Response to concerns about Piper methysticum Forst. f., Kava. A submission prepared by the Traditional Medicines Evaluation Committee (TMEC), a subcommittee of the European Herbal Practitioners Association.

Submission Date: 11/1/02

Introduction

This submission has been written by TMEC in response to a report recently circulated by the German BfArM. This agency has recently advised that there have been a number of adverse events associated with the use of concentrated standardised preparations of kava reported from Germany and Switzerland.

Kava is a significant herbal medicine with some unique properties and the ability of herbal practitioners to care for their patients would be seriously affected if its use were restricted and they were unable to use it. This TMEC submission argues that many of the adverse events cited by BfArM ought not to be attributed to kava and that, in addition, the properties of concentrated standardised extracts, as opposed to those preparations which approximate to traditional kava use, may be a contributory factor in causing adverse events. This paper proposes a number of simple measures that will ensure that kava may continue to be safely available in the UK.

Benefits of Kava

Kava has been used in Britain by herbal practitioners since the early 1900's mainly for urinary problems (Ellingwood, 1919). The indications given in the *British Herbal Pharmacopoeia* (Anon, 1983) are "Cystitis. Urethritis. Rheumatism. Infection of the genito-urinary tract". More recent texts emphasize its usage as a nervine. For example, indications given by Mills, Bone (2000) are "anxiety of nervous origin, nervous tension, restlessness or mild depression of non-psychotic origin, menopausal symptoms (Indications supported by clinical trials) " and "inflammation and infections of the genitourinary tract of both men and women; pain of muscular and nervous origin; insomnia. (Traditional therapeutic uses)." The use of kava as a nervine has increased markedly in recent years partly due to the evidence for effectiveness found in clinical trials (Pittler, Ernst, 2000). However, it is interesting to note that such usage is not completely new. Felter (1905) notes its application, *inter alia*, in neuralgia, dizziness and despondency. It has a particular value in agitation and anxiety (Spinella, 2001), being useful when other nervines have proved ineffective.

Clinical trials have been reviewed most recently by Pittler & Ernst (2000) who state that for treating anxiety superiority over placebo was suggested by all seven trials under review and that, for the three trials included in the meta-analysis, there was a significant reduction in score on the Hamilton Anxiety Scale. The clinical trials were all carried out in Germany where kava is prescribed both by doctors and sold OTC in pharmacies for anxiety and insomnia. This usage is backed by evidence derived from eight double-blind randomised clinical trials, involving 663 patients, which are reviewed in the draft submission to BfArM by two pharmaceutical associations, the *Bundesverband der Arzneimittel Herstell e.V. (BAH)* and *Bundersverband der Pharmazeutischen Industrie e.V. (BPI)* This document refers to three recent trials which are awaiting publication. These trials have used a range of products standardised on 15-70% kava lactones giving a daily dosage of 60 - 210mg daily of kava lactones. The use of kava is being increasingly advocated for use in anxiety as an alternative to benzodiazepines. For example, De Leo *et al*, (2001) showed a significant relative decrease in anxiety in a double-blind randomised trial on 40 menopausal women when kava was combined with hormone replacement therapy.

The modern use of kava as a nervine is in accordance with its traditional usage in the South Pacific. Kava drinkers report a sense of relaxation and tranquility and a sociable attitude (Chanwai, 2000). It is used as a social and ceremonial drink amongst men in Polynesia. In modern times as the influence of the church decreased, its use has become more widespread and frequent. Kava is an important part of social life in Fiji for instance. Fijian spiritual leaders are called *dauvaguna* the literal translation of which means “expert at drinking kava”. (Greenwood-Robinson, 1999). Kava is said not to be addictive and not to appear to have the violent antisocial effects of use of alcohol (Lebot *et al*, 1997). However (see below), there are serious concerns in Australia (Clough, *et al*, 2000) about its abuse as a recreational drug when used to excess.

What is kava?

Root bark and root of kava are used, either fresh or dried. Based on an archaeological study of the characteristic drinking bowls, it is proposed that it was first domesticated in Polynesia over 2,000 years ago (Green, cited in Lebot *et al*, 1997). A comprehensive survey by Lebot and Levesque in 1984 (cited by Lebot *et al*, 1997) suggests that it was originally domesticated in Vanuatu. Kava is now obtained from a range of cultivars in the South Pacific. It is always vegetatively propagated from stem cuttings as it is sterile. There are many cultivars and new strains continue to be developed by Polynesian farmers as each is considered to have different psychoactive effects. In recent years, there has been increasing pressure on the market because of the increased worldwide demand for kava. In 1998, it was amongst the top-selling herbs in the USA with a turnover of eight million dollars representing a growth rate of 473% (Pittler, Ernst, 2000). It is possible that the current hepatotoxity problems are to some extent consequent on poor quality control caused by a rapid and extraordinary increase in the size of the market (Murray, 2000). However since a range of products is implicated, this is unlikely to provide a satisfactory explanation for all the reported adverse reactions. It is to be hoped that the German BfArM will release relevant data about the source and quality assurance of supply in due course.

