Review

Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.)

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Abstract

Kava kava, a beverage or extract prepared from the rhizome of the kava plant (*Piper methysticum* Forst. f.), was used for many centuries as a traditional beverage in the Pacific Islands. During the past few decades, kava has also gained popularity in Western countries as well, due to its anxiolytic and sedative properties. However, in recent years, kava has been implicated in several liver failure cases which led to its ban in many countries and this has prompted wide discussion on its relative benefits and risks as a social beverage and a herbal remedy. Recently, it has been shown that several kavalactones, the assumed active principles of kava extracts, are potent inhibitors of several enzymes of the CYP 450 system (CYP1A2, 2C9, 2C19, 2D6, 3A4 and 4A9/11). This indicates that kava has a high potential for causing pharmacokinetic drug interactions with other herbal products or drugs, which are metabolised by the CYP 450 enzymes. In addition, several pharmacodynamic interactions have been postulated and indeed observed. Nevertheless, evidence of true pharmacokinetic and/or pharmacodynamic interactions remains unsubstantiated, and only few investigations of the potential of kava preparations to interact with specific drugs have been carried out. This review provides a critical overview of the existing data on interactions of kava with other drugs and concludes that there is an urgent need for further in vitro and in vivo investigations to fully understand clinically significant interactions with kava that have the potential to cause adverse effects or toxicity in kava users.
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Keywords: Kava kava; *Piper methysticum*; Herb–drug interactions; CYP 450 inhibition; Adverse effects/toxicity

1. Introduction

Kava kava, a beverage or extract prepared from the rhizome of the kava plant (*Piper methysticum* Forst. f.), was used for many centuries as a traditional beverage in the Pacific Islands (Lindstrom, 2004). Kavalactones, the assumed active principles, are predominantly concentrated in the plant's rhizome rather than in its upper stems or leaves; stem peelings and aerial parts contain some toxic alkaloids, such as pipermethystine (Nerurkar et al., 2004). Traditionally, Pacific Islanders avoid stem peelings and aerial parts and use only the rhizome for preparing aqueous extracts (Lindstrom, 2004). Some kava cultivars have been used for ceremonial occasions, others for medicinal purposes with particular cultivars being used to treat specific illnesses (Lebot and Lévesque, 1996). During the past few decades,

kava has also gained popularity in Western countries as well due to its anxiolytic and sedative properties (Singh and Singh, 2002). Solvents used for commercial kava extracts are usually ethanol–water or acetone–water mixtures (Singh, 2004a). Several clinical studies have assessed the therapeutic potential of kava in controlling anxiety. These studies have been recently reviewed by Pittler and Ernst (2003). They conclude that compared with placebo kava extract appears to be an effective treatment for anxiety. However, in recent years, kava has been implicated in several liver failure cases (Strahl et al., 1998; Russmann et al., 2001; Campo et al., 2002; BfArM, 2002; Brauer et al., 2003; Gow et al., 2003; McGhee, 2003). This led to its ban in many countries, which has prompted wide discussion on its relative benefits and risks as a social beverage and a herbal remedy (Schulze et al., 2003). Although kava is a widely studied herbal product that has gained even more attention after it was suspected of being hepatotoxic, only few investigations on its potential for herb–drug interactions have been carried out. This review provides a critical

Table 1
Summary of pharmacokinetic and/or pharmacodynamic interaction studies with kava and kava products

