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A Systematic Review of the Safety of Kava Extract in the Treatment of Anxiety

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Abstract

This paper systematically reviews the clinical evidence relating to the safety of extracts of the herbal anxiolytic kava (*Piper methysticum*). Literature searches were conducted in four electronic databases and the reference lists of all papers located were checked for further relevant publications. Information was also sought from the spontaneous reporting schemes of the WHO and national drug safety bodies and ten manufacturers of kava preparations were contacted.

Data from short-term post-marketing surveillance studies and clinical trials suggest that adverse events are, in general, rare, mild and reversible. However, published case reports indicate that serious adverse events are possible including dermatological reactions, neurological complications and, of greatest concern, liver damage. Spontaneous reporting schemes also suggest that the most common adverse events are mild, but that serious ones occur. Controlled trials suggest that kava extracts do not impair cognitive performance and vigilance or potentiate the

effects of central nervous system depressants. However, a possible interaction with benzodiazepines has been reported.

It is concluded that when taken as a short-term monotherapy at recommended doses, kava extracts appear to be well tolerated by most users. Serious adverse events have been reported and further research is required to determine the nature and frequency of such events.

Kava kava (*Piper methysticum* Forst.) is a perennial shrub native to some islands of the South Pacific. The name kava derives from the Polynesian word awa meaning bitter, referring to the characteristic taste of the psychoactive beverage prepared from the rhizome of the plant. Kava drinking is an integral part of traditional ceremonies and informal social occasions in many Pacific island societies.

In addition to its recreational use, kava has traditionally been employed for a range of medicinal purposes including the treatment of gonorrhoea, syphilis and cystitis and the induction of relaxation and sleep. In Europe, kava extracts are widely used for treating anxiety disorders and the results of clinical trials suggest that they are effective anxiolytics.[1] In order to make a balanced assessment of the value of kava extracts, evidence of efficacy must be weighed against information on safety. Heavy long-term consumption of kava has been shown to be associated with poor health status including malnutrition and bodyweight loss, liver and renal dysfunction, altered blood biochemistry and symptoms suggestive of pulmonary hypertension.[2] A distinctive reversible ichthyotic rash known as kava dermopathy is observed with heavy consumption of the beverage[3] and repeated episodes of generalised choreoathetosis secondary to kava bingeing have been reported.[4] Acute kava intoxication upon heavy chronic consumption has resulted in headache, sore eyes, generalised muscle weakness, abdominal pain, disorientation and hallucinations.[5] The amount of kava consumed in these cases is, however, at least 100 times higher than recommended therapeutic doses. As yet there has been no systematic attempt to document all the available safety data on kava extracts. This review was conducted in order to provide such an evaluation.

1. Method

Systematic literature searches were conducted in the following electronic databases to locate papers with information relating to the safety of kava extracts in humans: Medline, Embase, Amed (from their respective inceptions up to November 2000) and The Cochrane Library (search date November 2000). The search terms were: adverse drug reaction, adverse effect, adverse event, drug interaction, safety, tolerability, toxicity, kava, *Piper methysticum*, intoxicating pepper, kawa, Rauschpfeffer and yangona. Further relevant publications were located by checking the reference lists of all papers, contacting colleagues with interest in herbal medicine and searching departmental files. In addition, data were requested from the spontaneous reporting schemes of the WHO (Collaborating Centre for International Drug Monitoring) and the drug safety bodies of the US [Food and Drug Administration (FDA)], UK [Committee on Safety of Medicines (CSM)] and Germany [Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)]. Ten manufacturers of kava preparations were contacted and asked for any information held on file.

Data relating to adverse events associated with kava extracts in humans from post-marketing surveillance studies, clinical trials, case reports, spontaneous reporting schemes and phase I studies were included in the review. *In vitro* and animal data were excluded, as were data relating to raw kava material (e.g. kava beverages) or products consisting only of isolated constituents of kava. No language restrictions were imposed. All sources of in-

formation obtained were read by two reviewers (CS and AH) who independently extracted information relating to patients, preparations, adverse events, treatment and outcome, where available. Any discrepancies were settled by the third author (EE). No formal assessment of causality was attempted since no validated tools yet exist for performing such evaluations for herbal medicines and most sources of information contained insufficient detail for a meaningful assessment. However, the issues involved in interpreting the available data were outlined in the discussion section of the review. The various forms of evidence obtained were described in the text and summarised in tables.

