

Abstract

In recent years, kava kava (*Piper methysticum*, Forst. f., Piperaceae) has been implicated in a number of liver failure cases. Ever since this has kept the scientific world busy. Even though, on closer inspection, the majority of the case reports are probably not connected to kava intake, hepatotoxic effects of kava cannot generally be ruled out. In this article the major theories

as to the mechanism of kava hepatotoxicity are summarized. But in spite of all these hypotheses, there is still no satisfactory answer. In any case, further studies, that might hopefully restore the reputation of kava, are required.

Key words

Kava kava · *Piper methysticum* · Piperaceae · kavalactones · hepatotoxicity · herb-drug interactions · pipermethystin · alkaloid

Introduction

A worldwide discussion on the potential liver toxicity of kava kava (roots of *Piper methysticum* Forst. f., Piperaceae) was initiated by a number of published liver failure case reports after kava usage [1], [2], [3], [4], [5], [6], [7], [8]. This resulted in the ban of kava products in several countries. Several of these reports referred to the same cases and many reports were far from being undisputed and some just included already known errors and inconsistencies [7]. Thus the evidence that kava is actually hepatotoxic still has to be provided and most experts declare that only a negligible fraction of the case reports are attributable to kava [9], [10]. In particular herbal medicine experts in Germany, like the members of the Commission E (responsible for the appraisal of herbal drugs in Germany) or the Society for Medicinal Plant Research, are eager to point out that they regard kava extracts and kavalactones, the active principles of kava extracts, as being quite safe [11], [12], [13], [14], [15].

Several toxicological studies have shown no evidence of liver toxicity from kava extracts or kavalactones. Singh and Devkota

tested aqueous kava extracts in rats with a daily oral dose of 200 or 500 mg kavalactones/kg for two or four weeks. The data revealed that none of the liver enzymes (ALT, AST, ALP, LDH) were elevated; in fact, in some cases they were significantly reduced. This suggested a hepatoprotective rather than a hepatotoxic property of the kava extract; many Pacific Islanders have believed in this beneficial effect for a long time [16].

Other studies, some *in vivo* in animals and some with human hepatocytes, confirm these findings of Singh and Devkota. Gebhardt [17] examined the toxicity of kava extracts and kavalactones in isolated human and rat hepatocytes using the MTT test, which quantifies viable cell numbers using a dye reduction technique [18]. The EC₅₀ value was defined as the concentration of the test substance that left 50% of the hepatocytes viable. In human hepatocytes no cytotoxicity of kava extract or kavalactones was detected. Kavain exhibited an EC₅₀ of 45 µg/mL (~196 µM), the lowest value of all tested kavalactones in rats [11]. This concentration was much higher than any realistic kavalactone concentration in human blood after kava intake (< ~3 µg/mL or 15 µM) [11]. Toxicological studies by Hapke et al. (1971) [19] and

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Received December 1, 2003 · Accepted January 31, 2004

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Planta Med 2004; 70: 193–196 · © Georg Thieme Verlag Stuttgart · New York · ISSN 0032-0943 ·
DOI 10.1055/s-2004-815533

Sorrentino (1990) (unpublished report cited in [11]) show complete lack of toxicity on chronic oral dosing in rats and dogs and rats, respectively. Furthermore, hepatic failure has never been observed with the traditionally used kava extracts in the Pacific Islands [20]. Two studies with Australian Aboriginals documented minor abnormalities in liver function tests in heavy kava drinkers [21], [22]; however, these findings could not be directly compared with the case reports of liver failure in Western countries due to other confounding variables. In addition, due to a long tradition of kava ingestion without any hint of liver toxicity, these results led to the hypothesis that kavalactones alone cannot be the hepatotoxic agents. Furthermore, if kavalactones were hepatotoxic by themselves, then liver failure would probably occur more often [23]. In many of the case reports other drugs with hepatotoxic potential, that may have caused the observed liver failure, were also used by the patients.