Phamacology

Kava is an unusually well-researched herb. The crystalline resin was first isolated in 1857 by a French naval pharmacist and a detailed monograph was published in 1886 (Lewin, cited by Lebot et al, 1997). The kava lactones are considered to be the active constituents and have been shown in animal studies to have a sedative action (Grunze, *et al*., 2001), although the mechanism is unclear (Spinella, 2001). The kava lactones are found in the resinous portion (5-9%) of the plant material and are thus poorly soluble in water. This fact may have important implications for its safe use (see below

Kava lactones are 4-methoxy-2-pyrones with phenyl or styryl substituents at the 6th position (Lebot et al, 1997) and are found in the resinous plant material. Total kava lactone content varies from 3-20% dry weight and eighteen lactones have so far been isolated (He, *et al*, 1997) with the following six compounds being considered most important:

chiral enantiomers (Haberlein, et al, 1997) (STRUCTURES)
(+)-kavain (+)-dihydrokavain
(+)-methysticin (+)-dihydromethysticin
achiral dienolides:
yangonin demethoxyangonin

Traditional preparation techniques.

Kava is traditionally prepared in the South Pacific by grinding and mixing the root or root bark with cold water. This makes an emulsion that is a suspension of the resinous constituents in water (Lebot *et al*, 1997). It is also prepared as an emulsion (also traditionally prepared without heating) in coconut milk (Johnson, 1999).

Modern preparation techniques

The bioavailability of kava constituents varies substantially depending on the method of extraction employed (Hansel *et al*, 1994 cited in Schulz *et al*, 1997). Kava is predominantly available in Germany as a so-called concentrated standardised extract seemingly designed to maximize extraction of the kava lactones. For these concentrated standardised extracts, Schulz (1997) states that kava is dissolved in a high percentage of ethanol- to-water

mixture to obtain extracts containing about 30% kava lactones or alternatively using an acetone-water mixture to obtain extracts containing about 70% kava lactones. Both types of product have a herb-to-extract ratio of about 12-20:1 (Schulz, 1997). The dosage recommended by Commission E is expressed as the equivalent of 60-120mg kava lactones daily. A paper by Whitton, Whitehouse and Evans (see Appendix 1) makes the same point about enhanced kava-lactone extraction using a high ethanol or acetone medium but details somewhat different extraction values.

The preparation methods used for standardised products are highly technical and extraction rates vary (Kubatova, *et al*, 2001) depending on solvent and temperature. As the paper (Appendix 1) by Whitton *et al* demonstrates, both efficacy and safety depend on the kava lactones remaining in their natural form and on the extraction of the other natural constituents of the plant.

Varying extraction techniques and preparation methods may result in:

- An unnatural variation in the relative concentration of each lactone.
- Artefacts of production which may have a potential hepatotoxic action.

It should be noted that commercial kava products may also contain synthetic racemic kavain that may have other characteristics than the naturally occurring product.

It is clear that these technical matters related to extraction techniques require further elucidation and we await further data from BfArM and manufacturers of kava products.

Proponents of concentrated standardised products assert that they provide an effective dose within a consistent range. The traditional water-based kava preparations of the Polynesian peoples and low-alcohol kava tinctures employed by herbal practitioners have been considered unreliable because the concentration of active constituents varies from kava batch to batch. However, there are three relevant counter-arguments:

1. The whole range of the constituents may produce a more effective and safe medicine which has been demonstrated in kava (Williamson, 2001).

2. Some constituents, not necessarily considered active, may enhance the safety of the medicine. (See the specific point about glutathione made by Whitton *et al* in the paper in Appendix 1).

3. Definitive isolation of the active constituent has proved elusive in other medicinal plants such as *Hypericum perforatum* (Barnes *et al*, 2001).

4. Herbal practitioners rely on the synergy between a whole range of constituents in the herb(s) within a herbal prescription which is individually prescribed for the patient. This positive interaction also has the benefit of keeping levels of any one constituent below the safety threshold.

The advantages of low alcohol tinctures

TMEC strongly advocates the employment of extraction techniques which closely resemble those traditionally used in Polynesia. This would require the use of low-alcohol tinctures made by the traditional cold maceration processes common to UK tincture making. (Evidence for the safety implications of such tinctures is set out in detail in the paper by Whitton *et al.* See Appendix 1). The reasons for this opinion are set out below.
Tinctures used by herbal practitioners are prepared by macerating dry kava in a mixture of water and ethanol. It has been shown that such extracts using 25% ethanol /75% water contain up to 30 times less lactones that the concentrated standardised preparations (See Appendix 1). The traditional preparation method in a mixture of 25% ethanol/water extracts a much wider range of the natural kava constituents, Whitton *et al* (2002). Whitton *et al* (2002) have also reported the presence of glutathione in kava which is likely to be important in the metabolism of kava lactones in the liver, reducing any chance of potential toxicity. The same authors have demonstrated that the glutathione present in the plant is not extracted in high-alcohol or high-acetone extracts. In the cases of alleged toxicity due to kava, there are instances where concomitant use of drugs or alcohol are likely to have

depleted the reserve of glutathione in hepatocytes. This may predispose the individual to sensitivity to kava products with high kava lactone concentrations such as are found in standardised extracts, particularly when such an individual is also taking an orthodox medicine that may itself put pressure on the liver. On the other hand, not only would the kava lactones in the traditional extract be at lower concentration, but the glutathione present in the extract may allow the kava lactones to be metabolised in the liver even in conditions of glutathione depletion. This may explain the absence of kava toxicity from traditional preparations which have been used extensively and long-term even at high concentrations. In addition, research by Whitton *et al* currently in progress (See Appendix 1) proposes that low ethanol extracts of kava contain glutathione which may have a hepatoprotective effect if the person is, for any reason, in danger of saturation of the hepatic enzymatic detoxification pathways (see below).

