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Kava hepatotoxicity in traditional and modern use: the presumed Pacific kava paradox hypothesis revisited

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The rhizome of the Pacific kava plant (*Piper methysticum*) contains as its active constituents numerous kavalactones known for their relaxing properties. Kavalactones are found in aqueous, acetonic and ethanolic extracts of the kava rhizomes. These kava extracts are consumed worldwide and used for recreational purposes as well as to treat general anxiety. Kava use is associated with rare hepatotoxicity.

WHAT THIS PAPER ADDS

- Kava is a Pacific herb consumed worldwide and used for recreational purposes and to treat general anxiety. Kava use is associated with rare hepatotoxicity. The previously proposed Pacific kava paradox was based on kava hepatotoxicity, not observed following use of traditional aqueous extracts in the Pacific region but restricted to use of Western acetonic and ethanolic extracts. However, cases assessed by the WHO report and additional published case reports revealed that traditional aqueous extracts used in New Caledonia, Australia, the USA and Germany may also be hepatotoxic; hence, there is no longer a basis to sustain the previously proposed Pacific kava paradox. It appears that the primary cause of toxicity may be attributed to poor quality of the raw material caused by mould hepatotoxins.

Kava, a Pacific herb consumed worldwide for medicinal, recreational and cultural purposes, has been associated with rare hepatotoxicity, and there is currently a critical need to determine this causation. The previously proposed Pacific kava paradox was based on the theory that kava hepatotoxicity was not observed following use of traditional aqueous extracts in the Pacific region, but was restricted to use of Western acetonic and ethanolic extracts. Subsequent cases analyzed by the World Health Organization and published case reports revealed that traditional aqueous extracts used in New Caledonia, Australia, the USA and Germany may also be hepatotoxic; thus, there is no longer a basis to sustain the previously proposed Pacific kava paradox. It appears that the primary cause of toxicity may reside in the time before the preparation of the various kava extracts, possibly attributed to poor quality of the raw material caused by mould hepatotoxins. Rigorous testing of kava raw material is urgently advised, in addition to Pan-Pacific kava manufacturing quality standards.

Introduction

Kava (*Piper methysticum* G. Forster) is a recreational Pacific herb consumed worldwide [1, 2]. The beverages prepared from its rhizomes/roots are also used for cultural purposes by Pacific Island communities [3], and in Australia, the tablet or capsule form is used for the treatment of anxiety [4, 5]. Considerable global interest emerged when reports of toxic liver injury appeared, possibly related to Western acetonic and ethanolic kava extracts [6–8]. In 2002, this led to kava withdrawals from various European countries [8]; to Food and Drug Administration (FDA) consumer advice in the USA [9]; and to a practitioner alert, consumer advice and voluntary recall in Australia [6]. Since 2005, aqueous kava products have again become available in Australia as a Therapeutic Goods Administration approved over-the-counter product [4, 5]. In New Zealand, consumer advice was issued in 2002, with aqueous and solvent-based kava products remaining on the market [1]. In the USA, there is no particular solvent specification issued by the FDA for kava extracts; consequently, production and use of hydro-ethanolic kava products are not restricted [2, 9].

Although initially questioned [8], the subsequent use of the structured, quantitative and liver-specific assessment method of the Council for International Organizations of Medical Sciences [10], in the updated form [11], established causality for kava in a few patients with liver injury [12, 13]. The appearance of these cases was unexpected and created concern, because the mechanistic understanding of causation was not identified [6, 7].

In addition to these uncertainties, other aspects emerged early in the discussion around kava hepatotoxicity and centred on the interesting issue of the proposed Pacific kava paradox hypothesis; that is, while Western formulations of kava may be hepatotoxic, traditional kava use is safe [6].

Previously proposed Pacific kava paradox

In 2003, cases of hepatotoxicity in connection with the use of Western acetonic and ethanolic kava products were reported; at the same time, it was observed that liver toxicity had not been documented with traditional water-based kava extracts used in Pacific countries, such as the South Pacific Islands and Australia [6, 7]. In support of this proposed Pacific kava paradox, three Australian studies involving Aborigines in Arnhem Land who consumed traditional aqueous kava extracts prepared with kava raw material imported from Pacific Islands did not report cases of hepatotoxicity [14–16]. A fourth and a fifth study also supported the proposed Pacific kava paradox [17, 18]. The fourth report concerned inhabitants of New Caledonia who consumed traditional aqueous kava beverages prepared from plants imported from Vanuatu [17], and the fifth study provided data of a predominantly Tongan population of Hawaii, consuming traditional aqueous kava extracts prepared from plants of Hawaii [18].

