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Kava: a review of the safety of traditional and recreational beverage consumption

Technical Report

Kava: a review of the safety of traditional and recreational beverage consumption

Food and Agriculture Organization of the United Nations
World Health Organization
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Summary

Background to this review

This review of existing information on the safety of kava when consumed as a beverage, and associated data gaps, has been prepared by FAO/WHO in response to a request from the 12th session of the FAO/WHO Coordinating Committee for North America and the South West Pacific (CCNASWP, 19-20 September 2012). It is in relation to the proposal for the development of a regional standard for kava as the dried product that can be used as a beverage when mixed with water.

Kava beverage has a long history of consumption in the South Pacific and has an important role in traditional community ceremonies. In recent times, it has become more widely consumed as a recreational beverage in both the South Pacific islander community as well as in the wider international community. Within these communities, kava is considered to be a safe and enjoyable beverage, based on a long tradition of use and little evidence of harm.

This review has examined existing data relevant to the safety of kava beverage and identified any gaps in the available data, as well as steps that are needed to ensure the safe use of kava beverage. Consideration has been given to the method of preparation of kava beverage, the toxicity of its chemical components, the levels of consumption and the adverse health effects observed in consumers. Consideration has also been given to the relevance of the cases of hepatotoxicity that have been associated with consumption of kava medicinal products in non-Pacific island countries.

Kava varieties and beverage composition

Kava beverage is traditionally prepared from the peeled rhizome/root of the noble kava variety; however, available information indicates that other varieties are being used either alone or mixed with noble kava to prepare kava beverage. In some circumstances, other parts of the kava plant such as stems or peeling are also mixed with the rhizome/roots used to prepare kava beverage. The kava plant components vary between different parts of the plant and between kava varieties. Thus, the composition of kava beverage can be highly variable, depending on both the kava variety and the kava plant material used to prepare the beverage. There is also potential for other contaminants, such as moulds, to grow on stored kava material, some of which can produce mycotoxins such as aflatoxins.

In relation to kava varieties and beverage composition, the data gaps and their impact on a safety assessment of kava beverage are as follows:

Data gaps

- i. Comprehensive information on the source and composition of material used to prepare kava beverage.
- ii. Information on the composition of kava beverage, both with regard to pharmacologically active and non-active components.
- iii. Availability of practical and reliable analytical methods for monitoring kava components (kavalactones, alkaloids and flavokavins) and potential contaminants.

In order to assess the safety of kava beverage, there is a need for:

- i. Improvements in agricultural and supply chain controls, to provide a consistent high-quality raw material for kava beverage preparation.

- ii. Further development of analytical techniques capable of identifying the chemical components of the kava plant, as well as contaminants, to ensure the compositional control of kava beverage preparations.

Kava components and their properties

The kava plant contains six major kavalactones (the active pharmacological components) as well as alkaloids and flavokavins. The metabolism of kavalactones is reasonably well understood and involves cytochrome P450 2D6, which has the potential for polymorphism. Little is known about the metabolism of the kava alkaloids or flavokavins. Kavalactones can also inhibit some P450 enzymes, raising the possibility of affecting the metabolism and toxicity of co-medications. There is little evidence for kavalactone-associated *in vitro* cytotoxicity or *in vivo* hepatotoxicity in animals. Evidence of significant *in vitro* cytotoxicity with alkaloids and flavokavins, as well as hepatotoxicity in animals with flavokavins, has been noted and there is a case for minimizing human exposure to these components via kava beverage.

In relation to kava components and their properties, the data gaps and their impact on a safety assessment of kava beverage are as follows:

Data gaps

- i. An understanding of the potential for formation of reactive metabolites of kavalactones, alkaloids and flavokavins, and their role in kava toxicity.
- ii. An understanding of the potential for kavalactones to inhibit P450 enzymes, and to potentially enhance the hepatotoxicity of co-administered medication.
- iii. An understanding of the potential *in vitro* and *in vivo* toxicity of kava alkaloids and flavokavins, and their mechanisms of action.
- iv. The *in vivo* toxicity threshold levels for kava alkaloids and flavokavins.

In order to assess the safety of kava beverage, there is a need for:

- i. Further data on the metabolism of kavalactones, alkaloid and flavokavins and their significance in the observed toxicity *in vitro* and *in vivo*.
- ii. Further *in vivo* data to establish threshold levels for toxicity of the alkaloids and flavokavins.

Human health effects

There is little documented evidence of adverse health effects associated with traditional moderate levels of consumption of kava beverage, with only anecdotal reports of general symptoms of lethargy and headaches. Whether this reflects genuine low incidence or an under-reporting of adverse health effects is unclear. Clinical trials examining the efficacy of aqueous extracts of kava in treating anxiety, although limited, have also not identified adverse health effects. On the other hand, there is strong evidence that high levels of consumption of kava beverage can result in scaly skin rash, weight loss, nausea, loss of appetite and indigestion. These adverse health effects, while significant, are considered to be reversible upon cessation of kava use. Other possible effects include sore red eyes, laziness, loss of sex drive and general poor health. No effect on cognition, which might be associated with the pharmacological activity of kava, has been identified. No information is available on the potential for kava beverage consumption to impact on the incidence of chronic disease. Moderate to high kava beverage consumption also produces a reversible increase in the liver enzyme gamma glutamyltransferase (GGT), which may be an early indicator of cholestasis. Clinical surveys in Aboriginal communities in northern Australia with a history of heavy kava use have not revealed any evidence of long-term liver damage associated with consumption of kava beverage.

Three case studies of individuals presenting with hepatotoxicity following consumption of kava beverage have been documented. Other cases of kava-related hepatotoxicity (mainly in Europe) were associated with consumption of kava medicinal products prepared from organic extracts of kava. Whether the etiology of the observed hepatotoxicity is the same following consumption of kava beverage and kava medicinal products is still unknown. Research is ongoing in relation to kava-related hepatotoxicity and a number of possible mechanisms are being investigated.

In relation to human health effects, the data gaps and their impact on a safety assessment of kava beverage are as follows:

Data gaps

- i. The effect of regular kava consumption on general health parameters over time, including weight loss and adverse effects on the liver and skin, and the threshold intake for these effects.
- ii. An understanding of the mechanism of kava-related hepatotoxicity, for both organic and for aqueous extracts.
- iii. An understanding of the mechanism of the kava-induced increase in GGT and its relationship, if any, with long-term hepatotoxicity, and the intake threshold for this effect.
- iv. An understanding of the mechanism for kava-induced skin rashes (kava dermatopathy) and the intake threshold for this effect.
- v. An understanding of the relationship between the pharmacological effects of kavalactones and the observed toxicity in humans.
- vi. The effect of kava beverage consumption on the incidence of chronic diseases, if any.

In order to assess the safety of kava beverage, there is a need for:

- i. More systematic monitoring of the general health outcomes of regular consumers of kava beverage in order to better understand the range of potential health effects and to identify any susceptible subpopulations.
- ii. Studies to examine the threshold intake for the observed adverse health effects.
- iii. Studies to better understand kava-related hepatotoxicity.
- iv. Studies on the potential impact of co-medication with herbal preparations and drugs.
- v. Detailed examination of any future cases of hepatotoxicity to determine exposure to kava components, contaminants and/or co-medication.

Consumption

The consumption of kava beverage is highly variable between individuals, sexes and communities. This, together with the variability in the composition of kava beverage, makes it difficult to establish correlations with potential adverse health effects. The limited information available indicates that adverse effects begin to appear at an average consumption of 240-440g kava powder/week. The amount of kava alkaloids and/or flavokavins or other substances in these preparations is unknown.

In relation to consumption, the data gaps and their impact on a safety assessment of kava beverage are as follows:

Data gaps

- i. Comprehensive information on the level and frequency of consumption of kava beverage in South Pacific island communities.
- ii. Detailed information on the concentration range of active components (kavalactones, alkaloids and flavokavins) and potential contaminants in kava beverage preparations.
- iii. The extent to which alkaloids and flavokavins are extracted by the aqueous solvent during preparation of kava beverage.
- iv. Adequate data upon which to estimate the levels of intake of kavalactones, alkaloids and flavokavins, as well as potential contaminants, and to establish a safe level of intake.

In order to assess the safety of kava beverage, there is a need for:

- i. More reliable estimates of the level and frequency of consumption of kava beverage to determine the threshold level for adverse health outcomes.
- ii. Analytical information of the range of concentration of kavalactones, alkaloids and flavokavins in kava beverage, as well as the concentration range of potential contaminants.

Harm minimization

Based on the information considered in this review, a full understanding of the potential for consumption of kava beverage to impact on the health outcomes of consumers is not possible in the absence of the additional data indicated above. However, even in the absence of this additional data, a strategy to minimize any harm associated with moderate to high kava beverage consumption should include:

- using only the noble kava variety for beverage preparation
- restricting the plant material for kava beverage preparation to peeled rhizomes/roots
- monitoring kava storage conditions and employing surveillance for contaminants, in particular, aflatoxins.
- discouraging heavy consumption of kava beverage.

