Kava Kava: Gift of the Islands

Gary Piscopo, N.D. (Candidate)

Abstract

Piper methysticum, also known as kava kava, is a highly esteemed medicinal herb that has been at the center of social and ceremonial life in the Pacific islands from before the time of written language. Recent scientific investigation indicates kava can be of value as an anxiolytic, myorelaxant, and analgesic. Unlike other substances used for these purposes, kava has been shown to have minimal negative effect, and possibly a positive effect, on reaction time and cognitive processing. Possible uses as an anticonvulsant, antimycotic, and neuroprotectant have also been described. Although kava has been found to be effective, well tolerated, and non-addictive at therapeutic dosages, potential side-effects can occur when very high doses are taken for extended periods. Use of extracts made from the whole plant have been found to be superior to the use of individual constituents.

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Introduction

Within the realm of phytomedicine, flora that engender a psychoactive effect are historically among the most sought after herbs in the materia medica. Rising interest, both publicly and professionally, in herbs such as Hypericum and Yohimbe illustrates that this ancient inclination continues unabated. As its patterns of cultivation and impact on Pacific Island cultures clearly show, kava is an herb which fits prominently into this group of prized substances. Kava (*Piper methysticum Forst. f.*) is both the name of the herb and the intoxicating beverage prepared from its roots. It is a member of the pepper family Piperaceae, of the order Pieperales in the class Dicotyldonae. The family includes five genera and more than 2000 species of plants growing throughout the tropics, ten members of which have been classically utilized as spices or medicinal substances. These include black pepper (*P. nigrum*), betel (*P. betel*), matico (*P. angustifolium*), and the long peppers (*P. officinarum* and *P. longum*).[1]

Ethnobotany

Kava is a perennial plant indigenous to the tropical Pacific island region (Melanesia, Micronesia, Polynesia) which grows best at altitudes of 150-300 meters above sea level.[2] It is cultivated for the resins found in its root stock, also called the stump, which has often been erroneously referred to as a rhizome by some botanists. The plant is unable to reproduce itself sexually, being the sterile cultivar of its wild ancestor *P. wichmannii*, with which it is frequently confused. Propagation is therefore vegetative and based exclusively on human design.[1] There

Gary Piscopo, N.D. (Candidate- Bastyr University).—Correspondence address: Alpine Valley Natural Health Clinic. 1214 - 5th Street. Wenatchee, WA 98801. Whyterose3@aol.com

are several different varieties of the kava plant classified by the indigenous populations, based mainly upon morphological characteristics. Distinct varieties were used for distinct purposes within the culture. A rare variety, for example, might be used exclusively for ceremonial purposes, whereas a common variety would have more informal uses.[2]

Credit for the first detailed description of kava is usually given to Johann Georg Forster, a botanist on Captain James Cook's second voyage (1772-1775). Forster, who named the plant *Piper methysticum*, or "intoxicating pepper," is also credited with the first description of the kava drinking ceremony.[3] Kava is typically consumed at dusk, before the evening meal, so food will not hinder appreciation of the psychoactive properties. The fresh root, typically harvested in its fourth to sixth year of age, is cleaned thoroughly and cut into pieces. It is then prepared either via mastication ("Tongan method") by virgin members of the community or through pounding or grating ("Fijian method"). Once it has been reduced to pulp, a cold infusion made with water or coconut milk is prepared, the resulting mixture being strained through coconut fronds or palm fibers into coconut shells. One to three "shells" are typically consumed at a sitting, each shell being drained without stopping.[2] Generally, the first result of drinking kava is a local anesthetic and astringent effect on the tongue and inner lining of the mouth, followed by an overall sense of well being and a sharpening of the senses, particularly hearing. A relaxed, pleasant, social attitude generally ensues for up to several hours and often a particularly fitful sleep is described.[4] Half a coconut shell (roughly 100-150 ml, containing approximately 1.0-1.5 g of kava resin) of certain varieties of kava is strong enough to induce sleep within thirty minutes.[1]