Dosage

Assuming a 1:5 25% tincture and an upper limit of 20% lactones in the dried herb (concentrations stated as 3-20%, see section on Pharmacology, page 2), then 500 ml would contain (100 x 0.2 x 0.15) = 3 g (3000 mg) of kava lactones. Further assuming a daily dosage of 5-10ml of the 1:5 25% tincture, the daily dose of kava lactones amounts to a maximum of 30-60mg. If the concentration of kava lactones were lower, e.g. at around 10% as appears to be the case with regard to Australian kava discussed by Clough *et al*. (2000), then this figure falls to 15 –30 mg per day. It is noteworthy that the maximum daily dosage here is equivalent to the minimum daily dosages of the 60-210 mg kava lactones given in clinical trials of kava conducted in Germany.

Although standardised extracts provide a higher dosage of kava lactones than low-alcohol tinctures, over-dosage in itself is unlikely to be the cause of hepatotoxicity. Strong evidence for this is the fact that kava is taken daily at high doses as a normal part of daily life in large areas of the South Pacific. Indeed, some of the accounts of high kava intake are remarkable. For example Chanwai (2000) describes the case of a man who was admitted to casualty after an overdose but slept off his symptoms, who admitted to consuming up to 40 bowls a day for the last 14 years. In Australia, missionaries introduced kava to the aborigines in the 1980s as a substitute for alcohol. Since that time kava has been abused like alcohol and it is claimed that many people consume as much as fifty times the amount typically drunk by South Pacific islanders (Green-Wood-Robinson, 1999). Clough *et al* (2000) discuss concern over heavy usage of kava in Australia and describe normal use of kava in the Northern Territory as 37g of kava powder (containing around 3800 mg of kava lactones) per hour with heavy consumers using around 610g weekly prepared as a drink. The incidence of serious illness resulting from hepatotoxicity associated with regular kava usage would surely have been observed by the medical services in Polynesia and Australia if over-dosage of lactones were the main cause of hepatotoxicity.

There is a justified concern in Europe that idiosyncratic hepatotoxicity associated with use of herbal medicines may not be identified because the population taking herbal medicines is not large enough to produce sufficient cases for the association to be noted. But the fact that kava remains in traditional usage to such a wide extent is a powerful argument that idiosyncratic hepatotoxicity would have been noted.

Two post-marketing observation studies in Germany each on over 3,000 people are cited by Pittler & Ernst (2000), in addition to the clinical trials already mentioned above. In these observational studies, the rate of adverse events was 2.3% (daily dose of kava lactones 120-240mg) and 1.5% (daily dose 105 mg) lactones. The most frequent adverse reports were gastrointestinal complaints, allergic skin reactions, headache and photosensitivity. There is evidence in the South Pacific of a characteristic kava-induced skin disease which is described as a scaly rash suggestive of icthyosis (Ruze, 1990) - a condition called “kava dermopathy”. Although the skin becomes yellow, the description does not suggest an underlying hepatic condition in that the patient remains well, the rash is not itchy and the condition improves without treatment if the heavy use of kava is reduced.

Discussion of alleged Kava hepatotoxicity and the cases reported by BfArM

Hepatotoxicity

The German and Swiss reports cited by BfArM are of concern because there have been previous reports of hepatotoxicity associated with the use of medicinal plants (Larrey, 1997). The kava case reports from BfArM include all three of the main forms of acute damage to the hepatocyte which can result from adverse drug reactions i.e. necrosis, drug - induced hepatitis and cholestatic hepatitis (Hodgson & Levi, 1997). This suggests that there is a range of causes rather than just one cause in the reported cases.

Discussion of the cases reported by BfArM

The cases are numbered on the basis of the identifier in the table in English provided by BfArM to the Medicines Control Agency. They are discussed on the basis of our translation of the section describing the cases "Draft statement of two German pharmaceutical associations, *Bundersverband der Arzneimittel Herstell e. V.* (BAH) and *Bunderverband der Pharmazeutischen Indusctrie e. V.* (BPI)" subsequently referred to as BAH. The cases are identical except for case 3 which is not included in the BAH report. The BAH report claims that a number of the cases have been reported in the literature more than once, including case 28, and, in particular that cases 7 and 8 (BAH 5.16) are the same case and that cases 26 and 27 (BAH 5.12) are the same case. The details agree except for case 4 (BAH 5.8) where a different time before onset is given and for cases 23 and 25 (both included as BAH 5.6) where the time before onset of the two cases is reversed.

These discrepancies in numbering are unsatisfactory and tend to undermine confidence in the accuracy and veracity of the information provided by BfArM.

