Kava: herbal panacea or liver poison?

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EXTRACTS OF KAVA (*Piper methysticum*), a Pacific islands plant, have been used in the Pacific islands for centuries. Historically, use of kava was restricted to ceremonial occasions, but in the 20th century it has been increasingly used by the general population. Kava has always been considered to have a calming effect, and users are described as becoming mellow and reflective, rather than stimulated or combative.[1-3]

Ever since Europeans first reached the Pacific, there has been interest in the use of kava.[1,2] As early as the 19th century, Germans incorporated kava into their herbal medicine repertoire. More recently, with greater interest in herbal medicines, the use of kava has increased enormously worldwide. However, the kava used in Western countries is not the water extract of powdered roots that is traditional in the Pacific islands. Instead, in Western countries, kava is usually a dried ethanol or acetone extract of kava made up as capsules.

The increase in Western use of kava was an economic boon for Pacific island nations. However, this export boom halted with the banning of kava products in most Western countries. The ban followed reports of liver toxicity, first from Switzerland and Germany, and later from most other Western countries, including Australia.[4-9] The continuation of this ban has been predicted to have dire economic consequences for struggling Pacific island economies.[10,11]

The response to the ban has varied enormously. Several kava marketing agencies in the Pacific islands and some herbal practitioners have responded with a mixture of outrage ("*How could a natural Pacific icon which has been used for centuries without any suggestion of liver toxicity possibly be so harmful?*") and distrust ("*It is no coincidence that kava was starting to eat into the profits of the multinational pharmaceutical industry*"). On the other hand, cynics have observed that every boom is followed by a bust, and that the promotion of kava extracts as an anxiolytic with no adverse effects, in the absence of rigorous toxicology testing, was an invitation to disaster.

Where does the truth lie? Have people in Western countries been saved from an epidemic of liver toxicity by vigilant regulators, or are they now being denied the benefits of a Pacific panacea? And what about the Pacific Islanders? Have they been unwittingly exposing themselves to a nasty liver toxin, and should they now change traditional habits?

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ABSTRACT

- Following reports of liver toxicity, including liver failure, associated with extracts from the Pacific islands plant kava (*Piper methysticum*), these have been banned from sale as a herbal anxiolytic in many Western countries, to the detriment of Pacific island economies.
- Pacific Islanders have used kava extensively for centuries, without recognised liver toxicity. However, the population is small, and there has been no systematic evaluation of possible liver damage.
- For both economic and public health reasons, it is important to determine if kava is inherently hepatotoxic, and what the mechanisms of toxicity are.
- Such research could lead to safer kava extracts for sale in Western countries, or identification of a subpopulation who should not consume kava.

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Common ground

As in most debates, the common ground is extensive, and the argument is largely over interpretations and emphases.

For kava as marketed in Western countries, there is probably general agreement that:

- Despite the poor documentation of some of the reported cases of liver toxicity, kava preparations available in Western countries (ethanol or acetone extracts) very likely do cause severe liver toxicity in some patients.[4-9] The frequency of such severe toxicity is unknown.

For kava prepared and consumed in the traditional manner, there is probably general agreement that:

- There has been no recognition of severe liver toxicity, including in more recent times when clinicians were alerted to the possibility of liver toxicity. Thus, toxicity of the severity reported from Europe and Australia must be rare, and might well not occur at all in Pacific Islanders.
- There have been no systematic studies into milder forms of liver toxicity in Pacific island countries, so mild toxicity could be present without having been recognised.
- Kava prepared in the traditional manner and heavily used by Indigenous Australians is associated with moderately raised liver enzymes — mainly γ-glutamyl transferase (GGT).[12]

Issues of contention

Despite this common ground, there are major points of contention between the kava "stakeholders".

- How relevant is the Pacific island experience to the interpretation of the cases of liver toxicity in Western countries?