Although kava's primary use is its social ceremonial capacity, it also plays an important medicinal role in many indigenous cultures. Some of the conditions treated with kava include gonorrhea, menstrual problems, lactation problems, headache, general weakness, rheumatism, tuberculosis, leprosy, insomnia, asthma, certain skin conditions, and migraine.[1] As a matter of historical record, the use of kava for some of these conditions eventually made its way into the European pharmaceutical codex. Kava was listed in the British Pharmacopoeia as "kava rhizome" in 1914, and in 1950 it appeared in the US Dispensary as a treatment for both gonorrhea ("Gonosan") and nervous disorders ("Neurocardin").[5] While some of the medicinal applications of kava, such as its use in increasing lactation, could be attributed largely to the symbolic properties attributed to it by the Pacific Island culture (in this case, fertility), other uses, such as its effects on fungal skin diseases and sleep disorders, have been borne out by scientific investigation.[1]

Chemical Constituents

The pharmacologically active constituents of *Piper methysticum* are mainly composed of a group of lactonic molecules that can be organized around an arylethylene-alpha-pyrone skeleton.[3] The lactones are typically 4-methoxy-2-pyrones with phenyl or styryl substitutes at the 6- position,[1] and are similar in structure to myristicin, which is found in nutmeg.[6] These kava pyrones, or kava lactones as they are also known, can comprise between 3-20% of the root stock dry weight depending on age of the plant and specific cultivar.[7] The concentration of kava pyrones is generally highest in the lateral roots (15%) and decreases progressively toward the aerial part of the plant (10% in the stump; 5% in the basal stems).[1] Although a small amount of work has been conducted on the water-soluble fraction of the rootstock, the main body of research has been done on the resin, which contains most, if not all, of the active principles.[1]

Fifteen lactones have been isolated from *Piper methysticum*, nine of which have been fully identified. The six compounds

present in the highest concentration in the rootstock are: methysticin, yangonin, dihydromethysticin, kawain, dihydrokavain, and demethoxy-yangonin.[1] The first of these lactones, methysticin (also called kavakin, kawakin, kavatin, or kanakin), was isolated in 1860, followed by yangonin in 1874, and kawain (also known as kavain), and dihydrokawain (also called dihydrokavain) in 1914-1933.[2] Other compounds isolated from *Piper methysticum include* alkaloids (two from the roots and one, pipermethystin, from the leaves), flavokawins, an alcohol, a phytosterol, ketones, and organic acids.[1] Based on the chromatographic and spectrophotometric data available at the time, Shulgin separated the kava isolates into three categories: major (dihydrokawain, kawain, and methysticin), minor (yangonin, dihydromethysticin, desmethoxyyangonin, flavokawin A, pinostrobinchalcone, dihydrotectochrysin, aplinetinchalcone, aplinetin, dihydrooroxylin A), or trace (11-methoxy-nor-yanonin, 11-methoxyyangonin, flavokawin B).[3]

Recent work in the comparative chemistry of various kava plants indicates different cultivars have different mixtures of kava pyrones. Research by Lebot and Lévesque indicated morphological characteristics of the plant are a good indicator of the type, quantity, and composition of its active ingredients.[7] In order to define various cultivar chemotypes, Lebot and Lévesque divided the active ingredients of *Piper methysticum* into major and minor kava lactones. After demonstrating the major kava lactones comprised 96% of the lipid extract, they numbered and used only these constituents to define the chemotypes (1 = desmethoxyyangonin, 2 = dihydrokavain, 3 = yangonin, 4 = kavain, 5 = dihydromethysticin, 6 = methysticin).[3] The chemical composition of each cultivar was then coded by listing the proportion of the six major kava lactones in decreasing order of content (521364, for example, indicates dihydromethysticin was in the highest proportion in the cultivar, followed by dihydrokavain, etc.). Comparison of the chemotypic analysis with the ethnobotanical data demonstrated a strong correlation between traditional use of a cultivar and its chemical composition. Chemotype 256431, the infamous tudei ("two day" because it makes the drinker feel drunk for two days) and most of the P. wichmannii cultivars (chemotype 521634), for example, were largely avoided due to the unpleasant nausea they caused owing to their high proportion of dihydromethysticin and dihydrokavain. Cultivars traditionally used for medicinal and exchange purposes belonged to the chemotype 265431.[7] While there is some cultural variability concerning which cultivars were the most highly prized, generally those with a high percentage of kavain and a low percentage of dihydromethysticin (cultivars beginning with 426, 462, and 246) were the most sought after.[1] It is not clear if this information is currently being taken into account in the commercial preparation of *Piper methysticum* products.