The BfArM document is deficient in other respects too. The detail it provides is inadequate to evaluate most of the cases cited. In particular, no detail is provided regarding other medical conditions from which the patients mentioned in the report may have been suffering. In addition, the data provided on the eventual outcome of the cases is incomplete. It is also unclear whether the term "liver damage" refers to the results of a liver biopsy or to the finding of raised alanine aminotransferase (ALT) blood levels which are interpreted as indicating damage to hepatocytes in hepatocellular disease (Pagana, 1999). However, in the light of the need for the UK Medicines Control Agency to make an informed decision on these cases, we have endeavoured to interpret the evidence as presented. Unless noted otherwise, references to possible drug-induced hepatoxocity is taken from the *British National Formulary*, March 2001.

Cases analysed and categorised by common factors of note

Case Nos 1,2,19,28

Patients were taking a product made from synthetic kavain. Although, the outcome was hepatitis in all four cases, kavain cannot be equated with the naturally occurring form of kava and therefore no inference should be drawn from these cases. Traditional usage should not be taken as evidence for safe usage of synthetic products.

1. Cases who were taking the oral contraceptive pill or Hormone Replacement Therapy together with a drug which can also be associated with liver damage

Six Cases: Nos 4, 10, 12, 20, 21, 28

Cholestatic jaundice associated with use of oestrogen-containing medications is extremely rare (Lindberg, 1992) but does occur. In these 6 cases, the woman was also taking a drug which can also be associated with jaundice:

Case 4: (BAH 5.8, woman, 39, jaundice) diazepam 10mg PRN for 6 months

Case 10: (BAH 4, woman, 39, necrotizing hepatitis) "several antidepressants including paroxetine"

Case 12: (BAH 5.15, woman, 37, hepatitis) diclofenac 150mg by intramuscular injection. Hepatotoxic reactions associated with NSAID use are extremely rare and concomitant exposure to other hepatotoxic drugs is considered an important factor (Bareille et al, 2001).

This case is of hepatitis is difficult to interpret as it occurred in Brazil and as “re-exposure was said to be negative for all three drugs”.

Case 20: (BAH 3, woman, 50, necrosis, liver transplant) this woman had a 20-year history of combined oral contraceptive use but had changed months earlier to oestradiol valerate (apparently taken alone) as hormone replacement therapy. She had also started glimepride 8 months earlier. This is used for type II diabetes and is rarely associated with cholestatic jaundice and liver failure.

Case 21: (BAH 2, woman, 22, necrosis, liver transplant) this woman had changed from Valette (dienogest 2mg and ethinlestradiol 0.03 mg) to Pramino (norgestimate 180/215/250mcg and ethinylestradiol 25mcg). She also took rizatriptan if required for migraine relief. Rizatriptan is contra-indicated in hepatic impairment

Case 28 (BAH 5.4, woman, age unknown, hepatitis) this case is hard to interpret as no age is given and the woman was taking oestradiol valerate “twice weekly”, acetylcysteine, losartan which is rarely associated with hepatitis and omeprazole which can be associated with liver disease although, again this is rare (Paseka, 2000). Omeprazole is metabolised by the polymorphic CYP2C19 which is absent in 3% of Caucasians (Flockhart, 2000). The woman was also taking Esberitox (Echinacea) and 5 products which appear to be for upper respiratory problems - making a total of 11 products. As noted above this patient was taking synthetic kavain, not kava.

2.Cases who were taking a drug which can be associated with liver damage

Ten Cases: Nos 1,6, 9,14, 15, 17, 19,23, 26/27, 29

Case 1: (BAH 5.10, woman, 69, cholestatic hepatitis) was taking pentoxifylline which can be associated with intrahepatic cholestasis and a diuretic including the potassium-sparing triamterene which can be associated with jaundice. As noted above this patient was taking synthetic kavain, not kava.

Case 6: (BAH 5.10, woman, 50, hepatitis) was taking frusemide which can be associated with cholestatic jaundice, and triamterene (as above), atenolol, and a large dose of terfenadine 300mg. The recommended dose in the BNF is 60-120mg and terfenadine should also be avoided in hepatic impairment. The IKS considered this case to be caused by terfenadine.

Case 9: (BAH 5.1, woman, 81, liver failure and subsequent death). She was taking hydrochlorothiazide which can occasionally be associated with intrahepatic cholestasis. However, the autopsy showed chronic pancreatitis, characteristic of alcohol abuse and the report says that symptoms must have occurred over a period of at least 18 months. The report concedes “hepatic impairment by alcohol not excluded”. In these circumstances, it seems entirely reasonable to hold that this case is unrelated to kava use.

Case 14: (BAH 5.11, woman, 33, hepatitis) Cisapride, may have been taken which can cause reversible changes in liver function tests. Cirrhosis in a woman of 33 is an unexplained finding and the detail is inadequate to elucidate this case.

Case 15: (BAH 5.13, woman, 46, jaundice) had been taking hydrochlorothiazide for 5.5 months which can be associated with intrahepatic cholestasis and valsartan 80mg and propanolol 80mg daily.

Case 17: (BAH 5.14, woman, 59, jaundice) Celecoxib, a cyclooxygenase-2 inhibitor, was taken at 100-200mg daily.

