KAVA

A Human Health Risk Assessment

TECHNICAL REPORT SERIES NO. 30

FOOD STANDARDS AUSTRALIA NEW ZEALAND
June 2004

ISBN 0 642 34557 0
ISSN 1448-3017

Printed January 2005

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CONTENTS

SUMMARY

Kava is an intoxicating non-alcoholic water-based beverage prepared from the root of the plant *Piper methysticum*. Kava has a long history of use as a beverage in social ceremonies, particularly by South Pacific communities. Kava was also introduced into Australian Aboriginal communities, predominantly in Arnhem Land in the 1980s as an alternative to alcohol.

The kava plant (*Piper methysticum*) is a member of the pepper family. The term 'kava' is primarily used to refer to the kava plant and the drink prepared from the fresh or dried roots of that plant. The term 'kava', however, is also used to refer to other preparations such as powdered kava made up as the traditional drink and for use in medicinal products, and acetone or ethanol extracts of the plant for use in medicinal products.

Uses and preparation of kava

Kava is traditionally prepared from fresh or dried roots. Fresh material is chewed or ground until it is fine and fibrous, soaked in water, strained and drunk. Dried material is ground finely, wrapped in cloth and infused in water. The degree of dilution affects the potency of the kava preparation.

Extracts of kava are also used in complementary medicines/dietary supplements are generally prepared from the root, although more recently stem peelings have been used. These organic solvent extracts are generally standardised to contain approximately 30% kavalactones. The extracts of kavalactones are used primarily in complementary medicines such as capsules, powders/teas, liquids, and in combination products containing a variety of herbs and/or vitamins. Low alcohol tinctures used by herbal practitioners are prepared by macerating dried kava in a mixture of water and ethanol. Such extracts use 25% ethanol solvent for extraction and contain lower concentrations of kavalactones than the standardised preparations.

Chemical and pharmacological properties

The active ingredients of kava are kavalactones, pharmacologically active compounds naturally present in the kava plant. Nineteen kavalactones have been isolated from the kava root, of which six are major constituents (kawain, dihydrokawain, methsticin, dihydromethsticin, yangonin and demethoxyangonin).

Kava is known to have several actions; the primary action is as a mild sedative. Other actions include local anaesthesia of the mouth and tongue, analgesia, ocular effects, anticonvulsive effects and antimycotic properties. It has been reported as an effective anti-anxiety treatment.

The proportions and potency of kavalactones can vary according to the plant variety and also the method of preparation. The kavalactone content varies from 3% to 20% dry weight, even within the same subspecies. The effects of kava may also depend on how it is consumed - whether it is consumed with other drugs, food or alcohol or together with physical activity.

The absorption of kavalactones in the gastrointestinal tract is poor and variable. Kavalactones appear to be hydroxylated by the cytochrome P450 system and are eliminated by the kidneys and in the faeces.

Human health effects

Traditional kava beverage

The most common side effect of heavy kava consumption over an extended period is an ichthyosiform skin rash known as kava dermopathy or kani kani, characterised by flaky, dry skin with a yellowish discolouration of both the skin and nails. This condition is reversible when kava consumption is discontinued.

There have been no reported cases of liver toxicity associated with consumption of the traditional kava beverage. Reversible changes in liver function parameters have been reported with the traditional kava beverage, however, these are not indicative of acute liver inflammation. Other effects sometimes experienced by occasional kava drinkers include such as headache, loss of appetite, indigestion, and visual effects..

Reported adverse effects of heavy use of kava beverage include headache, chest pain, loss of appetite, loss of weight, impaired visual functions, indigestion, and loss of coordination. These effects were reversible following discontinuation of use. Cognitive and saccade (eye movement) function tests were performed on a group of current, ex and non-kava users among an indigenous population in northern Australia. No impairment was found in individuals who were currently heavy users, or those who had been heavy kava users in the past.

Kava extracts

There have been 82 case reports of liver toxicity world-wide associated with dietary supplement preparations containing kava extracts. In all of these reported cases, the kava had been prepared as a concentrated ethanol or acetone extract. The toxic effects ranged in severity from liver abnormalities to liver failure associated with liver transplantation and, in some cases, death. The elevated ALT levels noted in these cases of hepatotoxicity were not seen with the heavy consumers of the traditionally prepared kava drink.

The mechanism of kava extract-related liver toxicity is not clear but may be linked with the high kavalactone concentration in these preparations, the absence of glutathione (which is naturally present in the root of the kava plant) and individual variability in drug absorption, disposition and metabolism.

Constituents of kava

It has been noted that the aerial parts of the kava plant have been used for kava containing herbal preparations. The aerial parts of the plant contain piperidine alkaloids, the structure of which is similar to pyridine alkaloids which have been shown to be cytotoxic and can also affect DNA integrity. There is no direct evidence of piperidine alkaloids in kava dietary supplements at this time however, research has identified the potential for adverse effects should the aerial parts of the plant be used in preparations.

Dietary intake

Kava, as a food (i.e. raw, ground or dried root), is not widely used in Australia except in communities such as some Pacific Islander or Aboriginal communities. In the broad

community, the predominant use would be as a dietary supplement (New Zealand) or complementary medicine (Australia).

The weekly consumption of kava in the aboriginal population in Arnhem Land is similar to the consumption levels in Pacific Island populations, with heavy consumers drinking approximately 610 g/week.

