

## **Relevant Hepatotoxic effects of Kava still need to be proven**

### **A statement of the Society for Medicinal Plant Research**

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On June, 14, 2002 the German Federal Institute of Drugs and Medical Devices took the decision to withdraw all drug registrations for all products containing kava. The consequences of this ban were felt worldwide and led to an economic disaster in many South Pacific states. Within Europe, the kava ban deprived the physicians of an effective and comparatively safe medication, creating a “therapeutic gap nobody wished for” (Anon., 2002).

The decision to ban kava was rigorously debated in Europe, as many experts questioned the causality of the case reports of liver toxicity. The Grünwald report comes to the conclusion that relevant hepatotoxic properties of kava are not proven. In most cases retrospective analysis casts considerable doubt on the official causality assessment. Corresponding reviews and papers were published prior to and after the kava ban (Ernst, 2003; Loew and Gaus, 2002; Pittler and Ernst, 2003; Schmidt et al., 2002; Schmidt, 2003; Schmidt and Nahrstedt, 2002; Stevinson et al., 2002; Teschke et al., 2003; Teschke, 2003a; Teschke, 2003b).

According to the results of the most recent analysis, kava can potentially cause liver toxicity. However, the incidence of such effects appears to be extremely low: less than one case in one million of monthly doses (Teschke, 2003a). If indeed hepatotoxic effects of kava exist, they might be related to a rare immunologic reaction to a kava metabolite in a small subgroup of the European Caucasian population lacking the metabolizing liver enzyme cytochrome P450 D26 (Teschke, 2003a). This theory still needs further confirmation, as the discussion of hepatotoxicity is mainly based on only four more or less adequately documented case reports of liver reactions possibly caused by kava. In two of the patients a lack of cytochrome P450 2D6 was found. Compared to the millions of kava doses ingested within Europe, the number of only two confirmed allergic reactions in patients with an unusual metabolic pattern does not allow deducting a general threat to the patients' health.

The kava ban was not only based on the possibility of severe adverse effects, but at the same time on the supposed lack of appropriate clinical studies by most recent standards demonstrating efficacy. Mind that the focus is on “most recent standards”, which generally puts phytotherapy in a disadvantage in comparison to chemically defined drugs. For herbal drugs there is mostly a long dating experience concerning efficacy as well as tolerability. The studies performed with kava within the last decades can of course not be compliant to the most recent GCP standards, as those were defined much later. In contrast, new chemical entities may have proofs of efficacy according to the latest standards. However, a chemically defined drug with a recent, GCP compliant proof of efficacy is not necessarily safe, as rare adverse reactions are only detected after administration to a large number of patients.

Kava was thus not only officially judged as potentially dangerous, but in addition its efficacy was denied. The combination of both factors clearly shifted the risk-benefit evaluation towards the negative side. The *Society for Medicinal Plant Research* does neither accept the official conclusions drawn from the presentation of fragmentary safety data, nor a negative benefit-risk-ratio of kava on the grounds of missing proofs of efficacy. Scientists who are members of the *Society for Medicinal Plant Research* created a large part of the published pharmacological and clinical knowledge on kava. Like the members of the commission E,

who published a complaint about the way their expertise was bypassed in the decision making process, the *Society for Medicinal Plant Research* would have been happy to be involved in the discussion of kava (adverse) effects.

The Society feels that the rationale for the kava ban does not sufficiently take into account the huge body of positive evidence of efficacy and tolerability of kava. Instead it focuses entirely on a small number of case reports, and completely ignores all clinical, pharmacological, toxicological and ethno-pharmacological evidence. The Society for Medicinal Plant Research feels that the public verdict on kava without a rational analysis of the backgrounds of the case reports is somehow representative for the unequal treatment of herbal medicines and chemically defined drugs when it comes to benefit-risk assessments. Kava is only one rather tragic example of this evolution within the EU. Positive proofs of efficacy were neglected, whereas the possibility of adverse effects seemed to outweigh all advantages, even though the therapeutic alternatives are in no way safer than kava.

The European scientific community is following with keen interest the struggle for kava in the South Pacific states and Australia. The ideas recently discussed, e.g. the influence of glutathione contents in traditional kava drinks (Denham et al., 2002; Schmidt, 2003), or the potential pipermethysticine content in aerial parts of some kava cultivars surely merit a closer look and an international scientific collaboration. One should, however, always keep in mind that the drug safety protocol implemented by the German health authorities is hotly debated, as a relevant liver toxic potential of kava was never scientifically proven! The case reports discussed for kava are mostly inhomogeneous, and in most cases alternative causes could be identified (Loew and Gaus, 2002; Schmidt et al., 2002; Teschke, 2003a).

Thus, before the question whether the European registered pharmaceutical extracts are really differing from the traditional kava drinks in the South Pacific is addressed, and what potential adulterant might have caused the toxicity, one should first agree that there really is a relevant toxicity. The available details do not allow drawing this conclusion. The German health authorities clearly should present the additional data they claim to possess in order to allow the question to be addressed scientifically.

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