Potential for standard development

While there is a high level of variability in relation to kava beverage preparation, composition and consumption, there is also a significant body of evidence based on long-term use and more recent research results that indicate it should be possible to establish parameters to ensure a reasonable certainty of no harm from consumption of kava beverage. These will need to include:

- controls to provide a consistent high-quality raw material for kava beverage preparation, taking into account kava varieties, kava plant material, and preparation and handling techniques.
- establishing permissible daily intake levels for kava beverage components (kava lactones, alkaloids and flavokavins) as well as for potential contaminants (eg, aflatoxins). This will require further research, but not necessarily a full understanding of the metabolism and toxicity of each component.

Public health advice may also be necessary to accompany standard development in order to ensure safe consumption of kava beverage. This could include:

- advice on appropriate levels of consumption to avoid the harmful effects associated with excessive exposure.

- advice on hygienic practices appropriate for consuming a shared beverage.

When considering the establishment of a regional standard, the CCNASWP will need to consider:

1. The significance of the identified data gaps in relation to establishing a standard for kava beverage which provides a reasonable certainty of no harm for the majority of people:
 - whether information based on traditional use of kava beverage can be used to address some data gaps.
 - whether the use of existing data together with conservative assumptions can be used to address some data gaps.
 - whether some of the data gaps are more important or relevant to setting a standard.
2. The range of controls which need to be specified in a regional standard and their significance in addressing the safety of kava beverage consumption. These controls include the selection of kava varieties, the use of plant parts, the quality of raw material, handling and storage techniques, kava beverage preparation and compositional parameters.

1 Introduction

Kava beverages are produced from the kava plant (*Piper methysticum*), a pepper plant indigenous to Polynesia, Micronesia and Melanesia. Kava beverage has long been associated with traditional ceremonies on South Pacific islands, as well as being used as a recreational drink. More recently, kava organic solvent extracts have been marketed as medicinal anxiolytic products in other parts of the world.

The term 'kava' is used to describe the traditional beverage, but it is also commonly used to refer to the plant itself, and to the medicinal products containing organic solvent extracts. This report distinguishes the different uses of this term when necessary.

1.1 Background

At the 12th session of the FAO/WHO Coordinating Committee for North America and the South West Pacific (CCNASWP, 19-22 September 2012), the Coordinating Committee made the following conclusions:

1. The Coordinating Committee agreed to focus the proposal for the development of a regional standard for kava as the dried product that can be used as a beverage when mixed with water.
2. Regarding the safety of kava, the Coordinating Committee accepted FAO and WHO's offer to assist by:
 - Reviewing the existing information on kava as the dried product that can be used as a beverage when mixed with water in the context of a safety assessment; and
 - Identify data gaps (if they exist) and their impact on conducting a safety assessment.

This review has been prepared on behalf of FAO/WHO in response to the Coordinating Committee's request.

1.2 Focus of the report

This report focuses on the safety of kava consumption as a water-based beverage preparation in both traditional ceremonies and in recreational settings. Its purpose is to review existing data relevant to the safety of kava beverage and to identify, if necessary, any gaps in available data or steps that are needed to ensure the safe use of kava beverage.

The report will not re-examine the safety of kava medicinal products that have been reviewed previously by WHO (2007) and others; however, some of the safety issues that are raised in the WHO report and in more recent publications regarding these products are relevant to the safety of kava beverage consumption and need to be addressed. It is normal practice in risk assessment to consider information from all sources that can contribute to a comprehensive analysis of potential human health risks.

1.3 Traditional and recreational use of kava beverage

Kava beverage has been consumed for more than 2000 years in traditional ceremonies (Singh 1992) by (mostly) men in Polynesian, Melanesian and Micronesian cultures, with the exception of New Zealand, New Caledonia and most of the Solomon Islands. Kava beverage is said to have mild, pleasant psychoactive and intoxicating effects (Ulbricht et al 2005). Traditionally, consumption of kava beverage is used to mark important social events or to welcome guests. It has also been used traditionally as a medicine (a sedative, as well as treatment for various ailments, including anxiety). Consumption of traditionally-prepared kava beverage is characterized by a state of mild intoxication, followed by muscle relaxation and eventual sleepiness (Singh 2004).

Today, kava beverage is consumed more widely – even on a daily basis on many South Pacific islands – at kava bars as part of social activities. It is used recreationally to promote friendly social discourse during relaxation with friends (Brown et al 2007).

Kava's recreational use has spread to Pacific Islander communities in Hawai'i, California, Australia, New Zealand, and European countries, who are using kava imported from the Pacific islands. In Hawai'i, kava drink is known as 'awa'. Other names used to refer to kava include kava kava, kawa, ava, yati, jagona and yangona (Singh 1992).

Kava beverage was also intentionally introduced into Australian Aboriginal communities in 1982, predominantly in the northern central region known as Arnhem Land, as an alternative to alcohol, and has had wide recreational use (Clough 2003, Clough et al 2002b, Prescott 1990).

Kava usage is continuing to evolve both in the South Pacific islands as well as in other countries, leading to exposure scenarios that may differ from the traditional use. A consideration of the safety of kava therefore needs to take into account these different exposure scenarios (Baker 2011).

1.4 Use of kava extracts in medicinal products

Use of kava extracts in non-Pacific island countries began in the 1990s with the promotion of medicinal products (pills and liquid preparations) containing organic solvent extracts of kava to treat anxiety (Teschke et al 2008). In a systematic (Cochrane) review, kava extract was shown to produce a small, but significant reduction in the symptoms of anxiety (Pittler and Ernst 2003).

The emergence of cases of hepatotoxicity in Europe related to use of medicinal products containing kava extracts in 1998 (Loew and Franz 2003, Teschke et al 2003) led to the withdrawal of these products from the markets in Europe and North America in 2002 due to health concerns. This action prompted extensive research focused on identifying the mechanism(s) of this kava-associated hepatotoxicity. In 2007, WHO convened an expert group to examine the evidence for an association between hepatotoxicity and the consumption of kava medicinal products (WHO 2007). The conclusions of this review together with other on-going research have provided information that is relevant to an understanding of the safety of all forms of kava consumption.

The health concerns identified following the use of kava medicinal products have raised questions regarding the safety of kava consumption in all its forms, including the traditional water-based beverage (Currie and Clough 2003, Moulds and Malani 2003, Teschke et al 2003).

2 Kava varieties / beverage preparation

2.1 Kava varieties

There are more than 200 kava plant varieties (Singh 1992). The kava varieties used to prepare kava beverage belong to one of two basic groups: noble and two-day ('tu dei') kava. Traditional beverages are made from noble kava. Two-day kava is higher in kavalactones and alkaloids, and is named for its longer lasting psychotropic effects. It is also known to cause nausea (Lebot and Levesque 1998). Wichmannii kava varieties are wild-type varieties and elicit strong pharmacological effects (Lebot et al 1997). Traditional Pacific herbalists use medicinal kava varieties for specific therapeutic benefits, but these varieties are not used recreationally.

In Vanuatu, the Kava Act No. 7 of 2002, which came into effect in 2008, prohibits the sale and export of non-noble or non-medicinal kava varieties – namely, two-day kava and wichmannii kava (wild kava) (Republic of Vanuatu 2002). However, there are anecdotal reports that the regulations are not strictly followed, possibly due to the absence of adequate guidelines to assist farmers to distinguish the kava cultivars, but also because of demand for two-day kava and its high kavalactone content (Vergano et al 2012). Other South Pacific island countries do not have similar regulation.

Vergano et al (2012) noted the following anecdotal information about the availability of kava varieties used to prepare kava beverage, based on observations made during the international kava conferences in 2004 (Fiji) and 2012 (Vanuatu):

Kava consumption commonly takes place in kava bars where the responsibility for preparing the kava drink is in the hands of the owners of the kava bars. The owners rely on their experience with regard to preparation technique, but are generally unaware of the kava variety they are using, which is sourced from the local market. The situation varies between countries and the kava varieties available can include the two-day cultivar Palisi as well as noble cultivars. In Vanuatu, the markets contain both kava varieties. In Fiji, the markets distinguish between roots, chips and peelings, as well as between noble and non-noble varieties. In Samoa and Tonga, most of the kava grown is considered to be the noble cultivars.

Some researchers have proposed that noble kava only should be used for kava beverage preparation as well as for preparation of kava medicinal products (Teschke and Lebot 2011, Teschke et al 2011c). The need for quality control (standard operating procedures for growth, harvesting and processing) of raw kava root and rhizomes was also noted by the WHO expert group, who recognised that kava material produced for export and production of kava medicinal products is also likely to find its way into local markets. Quality control procedures are therefore also relevant for the preparation of suitable kava beverage (WHO 2007).

Lebot et al (2014) have described a high-performance thin layer chromatography methodology for the unambiguous identification of noble kavas and the exclusion of two-day kavas (based on the ratio of flavokavins to kavalactones) which could be used for rapid and cost-efficient routine analysis of kava used for the preparation of beverage. Other methods for identifying kavalactone composition have been developed based on high-performance liquid chromatography, gas chromatography or near infrared spectroscopy, but rely on more complex equipment which is not readily available or cost-efficient (Bilia et al 2004, Wang et al 2010).