Risk characterisation

The available data indicates that traditional kava beverage prepared from the root has a long tradition of safe use in the South Pacific Islands. It is compositionally different from kava products prepared by extraction using organic solvents.

While excessive consumption of the traditional kava beverage may lead to adverse health effects, such as kava dermopathy, there is no evidence that occasional use of kava beverage is associated with any long-term adverse effects, including effects on the liver.

In both Australia and New Zealand, the use of traditional kava beverage (ie, food use) is limited to a small proportion of the population, namely, the South Pacific Islander population and the Australian aborigines. The health impact of kava use in these populations is difficult to assess since, in some cases, the population may already have poor nutritional habits. The available data, however, does not suggest any specific health problems associated with moderate use of kava beverage.

KAVA

A Human Health Risk Assessment

INTRODUCTION

Traditional use of kava

Kava has a long history of use as a beverage in social ceremonies, particularly by South Pacific communities, and as a traditional medicine in several cultures. The drink is consumed for the sense of relaxation and tranquillity and to manifest a sociable attitude. Traditional medicinal uses include the treatment of gonorrhoea, syphilis, cystitis, boils, asthma, headache and urinary infections, and the induction of muscle relaxation and sleep. Kava was introduced into Australian Aboriginal communities, predominantly in Arnhem Land, in the 1980s as an alternative to alcohol. Kava is consumed by Pacific Islanders living in both Australia and New Zealand, but it is not used by the Maori people in New Zealand. Kava, in the *Australia New Zealand Food Standards Code*, means the plant, or a derivative of the plant, Piper methysticum, whether or not mixed with water.

Botanical characteristics

The kava plant (*Piper methysticum* Forst.) is a robust, fairly succulent, well-branching and erect, perennial shrub belonging to the Black pepper family *Piperaceae*. The generic name *Piper* comes from the Latin for "pepper", and the species name *methysticum* from the Greek meaning "intoxicant", thus *Piper methysticum* when translated into English means "intoxicating pepper". Other names used to refer to kava include: kava kava; kawa; ava; awa; yati; yagona; and yangona.

The leaves are heart shaped, pointed, smooth and green on both sides, being about 15 cm in length. The root becomes 5 to 8 cm thick at maturity at about 60 cm above the ground,. The plant reaches maturity about 3-5 years after planting and the plant is usually cultivated at around this age. The plant is usually about 2 to 2.5m tall when it is harvested (Singh, 1992).

Although kava is a dioecious species, only male plants are known and no fruits or seeds have been reported. The plant is cultivated through vegetative propagation.

Varieties

There are approximately 115 different cultivars of *Piper methysticum*, with 80 in Vanuatu, 7 in Tonga, 12 in Fiji, 5 in Samoa and 11 in Hawaii (SPC report, 2001). The Vanuatu government passed the *Kava Act* No. 7 of 2002, which identifies and categorises the different chemotypes or cultivars into: (i) Noblea kavas which have a long history of safe use as a traditional social beverage; (ii) medicinal varieties which have a long and proven history of beneficial properties amongst traditional Pacific herbalists; (iii) 'Tu Dei' kavas (two day intoxication) which, in the absence of direct requests, are banned as an export commodity; and (iv) 'Wichmannii' varieties (wild kava) which are also banned as an export commodity. Medicinal kavas are rarely used as a social beverage because they do not satisfy the kava

drinker's desire for the required physiological effect. The categorisation of kava varieties is at Appendix 1.

Geographical distribution

Kava is indigenous to the tropical Pacific Island region including Melanesia, Micronesia and Polynesia, with the exception of New Zealand, New Caledonia and most of the Solomon Islands (Singh, 1992). It thrives at altitudes of between 150m and 300m above sea level and grows well in stony ground.

Preparation of traditional kava beverage

The traditional kava beverage is prepared by soaking the pulverized root in a bowl of water and/or coconut milk solution and filtering the mix to produce a brew in a communal bowl. The kava is then drunk from a cup, sometimes a coconut shell. In parts of Vanuatu and Papua New Guinea today, and in other regions across the Pacific in the past, the root is pulverised through mastication, whereas the 'Fijian method' involves pounding the root rather than chewing it (Cairney et al. 2002). Alternatively, dried powdered kava is mixed with water and/or coconut milk solution and consumed from a cup.

Other uses of kava

Apart from the traditional uses of kava as a food, humans may be exposed to kava or components of kava through its use as a dietary supplement in New Zealand or as a complementary medicine in Australia. Such kava-containing products are commonly marketed for the treatment of anxiety, insomnia, premenstrual syndrome and stress.

Preparation of kava extracts

Commercial extracts of kava are generally prepared from the root, although more recently stem peelings have been used as raw material in kava products due to the high demand of the pharmaceutical industry. This extract is generally standardised to contain approximately 30% kavalactones compared to between 3-20% kavalactone content in root material. However various dosage forms with a range of indications are available. Organic solvents, primarily acetone or ethanol, are used as solvents for the extraction of kavalactones. Such extracts are used primarily in complementary medicines such as in capsules, powders/teas, liquids and in combination products that contain a variety of herbs and/or vitamins.

