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REVIEW

Role of Ethanol in Kava Hepatotoxicity

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Kava is known for its recreational, ceremonial and medicinal use in the Pacific. The aqueous non-alcoholic drink of kava rhizome produces intoxicating, relaxing and soothing effects. While kava's medicinal effects receive worldwide recognition, kava-containing products came under scrutiny after over 100 reports of spontaneous adverse hepatic effects. Many mechanisms have been postulated to explain the unexpected toxicity, one being pharmacokinetic interactions between kavalactones and co-administered drugs involving cytochrome P450 enzyme system. Alcohol is often co-injested in kava hepatotoxicity cases. This review evaluates the possible hepatotoxicity mechanisms involving alcohol and kava. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: kava; hepatotoxicity; alcohol; interactions.

INTRODUCTION – PAST AND PRESENT KAVA USE

Traditional and modern use

The name 'kava' is derived from the Polynesian word *awa* meaning 'bitter' which describes the characteristic taste of the intoxicating water-based non-alcoholic beverage prepared from kava rhizome (MHPRA, 2006). This traditional kava drink is claimed to reduce fatigue, ease pain, allay anxiety, induce sleep and produce a sociable attitude (MHPRA, 2006). In the Pacific, where alcohol fermentation did not evolve early, kava has been consumed for centuries for ceremonial and recreational purposes without serious adverse effects (Whitton *et al*., 2003).

In the 1990s, based on favorable clinical studies (Munte *et al*., 1993; Volz and Kieser, 1997) standardized kava preparations were approved as hypnotics and anxiolytics in Europe (MHPRA, 2006). These products are generally dried acetone and/or ethanol extracts rather than aqueous extracts in traditional kava drink (Bilia *et al*., 2002). Kava plant parts, other than the rhizome, may be used in these commercial preparations (Whitton *et al*., 2003).

Australian Aboriginal communities in the Northern Territory use the traditional kava water extract as an alternative to alcohol (Mathews *et al*., 1988). Recently there have been concerns of kava abuse in these communities, particularly the concurrent use of kava and alcohol (Clough *et al;* 2003; 2004).

Epidemiology of concomitant alcohol and kava use

Epidemiological data for alcohol and kava co-ingestion in western societies are lacking. In the USA, where kava is freely available, 67% of the adult population drinks alcohol (Sass and Shaikh, 2006). Similarly in Australia, where kava products are available below the suggested harmful amount, 1 in 2 adults drink alcohol regularly (National Health and Medical Research Council, 2001). Kava-alcohol combination has twice been noted in kava hepatotoxicity case reports (MHPRA, 2006) and is prevalent in remote Aboriginal communities (approximately 20% of participants used kava and alcohol concomitantly in the Eastern Arnhem Land study) (Mathews *et al*., 1988).

ACTIVE CHEMICALS AND METABOLISM

Chemical composition

Kavalactones are the actives responsible for the observed kava pharmacological activities as well as the inhibition of cytochrome P450 (CYP450) enzymes (Fu *et al*., 2008a). Six of the 18 kavalactones (Fig. 1), found in kava rhizomes represent ~96% of the total kavalactones (MHPRA, 2006).

Alkaloids and amides are also found in kava. Pipermethystine and 3α, 4α–epoxy-5β-pipermethystine (Fig. 2), are concentrated in the stem peelings (Dragull *et al*., 2003) and are implicated in kava hepatotoxicity (Lim *et al*., 2007).

Kavalactone and alcohol metabolism

Kava metabolism. The principal metabolic transformations of kavalactones are proposed to be (Fig. 3) (Duffield *et al*., 1989; Rasmussen *et al*., 1979):

1. Reduction of the 3–4-double bond and/or demethylation of the 4-methoxyl group of the alpha-pyrone ring.
2. Hydroxylation at C-12 of the aromatic ring. Hydroxylated kavain and dihydrokavain are the most abun-

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dant urinary metabolites excreted as glucuronide and sulphate conjugates.
3. Reduction of 7,8 double bond in kavain, yangonin and methysticin.
4. Hydroxylation of the C-11,12 of the aromatic ring in methysticin.