- How relevant is the finding that some Indigenous Australians who are heavy kava drinkers have raised serum GGT levels?[12]
- Is the liver toxicity in people taking kava in Western countries related to the different preparation procedures? In particular, does the ethanol or acetone extraction procedure either concentrate or select toxic compounds, or diminish protective compounds (such as glutathione)?
- Is the liver toxicity in people taking kava in Western countries related to genetic differences in liver metabolic enzymes not expressed in Pacific Islanders?
- How significant is it that nearly all the patients with liver toxicity attributed to kava have also been consuming other drugs or herbs, some of which have also been associated (albeit rarely) with liver toxicity?[13]
- What are the comparative doses of kava when prepared and ingested by the traditional method and by the extracted methods?
- Is kava a sufficiently valuable herb (that is, does it have sufficient efficacy) to warrant acceptance of a degree of liver toxicity?

Relevance of the Pacific experience

The Pacific experience is relevant in that it shows that kava is not a common liver toxin. However, the Pacific experience is also clearly not sufficient to sustain the argument that, because toxicity has not been observed in the Pacific, kava cannot be the cause of the liver disease seen in Western countries.

A major deficiency of the Pacific experience is that liver toxicity, possibly caused by kava, has never been systematically looked for. Apart from its important implications in trying to unravel the problem of toxicity seen in Western countries, this is a major public health question in Pacific island countries, and needs to be addressed.

The population of the Pacific islands is small compared with Western countries. An adverse event rate from kava of (say) 1 in 100 000 is likely to be recognised when the exposed population is large (such as in Western countries), but would not be recognised in the Pacific, where the total population with heavy kava intake is probably less than 100 000 (it is unlikely to be more than 10% of the total population, which is little more than one million). More information on the total exposed population, both in the Pacific islands and in Western countries, would be very useful in further exploring this issue.

Finally, a natural product can be used widely for many years before its toxicity is recognised. Alcohol is the prime example of a product that has been used for centuries, but only relatively recently accepted as a liver toxin.

The Indigenous Australian experience

The relevance of studies of Aboriginals who are heavy kava drinkers depends on the degree to which the findings might be confounded by alcohol, and the degree to which raised serum GGT levels reflect significant liver toxicity.[12]

The investigators went to considerable lengths to ensure that alcohol intake did not confound their results, and it is reasonable to accept their conclusion that heavy kava consumption in Indigenous Australians is associated with raised serum GGT levels.

The clinical relevance of raised serum GGT levels is more difficult to determine.[14] Alcohol causes raised serum GGT levels and can cause acute hepatitis and acute liver failure as well as chronic cirrhosis of the liver. However, other drugs (eg, phenytoin) also commonly cause raised GGT levels, reflecting CYP450 enzyme induction, yet seldom (if ever) cause acute liver failure or cirrhosis of the liver. Hence, raised GGT levels do not necessarily imply "subclinical" liver toxicity.

Extraction procedure

Many commentators have concluded that the liver toxicity in Western countries is a result of the extraction procedures. These commentators mainly follow the argument that water extractions used in the Pacific do not cause toxicity, so toxicity must be caused by the alcohol or acetone extraction procedures. As outlined above, this argument is not necessarily valid.

Clearly, the lack of toxicological studies on kava extracts is a major deficiency in the debate. These extracts have been marketed in Western countries as herbal preparations. Different countries regulate traditional herbal medicines in slightly different ways, but common to all is the recognition that traditional use is of value in ensuring an acceptable degree of safety, so herbal preparations do not require the same rigorous toxicity testing as new pharmaceuticals. Thus, in the case of kava extracts, we do not have the toxicological data to assist us in making judgements on the possible human liver toxicity.

Genetic differences in liver metabolism

At least two of the European individuals with kava-associated liver toxicity were reported to have a genetic deficiency of the liver metabolic enzyme CYP2D6.[9] This enzyme deficiency occurs in about 10% of Europeans, but has been reported not to be present in Pacific Islanders.[15] This raises the possibility of genetic susceptibility of some Europeans, although it is not known how the enzyme deficiency might lead to toxicity.

