

Kava Hepatotoxicity and Raw Material Quality

Availability of phytomedicines made from Kava (*Piper methysticum*) has been restricted in many countries for several years, following reports of hepatotoxicity associated with its use particularly in Europe^(1,2).

Initially these reports all involved modern versions of Kava extracts prepared by organic solvents including acetone or ethanol, and it was observed that liver toxicity had not been documented with traditional water based extracts used in Pacific countries. This led to a proposal that while western formulations of Kava may be hepatotoxic, traditional Kava use is safe^(3,4). In support of this hypothesis was the absence of reports of hepatotoxicity found in studies involving traditional use by Australian⁽⁵⁻⁷⁾, New Caledonian⁽⁸⁾, and Hawaiian⁽⁹⁾ populations.

In a move which gave significant weight to this so called 'Pacific Kava paradox', in 2005 the Australian TGA approved the manufacture and sale of aqueous Kava extracts only, while continuing restrictions on non-aqueous extracts. Production and use of hydroethanolic Kava products is still permitted in New Zealand and the United States.

Soon after the Pacific Kava paradox was proposed, however, case reports began to appear associating hepatotoxicity with use of Kava as a traditionally prepared water extract. The first of these, in 2003, described severe hepatotoxicity following the use of traditional aqueous extracts derived from Kava imported from Vanuatu⁽⁶⁾. Further case reports emerged from Australia^(10,12), the U.S.^(11,12), and Germany⁽¹²⁻¹⁴⁾. In all these reports, causality for Kava was implicated through use of the same structured, quantitative, liver specific and updated CIOMS scale^(15,16) that was used to assess cases of liver disease associated with acetic and ethanolic extracts^(13,14). Also, in 2007 the World Health Organisation (WHO) reported five cases of hepatotoxicity associated with use of aqueous Kava extracts, although only two were from traditionally prepared Kava⁽¹⁷⁾.

Another study compared typical clinical features of Kava hepatotoxicity associated with five case reports involving aqueous extract use, with those associated with nine cases of acetic or ethanolic extract use from Germany and Switzerland. This found a similar

clinical picture in all fourteen patients, independent of which type of extract was used^(12,14).

While the above numbers and the total number of reported cases of hepatotoxic reactions linked with traditional aqueous extract use to date are small, these studies suggest that the solvents used to produce Kava extracts may not contribute to this problem as was previously thought. Other potential causes of hepatotoxicity related to the herb itself, or a rare idiosyncratic reaction, therefore seem more likely.

To date there is little experimental evidence that Kava lactones themselves may be hepatotoxic⁽¹⁸⁻²⁰⁾. Two non-Kava lactone constituents have been identified as potential culprits, the alkaloid pipermethystine⁽²¹⁾ and the chalcone flavokavain B⁽²²⁾. However, pipermethystine failed to cause experimental liver injury even in high doses, and was not found in commercial Kava extracts⁽²³⁾. Flavokavain B produces modest signs of hepatotoxicity in experimental animals, but only at doses far in excess of those found in ethanolic Kava extracts⁽²²⁾.

While traditionally the peelings of rhizomes and roots were not used to prepare customary Kava drinks, during the lead-up to the first reports of liver toxicity from Europe, high demand led to these peelings being sometimes supplied to product manufacturers^(24, 25). Two new papers on this subject by Professor Rolf Teschke, a renowned German researcher into Kava hepatotoxicity, now suggest that contamination of raw material during storage with hepatotoxic fungi and moulds, could be at least partly contributory to these cases^(26, 27).

The high temperatures and humidity in many South Pacific countries are ideal conditions for growth of moulds, which can develop soon after harvest, particularly during the poor drying and storage conditions often prevalent in these countries. This could encourage the development of moulds within the bags and containers in which Kava is exported. Without adherence to good agricultural and manufacturing practices, or robust sampling and quality assurance systems by manufacturers, this problem may not be picked up prior to extraction taking place. Mould growth can lead

to the production of hepatotoxins such as aflatoxins and ochratoxin A, which could conceivably be carried through into Kava finished products, particularly if peelings are used.

Aflatoxins are a group of mycotoxins principally produced by *Aspergillus flavus* and *A. parasiticus*, both natural contaminants of food and feedstuff. These toxins can have various negative health effects including acting as liver carcinogens, especially in combination with chronic hepatitis C virus infection⁽²⁸⁾. Epidemic outbreaks of hepatitis due to consumption of maize heavily contaminated with *Aspergillus flavus* and aflatoxins, have previously been reported in western India⁽²⁹⁾.

While the potential role of mycotoxins in Kava-associated hepatotoxicity seems quite plausible, a wide range of studies are required in order to further investigate this as well as other potential aetiological factors. Professor Teschke calls for toxicological studies into various Kava cultivars, possible adulterants, suspected contaminants including fungi and bacteria, and diseases of the Kava plant such as Kava dieback^(17, 26, 30). However, even prior to the results from these studies becoming known, more attention should be given by regulators and manufacturers to ensure properly dried and processed raw materials, free of mould contamination, are used.

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