Kavalactones are usually metabolized in liver by CYP450 enzymes (Whitton *et al*., 2003) particularly CYP3A and 1A (Guo *et al.,* 2009). Several kavalactone reactive metabolites have been implicated in kava hepatotoxicity. Amongst these, two electrophilic quinoid metabolites have been identified *in vitro* (Johnson *et al*., 2003; Zou *et al*., 2004) and another reactive metabolite (6-phenoxy-3-hexen-2-one, 6-PHO) has been identified as a mercapturic acid derivative in human urine (Zou *et al*., 2005).

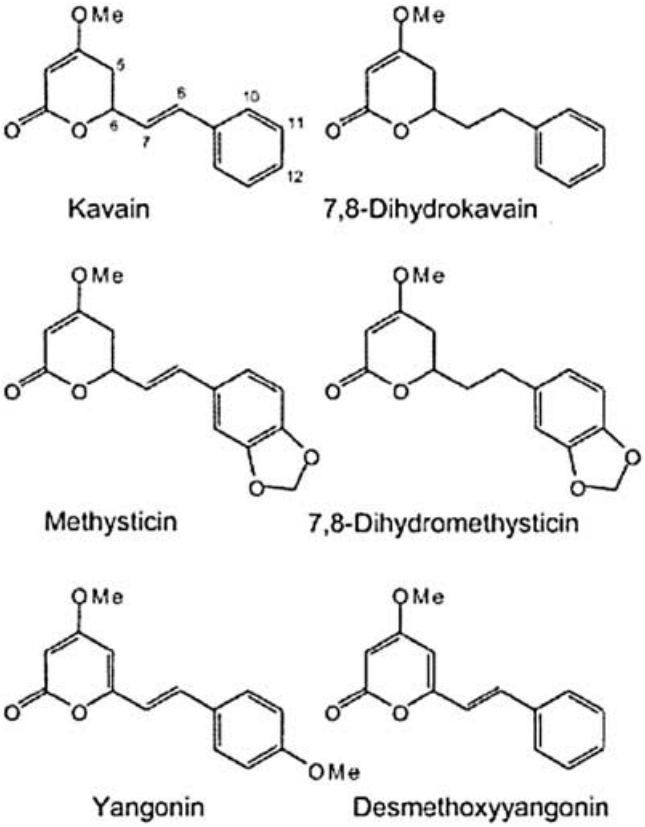

Figure 1. Structures of the six main kavalactones (MHPRA, 2006).

Alcohol metabolism. More than 90% of alcohol is metabolized to acetylaldehyde by three oxidizing enzymes: (1) Alcohol dehydrogenase (ADH); (2) Microsomal ethanol oxidizing system (MEOS) involving CYP 2E1 and (3) Catalase (Rockerbie, 2001). Although MEOS plays a less significant role compared to ADH in naive drinkers (Rockerbie, 2001), at high alcohol concentrations it accounts for more than 40% of alcohol oxidation (Rockerbie, 2001). Chronic alcohol intake induces MEOS activity (Rockerbie, 2001); CYP 2E1 expression increased 4–10-fold in chronic alcohol drinkers (Lieber, 1997). Increased CYP 2E1 levels are associated with enhanced oxidative stress due to the unique capacity of CYP 2E1 to generate reactive intermediates and to activate many xenobiotics to their toxic metabolites (Lieber, 1997).

KAVA HEPATOTOXICITY

Prior to 1998 there were no major safety concerns with kava (MHPRA, 2006). Adverse events observed in kava clinical trials and post-marketing surveillance studies included kava dermopathy, allergic reactions, gastrointestinal symptoms, tiredness, tremor, weight changes, tachycardia and headache (Ulbricht *et al*., 2005). None of the studies reported hepatotoxicity, which may have been due to lack of liver function monitoring, short study durations and limited variety and strength of kava preparations being studied (Barnes *et al*., 2007; Stevinson *et al*., 2002). While these clinical trials failed to identify the adverse hepatic effects, spontaneous case reports emerged in the late 1990s; to date there are over 100 cases worldwide (MHPRA, 2006). These reports comprise the substantial evidence against kava leading to restricted kava sales in many countries (MHPRA, 2006).