Kava used for medicinal purposes is a concentrated standardized extract designed to maximise extraction of the kavalactones that have been identified as the 'active constituent'. In the manufacture of the concentrated extract either ethanol (60% or above) or acetone (60% or above) and water is used as the solvent to obtain the maximum yield of kavalactones. Kavalactone standardized extracts are likely to contain only kavalactones and no proteins, amino acids, or sugars. Kava root extracted in: acetone yielded 100% kavalactones; 96% ethanol yielded 100% kavalactones; 25% ethanol yielded 15 % kavalactones; water yielded 2.97% kavalactones (Denham et al. 2002). Extraction rates also vary depending on the temperature at which the products are prepared.

Low alcohol tinctures

Tinctures used traditionally in Polynesia and by herbal practitioners are prepared by macerating dried kava in a mixture of water and ethanol. Such extracts using 25% ethanol/75% water contain up to 30 times fewer kavalactones than the concentrated standardised preparations. A wider range of other natural kava constituents is extracted.

CHEMICAL AND PHARMACOLOGICAL PROPERTIES

Chemistry

More than 40 compounds belonging to the classes of kavapyrones, alkaloids, steroids, chalcones, long-chained fatty acids and alcohols have been isolated and identified from *Piper methysticum* (Palmer et al. 1997). Fresh kava rootstock contains 80% water, while dried rootstock consists of approximately 43% starch, 20% fibre, 12% water, 3.2% sugars, 3.6% proteins, 3.2% minerals and 15% (3-20%) kavalactones (Lebot et. al., 1992). Among these compounds, kavalactones have been recognized as the constituents responsible for the reported biological activities in kava.

Kavalactones

Kavalactones are 4-methoxy-2-pyrones with phenyl or styryl substitutes at the 6^{th} position (Lebot et al., 1997). They are found in the lipid soluble portion. Total kavalactone content varies from 3% to 20% dry weight, even within the same subspecies. Different cultivars have different mixtures of kavalactones. The concentration of kavalactones is generally highest in the lateral roots (15%) and decreases progressively toward the aerial part of the plant (10% in the stump and 5% in the basal sterns (Lebot et al., 1992)).

Nineteen different kavalactones have been reported from the root extracts of kava, with the nineteenth reported in 2002 (Dharmaratne et al., 2002). The most abundant kavalactones are: demethoxyangonin, yangonin (achiral enantiomers); and chiral enantiomers (+)-dihydrokawain, (+)-kawain, (+)-dihydromethysticin, and (+)-methysticin. Structures of these kavalactones are at Appendix 2.

Duve and Prasad (1983) investigated the stability of kavalactones in powdered kava root stored in screw-capped glass bottles at room temperature for 22, 36 and 39 months. After 39 months of storage 93.9% of dihydrokavain, 81.6% of kavain, 72.4% of dehydrokavain, 54.9% of tetrahydroyangonin, 25.8% of dihydromethysticin, 32.1% of yangonin and 29.5% of methysticin had deteriorated in the powdered root samples.

Alkaloids

Two alkaloids were isolated from a methanolic extract of kava root and were identified as 1-cinnamoylpyrrolidine and 1-(*m*-methoxycinnamoyl)pyrrolidine (Achenbach and Karl, 1970). A third alkaloid, pipermethystine, was isolated from leaves by Smith (1983). Singh (1992) reported that this compound is also present in small amounts in the stems and roots of the plant. Dragull et al. (2003) report the presence of pipermethystine in the stem peelings and leaves. These authors also report 2 new piperidine alkaloids, namely, 3α, 4α-epoxy-5β-pipermethysticine and awaine.

Pharmacology and pharmacokinetics

Kava lactones have muscle relaxant, local anaesthetic, anxiolytic and anticonvulsive properties (Cairney et al., 2002). Drinkers of the traditionally prepared kava beverage in the South Pacific report a sense of relaxation and tranquillity, and the drink manifests a sociable attitude (Chanwai, 2000). Herbal preparations are marketed for the treatment of anxiety, insomnia, premenstrual syndrome and stress (Centres for Disease Control and Prevention, 2002). The traditional medicinal uses of kava include treatment of gonorrhoea, syphilis, and cystitis, induction of muscle relation and sleep (Ernst et al., 2001), treatment of boils, asthma, headache and urinary infections (Harvard Medical Health Letter, 2000).

Animal studies have established that kavalactones act to directly alter neuronal excitability through voltage-dependent ion (probably Na+) channels, causing a release of muscle tension. Inhibition of voltage-operated ion channels can account for the anaesthetic and anticonvulsive pharmacological actions of kavalactones (in Cairney et al., 2002).

Psychopharmacological effects of kava have also been reported and the mood-altering effects of kavalactones have been described as hypnotic (Schultes and Hoffman, 1992). The pharmacological properties of kavalactones are comparable to those of benzodiazepines, however, kavalactones bind very weakly to the gamma-aminobutyric acid ($GABA_A$) and benzodiazepine (Bilia et al. 2002). The authors propose that N-methyl-D-aspartate receptors and/or voltage dependent calcium channels may also be involved in the elementary mechanism of action.

Kavalactones are poorly soluble in water and their absorption in the gastrointestinal tract is poor and variable (Rasmussen et al., 1979), although it is remarkably rapid given their lipophilic nature (Malani, 2002). Kavalactones appear to be hydroxylated by the cytochrome P450 system and their metabolism may be enhanced by the presence of glutathione (Russmann et al., 2001; Tinsley, 1999; Whitton et al., 2002).

Kavalactones are eliminated in part by the kidneys (metabolites and unchanged pyrones) and in part by the faeces (unchanged pyrones). In humans, a complex mixture of metabolites and unchanged kavalactones have been identified in human urine following ingestion of kava prepared by the traditional method of aqueous extraction of *Piper methysticum* (Duffield et al., 1989).