Case 19: (BAH 5.3, woman, 21, hepatitis) was taking pantoprazole which, as with omeprazole, can be associated with liver disease. She was also taking paracetamol and metoclopramide and had overdosed on Kavain. More detail is needed on other medical conditions suffered by this patient in order to interpret this case. *Further important*

*information regarding this case has come to light as this paper is being submitted and is presented in a footnote.**[1]***

Case 23: (BAH 5.6 ii, woman, 35, jaundice) paracetamol was also taken but no dosage or details are provided.

Case 26/27: (BAH 5.12, woman 38 or 39, hepatitis) The confusion of cases here is an example of inaccurate data records provided by BfArM. . This case or cases depending on whether the two reports are of the same woman is unclear. Penicillin can be associated with hypersensitivity and cholestatic jaundice but the information given is inadequate.

Case 29: (BAH 1, woman, 60, liver transplant) this woman of 60 was taking piretamide which is a loop diuretic. Frusemide, another loop diuretic, can be associated with cholestatic jaundice. She was also taking a sympatheticomimetic, Etilefrine. The dosage varied but was up to 480mg (four times the recommended dose).

> [1] The young woman in case #19 apparently used a product called "Kavain Harras plus." An article published late last year by Schmidt (see *Journal fur Orthomolecular Medizin* 9(4):379-391; the article is titled: "Lebernebenwirkungen durch Kava-Extrakt") states that this product is a combination of 30mg synthetic d-l kavain and 250mg of an ethanol extract concentrated to 8% kavalactones, so delivering an additional 20mg kavalactones. Schmidt also states that this woman was using up to 10 tablets per day of the product (it seems that the manufacturer suggest 6 tablets daily) and that there was some discussion, apparently in her medical record or the BfArM file, that she may also have used Ecstasy (i.e., MDMA - see Brauer et al. 1997. Liver transplantation for the treatment of fulminant hepatic failure induced by the ingestion of ecstasy. Transpl. Int.10:229-233).
>
> *Source personal correspondence from Michael McGuffin, President, American Herbal Products Assoc.*

2. Cases where drugs not associated with liver damage, herbal medicines or dietary supplements or Kavain alone were taken

Seven Cases: Nos 2, 7/8, 11, 13, 22, 24, 25

In these cases, detail is limited and no other drug or medication can be implicated.
All cases apart from 7/8, where no information is given, are stated to have made a full recovery. In some of these cases, it is not clear whether the person was ill or whether liver function tests were found to be raised when monitoring.

Case 2: (BAH 5.17, man, 35, cholestatic hepatitis) was taking no other medication

Apart from Cases 18 & 30, this is the only case where no other medication was taken. As noted above this patient was taking synthetic kavain, not kava.

Case 5: (BAH 5.9, woman, 68 or 69, cholestatic hepatitis) was taking Neuroplant forte (Hypericum) which has been associated with induction of CYP3A4. Biopsy showed “immunological hypersensitivity”.

Case 7/8: (BAH 5.16, woman or women, age 72 and/or 75, cholestatic hepatitis) was taking two herbal/vitamin products one of which included 0.6mg of kava lactones.

Case 11: (BAH 5.19, woman, 59?) was taking Buscopan

Case 13 (BAH 5.18, woman, 62, jaundice) there was concomitant medication but no details and no detail of Kava dosage which makes interpretation impossible

Case 22: (BAH 5.20, woman, 34, hepatitis) was taking L-thyroxine

Case 24: (BAH 24, woman, 47, raised liver function test results) was taking fish oils. The report states that the liver enzymes returned to normal when the fish oils

were stopped but again the detail is insufficient. However, this case would appear to support the safe use of kava for the report states that the patient was “restored to health after discontinuation of the concomitant medication and continuation of the (kava) medication”.

Case 25: (BAH 5.6 I, woman, 34, hepatitis) was taking *Hypericum perforatum*

4.Associated with an overdose of alcohol

Case 16: (BAH 5.21, woman, 33, jaundice) took an overdose of alcohol, 60g. This case is described in detail by Russman et al (2001) and is discussed below as the woman was shown to be a poor metaboliser of CYP 2D4.

See also case 9 mentioned above.

5.Cases not associated with other drug usage

Cases 18, 30

The final two cases are men both of whom required liver transplants and both of whom appear not to have been taking other medication. In these two cases, Kava would appear to be implicated but again more detail of the medical history is required for a proper assessment.

Case 18: (BAH 5.22, man, 50, necrosis, liver transplant) took Laitan 210-280mg daily for 1.5 months, “moderate alcohol” and a yeast preparation. This is above recommended dose of kavalactones

Case 30: (BAH 5.2, man, 32, necrosis, liver transplant) took Antares, 240mg daily for 3 months and occasionally Baldrian-phyton (Valerian) at night. This too is above the recommended dose of kavalactones.