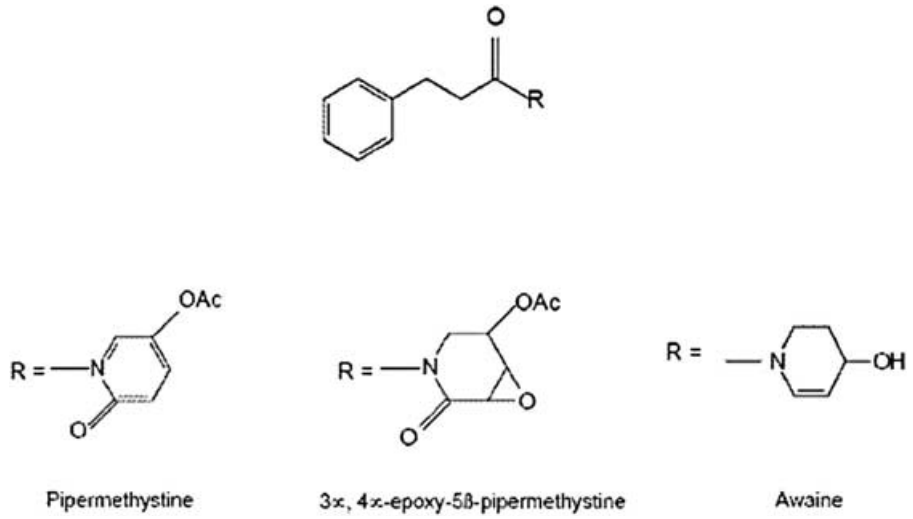

Figure 2. Structures of the alkaloidal constituents in kava plant (MHPRA, 2006).

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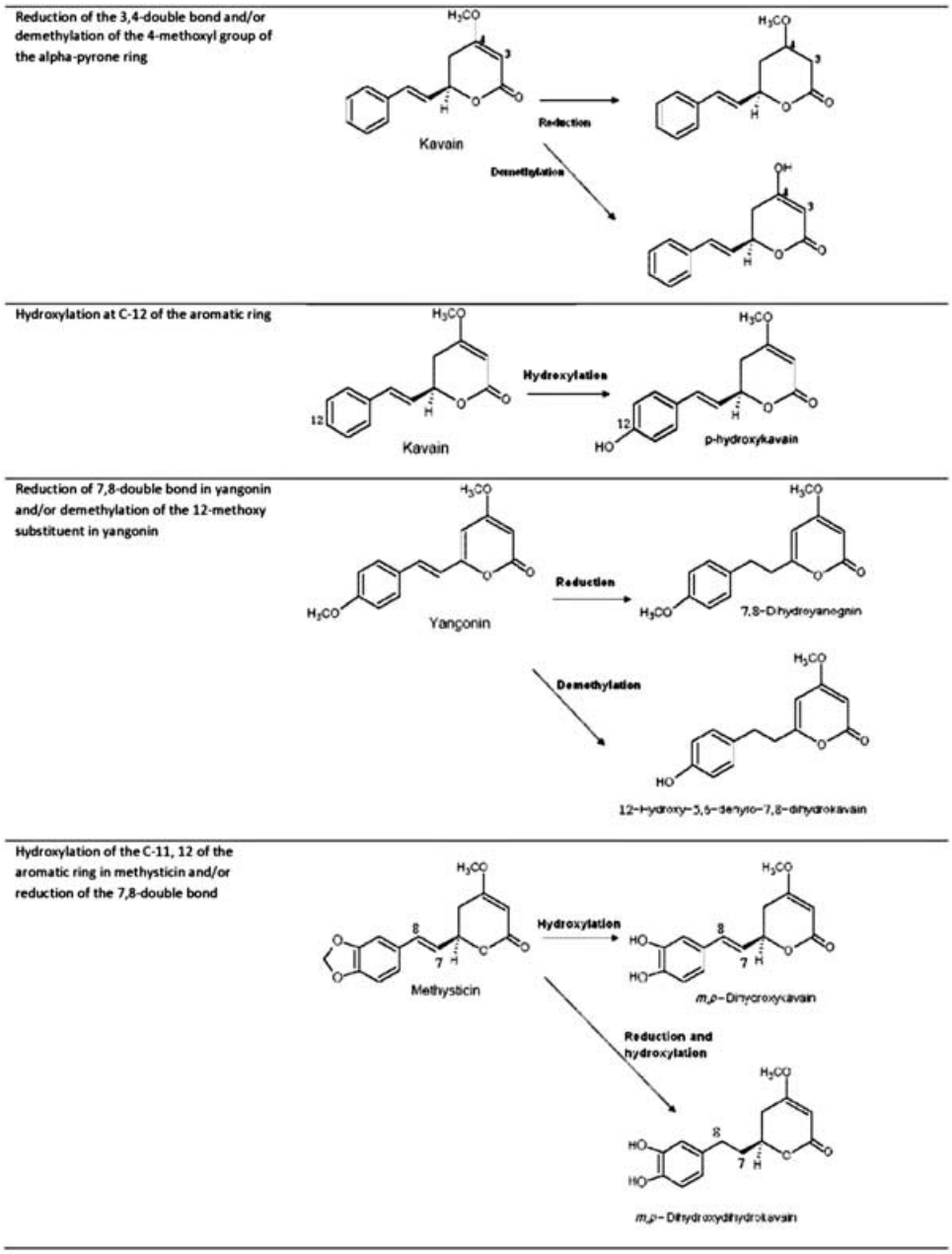