HUMAN HEALTH EFFECTS

Traditional kava beverage

Skin conditions

The most commonly observed side effect of heavy kava consumption over an extended period is an ichthyosiform skin rash known as kava dermopathy or kani kani in Fijian (Lebot et al., 1992), characterised by flaky, dry skin with a yellowish discolouration of both the skin and nails. The onset typically begins in the face and moves in a descending fashion towards the feet, with subsequent dequarnation and cracking in a scaly pattern. In addition to the desquamating keratosis, palmar and plantar keratoderma andocular photosensitivity can also develop (Singh, 1992). Kava dermopathy should not be confused with skin conditions that

can be the result of acute allergic effects of *Piper methysticum*, which have also been reported in the literature (Suss and Lehmann, 1996).

The possibility of kava dermopathy being caused by niacin deficiency has been investigated (Ruze, 1990). The results of the study indicated that niacin deficiency was not responsible for the scaly rash and that the rash is characteristic of an acquired ichthyosis.

Liver effects

Clinical evidence of liver toxicity from traditional use in Pacific countries has not been documented. However, there have been no systematic studies into sub-clinical forms of liver toxicity in Pacific Island countries, so it is possible that mild toxicity could be present without having been recognised (Moulds and Malani, 2003). An early study of the health effects of kava use in Aboriginal communities documented consistent changes in liver function tests in heavy kava drinkers, characterised by elevated serum γ-glutamyl transferase (GGT) (Mathews et al., 1988).

A recent study confirmed these findings, with elevated levels of GGT and alkaline phosphatase (AP) activity in 61% and 50% of kava users respectively. GGT and AP levels generally returned to normal within 1-2 months of cessation of kava use (Cairney et al., 2003). Serum alanine aminotransferase (ALT) activity, however, was not raised in any kava drinkers. In contrast, ALT levels were high in cases of hepatotoxicity associated with herbal products. This suggests that elevated ALT levels provide evidence that liver function changes (increased GGT and AP) in users of aqueous kava extracts are reversible and begin to decrease after 1-2 weeks abstinence from kava. In this case no evidence for irreversible liver damage was found even in those who had used kava more or less continuously for up to 18 years.

General physical health effects

A survey conducted in Fiji examined the physical health of kava drinkers (Kava, 2001). Kava consumption was graded according to the classification system used in the study on the impact of kava use on Australian Aborigines, as follows: Non-user; occasional user (100g/week); heavy user (310g/week); and very heavy user (440g/week) (Mathews et al., 1988). The occasional user experienced little side effects: 3% experienced headaches; 10% experienced indigestion; and 7% experienced lack of coordination. Increasing health problems were associated with heavy and very heavy use: 78% of very heavy users and 65% of heavy users experienced kani kani; 72% of very heavy users and 57% of heavy users experienced watery eyes. Other symptoms experienced by heavy and very heavy users included: headache; chest pain; loss of appetite; indigestion; and loss of coordination.

The health status of 39 kava users and 34 non-users in a coastal Aboriginal community in Arnhem Land was assessed in 1988 (Mathews et al., 1988). Kava users were more likely to complain of poor health and a 'puffy' face and were more likely to suffer from kani kani. Very heavy users were 20% underweight and their levels of γ-glutamyl transferase were increased greatly. Albumin, plasma protein, urea and bilirubin levels were decreased in kava users, and high-density lipoprotein cholesterol levels were increased. Kava users were more likely to show haematuria, and to have urine which was poorly acidified and of low specific gravity. The use of kava was also associated with an increased red-cell volume, with a decreased platelet volume and a decreased lymphocyte count. Shortness of breath in kava

users was associated with an altered resting electrocardiogram suggestive of pulmonary hypertension.

Gastric effects

Use of kava has been shown to be associated with gastritis, an inflammation of the stomach. Kava was also shown to have synergistic effects when used with alcohol. Kava users aged 15-24 years were found to have an increased risk of developing gastritis than others (Ngirasowei and Malani, 2002).

Visual Effects

Visual functions have been measured (in one subject) following consumption of the kava beverage. A reduced near point of accommodation and convergence, an increase in pupil diameter and disturbance to the oculomotor balance were observed. No changes were recorded in visual or stereoacuity, or ocular refractive error (Garner and Klinger, 1985).

Melioidosis

Kava consumption has been implicated as a risk factor for Melioidosis, or infection with *Burkholderia pseudomallei,* in the Northern Territory. Kava consumption occurred in 8% of the subjects with Melioidosis (Currie et al., 2000). Melioidosis is a common cause of community-acquired pneumonia in the tropical north of the Northern Territory and cases occur in the wet season.

A recent cross-sectional study within a kava using East Arnhem Land Aboriginal community established that kava use (both current and recent users) was associated with lower lymphocyte counts with 51% of users below the normal range (personal communication from Alan Clough). The authors suggest a possible kava related immunological predisposition to certain infections such as melioidosis.

Social effects

The survey into the physical health of kava drinkers in Fiji (Kava, 2001) also investigated the social and economic impact of kava drinking on the families of kava drinkers and employment performance.