2.2 Preparation and composition of kava beverage

2.2.1 Preparation

Traditional ceremonial beverage preparation involves maceration, grinding or pounding fresh or dried rhizome/root (1.0–1.5 g), and then mixing it with water or coconut milk (100–150 mL) to form an emulsion. The mixture is agitated, and then strained through a cloth or bark filter into a communal bowl. The beverage is grey with a slightly pungent taste. Kava beverage prepared from fresh rhizome/root produces a stronger beverage than kava beverage prepared from dry rhizome/root (Cairney et al 2002, Norton and Ruze 1994).

Kava preparation for recreational use is essentially the same as for ceremonial use (Shimoda et al 2012), although the beverage may be prepared from powdered kava rhizome/root or from fresh rhizome/root rather than dried rhizome/root. Kava beverage prepared from fresh rhizome/root is a more complex beverage because numerous volatile components are lost in the drying process. Kava beverage prepared from fresh rhizome/root is commonly consumed in Vanuatu (Lebot 2006).

In non-Pacific island countries, kava beverage is usually made from kava rhizome/root powder, which is prepared by drying the rhizome/root and then grinding it. The powder is soaked in water (at least one tablespoon per cup) for about 30 minutes before straining the mixture through cloth to prepare the beverage for consumption.

On the island of Pohnpei in Micronesia, kava beverage is prepared by mixing kava root with the fibrous bark of a local tree, *Hibiscus tiliaceus*, before pressing out the beverage (Balick and Lee, 2002).

2.2.2 Composition

Although kava beverage is traditionally prepared from rhizome/root material (which contain high levels of kavalactones), if stems and/or peelings are present, the kava beverage can also contain kava alkaloids. These alkaloids are present only in plant parts exposed to sunlight - traditionally, these parts would be peeled if used for kava beverage preparation.

The more recent availability of kava biomass (i.e. roots, stumps, stems and/or peelings) for export and subsequent organic solvent extraction of kavalactones may not be subject to the same quality control, and could enter the local market for kava beverage preparation (Lebot 2006, Teschke et al 2011a). Vergano et al (2012) reported the following anecdotal information regarding quality control of kava beverage, based on observations made during the Kava conferences in 2004 (Fiji) and in 2012 (Vanuatu):

In the kava bars visited in the course of the mission to Vanuatu, the plant material was superficially washed and cut in pieces, which went directly to a meat mincer, without prior peeling or appropriate cleaning. This material is then directly used for the preparation of kava. As a consequence, the taste suffers from the peelings, and the kava drinkers are exposed to hitherto unknown phytochemicals present in the skins, but not necessarily in the peeled roots. One can safely assume that the traditional habit of peeling must have made some sense, or otherwise it would not have been done. Today the worst black spots on the traded roots caused by mould formation are sometimes removed by rubbing the roots with a toothbrush, with limited success.

Kava quality refers to both the general quality of the material used, that is, the presence of contaminants and impurities which impact on the toxicological effects, as well as to the level and range of kavalactones which impact on the pharmacological effects. Both of these aspects of quality may impact on the overall safety of kava beverage consumption. In relation to the kavalactones composition, Lebot and Levesque (1989) reported that two-day kava cultivars are rich in two particular kavalactones (dihydrokavain and dihydromethysticin) that can produce nausea when consumed.

Another potential source of contamination of kava beverage is from mould growth on kava material as a result of poor storage conditions (see Section 4.2.4), which may impact on kava safety (Teschke et al 2011, 2013). Similarly, phytochemicals with unknown toxicity from kava plant stems or leaves or from other plants may impact on safety of kava beverage.

2.3 Preparation and composition of medicinal products

Kava medicinal products are sold as powdered extracts, capsules, tinctures and fluid extracts. They are made from a concentrated kavalactones mixture prepared by extracting the dried peeled rhizome/root (and possibly other plant parts) with either ethanol or acetone.

The total amount of kavalactones extracted using ethanol or acetone (i.e. organic extraction) is 2-10 times the amount extracted with water (i.e. aqueous extraction) (Cote et al 2004, Whitton et al 2003; Xuan et al 2008). Organic extracts may contain 30–70% kavalactones (Olsen et al 2011). Although the same kavalactones are found in both aqueous and organic solvent extracts, the hydrophilic components are found in negligible amounts in the organic extracts (Loew and Franz 2003). The ratio of the six major kavalactones in the aqueous extract is also significantly different to the ratio of kavalactones in the organic extract (Cote et al 2004). Commercial kava extracts are generally standardised to contain approximately 30% kavalactones (Brown et al 2007, Whitton et al 2003).

2.4 Limitations of the available data on kava varieties / beverage composition

- Further information is needed on the source and composition of material used to prepare kava beverage.
- Further information is needed on the composition of kava beverage, both with regard to pharmacologically active and non-active components.
- There is a need for practical and reliable analytical methods for monitoring kava components (kavalactones, alkaloids and flavokavins) and potential contaminants.

3 Kava components and their properties

3.1 Chemistry and pharmacology

Kava rhizome contains 80% water; dried rhizome consists of about 43% starch, 20% fibre, 12% water, 3.2% sugars, 3.6% proteins, 3.2% minerals and 3–20% kavalactones (Lebot and et al 1992). The kavalactone content is dependent on plant weight and cultivar. The roots contain the highest concentration of kavalactones, which decrease progressively towards the aerial parts of the plant (Fu et al 2008, Lebot and et al 1992).

Kavalactones are 4-methoxy-2-pyrones with phenyl or styryl substitutes at the 6th position, and are lipid soluble (Lebot et al 1997). They are responsible for kava's pharmacological effects. Eighteen kavalactones have been identified, but six kavalactones – kawain, methysticin, 7,8-dihydromethysticin, yangonin, desmethoxyyangonin and 5,6-dihydrokawain – comprise about 96% of the active pharmacological components of kava (Lebot and Levesque 1989b, Sarris et al 2011, Singh and Singh 2002). Noble kava has a relatively high content of kavain (Lebot 2006).

A range of pharmacological effects have been reported to be associated with the use of kava, including anxiolytic, anti-stress, sedative, muscle relaxant, antithrombotic, neuroprotective, mild anaesthetic, hypnotic and anti-convulsive actions, although the mechanisms of action are not well established (Gounder 2006, Sarris et al 2011).

Kava also contains alkaloids, three of which have been characterised – pipermethystine, 3 α ,4 α -epoxy-5 β -pipermethystine and awaine. These alkaloids occur more commonly in the aerial parts of the plant, the stem and leaves, rather than in the roots, but can be incorporated into kava beverage during preparation (Dragull et al 2003, Lebot 2006, Nerurkar et al 2004, Rowe et al 2011).

Minor kava chemical components (less than 1% dry weight) include the dihydrochalcones, flavokavins A, B, and C (also known as flavokawains) and a range of other minor compounds (Teschke and Lebot 2011, Teschke et al 2011a, Teschke et al 2011c, Xuan et al 2008, Zhou et al 2010; Lebot et al 2014).

3.2 Pharmacokinetics

The main metabolic pathways for kavalactones in humans and rats are reasonably well understood. The aromatic ring is broken and the lactone ring hydroxylated, followed by dehydration, reduction of the 7,8-double bond and demethylation of the 4-methoxy group (Duffield et al 1989b, Fu et al 2008). The hydroxylation and demethylation steps are known to be a function of cytochrome P450 (CYP) 2D6, and excretion is mainly via the urine as glucuronide and sulphate conjugates (Duffield et al 1989a).

Little is known about the metabolism of kava alkaloids or flavokavins (Rowe et al 2011); however, CYP2D6 is known to have a high affinity for alkaloids (Ingelman-Sundberg 2005). CYP2D6 is absent in 7% of Caucasians and in less than 1% of Polynesians. It has been suggested that low CYP2D6 might lead to an accumulation of kavalactones or alkaloids, resulting in toxicity (WHO 2007). However, there is currently insufficient information available on P450 enzymes involved in metabolism of kavalactones or kava alkaloids to further examine this hypothesis (Olsen et al 2011).

There is limited knowledge about the potential for specific kavalactone metabolites to alkylate DNA, or disrupt enzymatic or metabolic activity (Ulbricht et al 2005). Johnson et al (2003) showed that reactive metabolites such as quinones, quinone methides and epoxides could be formed *in vitro*, but analysis of metabolites in human urine did not indicate formation of substantive quantities of reactive metabolites *in vivo*. On the other hand, Zou et al (2005) identified 6-phenyl-3-hexen-2-one, a reactive metabolite of kavain and dehydrokavain, in human urine following consumption of kava beverage prepared from 10 g of powdered rhizome. Kavain and dehydrokavain are present in relatively higher concentrations in kava extracts prepared using organic solvents than in aqueous extracts.