CNS effects

In animal studies, kava pyrones have been shown to have analgesic, sedative, anxiolytic, anticonvulsant, and local anesthetic effects.[1,4] While research concerning kava pyrones' mechanism of action on the central nervous system (CNS) is suggestive, no clear consensus has been reached. Due to the overlap in CNS effects with benzodiazepines, one hypothesis suggests the kava pyrones produce pharmacological effects by potentiation of GABA or benzodiazepine receptors. One study which addressed this issue found little evidence to support this contention. In both *in vitro* and *in vivo* binding studies on rat brains, only weak GABA or benzodiazepine binding activity was observed, neither of which correlated with pharmacological activity.[8]

A more recent study, however, concluded kava pyrones do mediate sedative effects by way of GABA receptor binding. The

authors suggest the previous study might have seen little effect on GABAA binding activity for a number of reasons including: 1) the previous authors looked at areas atypical for kava pyrone effect (frontal cortex and cerebellum) as opposed to the usual target brain centers for its actions (hippocampus, amygdala, and medulla oblongata), 2) only two kava pyrone concentrations (100 µM and 1 mM) were used, and 3) investigators used pure compounds of methysticin, dihydromethysticin, kawain, and dihydrokawain rather than an enriched extract which more closely estimates its pharmacological effect *in vivo*. Other research has revealed synergistic effects in animal studies when kava resin was used as opposed to individual constituents.[9] An extract of 58% kava pyrones and 42% other lipid soluble compounds enhanced binding of [3H] muscimol (a GABA- agonist) in a concentration-dependent manner within target brain centers, with the hippocampus and amygdala showing the highest levels of enhancement. Scatchard analysis revealed the observed effects of kava pyrones were due to an increase in the number of GABAA binding sites rather than to a change in affinity. The authors also observed that the effects of kava pyrones and pentobarbital or pregnane steroid were more than additive.[10]

It has been known for some time that kava pyrones inhibit convulsions caused by strychnine, maximal electroshock, and pentylenetetrazole in animals, and are superior in this capacity to mephenesin, a conventional countermeasure.[11-13] Recent work in this area indicates this property of *Piper methysticum* might be mediated by way of Na+ channel receptor sites, which is a common target of anti-epileptic drugs. In a series of investigations aimed at elucidating kava's anticonvulsant mechanism, the synthetic kava pyrone (+/-) kavain was shown to block both 4-aminopyridine elevated Na+ levels and veratridine elevated Ca^{2+}in rat cerebrocortical synaptosomes. Because the pathways involved in Ca^{2+} homeostasis appeared to be unaffected by (+/-) kavain, the authors suggest it interacts specifically with Na+ channel subtypes and influences Ca^{2+} levels indirectly. They note the anticonvulsive properties of kava pyrones are similar to local anesthetics, especially procaine.[14-16] These studies were consistent with a published report that (+)-methysticin blocked epileptiform activity in hippocampal and entorhinal cortex slices in the rat, possibly by interfering with processes responsible for frequency potentiation.[17] Similar work in guinea pigs analyzing the effects of kava pyrones on field potential changes mediated by omission of Mg^{2+} confirms that voltage dependent calcium channels might be involved in the anticonvulsant effect of *Piper methysticum*. Here, as in other studies,[9] the authors note multiple constituents of *Piper methysticum* have an additive or synergistic effect compared to individual isolates.[18]

Analgesic effects

An investigation comparing an aqueous extract of *Piper methysticum* against a lipid soluble extract was consistent with other studies which showed the main pharmacological effects of kava ingestion, including its antinocioceptive activities, are due to the lipid soluble fraction.[19] In another study, eight purified pyrones from the lipid soluble extract were tested for analgesic activity using the tail immersion and abdominal constriction tests in mice. Kawain, dihydrokawain, methysticin, and dihydromethysticin were found to be very effective in producing analgesia. It was found that dihydrokawain was the most potent of the pyrones, but its activity was transient, while dihydromethysticin was less potent but more prolonged in its action than dihydrokawain. Kawain had only half the potency of dihydrokawain, but a slightly longer effect, while methysticin was very similar to dihydromethysticin in both its potency and length of action. Naloxone, in doses which inhibited morphine-induced analgesia in both

tests, was ineffective in reversing the antinocioceptive activities of the kava extracts, showing that analgesia produced by kava occurs via non-opiate pathways.[20] An earlier study measuring the analgesic effect of dihydrokavain and dihydromethysticin showed a dose of 120 mg/kg of either dihydrokavain or dihydromethysticin was equivalent to 2.5 mg/kg of morphine.[21]