Wives of kava drinkers interviewed indicated loss of libido and impotence. Some heavy consumers spent as much as 20% of household income on kava, putting an additional financial burden on the family. It was also noted that the children of heavy kava drinkers perform poorly at school due to lack of proper educational materials and parental supervision. Some employers stated that because of heavy consumers of kava tended to be irregular and not punctual for work, they were against the consumption of kava by their employees. Driving an automobile under the influence of kava was also noted as a concern.

Cognitive and saccade function

There is some evidence to suggest that kava use is associated with brain impairment. There have been case reports of severe choreoathetosis (involuntary movements) following kava use (Schelosky et al., 1995; Spillane et al., 1997) and an association has between heavy kava

use and seizures either from toxicity or on withdrawal has been raised (Clough et al., 2001). Cognitive tests and saccade function (eye movement) tests were performed on a group of current, ex, and non-kava users among an indigenous population in northern Australia, with some of the current kava users being identified as heavy users (Cairney et al., 2003). No impairment in cognitive or saccade function was found in individuals who were currently heavy kava users or those who had been heavy kava users in the past. No cognitive indicators of dysfunction were found that may precede, or lead to, the choreoathetotic movements reported among kava users in the literature, suggesting that these involuntary movement reactions occur from acute rather than chronic changes.

Kava extracts

Liver Toxicity in humans

There have been reports of liver toxicity associated with use of kava extracts, initially from Switzerland and Germany and later from other western countries, including Australia. In November 2001, the German health authority *Bundesinstitut für Anrzneimittel und Medinzinprodukte*, or German Federal Institute for Drugs and Medical Products (BfArM) published evidence that suggested an association between kava consumption and liver damage in 24 case studies reported from Germany and Switzerland. These included one death and three liver transplants. The case reports from the BfArM include all three of the main forms of acute liver damage that can result from adverse drug reactions: necrosis; drug-induced hepatitis; and cholestatic hepatitis (Hodgson and Levi, 1997).

However, a detailed review of the original cases published by BfArM, particularly by German industry, suggested that a causal link between kava and liver toxicity was not established. Although kava was implicated in causing these adverse effects, the evidence in some cases was compounded by other factors including the concomitant use of drugs also linked with liver problems (e.g. alcohol), and previous history of compromised liver function. Detailed information on the patients' history, co-medication, consumption of alcohol and other particulars were missing (Mills and Steinhoff, 2003).

At the end of 2002, the UK Medicines Control Agency and Committee on Safety of Medicines (MCA/CSM) had compiled a total of 68 cases of liver toxicity associated with kava consumption. Of these cases, the association between kava and liver damage was judged to be 'probable' in 14 cases (including 3 liver transplants) and 'possible' in 30 others, the remainder could not be assessed.

Since these case studies were published, the acute liver failure and death of an Australian woman has been described which was associated with the use of a preparation containing *Piper methysticum* and passionflower (*Passiflora incarnate*) (Gow et al., 2003). The woman received a liver transplant after she presented with jaundice and a liver biopsy showed non-specific severe acute hepatitis with pan-acinar necrosis and collapse of hepatic lobules. The liver transplantation was unsuccessful. Histological examination of the explanted liver confirmed the presence of massive hepatic necrosis. There are now a total of 82 cases of liver toxicity associated with kava-containing medicines internationally, including 4 deaths.

While not conclusive, there is a reasonable possibility of a causal relationship between consumption of kava-containing products and hepatotoxicity. Many of the case reports described kavalactone doses in the range of 180-240 mg/day, although there are reports at

doses as low as 60-70 mg/day, which is less than the previous maximum recommended daily dose of 250 mg/day for kavalactones in listed medicines. All but one of the reports described a duration of use of 2 months or more.

Factors affecting kava extract-induced liver toxicity

While the exact causative factors in kava extract-induced liver toxicity remain unknown, possible contributing factors are discussed below.

Kava constituents

Kava contains a wide range of chemical components as well as the active constituents, kavalactones. These other components of plants can affect the stability, solubility and bioavailability of the active components (Denham et al., 2002). The use of non-traditional methods of preparation can change the component profile, which may potentially affect the toxicity of the kava preparation. Different extraction techniques and preparation methods may result in extracts where the presence and relative concentration of each kavalactone is altered considerably compared to the kava root and the traditionally prepared kava beverage.

Research currently in progress is assessing the profiles of kava constituents with non-traditional extraction methods and the hepatotoxicity of kava constituents using Hep G2 cells and human hepatocytes with different markers, and investigating different solvent extraction techniques. Preliminary results indicate an altered profiles of kava constituents using non-traditional extraction methods and that traditional methods of preparation in water are considerably safer than kava prepared in organic solvents (ethanol, acetone and hexane) (personal communication from Professor Stephen Myers[1]).

Absence of glutathione in kava extracts

Whitton et al. (2002) suggest that extraction procedures using high concentrations of either acetone or ethanol in order to maximize and standardize kavalactone content are likely to contain only kavalactones and no protein, amino acids or sugars. The authors identified glutathione in both aqueous extract and 25% ethanol extract while negligible amounts of glutathione are present when higher concentrations of ethanol or acetone are used. It is postulated that glutathione may have an important role in the metabolism of kavalactones.

Kavalactones are normally metabolised by lactone hydrolases, the activity of which is increased by the presence of glutathione. Glutathione occurs naturally in kava root in approximately the same concentration as kavalactones. In contrast, standardised extracts contain negligible amounts of glutathione while the kavalactone concentration is concentrated some 30-fold (Denham et al., 2002). Glutathione is not soluble in ethanol extractions above 50% (Merck Index, 1996).