Summary

In most of the case reports, the patient was also taking drugs concomitantly. Assuming the medication were responsible for the adverse event, and not some other factor such as other disease or excessive use of alcohol, it is possible that the hepatotoxicity was caused by the conventional drug, by the kava, by both the drug and the kava or mainly by the drug but the kava as a co-factor. However, in assessing these cases, we should take into account the increased risk of adverse effects on the liver where kava lactone concentration is enhanced in a product and glutathione presence is reduced due the extraction techniques employed as explained in the paper by Whitton *et al* (see Appendix 1). Such stress on the liver is still further likely to be enhanced due to individual variability in the metabolic cytochrome P450 processes that are discussed below.

Inter-individual variability in cytochrome-P450 metabolism of xenobiotics

Inter-individual variability in drug response is now increasingly recognised as a major cause of adverse drug reactions. Much of this variability is now ascribed to genetic differences in drug absorption, disposition, metabolism or excretion. The variability which has been most investigated and which is considered to be of most significance is genetic polymorphism in drug metabolising enzymes in the hepatocyte. This is considered to be an adaptive response to environmental challenge (Wolf, Smith, 1999) so it is not in itself surprising that individuals vary and failure of metabolism of xenobiotics (“foreign” compounds, whether natural or synthetic) is associated with the use of medicines either from natural or synthetic sources.

Cytochrome P450 (CYP) enzymes are mixed function microsomal monooxygenases located on smooth endoplasmic reticulum throughout the body primarily in hepatocytes and the wall of the small intestine. There are 12 families and a single hepatocyte can contain a range of CYP enzymes which metabolise a range of drugs. They are responsible for Phase I

(oxidation, reduction and hydrolysis) metabolism of a wide number of compounds and transform lipophilic drugs to more polar compounds that can be excreted by the kidneys. Phase II of detoxification occurs if the product conjugates in the hepatocyte cytoplasm with the tripeptide glutathione. The resulting soluble compound is excreted via the bile or urine. This conjugation is catalysed by cytoplasmic glutathione S-transferases. Interindividual variations exist in concentration of hepatocyte glutathione and in relative concentration of individual glutathione S-transferases (Mannervik, Widdersten, 1995). and in levels of other compounds associated with drug metabolism.

CYP2D6 Deficiency

Many CYP enzymes are genetically polymorphic and thus there is marked inter-individual variation in drug metabolism (Wolf, Smith, 1999). One of the most extensively studied genetic polymorphism is that of CYP2D6 and it is considered to cause much of the individual variation seen in drug response, side effects and drug interactions (Poolsup et al, 2000). Individuals may be poor (slow) metabolisers, intermediate, extensive (fast) or ultra-fast metabolisers. In a Caucasian population 7-9% of individuals are homozygous deficient in CYP2D6 and are thus poor (slow) metabolisers (Poolsup, et al, 2000). The incidence of CYP2D6 deficiency in Asian populations is 1% and it is thought that much ethnic variation in drug response is associated with CYP polymorphism (Poolsup, *et al*, 2000). Drug substrates for CYP2D6 include: antidepressants, antipsychotics, beta-blockers eg propanolol and anti-arrythmics. CYP2D6 metabolizes a range of antidepressants (Fromm, *et al*., 1997). Poor metabolisers are at risk of adverse reactions if the rate of biotransformation is inadequate.

If xenobiotics are inadequately metabolised they may make covalent bonds with DNA, RNA, nuclear proteins or cytoplasmic proteins and breakdown of function occurs within these cells. Above a certain rate, the result of this is damage to the hepatocyte leading to centrilobular necrosis (Kaplowitz, 1997).

Russmann et al (2001) discuss Case 16 in detail. It is noteworthy that the woman had restarted kava for three weeks after an initial course of treatment two months earlier and then became ill three weeks later after an overdose of alcohol. The woman was shown to be CYP2D6 deficient using phenotyping with debrisoquine. The authors then tested Case 10, described by Strahl *et al* (1998) and found her to also be CYP2D6 deficient and argue that CYP2D6 deficiency is a risk factor for hepatotoxicity ascribed to kava.

This finding may help to explain the lack of hepatotoxicity due to Kava recorded in the South Pacific. Wanwirolmuk et al (1998, cited in Poolsup *et al*, 2000) tested the phenotype of 100 Polynesians using a debrisoquine probe and found a 0% incidence of CYP2D6 deficiency.

As stated, many antidepressants are metabolised by CYP2D6 and it is likely that the use of antidepressants with kava is not uncommon. Yet only one of the above cases involved antidepressants which suggests that CYP2D6 deficiency is more likely to be relevant than competition between CYP2D6 substrates.

This finding is significant but difficult to predict as most people are unaware of their CYP2D6 phenotype. It should be noted that where CYP2D6 deficiency occurs, kava products with enhanced kava lactones might have implications for the liver particularly when a concomitant orthodox medicine or substantial amounts of alcohol are regularly taken. Such risks are likely to be small if low-alcohol tinctures are employed within the normal therapeutic dosage range.

Recommendations from TMEC:

1. **Products made from synthetic Kavain are synthetic drugs not herbal medicinal products and should be excluded from the analysis.**

2. **None of the cases cited by BfArM involved traditionally prepared tinctures. In the light of evidence presented above and in**

Appendix 1, the safety of concentrated standardised products made from acetone extracts and high alcohol concentrations needs re-evaluation. Low-alcohol tinctures appear to provide a safe alternative. TMEC recommends the adoption of extraction methods using 25% alcohol that will ensure the extraction of the full spectrum of constituents and a substantially lower concentration of kava lactones thus ensuring the safe use of kava as a medicine.