2. Results

Forty-six papers were located and considered for inclusion in this review.[2-47] Sixteen were excluded because they did not report data for therapeutic kava whole-plant extracts: nine related to consumption of raw kava material[2-10] and seven were of an isolated constituent of kava.[11-17] Thirty papers were included in the review: two reported drug monitoring studies;[18,19] nine described clinical trials;[20-28] 11 were case reports including 20 individual cases[29-39] and eight papers described phase I studies.[40-47] Data from four spontaneous reporting schemes were also included.

2.1 Drug Monitoring Studies

A postmarketing surveillance study monitored 4049 adults taking 150mg daily of kava extract (Laitan®;[1] WS 1490) corresponding to 105mg daily of kavapyrones, for 6 weeks.[18] According to the assessment by the treating physician, the tolerability of kava was rated as 'good' or 'very good' in 96% of patients. A total of 61 adverse events were reported (1.5%). These were mainly gastrointestinal complaints or allergic reactions and were all mild and reversible. A causal relationship was rated as probable by the treating physician in approximately half these cases. For the remainder, causality was considered improbable or was not evaluated. No herb-drug interactions were observed in patients taking concomitant medication.

A further drug monitoring study involved 3029 adults taking one or two tablets daily of a kava extract (Antares®120) standardised to 120mg kavapyrones.[19] Tolerability was judged to be 'good' or 'very good' in 93% of patients. Adverse events were reported in 69 patients (2.3%), of whom 37 (1.2%) withdrew from the study. The most common reports were of allergic reactions (nine reports), gastrointestinal complaints[31] and central nervous system symptoms such as headache or dizziness.[22] In all cases, symptoms disappeared when kava was discontinued and none was considered serious.

2.2 Clinical Trials

Nine randomised clinical trials were included, all investigating the effect of kava extracts on anxiety symptoms. Eight were placebo controlled[20-27] and one compared kava with conventional anxiolytics.[28] The longest treatment period was 6 months[24,27] with the others all lasting 8 weeks or less. The highest daily dose of kava was 800mg,[25] with 300mg being most common. Three trials reported no adverse events in any patients and from the other six studies the following adverse events were reported: gastrointestinal symptoms, tiredness, restlessness, tremor and headache (table I). The numbers of patients reporting adverse events and the types of complaint were similar to the placebo groups.

2.3 Case Reports

2.3.1 Dermatological Reactions

Two cases of sebotrophic reactions following treatment for anxiety with kava extracts were described.[29] A 52-year-old woman was seen with papules and plaques on the face and later on her dorsal and ventral thorax and arms after taking a kava product for 3 weeks. A kava patch test was positive. A 70-year-old man experienced erythematous infiltrated plaques on the ventral and dorsal thorax and the face following several hours of sun-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

Table I. Randomised clinical trials of kava extracts for anxiety symptoms

Study	n	Preparation and daily dose (total kavapyrones)	Treatment duration	Adverse events reported (no. of patients)	
				kava group	control group
Placebo-controlled trials					
Bhate et al.[20]	59	Kavosporal® 300mg (60mg)	2 days (pre-operative)	Postoperative hangover (2)	Postoperative hangover (4)
Warnecke et al.[21]	40	Kavosporal® 300mg (60mg)	4 wks	Tiredness, low energy headache (5), gastrointestinal symptoms (3)	Gastrointestinal symptoms (2)
Warnecke[22]	40	Laitan® (WS 1490) 300mg (210mg)	8 wks	Restlessness, tiredness, tremor, gastrointestinal symptoms (4)	Restlessness, tiredness, tremor, gastrointestinal symptoms (6)
Kinzler et al.[23]	58	Laitan® 300mg (210mg)	4 wks	None	None
Volz and Kieser[24]	100	Laitan® 300mg (210mg)	24 wks	Gastrointestinal symptoms (2)	Vertigo, palpitation (3)
Singh et al.[25]	60	Kavatrol™ 800mg (240mg)	4 wks	None	None
Lehmann[26]	20	Kavosporal® 450mg (150mg)	1 wk	Not specified (1)	Not specified (3)
De Leo et al.[27]	40	Not specified 100mg (55mg)	24 wks	None	None
Comparative trial against anxiolytics					
Woelk et al.[28]	172	Laitan® 300mg (210mg)	6 wks	Gastrointestinal symptoms (1)	Tiredness; vertigo, pruritus (7)

n = number of patients; **wk(s)** = week(s).

light exposure. He had been taking a kava preparation along with six other medications for 2 to 3 weeks. Lymphocyte-transformation testing with suspected drugs in serial dilution revealed significant proliferation only with kava.