Psychoactive effects

Several studies have investigated the anxiolytic properties of kava. In one randomized, placebo-controlled, double-blind study, two groups of 29 patients were treated for a period of four weeks with the standardized kava extract WS 1490 (100 mg tid), containing 70% kava lactones, or a placebo. The group receiving WS 1490 showed a significant reduction of symptoms after one week of treatment as measured by the Hamilton Anxiety Scale (HAMA) and other secondary scales. The difference in symptomatology continued to increase between the two groups over the course of the study, and no adverse experiences were reported by the medication group.[22] A similar placebo-controlled, double-blind study, also using WS 1490 (100 mg tid), was done on two groups of 20 patients with menopausally-related symptomatology. Again a significant difference in symptomatology was seen in the WS 1490 group after only one week of treatment as measured by the HAMA. Over the eight-week study period, the authors noted a high level of efficacy for the kava extract compared with placebo in addressing neurovegetative and psychosomatic dysfunctions of the peri-menopausal period.[23] A third study, comparing WS 1490 with either oxazepam (15 mg/day) or bromazepam (9 mg/day), found similar improvement in anxiety symptoms for all three medications.[24]

The most recent study involving kava extract was also the first to address both short- and long-term efficacy. One-hundred-and-one outpatients suffering from anxiety of non-psychotic origin were included in a 25-week multi-center, randomized, placebo-controlled, double-blind trial with WS 1490. Unlike the studies mentioned above, significant improvement in symptoms was not noted until the eighth week of the study. The results, as measured by the HAMA and a variety of secondary scales, supported both the short-term and long-term efficacy of WS 1490 as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety disorders. None of the side-effects generally associated with these classes of drugs was observed with the kava extract. The authors also call attention to the fact that, despite widespread use for anxiety disorders, there are very few long-term efficacy data based on placebo-controlled trials for either benzodiazepines or anti-depressants.[25]

Two other studies highlight the observation that, not only does *Piper methysticum* not impair reaction time or the ability to concentrate, but at therapeutic doses it might actually improve performance. In one double-blind study comparing oxazepam (Serax) with WS 1490 on reaction time in event-related potentials (ERPs or scalp-recorded electrical potentials generated by neural activity) in a visual search paradigm, the authors determined a reduction of processing capacity occurred under the influence of oxazepam, while an enhancement of processing capacity occurred under WS 1490.[26] The second study also compared kava extract with oxazepam, this time in a double-blind, cross-over design involving a recognition memory task. Using several parameters, oxazepam was shown to slow reaction time and reduce the number of correct answers while the kava extract was shown to slightly increase word recognition rate and generate a larger ERP difference between old and new words.[27]

Myorelaxant effects

Research in this area is consistent in its agreement that kava pyrones are superlative

muscle-relaxing agents.[29,30] One study concluded dihydrokavain and dihydromethysticin were superior to other agents normally used for this purpose, including propanediol, benzazoles, and benzodiapines.[30] In a study involving mouse phrenic nerve-hemidiaphragm and frog sartorius muscle preparations, it was demonstrated kava pyrones depressed the amplitude of both miniature end plate potentials (mepps) and end plate potentials (epps), but had no effect on the frequency of mepps. These effects were poorly reversed by calcium or neostigmine, suggesting kava pyrones act on the ionic mechanisms that produce skeletal muscle contractions.[31] (+/-) Kavain seems to have a similar effect on relaxing smooth muscle, apparently by raising the extracellular K+ concentration and by blocking K+ channels.[32]

Local anesthetic effects

Of the kava pyrones that produce anesthesia, kavain appears to be the most effective surface anesthesia and is comparable to cocaine in its effects and duration of action.[1] In a study using a preparation of kavain in alcohol, subcutaneous injections produced local anesthesia from several hours up to several days. It was observed, however, that too high a dose induced paralysis in the peripheral nerves. It was therefore concluded that kavain was unsuitable for most instances of local anesthesia.[33]