It is postulated that the ring-opened kavalactones may bypass the phase I enzymatic detoxification pathway in the liver thus not causing any depletion of intracellular glutathione in the hepatocyte (Denham et al., 2002). Glutathione is required for phase II conversion of kavalactones into excretable waste products. The high concentration of kavalactones

[1] Australian Centre for Complementary Medicine, Education and Research, a joint venture of the University of Queensland and Southern Cross University.

introduced by concentrated standardised extracts has the potential to saturate the enzymatic detoxification pathways by depleting stores of glutathione and resulting in undue stress on the liver.

Glutathione is normally present in adequate amounts in most cells in the body but some individuals have a genetic deficiency (Lomaestro and Malone, 1995). In these cases, high doses of kavalactones will lead to rapid depletion in glutathione levels and result in free lactone exposure in the hepatocytes and potentially tissue damage (Zheng et al., 2000). Oral glutathione supplementation has been shown to correct the deficiency (Kidd, 1997).

In summary, it appears that the high kavalactone content in concentrated standardised extracts and the absence of the glutathione (which is naturally present in the root of *Piper methysticum*) may deplete the endogenous reserves of glutathione in the hepatocytes, which could contribute to toxicity. Individuals with glutathione deficiency may be at increased risk of depletion of glutathione stores if a high concentration kavalactone extract is taken.

Genetic polymorphism in drug metabolizing enzymes

Inter-individual variability to drug response ascribed to genetic differences in drug absorption, disposition, metabolism or excretion can be a factor in adverse drug reactions. The most studied variability is genetic polymorphism in drug metabolizing enzymes in the hepatocyte. Cytochrome P450 enzymes are responsible for phase I (oxidation, reduction and hydrolysis) metabolism of a wide number of compounds and for transforming lipophilic drugs into more polar compounds that can be excreted by the kidneys (Denham et al., 2002).

CYP2D6 is one of the most extensively studied genetic polymorphisms involving cytochrome P450 enzymes. Individuals may be poor (slow) metabolisers, intermediate, extensive (fast) or ultrafast metabolisers. In a Caucasian population 7-9% of individuals are homozygous deficient in CYP2D6 and are, thus, poor metabolisers, while the incidence of CYP2D6 deficiency in Asian populations is 1% (Poolsup, 2000), and in a sample of 100 persons of pure Polynesian decent, there was no CYP2D6 deficiency (Wanwirolmuk et al., 1998). A poor metaboliser is at risk of having adverse effects to drugs if their rate of biotransformation is inadequate. In some of the cases of liver toxicity reported by BfArM, the individuals were CYP2D6 deficient.

When CYP2D6 deficiency occurs, use of kava products with enhanced kavalactones has the potential to affect the liver as a result of slow metabolism, particularly when a concomitant medication or alcohol are also taken.

Other kava extract-induced adverse reactions in humans

Aside from liver abnormalities or toxicity, adverse effects attributed to kava extracts include: gastrointestinal complaints; restlessness; mydriasis; allergic skin reactions; dermatomyositis (Ernst et al., 2001); visual accommodation disorders; pupil dilation; and disorders of oculomotor equilibrium (Singh and Blumenthal, 1997). Toxic doses (several times the therapeutic dose of approximately 70 mg of kavalactones three times daily) can cause progressive ataxia, muscle weakness, and ascending paralysis (Spillane et al., 1997). Chronic heavy consumption can cause kani kani, or kava dermopathy, previously described. All of these symptoms are reversible and disappear within several weeks of discontinuation of kava extract.

Various clinical trials have been carried out to determine whether kava is an effective symptomatic treatment for anxiety and a number of these trials have reported adverse effects. A Cochrane review by Pittler and Ernst (2003) reviewed 11 clinical trials. Eight of the 11 clinical trials reviewed reported adverse events experienced by patients receiving kava extract. The most frequent reports were stomach complaints, restlessness, drowsiness, tremor, headache and tiredness. Six of the trials reviewed measured liver enzyme levels, and these did not demonstrate hepatotoxicity. Bilia et al. (2002) reviewed nine clinical trials and found that three of these trials reported no adverse events, while the other six studies reported gastrointestinal symptoms, tiredness, restlessness, tremor and headache, but the authors point out that the number of patients reporting the complaints was similar in the placebo groups.

Contraindications

Several pharmacological effects of kava have been observed, including platelet inhibition, difficulties with visual accommodation and photosensitivity, and possible dopaminergic antagonist activity. Recommendations have been made that kava not be used in conjunction with anticoagulants, antiplatelets or antipsychotics because of potential additive effects, or in patients with Parkinson's disease, apparently because of dopamine antagonist (MacKinnon, 2000; Meseguer et al., 2002). Kava may also enhance the effects of other centrally acting agents such as benzodiazepines and alcohol (Almeida and Grimsly, 1996).

Cautions on use

Use of kava during pregnancy or lactation has been cautioned since kavalactones may be present at concentrations, which would likely have an effect on the foetus or infant (Brinker, 1998). Despite this caution, it has been reported that Pacific Island women have, at least in the past, drunk kava during pregnancy in the hope that it will give an easy labour and produce a fine child, and also during lactation to induce milk flow (Frater, 1952).

Use of kava in patients with endogenous depression should be avoided, since it has been speculated that the herb may increase these patients' risk of suicide (Pepping, 1999). Use of kava by children is generally not recommended. In some patients therapeutic doses of kava can affect motor function and may impair the ability to operate machinery, including driving a car.