Figure 3. Proposed metabolic transformations of kavalactones.

Many theories on the mechanism of kava-induced hepatoxicity have been proposed. However, the fundamental question remains as to whether or not kava is hepatotoxic (Anke and Ramzan, 2004). Some argue that causality cannot be established with sufficient certainty from spontaneous reports particularly in view of the co-ingestion of other potentially hepatotoxic agents, such as alcohol, and/or pre-existing liver disease (Ernst, 2007).

HEPATOTOXICITY MECHANISMS

Hepatotoxicity is broadly categorized into two types: (1) Dose-related direct toxicity caused by the parent drug and/or metabolites; (2) Idiosyncratic reactions, which do not have a clear dose-response relationship (Li, 2002).

Direct toxicity

On the basis of case reports, German kava sales figures and two drug monitoring studies, Ernst (2007) estimated that the incidence of liver injury is one in 60–125 million kava doses or less than one in 2500 individuals. This rate is high in view of the long history of apparent safe use of kava, and arguably this is also a high incidence to fit into an idiosyncratic reaction, which occurs in less than one in 5000 individuals (Li, 2002). Kavalactones can be biotransformed into reactive metabolites, which, similar to paracetamol, may deplete liver glutathione (GSH). Moreover, heavy kava use has been associated with liver damage suggesting the possible dose related nature of injury (Mathews *et al*., 1988).

Mechanisms of direct kavalactone cytotoxicity. Only a few studies have investigated direct kavalactone toxicity; *in vitro* no cytotoxicity of kava extracts and kava-

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lactones were noted in isolated human hepatocytes (unpublished data, 2003, cited in *J Altern Complement Med* **2:** 183–188). Similarly Zou *et al.* (2004) tested the toxicity of methysticin, yangonin and desmethoxyyangonin in human cH2 cells; only moderate cytotoxicity was noted at concentrations unlikely to be reached with therapeutic doses. In contrast, a recent study with kavain demonstrated severe liver vascular and endothelial damage in rat liver (Fu *et al*., 2008b). This study, for the first time, implicated kavain in directly causing liver ultrastructual damage either via direct interaction with endothelial lining and/or by activation of local liver-associated macrophages leading to release of cytotoxic substance (Fu *et al*., 2008b).