Reference	Nature of study	Number of subjects/replicates	Study topic	Result	Kava preparation	Kava dose	Duration of kava treatment	Study deficiencies
Mathews et al. (2002)	In vitro	No data	CYP inhibition	Inhibition of CYP1A2, 2C9, 2C19, 2D6, 3A4, 4A9/11	40% methanol or acetone extract	100 μM kavalactones	10 min incubation	No data on number of replicates and variability
Unger et al. (2002)	In vitro	No data	CYP inhibition	Inhibition of CYP3A4	Methanol, acetone and ethyl acetate extracts	1 mg/ml	30 min incubation	Only graphical results, no data on number of replicates, variability or P-values, no data on kavalactone content in extracts
Zou et al. (2002)	In vitro	Four replicates	CYP inhibition	Inhibition of CYP1A2, 2C9, 2C19, 2D6, 3A4	Individual isolated kavalactones	Several concentrations	Various times	No P-values and variability
Almeida and Grimsley (1996)	Human case-report	1	Interaction with alprazolam	Coma, maybe due to interactions between kava and alprazolam	Tablets	No data	3 days	No data on kava preparation or dose
Klohs et al. (1959)	In vivo (mice)	10	Interaction with pentobarbital	Increased sleeping times with pentobarbital	Individual isolated kavalactones and chloroform extract, p.o.	60 or 160 mg/kg	Single dose, 30 min prior to pentobarbital injection	No data on kavalactone content of extract
Meyer (1962)	In vivo (mice)	10	Interaction with various CNS-depressants	Increased sleeping times with pentobarbital, hexobarbital, urethane and glutethimide	Dihydrokavain and dihydromethysticin, p.o.	20–240 mg/kg	Single dose, 30 min prior to injection	No P- values
Herberg (1996)	Volunteer clinical study	18	Interaction with bromazepam	No effects	Tablets	120 mg kavalactones per tablet, two per day	14 days	–
Jamieson and Duffield (1990)	In vivo (mice)	5–14 per group	Interaction with alcohol	Increased sleeping times and increased toxicity	Lipid soluble extract, p.o.	200–600 mg/kg	Single dose	Only graphical results for sleeping-times and variability, no data on kavalactone content of extract
Foo and Lemon (1997)	Volunteer clinical study	40 (9–11 per group)	Interaction with alcohol	Kava appeared to potentiate sedation, intoxication and impairment of cognition/co-ordination when combined with alcohol	Aqueous extract, p.o.	1 g/kg	Single dose	–
Herberg (1993)	Volunteer clinical study	40 (20 per group)	Interaction with alcohol	No effects	Tablets	100 mg kava per tablet, 70% kavalactones, three per day	8 days	–
Schelosky et al. (1995)	Human case-report	1	Interaction with levodopa	Reduced effectiveness of levodopa	Tablets	150 mg kava extract per tablet, two per day	10 days	No data on kavalactone content of tablets
Baum et al. (1998)	In vivo (rats)	5–12 per group	Modulation of dopamine system	Dopamine–agonistic and –antagonistic properties of various kavalactones, increased dopamine concentration with kava extract	Kava extracts and individual kavalactones, i.p.	20–220 mg/kg	Single dose	No data on nature of kava extract or kavalactone content of extract
Donadio et al. (2000)	Human case-report	1	Interaction with caffeine	Rhabdomyolysis	Tablets	100 mg	Single dose	No data on kavalactone content of tablets
Klohs et al. (1959)	In vivo (mice)	10	Effect of kava extract and kavalactones on strychnine-induced convulsions	Anticonvulsive properties of kavalactones and chloroform extract	Chloroform kava extract and individual isolated kavalactones, p.o.	Various doses	Single doses, 15 min prior to strychnine injection	–

Reference	Study type	Replicates	Effect	Properties	Preparation	Dose	Notes	
Kretzschmar and Meyer (1969)	In vivo (mice)	10–20 per group	Effect of kavalactones on maximal electroshock and pentylenetetrazole-induced convulsions	Anticonvulsive properties of all tested kavalactones	Individual isolated kavalactones dissolved in peanut oil, p.o and i.p.	70–750 mg/kg	Single dose	–
Kretzschmar et al. (1970)	In vivo (mice)	10–30 per group	Effect of kavalactones on strychnine-induced convulsions	Anticonvulsive properties of all tested kavalactones	Individual isolated kavalactones dissolved in peanut oil, i.p.	Various	Single dose, 30 min prior to strychnine injection	–
Schmitz et al. (1995)	In vitro	4–10 replicates	Effect of methysticin on different seizure models	Anticonvulsive properties of methysticin	Methysticin dissolved in DMSO	1–100 µM	Single dose	–
Gleitz et al. (1996)	In vitro	4–15 replicates	Effect of (±)-kavain on Ca^+ and Na^+ channels	Anticonvulsant properties of (±)-kavain, possible mechanism: inhibition of voltage-dependent Ca^+ and Na^+ channels	(±)-Kavain dissolved in DMSO	Various	Single dose	–
Uebelhack et al. (1998)	In vitro	2–8 replicates	Effect of kava extracts and kavalactones on human platelet MAO-B	Reversible inhibition of platelet MAO-B	Kava extracts (67.6%) and synthetic kavalactones	Kava extract: 2–225 µM for intact platelets, 0.25–45 µM for disrupted platelets; kavalactones: 0.05–200 µM	Single dose	–
Gleitz et al. (1997)	In vitro	4–15 replicates	Effect of (±)-kavain on human platelets	Antithrombotic properties of (±)-kavain	(±)-Kavain	Various	Single dose	–

