Kava, the anxiolytic herb: back to basics to prevent liver injury?

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The use of the anxiolytic herb kava has caused toxic liver injury in Western countries and economic problems in South Pacific Islands due to the regulatory ban on kava. This analysis shows poor quality of kava raw material as a cause for its toxicity and suggests preventative measures by going back to the traditional use of kava for the sake of the patients and the South Pacific economy.

Introduction

The credit for the first detailed description of the kava plant is given to George Forster [1, 2], a member of the sailing crew of Captain James Cook on his second voyage around the world on the 'Resolution' (1772–1775) [3]. In 1777 George Forster named the kava plant *Piper methysticum* or 'intoxicating pepper' [2]. Its extracts are used as recreational beverages for social events in South Pacific Islands [1–6], as unregulated dietary supplements in the United States [4–6] and also worldwide due to internet access [5], or as regulated herbal anxiolytic products approved in Australia [7]. A Cochrane study confirmed the efficacy of kava extracts for anxiety disorders, and also considered major side effects such as drug tolerance observed with synthetic alternatives like benzodiazepines [8]. Since 2002 due to concerns of liver toxicity, kava has been banned from consumption in several countries including the United Kingdom, Germany, Switzerland, France and Canada, but surprisingly not in the United States [5]. This has caused profoundly harmful socioeconomic effects on poor Pacific Island countries that rely on this export [5, 6]. Furthermore, patients with anxiety disorders in restricted areas may receive this effective anxiolytic herb only illegally via the internet. As a consequence, a highly qualified WHO expert group recently convened to assess the hepatotoxic risks of kava, and to provide potential solutions [5]. This was a critical WHO imperative as the kava ban has caused economic problems in the South Pacific which are

causing follow-on public health ramifications from the resultant increase in poverty.

Issue of unexpected toxic liver injury

Reports of toxic liver injury due to the treatment with the anxiolytic herb kava first appeared in 1998, and were unexpected in Western countries [8–13] since kava has had a tradition for safe use in the South Pacific Islands for centuries [4–8]. There were, however, differences in the manufacturing process: the traditional kava extract in the South Pacific Islands is water based [4–8, 14], whereas Western countries commonly use ethanol and acetone extraction media and various solubilizers [13–15]. For both medicinal and traditional kava extracts, the preferred raw materials are the peeled rhizomes derived from the kava plant in the South Pacific Islands, as opposed to aerial plant parts and the peelings of roots and stems sometimes used by European manufacturers [5, 14].

First a quantity issue, then a problem of quality

The initial cases of kava hepatotoxicity emerged concurrently with the booming kava market at the end of the last

century [4–6]. To cope with increased demand, quality criteria for kava raw material may have partially been neglected [4–6, 14]. Resulting quality problems were substantiated by hepatotoxicity reports associated even with the use of traditional aqueous kava extracts in New Caledonia [5, 6, 14]. Accordingly, safety concerns were expressed that inappropriate kava raw material may have been responsible rather than solvents or solubilizers [14–17].

The problem of kava hepatotoxicity not being confined to Western countries, but extending to the South Pacific Islands region [14], led to the new issue about going back to basics and to the traditional use of kava before the kava boom. Thus, using peeled rhizomes and roots of a traditional noble kava plant that has a safe toxicity record was recommended [5, 14, 16, 18].

Feasible quality problems: kava cultivars and plant parts

Uncertainties regarding the quality of raw material included the plant variety itself and the plant parts used for traditional and medicinal kava extracts [5, 12–18]. These issues are complex since numerous different kava varieties exist and various plant parts other than the rhizome and roots have been harvested and sold in the past [4–6, 11, 14, 18–20].

At present up to 200 different kava varieties, also called cultivars, are known in the South Pacific Islands, with their number still rising [5, 6, 18]. In 2002 the Vanuatu government passed the Kava Act no. 7 [19] which identified and categorized the different cultivars into: (i) Noble kava cultivars with a long history of safe use as a traditional social beverage, (ii) medicinal varieties with a long and proven history of beneficial properties amongst traditional Pacific herbalists, and banned as export commodities are (iii) 'Tu Dei' kava cultivars (2 day intoxication) and (iv) 'Wichmannii' varieties (wild kava). Medicinal kavas are rarely used as a social beverage because they do not satisfy the desired physiological effect of the kava drinker [19]. Therefore, kava cultivars used for traditional kava beverages in the South Pacific Islands were different from those used for medicinal purposes in Western countries. This raises the question as to whether noble cultivars may be better and safer regarding hepatotoxic effects than the medicinal kava varieties.

Each kava cultivar may readily be identified by its individual chemotype signature consisting of various kavalactones (the active chemical compounds) [1, 6, 18]. Out of 18 kavalactones the following six are required to establish the signature: kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin and desmethoxyyangonin [18]. Surprisingly, no batch analysis was made in any of the kava extracts used by patients with established kava hepatotoxicity [13–15]. In studies with medicinal kava extracts,

however, adulteration by non-medicinal kava cultivars was detected as evidenced by chemotype analysis [18].

The parts of the kava plant previously used to prepare extracts may not have been peeled, and may have included not only the underground parts such as rhizomes and roots, but also aerial parts like stems, adventitious roots and peelings [5, 17–20]. Aerial parts occasionally used for traditional and medicinal extracts are known to be hepatotoxic and have been a matter of concern [5, 6, 14, 18].