Alcohol and the generation of reactive metabolites. CYP 2E1 may also be involved in kavalactone metabolism; it catalyzes oxidative reactions (demethylation and hydroxylation) as well as reductive reactions and has a relatively wide substrate specificity including several aromatic compounds (Lieber, 1997). CYP 2E1-mediated metabolism often generates more toxic metabolites than the parent compound (Lieber, 1997). This may be the mechanism for the increased susceptibility to liver injury with the co-administration of alcohol with isoniazid, and perhaps kavalactones, although only a few studies have explored such a mechanism for kavalactones (Fraser, 1997). Zou *et al.* (2004) studied the metabolic toxicity of kava using MCL-5 cells transfected with several human CYP450s (CYP 1A1, 1A2, 2E1 and 3A4) and human epoxide hydrolase. This study, however, found that kavalactones are not bioactivated by CYP 2E1 or other CYP enzymes. This study did only examine a limited number of CYPs and three of the six main kavalactones (methysticin, yangonin and desmethoxyyangonin) (Zou *et al*., 2004). Futhermore, the generation of toxic metabolites may require sequential metabolism or kava-hepatotoxicity may be an immune-mediated idiosyncratic reaction (Zou *et al*., 2004).

Alcohol and paracetamol-like hepatotoxicity mechanism for kavalactones. Induction of CYP 2E1 by alcohol is proposed as a mechanism augmenting the formation of reactive paracetamol metabolites and its hepatotoxicity (Fraser, 1997; Lieber, 1997). There is a characteristic delayed onset of paracetamol toxicity which peaks after alcohol withdrawal when toxic metabolite levels are highest resulting in subsequent depletion of hepatic GSH (Lieber, 1997).

Kava-induced hepatotoxicity, similar to that of paracetamol, is also characterized as a delayed phenomenon (Whitton *et al*., 2003; MHPRA, 2006), and the metabolism of kavalactone is thought to be enhanced by GSH. As in alcoholics, elevated gamma glutamyltransferase (GGT) has been reported in heavy kava users (Mathews *et al*., 1988; Russmann *et al*., 2003), as well as in animals (Russmann *et al*., 2003; Clayton *et al*., 2007). GGT elevation indicates the involvement of GSH in metabolism since GGT facilitates GSH conjugate disposition and ensures high intracellular GSH (Sass and Shaikh, 2006).

As with paracetamol, reactive kavalactone metabolites that conjugate with GSH have been identified. Johnson *et al.* (2003) identified two GSH conjugated electrophilic reactive metabolites (σ-quinones) of kavain and 7,8-dihydrokavain. Quinones are electrophilic reactive phase I metabolites that react with GSH and can cause toxicity via covalent modification of biological proteins and/or through redox cycling leading to formation of reactive oxygen species (Johnson *et al*., 2003). In another study, Zou *et al.* (2005) identified a mercapturic acid derivative in human urine; the authors proposed 6-phenyl-3-hexen-2-one (6-PHO) as the reactive metabolite that reacts with GSH. Thus GSH conjugation of kavalactones may represent a detoxification pathway which alleviates the oxidative stress caused by σ-quinones and 6-PHO (Johnson *et al*., 2003).

Interestingly, GSH is present in traditional kava beverage in a 1:1 ratio with kavalactones (Whitton *et al*., 2003); it is absent in commercial kava preparations (Whitton *et al*., 2003). While this lack of GSH has been proposed to contribute to kava hepatotoxicity (Whitton *et al*., 2003), an opposing view is that the presence of GSH would deactivate kavalactones and reduce their pharmacological activity (Schmidt *et al*., 2002). However, since kavalactones are only weak electrophiles, this hypothesized deactivation by GSH requires further testing.

Idiosyncratic reactions

While the evidence surrounding direct kava toxicity is conflicting, kavalactones appear to satisfy all the hypothesized endpoints for the idiosyncratic hepatotoxicity mechanism (Li, 2002). That the clinical studies failed to detect kava hepatotoxicity reflects a critical feature of the idiosyncratic reaction such that the toxicity is often delayed (MHPRA, 2006) and not able to be detected in clinical trials (Pittler and Ernst, 2003), animal (Singh, 2003) and cellular studies (Zou *et al.,* 2004). Moreover, dihydrokavain and yangonin inhibit COX-II (Wu *et al*., 2002) and classic COX inhibitors, like diclofenac and lumiracoxib are associated with idiosyncratic hepatotoxicity (Aithal and Day, 2007). COX-II-derived mediators are hepato-protective (Aithal and Day, 2007) and COX inhibition may thus predispose individuals to kava liver injury.