overview of the existing data on interactions of kava with other drugs and concludes that there is an urgent need for further in vitro and in vivo investigations to fully understand clinically significant interactions with kava that have the potential to cause adverse effects or toxicity in kava users. A detailed summary of published pharmacokinetic and/or pharmacodynamic interaction studies and case-reports are summarized in Table 1. These studies will now be reviewed critically.

2. Methods

All publications which might describe case-reports of interactions between kava kava and other drugs, or in vitro or in vivo studies investigating such interactions were identified by searches using databases such as MEDLINE, EMBASE, BIOSIS, Australasian medical index (AMI) and international pharmaceutical abstracts. Search terms were kava, kawa, *Piper methysticum*, kavalactones, kava–drug and kava–herb interactions. In addition, manual searches of the references cited in these publications and our own files were conducted.

3. Pharmacokinetic interactions

3.1. Potential for pharmacokinetic interactions attributable to CYP 450 inhibition

In recent years, several studies have shown that kavalactones, especially those with a methylenedioxyphenyl group, like methysticin and dihydromethysticin, are potent inhibitors of CYP 450 enzymes (Mathews et al., 2002; Unger et al., 2002; Zou et al., 2002). Mathews and co-workers tested kava extract, as well as individual kavalactones that were isolated from kava, for their potential to inhibit various CYP enzymes in vitro using human liver microsomes. Methanol or acetone kava extract (40%) normalized to a concentration of 100 µM (assuming an average molecular weight of the active components of 250 g/mol) showed statistically significant CYP2C9 (92% compared with control), 2C19 (86%), 3A4 (78%), 2D6 (73%), 4A9/11 (65%) and 1A2 (56%) inhibition ($P < 0.001$ for all CYPs). Lower kava concentrations (10 µM) were still significantly inhibitory towards the various CYP's, but the enzymes where inhibited to a lesser extent: CYP2C9 (53%, $P < 0.001$), 2C19 (30%, $P < 0.01$), 3A4 (42%, $P < 0.001$), 2D6 (22%, $P < 0.01$) and 1A2 (36%, $P < 0.01$). To further investigate the inhibitory effects of the individual kavalactones, 10 µM concentration of each component was used. Kavain did not inhibit any of the enzymes, but there was significant inhibition of CYP2C9 by desmethoxyyangonin (42%, $P < 0.001$), methysticin (58%, $P < 0.001$) and dihydromethysticin (69%, $P < 0.001$); of 2C19 by dihydromethysticin (76%, $P < 0.001$); of 3A4 by desmethoxyyangonin (40%, $P < 0.001$), methysticin (27%, $P < 0.01$) and dihydromethysticin (54%, $P < 0.001$); and

