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Kava update: a European perspective

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Kava is the beverage prepared from the rhizome of the kava plant (*Piper methysticum* Forster), and is traditionally used for recreational or medicinal purposes by the islanders of the South Pacific. Its active ingredients are kava pyrones (eg, kavain[1]), which are thought to mediate effects on $GABA_A$ receptors, particularly in the hippocampus (region of the brain) and amygdale complex. Numerous clinical trials have shown kava to be an effective anxiolytic, and a Cochrane Review leaves little doubt about its efficacy.[2]

Kava was also deemed to be a safe remedy,[3,4] but recent case reports associate it with liver damage which was severe (hepatic failure) in some instances.[5] Today, about 70 cases of various degrees of liver damage have been documented worldwide.[6] Kava-containing products were therefore banned, first in Germany and Switzerland and subsequently in several other countries.[6] Australia also currently bans kava supplements while New Zealand authorities recommend that labels should warn against the possibility of liver damage and a watching brief should be kept over the issue.[7] This article is an attempt to summarise recent developments on the safety of kava.

Several experts have implied that the German authorities' decision to withdraw kava from the market was politically, not scientifically, motivated.[8] Since Germany has the reputation of having generally sound expertise on herbal medicine, other national authorities tended to follow the German example of a ban. There is, however, evidence from Canada that the ban is less than effective.[9] In several countries, the regulatory authorities are being taken to court by lobbyists who argue that the ban was not justified. In the United Kingdom (UK), a recent judgement rejected the challenge to the kava ban by 420 health stores.[10]

Meanwhile, several in-depth analyses of the known cases of hepatotoxicity have emerged.[11,12] They conclude that about 80% of these patients took kava overdoses and/or self-medicated kava for longer than 3 months. Most patients administered comedications with known hepatotoxicity. A typical Australian case was published recently[13] in which a 56-year old woman developed fatal liver failure after taking a kava preparation for 3 months. The fatality was rated as 'probably' caused by kava toxicity, even though the patient had taken two other herbal remedies associated with liver damage and the cause of death was progressive blood loss after liver transplant which is clearly not directly related to kava. Generally speaking, causality is not well established and kava taken as recommended may not be as toxic as the regulators seem to believe.

Others have pointed out that liver damage is likely to be the result of non-traditional ways of production of commercially available kava supplements. The traditional kava beverage is essentially a water extract. Australian epidemiological studies suggest that regular users of the traditional water extract consume quantities equivalent to 10–50 times the recommended daily dose without signs of liver damage.[14] Yet two cases of

hepatitis have been recently associated with ingesting traditional aqueous kava extracts for 4–5 weeks.[15] Commercial kava supplements are produced through alcohol or acetone extraction. It is conceivable that different methods yield different kava alkaloids.[16,17] UK scientists suggested that differences between aqueous and acetonic extraction are associated with differences in toxicity; indeed, only water extraction delivers sufficient glutathione which seems to be essential for protection against hepatotoxicity.[18]

Another possible explanation for liver damage is that suboptimal raw material was used during the 'kava boom' of the late 1990s. For instance, manufacturers purchased peelings of the kava stump which contain the hepatotoxic alkaloid pipermethystine not normally contained in good quality kava supplements.[19] A further explanation is the possibility of a genetic difference between Europeans and Pacific Islanders, which could protect the latter group from kava-induced liver damage.[17] Comparative toxicity studies are required to improve our understanding of these issues.

The mechanism of kava hepatotoxicity (if any) is not yet understood. Direct toxicity is unlikely but an immunologically mediated idiosyncratic mechanism appears the most likely explanation, particularly at high doses of kava intake.[20] Kava also has the potential for causing drug interactions through inhibition of P450 enzymes responsible for the metabolism of numerous pharmaceuticals.[21] The importance of this finding is, however, not clear at present.

Even though few direct comparisons have been published, the efficacy of kava seems to be similar to that of benzodiazepines.[2] Therefore it is relevant to note that a rough estimation of the incidence of liver damage yields similar results for kava and benzodiazepines.[20] There seems to be little difference between the reported incidence of kava-induced hepatotoxicity and that of other psychoactive drugs such as valproic acid, fluoxetine, paroxetine, sertraline, fluvoxamine, impiramine, and codeine.[22] Of course, the seriousness of the liver damage also needs consideration, but there are only very few cases of serious hepatoxicity associated with kava.[3–8] The many adverse effects (other than hepatotoxicity) of psychoactive drugs (eg, sedation, dependence, memory impairment, accidents) should also be taken into account.[23]

Meanwhile more positive trial data have emerged, which were not available when kava was banned in Germany. They showed that kava reduces anxiety in perimenopausal women[24] and is as effective as opipramol or buspirone for generalised anxiety disorder.[25] A further randomised, placebo-controlled trial demonstrated that kava is more effective than placebo in improving sleep in patients suffering from sleep disturbances associated with non-psychotic anxiety disorders.[26] In none of these studies was there evidence of liver toxicity or other adverse events, but clinical studies are of course too small for detecting rare adverse events.

Vis a vis the totality of this new evidence, German physicians now recommend kava as an herbal anxiolytic at a dose of 120–210 mg kavapyrone/day. The length of medication should be limited to 1–2 months, and liver enzymes should be checked before and during kava medication.[27] This recommendation is, of course, more theoretical than practical: in Germany, kava remains 'off limits' and, in other countries, it is marketed as a food supplement for which such advice is not legally enforceable. Food Standards Australia and New Zealand (FSANZ) currently propose

to prohibit the use of organic solvents or root peelings of the plant in the production of kava products.[28]

Based on the data available to date, my personal impression is that the traditional water extract seems to have no or only low hepatotoxicity. Commercial acetone or alcohol extracts are associated with serious liver damage in extremely rare cases. The risk/benefit balance of such products may nevertheless turn out to be positive, particularly in comparison to that of synthetic psychoactive drugs. But, to err on the safe side, I would recommend caution until our knowledge is more complete.

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