In the first Australian study, published in 1988, heavy use of traditional aqueous extracts caused greatly increased levels of γ-glutamyltranspeptidase (γGT) and a concomitant decrease of bilirubin, but values for alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP) were lacking [14]. In the two other Australian reports concerning traditional aqueous extracts, published in 2003, serum γGT and ALP levels were increased, with normal values of ALT [15, 16] and bilirubin [15], but AST data were lacking [15, 16]. In 2003, the fourth study, from New Caledonia, showed that heavy users of traditional aqueous extracts had marginally elevated ALT and AST activity in a few cases, but there were high serum γGT levels in most heavy users, with a lack of ALP values [17]. Finally, in 2007, the fifth study, from Hawaii, revealed elevated activities of γGT and ALP and unchanged ALT and AST values in consumers of the traditional aqueous beverages [18].

Therefore, the five studies all showed either normal or slightly increased ALT and AST values, and in none of these studies was there evidence for clinically relevant hepatocellular injury [14–18]. This is in contrast to high ALT and AST values observed in patients who used ethanolic or acetonic kava extracts [12, 13]. However, the changes of increased γGT [14–16, 18] and ALP [15, 18] deserve further evaluation and are likely to be due to malnutrition, alcohol, hepatic enzyme induction, enzyme adaptation or cholestasis [13]. The rare possibility exists that increased γGT and ALP values [14–16, 18] may signify incipient, subclinical hepatic injury of the cholestatic type; this constellation is observed in some forms of drug-induced hepatotoxicity. Although details of the cases and the used kava cultivars are lacking, all these five studies seemed to support the concept of the proposed Pacific kava paradox.

Cases of hepatotoxicity caused by traditional aqueous kava extracts

In 2003, when the Pacific kava paradox was first proposed [6, 7], the first case reports appeared showing hepatotoxicity due to kava use prepared traditionally as water extracts rather than by organic solvents. In two cases from New Caledonia, severe hepatotoxicity was described following the use of traditional aqueous extracts derived from kava imported from Vanuatu [17], with clinical features akin to those detailed for the corresponding German and Swiss cases of patients who used acetonic and ethanolic extracts [13]. Similar reports of single cases came from other countries [12, 13, 19–21]: Australia [19, 21], the USA [20, 21] and Germany [12, 13, 21]. In all these reports [12, 13, 19–21], causality for kava has been established by the structured, quantitative, liver-specific and updated scale of

the Council for International Organizations of Medical Sciences [10, 11] that was also applied to cases of patients with liver disease due to acetonic and ethanolic extracts [12, 13]. In 2007, the World Health Organization (WHO) kava hepatotoxicity study listed five cases due to aqueous kava extracts; three were coded for kava with a causality of possible and two probable; two were from traditionally prepared kava [1]. The WHO report also referred to other cases of patients with liver disease, but a relation to the use of traditional aqueous kava extracts was not established using the WHO scale [1]. Essentially, the WHO kava report confirmed that traditional aqueous kava extracts may exert rare potential hepatotoxicity similar to acetonic and ethanolic extracts. These observations have cast doubt on the Pacific kava paradox.

In a recent study, typical features of kava hepatotoxicity caused by aqueous, acetonic and ethanolic extracts were compared [21]. Clinical characteristics included assessment of gender, age, daily use of kavalactones, daily kava overdose, duration of kava use, co-medication with synthetic drugs and other herbs including use of herbal mixtures, outcome and requirement for a liver transplant. The assessed features were fairly comparable with respect to all used extracts, substantiating that the solvents employed to prepare the various kava extracts are not causally related to the development of liver injury in these cases.