3.2.1 Pharmacokinetic drug interactions

Kavalactones, especially methysticin and dihydromethysticin, have been shown to be inhibitors of CYP450 enzymes, which suggests a possibility of pharmacokinetic interactions with substances (herbal substances or drugs) that are metabolized via the CYP450 pathway (Anke and Ramzan 2004, Ulbricht et al 2005). In three different studies, the different kavalactones were shown to have significant negative effects on some or all of the CYP450 isoforms 2C9, 2C19, 3A4, 2D6, 4A9/11 and 1A2 (Anke and Ramzan 2004). Coté et al (2004) proposed that the different proportions of kavalactones between aqueous and organic extracts, and thus the difference in inhibition of P450 enzymes, was related to their differential biological activity.

In *in vitro* studies, there was no difference between IC₅₀ values for aqueous (0.9–9.7 µg lactones/mL) and acetonic kava extracts (1.2–15.3 µg lactones/mL) towards inhibiting isoforms 3A4, 1A2, 2C9 and 2C19 (Coté et al 2004). Individual lactones showed varying abilities to inhibit P450 enzymes, although it is unclear if clinically relevant concentrations are reached *in vivo* in humans (Olsen et al 2011).

Another study has shown that kava extract significantly induces the CYP1A1 isoform; specifically, the kavalactones methysticin and dihydromethysticin (Li et al 2011), and that this can occur within the clinically relevant range (60–160 µM) of kavalactone plasma concentrations (Pittler and Ernst 2003). The authors suggest the possibility of an association between kava and CYP1A1-mediated induction of the aryl hydrocarbon receptor (AhR), which is involved in cell regulation (Li et al 2011).

3.3 Toxicity

3.3.1 Kavalactones

The cytotoxic effects of individual kavalactones have been examined *in vitro*. These studies showed differences in cytotoxicity which did not correlate between a human lymphoblastoid cell line (Zou et al 2004a) and cryopreserved human hepatocytes (Zou et al 2004b). Tang et al (2011) also examined kavalactone-induced cytotoxicity in HepG2 cells and showed kavain had minimal cytotoxicity while yangonin showed marked cytotoxicity. Overall, the *in vitro* studies do not show consistent cytotoxicity for individual kavalactones in different cell lines.

The available *in vivo* animal studies with kava extracts do not provide evidence of kava-induced hepatotoxicity, even at high dosages. Rats treated with an acetone or ethanol extract of kavalactones at up to 133 mg/kg/day for three months produced no enzymatic or histological evidence of hepatotoxicity (DiSilvestro et al 2007). In a similar study over

90 days and, subsequently, 2 years, rats treated with an ethanol extract of kavalactones at 1-2 g/kg/day had elevated gamma-glutamyltransferase (GGT) levels and liver hypertrophy, but no histological evidence of hepatotoxicity (Clayton et al 2007, National Toxicology Program 2012). Rats treated with an aqueous extract of kavalactones at 500 mg/kg/day for four weeks produced no increases in the liver function enzymes alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) or lactate dehydrogenase (LDH) (Singh and Devkota 2003). Overall, the *in vivo* studies do not provide clear evidence of kava-induced hepatotoxicity in rats, even at high dosages.

Reactive kavalactone metabolites have also been proposed as an explanation for kava-induced skin rash due to the formation and immune recognition of skin protein adducts (Olsen et al 2011).

3.3.2 Alkaloids

The kava alkaloids, particularly pipermethystine, are possibly more cytotoxic than the kavalactones. In a study by Nerurkar et al (2004) in HepG2 cells, pipermethystine showed considerably higher cytotoxicity than the lactones dihydromethysticin and desmethoxyyangonin after 24 hours of exposure.

In a two-week study in rats, pipermethystine (10 mg/kg/day) did not produce any changes in liver enzymes or cause hepatotoxicity, as measured by lipid peroxidation and apoptosis markers, but did increase markers of oxidative stress (Lim et al 2007).

3.3.3 Flavokavins

The potential toxicity of the dihydrochalcone flavokavin B (FKB) has been examined in HepG3 cells where it is reported to induce hepatocellular apoptosis by the induction of oxidative stress, depletion of glutathione, and altering the balance of the IKK/NF- κ B and MAPK signalling pathways. The addition of exogenous GSH was able to normalise NF- κ B and MAPK signalling in HepG3 cells and prevent the flavokavin B-induced toxicity. A further study evaluated the hepatotoxic effects of FKB *in vivo* in mice at an oral concentration of 25mg/kg/day for 7 days, resulting in liver damage demonstrated by diffuse cloudy hepatocellular swelling and vesiculated cytoplasm, together with raised serum AST and AKP levels (Zhou et al 2010). The authors suggest that flavokavin B is a major hepatotoxin in organic kava extracts, although Teschke et al (2011b) have questioned whether the levels in kava organic solvent extracts are high enough to produce hepatotoxicity *in vivo*.

Vergano et al (2012) have used the *in vivo* toxicity information on flavokavin B (Zhou et al 2010) to establish a permitted daily exposure (PDE) of 10.4 mg/day, using the ICH guideline on solvent impurities¹ and a LOEL of 25mg/kg/day. The calculation provided by Vergano et al (2012) indicates that a heavy kava drinker of noble cultivar Borogu would be below the estimated PDE, while the same drinker of the two-day cultivar Palisi would be well above the estimated PDE. While there are many assumptions in this calculation, it provides a route to establish safe levels of exposure for flavokavin B.

¹ CPMP/ICH/283/95: Impurities – Guidelines for Residual Solvents

3.4 Limitations of the available data on kava components and their properties

- Further data is needed on the potential for formation of reactive metabolites of kavalactones, alkaloids and flavokavins, and their role in kava toxicity.
- Further data is needed on the potential for kavalactones to inhibit P450 enzymes, and to potentially enhance the hepatotoxicity of co-administered medication.
- Further data is needed on the potential *in vitro* and *in vivo* toxicity of kava alkaloids and flavokavins, and their mechanisms of action.
- Further data is needed on the *in vivo* toxicity threshold levels for kava alkaloids and flavokavins.

4 Reported human health effects

4.1 Effects on general health

4.1.1 Traditional kava beverage consumption

There are very few published reports of adverse health effects arising from the traditional consumption of kava beverage in the South Pacific islands. This may reflect a genuine low incidence level of adverse effects or a lack of reporting and systematic data collection. There are anecdotal reports of general symptoms such as feeling unwell, headaches, sleeplessness, tiredness and feeling lethargic (Kava 2001, Singh 1992).

Preparations of kava beverage vary with plant variety (Lebot et al 1997; Lebot et al 2004) which can affect the pharmacological potency and, in some cases, the potential toxicity. This may be due to differences in potency, absorption rate and pharmacokinetics of the various kavalactones and other components (Olsen et al 2011, Rowe et al 2011).

In a study of 12 Tongan men living in New Zealand who regularly consume kava beverage, the participants reported feeling tired and lazy after consuming kava, which affected their work and sexual activity (Nosa and Ofanoa 2009).

4.1.2 Clinical trial outcomes

Clinical studies have been conducted to examine the effectiveness of kava as a treatment for anxiety. These studies have been conducted using both aqueous and organic extracts of kava. The vast majority of medicinal products available to consumers in the form of dietary supplements use kava organic extracts as the active ingredient. However, some clinical studies on patients with anxiety have also been conducted using tablets prepared with kava aqueous extracts (see below).

Using kava aqueous extracts

In a study of the clinical efficacy of kava aqueous extract, 60 patients with elevated generalized anxiety disorder were administered five tablets per day containing an aqueous extract of kava for three weeks (dosage 250 mg kavalactones per day). The aqueous extract of kava resulted in a reduction in participants' anxiety and depression levels. There was no evidence of serious adverse health effects and no clinical hepatotoxicity. A few of the participants reported nausea and/or gastrointestinal side-effects (Sarris et al 2009). In a subsequent study, 75 patients with generalised anxiety disorder were administered a tablet containing an aqueous extract of kava for 6 weeks (dosage 120/240 mg kavalactones per day). More headaches were reported in the kava group but no other adverse effects or changes to liver function test were reported (Sarris et al 2013b, Sarris et al 2013c).

Using kava organic extracts

There have been a number of randomised controlled trials (RCTs) conducted to examine the efficacy of kava organic solvent extracts in treating anxiety. The incidence of adverse effects was measured as a secondary outcome in these trials.

In a Cochrane Collaboration study, Pittler and Ernst (2003) examined 12 double-blinded RCTs ($n = 700$). Six trials reported adverse events experienced by patients receiving kava

organic extract – most frequently stomach complaints, restlessness, drowsiness, tremors, headaches and tiredness. Four trials (comprising 30% of patients in the reviewed trials) report the absence of adverse events while taking kava extract. None of the trials reported any hepatotoxic events. Seven of the trials measured liver enzyme levels as safety parameters and reported no clinically significant changes.

4.1.3 Excessive kava beverage consumption

Kava drinking was introduced into Australia Aboriginal communities in Arnhem Land in the Northern Territory in 1982, partly as a substitute for alcohol. Over time, kava has become widely used in a recreational setting, with excessive use in some circumstances. Rychetnik and Madronio (2011) examined the available studies conducted in these communities for evidence of health and social effects of kava consumption, together with studies conducted on South Pacific islanders. The evidence was appraised on study design (level of evidence) and standard epidemiological criteria for causality (Table 4.1).

