ARE KAVALACTONES THE HEPATOTOXIC PRINCIPLE OF KAVA EXTRACTS? THE PITFALLS OF THE GLUTATHIONE THEORY

Dear Editor:

Recently, in this journal Denham et al. (2002) and (within the same paper) Whitton et al. published their ideas about the influence of glutathione in aqueous preparations respectively low alcoholic tinctures of kava (Piper methysticum roots.html) on the safety of intake regarding adverse liver reactions. Even though the theory presented is highly interesting, and deserves a closer inspection, the weak point of the argumentation is that it is based on the hypothesis that kavalactones are hepatotoxic. There is, however, currently no evidence to back up this theory.

The worldwide discussion on potential liver toxicity of kava was triggered by the risk–benefit reevaluation of the German health authorities, on the assumption of hepatotoxic effects, which finally led to the ban of kava products in Germany in June 2002 (for details, see www.uni-muenster.de/Chemie/PB/Kava/kavaroot.html). One should keep in mind, however, that the circumstances of the case reports and the existing preclinical and clinical data still do not allow a deduction of a specific hepatotoxic potential of kava extracts, even though several case reports have been cited with the evaluation of a “probable” causality in a most recent approach by Teschke (2002). However, the potentially hepatotoxic concomitant treatment of the patients was still largely left out of the discussion (Teschke, 2002). The outcome of the official German assessment was heavily criticized by experts in phytomedicine and toxicology, including the members of the German Commission E (who would normally have been consulted in the decision-making process), because the kava ban would not decrease, but rather increase the risk of potentially serious adverse effects, including liver diseases, for individual patients (Anonymous, 2002a, 2002b, 2002c). The experts of the German Commission E filed their protest against the decision in the media, however, without success.

Toxicologic studies with kava extract and isolated kavalactones

Efforts to elucidate the liver damaging mechanisms (if existent!) are highly appreciated in the discussion. Up to now, neither clinical nor preclinical or toxicologic studies have yielded any hint on potential toxicity of any kind for kava preparations and their components. Denham et al. (2002) indicate dose-dependant cytotoxicity of isolated kavalactones on Acanthamoeba cells. Similar experiments were carried out in more relevant test systems on human hepatocytes, testing isolated kavalactones and standardized total extracts, with no signs of hepatotoxicity or clinically relevant cytotoxicity produced. Moreover, kavalactones and kava extracts display a rather low toxicity in toxicologic testing in animals (see Table 1).

In addition to acute toxicity, chronic toxicity was tested. An application of 50 mg/kg three times a week in rodents over a time of 3 months did not yield signs of toxicity (Meyer, 1965). A kava extract with 70% kavalactones based on acetone as the extraction medium was tested over 26 weeks in rats (maximum dose 320 mg/kg and day) and dogs (maximum dose 60 mg/kg and day) (Schulz and Hänsel, 1999). Daily doses of 24 mg/kg in rats and 20 mg/kg in dogs did not cause adverse effects. Only with the highest dosage regimens slight histopathologic changes in the liver and kidneys were seen (Schulz and Hänsel, 1999). No lethality was found.

Dihydrokavain and desmethoxyyangonin were tested in mice and Wistar rats on oral ap-
application. Among other parameters, liver functions, with tests for transaminases and alkaline phosphatase, were screened as well as histopathologic changes. An application of 30, 100, and 300 mg/kg twice a day over 2 weeks in mice did not yield any clinically relevant changes in the laboratory parameters or organ structures. Rats were given the same dosage scheme over 3 months. Only with the use of desmethoxyyangonin were transient changes of serum glucose, cholesterol, and triglycerides found, however, without a clear dosage–effect relationship (Hsu et al., 1994). Overall, the experiment did not yield hints on toxic effects of kavalactones (Hsu et al., 1994).

In an unpublished toxicologic study of L. Sorrentino* the effects of chronic application of an ethanolic kava extract standardized to 50 mg of kavalactones per capsule (Kavasedon®, Harras Pharma Curarina, Munich, Germany) on Wistar rats were tested over three, respectively 6 months. Based on the amount of food intake, the rats consumed either 7.3 or 73 mg/kg of kavalactones per day. The parameters examined included transaminases, glucose, nitrogen, total protein, total blood lipids, cholesterol, hematology, body weight, organ weight, histology and lipid content in the liver. Even after 6 months, no increase in liver function tests or the fat content in the liver was noted and all physiologic and histologic parameters were normal (see Table 2).

