New Zealand Association of Medical Herbalists

SUBMISSION ON PROPOSED RECLASSIFICATION OF KAVA AS A PRESCRIPTION MEDICINE – MEDICINES CLASSIFICATION COMMITTEE, June 2005

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SUBMISSION TO THE MEDICINES CLASSIFICATION COMMITTEE, CONCERNING PROPOSAL TO HARMONISE THE CLASSIFICATION OF KAVA WITH THAT OF AUSTRALIA

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Kava and its Use in New Zealand.

Kava (*Piper methysticum*) has been used in the New Zealand supplement market since 1998 or earlier. It has been both an imported product as well as manufactured locally since that time. We are aware of 5 suppliers using a 90% Ethanol/water extracted solid herbal extract, one manufacturing and supplying a 60% ethanol/water liquid extract to practitioners only, and one supplying a TGA compliant aqueous liquid extract.

Use amongst the Polynesian community in New Zealand, is also prevalent.

Reports of Liver damage and Regulatory responses

The first case report of liver damage linked with kava consumption appeared in the German literature in 1998 (1). This case involved hepatitis in a 39 year old woman who had taken kava for 6 months. Concurrent drug treatment included the progestogenic agent desogestrel and the antidepressant paroxetine, for which reports of severe hepatotoxicity have been previously documented (2).

A Swiss report published in 2000 described nine cases of hepatotoxicity which were attributed to kava (3), and this was followed in November 2001 by a report by the German Health Authority Bundesinstitut fur Arzneimittel und Medizinprodukte (BfArM) of 24 cases. This included one death and 3 cases of liver transplants.

Further reports occurred, and in total, 39 cases of adverse hepatic reactions were reported to the BfArM from 1990 to 2002 (4). Of these, insufficient data was available or kava was excluded as the aetiological cause in 12 patients (4).

In June 2002 BrArM withdrew the marketing authorizations of all kava and kavain-containing medicinal products. Due to the reputation of Germany as having generally sound expertise on herbal medicine, other national authorities tended to follow the German ban. In the UK, the Medicines Control Agency (MCA) and Committee on Safety of Medicines (CSM) in Britain enacted a formal prohibition in January 2003. Recalls or effective withdrawal of kava also subsequently occurred in many other countries including the U.S., Switzerland, Canada, Singapore and Australia.

In August 2002 the New Zealand Food Safety Authority considered the issue and declined to issue recall notices. It appears from this notification that the Medicines Classification Committee considered the issue on 10 September 2002 and declined to take action.

Since these earlier reports, a small number of additional case reports have also been made. These include one case of acute liver failure and death in Australia (5), attributed to the kava content of a product also labeled as containing Passionflower (*Passiflora incarnata*) and Scullcap (*Scutellaria lateriflora*), despite the fact that presence of Scullcap could not be established by HPLC (6). The possibility of potentially hepatotoxic unknown adulterants or contaminants in this product, therefore remains.

A total of around 80 cases of various degrees of liver damage have now been documented worldwide (7, 8, 9).

Possible mechanisms of toxicity:

Virtually no reports of kava-related liver damage in traditional communities have been made, despite large doses of the crude root and the kava lactones it contains often being consumed. While two cases of liver injury linked to kava use in New Caledonia were reported in 2003, in one case the patient was also taking phenobarbitone (a known potential hepatotoxin), and in neither case was the patient rechallenged with kava to confirm that it was responsible (10).

A survey conducted in Samoa in 2002 failed to find one case, even in heavy kava drinkers (11). An Australian cross sectional study involving liver function tests in 98 aboriginal participants who had taken an average quantity of 118g per week of kava powder for a medium period of 12 years, found an association between more recent kava use and higher levels of GGT and ALP, but not with ALT or bilirubin. These small elevations were shown to be reversible and a return to baseline levels became apparent after 1 to 2 weeks abstinence. No evidence for irreversible liver damage was found (12).

Traditionally it is mainly men who drink kava, yet their incidence of liver toxicity is low and similar to that of island women who do not take kava (13).

In the years prior to kava's withdrawal, a competitive drive to produce high lactone-containing products, and the associated introduction of synthetic solvents and use of less natural manufacturing processes became widespread. Several of the German case reports also involved patients who were taking a product made from *synthetic* kavain (a kava lactone), rather than a naturally-produced kava extract. All Swiss and most German cases involved consumption of a high dose of an extract standardized to contain 70% kava lactones, manufactured using

acetone rather than ethanol as a solvent. None of the early cases cited by the German authorities involved traditionally prepared tinctures made using low or moderate percentages of alcohol.