of 2D6 by methysticin (44%, $P < 0.001$). Unfortunately, the authors did not report the number of times the inhibition studies were replicated, the variability in their results or any other details on the inhibition calculations, so that the reliability of their study results cannot be assessed. While such in vitro studies may predict if interactions might be possible in vivo, clinical studies or case-reports in humans are far more important in establishing if interactions actually occur. The recommended daily dose for kava is equivalent to 120 mg kavalactones (Kommission E, 1990); dosages used in several clinical trials have been equivalent to 240 mg or more kavalactones daily (Schmidt, 2003). Assuming complete oral absorption and a theoretical blood volume of 6 l, an average blood/plasma concentration of 20–40 µg/ml (80–160 µM) kavalactones may be predicted. In humans, a single oral dose of 200 mg synthetic (±)-kavain resulted in a maximum plasma concentration of 18 µg/ml (Singh, 2004b); thus bioavailability appears to be approximately 50%. However, other studies have shown that the administration of the complete kava extract compared to the administration of pure single kavalactones increases the bioavailability by 2-fold (for kavain) to more than 20-fold (for yangonin) (Keledjian et al., 1988). Therefore, the kavalactone concentrations used by Mathews et al. (2002) in their CYP inhibition studies are clinically realistic. Unger et al. (2002) tested several fractions with different polarity from a crude ethyl acetate extract of kava kava root powder (1 mg/ml) for CYP3A4 inhibitory effects. A significant inhibition (~80%, interpolated from graphical results) of CYP3A4 was observed with the methanolic fractions (50/75/100% methanol) and the acetone (~78%) and ethyl acetate (~70%) fractions. Further fractionation and analysis with liquid chromatography/electrospray ionisation–mass spectrometry identified the kavalactones kavain, dihydrokavain, methysticin, dihydromethysticin and dihydroyangonin as the main inhibitory principles. However, these authors also did not give any information on the number of replicates, variability, or any details on CYP inhibition calculations. In addition, no information on kavalactone inhibitory concentrations (such as IC_{50} values) was reported. Therefore, it is difficult to evaluate their results critically. Zou et al. (2002) investigated the influence of the isolated kavalactones kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin and desmethoxyyangonin on recombinant human CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) and calculated IC_{50} values from the mean of four determinations for the most potent inhibitory active compounds. Desmethoxyyangonin inhibited CYP1A2 ($IC_{50} = 1.7$ µM), CYP2C9 ($IC_{50} = 50.12$ µM), CYP2C19 ($IC_{50} = 0.51$ µM) and CYP3A4 ($IC_{50} = 20.02$ µM); dihydromethysticin inhibited CYP1A2 ($IC_{50} = 14.8$ µM), CYP2C9 ($IC_{50} = 13.35$ µM), CYP2C19 ($IC_{50} = 0.43$ µM), CYP2D6 ($IC_{50} = 37.03$ µM) and CYP3A4 ($IC_{50} = 2.49$ µM); methysticin inhibited CYP1A2 ($IC_{50} = 12.53$ µM), CYP2C9 ($IC_{50} = 16.39$ µM), CYP2C19 ($IC_{50} = 0.93$ µM), CYP2D6 ($IC_{50} = 153.20$ µM) and CYP3A4 ($IC_{50} = 1.49$ µM); kavain

inhibited CYP1A2 ($IC_{50} = 44.66$ µM), CYP2C9 ($IC_{50} = 128.30$ µM), CYP2C19 ($IC_{50} = 4.86$ µM) and CYP3A4 ($IC_{50} = 34.48$ µM) and dihydrokavain inhibited CYP2C9 ($IC_{50} = 130.95$ µM), CYP2C19 ($IC_{50} = 10.05$ µM) and CYP3A4 ($IC_{50} = 78.59$ µM). Yangonin could not be evaluated for its CYP inhibitory effect using the fluorimetric assay employed due to its high native fluorescence. Kavain, methysticin, dihydromethysticin and desmethoxyyangonin were even more potent inhibitors of the isoform CYP2C19 than the positive control (tranylcypromine, $IC_{50} = 5.46$ µM) used in the assay, which is known to produce clinically significant drug interactions. Zou et al. (2002) also determined the IC_{50} values for several grapefruit juice components such as bergamottin (0.48 µM for CYP1A2, 0.33 µM for CYP2C9, 0.19 µM for CYP2C19, 0.35 µM for CYP2D6, 1.47 µM for CYP3A4); 6,7-dihydroxybergamottin (10.23 µM for CYP1A2, 1.17 µM for CYP2C9, 0.097 µM for CYP2C19, 1.19 µM for CYP2D6) and naringenin (83.09 µM for CYP1A2, 2.57 µM for CYP2C9, 3.48 µM for CYP2C19, 159.12 µM for CYP2D6, 11.90 µM for CYP3A4) that are known to interact with several drugs in vivo. These reported IC_{50} values for kavalactones and grapefruit juice components are similar, indicating a comparable potential for interactions in vivo. However, again no statistical information or extent of variability were provided for these inhibition data. Nevertheless, all these three studies collectively lead to the hypothesis that there is a high risk of pharmacokinetic herb–drug interactions with kava as many of these CYP 450 enzymes that kava components inhibit to varying extents are responsible for the metabolism of majority of the pharmaceutical agents used currently. Co-ingestion of kava with prescribed or over-the-counter medications or other herbal remedies that are metabolised by one of these enzymes might then result in elevated and potentially toxic plasma concentrations of the co-administered drugs or their metabolites. Nevertheless, no systematic studies investigating pharmacokinetic interactions between kava and specific drugs or other herbs have been carried out.