3. **Consumers need to be informed that Kava products should not be taken whilst taking conventional medicines without the advice of a health professional.**

Kava should not be taken without consulting a health professional if the user has a history of liver disease.

4. **Maximum doses for Kava should be set after consultation with interested parties.**

5. **Doctors, nurses, pharmacists and other health professionals should be adequately informed about herbal medicines and possible herb/ drug interactions (Jobst *et al*, 2000).**

Comment

The training of health professionals is outside the scope of the Medicines Control Agency. However, the achievement of statutory self-regulation of herbal practitioners would support the endeavours of the professional associations which form the European Herbal Practitioners Association to assure high standards of training and mandatory continuing professional development for those who regularly prescribe herbal medicines to patients.

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APPENDIX 1. To submission of Traditional Medicines Evaluation Committee (a subcommittee of the European Herbal Practitioners Association).

Response to Reported Hepato-toxicity of High Lactone Extractions of *Piper methysticum* Forst. (Kava)

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Introduction

This paper (the result of work currently in progress) is produced in response to the reports by the German BfArM of possible hepatotoxic effects of kava extracts that has lead to concerns regarding the safety of kava products on sale in the United Kingdom. There have been thirty cases of hepatotoxicity reported to German and Swiss regulators including three transplants and one death allegedly associated with the use of concentrated standardised kava extracts.

In the Oceanic Islands of the South Pacific kava is drunk as an alternative to alcohol or for ceremonial purposes and studies have shown that in islanders who regularly drink up to ten times the recommended therapeutic dose, the only recorded abnormality is a slightly raised gamma-glutamyltransferase (Barguil, 2001).

Analysis presented in this paper, based on as yet unpublished research by the authors, demonstrates the presence of glutathione in the traditional extract, which, it is postulated, may have a hepato-protective effect. Concentrated standardised extracts do not contain glutathione (see below).

Extraction Techniques

In the Oceanic Islands, kava is traditionally prepared by macerating the root or root bark in a cold water and/or coconut milk solution. However, in the manufacture of concentrated extracts either ethanol (60% and above) or acetone (60% or above) are employed as solvents to obtain the maximum yield of kava lactones (source Lamberts Ltd) that have been identified as the “active constituent”.

Research Data (The result of as yet unpublished work in progress)

Analysis of Kava Extraction in Different Solvents

Kava *(Piper methysticum)* root was extracted in different solvents and analysed by High Performance Liquid Chromatography (HPLC) with diode array detection. Different solvents were used to extract the kava lactones, and their extraction is shown in **Table 1** below.

Table 1: *Extraction of kava lactones in different solvents, summary of results for ten samples in each solvent.*

Extract	% Kava lactones in dried extract
Acetone extract	100
96% Ethanol extract	100
25% ethanol	15
Water	2.97

The extraction was carried out by reflux percolation for one hour for each sample of 5% w/v *Piper methysticum* root. The resulting liquids then had their specific gravity and percentage dry extract determined by the techniques described in the *British Pharmacopoeia,* 1999. The total kava lactones were measured by HPLC using an acetonitrile/ water solvent gradient (Whitton 2001)

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Kava lactone standardised extracts are produced using a high acetone or ethanol concentration, and are likely to contain only kava lactones and no proteins, amino acids or sugars.

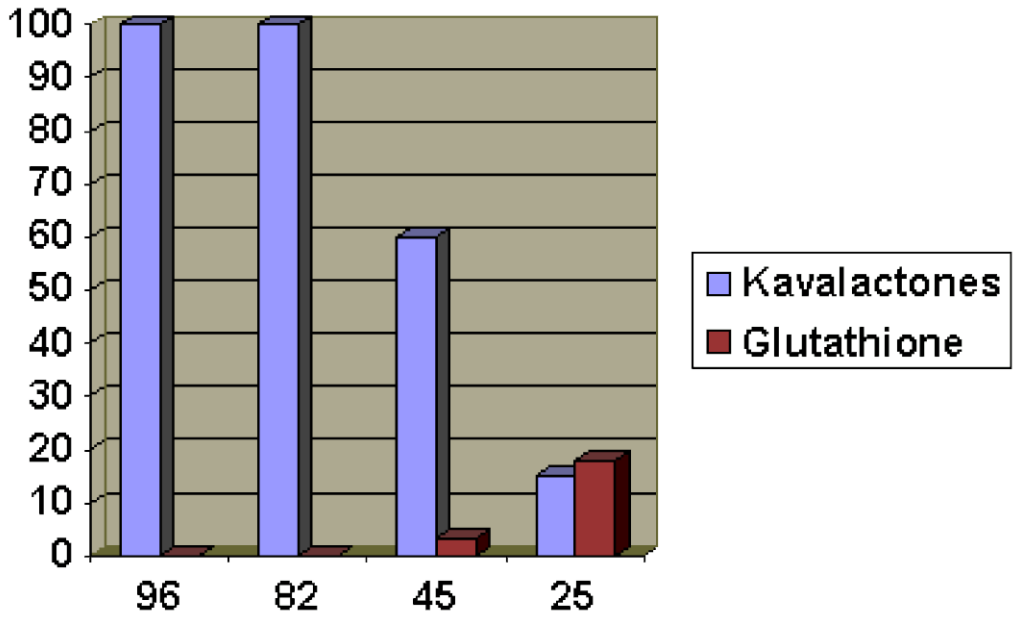
Further analysis identified one of the other compounds in the aqueous extract and in the 25% ethanol extract as glutathione by comparison with a reference sample obtained from Sigma-Aldrich (Poole).