A 47-year-old woman presented with an erythematous rash on her back, upper extremities and face accompanied by proximal muscle weakness 2 weeks after starting a kava preparation.[30] The patient's condition improved following treatment with prednisone and discontinuation of kava.

A 36-year-old woman presented with a generalised rash, severe itching with erythema and papules, 4 days after discontinuing a kava preparation (Antares®) which she had taken at a dose of 120mg daily for a 3-week period.[31] The condition was resolved with corticosteroids and antihistamines, although the itching lasted several weeks. Patch tests with the kava extract administered 6 weeks later were positive after 1 day.

A 51-year-old woman presented with an itchy erythematous rash on the face, arms, neck and upper body.[32] She had been taking a kava preparation (Antares®), chlorprothixene and diazepam for several weeks and diclofenac for 6 days. Three weeks later she experienced a generalised symmetrical urticarious erythema after taking a single tablet of an isolated constituent of kava, the kavopyrine kavain (Neuronika®). Histological tests indicated an interface dermatitis consistent with a drug allergy. Skin patch testing was positive for kava. She made an uneventful recovery following treatment with antihistamines and corticosteroids.

2.3.2 Neurological Manifestations

Four cases of patients with extrapyramidal symptoms suggestive of central dopaminergic antagonism after ingestion of kava extracts have been described.[33] A 28-year-old man experienced an acute attack of involuntary neck extension and upward deviation of the eyes beginning within 90 minutes of taking 100mg kava (Laitan®). A 22-year-old woman experienced involuntary oral and lingual dyskinesias, tonic rotation of the head to the right and painful twisting movements of the trunk 4 hours after ingesting 100mg kava (Laitan®). A 63-year-old woman experienced forceful involun-

tary oral and lingual dyskinesias of sudden onset after taking 450mg daily of kava (Kavasporal forte®) for 4 days. A 76-year-old woman with idiopathic Parkinson's disease noted a pronounced worsening in the pattern of motor fluctuations and episodes of dyskinesias after 10 days of taking 300mg kava (Kavasporal forte®) concomitantly with levodopa and benserazide. In all patients, improvements were reported following treatment with biperiden or discontinuation of kava.

2.3.3 Liver Damage

Nine cases of liver damage occurring in association with ingestion of kava extracts have been reported.[34] Histological data from four patients were consistent with an immuno-allergic mechanism. Symptoms generally occurred between 3 weeks and 4 months of starting the kava extract with doses ranging from 60 to 210mg kavapyrones/day. In several cases other medications with hepatotoxic potential were being taken concurrently. The majority of cases involved acetone extracts, but one appeared to refer to an alcoholic extract of kavapyrones. This patient was a 39-year-old woman who developed necrotising hepatitis after taking 60mg kavapyrones daily for 6 months alongside other medications.[35] Following normalisation of liver values with discontinuation of all medications, a marked increase in transaminase levels occurred 14 days after she resumed use of the same herbal product. This increase was reversed upon discontinuation. Further information is available for two more of the nine cases. A 50-year-old man developed jaundice and subsequent liver failure following consumption of 300 to 400mg daily of kava extract (Laitan®) for 2 months.[36] He was taking no other medication and did not drink alcohol. The patient recovered uneventfully after a liver transplant. A 33-year-old woman developed jaundice after taking 300mg kava (Laitan®) for 3 weeks.[37] She took no other drugs but had consumed 60g of alcohol the day before she felt unwell. Liver values returned to normal within 8 weeks of discontinuing the herbal extract.

2.3.4 Myoglobinuria

The case of a 29-year-old man who experienced diffuse severe muscle pain and passed dark urine a few hours after ingesting a herbal combination product was reported.[38] Blood creatine kinase and myoglobin were raised considerably above normal values. No signs of an underlying metabolic myopathy could be found. The patient's condition improved within 6 weeks. The herbal preparation (Guaranaginko Plus) contained 500mg guarana, 200mg ginkgo and 100mg kava. The authors believed that the methylxanthine effects of guarana and the antidopaminergic and neuromuscular blocking activities of kava to be pathologically relevant to the rhabdomyolysis observed in the patient.