In nearly all cases, extracts high in kava lactones had been taken, and the dosages for these were at the top end of the normal recommended range (three of the four people requiring liver transplants were believed to have been consuming greater than 240mgs kava lactones per day (3), while most manufacturers recommend intake of between 60 to 120mgs kava lactones daily).

It is therefore quite conceivable that these developments contributed to the use of products with a higher incidence of adverse effects than preparations made according to more traditional methods, such as aqueous infusions or hydroethanolic liquid extracts (14, 33).

A submission prepared by the European Herbal Practitioners' Association, asserted that safety may depend on the kava lactones remaining in their natural form (14). It has been postulated that certain modern extraction techniques then in vogue, could have resulted in an unnatural variation in the phytochemical balance of each lactone, and possibly artefacts of production with potential hepatotoxicity. High lactone kava preparations are also postulated to deplete glutathione levels in the body, and thus reduce the ability of hepatocytes to metabolise lactones. The Michael reaction between glutathione and kava lactones, resulting in opening of the lactone ring, has been associated with protection against hepatotoxic effects (15).

Despite this, TLC analyses have found there to be little difference between the composition of an aqueous, ethanol or acetone extract of Kava, the major difference appearing to be the amount of material extracted rather than the composition (16).

Use of non traditional parts of the plant (root peelings and aerial parts) by European pharmaceutical companies, also became common during 2000 and 2001 (17, 18). It has been suggested that the usage of these plant parts, traditionally avoided by Polynesian kava drinkers, may also account for the sudden appearance of case reports of hepatotoxicity in Europe during this time.

The most likely explanation for possible hepatotoxic effects attributable to kava ingestion, is that such episodes occur as a rare idiosyncratic reaction. Idiosyncratic reactions have been reported for a number of other herbal medicines, just as they have for numerous drugs. A genetically-determined lack of particular metabolising enzymes, could be involved in some individuals.

The fact that all three of the main types of hepatocyte damage which occur through drug-related adverse reactions (necrosis, drug-induced hepatitis and

cholestatic hepatitis) have been seen in these case reports however, suggests the contribution of more than one cause.

The possible contribution of other drugs being taken concurrently, known to be a factor in a large percentage of case reports, also implicates the possibility of interference with their metabolism and subsequent potentiation of their toxicity. In all but 5 of the 24 cases originally reported in Germany, other drug therapies were being taken at the same time as kava. Thus adverse drug interactions involving kava, rather than kava toxicity itself, may be responsible for many case reports of hepatotoxicity.

Appraising the evidence and quantifying the risk

Determining the exact numbers of cases reported to date, is difficult, due to the lack of provision of adequate data to establish a causal relationship in many cases and inclusion of previously reported cases by some authors (8, 9).

A full evaluation of all reports has not been undertaken by this submission's authors, due to time and other constraints. Several points about the earlier reports however, as well as conclusions of recent reviews, should be considered.

Various sets of authors have evaluated these reports. A critical analysis of the suspected 19 cases of hepatotoxicity reported in Germany prior to 2003, revealed that only in a single patient a very probable causal relationship could be established between kava treatment and the development of liver disease, whereas in another patient a possible association was identified (9). Of the remaining 17 cases, 12 patients were not assessable due to insufficient data, and in 5 other cases a causal relationship was unlikely or could be excluded. An incidence calculation from these case reports indicates that hepatotoxicity from kava could occur in 0.008 cases per million daily doses (9), which represents an extremely low risk of adverse reactions associated with kava.

The most recent independent evaluation of kava toxicity, published in the April 2004 issue of the journal *Toxicology Letters* (8) identified a total of 78 cases of hepatotoxicity reputedly linked to kava ingestion, from various databases. This American author cited the most thorough evaluation of adverse event reports regarding kava, conducted by Mathias Schmidt and Adolf Nahrstedt of the University of Munster. Originally published in the *Deutsche Apotheker Zeitung* in February 2002, a much expanded version of this article is available on the Internet in an updated English translation (19).

