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File: ■ Kava (*Piper methysticum*)
■ Cultivar Variations
■ Hepatotoxicity

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RE: Review Clarifies Factors Involved with Hepatotoxicity Cases Involving Kava

Teschke R. Kava hepatotoxicity: pathogenetic aspects and prospective considerations. *Liver Int*. Jul. 11, 2010. [Epub ahead of print] doi: 10.1111/j.1478-3231.2010.02308.x

Kava (*Piper methysticum*) has been associated with reports of hepatotoxicity, leading to a ban by the German government in 2002. The cause of hepatotoxicity associated with kava is not clear.[1] The purpose of this review was to analyze the pathogenesis of kava hepatotoxicity and strategies "to overcome the problem of hepatotoxic effects associated with kava use in the future."

Hepatotoxicity has been linked to kava use in 14 of 31 suspected cases. For cases involving kava used by itself, causality was determined as highly probable in one case, probable in two cases, and possible for four cases. For cases involving kava and known comedication with drugs or herbal medicines, causality was probable for kava and the comedication in one case, probable for kava and possible for comedication in one case, and possible for kava and the comedication in five cases. The patients in these cases were from Germany (n=8), Switzerland (n=2), United States (n=1), Australia (n=1), and New Caledonia (n=2), reducing the likelihood of ethnicity influencing outcome. The kava preparations included ethanolic extracts (n=5), acetone extracts (n=4), aqueous extracts (n=3), and herb-kava mixtures (n=2). The patients' liver enzymes were "compatible with hepatocellular injury and not with cholestatic or mixed type of liver disease." Liver histology revealed liver cell necrosis and hepatitis. A positive re-exposure test was reported for one case. Favorable outcomes were reported for 13 out of 14 patients, but three patients required liver transplants. A World Health Organization (WHO) assessment of 93 cases found probable associations between kava and hepatotoxicity in eight cases, but used an unvalidated assessment method that is not specific for hepatotoxicity.

Determining the cause of hepatotoxicity linked to kava has been hampered by the lack of reproducibility, inadequate animal studies for assessing pathogenesis, and the dearth of chemical analyses of implicated kava products. There is a possibility that ethanol and acetone kava extracts may have higher levels of toxic compounds and lower levels of protective compounds from kava in comparison to traditional water extracts. The 14

verified kava hepatotoxicity cases included aqueous extracts, which seems to make this possibility unlikely. There is no evidence that the multiple solubilizers used in the ethanol and acetone extracts directly cause kava-associated hepatotoxicity.

The use of substandard cultivars has been implicated in kava-associated hepatotoxicity. For example, the "Tu Dei" cultivar is a cheaper and fast-growing cultivar that is not recommended for daily consumption. The Vanuatu government's 2002 Kava Act No. 7 categorizes the various kava chemotypes and cultivars into noble cultivars, medicinal varieties, Tu Dei kavas, and wild kavas. Noble cultivars have a long history of use as social beverages, and the medicinal varieties have a long history of traditional use by Pacific herbalists. Both of these types are available for export. The export of Tu Dei and wild kavas is no longer permitted. The noble cultivars that are more commonly used in traditional beverages are different from the medicinal varieties that are found in Western kava products. It is possible that the noble cultivars have lower hepatotoxicity compared to the medicinal varieties.

Germany's Commission E recommends the use of dried rhizome chips in the preparation of kava products,[2] and different groups of Pacific Islanders have traditionally used either fresh or dried roots and rhizomes. Root peelings and stem peelings have been used as cheaper sources of kavalactones by some manufacturers. There are also reports of products made with kava leaves, adventitious roots from the stems, and aerial parts. In traditional kava use, the rhizomes or roots are often peeled, and there is speculation that the peeled rootstock may be the best for avoiding hepatotoxicity. Adulteration with synthetic racemic kavain has been reported, and adulteration with other species of kava or other contaminants is possible but unverified. On the other hand, 10 out of the 14 verified cases of hepatotoxicity occurred in Germany and Switzerland, where effective regulation has ensured that kava products are made with *Piper methysticum*.

More research is needed to establish the possible role of hepatic glutathione depletion in kava-associated hepatotoxicity. In vitro studies have shown that constituents of kava (not including kavalactones) inhibit cyclooxygenase-1 (COX-1) and COX-2, and more research is needed to determine if this speculative mechanism is truly related to kava-associated hepatotoxicity. Kava extracts and kavalactones have been shown to both stimulate and inhibit P-glycoprotein in vitro. More research is needed to clarify the in vivo effect of kava and its constituents on P-glycoprotein, as well as the possibility that genetic enzyme deficiencies may be involved in kava-associated hepatotoxicity.

The vast majority of hepatotoxicity cases have involved comedication. Kavalactones, with the exception of kavain, inhibit cytochrome P450 (CYP P450) enzymes in vitro. It is possible that the hepatotoxicity associated with kava is the result of effects on CYP P450 enzymes coupled with comedication. A clinical study on the chronic use of kava found only inhibition of CYP P450 2E1, with no increase in serum liver enzymes, but more research is needed. Daily overdose may also be a source of hepatotoxicity, and the majority of hepatotoxicity cases involved patients who were not following the recommended dose and/or duration. Alcohol consumption may also play a role because alcohol is partially metabolized by CYP P450 2E1, and in vitro evidence suggests that kavalactones are also CYP P450 substrates. Pipermethystine from stem peelings of the Isa cultivar, flavokavain B from Isa cultivar roots, and the kavalactones methysticin and yangonin are individual components proposed as potential sources of kava-associated hepatotoxicity, but more research is needed.

The author recommends the use of peeled kava rhizomes and roots and aqueous extracts in kava products. Prolonged use of high kava doses and consumption of comedication(s) are not recommended. More study is needed on the ideal kava cultivar for kava extracts, but the author suggests a move away from medicinal varieties towards the noble cultivars that are more commonly used in the Pacific. He suggests the Borogu cultivar with chemotype 423561, which has high levels of kavain and a long history of daily use without adverse effects.

An important issue that this article fails to adequately address is the discrepancy between dosage and hepatotoxicity. In regard to total kava and/or total kavalactone doses consumed, the hepatotoxicity cases implicating water extracts involved consumption of much greater amounts than those associated with ethanolic or acetonic extracts, thereby suggesting that solvent influence on total phytochemical content is likely a contributing factor. However, this issue remains confounded by specific cultivar/kavalactone intake. Nonetheless, this review stands as the most comprehensive and balanced to date.

—Marissa Oppel-Sutter, MS

References

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