2.3.5 Herb-Drug Interaction

One report has been published reporting a suspected interaction between kava and a benzodiazepine.[39] A 54-year-old man whose medication included alprazolam as well as cimetidine and terazosin, was hospitalised in a lethargic and disorientated state after taking a kava extract for 3 days. His vital signs were normal and he regained alertness after several hours. His alcohol level was negative and he denied taking an overdose of kava or alprazolam.

2.4 Spontaneous Reporting Schemes

The WHO Collaborating Centre for International Drug Monitoring had received reports of adverse events relating to kava preparations from the national drug safety bodies of Austria and Germany as of November 2000. The WHO state that the information is not homogenous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and that the information does not represent the opinion of the WHO. Reports of 78 adverse events were received from Germany and two from Austria. The adverse events reported from Austria were anxiety and increased sweating, but no further details were available. The adverse events reported from Germany (table II) related to 47 individual patients. In 44 of these cases, kava was the only suspected drug

Table II. Reports of adverse events associated with kava extracts from the database of the WHO Collaborating Centre for International Drug Monitoring

Type of adverse event (no. of reports)
Body as a whole – general disorders (5)
Anaphylactic shock (2)
Allergic reaction (2)
Chest pain substernal (1)
Skin and appendages disorders (29)
Stevens-Johnson syndrome (1)
Angio-oedema (1)
Dermatitis (3)
Erythema (2)
Aggravated psoriasis (1)
Pruritus (6)
Rash (9)
Increased sweating (1)
Urticaria (5)
Cardiovascular disorders, general (1)
Hypotension (1)
Central and peripheral nervous system disorders (7)
Abnormal coordination (1)
Dizziness (2)
Headache (3)
Speech disorder (1)
Gastrointestinal disorders (10)
Abdominal pain (3)
Dyspepsia (1)
Nausea (3)
Tongue discolouration (1)
Vomiting (2)
Heart rate and rhythm disorders (2)
Tachycardia (2)
Liver and biliary system disorders (6)
Increased hepatic enzymes (1)
Hepatitis (2)
Hepatocellular damage (1)
Jaundice (2)
Metabolic and nutritional disorders (2)
Hyperglycaemia (1)
Generalised oedema (1)
Psychiatric disorders (8)
Aggressive reaction (1)
Agitation (1)
Anxiety (4)
Hallucination (1)
Nervousness (1)
Respiratory system disorders (4)
Asthma (1)
Dyspnoea (2)
Rhinitis (1)
Urinary system disorders (3)
Face oedema (3)
Vision disorders (5)
Abnormal accommodation (1)
Abnormal vision (3)
Chromatopsia (1)

although ten patients were taking other medications concomitantly. No interactions with other drugs were reported. All reports referred to kava monopreparations. In 22 cases a definite improvement was reported following dechallenge. In the five cases where there was a rechallenge, four resulted in a recurrence of symptoms. In 21 cases causality was rated as possible while the remainder were unclassified (see table III for definitions). Twenty-six patients recovered without sequelae, two had not yet recovered at the time of reporting and in the remaining 19 patients the outcome was unknown.

The data provided by the BfArM in Germany consisted of 19 reports of liver-related adverse events received between December 1993 and February 2001. Thirteen of these related to monopreparations of kava. three reports were of hepatic failure, three of hepatitis, one of cholestatic hepatitis, one of jaundice, two of hepatocelluar damage, one of increased hepatic enzymes, one of haematemesis and one of abdominal pain. In seven cases, kava was the only suspected drug. A more recent document available since November 2001 on the BfArM website (http://www.bfarm.de) stated that a total of 24 cases of liver-related adverse events had been reported, including one fatality. Three patients underwent liver transplants. Five patients were taking no co-medication. In 18 patients causality was rated as likely or possible.

As of May 2001, the CSM had received reports of suspected adverse reactions associated with kava extracts in two middle-aged patients. The first report related to confusion and auditory and visual hallucinations associated with a suspected interaction between kava and flunitrazepam; the patient recovered after the drugs were discontinued. The second report was of myalgia, increased creatine phosphokinase and leucopenia following administration of a kava preparation for 1 month and St John's wort for 2 months.