Formation of reactive metabolites. As discussed, reactive metabolites are also capable of mediating immune toxicity by forming protein adducts which serve as neoantigens leading to idiosyncratic reactions. Many xenobiotics that cause immune-induced hepatotoxicity are bioactivated by CYP 2E1, 2C9 and 3A (Li, 2002). The latter plays an important role in kavalactone metabolism, and CYP 2E1 is induced 3–4-fold during chronic alcohol intake (Lieber, 1999). Thus, kavalactone intake during chronic alcohol may accelerate generation of reactive metabolites resulting in a greater risk of kava hepatotoxicity.

Extent of exposure. A threshold dose/concentration exists above which it is more likely to initiate a cascade of events leading to a toxic immune response (Li, 2002).

Many factors can increase exposure to kavalactones. First, kavalactone content in standardized extracts are 30 times more than that of the traditional aqueous extract (Whitton *et al*., 2003). Secondly, enzyme interactions of kava with co-administered xenobiotics, such as

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alcohol, can also increase kava organ concentration. Acute alcohol ingestion is known to decrease the metabolism of some xenobiotics probably via direct competition for CYP 2E1, 1A and 3A enzymes (Mattila, 1990; Fraser, 1997). CYP 2D6 deficiency is also linked with higher kavalactone exposure.

CYP450 activity. Reduced CYP450 activity due to inhibition, either via acute alcohol ingestion or other xenobiotic interactions, may lead to increased exposure to kavalactones, hence contributing to hepatic risk. Induction of liver enzymes is also a well-recognized toxicological phenomenon (Li, 2002); CYP450 induction by kavalactones has been demonstrated in some studies. Daily oral doses of kava extract for 7 to 14 days significantly enhanced hepatic CYP 1A2, 2B1, and 3A, and moderately induced CYP 2E1 (Mathews *et al*., 2005; Clayton *et al*., 2007). Thus although CYP450 induction may be beneficial by limiting kava exposure, increased CYP450, particularly those that generate reactive/toxic metabolites, may produce higher concentrations of toxic metabolites.

Genetic factors. CYP 2D6 deficiency has been documented in two hepato-adverse case reports (Russmann *et al*., 2001). CYP 2D6 deficiency occurs in 7–9% of Caucasians, 5.5% of Western Europeans, 1% of Asians and less than 1% of Polynesians (Ingleman-Sundberg, 2005). These genetic differences, particularly between Polynesians and Caucasians, may increase predisposition to hepatotoxicity in Caucasians (Singh, 2005) This hypothesis however, requires further testing to see if CYP 2D6 plays a major role in kavalactone metabolism.

Cultivation and environmental factors. It remains to be established if the commercial kava extracts incorporate different cultivars (MHPRA, 2006) and different parts of kava plants (Dragull *et al*., 2003; Food Standards Australia New Zealand, 2004). It is suspected that kava-induced hepatotoxicity may be due to the presence of kava alkaloid (pipermethystine) which is found only in the stem peelings and aerial parts – the kava plant components that are avoided in traditional kava drink (Dragull *et al*., 2003; Anke and Ramzan, 2004). Nerurkar *et al.* (2004) demonstrated disruption of mitochondrial function by pipermethystine in HepG2 cells.

SUMMARY

No single mechanism explains kava hepatotoxicity and its unpredictable nature. This review has evaluated the possible mechanisms and the strength of literature evidence available to support or refute a particular mechanism; in particular, how alcohol may play a role in kava-hepatotoxicity by generating reactive metabolites via CYP 2E1 during chronic alcohol intake or by hepatic enzyme inhibition during acute alcohol ingestion leading to enhanced kavalactone exposure. There are reasonable grounds to suggest that a metabolic interaction of kava with alcohol might be a possible mechanism of kava hepatotoxicity.

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REFERENCES

Aithal G, Day C. 2007. Nonsteroidal anti-inflammatory drug-induced hepatotoxicity. *Clin Liver Dis* **11**: 563–575.

Anke J, Ramzan I. 2004. Kava Hepatotoxicity: Are we any closer to the truth? *Planta Med* **70**: 193–196.