Table 4.1 Summary of evidence on the health effects of kava beverage consumption

Studies	Health or social effect	Level of evidence ^a	Review finding based on 'body of evidence' ^b
Clough 2003, Clough et al 2003b, Kava 2001, Mathews et al 1988, Riley et al 1987	Scaly skin rash	III-2	A1 – Causality indicated: Association found, additional criteria indicate causal relationship
Alexander et al 1988, Chanwai 2000, Grace 2003, Russmann et al 2003		IV	
Clough 2003, Mathews et al 1988, Clough et al 2003b, Clough et al 2004a, Mathews et al 1988, Riley et al 1987	Weight loss	III-2	A1 – Causality indicated: Association found, additional criteria indicate causal relationship
Brown et al 2007, Clough 2003, Clough et al 2003b; Mathews et al 1988, Riley et al 1987	Raised GGT liver enzyme	III-2	A1 – Causality indicated: Association found, additional criteria indicate causal relationship
Chanwai 2000, Russmann et al 2003		IV	
Kava 2001, McDonald and Jowitt 2000	Nausea, loss of appetite or indigestion	III-2	A1 – Causality indicated: Association found, additional criteria indicate causal relationship
Kava 2001, Mathews et al 1988	Sore red eyes	III-2	A2 – Association indicated: causality unclear
Chanwai 2000		IV	
Kava 2001	Impotence /loss of sex drive	III-2	A2 – Association found
Gregory 1988		IV	
Kava 2001, Mathews et al 1988	Self-reported 'poor health'	III-2	A2 – Association found
Clough 2003, Clough et al 2003b, Clough et al 2004a	Raised cholesterol	III_2	A2 – Association found
Clough et al 2004b	Ischaemic heart disease	III-2	A3 – Unclear association
Young et al 1999		IV	
Foo and Lemon 1997, Prescott et al 1993	Cognitive performance	II	N1 – No association found
Cairney et al 2003a, Cairney et al 2003b, Russell et al 1987		III-3	
Clough 2003	Permanent liver damage	III-2	N2 – No association found
Russmann et al 2003		IV	
Clough 2003	Pneumonia	III-3	N2 – No association found

GGT, gamma-glutamyltransferase.

^a See Appendix 1.

^b Categories of 'association' based on level of evidence other criteria for assessing the evidence for a causal relationship, namely, consistency, strength, dose-response, temporal relationship, biological plausibility, analogy/coherence and reversibility/experiment.

Source: Rychetnik and Madronio (2011).

The analysis by Rychetnik and Madronio (2011) strongly suggests that scaly skin rash, weight loss and raised GGT levels are all caused by heavy kava beverage consumption; however, the reversibility of these effects suggests that these changes need not lead to longer term adverse health outcomes. Nausea, loss of appetite and indigestion also appear to be caused by heavy kava beverage consumption, even though the criteria for supporting causality are less strong in these cases. Anecdotal evidence also suggests that nausea, loss of appetite and indigestion can result from heavy kava beverage consumption.

Other self-reported symptoms and clinical findings in Aboriginal Australians consuming kava beverage, some which may be subject to bias, included complaints of being unwell; shortness of breath; a puffy face, red eyes and a rash; and to have brisk patellar reflexes, which the authors suggest may be variously caused by symptoms of anxiety, by the pharmacological effects of kava or by transient allergic manifestations (Mathews et al 1988). Clough et al (2003c) also reported reduced lymphocyte counts in Aboriginal kava beverage drinkers ($P<0.001$), but there have been no subsequent reports of this effect.

Possible confounding factors in evaluating the evidence for an association between kava beverage consumption in Aboriginal communities and adverse health effects include alcohol and other drug misuse, and general malnutrition.

4.2 Effects on the liver

There have been a small number of case study reports indicating a relationship between hepatotoxicity and consumption of kava beverage. A larger number of case study reports have provided evidence of an association between hepatotoxicity and consumption of medicinal products/herbal supplements containing kava organic solvent extract (WHO 2007), although the validity of a number of these case studies has been disputed (Teschke 2010b). The subsequent bans on kava herbal supplements in most non-Pacific island countries have focused attention on the possible mechanisms of this kava-associated hepatotoxicity. While the focus of these health concerns has been largely directed towards kava medicinal products based on organic solvent extracts, questions have also been raised regarding the safety of kava beverage consumption (Currie and Clough 2003, Ernst 2006, Moulds and Malani 2003).

Table 4.2 summarizes the *in vivo* evidence for kava beverage-associated effects on the liver. The following sections examine some of the recent evidence and hypotheses regarding the mechanism of kava-associated hepatotoxicity.

Table 4.2 Summary of the evidence on the effects on the liver following consumption of kava beverage

Study	n	Effect of kava	Type of study Level of evidence ^a	Preparation
Liver enzyme levels				
Brown et al 2007	62	Significant association with raised GGT levels Probable association with raised ALP levels	Cohort III-3	Traditional beverage – aqueous based (Tongan population in Hawaii)
Clough et al 2003b	101	Causality indicated with raised GGT and ALP levels No increase in ALT or bilirubin	Cross-sectional III-2	Beverage prepared from powdered rhizome (Aboriginal Australians)
Mathews et al 1988	73	Causality indicated with raised GGT and ALP levels	Pilot survey III-2	Beverage prepared from powdered rhizome (Aboriginal peoples)
Russmann et al 2003	27	Causality indicated with raised GGT Minimal increase in ALT and AST	Consequent survey III-3	Traditional beverage – aqueous based (New Caledonia)
Hepatotoxicity				
Clough et al 2003b		No documented cases of liver injury over 20 years' clinical surveillance	-	Beverage prepared from powdered rhizome (Aboriginal Australians)
Clough et al 2003a, Clough et al 2003b	101	No association with long-term liver injury	Cross-sectional III-3	Beverage prepared from powdered rhizome (Aboriginal Australians)
Russmann et al 2003	27	No association with long-term liver injury	Consequent survey III-3	Traditional beverage – aqueous based (New Caledonia)
WHO 2007	2	Jaundice (1), hepatocellular injury (1)	Case studies IV	Traditional beverage – aqueous based
Christl et al 2009	1	Associated hepatotoxicity	Case study IV	Traditional beverage – aqueous based (Samoa)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase.
a See Appendix 1.

4.2.1 Hepatotoxicity and kava beverage consumption

South Pacific island communities

Although there has been long and extensive use of kava beverage in communities of the South Pacific islands, there are only three published case reports of liver toxicity associated with consumption of kava beverage. Two of these cases occurred in residents of New Caledonia, and the other was in a European tourist visiting Samoa (see Box 4.1).

Box 4.1 Case study reports of hepatotoxicity from kava beverage consumption

Case 1

A 59-year-old female of Oceanian origin had symptoms of liver injury following four weeks of drinking kava beverage prepared from dried kava imported from Vanuatu (dosage unknown). The patient did not consume alcohol but was a long-term user of lisinopril, phenobarbital and fenofibrate (for treatment of hypertension, anxiety and high cholesterol, respectively). There was markedly elevated transaminases (AST and ALT) and bilirubin in the blood, together with changes in other clinical pathology parameters indicative of liver damage. The patient recovered after cessation of kava consumption and laboratory values return to normal after three months.

Source: Russmann et al (2003)

Case 2

A 55-year-old female of Oceanian origin had symptoms of liver injury following five weeks of kava beverage consumption (four cups per evening, approximately 18 g kavalactones per week). The patient did not take any medication. There was markedly elevated transaminases (AST and ALT) and bilirubin in the blood, together with changes in other clinical pathology parameters indicative of liver damage. The patient recovered following cessation of kava consumption and laboratory values returned to normal after three months.

Source: Russmann et al (2003)

Case 3

A 42-year-old male presented with serious liver disease three weeks after holidaying in Samoa and repeatedly taking part in traditional kava ceremonies where he consumed a cumulative volume of 2–3 L of kava beverage. There was marked elevation of liver enzymes (AST, ALT, GGT, AP, LDH) and bilirubin. All other routine parameters were normal. Histology of a liver puncture showed a pattern consistent with toxic liver injury. Laboratory tests returned to normal after 36 days.

Source: Christl et al (2009)

Australian Aboriginal communities

Clinical surveillance of Aboriginal people in northern Australia using kava beverage for 20 years has not documented any cases of hepatic failure attributable to kava, despite clear evidence of excessive consumption (Clough et al 2002a, Clough et al 2003a, Mathews et al 1988).

4.2.2 Liver enzyme changes and kava beverage consumption

Russmann et al (2003) surveyed 27 heavy kava drinkers from New Caledonia. All had been regularly consuming kava beverage for at least five years with a mean intake of about 32 g kavalactones per week (approximately 70 mg/kg/day). Dry skin occurred in 15 individuals, which is known to occur with excessive kava consumption (Norton and Ruze 1994). The authors reported an increase in gamma glutamyl transferase (GGT) in 23 individuals, which they considered to be related to the induction of CYP450 enzymes and was reversible upon cessation of kava consumption. Five individuals showed a minimal increase in ALT, and seven individuals showed a minimal increase in AST. All individuals had normal ALP and bilirubin levels, and were considered to be in good general health with no symptoms of liver disease.