The Kava Alkaloid Pipermethystin

Several theories have been postulated as to why liver failure may have occurred after kava ingestion. Recently University of Hawaii scientists announced that they had solved the kava mystery: they suggested that the kavalactones were not the hepatotoxic agents of kava kava but rather the kava alkaloid, pipermethystin, that is found in the stem peelings and aerial parts of *Piper methysticum* from different cultivars and countries [24]. Traditionally, peelings are avoided by the Pacific Islanders, but Dragull et al. claimed that they were used to obtain the extracts for commercial kava products [25]. In Germany the kava raw material is total roots so adulterations with aerial parts/leaves/stem peelings are unlikely. Nerurkar showed that pipermethystin had a strong negative effect on liver cell cultures (cited in [24]). This is supported by evidence from several alkaloids with structures similar to pipermethystin, like the four alkaloids from *Piper arborescens* Roxb. (Piperaceae), that are known to be cytotoxic [26]. Dragull et al. suggested that the possible enzymatic epoxidation of pipermethystin may lead to hepatotoxic products. This theory of kava hepatotoxicity appears plausible, as kava-based food supplements were available previously without any quality control. However, there is very strict quality control of registered herbal medicines in Germany. Since most kava products involved in the reported cases of liver toxicity were German in origin, such adulterations would not have escaped detection by either German regulatory agencies or the pharmaceutical industry in Germany because of the strict German regulatory requirements [23]. On the other hand, University of Hawaii researchers pointed out that the analytical methods used by some herbal manufacturers and regulatory agencies might not have been capable of detecting differences between alkaloids and kavalactones [25]. However, German regulatory agencies or manufacturers have not encountered any problems in differentiating between kavalactones and kava alkaloids and there is batch to batch consistency of kava raw materials (International Kava Stakeholder Meeting, 2003). It does appear, though, that there is indeed a possibility that at least some hepatic adverse effects may have been caused by contaminated kava products containing its alkaloids.

The Glutathione Theory

Whitton et al. recently presented another theory concerning the differences between traditionally used kava extracts and commercially used products [27]. They found that aqueous extracts contain glutathione, which has the potential to react with the kavalactones to provide protection against hepatotoxicity, especially when detoxification pathways are saturated. However, as kavalactones have been identified as the active principles of kava kava, this *in vivo* reaction may also lead to a complete loss of pharmacological activity. In addition, this study was based on the assumption that kavalactones themselves have hepatotoxic potential, which has not been proven yet. Furthermore, the experiments of Whitton et al. were carried out with *Acanthamoebae castellanii* (amoeba cells), where cytotoxicity was noted with isolated kavalactones. However, as stated before, no cytotoxicity was observed either with isolated kavalactones or kava extracts in human hepatocytes [11]. Thus, it is possible that amoeba cells and human hepatocytes may respond differently to kava.

Herb-Drug Interactions

A prominent feature of all case reports was that almost all patients used other medications [1], [23], [28]. This leads to the hypothesis that herb-drug interactions might be responsible for the observed liver toxicity. Nevertheless, ingesting kava concomitantly with other drugs is the norm rather than the exception, thus interactions alone cannot be responsible for the reported liver failures as the observed frequency would be much higher than reported. There are two possibilities: either toxic metabolites of kavalactones are generated or plasma concentrations of drugs with potential liver toxicity are elevated. Several studies have shown that kavalactones are potent inhibitors of several enzymes of the CYP P450 system [29], [30], which confirms the possibility of herb-drug interactions. Mathews et al. showed that kavalactones with a methylenedioxyphenyl group, such as methysticin and dihydromethysticin, inhibit CYP P450 enzymes after metabolic activation by forming metabolic intermediate complexes [30]. As many different cultivars of kava with various major constituents have been identified so far [31], those cultivars with high methysticin and dihydromethysticin concentrations have the highest potential for causing such drug interactions. These may result in increased plasma concentrations of co-administered drugs that are metabolized by the CYP P450 system. This event was suspected for alprazolam, which caused coma in combination with kava [32]. Even though this case report was criticized by certain experts since the side effect might well have occurred without kava intake (cited in [23]), alprazolam as a benzodiazepine is suspected to have a hepatotoxic potential [33]. In other case reports, drugs with potential hepatotoxicity have been used together with kava as well, for example, fluoxetine, paroxetine, acetylsalicylic acid, oral contraceptives, celecoxib, omeprazole and others [1], [23].