Piperidine alkaloids from kava plant stem and leaves

The major plant parts in traditional use of kava have been the rootstock and roots although leaves and branches have been used in folk medicine primarily for topical applications (Cambie and Ash, 1994). There are suggestions that in recent years, stem peelings have been included as raw material in kava products due to the high demand by the pharmaceutical industry. Also, kava leaf tea has recently appeared in health food stores in Hawaii (Dentali, 1997).

Piperidine alkaloids in *Piper methysticum* and their potential activities on human physiology were investigated by Dragull et al. (2003). Pipermethysticine (**1**), 3α, 4α-epoxy-5β-pipermethysticine (**2**) and awaine (**3**) have been isolated from the aerial parts of Piper methysticum. **1** was concentrated in the stem peelings and leaves, **2** and **3** are new alkaloids with **2** only found in one cultivar of those examined, and **3** occurred primarily in young

leaves of all cultivars investigated. The authors note that while the effects of these piperidine alkaloids on human physiology are unknown and their possible toxicity on the liver has not been investigated, however, several pyridine alkaloids with structures similar to **1** have been shown to be cytotoxic (Duh and Wu, 1990; Duh et al., 1990). Furthermore, **1** decomposes on standing at room temperature due to hydrolysis of the amide, to give 3-phenylpropionic acid and the dihydropyridone **4** (Smith, 1979). Compounds **1** and **4** exhibit structural features of 2,5-dihydroxypyridine, which has been shown to affect DNA integrity in vitro due to its ability to redox cycle (Kim and Novac, 1990). None of the three piperidine alkaloids were detected in the commercial root powders from Fiji, Tonga or Hawaii in the analyses by the authors (Dragull et al, 2003). The use of the alkaloid-rich stem peelings is generally avoided by the Pacific peoples. Dragull et al. (2003) do not have any direct evidence of the presence of piperidine alkaloids in kava dietary supplements however, caution is advised on using the aerial plant parts for human consumption.

Animal toxicity data on kavalactones

Animal toxicity studies on kava have been limited mainly to acute and subchronic studies in rats and mice. Toxicology studies in animals indicate that the oral LD_{50} is between 800 and 1000 mg/kg bw for the different kavalactones investigated. An NIH report on Kava Chemistry and Toxicology (1998) summarised acute toxicity LD_{50} values for 6 major kavalactones that were obtained from the Registry of Toxic Effects of Chemical Substances. These values are shown in Table 1. There are no long-term toxicity studies of kava in animals available and no information on its genotoxic potential.

Table 1: LD_{50} (mg/kg) values for kavalactones (NIH Report, 1998)

Species (route)	Kavain	Dihydro-kavain	Methysticin	Dihydromet-hysticin	Yangonin	Demethoxy-yangonin
Mouse (oral)	1130	920	-	1050	>1500	>800
Mouse (ip)	420	325	530	420	>1500	>800
Mouse (iv)	69	53	49	-	41	55
Dog (ip)	-	>200	-	>200	-	-
Cat (ip)	-	>250	-	-	-	-
Rabbit (ip)	-	>350	-	300	-	-

DIETARY INTAKE

Kava (i.e. raw, ground or dried root) is not widely used as a food in Australia or New Zealand except in some Pacific Islander communities or Aboriginal communities in Australia. In the broad community, the predominant use would be as a complementary medicine in the form of an extract. Kava is not permitted as an ingredient in other foods.

Weekly consumption of kava in the Arnhem Land region of the Northern Territory appears similar to the consumption levels in Pacific Island populations. Kava is not listed as a food in the 1995 National Nutrition Survey. The following information on import data, consumption data and kavalactone content provides some indication of the dietary exposure.

Import data

Some data on the extent of kava consumption in the Northern Territory is available. Total kava sales to Aboriginal communities were reported for 1986 (3,688 kg), 1987 (7,216 kg),

1988 (11,165 kg), 1989 (23,893 kg), 1990 (23,077 kg), 1991 (19, 235 kg) and 1992 (10 months only) (15,263 kg). Total kava imports were estimated in 1998 to be 23,405 kg, imported mainly through NSW, Queensland and Victoria. Estimates from imported food data are less reliable because only a small fraction of kava imports are referred to Australian Quarantine Inspection Service for testing. No data is available on consumption in New Zealand.

Consumption data

Early studies (1986-87) reported a prevalence of kava use of 42% of the population and more recently 56% and 66% with a greater proportion of males (from 53% to 71%) than females (from 6% to 51%.

Recent changes in the diversity and patterns of substance use, including kava, in eastern Arnhem Land was recently investigated, with consumption measured in both 1999 and 2000 (the samples surveyed differed). In 1999 46% of males and 18% of females were kava users, while in 2000, 52% of males and 11% of females were kava users. However, when comparing kava use in the Miwatj region only, men's kava consumption had declined. During this time, the estimated size of the informal kava trade in Arnhem Land has dropped from $6-8 million in 1997-98 to $5 million in 1999 to $3.8 million in 2000.