Brown et al (2007) examined the effects of traditional kava beverage on liver function tests in 31 regular adult kava consumers and 31 adult non-kava consumers in a population of Tongan and non-Tongan male residents in Hawaii. Chronic kava beverage consumption was associated with elevated GGT in 65% of kava drinkers, compared to 26% in the controls ($P = 0.005$), as well as elevated alkaline phosphatase (ALP) in 23% of kava drinkers compared to 3% in the controls ($P = 0.053$). There was no significant difference in ALT, AST, bilirubin, albumin or total protein. The authors did not examine the effect of cessation of kava consumption.

In kava beverage-consuming Aboriginal communities in northern Australia, a clear association was found between kava consumption and elevated GGT (Clough 2003, Currie and Clough 2003, Clough et al 2003b, Mathews et al 1988, Riley et al 1987, Rychetnik and Madronio 2011). There was also an increase in ALP in 50% of participants in clinical studies who reported using kava at least once in the month before measurement, compared to less recent or non-users (Clough et al 2003b). ALT and bilirubin levels were normal, and both GGT and ALP returned to normal levels after 1–2 months of abstinence (Clough et al 2003a).

Based on the above observations, Clough et al (2003b) proposed that these results indicate a non-inflammatory response pattern. Rowe et al (2011) suggest that the increases in GGT and ALP without corresponding ALT or AST elevation are indicative of cholestasis rather than a hepatocyte inflammatory response. Cholestasis could arise from a non-inflammatory process resulting from direct inhibition of proteins or transporters or from an inflammatory process via Kupffer cell activation. Further research is necessary to examine the mechanisms involved and the extent of biliary excretion of kavalactones in order to better understand the significance of the kava-related elevated GGT levels (Rowe et al 2011).

4.2.3 Human cases of kava-associated hepatotoxicity

WHO reviewed suspected case studies of kava-related hepatotoxicity following reports of a number of such cases in Germany and Switzerland in 1998 (WHO 2007). Of the 93 case reports initially identified by WHO, eight were identified as having a ‘probable’ association with the use of kava (six with kava organic solvent extract and two with kava beverage). Reported dosages ranged from 45 mg to 1200 mg kavalactones per day, taken for one week to twelve months. The WHO report concluded that:

- the relationship (causality) ratings provide a significant concern of a cause-and-effect relationship between kava products and hepatotoxicity; a non-random effect is indicated by a higher rate for the organic extracts than for synthetic products
- chemicals other than kava lactones might be responsible for hepatotoxicity with the organic extracts
- kava products have a strong propensity for kava–drug interactions
- risk factors for hepatic reactions appear to be the use of organic extracts, heavy alcohol intake, pre-existing liver disease, genetic polymorphisms of cytochrome P450 enzymes and excessive dosages. Also, co-medication with other potential hepatotoxic drugs and interacting drugs, particularly anxiolytics, antipsychotics and antithrombotics, might lead to harm.

Teschke and Wolff (2009) have criticized the WHO report, particularly in relation to the method used to apply causality to kava. This has led to further analysis of case studies of hepatotoxicity where kava involvement was suspected.

More recent reports have examined 31 case reports of hepatotoxicity suspected to be associated with kava consumption, using the Council for International Organizations of Medical Sciences (CIOMS) scale for causality assessment. Causality for kava ± co-medicated drugs and dietary supplements was highly probable ($n = 1$), probable ($n = 4$) or possible ($n = 9$) in 14 patients with liver disease. Risk factors included overdose, prolonged treatment, and co-medication with synthetic drugs and herbal dietary supplements. In 5 of the 14 patients, the kava used was an aqueous extract (Teschke et al 2009, Teschke 2010a, b). Teschke (2010b) proposed that these results show that kava hepatotoxicity occurs independently of the extract medium, and may primarily be attributed to daily overdose, prolonged treatment, co-medication and poor-quality kava extracts.

4.2.4 Mechanisms/risk factors - kava-associated hepatotoxicity

The initial observation of cases of kava-associated hepatotoxicity following consumption of medicinal products containing organic solvent extracts of kava and the subsequent observation that there were also cases of hepatotoxicity associated with consumption of kava beverage has led to speculation regarding possible mechanisms and/or associated risk factors. Teschke (2010a) noted that these possible mechanisms/risk factors may apply to both organic and aqueous kava extracts, even though there may be factors that make the likelihood of developing hepatotoxicity from either organic or from aqueous extracts greater under certain circumstances.

Mechanisms and/or risk factors that may be relevant to kava hepatotoxicity has been proposed since the first reports of hepatotoxicity in 1998. These potential factors are briefly discussed in the following subsections, which are partially based on the critical reviews of Olsen et al (2011) and Teschke et al (2011a).

Specific kavalactones or mixtures of kavalactones

The composition of kava beverage and extracts varies depending on the species of plant, which part of the plants are used, and the preparation method; however, no correlation has been made between specific kavalactones and hepatotoxicity in *in vitro* cell cultures (Zou et al 2004b) or *in vivo* in rats (Clayton et al 2007, Singh and Devkota 2003). Although organic extraction yields higher kavalactone concentrations than aqueous extraction (Loew and Franz 2003) – as well as differences in the ratio of major kavalactones (reduced levels of yangonin and desmethoxyyangonin) (Cote et al 2004) – no correlation has been made between exposure to total or specific kavalactones, and the incidence of hepatotoxicity.

Inhibition or induction of major metabolising enzymes

In *in vitro* studies, there was no difference between IC₅₀ values for aqueous (0.9–9.7 µg lactones/ml) and acetic kava extracts (1.2–15.3 µg lactones/ml) towards P450 3A4, 1A2, 2C9 and 2C19 enzymes (Coté et al 2004). Individual kavalactones showed varying ability to inhibit P450 enzymes, although it is unclear if clinically relevant concentrations are reached in humans *in vivo* (Olsen et al 2011). Induction of various P450 enzymes, particularly 1A1, has also been observed *in vivo*, which led Yamazaki et al (2008) to propose a role for P450 1A1 in kava hepatotoxicity based on its role in bioactivation of polycyclic aromatic hydrocarbons.

Cytochrome P450 polymorphisms

Given the apparent very low incidence of kava hepatotoxicity (Ernst 2006), polymorphisms in P450 have been proposed as being responsible for the observed cases of hepatotoxicity – or at least a risk factor. Cytochrome P450 2D6 is responsible for hydroxylation of the aromatic ring and demethylation of kavalactones and may be involved in the metabolism and detoxification of kava alkaloids. CYP2D6 has four human phenotypes (ultrarapid, efficient, intermediate and poor) and is absent in 7% of Caucasians and in less than 1% of Polynesians. These differences are likely to contribute to different rates of metabolism of kavalactones, and could lead to accumulation of alkaloids in poor metabolisers, thus influencing individual susceptibility to kava-associated hepatotoxicity. Further research is needed to clarify pharmacogenomic differences in kava metabolism.

Formation of reactive kavalactones metabolites

There is some evidence for the formation of reactive metabolites from kavalactones catalysed by P450 enzymes (Johnson et al 2003, Ulbricht et al 2005, Zou et al 2005), however, there is currently insufficient information to relate these results to the *in vitro* or *in vivo* toxicity data which show little evidence of kava-induced hepatotoxicity.

Toxicity of minor kava components

Kava alkaloids, particularly pipermethystine and flavokavain B, display higher cytotoxicity *in vitro* than the kavalactones (discussed in Section 3.3). The amount of these minor components, however, is highly variable, depending on the extraction medium and the kava cultivar used (DiSilvestro et al 2007, Jhoo et al 2006, Teschke et al 2011c, Xuan et al 2008, Zhou et al 2010). It is unclear from the data available whether pipermethystine or flavokavain B display toxicity *in vivo* (Lim et al 2007) or would be present in the plasma at sufficiently high levels to produce toxicity in human-exposure scenarios (Teschke et al 2011a).

Depletion of GSH and subsequent reaction of active metabolites to cellular macromolecules

Whitton et al (2003) proposed a role for glutathione in protecting consumers of kava beverage from hepatotoxicity, since glutathione is extracted by water but not organic solvents. However, the proposal that glutathione binds irreversibly to kavalactones and thus protecting kavalactones from P450 metabolism has not been demonstrated (Olsen et al 2011). Zhou et al (2010) demonstrated that flavokavain B depletes hepatocellular GSH, which may contribute to sensitization of the liver to hepatotoxin-induced injury because of its role as a scavenger of reactive oxygen species.