Pacific kava paradox rejected

Since the Pacific kava paradox was suggested in 2003 [6, 7], compelling evidence has accumulated that traditional kava extracts may rarely be toxic to the liver [13]; and toxicity was not restricted to Western populations in Australia [13, 19, 21], the USA [13, 20, 21] and Germany [13, 21], but occurred also in New Caledonia [17, 21]. Considering the various case reports [12, 13, 17, 19–21] and the proposals made by the WHO [1], it is apparent that any type of kava product, including traditional aqueous kava extracts, acetonic and ethanolic kava extracts may rarely cause hepatic adverse reactions [13, 21]. Consequently, it is now reasonable to reject the Pacific kava paradox. Further research is required to ensure safe human use of kava extracts [5, 22, 23]. It is possible that the problem of kava hepatotoxicity resides at an early level of its production, perhaps at planting, harvesting or storage of kava plants. Selection of the appropriate kava cultivars and ensuring plant parts of good quality are required for safety reasons [23] in all counties where kava products are available, including Pacific Islands, Australia and the USA [1–5, 9, 17–21].

There has been worldwide interest in kava and associated liver injury [1, 24–26], as well as research activities attempting to elucidate pathogenic factors of kava hepatotoxicity [22, 23]. At present, little evidence exists that the primary psychoactive constituents (kavalactones) or other constituents (pipermethystine and flavokavain B) of the kava plants are the toxicological culprits for kava hepatotoxicity [13, 22, 23, 27, 28]. Rather, it appears that poor kava material containing adulterants or impurities, including mould hepatotoxins as contaminants, are more likely to be responsible [22, 23]. There is the possibility that mouldy kava raw material may have been used in the past, contaminated by *Aspergillus* species, producing aflatoxins, other fungal species, bacteria or viruses, all being potentially hepatotoxic [23, 26–28].

As a matter of fact, in three aqueous extracts prepared from the internal part of the kava rhizome to minimize soil contamination, various species of bacteria were isolated: *Bacillus*, *Cellulomonas*, *Enterococcus*, *Pectobacterium* and *Staphylococcus*; the conclusion was reached that the *Bacillus cereus* group and *Staphylococcus* species may produce toxins and cause food-borne illness [29]. These and additional species of bacteria may elicit hepatotoxicity, provided quantities are sufficient [23].

Furthermore, data have emerged revealing kava contamination by *Aspergillus* species producing mycotoxins such as ochratoxin A [30] and aflatoxins [31] that create concern [23, 26, 28]. Kava roots obtained from a botanical supplier were found to contain ochratoxin A at a level of 10.3 ng g^{-1}; corrected for about 50% recovery, the actual concentration was 20 ng g^{-1} [30]. In other studies, kava was found to be naturally contaminated with aflatoxins at concentrations of at least 0.5 ng g^{-1} [31]. These are potentially toxic to the human liver in analogy with epidemic toxic hepatitis caused by food contaminated with aflatoxins reported from India and Kenya [32–34]. Other fungal candidates with similar hepatotoxic potency have to be considered, and future assessment has to include parts of mouldy kava plants, with preference for rhizomes and roots as peeled organs and their separate peelings [23]. It is conceivable that the bark of kava rhizomes and roots contains higher amounts not only of bacteria but also of fungi, which is an important aspect because quantity is a major parameter for hepatotoxicity.

It should be noted that kava products available in Australia and New Zealand are manufactured with Pharmaceutical Good Manufacturing Practice, ensuring that the kava material is screened for contaminants. If the liver toxicity is due to poor material and contaminants, it is potentially preventable. Alternatively, the small number of cases of kava hepatotoxicity may be due to an idiosyncratic reaction of the metabolic type, thus not being preventable [6, 13, 27]. This issue requires urgent research.

Outlook

Reassessment of the previously proposed Pacific kava paradox reveals that there is no longer a convincing basis for this proposal and the assumption that cases of

hepatotoxicity are restricted to Western use of acetonic and ethanolic kava extracts. Case reports have now shown that traditional aqueous kava extracts also are potentially hepatotoxic, suggesting that kava hepatotoxicity is either a problem primarily of poor quality of the kava raw material rather than of synthetic solvents or due to an idiosyncratic reaction. Regardless, it is still advisable preferentially to use an aqueous solvent [4, 5], which is also in concert with the traditional preparation of kava [1, 3]. Global kava use remains prevalent; therefore, investigation is urgently advised to compare different raw kava material to assess potential hepatotoxic effects [22, 23, 26, 35], in addition to application of a Pan-Pacific kava manufacturing quality standard and a general Kava Quality Standardization Code [26].

Competing Interests

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