The most recent update available (October 1998) of the web report of the Special Nutritionals Adverse Event Monitoring System of the FDA included 35 reports of adverse events associated with

Table III. WHO definitions for causality assessment of suspected adverse reaction

Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable/likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Conditional/unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
Unassessible/ unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

products containing kava, including one death. In all but one case, these were combination preparations of which kava was listed as one of a large number of ingredients. Most reports referred to an overdose of a preparation called 'FX' that is promoted for recreational purposes. The one report relating to a kava monopreparation was of deep somnolence, but no further details were provided.

2.5 Phase I Studies

2.5.1 Effects on Performance

In three studies testing the effect of kava on various cognitive and personality variables, doses of up to 600mg daily of kava extract (Laitan®) taken for one week had no detrimental effect on vigilance, reaction time, memory or coordination.[40-42] The results of another small, placebo-controlled trial indicated no deterioration in psychomotor test parameters following a single dose of kava extract (Antares 120®) containing 120mg kavapyrones.[43]

A further double-blind, randomised placebo-controlled trial investigated the effect on driving ability of taking 300mg daily of kava (Laitan®) for 15 days.[44] Results from a battery of tests including measures of optical orientation, concentration, reaction time under stress, vigilance and motor coordination indicated no deterioration in performance.

2.5.2 Effects with Alcohol

The effect of combining kava with alcohol on psychomotor performance was tested in a double-blind, placebo-controlled randomised trial involving 40 volunteers.[45] Participants took 300mg daily of kava (Laitan®) or placebo for 8 days, consuming alcohol on 3 separate days to reach a blood alcohol concentration of 0.05%, then undergoing a battery of tests measuring vigilance, coordination, reaction time and concentration. No potentiation of alcohol with the kava extract could be detected in comparison with placebo. Adverse events consisting of gastrointestinal symptoms, tiredness and headache were reported by ten volunteers from the kava group and 12 of those receiving placebo.

2.5.3 Effects with Anxiolytic Drugs

A further double-blind, randomised crossover trial examined the effects of combining a kava extract and conventional anxiolytic medication.[46] Eighteen volunteers participated receiving either 800mg daily of kava (Antares®) or 9mg daily of bromazepam or both for 14 days each. Results from a battery of tests indicated no significant differences between bromazepam alone and the com-

bination with kava. Performance was no different to baseline with kava alone. Seventy-seven adverse events were reported, of which 22% were related to kava, 36% to bromazepam and 42% to the combination. Tiredness was the most common complaint, reported in four volunteers while taking kava, 11 with bromazepam and 14 with the combination.

2.5.4 Effects on Sleep

A double-blind, randomised placebo-controlled trial examined the effect of a 150mg or 300mg dose of kava (Latain®) on the sleep pattern of 12 volunteers.[47] With the higher dose, superiority over placebo was reported in sleep latency, duration and quality according to objective measures and subjective reports with no adverse events reported.

3. Discussion

Most of the information included in this review has to be interpreted with caution because of its anecdotal nature. A temporal association between adverse events and the ingestion of kava extracts does not provide sufficient evidence that kava was responsible for the symptoms experienced since other (sometimes unknown) factors may be involved.

Despite the comprehensive search procedures, the material uncovered is likely to under-represent the frequency of suspected adverse events associated with kava due to under-reporting. This is a problem that is even more pronounced with herbal medicines than conventional pharmaceutical agents. This may be partly due to the common misconception that since herbs are natural, they are necessarily safe – a belief that may prevent an association being made between an adverse event and use of an herbal extract. However, there is also evidence that patients are less likely to report adverse events from herbal remedies to physicians than those from conventional medication.[48]

Some sources of information provide only limited information on safety.[49] For example clinical and phase I trials study relatively small numbers of patients for short time periods so are unlikely to detect rare or delayed adverse events. Furthermore, the number of adverse events reported varies with use of active or passive methods of data collection. Post-marketing surveillance studies have larger samples than trials, but similar time frames. There is therefore a lack of data on the long term therapeutic use of kava extracts and the German Commission E monograph suggests no more than 3 months use without medical advice.[50] Similarly, in the absence of data on the its use during pregnancy and lactation, kava should be regarded as contraindicated at these times.

The data from drug monitoring studies and clinical trials suggest that, at least in the short-term, kava extracts are well tolerated by the majority of users with adverse events being generally rare, mild and reversible. Similar frequencies and types of adverse event have been reported in studies involving preparations of the kavopyrine kavain.[11,12]

The information from spontaneous reporting schemes also suggests that the most common adverse events are non-serious, but indicates the possibility of graver outcomes.