4. Pharmacodynamic interactions

Several pharmacodynamic interactions with kava have been postulated. However, the evidence for true pharmacodynamic interactions is poor; only a few clinical case-reports, in vivo and in vitro studies exist. Most pharmacodynamic recommendations for the use of kava products in combination with other drugs are therefore based on theoretical considerations rather than on actual experimental data generated either in animals or humans.

4.1. Interactions with CNS-depressants

The known sedative effects of kava (reviewed by Singh and Singh, 2002) have led to the assumption that

kavalactones potentiate the effects of CNS-depressants like benzodiazepines, barbiturates or alcohol, as stated in reviews by Pepping (1999) and Bilia et al. (2002). One case-report (Almeida and Grimsley, 1996) described coma in a 54-year-old male patient taking alprazolam, cimetidine and terazosin without any observable adverse effects until he self-medicated with kava 3 days prior to his hospitalisation. The drug screen in this patient was negative for alcohol but positive for benzodiazepines. Prior pharmacological studies, indicating additive effects between kava constituents, pentobarbital and pregnane steroids (Klohs et al., 1959; Meyer, 1962), led these authors to suggest a possible pharmacodynamic interaction between kava and alprazolam. However, the assumption of interactions between kava and alprazolam was criticised by The American Botanical Council (cited in Schmidt, 2003). In their opinion, coma might well have occurred as a side-effect of alprazolam even without kava intake. In addition, as alprazolam, a benzodiazepine, is metabolised by CYP3A4 (Gorski et al., 1999) and cimetidine is a potent inhibitor of CYP1A2, 2C9, 2C19 and 3A4 (Tredger and Stoll, 2002), this might have been the reason for higher alprazolam or kavalactone concentrations which then led to the observed coma. As CYP3A4 is also inhibited by kava and kavalactones (Mathews et al., 2002; Unger et al., 2002; Zou et al., 2002), a pharmacokinetic interaction between alprazolam and kava is another plausible explanation. However, pharmacodynamic interactions might well have occurred, as animal studies with the barbiturates, pentobarbital and hexobarbital, and other non-barbiturate CNS-depressants like urethane and glutethimide suggest synergistic, not simply additive, effects with kavalactones (Klohs et al., 1959; Meyer, 1962). In an early study, Klohs et al. (1959) found increased pentobarbital-induced sleeping times (410% compared to controls, groups of at least 10) in mice after oral administration of 60 mg/kg dihydromethysticin. Methysticin, kavain, dihydrokavain and yangonin (160 mg/kg, p.o.) also prolonged sleeping times, but not to the same extent (by 250, 235, 150 and 150% over controls, respectively). Meyer (1962) confirmed these findings and observed prolonged sleeping times in mice (10 in each group) with the kavalactones, dihydrokavain and dihydromethysticin, in combination with either hexobarbital, pentobarbital, urethane or glutethimide. The lowest i.p. dose of dihydromethysticin that increased a 70 mg/kg (i.p.) hexobarbital-induced sleeping time significantly (from 45 ± 6 to 87 ± 5 min) was 20 mg/kg. In comparison, the lowest active dose of dihydrokavain was approximately three times higher. With higher doses of dihydromethysticin and hexobarbital, longer sleeping times, up to 27 ± 1 h with 240 mg/kg dihydromethysticin and 150 mg/kg hexobarbital in combination, could be reached. Pentobarbital (70 mg/kg i.p., equivalent to 100 mg/kg hexobarbital) and urethane (1000 mg/kg i.p., equivalent to 110 mg/kg hexobarbital), in combination with 60 mg/kg dihydromethysticin, respectively, resulted in sleeping times of 310 ± 18 and 233 ± 17 min, respectively (controls: 85 ± 13