Of these 78 case reports of adverse events, 37 cases derived from the German BfArM (plus five duplicate/triplicate entries of otherwise identical case reports), 5 cases from the Swiss SWISSMEDIC, 2 case reports published in the German public press, 5 cases from the medical literature, 20 cases from the US FDA, 2

cases from the British MCA, one from the TGA, 3 from Canada, 2 from France and 1 case from the Pharmacovigilence Working Party of the EMEA (European Agency for the Evaluation of Medicinal Products).

Of the 78 reports, the following conclusions were made:

a) 5 reports appear to be double or triple entries
b) 14 reports have no connection to kava usage.
c) 29 cannot be assessed due to the insufficiency of the documentation.

Of the cases showing a "possible connection", only one appears to involve use in strict conformity with German Commission E recommendations of no more than 120mg kavalactones per day for 3 months or less. Three others were deemed "plausible", although in two of these three, higher dosage and longer term treatment may have been employed. Using their very narrow criteria for inclusion, Schmidt and Nahrstedt concluded that only 4 out of the 78 cases constitute reasonable acceptable adverse events reports against kava. By this they meant evidence of direct toxicity, as opposed to potentiation of the toxicity of other drugs (19).

These and other recent reviews on kava hepatotoxicity by a number of prominent toxicologists, hepatologists and medical herbalists (7, 20, 21), all conclude that the incidence of this problem is extremely rare. Furthermore, several experts have implied that the German authorities' decision to withdraw kava from the market was politically, not scientifically, motivated (22). The impressive level of efficacy for this phytomedicine in comparative trials involving benzodiazepine controls, along with a more favourable adverse events profile than that of these widely prescribed drugs (31), means that such claims deserve a serious and objective consideration.

In attempting to quantify the significance of these reports, the scale of usage of kava-containing products as a dietary supplement or herbal medicine in western countries during the late 1990's and early 21st century, should also be considered. Information from various sources, indicates that regular usage of kava as a popular natural anxiolytic agent was highly popular, particularly in Europe and the U.S., in the years prior to its withdrawal.

A comparison with paracetamol hepatoxicity

As part of an objective risk versus benefit assessment of the potential hepatotoxicity of kava, a comparison with the drug paracetamol (acetaminophen), is warranted. This drug has been available since the 1950's yet hepatotoxicity leading to liver failure was not recognized in significant numbers in the U.S. prior to 1980.

True incidence studies on paracetamol-induced acute liver failure are not available, despite it being sold for the past 50 years (23). Nevertheless, in the United Kingdom, paracetamol accounted for 73% of all acute liver failure cases between 1987 and 1993 (24). Retrospective studies from the Acute Liver Failure (ALF) Study Group in the U.S. covering the period 1994-1996 (25), and a 13 year retrospective study (26) found 20% of cases to be related to paracetamol use. These studies may have underestimated the number of cases however, and the ALF Study Group recorded that 39% of all acute liver failure cases were considered due to paracetamol between 1998 and 2001 (27), an incidence which increased to 49% in 2003 (23). Paracetamol overdosage accounts for an estimated 458 deaths due to acute liver failure in the U.S. each year (23), and liver injury even at therapeutic doses is well documented (28).

These figures cannot be equated to actual incidence figures of liver toxicity, and somewhat unbelievably, it appears that these are not available, despite more than 50 years of use (23). They also implicate either an increased incidence of paracetamol-associated liver damage, and/or increased awareness and reporting of such problems in more recent years.

A recently developed assay that reliably detects paracetamol-containing protein adducts released into the plasma by dying hepatocytes, found that in 20% of ALF patients with indeterminate aetiology, unrecognized paracetamol poisoning was shown to be responsible (29).

Researchers from Massey University's Centre for Public Health Research in Wellington have also recently published evidence of use of paracetamol by children being associated with a higher risk of asthma in later years (30).

Paracetamol is widely regarded as safe, but hepatologists now describe it as having a narrow therapeutic window for such a popular over-the-counter drug (Lee). Leading hepatologists have recently published concerns regarding the current availability and packaging of paracetamol products, and even asked the question whether this drug should be withdrawn from the market (23, 28).

Summary:

Quantification of the risk of hepatotoxicity for kava is very difficult based upon present evidence. Nevertheless, a number of reviews of the risks of hepatotoxicity by prominent herbal experts have concluded that these risks are at best very low, and convincing evidence of a causative link lacking in most cases.

A comparison with paracetamol-associated hepatotoxicity, results in the conclusion that these potential risks for kava are dramatically less than that of a popular non prescription drug widely sold through grocery outlets.