Samples of commercially available kava extracts were examined and the ratio of kava lactones to glutathione was calculated, the results are shown below in **Table 2.**

Table 2: ***Kava lactone /Glutathione ratios (results summarised from ten samples of each type)***

Sample	Kava lactone content (expressed as absorbance)	Glutathione content (expressed as absorbance)	Kava lactone / glutathione ratio
Kava standardised extract powder (30% kava lactones) dissolved in 25% ethanol	4.031712e6	1.346769e3	1/0.0003
82% ethanol extraction	3.168906e5	5.3813e3	1/0.017
25% ethanol extraction (1 part plant to 3 parts solvent)	1.63689e4	1.88736e4	1/1.15
25% ethanol extraction (1 part plant to 1 part solvent)	2.49798e4	5.1525e4	1/2.2

Fig 1 ***Kava lactone & Glutathione extraction (expressed as a percentage of dry extract) against ethanol percentage in solvent***



Importance of Glutathione in Kava Extracts

Lactones may be hepatotoxic, if not mediated by glutathione and are usually metabolised in the liver by enzymes called lactone hydrolases (Schmidt *et al*. 1999). It is likely that the high concentration of lactones introduced by concentrated standardised extracts has the potential to saturate the enzymatic detoxification pathways resulting in hepatotoxicity. Glutathione has an essential role in the phase II conversion of lactones into excretable waste products. Increased toxicity of the lactones may occur on glutathione depletion. Glutathione is not soluble in ethanol concentrations above 50% (*Merck Index*). There has been relevant work on a related group of compounds, sesquiterpene lactones. It has been demonstrated that sesquiterpene lactones react with the sulphide group on the glutathione molecule in a reversible pH dependent reaction (Schmidt *et al.* 1999). The binding of the sesquiterpenes lactones to the glutathione molecule allows for faster clearance by the lactone hydrolases present in the hepatocytes (Schmidt *et al*. 2001). It has been demonstrated that glutathione prevents toxicity from other sesquiterpene lactones if

administered at the same time (Lautermann *et al*). It has also been documented that glutathione has to be present at the time of ingestion of the kava in order to potentiate the metabolism of the lactones.

Glutathione is present in adequate amounts in most cells in the body but some individuals can have a deficiency linked with cytochrome P450 (Lomaestro BM, Malone M, 1995). In these cases, high doses of lactones will lead to rapid depletion in glutathione levels and result in free lactone exposure in the hepatocytes and consequent tissue damage (Zheng *et al*). Glutathione supplementation has been shown to correct the deficiency (Kidd, 1997). It is suggested that the glutathione molecule may not be absorbed intact but may be broken down into its constituent amino acids and regenerated within the hepatocyte. It has been demonstrated that glutathione prevents toxicity from other sesquiterpene lactones if administered at the same time (Lautermann *et al*).

Summary

Hepatotoxic lactones are normally metabolised by lactone hydrolases, which are enhanced by the presence of glutathione.
Glutathione naturally occurs in kava, (*Piper methysticum* Forst.) in a 1:1 ratio with kava lactones and is likely to reduce the likelihood of potential lactone toxicity. In contrast to the traditional crude extract, standardised extracts contain no glutathione whilst containing up to 30 times the kava lactone concentration.
It appears that the high kava lactone in standardised extracts depletes the reserves of glutathione in the hepatocytes which could result in liver damage. It would therefore seem prudent to limit the organic solvent level in the extraction of kava to 25% ethanol in order to ensure the preservation of the hepato-protective effect of the glutathione. Tinctures made with 25% ethanol would appear to be safe as a result of this synergistic effect of the glutathione and kava lactones.

Conclusions

Traditional preparations have had many years of safe usage (Tyler, 1995) and toxicity has only been reported in Europe with concentrated standardised extracts (Escher, 2000).

This paper argues that there are significant differences between concentrated extracts and those produced by traditional methods that maintain a satisfactory ratio between glutathione and kava lactones. In traditional extracts, ratios of at least 1:1 kava lactone: glutathione should provide a safe product with hepato-protective action. It would appear that glutathione has an important synergistic action in protecting the liver from potential lactone toxicity.

This study suggests that standardised herbal extracts which do not contain all components of the traditional plant extract may have a potential to induce hepatotoxicity in susceptible people (e.g. those taking concomitant orthodox medicines).

It is proposed that tinctures manufactured using a traditional cold-maceration process (in 25% ethanol and 75% water) that more nearly approximate to traditional water or coconut milk extracts, or raw plant material are safe in normal subjects.

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