Cardiovascular effects

Based on its deduced effects on arachidonic acid (AA), ATP, cyclooxygenase, and thromboxane synthase, (+/-) kavain was recently investigated for its anti-thrombotic effect on human platelets. Application of (+/-) kavain five minutes before exogenously applied AA resulted in a dose-dependent decrease in platelet aggregation and ATP release, as well as synthesis of thromboxane A2 and prostaglandin E2. Based on their analysis, the authors concluded the primary target of (+/-) kavain is the inhibition of cyclooxygenase, leading to a suppression of thromboxane A2-induced platelet aggregation.[34] In a study which investigated the extent to which *Piper methysticum* was protective against ischemic brain damage, the effects of WS 1490 were compared to those of memantine, an anticonvulsant with neuroprotective properties. It was found the kava pyrones were capable of reducing infarct area and volume in rat and mouse brains in a manner comparable to memantine. The authors determined this neuroprotective activity was probably mediated by the methysticin constituents of the kava extract.[35]

Antimicrobial Activity

The research concerning *Piper methysticum*'s antimicrobial properties is contradictory and fragmented. Early reports indicated kavain possessed bactericidal properties, especially against gonococcus.[36] However, an observation that large numbers of gram-positive, gram-negative, pathogenic, and non-pathogenic bacteria were found to grow uninhibited in nutrients containing kava pyrones probably indicates they are not bacteriostatic in nature.[2] One source indicates dihydrokavain inhibits the growth of *Aspergillus niger*,[1] and a study of plants used in Polynesian traditional medicine for treatment of infectious diseases maintains that *Piper methysticum* showed some anti-fungal activity.[37]

Other uses

Other empirical uses for kava include its use in the treatment of asthma, its use for facilitating chiropractic adjustments, and its use in the treatment of urogenital disorders. Claims that kava acts as an aphrodisiac, often made by distributors of kava products, runs counter to the observations of indigenous peoples. The Tongans, for example, observe

kava can actually have anaphrodisiac effects.[38] Many of the customs around the preparation and participation in kava ceremonies, such as the injunction that only virgin members of the tribe chew the kava, are aimed at separating sexuality and kava, perhaps in recognition that this combination could be a treacherous brew indeed.[1]

Toxicology

Dermopathy: The most common side-effect of heavy kava consumption over an extended period of time is an ichthyosiform skin rash, known as kava dermopathy or kani kani in Fijian.[2] The onset typically begins in the face and moves in a descending fashion toward the feet, with subsequent desquamation and cracking in a scaly pattern. In addition to the desquamating keratosis, palmar and plantar keratoderma and ocular photosensitivity can also develop.[39] Doses of 300-800 mg per day of dihydromethysticin were sufficient to produce kava dermopathy in a high percentage of patients.[40] The etiology of the condition is unknown, although several hypotheses have been proposed. These include accumulation of kava lactones in the skin, chronic allergic dermatitis, and a reduction of "glandular secretions."[41] One prevalent theory was that the condition was due to a niacin deficiency. This hypothesis was recently tested in a double-blind, placebo-controlled trial of 32 kava drinkers afflicted with kava dermopathy. During the three-week study period, the diet of the medication group was supplemented with 100 mg of nicotinamide daily. The author noted no significant difference between the medication and control groups, and concluded the dermopathy is not caused by niacin deficiency.[39] Kava dermopathy should not be confused with skin conditions that can be the result of acute allergic effects of *Piper methysticum*, which have been reported in the literature.[42]

Potentiation of other substances: It has been reported that kava pyrones have a potentiating effect on barbituric narcosis.[1] Of the kava constituents, dihydromethysticin has the greatest potentiating effect based on studies done with mice.[1] One case of an interaction between kava and alprozolam (Xanax) in a 54-year-old male that resulted in a semicomatose state has also been reported.[43] These effects are not surprising given the observed activity of kava pyrones on GABAA binding sites and, in the case of barbituric narcosis, its ability to potentiate the binding of pentobarbital to these sites.[10]

The potentiating effects of kava on alcohol are less clear. One double-blind, placebo-controlled study looked to establish whether there were any adverse effects in combining kava extract WS 1490 (100 mg tid) with ethyl alcohol (0.05% blood alcohol concentration) in two groups of 20 human volunteers. The results showed no negative multiplicative effects of this combination over the eight-day period of the study.[44] An earlier study with mice, however, found an interaction of considerable magnitude existed between ethanol and kava resin. The authors found a ten-fold prolongation of mean sleeping time of mice treated with kava extract when alcohol was added, and a three-fold prolongation of sleep time when subhypnotic doses of kava resin were administered with hypnotic doses of ethanol. Kava and ethanol also increased each other's toxicity. The authors note the potentiation between kava and ethanol occurred in a dose-dependent manner,[45] which could partially explain the lack of multiplicative effects in the first study.