Barnes JA, Linda A, Phillipson JD, Newall CA. 2007. *Herbal Medicines* (3rd edn). Pharmaceutical Press: London.

Bilia AR, Sandra G, Vincieri FF. 2002. Kava-kava and anxiety: growing knowledge about the efficacy and safety. *Life Sci* **70**: 2581–2597.

Clayton K, Kissling G, Burka L, Chan P, Nyska A. 2007. Immunohistochemical analysis of expressions of hepatic cytochrome P450 in F344 rats following oral treatment with Kava extract. *Exp Toxicol Pathol* **58**: 223–236.

Clough AR, Jacups SP, Wang Z, Burns CB, Bailie RS, Cairney SJ, Collie A, Guyula T, McDonald SP, Currie BJ. 2003. Health effects of kava use in an eastern Arnhem Land Aboriginal community. *Intern Med J* **33**: 336–340.

Clough AR, D'Abbs AP, Cairney S, Gray D, Maruff P, Parker R, O'Reilly B. 2004. Emerging patterns of cannabis and other substance use in Aboriginal communities in Arnhem Land, Northern Territory: a study of two communities. *Drug Alcohol Rev* **23**: 381–390.

Dragull K, Yoshida WY, Tang CS. 2003. Piperidine alkaloids from Piper methysticum. *Phytochemistry* **63**: 193–198.

Duffield AM, Jamieson DD, Lidgard, RO, Duffield PH, Bourne DJ. 1989. Identification of some human urinary metabolites of the intoxicating beverage kava. *J Chromatogr A* **475**: 273–281.

Ernst E. 2007. A re-evaluation of kava (Piper methysticum). *Br J Clin Pharmacol* **64**: 415–417.

Food Standards Australia New Zealand. 2004. *Kava. A Human Health Risk Assessment (Technical report series No. 30).*

Fraser AG. 1997. Pharmacokinetic interactions between alcohol and other drugs. *Clin Pharmacokinet* **33**: 79–90.

Fu PP, Xia Q, Guo L, Yu H, Chan PC. 2008a. Toxicity of kava kava. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* **26**: 89–112.

Fu S, Korkmaz E, Braet F, Ngo Q, Ramzan I. 2008b. Influence of kavain on hepatic ultrastructure. *World J Gastroenterol* **14**: 493–656.

Guo L, Li Q, Xia Q, Dial S, Chan P, Fu P. 2009. Analysis of gene expression changes of drug metabolizing enzymes in the livers of F344 rats following oral treatment with kava extract. *Food Chem Toxicol* **47**: 433–442.

Ingelman-Sundberg M. 2005. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* **5**: 6–13.

Johnson BM, Qiu SX, Zhang S, Zhang F, Burdette JE, Yu L, Bolton JL, Van Breemen RB. 2003. Identification of novel electrophilic metabolites of piper methysticum Forst (Kava). *Chem Res Toxicol* **16**: 733–740.

Li AP. 2002. A review of the common properties of drugs with idiosyncratic hepatotoxicity and the 'multiple determinant hypothesis' for the manifestation of idiosyncratic drug toxicity. *Chem Bio Interact* **142**: 7–23.

Lieber CS. 1997. Cytochrome P-4502E1: its physiological and pathological role. *Physiol Rev* **77**: 517–544.

Lieber CS. 1999. Pharmacology and metabolism of alcohol, including its metabolic effects and interactions with other drugs. *Clin Dermatol* **17**: 365–379.

Lim STS, Dragull K, Tang CS, Bittenbender HC, Efird JT, Nerurkar PV. 2007. Effects of kava alkaloid, pipermethystine, and kavalactones on oxidative stress and cytochrome P450 in F–344 rats. *Toxicol Sci* **97**: 214–221.