Kava mould contaminants

A recent hypothesis has focused on the quality of the kava material used for both medicinal product preparation and kava beverage preparation, suggesting that contaminant hepatotoxins, such as the mycotoxins, specifically aflatoxins, might be responsible for cases of kava hepatotoxicity (Teschke et al 2011a, Teschke et al 2012, Teschke et al 2013). There is significant potential for contamination of kava material by *Aspergillus* species during postharvest storage, resulting in the formation of aflatoxins, which are known to be hepatotoxic and carcinogenic in humans, particularly in regions of high hepatitis B prevalence. Further analytical and possibly epidemiological research will be required to explore this hypothesis (Rowe and Ramzan 2012, Teschke et al 2011a).

4.3 Effects on cognitive function

Cairney et al (2002) and, more recently, LaPorte et al (2011) and Sarris et al (2011) reviewed the neurobehavioural effects of kava.

The study by Cairney et al (2002) examined users and non-users of kava beverage in Australian Aboriginal communities and concluded that there was evidence that kava has muscle relaxant, anaesthetic, anxiolytic and anticonvulsive properties, but no conclusive evidence that kava interferes with normal cognitive processes.

LaPorte et al (2011) reviewed 10 human clinical trials (7 acute/extract and 3 chronic/beverage), supported the conclusion that kava had no replicated significant effects on cognition, although visual attention may be impaired during high cognitive demand.

Sarris et al (2011) examined the available clinical trials and concluded that the limited studies available indicated equivalent clinical efficacy between kava and more traditional pharmaceutical agents in the treatment of generalized anxiety disorder, but that further randomized double-blinded trials were necessary to fully establish the efficacy and safety of long-term clinical use of kava.

Table 4.3 summarizes the *in vivo* evidence for kava beverage-associated effects on cognitive function.

Table 4.3 Summary of evidence on the cognitive function effects of kava beverage consumption

Study	n	Effect of kava	Type of study Evidence level ^a	Preparation
Cairney et al 2003a	101	Chronic kava users – no effects seen on motor function task, visual search, pattern recognition or pattern-location associate learning	RCT II	Beverage prepared from powdered rhizome (Aboriginal Australians)
Cairney et al 2003b	28	Chronic kava users – decreased visual accuracy under high load, but basic motor skills and memory were not affected	RCT II	Beverage prepared from powdered rhizome (Aboriginal Australians)
Clough et al 2003b	101	Chronic kava use – no neurocognitive effects seen	Cross-sectional III-3	Beverage prepared from powdered rhizome (Aboriginal Australians)
Garner and Klinger 1985	1	Acute kava use – visual effects (reduced the near point of accommodation and convergence, increased pupil diameter, and disturbed oculomotor balance)	Case study IV	Traditional aqueous beverage
Mathews et al 1988	73	Chronic kava use – no effects seen on memory, cognition and coordination	Pilot survey III-3	Beverage prepared from powdered rhizome (Aboriginal Australians)
Sarris et al 2013a	22	Acute kava use – no effects seen on motor skills and cognitive function	RCT/cross-over II	Herbal extract (180 mg of kavalactones)
Thompson et al 2004	20	Acute kava use – improved accuracy and speed of working memory and visual attention tasks	RCT II	Herbal extract (90 mg of kavalactones)

RCT, randomised controlled trial.

^a See Appendix 1.

In general, available reports support the conclusion that kava does not affect cognitive function, although one study reported improved visual attention and cognitive tasks (Thompson et al 2004), and another reported decreased visual attention (Cairney et al 2003a). A kava medicinal preparation containing 180 mg kavalactones did not impair driving ability; however, the effect of higher consumption levels is not known (Sarris et al 2013a).

4.4 Effects on skin

Heavy kava drinkers, including traditional Pacific islanders, have long reported effects on skin, including rashes and other dermatitis conditions, such as dry, scaly, yellow skin on the hands (palms), feet (soles) and back (Rowe et al 2011). The condition is accompanied by hyperpigmentation, which *in vitro* studies have linked with the kavalactones, yangonin and 7,8-epoxyyangonin (Matsuda et al 2006). The skin condition has been referred to as ‘kava dermatopathy’ and occurs as a result of sustained heavy kava drinking (more than 435 g kava powder/week) (Clough et al 2003b, Lebot et al 1992, Norton and Ruze 1994, Ruze 1990). The condition is reversible after drinking kava has ceased.

One proposed mechanism for skin rash is the immune recognition of skin protein adducts formed by reaction with kavalactone metabolites. Ruze (1990) proposed a relationship with niacin deficiency, but this has not been supported by other research (Fu et al 2008);

Teschke et al 2011). A more recent study has proposed a role for mast cell activation in an *in vitro* assay by an aqueous kava extract, but not for isolated kavalactones (Shimoda et al 2012). Further research is required to identify the responsible active component(s) in aqueous extract and to assess the potential for a similar *in vivo* response.

Table 4.4 summarises the *in vivo* evidence for kava beverage-associated effects on the skin.

Table 4.4 Summary of evidence of skin effects of kava beverage consumption

Study	<i>n</i>	Effects of kava	Type of study Evidence level ^a	Preparation
Clough et al 2003b	101	Dermopathy observed 45% of current users	Cross-sectional III-3	Beverage prepared from powdered rhizome (Aboriginal peoples)
Mathews et al 1988	73	A scaly skin rash was associated with heavy kava drinkers	Pilot survey III-3	Beverage prepared from powdered rhizome (Aboriginal peoples)
Ruze 1990	200	A scaly rash and eye irritation were seen in some heavy kava drinkers	IV	Traditional aqueous preparation (Tonga)
Shimoda et al 2012	24	13 out of 14 respondents reported having a scaly skin rash	Survey ^b	Traditional aqueous preparation

–, unknown.

^a See Appendix 1.

^b Individuals were surveyed from Vanuatu, Marshall Islands, Kiribati, Solomon Islands, Hawaii, Samoa, Fiji, Palau and Guam.

4.5 Effects on chronic diseases

No clinical trials or epidemiological studies have examined the potential for kava beverages to impact on the incidence of chronic diseases, such as cardiovascular disease, diabetes or kidney disease. However, there are also no anecdotal reports of an increased incidence of these diseases, despite the long history of kava beverage consumption in the South Pacific.

Longer term health effects associated with heavy use of kava beverage described by Clough et al (2003b) include seizures and extreme weight loss. Early studies provided circumstantial evidence that kava beverage consumption was associated with ischaemic heart disease (IHD) among young Australian Aboriginal people in Arnhem Land (Young et al 1999). Further analysis of hospital cases of IHD during 1992–97, however, did not provide any evidence for an association between kava beverage consumption and IHD (Clough et al 2004b). In the Australian Aboriginal community, there is some evidence of malnutrition being associated with kava beverage consumption (Clough et al 2004a).

4.6 Limitations of the available data on human health effects

- Further information is needed on the effect of regular kava consumption on general health parameters over time, including weight loss and adverse effects on the liver and skin, and the threshold intake for these effects.
- Further information is needed in order to understand the mechanism of kava-related hepatotoxicity, for both organic and for aqueous extracts.

- Further information is needed to understand the mechanism of the kava-induced increase in GGT and its relationship, if any, with long-term hepatotoxicity, and the intake threshold for this effect.
- Further information is needed to understand the mechanism for kava-induced skin rashes (kava dermopathy) and the intake threshold for this effect.
- Further information is needed to understand the relationship between the pharmacological effects of kavalactones and the observed toxicity in humans.
- Further information is needed to understand the effect of kava beverage consumption on the incidence of chronic diseases, if any.

5 Consumption of kava beverage

The level of consumption of kava beverage, as well as the frequency of consumption, varies between individuals, between sexes, within communities and between South Pacific islands, and also depends on the social context of the beverage consumption (Balick and Lee 2002, Lebot 2006). This, together with high variability in the composition of kava beverage, which depends on the variety of the kava plant, the plant parts used and the preparation procedures, makes it difficult to correlate the effects observed with the level of intake of kava beverage or its components.

5.1 Level and frequency of consumption

In a study of 150 men and women in Vanuatu who regularly consumed kava beverage (at least weekly in 51% of men and 11% of women), the mean consumption was 4.1 shells per day for men and 3.0 shells per day for women. Kava was consumed in 27% of males and 17% of women on a daily basis. The majority of kava drinkers consumed kava at least weekly (Grace 2003). Based on an average of 250 mg kavalactones per shell (Balick and Lee 2002), this is equivalent to 750 mg per session for females and 1000 mg per session for males.

The report by Vergano et al (2012) has anecdotal information on the consumption of kava beverage, suggesting that a heavy kava drinker would ingest 5 cups of kava beverage daily, corresponding to 500 ml or 333 g of fresh kava root, which is equivalent to approximately 200 g of kava powder (assuming 60% water content). Based on an average of 250 mg kavalactones per cup (shell) (Balick and Lee 2002), this is equivalent to 1250 mg per day.

A survey ($n = 24$) across nine Pacific islands indicated that the starting material was ground kava root and stem mixture diluted with water giving a 0.5–1.0% weight/volume preparation on most Pacific islands, but up to 3% (w/v) on Vanuatu and up to 5% (w/v) on Kiribati. Consumption per person was 1.5–5.0 L per session. Consumption frequency was daily in 29% of respondents and monthly in 54% of respondents (Shimoda et al 2012).