Extrapyramidal side-effects: There has been one report of four patients who developed clinical signs suggestive of central dopaminergic antagonism after exposure to two kava preparations: Laitan (100 mg kava extract, 70% kava lactones) and Kavasporal forte (150 mg kava extract). In the cases involving Laitan, the symptomatology occurred soon after the first dose. In the cases involving Kavasporal forte, onset of symptoms

occurred after doses of 150 mg tid for four days and 150 mg bid for 10 days. The authors cite clinical findings of the beneficial effects of kava on schizophrenia to support their claim of dopaminergic antagonism.[46]

Abuse: Taken at moderate doses, kava is generally safe, effective, and non-addictive.[47] Like any herb that produces a psychoactive effect, however, the potential for abuse can arise, especially in circumstances where there is a lack of ceremonial or social constraints to control its use. A case in point was the introduction of kava in the early 1980's to the aboriginal (Yolngu) people of Arnheim Land in the Northern Territory of Australia. Learning of the herb from Pacific Island church workers, kava was imported in hopes that it would act as a less harmful alcohol substitute. By 1985, it had reportedly reached the proportions of a "social epidemic."[48] Quantities as large as 440 grams per week (2200 grams of fresh weight or 40-70 grams of resin) were being consumed by up to 80% of the adult men and 20% of adult women.[1] To put this intake in context, this amount of kava consumption would require well over a gallon of kava per day,[7] an amount up to a hundred times the quantity normally imbibed in the Pacific Islands.[48] One study arising from this situation attempted to establish that heavy consumption of kava in itself was harmful and produced serious deleterious side-effects. They found very heavy users of kava were 20% underweight, gamma-glutamyl transferase enzymes were increased, and albumin, urea, and bilirubin levels were decreased.[49] This research, however, was found to be flawed for several reasons. First, the study has been attacked as being politically motivated by commercial alcohol interests to pressure a government ban of kava.[2] Second, their conclusion that kava was harmful failed to take into account dosage levels or the drinker's psychological state and cultural setting.[1] Finally, the study did not control for the fact that many of the subjects were probably also heavy alcohol and tobacco abusers, nor did they address the fact that the health of aborigines is generally worse than that of other groups in Australia.[1] However, this does not negate the observation that potential for abuse of kava does exist, and that it may have harmful side-effects if consumed at levels described above.

Other, more sensational claims of negative effects from kava have not been substantiated in the literature. One report that kava resulted in a death on the island of Tanna in 1988 was found to be groundless, as was a claim that kava is addictive.[1] Another recent report concerned a product call "fX" that caused dizziness, nausea, dyspnea, and respiratory arrest in 50 people attending a Los Angeles New Year's Eve "rave" concert in 1997. Contrary to police claims that the main offending agent was kava, an analysis of the product revealed it contained two substances: a potentially toxic chemical (1,4 butanediol) and caffeine. Not even trace amounts of kava were detected.[50]

Conclusion

The dosage of kava needed for therapeutic purposes depends on the percentage of kava pyrones in the extract. A kava extract containing 70% kava pyrones (yielding 70 mg pyrones in 100 mg capsule) was the most often used extract in the studies noted above. An oral dose of a preparation yielding 50-70 mg kava pyrones three times per day is the usual dose for anxiolytic activity. Significant reduction of symptoms can take up to eight weeks. A single oral dose yielding 150-210 mg pyrones can be taken before bed to promote relaxation and sleep in cases of mild insomnia.[7]

Studies with mice confirm minimal tolerance to extracts of kava resin occurs at moderate doses.[51] The German Commission E monograph on kava indicates it is contraindicated in pregnancy, nursing, and endogenous depression.[2] Given the evidence presented above, it would be wise to avoid using kava

with other substances that act on the central nervous system, such as alcohol, barbiturates, benzodiazepines, and antidepressants.

