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Commentary

A re-evaluation of kava (*Piper methysticum*)

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Kava (*Piper methysticum*), a herbal anxiolytic drug was banned in the UK and other countries. About 70 case reports had suggested hepatotoxicity. This article summarizes the research since the ban. Several theories have emerged to explain possible mechanisms of toxicity. Yet uncertainty as to whether or not kava is hepatotoxic prevails. Some experts therefore believe that the prohibition was not justified. The evidence, however, continues to implicate kava, and the ban was recently upheld by the UK licensing authority.

In 2003, the UK government prohibited the sale of kava (*Piper methysticum*), a popular and effective herbal anxiolytic [1], marketed in Britain as unlicensed herbal products or food supplements. One year earlier, the German authorities had issued a similar prohibition [2]. The reason was an unacceptable risk of hepatotoxicity. The herbal sector, by and large, felt that a ban was an unnecessary and disproportionate over-reaction. The aim of this article is to summarize the new evidence.

About 100 cases of liver damage have now been associated with the intake of kava worldwide. This figure is comparable with those which in the past have led to the ban of mainstream drugs. Some experts, however, argue that causality between the adverse effect and use of kava has not been established with sufficient certainty. In several cases, liver damage could have been due to other drugs or alcohol taken concomitantly. In other instances, excessive doses of kava had been used. Only in 14 cases was causality deemed to be 'probable'. An incidence rate of one potential case of liver damage in 60–125 million kava doses was estimated on the basis of the number of reported cases and the sales figures of kava in Germany [2, 3]. Two drug monitoring studies, including a total of 7078 patients taking 120–150 mg kava extract per day, had not found a single case of kava-induced hepatotoxicity [4]. This seems to imply that the incidence of kava-induced hepatotoxicity is less than 1 per 2500 patients; arguably this could still be a relatively high figure. Other data suggest that kava does lead to an increase in liver enzymes [5, 6]. Moreover, none of the drug monitoring studies specifically evaluated signs or symptoms of hepatotoxicty, nor were they of long duration. The above-incidence estimate is less than reliable: neither the true number of cases, nor the total number of patients exposed, nor the cumulative duration of exposure are known with certainty.

Kava has been used for centuries in the South Pacific. Its main active principle seems to be a family of compounds called kavalactones. The Pacific Islanders used water extracts of kava, apparently without adverse effects [7]. Recent *in vitro* and animal studies have confirmed that water fractions of kava are less cytotoxic than organic solvent fractions [8, 9]. Modern commercial products rely on alcohol or acetone extraction, a process which may extract toxic compounds (e.g. alkaloids) from the plant. Some experts therefore believe that the extraction method is the key for understanding the liver damage observed with modern kava preparations [10]. The above-mentioned surveys [5, 6], however, seem to contradict this theory but imply that liver function is impaired even if kava is consumed as an aqueous extract.

Another theory holds that suboptimal raw material has contributed to the problem. At the height of the 'kava boom' prices were high and kava was in short supply. Thus kava cultivars (over 80 different cultivars exist) and parts (e.g. peelings of the stump instead of the rhizome), were used. This can yield potentially toxic raw material [11]. It is therefore conceivable that suboptimal raw material contains toxic ingredients which are absent in

optimal material. Kava preparations based on toxic raw material or unsafe extraction methods should, of course, be prohibited. Therefore these potential explanations of the observed toxicity could be seen as arguments in favour rather than against a ban.

The mechanism of kava hepatotoxicity (if any) is still not well understood [12]. An immunologically mediated idiosyncratic reaction appears to be the most likely explanation, particularly at high doses [13, 14]. Comedication with St John's Wort (*Hypericum perforatum*) extracts may potentiate the hepatotoxicity of kava [14]. The constituents of kava, flavokavin B and pipermethystine, have been shown to be cytotoxic *in vitro* [8], but other studies seem to show an absence of toxicity in therapeutic doses or even a hepatoprotective effect [15]. A recent overview of toxicological tests in animals implied that kavalactones and kava extracts have a low level of toxicity [9]. Kava has the potential for causing drug interactions through inhibition of the cytochrome P450 enzymes [16–19]. Such interactions could either generate toxic metabolites or increase the toxicity of concomitantly administered drugs. Cytochrome P2D6 deficiency was postulated to be a risk factor for kava hepatotoxity [20] but CYP2D6 deficiency cannot account for liver damage in patients not taking drugs metabolized by this route. No clinically significant interactions with kava have been confirmed *in vivo*. In any case, interactions would not account for those case reports where hepatotoxicity occurred without concomitant medications.

A crucial point of the ban in Germany where kava was fully licensed was that the anxiolytic efficacy of kava was deemed to be uncertain. An updated Cochrane review includes 11 placebo-controlled randomized trials with a total of 645 patients suffering for anxiety [1]. The pooled data of six studies using the Hamilton Anxiety Scale as a common outcome measure yielded a weighted mean difference of 5.0 (95% confidence interval 1.1, 8.8, $P = 0.01$) favouring kava over placebo. Similarly positive conclusions were reached by other investigators [21]. The anxiolytic effects of kava seem to be as powerful as those of conventional anxiolytics [22–24]. Other randomized controlled trials suggest that kava reduces anxiety in perimenopausal women [25], facilitates cognitive function and increases positive affectivity [26] and improves sleep quality [27]. Most of these trials did not monitor liver function; those that did, noted elevations of liver enzymes which, however, were usually not considered to be clinically relevant by the investigators.

The ban on kava in the UK and other countries (e.g. Austria, Germany, France) caused an estimated damage of US$1.2 billion to the industry [15]. Some experts now believe that, all things considered, the ban is no longer justified [15]. But expert opinion is, of course, notoriously unreliable. The UK National Association of Health Stores, together with the actress Jenny Seagrove, challenged the ban in the UK High Court, but the claimants lost the case and a subsequent appeal [12]. The Expert Working Group of the UK Medicines and Healthcare Products Regulatory Agency recently concluded that the prohibition order on kava remains justified and proportional [12].

In conclusion, emotional views about the safety of kava (or any other therapy) tend to distract from the facts. The evidence may be complex and uncertainty does prevail but, on the basis of existing evidence, hepatotoxicity cannot presently be ruled out. A number of theories have emerged which may deserve further investigation. These theories, however, do not throw the hepatotoxic potential of kava into serious doubt. The onus is now on the kava industry to generate data which are compelling.

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