Mathews JD, Reily MD, Fejo L, Munoz E, Milns NR, Gardner ID, Powers JR, Ganygulpa E and Gununuwawuy BJ. 1988. Effects of the heavy usage of kava on physical health:

Summary of a pilot survey in an aboriginal community. *Med J Aust* **148**: 548–555.
Mathews JME, Amy S, Valentine JL, Black SR, Coleman DP, Patel P So J, Burka LT. 2005. Pharmacokinetics and disposition of the kavalactone kawain: interaction with kava extract and kavalactones in vivo and in vitro. *Drug Metab Dispos* **33**: 1555–1563.
Mattila M. 1990. Alcohol and drug interactions. *Ann Med* **22**: 363–369.
MHPRA. 2006. *Committee on Safety of Medicine's Expert Working Group (Kava). Report of the CSM's expert working group on the safety of kava.* Medicines and Healthcare Products Regulatory Agency (MHPRA).
Munte TF, Heinze HJ, Matzke M, Steitz J. 1993. Effects of oxazepam and an extract of kava roots (Piper methysticum) on event-related potentials in a word recognition task. *Neuropsychobiology* **27**: 46–53.
National Health and Medical Research Council. 2001. *Australian Alcohol Guidelines: Health Risks and Benefits.* Canberra: AGPS. Available at: http://www.nhmrc.gov.au/publications/synopses/_files/ds9.pdf [Accessed 2 May 2008].
Nerurkar PV, Dragull K, Tang C-S. 2004. In vitro toxicity of kava alkaloid, pipermethystine, in HepG2 cells compared to kavalactones. *Toxicol Sci* **79**: 106–111.
Pittler MH, Ernst E. 2003. Kava extract for treating anxiety. *Cochrane Database Syst Rev (2)*. CD003383.
Rasmussen AK, Scheline RR, Solheim E, Hansel R. 1979. Metabolism of some kava pyrones in the rat. *Xenobiotica* **9**: 1–16.
Rockerbie RA. 2001. *Alcohol and drug intoxicatiom (*2nd edn). Alco Trace: Victoria, BC.
Russmann S, Lauterburg BH, Helbling A. 2001. Kava hepatotoxicity. *Ann Intern Med* **135**: 68–69.
Russmann S, Barguil Y, Cabalion P, Kritsanida M, Duhet D, Lauterburg BH. 2003. Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. *Eur J Gastroenterol Hepatol* **15**: 1033–1036.
Sass DA, Shaikh OS. 2006. Alcoholic Hepatitis. *Clin in Liver Dis* **10**: 219–237.
Schmidt M, Nahrstedt A, Lupke NP. 2002. Piper methysticum (kava) under discussion: observations on quality, effectiveness and safety. *Wien Med Wochenschr* **152**: 382–388.
Singh YN. 2003. Aqueous kava extracts do not affect liver function tests in rats. *Planta Med* **60**: 496–499.
Singh YN. 2005. Potential for interaction of kava and St. John's wort with drugs. *Journal of Ethnopharmacol* **100**: 108–113.
Stevinson C, Huntley A, Ernst E. 2002. A systematic review of the safety of kava extract in the treatment of anxiety. *Drug Saf* **25**: 251–261.
Ulbricht C, Basch E, Boon H, Ernst E, Hammerness P, Sollars D, Tsourounis C, Woods J, Bent, S. 2005. Safety review of kava (Piper methysticum) by the Natural Standard Research Collaboration. *Expert Opin Drug Saf* **4**: 779–794.
Volz HP, Kieser M. 1997. Kava–kava extract WS 1490 versus placebo in anxiety disorders – a randomized placebo–controlled 25–week outpatient trial. *Pharmacopsychiatry* **30**: 1–5.
Whitton PA, Lau A, Salisbury A, Whitehouse J, Evans CS. 2003. Kava lactones and the kava-kava controversy. *Phytochemistry* **64**: 673–679.
Wu D, Nair M, DeWitt DL. 2002. Novel compounds from Piper methysticum Forst (Kava Kava) roots and their effect on cyclooxygenase enzyme. *J Agric Food Chem* **50**: 701–705
Zou L, Harkey MR, Henderson GL, Dike LE. 2004. Kava does not display metabolic toxicity in a homogeneous cellular assay. *Planta Med* **70**: 289–292.
Zou LH, Martha R, Henderson GL. 2005. Synthesis, in vitro, reactivity, and identification of 6-phenyl-3-hexen-2-one in human urine after kava-kava (Piper methysticum) ingestion. *Planta Med* **71**: 142–146.

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