References

1. Lebot V, Merlin M, Linstrom L. *Kava the Pacific Drug*. New Haven, CT: Yale University Press; 1992:10.
2. Singh YN. Kava: an overview. *J Ethnopharmacol* 1992;37:13-45.
3. Shulgin AT. The narcotic pepper—The chemistry and pharmacology of Piper methysticum and related species. *Bull Narc* 1973;25:59-74.
4. Holm E, Staedt U, Heep J, et al. The action profile of D,L-kavain. Cerebral sites and sleep-wakefulness-rhythm in animals. *Arzneimittelforschung* 1991;41:673-683.
5. Kilham C. *Kava: Medicine Hunting In Paradise*. Rochester, VT: Park Street Press; 1996:60-68.
6. Wren RC. *Potter's New Cyclopaedia Of Botanical Drugs and Preparations*. Saffron Walden: C.W. Daniel Company Limited; 1988:201.
7. Lebot V, Lévesque J. The origin and distribution of kava (Piper methysticum Forst. g. and Piper wichmanni C. DC., Piperaceae): A phytochemical approach. *Allertonia* 1989;5:223-280.
8. Davies LP, Drew CA, Duffield P, et al. Kava pyrones and resin: studies on GABAA, GABAB and benzodiazepine binding sites in rodent brain. *Pharmacol Toxicol* 1992;71:120-126.
9. Keledjian J, Duffield PH, Jamieson DD, et al. Uptake into mouse brain of four compounds present in the psychoactive beverage kava. *J Pharm Sci* 1988;77:1003-1006.
10. 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* 1994:469-474.
11. Klohs MW, Keller F, Willimas RE, et al. A chemical and pharmacological investigation of Piper methysticum Forst. *J Medication Pharm Chem* 1959;1:95-103.
12. Kretzschmar R, Meyer HJ.[Vergleichende Untersuchungen uber die antikonvulsive Wirksamkeit der Pyronverbindungen au Piper methysticum Forst.] *Arch Int Pharmacodyn* 1969;177:261-267.
13. Meyer HJ. Pharmacology of kava. In: Efron DH, Holmsted B, Kline NS, eds. *Ethnopharmacologic Search for Psychoactive Drugs*. New York: Raven Press; 1979:133.
14. Gleitz J, Friese J, Beile A, et al. Anticonvulsive action of (+/-)-kavain estimated from its properties on stimulated synaptosomes and Na+ channel receptor sites. *Eur J Pharmacol* 1996;315:89-97.
15. Gleitz J, Beile A, Peters T. (+/-)-Kavain inhibits veratridine-activated voltage-dependent Na(+)-channels in synaptosomes prepared from rat cerebral cortex. *Neuropharmacology* 1995;34:1133-1138.
16. Gleitz J, Beile A, Peters T. (+/-)-Kavain inhibits the veratridine- and KCL- induced increase in intracellular Ca^{2+} and glutamate-release of rat cerebrocortical synaptosomes. *Neuropharmacology* 1996;35:179-186.
17. Schmitz D, Zhang CL, Chatterjee SS, Heinemann U. Effects of methysticin on three different models of seizure like events studied in rat hippocampal and entorhinal cortex slices. *Naunyn Schmiedebergs Arch Pharmacol* 1995;351:348-355.
18. Walden J, von Wegerer J, Winter U, et al. Effects of kawain and dihydromethysticin on field potential changes in the hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 1997;21:697-706.
19. Jamieson DD, Duffield P, Cheng D, Duffield A. Comparison of the central nervous system activity of the aqueous and lipid extract of kava. *Arch Int Pharmacodyn Ther* 1989;301:66-80.
20. Jamieson DD, Duffield PH. The antinocioceptive actions of kava components in mice. *Clin Exp Pharmacol Physiol* 1990;17:495-507.
21. Bruggemann F, Meyer HJ. [Die analgetische Wirkung der Kawa-Inhaltsstoffe Dihydrokawain und Dihydromethistizin.] *Arzneimittelforschung* 1963;13:407-409.
22. Kinzler E, Kromer J, Lehmann. Effect of a special kava extract in patients with anxiety-, tension-, and excitation states of non-psychotic genesis. Double blind study with placebos over 4 weeks. *Arzneimittelforschung* 1991;41:584-588.
23. Warnecke G. Psychosomatic dysfunctions in the female climacteric. Clinical effectiveness and tolerance of Kava Extract WS 1490. *Fortschr Med* 1991;109:119-122.