Based upon the information available, it appears likely that the particular type of kava-based preparations which were being consumed in many of these cases, may be of great relevance to these reports, rather than kava itself. Additional risk factors which appear to be associated with potential kava toxicity include concurrent use of prescription drugs.

This phytomedicine has been conclusively shown to be superior to placebo for the treatment of anxiety, and major clinical trials have found reported adverse events to be “mild, transient and infrequent” (22, 31). Restrictions on the availability of kava will lead to the increased use of chemical treatments such as benzodiazepines and antidepressants for anxiety disorders, many of which commonly produce adverse effects including liver toxicity and dependency.

Challenges to the UK ban have been made by industry groups, and minutes of the Fifth Standing Committee on Delegated Legislation meeting held in January 2003 to discuss the Kava in Food Regulations, 2002, make interesting reading (32).

The link between the ethanol extracts used in New Zealand and case reports of liver toxicity reported in other countries is tenuous, if it exists at all.

Recommendations

The Australian Decision

A review of the status of kava in the Australian market took place in 2003, with the convening of the Kava Evaluation Group. This group made recommendations to the Complementary Medicines Evaluation Committee (CMEC), which were then adopted as law. Australia subsequently issued a decision permitting the sale of aqueous extracted kava on the basis that this was the traditional method of preparation and was presumed safe. The TGA then classified all other Kava extracts as prescription medicines. This decision was accompanied by vigorous debate, and industry experts were most unhappy with it at the time.

The permission of the use of water extracted root and rhizome is much tighter than the traditional use.

We do not accept the decision of the TGA to withdraw products made from ethanolic extracts of kava, and believe that the evidence basis of these being hepatotoxic when used appropriately, is extremely small at the present time.

We also note from the Minutes of the December 2001 meeting of the Medicines Classification Committee, that the Minister’s Delegate at that time did not accept the proposal to apply a framework developed by the Committee to identify the appropriate classification for herbal medicines. Instead the Minister’s Delegate

accepted the advice submitted by Medsafe, that this proposal be rejected for the following reasons:

- *MCC expertise is in the practice of medicine and the practice of pharmacy: members are not skilled in the field of herbal medicines.*
- *The consultation process was limited in its effectiveness and therefore there is no assurance that all relevant information was considered.*
- *Accepting the recommendations would result in unavailability of products for which there is no evidence of consumer harm in New Zealand.*

"Medsafe recommends that consideration of these classifications be deferred until the outcome of the government decision on the joint agency proposal is known later in the year. If the decision is positive, consideration of classification will be dealt with as part of the pre-implementation process. An expert committee of Australian and New Zealand members with knowledge of herbal medicines could be convened for this purpose".

It is our impression that as yet no attempt has been made to convene the above expert committee to objectively evaluate the kava safety issue. Furthermore, any attempt to restrict the availability of this widely used herbal medicine without the above process being pursued, could have serious implications for the credibility of the consultation process with both industry and practitioner professional bodies, as part of preparations for a new joint agency with Australia.

This situation highlights the importance of the ongoing ability of New Zealand medicines regulators to retain the right to continue to implement country-specific legislation outside of the JTA framework, as has been promised to industry groups on a number of occasions.

The need for Practitioner-Only Scheduling

As the professional body representing qualified medical herbalists in New Zealand, we have argued for several years the case for establishment of a separate schedule of registered "practitioner-only" herbal products. As responsible medical herbalist practitioners, we believe that kava should be one such medicine to be reclassified in such a way, to enable ongoing access by properly trained complementary health practitioners and their ability to prescribe this safely to their patients.

It is of concern that reclassifying kava as a "prescription only" medicine based upon current legislation, would effectively result in it being prescribable by medical practitioners only, most of whom have little training or knowledge of the safety issues concerning this or other herbal medicines. This would in fact be seen as a highly significant precedent to future regulatory policy under a new Joint Agency environment, and could lead to key practitioner and industry bodies

possibly withdrawing their current provisional support for the JTA. Clearly, the need to actively encourage the statutory regulation of medical herbalists and thus facilitate our right to continue to safely prescribe both kava and certain other herbal medicines for which safety concerns exist when these are sold in an unrestricted manner, is a matter of urgency. Ministerial support for our association's preparations to hopefully become registered under the 1993 Health Practitioners Competence Assurance Act, is therefore requested.

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