Co-ingestion of other agents

Some commentators, in reassessing the cases of liver toxicity in Germany, have given prominence to the possibility that the liver dysfunction in each case could have been caused by co-ingested drugs or herbs.[13]

It is true that in some of the cases kava was mixed with other herbs. Some patients also co-ingested other agents (eg, frusemide or a benzodiazepine), which have very rarely been associated with liver dysfunction. It is therefore impossible to be certain that the kava, rather than one of the other agents, caused the liver dysfunction. However, more than one regulatory agency, with their inherent expertise, has examined the data and concluded that kava is the most likely culprit in enough of the cases to be of concern. This should at least give

reasonable confidence that kava is not being unfairly blamed for problems caused by other drugs or herbs.

Comparative doses from different extraction procedures

The active components of kava are considered to be kavalactones, several of which have been described.[2,16-18] Most products containing kava extracts specify a kavalactone content on the label, but there is little information on how this is determined, and there are anecdotal reports of products having quite different kavalactone content to that on their label. Kavalactone concentrations in traditionally prepared kava have been measured, but the results of these studies have not been replicated, or compared with those in commercial extracts.[19,20]

This lack of data has led to considerable confusion when attempts have been made to compare the "doses" of kava associated with toxicity and the "doses" considered efficacious and ingested when kava is consumed traditionally.[13] This issue needs attention, at least to the extent of documenting the content (and variability) of known kavalactones in traditional and extracted preparations.

The harm–benefit ratio for kava

Some herbalists (and others) have argued that kava is sufficiently beneficial that rare cases of liver toxicity should be tolerated in the same manner that rare cases of liver toxicity caused by benzodiazepines are tolerated.[13]

Good efficacy studies of kava in humans are rare,[21] and have only been performed on kava extracts. A reasonable conclusion is that the efficacy of kava is modest, and of a nature similar to the benzodiazepines. However, kava is probably not as potent as the benzodiazepines, as experience suggests that even in high doses it does not cause as profound effects.

Because the efficacy of kava is not well documented, and both the frequency and severity of the toxicity are contentious, it is impossible to make an accurate assessment on the harm–benefit ratio for kava.

The future

Pacific island countries are suffering economically from the current ban on kava, and feel that Western countries are not taking sufficient notice of their plight. Nevertheless, it would not be proper to continue marketing kava extracts without better evaluation of their safety. People in Pacific island countries can probably continue to consume kava in the traditional way, but their governments need to ensure that proper studies are undertaken to better evaluate the safety of kava before they push for resumption of large-scale exports.

It will be impossible to prove that kava is completely safe, but a good start would be to undertake a systematic evaluation of a large number of drinkers of kava prepared in the traditional manner, assessing them for liver dysfunction (and any other toxicity). If such a study shows no convincing liver dysfunction, then the Pacific island countries need not be concerned for their own populations. The debate (and future research) would then concentrate on the kava extraction procedures and the genetic basis of kavalactone metabolism, to determine the mechanisms of the toxicity seen in Western countries. In turn, this could lead to the development of less toxic extracts or the identification of a subpopulation in Western communities who should not consume kava.

If a systematic study of drinkers consuming kava in the traditional manner were to show significant liver dysfunction — or any other toxicity — then the focus would change to the public health implications for the population of the Pacific islands. Each country would need to decide what restrictions, if any, to impose on the availability of kava, and further research would be required to determine the extent and severity of the problem, and the mechanisms of the toxicity.

Conclusion

The banning of kava by most Western countries has had a detrimental effect on the economies of Pacific island countries. In addition to this economic imperative, there are important public health reasons for determining whether kava is inherently hepatotoxic. Once this is known, attention can focus on the mechanism of the toxicity. Knowledge of the mechanism of toxicity might then allow a safe preparation to be developed, and/or subpopulations identified who should not ingest kava.

Competing interests

None identified.

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