24. Woelk H, Kapoula S, Lehrl S, et al. Treatment of patients suffering from anxiety — Double-blind study: Kava special extract versus benzodiazepines. *Ztschr Allegemeinmed* 1993;69:271-277.
25. 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.
26. 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;27:224-230.
27. Munte TF, Heinze HJ, Matzke M, Steitz J. Effects of oxazepam and an extract of kava roots (Piper methysticum) on event-related potentials in a word recognition task. *Neuropsychobiology* 1993;27:46-53.
28. Meyer HJ, Kretzschmar R. Kawa pyrone—a new kind of substance group of central muscle relaxants of the mephenesin type. *Klin Wochenschr* 1966;44:902-903. [Article in German]
29. Kretzschmar R. [Kavain als Psychopharmakon.] *Munchen Med Wochenschrift* 1970:154-158.
30. Jossang P, Molho D. [Etude des constituants des feuilles de Piper methysticum Forst.] *Bulletin du Museum National d'Histoire Naturelle* 1970:440-447.
31. Singh YN. Effects of kava on neuromuscular transmission and muscle contractility. *J Ethnopharmacol* 1983;7:267-276.
32. Seitz U, Ameri A, Pelzer H, et al. Relaxation of evoked contractile activity of isolated guinea-pig ileum by (+/-)-kavain. *Planta Med* 1997;63:303-306.
33. Baldi D. [Sulle proprieta farmacologische del Piper methysticum.] *Terapia moderna* 1980:359-364.
34. Gleitz J, Beile A, Wilkens P, et al. Antithrombotic action of the kava pyrone (+)-kavain prepared from Piper methysticum on human platelets. *Planta Med* 1997;63:27-30.
35. Backhauss C, Krieglstein J. Extract of kava (Piper methysticum) and its methysticin constituents protect brain tissue against ischemic damage in rodents. *Eur J Pharmacol* 1992;215:265-269.
36. Steinmetz EF. *Kava kava (Piper methysticum): Famous drug plant of the South Sea Islands*. San Francisco: Level Press; 1960:24.
37. Locher CP, Burch MT, Mower HF. Anti-microbial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants. *J Ethnopharmacol* 1995;49:23-32.
38. Lemert EM. Forms and pathology of drinking in three Polynesian societies. *American Anthropologist* 1967:361-374.
39. Ruze P. Kava-induced dermopathy: a niacin deficiency? *Lancet* 1990;332:1442-1445.
40. Keller F, Klohs MW. A review of the chemistry and pharmacology of the constituents of Piper methysticum. *Lloydia* 1963;26:1-15.
41. Norton SA, Ruze P. Kava dermopathy. *J Am Acad Dermatol* 1994;31:89-97.
42. Suss R, Lehmann P. Hematogenous contact eczema cause by phytogenic drugs exemplified by kava root extract. *Hautarzt* 1996;47:459-461.
43. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996;125:940-941.
44. Herberg KW. Effect of Kava-Special Extract WS 1490 combined with ethyl alcohol on safety-relevant performance parameters. *Blutalkohol* 1993;30:96-105.
45. Jamieson DD, Duffield PH. Positive interaction of ethanol and kava resin in mice. *Clin Exp Pharmacol Physiol* 1990;17:509-514.
46. Schelosky L, Raffauf C, Jendroska K, Poewe W. Kava and dopamine antagonism. *J Neurol Neurosurg Psychiatry* 1995;58:639-640.
47. Khalsa KPS. Kava, the peaceful herb. *The Herb Quarterly* 1997:38-42.
48. Cawte J. Parameters of kava used as a challenge to alcohol. *Aust N Z J Psychiatry* 1986;20:70-76.
49. Mathews JD, Riley MD, Fejo L, 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;148:548-555.
50. *Los Angeles Times*, Jan 3, 1997.
51. Duffield PH, Jamieson DD. Development of tolerance to kava in mice. *Clin Exp Pharmacol Physiol* 1991;18:571-578.