The most serious concern identified in relation to kava extracts is the risk of liver damage. Cases published in the literature and reported to spontaneous reporting schemes suggest such an association. Case reports do not necessarily imply causality and in several cases other medications with hepatotoxic effects were being taken concurrently. However, because of its importance, this possible adverse effect of kava must be systematically investigated. The potential for hepatotoxic effects of kava was suggested by a study of aboriginal kava drinkers in whom γ-glutamyl transferase (GGT) was elevated.[2] Follow-up assessments of individuals who had reduced their kava consumption indicated improvements in liver function tests.[6] The relevance of these observations to the recent cases reported with kava extracts is unclear since these are not related to high doses or long term consumption of kava. There is some evidence that immunoallergic effects may explain the adverse events.[34] In many countries, kava products have been withdrawn from sale due to concern over liver toxicity.

Until further evidence emerges, hepatic impairment should be considered a contraindication for kava and monitoring liver function in all patients using kava extracts might be recommended.

Reports of dyskinetic reactions after ingestion of kava extracts, point to dopamine antagonistic properties of the herb.[33] Similar phenomena have been reported following kava drinking binges.[4] At least two of these individuals had a history of motor disturbances, one being parkinsonian in whom an interaction between kava and levodopa can not be ruled out. In the absence of conclusive data about the effects of kava on dopamine,[51] it is suggested that kava should be contraindicated in patients with neurological disorders or those treated with levodopa.

The information available from the spontaneous reporting scheme of the FDA contained only one report relating to a monopreparation of kava. The remainder were of combination products and most referred to a recreational supplement 'FX'. It seems likely that most of these cases relate to a reported incident in 1996 when the drug was distributed to concert-goers in Los Angeles.[52] It is reported that 50 people experienced symptoms such as dizziness, nausea and shortness of breath and many were hospitalised. When samples of 'FX' were analysed by the American Botanical Council, no kava could be detected. Cases of adverse events associated with the recreational use of 'herbal ecstasy' tablets have also been reported in New Zealand,[7] although none of the patients described were known to have taken preparations which listed kava among its ingredients. Most 'herbal ecstasy' products are based largely on sources of caffeine and ephedrine and also contain various herbs and vitamins.

Controlled trials on healthy volunteers suggest that neither single nor repeated doses of kava have detrimental effects on cognitive or motor performance. This is an important finding given the risks involved with driving or operating machinery when taking conventional anxiolytics.[53] However, these trials were all small and further investigation is required before kava can be regarded as safe to use in these circumstances. Studies examining the effects on cognitive performance of kava beverages also suggest that it is not significantly impaired[8-10] and the study of aboriginal kava drinkers found no effect of kava on memory, cognition and coordination.[2] Controlled trials of extracts of kavain in healthy volunteers have also demonstrated no impairment (and some improvements) in cognitive performance with doses ranging from 200 to 1000mg.[13-17]

The results of one trial suggested that, unlike most anxiolytics, kava extracts do not potentiate the effects of alcohol.[45] This is in contrast with a randomised trial examining the acute effects of a kava drink and alcohol.[10] Cognitive performance tests and subjective measures of intoxication indicated greater impairment with the combination of kava and alcohol, than either drink alone. These conflicting findings may be due to the quantity of kava rhizome consumed (1 g/kg bodyweight) being greater than the typical dose received in standardised extracts. However, until further studies clarify the situation, it would appear reasonable to avoid the concomitant use of alcohol and kava extracts. Similarly, the interactive effects of kava on conventional anxiolytic agents are unclear. one study indicated no potentiation of the effects of bromazepam.[46] However, at least one case has been reported in the literature of a suspected interaction between kava and alprazolam leading its authors to warn of 'potential for dangerous interactions between kava and prescription drugs'.[39] This conclusion has been strongly criticised[54] and it was suggested that the reported state of the patient was more likely to be attributable to alprazolam alone or an interaction between alprazolam and cimetidine or terazosin.[52] Nonetheless, in the absence of adequate data, the cautious approach would be to avoid concomitant use of kava extracts and medications acting on the central nervous system.

4. Conclusions

Although reliable evidence relating to the safety of kava extracts is limited, current data seem to suggest that monopreparations are generally well

tolerated by most users when taken as a short-term mono-therapy at recommended doses. However, serious adverse events have been reported some individuals, most notably liver damage. Further research is required to determine the nature and frequency of such events.

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