In another as-yet-unpublished study, Gebhardt examined the cytotoxicity of kava extract (Kavasedon) and isolated kavalactones on cultured human and rat hepatocytes.† The six isolated kavalactones produced a differential toxicity in rat hepatocytes, measured by MTT testing (see Table 3) but not in human cultured hepatocytes, where no cytotoxicity was detected up to the highest tested concentration (200 μg/mL). The alkaloids of Chelidonium majus (greater celandine) served as a positive control. The microscopic evaluation of the cells did not yield any deviation from the results of testing, based on the chemical reduction of 3-[4,5-dimethyl-thiazole-2-yl]-2,5-diphenyl-tetrazolium bromide to colored and analytically detectable formazine, a reaction that is very specific for cytotoxic processes.

The extract itself did not yield any indications of cytotoxicity on liver cells for rat or human hepatocytes. These results are directly relevant to the conditions in vivo: In full extracts, kavain, which, according to these experiments, has the lowest EC_{50} value in rat hepatocytes, is contained in kava extract in a concentration of approximately 20%, representing 10 mg per capsule and a maximum of 20 mg in the daily dose. Under the supposition of complete ab-

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† Gebhardt R. Hepatotoxic effects of kava extract (Kavasedon®) and kavalactones in primary cultured liver cells [unpublished data]. Munich, Germany: Harras Pharma Curarina, 2001.
sorption, 20 mg of kavain in a theoretical blood volume of 6 L would be equivalent to a theoretical blood concentration of 3.33 mg of kavain per mL of blood, which would be by a factor of 13.5 far from the EC\textsubscript{50} value in rat hepatocytes (which were not found in human hepatocytes anyway). In reality, the absorbed kavain would not be present in the bloodstream at 100%, because the highly lipophilic properties would ensure a fast repartition in other compartments, thus, even enlarging the safety range of intake of kava extract.

**Kavalactone-free preparations: efficacious and free of risks?**

The distinction made in the report by Denham et al. (2002) in natural extracts such as the Polynesian ritual kava bowl and/or low alcoholic tinctures, on the one hand, and “artificial” pharmaceutical extracts, on the other hand, was not really helpful. One has to keep in mind that all relevant clinical trials and toxicologic studies have been performed with standardized extracts and the kavalactones have always been considered to be the active constituents—which was also confirmed by Denham et al. It is, of course, a general rule in phytotherapy that the total extract is more than the sum of its constituents, and experience shows that this is so for kava. However, one cannot compare the situation for kava with that of *Hypericum perforatum* (St. John’s wort)—This is a typical example of a plant for which the active principle is still unknown, in contrast to kava. With kavalactones definitively being the carrier of the pharmacologic effects and proofs of efficacy missing for preparations with low kavalactone contents, one cannot assume that extracts that are poor in kavalactones would be as effective or would even enhance the safety of the preparations. The first assumption would require clinical studies, the latter would require a confirmation of a supposed hepatotoxic potential of the kavalactones.

The point of the kavalactone content in native kava drinks in contrast to artificially enriched kava extracts is misleading. First, the usual standardized extraction methods do not produce kava extracts infinitely enriched in

<table>
<thead>
<tr>
<th>Kavalactone</th>
<th>(EC_{50} ) ((mg/mL))</th>
<th>Reference-alkaloid</th>
<th>(EC_{50} ) ((mg/mL))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kavain</td>
<td>45</td>
<td>Sanguinarin</td>
<td>5</td>
</tr>
<tr>
<td>Dihydrokavain</td>
<td>ca. 150</td>
<td>Chelerythrin</td>
<td>8</td>
</tr>
<tr>
<td>Yangonin</td>
<td>ca. 200</td>
<td>Coptisin</td>
<td>13</td>
</tr>
<tr>
<td>Desmethoxy-Yangonin</td>
<td>&gt;200</td>
<td>Protopin</td>
<td>ca. 100</td>
</tr>
<tr>
<td>Methysticin</td>
<td>63</td>
<td>Chelidinon</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Dihydromethysticin</td>
<td>&gt;200</td>
<td></td>
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</tbody>
</table>

In human cultured hepatocytes, all six kavalactones did not show cytotoxicity up to the highest tested concentration (200 \(\mu g/mL\)) (Gebhardt, 2001: unpublished results).
kavalactones: The standardization in German pharmaceutical preparations guarantees not only a constant and reproducible content in kavalactones exactly as indicated on their labels (typically 45–60 mg per tablet or capsule) but also highly constant amounts among the different kavalactones. An example of batch-to-batch conformity can be found in Schmidt et al. (2002) and—translated into English—in the abovementioned internet site. Thus, the standardized extraction yielding a reliable extract composition is an asset in rational phytotherapy, for which patients and physicians are entitled to a constant and reliable drug quality.