and 103 ± 15 min.) In addition, the ED_{50} for loss of righting reflex with glutethimide in combination with dihydromethysticin was evaluated; 60 or 100 mg/kg dihydromethysticin decreased glutethimide ED_{50} from 120 to 100 and 80 mg/kg, respectively. As only sleeping times and not blood concentrations of either the kavalactones or the tested CNS-depressants were measured, pharmacokinetic interactions might be another plausible explanation. Some barbiturates, for example, hexobarbital, are metabolised by CYP2C9 (Guengerich, 1995), which is probably inhibited by kavalactones (Mathews et al., 2002). However, this cannot be the only reason as these four CNS-depressants show great chemical and metabolic diversity. Urethane, for example, is metabolised mainly by CYP2E1 (Hoffler et al., 2003), whose activity is not affected by kava (Mathews et al., 2002); glutethimide is metabolised mainly by CYP2B6 (Tredger and Stoll, 2002), whose inhibition by kava/kavalactones has not been examined so far. In contrast, a double blind, cross-over study in 18 healthy volunteers, investigating the possibility of interactions of kava (120 mg kavalactones, two tablets per day) with benzodiazepines (bromazepam: 9 mg/d), demonstrated that kava and bromazepam do not show either additive or synergistic effects (Herberg, 1996). No significant changes in safety-related performance, such as stress tolerance, vigilance or motor coordination, could be detected between bromazepam treatment alone and simultaneous treatment with bromazepam and kava (Herberg, 1996). As this was a randomised controlled trial (RCT), this adds more credibility to this observation than the animal studies mentioned earlier. However, with the small (18) subject number and a tendency for greater impairment with the benzodiazepine–kava combination that was observed in all performance tests, it would be desirable to conduct an additional study of this style with more volunteers.

4.2. Interactions with alcohol

Even though it may be predicted, based on theoretical considerations, that there may be either pharmacokinetic and/or pharmacodynamic interactions between alcohol and kava, resulting perhaps in increased toxicity of either kava or alcohol, only a few studies have examined such effects from co-ingestion of kava and alcohol. Jamieson and Duffield (1990) reported increased sleeping times in mice when alcohol and a lipid-soluble extract of kava were administered in combination. In a pilot experiment, the effect of kava on ethanol-induced hypnosis was investigated. A 3 g/kg ethanol i.p. dose failed to induce loss of righting reflex; a 3.5 g/kg dose caused hypnosis while 4 and 4.5 g/kg doses increased sleeping times. However, the latter dose killed 1 out of 14 (7%) mice. In the subsequent experiments, the effect of subhypnotic doses of kava resin on sleeping times in mice treated with 3.5 or 4 g/kg ethanol doses were investigated. A 200 mg/kg oral kava resin dose increased the sleeping time significantly ($P < 0.001$) for both ethanol doses. Further prolongation of sleeping times was noted when a 300 mg/kg

kava resin dose was used. However, this dose killed three of six (50%) mice treated with 4 g/kg of alcohol, implying an increased toxicity of the kava–alcohol combination compared to alcohol alone. In a subsequent experiment, the effect of ethanol on kava-induced hypnosis was investigated. Kava doses that elicited loss of righting reflex varied from 350 to 600 mg/kg orally; however, one of six (17%) mice died at the latter dose. Alcohol doses between 2 and 3 g/kg in combination with these kava doses prolonged sleeping times significantly ($P < 0.001$). However, administration of 450 mg/kg kava plus 2 g/kg of alcohol killed three of five (60%) mice rapidly, again implying increased toxicity of the kava–alcohol combination. The authors thus postulated a pharmacodynamic interaction between kava and ethanol involving hypnosis, with more than a simple additive effect, as well as increased toxicity when used in combination. However, the study did not include an isobolographic analysis using varying dose ratios of kava and alcohol, so it is difficult to conclude that a synergistic interaction, as suggested by the authors, did indeed occur. In addition, the pharmacodynamic effect was quantified as sleeping time, which would still be consistent with a pharmacokinetic interaction between kava and alcohol, for example, with either alcohol inhibiting kava metabolism or kava inhibiting alcohol metabolism, leading to increases in systemic concentrations of either agent. Schmidt (2003) also criticised these findings and argued that kava and alcohol doses used were much higher than those that yield realistic blood concentrations in humans. In a clinical study in 40 volunteers (10 × placebo, 11 × kava, 10 × alcohol, 9 × combination of kava and alcohol), Foo and Lemon (1997) examined the effects of alcohol (0.75 g/kg p.o., resulting in blood alcohol concentrations from 0.05 to ∼0.1%) and kava (1 g/kg kava powder in 500 ml water, p.o.) on cognition in humans. Kava alone had little effect but appeared to potentiate sedation, intoxication and impairment of cognition or co-ordination when combined with alcohol (significant differences in several tests, slight trends in others). In contrast, Herberg (1993) could not detect any influence of kava (three tablets per day containing 100 mg kava extract, standardized to 70% kavalactones) on mental concentration, vigilance and motor ability in human test subjects (40 volunteers; 20 × kava + alcohol, 20 × placebo + alcohol), beyond the effects of concomitantly administered alcohol. A possible explanation for these differing results might be the lower alcohol doses (yielding a maximum of 0.05% blood alcohol concentration) used in the study by Herberg (1993) compared to the doses in the clinical study of Foo and Lemon (1997). Thus, an unequivocal study on kava and alcohol pharmacodynamic interaction with respect to CNS pharmacological or toxic effects still needs to be carried out.