In Aboriginal communities in northern Australia, consumption has been estimated as 3800 mg kavalactones per hour, based on consumption of nearly 7 cups of 100 ml (670 ml total) kava beverage prepared from 37 g kava powder containing 12.5% kavalactones (assuming 82% efficiency of extraction) (Clough et al 2000).

Mathews et al (1988) estimated consumption to be 100 g of kava powder per week (occasional drinker), 310 g/week (heavy drinker) or 400 g/week (very heavy drinker).

5.2 Threshold intake levels for adverse effects

In a study by Clough (2003) examining the health and social impact of kava consumption in Aboriginal communities in Arnhem Land (approximately 6800 individuals), there was an increased frequency of skin rash, increased body mass index, increased GGT enzyme levels and increased lymphocyte counts in individuals with an average consumption level of 310–425 g kava powder/week. Overall, Clough (2003) suggests that average kava consumption in a community from 240 g kava powder/week up to 440 g kava powder/week is a level at which adverse health and/or social effects may begin to appear.

Based on the data from Clough et al (2000), this is equivalent to 3500-6440 mg kavalactones/day.

The available published and anecdotal information on kava beverage consumption indicates that the consumption level of kavalactones from recreational use of kava beverage can easily exceed the level of kavalactones in aqueous extracts used for the treatment of anxiety in a clinical setting (140–250 mg/day over 6 weeks), where no significant toxicity was observed (Sarris et al 2013b).

5.1 Limitations of the available data on consumption of kava beverage

- Further comprehensive information is needed on the level and frequency of consumption of kava beverage in South Pacific island communities.
- Further detailed information is needed on the concentration range of active components (kavalactones, alkaloids and flavokavins) and potential contaminants in kava beverage preparations.
- Further information is needed on the extent to which alkaloids and flavokavins are extracted by the aqueous solvent during preparation of kava beverage.
- Further data is needed upon which to estimate the levels of intake of kavalactones, alkaloids and flavokavins, as well as potential contaminants, and to establish a safe level of intake.

6 Conclusions and future directions

6.1 Evidence for harm associated with kava beverage

Kava beverage has been consumed in the South Pacific community for more than 2000 years and more recently in other nearby communities. During these times, there has been little documented evidence of adverse health effects associated with moderate consumption, indicating that if adverse health effects have occurred, the incidence is likely to be low.

On the other hand, there is clear evidence from documented and anecdotal reports that heavy consumption of kava beverage can result in the presence of scaly skin rash, weight loss, nausea, loss of appetite and indigestion. Other possible effects may include sore red eyes, laziness, loss of sex drive and general poor health. These effects are considered to be reversible upon cessation of kava use. An effect on cognition, which might be associated with the pharmacological activity of kava, has not been identified. No information is available on the potential for kava beverage consumption to impact on the incidence of chronic disease.

In all communities where kava beverage is used, there is a clear association between increased levels of the liver enzyme GGT and moderate-to-heavy kava beverage consumption. This effect is also reversible upon cessation of kava use and has been suggested to be associated with cholestasis rather hepatocellular damage, since no corresponding increase in transaminases ALT and AST, or in bilirubin, was observed. Clinical surveys in Aboriginal communities in northern Australia with a history of heavy kava use have not identified any evidence of kava-related, long-term liver damage.

There are three documented case studies of individuals presenting with hepatotoxicity following consumption of kava beverage. The lack of any evidence of kava beverage-related hepatotoxicity in communities with moderate-to-heavy kava consumption suggests that additional causative factors are involved in these three cases, such as quality of the kava raw material, co-medication with herbal products or drugs, genetic factors (enzyme polymorphism) or contamination of the kava during storage.

There are a number of other case studies of individuals (mainly in Europe) presenting with hepatotoxicity following consumption of kava medicinal products prepared from organic extracts of kava. Whether the etiology of the observed hepatotoxicity is the same following consumption of kava beverage and kava medicinal products is still unknown. The ongoing research on the causes of kava-related hepatotoxicity may assist in minimizing any further cases of hepatotoxicity in users of kava medicinal products, as well as in users of kava beverage.

On balance, the weight-of-evidence from both a long history of use of kava beverage and from the more recent research findings indicates that it is possible for kava beverage to be consumed with an acceptably low level of health risk; however, further studies are needed to define the parameters necessary to ensure safe use of kava beverage. These parameters include the selection of kava varieties, the method of kava beverage preparation, the compositional parameters for kava beverage, and the safe levels of kava beverage consumption.

6.2 Potential harm minimization strategies

The people of the South Pacific consider the traditional method of preparation and consumption of kava beverage islands to be safe and beneficial to the community. In recent decades, changes have occurred to the preparation methods for kava beverage, as well as to the level and frequency of consumption. Whether or not these changes have increased the potential for harm associated with kava beverage consumption is not known with any certainty. However, better understanding of the kava plant components, and their chemistry, toxicity and pharmacokinetics has led to a better understanding of some of the factors that impact on health outcomes of consumers of kava beverage. These factors include the following and should be part of a harm minimization strategy:

- **Choice of kava cultivar for kava beverage.** Traditionally, kava beverage has been prepared from peeled roots and rhizomes of the noble cultivar. The Vanuatu Act 2002 specifically prohibits the sale and export of non-noble or non-medicinal kava varieties – namely, two-day kava and *wichmannii* kava. The reason for peeling roots and rhizomes is not clear – possibly for organoleptic reasons. Noble kava has a relatively high content of kavain and a low capacity to inhibit P450 enzymes. There is a case for using noble kava only for kava beverage preparation.
- **Part of the plant used for kava beverage.** Analytical data indicate that the use of stem peelings and leaves in the kava material could introduce potentially toxic alkaloids and flavokavins. Anecdotal evidence suggests that some inappropriate use of stems and peelings has occurred when preparing kava beverages. There is a case for restricting the plant material for kava beverage preparation to peeled rhizomes and roots.
- **Quality of kava material used for kava beverage.** Postharvest storage of kava material in warm and humid conditions is a suitable environment for the growth of moulds, such as *Aspergillus* spp. which can produce aflatoxins. Direct evidence for the presence of aflatoxins is not available, but there is anecdotal evidence of poor quality kava material being used for beverage preparation. There is a case for better monitoring of kava storage conditions and additional surveillance for contaminants.
- **Excessive and frequent consumption of kava beverage.** There is abundant evidence that excessive and frequent consumption of kava beverage is associated with adverse health outcomes, even though many are reversible upon cessation of consumption. There is also data that indicates the pharmacological effects associated with recreational use of kava can be achieved at lower consumption levels than currently occur in some communities. There is a case for discouraging heavy consumption of kava beverage.

6.3 Further investigations to improve safety

6.3.1 General areas of investigation

To date, there have been three broad areas of investigation that have provided information leading to a better understanding of the nature of kava beverage and its potential to cause adverse health effects, namely:

- Analytical work on the kava plant and its chemical components. This research has identified the pharmacologically active ingredients, as well as ingredients that may cause potential toxicity.

- Studies on the mechanism of kava-associated hepatotoxicity, particularly as a result of consumption of kava medicinal products produced from organic solvent extracts of kava. This research has provided a better understanding of the compositional and other factors that may impact on the safe use of kava beverage.
- Studies in Aboriginal communities in northern Australia, where kava beverage has been widely consumed, often in excessive amounts, for many years. This research has more clearly identified potential adverse effects from kava beverage consumption.

6.3.2 Specific areas of investigation to address identified data gaps

The following specific investigative work is needed to address the data gaps identified in this report which impact on the safety assessment of kava beverage.

Kava varieties and beverage composition

- Improvements in agricultural and supply chain controls, to provide a consistent high-quality raw material for kava beverage preparation.
- Further development of analytical techniques capable of identifying the chemical components of the kava plant, as well as contaminants, to ensure the compositional control of kava beverage preparations.

Kava components and their properties

- Further data on the metabolism of kavalactones, alkaloid and flavokavins and their significance in the observed toxicity *in vitro* and *in vivo*.
- Further *in vivo* data to establish threshold levels for toxicity of the alkaloids and flavokavins.

Human health effects

- More systematic monitoring of the general health outcomes of regular consumers of kava beverage in order to better understand the range of potential health effects and to identify any susceptible subpopulations.
- Studies to examine the threshold intake for the observed adverse health effects.
- Studies to better understand kava-related hepatotoxicity.
- Studies on the potential impact of co-medication with herbal preparations and drugs.
- Detailed examination of any future cases of hepatotoxicity to determine exposure to kava components, contaminants and/or co-medication.

Consumption

- More reliable estimates of the level and frequency of consumption of kava beverage to determine the threshold level for adverse health outcomes.
- Analytical information of the range of concentration of kavalactones, alkaloids and flavokavins in kava beverage, as well as the concentration range of potential contaminants.

Appendix Levels of evidence

Table A.1 Ranking of studies to determine levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies (no control group), or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pretest/post-test.
Not ranked	Expert opinion

Source: (NHMRC 1999)

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