In addition, Denham et al. (2002) stated that the South Pacific use of kava often involves intakes of much higher doses of kavalactones than would be found in standardized extracts restricted to an intake of 60–120 mg kavalactones per day. This is supported by the analyses of Hänsel and Lazar (1985), who found exactly this range of kavalactones in cold aqueous macerations of kava roots (Hänsel and Lazar, 1985). In the indogenous preparations, these amounts are not dissolved in the extraction medium, but form suspensions of resinous droplets in the water phase. In the South Pacific islands, it is a well-known fact that the potency of the kava drink will increase when the bottom of the “tanoa,” where the kava drink was prepared, is reached. In addition, Polynesian and Melanesian people usually drink more than one coconut bowl of the drink in a “kava session,” thus providing an amount of kavalactones far superior to those of standardized kava preparations.

The idea of a Michael addition of glutathione or cysteine to kavalactones, thus, rendering them water soluble, sounds interesting. However, the opening of the lactone ring does not necessarily mean that the reaction product is harmless, because such deductions would have to be shown in toxicologic studies—preferably in clinically relevant models. It also does not mean that these premetabolized products are still effective. In addition, it is highly questionable that such reactions would take place within the kava bowl, because the kavalactones are concentrated in resinous droplets into which water and, thus, also glutathione, will not enter. It is hard to foresee what might happen in the duodenum under in vivo conditions. However, all pharmacologic data on kavalactones show that they are absorbed unchanged and act as such.

If relevant Michael additions to kavalactones took place in the gastrointestinal (GI) tract, these would not be restricted to alcoholic tinctures or the intake of ceremonial kava drinks. As already discussed, the consumption of kava in the South Pacific involves potentially much higher doses than those provided by pharmaceutical extracts. It is unlikely that the kavalactones in ceremonial kava drinking would be cleaved by GI Michael additions but the lesser amounts in standardized capsules would not be sufficiently premetabolized to render them harmless—in places where kavalactones may have an intrinsic hepatotoxicity (which would still have to be demonstrated). As the kavalactones are absorbed intact, and because these are undoubtedly the carriers of the pharmacologic effect of the ceremonial kava drink as well as pharmaceutical standardized extracts, the question of the relevance of the finding of a possible Michael addition of glutathione to kavalactones would have to be examined carefully to avoid preliminary conclusions.

Summary

Despite the official kava bans of diverse health authorities, there is still no indubitable evidence for kava hepatotoxicity. The only case reports that can be attributed clearly to the intake of kava extract could be shown to be caused not by a direct toxic mechanism but via an immunologic reaction (Russmann et al., 2001a, 2001b; Strahl et al., 1998), which has to be expected for a small but existing extent for virtually any ingested drug, herb, or food. Under these circumstances, the question should perhaps be: “Do kavalactones really possess a hepatotoxic potential?” rather than “How can supposedly toxic kavalactones be avoided?” Reports on hepatic adverse events caused by immunologic reactions can be found for almost any medicinal plant, including such herbal medicines as valerian (Mahady et al., 2001),
which are nevertheless and rightfully regarded as being safe (Klepser and Klepser, 1999; Mahady et al., 2001). Perhaps the problem with kava is not so much toxicity but more the current desire for absolute safety in the public opinion—a safety that can never exist and that gives way to a distorted view on the risks of herbal medicines compared to the accepted risks of daily life.

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RESPONSE TO SCHMIDT “ARE KAVALACTONES THE HEPATOTOXIC PRINCIPLE OF KAVA EXTRACTS? THE PITFALLS OF THE GLUTATHIONE THEORY”

Dear Editor:

Schmidt implies that there is no evidence of hepatotoxicity with use of kava whereas Denham et al. (Denham, 2002) and I and my coauthors in our Appendix in the Denham et al. paper have argued that toxicity is unlikely at traditional doses and for traditional preparations but that there may be toxicity at high dosages of standardized extracts.

Evidence of hepatotoxicity of kava was presented by Zou et al (Zou, 2002) when extracts of kava inhibited human cytochrome p450 enzymes (CYP1A2, CYP2C9, and CYP2C19) in vitro. This supports our evidence (Whitton et al. in Appendix of Denham et al., 2002) in Acanthamoeba cells. This suggests a possible mechanism for toxicity caused by kava use in certain individuals with concomitant use of other cy-