4.3. Interactions with levodopa

Interactions of kava with levodopa have been postulated. Schelosky et al. (1995) reported a case where kava was suspected to have reduced the effectiveness of levodopa in a 76-year-old female patient suffering from Parkinson's disease using a kava product (tablets containing 150 mg kava extract) twice a day for 10 days. This resulted in an increased duration and frequency of "off-periods"; she returned to her normal baseline disease pattern within 2 days of discontinuing the kava extract. In three other patients without Parkinson's disease, kava ingestion (one tablet containing 100 mg extract in two cases; tablets containing 150 mg kava extract three times daily for 4 days in one case) was related to dystonia and dyskinesia (Schelosky et al., 1995). Each time these patients received biperiden (2.5 or 5 mg, i.v.), an antimuscarinic drug used for Parkinson's disease, this led to immediate and complete relief of their symptoms, which were exacerbated with kava intake. This suggested an adverse pharmacodynamic interaction between kava and levodopa. Baum et al. (1998) demonstrated dopamine–antagonistic and also some dopamine–agonistic properties of different kavalactones in vivo in rats. Kava extracts (20, 120 and 220 mg/kg, i.p., kavalactone content of the extracts were not determined and the solvent for the extract was not reported) increased dopamine concentrations in the nucleus accumbens significantly ($P = 0.024$, 0.0001 and 0.0002, respectively). Yangonin (120 mg/kg, $P = 0.013$) and (±)-kavain (30 mg/kg with $P = 0.002$ but not 60 and 120 mg/kg) alone decreased dopamine concentrations, whereas desmethoxyyangonin (120 mg/kg, $P = 0.034$) increased neurotransmitter concentrations. Dihydrokavain, methysticin and dihydromethysticin (120 mg/kg each) failed to affect dopamine concentrations. However, large interindividual differences in the response to the kava extract or the individual kavalactones with no obvious explanation were noted in their study. Nevertheless, the modulation of the dopamine system by kava might be a possible explanation for the above-mentioned case-report, pointing to a pharmacodynamic interaction between kava and levodopa. As modulation of the dopaminergic system was observed both in vitro and in vivo (Schelosky et al., 1995; Baum et al., 1998), interactions with antipsychotic medications such as promethazine or haloperidol, resulting in, for example, increased Parkinson-like side-effects, might also be plausible.

4.4. Interactions with caffeine

Donadio et al. (2000) noted rhabdomyolysis in a 29-year-old male who took a herbal product containing 500 mg guarana, with the active constituent caffeine, 200 mg *Ginkgo biloba* and 100 mg kava. The patient suffered from severe muscle pain and passed dark urine a few hours after consuming the preparation. The authors believed that the methylxanthine effects of guarana and the antidopaminergic properties of kava (Schelosky et al., 1995; Baum et al., 1998) were pathogenetically relevant. Methylxanthines like caffeine might induce muscle contracture and in high doses myoglobinuria (Wrenn and Oschner, 1989); antidopaminergic medications like haloperidol may cause

neuroleptic malignant syndrome, a disorder associated with myoglobinuria (Adnet et al., 1996). It was concluded that a combination of such effects might have been responsible for the rhabdomyolysis in this patient (Donadio et al., 2000). However, no similar clinical cases are known, and as Schmidt (2003) states, if there were actual interactions between kava and caffeine, these effects might be observed more often since caffeine in similar amounts is consumed regularly by many kava users in the form of coffee or tea. Thus, it appears unlikely that pharmacodynamic interactions between kava and caffeine are associated with rhabdomyolysis.