Other co-administered drugs or herbal remedies with an influence on CYP enzymes, for example, St. John's wort (*Hypericum perforatum* with its constituent hyperforin) as an inducer [34] or grapefruit juice as an inhibitor of CYP3A4 [35], may be responsible for alterations in metabolic pathways for the kavalactones.

Another possibility is the altered metabolism of co-administered drugs to toxic products. Paracetamol was co-ingested with kava in at least three cases [23]; the conversion of paracetamol to its reactive/toxic metabolite may have been altered.

Interactions with Ethanol

The influence of kava on the metabolism of ethanol, for example, a decreased conversion to acetaldehyde, would also be a possible reason for the observed liver toxicity, as several kava users were co-ingesting alcohol [23]. On the other hand, hepatic elimination is frequently altered in alcoholics [23], so that alcohol may alter the metabolism of kava to possible hepatotoxic products. In addition, as the hepatic glutathione concentration is reduced by alcohol [36], co-ingestion of alcohol may decrease the detoxification of kavalactones or their metabolites. So far no studies have examined either kavalactone or alcohol metabolism in the presence of the other substance.

CYP 2D6 Deficiency

A deficiency in CYP 2D6, detected in two of the patients with liver failure [2], might be an additional risk factor as it may alter the metabolism of kavalactones. Genetic polymorphism of CYP2D6 has a prevalence of ~10% in Caucasian populations and probably does not exist in the Polynesian population [37]. Since this enzyme is suspected to be a major metabolizer of kavalactones, genetic differences between the two ethnic groups may be another explanation for the observed liver toxicity associated with commercial kava products [16].

Toxic Metabolite(s) of Kava?

Johnson et al. identified two novel electrophilic metabolites of kava, two *ortho*-quinoids, using *in vitro* experiments with both rat and human hepatic microsomes; however, these metabolites were not detected *in vivo* [38]. Instead corresponding catechols in the form of glucuronic acid and sulfate conjugates were found. These observations indicate that in all probability quinoid metabolites are usually not formed in substantial quantities *in vivo*. However, such metabolites might contribute to hepatotoxicity when phase I metabolic pathways are altered or if conjugation (phase II) pathways become saturated [38]. Usually the major metabolic pathway for kavalactones is hydroxylation followed by conjugation; opening of the lactone ring, demethylation, decarboxylation, dehydration and oxidation have been observed as well [39].

Genesis of Liver Failure

Either immunological and/or toxicological reactions resulting from any of the above mechanisms have been suggested as causing liver toxicity. The generally high kava dose ingested in the case reports tends to imply a dose-dependent toxic mechanism [1]. However, two of the four well-documented cases possibly related to kava intake were found to be allergic in nature [2],

[10], [23], [28]. Thus, most experts believe that the available data point to an idiosyncratic-immunological genesis for the liver failure [2], [10], [23], [28], especially since in one of the clear-cut cases (as re-analyzed and cited in [2]), a relatively low dose (60 mg daily) of kava was used [8].

Conclusions

In spite of all these observations, interpretations, hypotheses and theories as to the mechanism of kava hepatotoxicity, the reasons for the liver failure possibly due to kava intake remain unresolved. Further controlled clinical and non-clinical studies are necessary to determine the possible mechanisms of liver toxicity seen in Western countries. Such studies may then lead either to the development of less toxic kava extracts, to the identification of a subpopulation of individuals that should not use kava or to additional mandatory cautionary requirements with the use of kava either for recreational use or as herbal remedies (existing suggestions include a switch from OTC to prescription only, periodic laboratory tests during kava ingestion and avoidance of co-medication or alcohol).

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