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RE: German Court Lifts Kava Ban; Hepatotoxicity May Be Linked to Kava Cultivar


The social sharing of kava (*Piper methysticum*, Piperaceae) root and rhizome water extracts has been an integral part of Melanesian culture for over 1000 years. In Germany, ethanol extracts of kava were first mentioned in 1886 and over the next 113 years, no serious adverse effects were reported. Based on clinical evidence of efficacy and history of safe use, in 1990, kava ethanol extract was licensed in Germany for the treatment of situational anxiety. The first cases of alleged kava hepatotoxicity were filed in 1999, and many other case reports soon followed. By 2002, there were over 20 case reports of hepatotoxicity associated with German kava products, and the German regulatory authority, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), made an administrative decision to cancel all drug licenses for medicinal products containing kava; a number of other countries, including the US and Canada, quickly followed suit. The consequences of the kava ban were felt worldwide, as physicians and patients deprived of an effective and relatively safe medication, and the resulting crash of the market, wrought economic devastation in the kava-producing nations of the South Pacific (economic losses were estimated at over $3 billion USD in Samoa alone). In 2015, a German appeals court upheld the 2014 ruling that the kava ban was illegal, effectively restoring the marketing authorizations and ending the embargo on medicinal kava.

In this article, the authors provide an overview of the issues surrounding the kava ban and the rulings of the German courts that lifted the ban. They also provide a summary of the theories which have been proposed to explain the purported kava toxicity, and discuss the ethnobotany, cultivation, and future prospects of kava.

The German ban was based on the assessment that the risk-benefit ratio for kava had shifted to the negative. However, there is considerable misunderstanding of the major issues causing the shift. "Whereas the international debate was always focused on the risk side, the German authority had in fact based the withdrawal of marketing authorisation primarily on a denial of clinical efficacy." The BfArM deemed that there was a lack of clinical evidence of efficacy by the most recent Good Clinical Practice (GCP) standards. In other words, the
(previously accepted) evidence of efficacy provided in kava clinical trials conducted in the two decades before the ban was rejected because the trials did not conform to the current GCP standards. "With BfArM declaring kava not to be efficacious, any possible risk, even a minor one, automatically shifts the benefit to risk ratio to the negative side, thus justifying the regulatory decision to ban kava."

This decision placed German manufacturers in an impossible "Catch-22" situation. The BfArM would not authorize the performance of new clinical trials by the most recent GCP standards due to safety concerns. BfArM treated kava preparations as new products with no marketing history, which require the full set of product-specific preclinical data before a clinical trial could be conducted. Hence, the assessment of the clinical safety of kava could be delayed indefinitely on these formal grounds.

Following the ban, studies were conducted with water-extracted kava products and demonstrated efficacy. However, BfArM disregarded this evidence because the water extract and its dosage schedule were not equivalent to the ethanol extracts previously approved for marketing.

Legal options could not be pursued until BfArM issued a final decision on kava in 2012; this action finally opened the door for kava marketing authorization holders to challenge the ban in court. In June 2014, the German Administrative Court of Cologne ruled that the available data do not support the alleged hepatotoxicity, and the de facto "ban" was illegal. The judgment was appealed. The German Upper Administrative Court of Münster ruled against the appeal on February 25, 2015. According to the authors, the ruling can be considered final because no additional appeal has been pursued by German regulatory authorities.

The key points of the rulings of the German courts were as follows: (1) The number of hepatotoxicity case reports was inflated by the inclusion of duplicates. (2) The ad hoc process used to make the risk assessment is likely to produce different results if applied by different assessors. (3) The majority of the reports could be more easily explained by known co-medications or alcohol abuse. (4) The application of a suitable method for assessing liver damage in clinical research reduced the number of cases to three reports where the liver damage was possibly caused by kava, as there were not any obvious, more likely alternative explanations. (5) The number of possible cases was so small (less than one case/one million monthly doses) that it did not justify the ban. (6) Risk assessments must be performed in the context of their therapeutic environment. "A drug must not be removed from the market if all possible replacements for it carry (or might potentially carry) an even higher risk." Pharmaceutical alternatives to kava have known significant adverse effects that might be more harmful than those caused by kava. (7) A case report is not proof of causality. The regulatory authority cannot act on the mere suspicion of potential danger; it has the obligation to provide evidence for both the alleged dangers and the causal relationship with the suspected medication. (8) Once the regulatory authority has accepted clinical proofs of efficacy, a company having a licensed drug on the market is not obliged to continuously provide new evidence of efficacy, and the regulator cannot withdraw its approval just because new standards are published at a later date.

The court ruled that BfArM had not conclusively proven a causal relationship between the use of kava products and the alleged liver damage. Therefore, the risk to benefit ratio could not be negative given the previously accepted evidence of efficacy, and the ban of kava in Germany was illegal.

Although the number of case reports deemed possibly related to kava seems insignificant compared to the known kava exposure data (450 million daily doses in ten years), those
cases still deserve consideration. Most of the theories proposed to explain kava hepatotoxicity can be easily ruled out because they do not account for the facts that the case reports were largely restricted to German ethanolic extracts of kava, and these extracts had been used safely for over 100 years prior to 1999. The most plausible explanation is that the sudden occurrence of hepatotoxicity was due to a change in the quality of the kava raw material; most likely the introduction of "two-day kava" cultivars into German products which happened in the mid-1990s.

Selection by humans over the centuries has resulted in 120-150 cultivars of *P. methysticum* which may be divided into groups based on their phytochemical profiles. The cultivars in the "noble kava" group, which are considered to be the best, are closely related in terms of their kavalactone content, with relatively high levels of kavain and relatively low levels of the lipophilic kavalactones. The two-day kava cultivars contain relatively high levels of lipophilic kavalactones and are not used for daily kava drinking because they produce an unpleasant experience that lasts for two days.

While the differences in kavalactone content help differentiate the two-day and noble kava cultivars, they do not explain the hepatotoxicity. Kavalactones have been extensively researched and they have never been shown to exert hepatotoxic effects. This suggests that there may be other, as yet unidentified constituents of two-day kava which may have hepatotoxic effects. Research suggests that the constituent flavokavin B could possibly be used as a marker to discriminate two-day and noble kava material.

In summary, a causal relationship between the consumption of kava extracts and the occurrence of adverse liver reactions has not been scientifically demonstrated. The authors conclude that the rare, possible cases of hepatotoxicity were the result of "ill-defined herbal drug identity, a lack of appropriate quality control, and misguided regulatory politics." Now that the ban in Germany has been lifted, appropriate measures must be taken to ensure safe, high-quality kava products and prevent the re-occurrence of kava-associated hepatotoxicity. "To re-establish 'noble' kava to its rightful place as an essential anxiolytic drug in the European market, its botanical and phytochemical differentiation from the 'non-noble' kava varieties has to be established by pharmacopeial regulations."

However, the authors warn that there is not much time to act, as kava exports from the South Pacific are approaching the pre-ban levels. With one of the largest economies, New Caledonia has shifted to predominantly two-day kava based on the argument that it has higher kavalactone content and lower cost due to the shorter growth period. This could be playing with fire, they warn, as there are already isolated case reports of liver toxicity from New Caledonia.

—Heather S. Oliff, PhD

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