and lipid extract of kava (*Piper methysticum*). Arch Int Pharmacodyn 1989;301:66–80.

Jappe U, Franke I, Reinhold D, Gollnick HPM. Sebotropic drug interaction resulting from kava-kava extract therapy: a new entity? J Am Acad Dermatol 1998;38:104–6.

Jussofie A, Schmiz A, Hiemke C. Kavapyrone enriched extract from *Piper methysticum* as modulator of the GABA binding site in different regions of rat brain. Psychopharmacology 1994;116:469–74.

Keller F, Klohs MW. A review of the chemistry and pharmacology of the constituents of *Piper methysticum*. Lloydia 1963;26:1–15.

Kretzschmar R, Meyer HJ, Teschendorf HJ. Strychnine antagonistic potency of pyrone compounds of the kavaroot (*Piper methysticum* Forst). Experientia 1970;26:283–4.

Locher CP, Burch MT, Mower HF, Berestecky J, Davis H, Van Pool B, et al. Antimicrobial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants. J Ethnopharmacol 1995;49:23–32.

Mathews JD, Riley MD, Fejo L, Munoz E, Milns NR, Gardner ID, et al. Effects of the heavy usage of kava on physical health: summary of a pilot survey in an Aboriginal community. Med J Aust 1988;148:548–55.

Norton S, Ruze P. Kava dermopathy. J Am Acad Dermatol 1994;31:89–97.
Schelosky L, Raffauf C, Jendroska K, Poewe W. Kava and dopamine antagonism. J Neurol Nerosurg Psychiatry 1995;58:639–40.
Seitz U, Schule A, Gleitz J. [^{3}H]-Monoamine uptake inhibition properties of kava pyrones. Planta Med 1997;63:548–9.
Singh YN. Kava: an overview. J Ethnopharmacol 1992;37:13–45.
Singh YN. Effects of kava on neuromuscular transmission and muscle contractility. J Ethnopharmacol 1983;7:267–76.
Thorndyke A, Rhyne H. Kava. Available from: URL: www.unc.edu/~cebradsh/kava.html. Accessed 1998 Oct. 29.
Tyler VE, Brady LR, Robbers JE. Pharamcognosy, 8th edit., Philadelphia: Lea and Febiger, 1981.
Volz HP, Kieser M. Kava-kava extract WS 1490 versus placebo in anxiety disorders-a randomized placebo-controlled 25–week outpatient trial. Pharmacopsychiatry 1997;30:1–5.