4.5. Interactions with anticonvulsants

Other hypotheses on interactions with kava have been put forward, but again these claims remain unsubstantiated and the evidence is not exhaustive. The major kavalactones display anticonvulsive action against maximal electroshock, strychnine and pentylenetetrazole induced convulsions in mice (Klohs et al., 1959; Kretzschmar and Meyer, 1969; Kretzschmar et al., 1970). Consistent with this, methysticin also displayed anticonvulsive properties using rat hippocampal and entorhinal cortex slices as models of seizure-like events (Schmitz et al., 1995). Gleitz et al. (1996) determined inhibition of voltage-dependent Ca^+ and Na^+ channels as the possible mechanism of this anticonvulsant action. These results collectively led to the suggestion that additive therapeutic effects of kava with anticonvulsants and potentiation of their side-effects, such as lethargy and cognitive impairment, are possible (Spinella, 2001).

4.6. Interactions with MAO-inhibitors

Uebelhack et al. (1998) found reversible inhibition of platelet MAO-B in vitro by kava kava spissum extract containing ∼68% kavalactones ($IC_{50} = 24 \pm 12 \,\mu M$ for intact platelets and $1.4 \pm 0.6 \,\mu M$ for disrupted platelet homogenates). Desmethoxyyangonin ($K_i = 0.28 \,\mu M$; $IC_{50} = 28.1 \pm 12.9 \,\mu M$ for intact platelets and $0.12 \pm 0.02 \,\mu M$ for disrupted platelet homogenates) and ($\pm$)-methysticin ($K_i = 1.14 \,\mu M$; $IC_{50} = 39.5 \pm 17.9 \,\mu M$ for intact platelets and $0.67 \pm 0.12 \,\mu M$ for disrupted platelet homogenates) inhibited MAO-B. Yangonin, ($\pm$)-dihydromethysticin, ($\pm$)-dihydrokavain and ($\pm$)-kavain also produced MAO-B inhibition, but no details were reported. However, substantial differences in IC_{50} values between intact and disrupted platelets were observed (for example, for ($\pm$)-methysticin $39.5 \pm 17.9 \,\mu M$ versus $0.67 \pm 0.12 \,\mu M$), indicating that penetration of kavalactones across the cytoplasmic membrane may be a limiting factor in MAO inhibition in vivo. Nevertheless, based on these results, kavalactones may theoretically display additive effects with MAO-B inhibitors like selegiline used in the treatment of Parkinson disease (Pepping, 1999).

4.7. Interactions with antiplatelet medications or anticoagulants

In another in vitro experiment, Gleitz et al. (1997) detected dose-dependent antithrombotic actions of ($\pm$)-kavain on human platelets. IC_{50} values for suppressing aggregation, releasing endogenous ATP, formation of prostaglandin E_2 and formation of thromboxane A_2 were 78, 115, 86 and 71 μM, respectively. Similar IC_{50} values from the various assays led the authors to suggest an inhibition of COX-2 by ($\pm$)-kavain as primary mechanism of this antithrombotic action. Thus, interactions with antiplatelet medications like aspirin and dipyridamole or anticoagulants like warfarin and phenprocoumon might be postulated; no studies have, however, specifically examined such interactions. Of course, pharmacokinetic interactions with warfarin are also possible since warfarin is metabolised mainly by CYP3A4 (Guengerich, 1995), an enzyme inhibited quite substantially by kava extract and several kavalactones at clinically realistic concentrations (Mathews et al., 2002; Unger et al., 2002; Zou et al., 2002).

5. Conclusions

Kava appears to display a propensity for both pharmacokinetic and/or pharmacodynamic interactions with other drugs and/or herbs. However, there is paucity of well-documented unequivocal evidence and clinical recommendations are based mainly on theoretical considerations rather than on actual experimental data gathered in a systematic manner. Further, in vitro and in vivo investigations in animals as well as clinical studies in volunteers and patients are therefore required to fully understand clinically significant interactions with kava that have the potential to cause either adverse effects or toxicity in kava users.

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