Pathogenetic challenges

In addition to quality problems of the kava raw material itself, other possible causative mechanisms for kava hepatotoxicity have to be discussed [5, 21]. Adverse reactions may be caused by plant material contamination [5, 11, 21, 22], pipermethystine [5, 21], flavokavain B [21, 23], inappropriate preparation including adulteration [5] and use of organic solvents such as ethanol and acetone [5, 11], or misuse in respect to high dosage or concomitant use with alcohol [13]. Toxicity could be intrinsic, provided some of the herb constituents are toxic, or it could be idiosyncratic, because it occurs with low frequency [13, 21]. Major concerns are herb–drug interactions since 64% of the patients with established kava hepatotoxicity used up to 20 different synthetic drugs and dietary supplements including botanicals [11, 13, 21]. Therefore, other pathogenetic mechanisms cannot be totally ignored.

The WHO kava report

The WHO report analysed the problems of toxic liver disease associated with the kava extracts regarding causal relationship, role of solvents for aqueous, ethanolic and acetonetic extracts, kava raw material, comedication, dosage and duration of intake, impurities, and adulteration [5]. A causal relationship for kava was established using definitions of the WHO Collaborating Centre for International Drug Monitoring, but no attempt has been made for an in-depth clinical examination of individual reports. It was confirmed that liver injury occurred with ethanolic, acetonetic and aqueous kava extracts. For aqueous extracts the case numbers were smaller, an observation not unexpected since there are far fewer consumers of aqueous extracts in the South Pacific Islands than patients treated with ethanolic and acetonetic extracts in the Western world.

Recommendations outlined by the WHO report suggest the creation of a pharmacopoeial standard for kava which addresses the issues of quality, plant parts, dosage and methods used for preparation [5]. They included the use of the rhizomes and roots, but not of aerial parts or synthetic solvents. A good candidate for an appropriate traditional noble kava plant is the cultivar Borogu with the chemotype 423561, signifying high amounts of kavain [16]. Cultivated with a long tradition in

Table 1

Proposals to improve kava safety regarding liver injury

Items	Proposals
1 Quality of kava cultivar	Noble kava cultivar (A,B)
2 Minimum of plant maturation	5 years (A,B)
3 Kava plant part (A,B)	Peeled rhizomes and roots
4 Solvents used for kava extracts	Water (A,B)
5 Solubilizers	None (A,B)
6 Adulterations and impurities	Surveillance (A,B)
7 Maximum daily dose	To be determined (A,B)
8 Maximum duration of use	To be determined (A,B)
9 Comedication	Not recommended (A,B)
10 Alcohol use	Not recommended (A,B)
11 Prescription device	Obligate (A), not feasible (B)

The presented proposals are made for medicinal aqueous kava extracts (A) and traditional aqueous kava extracts (B), based on details derived from various references [4–7, 14, 16, 18–20]. Borogu is one of the traditional noble kava cultivars of choice [16].

Vanuatu (the area of origin of *Piper methysticum*), Borogu is well established for daily drinking without apparent side effects and is known for its rapid effect, and is thus a potential ideal candidate for future clinical studies.

The way forward: back to basics

To advance current research and the potential re-introduction of kava to restricted countries, going back to the traditional usage of a noble cultivar (e.g. Borogu) is recommended [16]. This is a prerequisite for further efficacy studies, as evidenced by a recent positive clinical study using a water extract of peeled roots from a noble kava cultivar [7]. Before the recognition of hepatotoxicity, European countries traditionally adhered to the use of peeled kava rhizomes, which were well tolerated and failed to cause toxicity. Rhizomes are clearly defined as the part below the stems and above the roots [5]. This excludes stems, leaves, and aerial adventitious roots with hepatotoxic properties [20]. Normal roots, which may have different properties compared with the rhizomes, require further research as suggested [5].

Unlike the mainstream of synthetic pharmaceuticals, kava is a heterogeneous collection of herbal products [4], requiring special regulatory, scientific and clinical attention (Table 1), in concordance with the WHO recommendations [5]. Use of one specific noble cultivar (such as Borogu) for research and export for medicinal kava products was recommended [5]. Only peeled rhizomes and roots should be used for aqueous kava extracts for both medicinal and traditional purposes in the Western world and the South Pacific Islands, respectively. Stringent strategies for minimizing hepatotoxic risks need to be implemented, including thorough regulatory and commercial surveillance at all manufacturing levels.

Conclusions

Liver injury caused by medicinal and traditional kava extracts as a consequence of inappropriate kava raw material has undermined consumer confidence in modern herbal medicine. A current approach is being made to overcome lack of standards and to suggest criteria for good kava quality, both in Western countries and in the South Pacific Islands. Thorough safety control measures are now required as mandatory for the sake of both the patients who want the anxiolytic herbal kava extracts and those individuals who like the relaxing properties of traditional kava drinks. This approach should also be of potential benefit to the future economy of the Pacific Islands. The critical next step forward in assisting the Pacific Island people with the re-introduction of their valuable export commodity and cultural icon, is to go back to basics, back to using water extracts of peeled noble kava rhizomes and roots.

Competing interests

There are no competing interests to declare.

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