Kavalactone dose from traditionally prepared beverage

Clough et al. (2000) estimated the quantity of kavalactones consumed by Aboriginal kava drinkers. Total kavalactone content of kava powder may be 10-15% (average 12.5%) of dry weight depending on factors such as plant growth conditions and age of plant at harvesting. The effectiveness of kavalactone extraction is not standardised and is subject to social-contextual as well as physical variations in the substance. The efficacy of extraction of the active constituents in infusions of 33 g/L of kava powder in water is from 81% to 83%. The major active constituents all seem to deteriorate at varying rates in storage. In one hour each person drank approximately 670 mL (633-715 mL) (i.e. just under 7 cups of 100 mL) of liquid containing 37 g (34 -39 g) of kava powder. Given that extraction efficiency is likely to be around 82%, approximately 3800 mg kavalactones would be consumed.

NUTRITIONAL IMPACT

Informal reports indicate that malnutrition is higher amongst kava users than non-users in some communities. This appears to be a result of kava abuse where some users fail to maintain adequate intake of other foods rather than a consequence of kava ingestion per se. There are no known nutritional problems associated with the moderate use of kava.

The possibility of kava dermopathy (skin condition also referred to as kani kani) being caused by a niacin deficiency was investigated. The results of the study indicated that niacin deficiency was not responsible for the scaly rash, which is characteristic of an acquired ichthyosis (Ruze, 1990).

Assessing the nutritional impact of kava consumption is difficult since the background diet of consumers is often compromised and may have been for a number of years. One research group has investigated kava use and the biomarkers of dietary quality and coronary heart disease and nutritional status in Australian Aborigines in Arnhem Land. Skin fold thickness,

body mass index and body fat were decreased in kava users compared with non-kava users. Total and LDL cholesterol were elevated in kava users compared to both former users and those who had never used kava. HDL cholesterol was higher in current users versus never users. Plasma levels of carotenoids were extremely low compared to other populations (e.g. non-Aboriginal populations) but did not vary with kava usage. High plasma homocysteine levels across all groups were consistent with low dietary folate intake and increased coronary heart disease risk (personal communication from Alan Clough[2]).

RISK CHARACTERISATION

The available data indicates that traditional kava beverage prepared from the root has a long tradition of safe use in the South Pacific Islands. It is compositionally different from kava products prepared by extraction using organic solvents.

Studies in Fiji indicate that occasional users experienced little side effects – there were low incidence reports of headache, indigestion and lack of coordination. For heavy users over an extended period, the most common side effect of heavy consumption is a skin rash known as kava dermopathy, characterised by flaky, dry skin with a yellowish discolouration of both the skin and nails. Other reported adverse effects of heavy use include headache, chest pain, loss of appetite, loss of weight, impaired visual functions, indigestion, and loss of coordination. These effects were reversible following discontinuation of use.

The cases of liver toxicity associated with kava extracts observed in Western countries in recent years appear to be associated with consumption of kava-containing dietary supplements only. There have been no cases of diagnosed liver toxicity associated with consumption of the traditional kava beverage although reversible increases in liver enzyme activity have been observed. The mechanism of kava extract-related liver toxicity is not clear but may be linked with the high kavalactone concentration in these preparations, the absence of glutathione and the different metabolic pathways that are utilized.

In both Australia and New Zealand, the use of traditional kava beverage (ie, food use) is limited to a small proportion of the population, namely, the South Pacific Islander population and the Australian aborigines. The health impact of kava use in these populations is difficult to assess since, in some cases, the population may already have poor nutritional habits. The available data, however, does not suggest any specific health problems associated with moderate use of kava beverage.

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Appendix 1

Kava varieties as classified in the *Vanuatu Kava Act* No. 7 (2002)

Table 1: Nobles kava

Variety	Origin	Variety	Origin
Melomelo	Ambae	Silese	Malekula
Asiyai Biyaj	Aneityum	Melmel Borogu Sese	Pentecost
Paliment Miela Olitao	Emae	Urukara Bir Sul Bir Kar Palarasul Palasa Poivota	Santo
Kelai	Epi	Pia Ahouia Leay Amon	Tanna
Ge wiswisket Gegusug	Gaua	Puariki Pualiu	Tongoa
Borogoru	Maewo	Naga miwok Ge vemea	Vanua Lava

Table 2: Medicinal kava

Variety	Origin	Variety	Origin
Mologugei	Ambae East	Meihang	Paama
Ngwangaru	Ambae East	Teiha	Paama
Bisuiboe	Ambae West	Toh	Paama
Mavute	Ambae West	Borogu tememe	Pentecost Central
Ketche	Aneityum	Bukulit	Pentecost Central
Mokom	Aneityum	Borogu temit	Pentecost Central
Riki	Aneityum	Borogoru maita	Pentecost North
Oleikaro	Emae	Borogoru memea	Pentecost North
Pualapa	Emae	Vabugai	Pentecost North
Ulutao	Emae	Bugolita	Pentecost North
Bagavia 1	Epi	Gorogoro entepal	Pentecost South
Bagavia 2	Epi	Gorogoro entemet	Pentecost South
Meoler	Epi	Kerakra	Pentecost South
Pakaewa	Epi	Tamaevo	Pentecost South
Purumbue	Epi	Aigen	Tanna Central
Tinbokai	Epi	Mita	Tanna Central
Liki	Erromango	Saosao	Tanna Central
Pic	Erromango	Tuan	Tanna Central
Pore	Erromango	Kiskisnian	Tanna Central
Bumalotu	Maewo North	Yalon	Tanna Central
Hawerara	Maewo North	Awor	Tanna Central
Malokai	Maewo North	Malamal	Tanna Central
Raimelmelo	Maewo North	Paama	Tanna Central
Resres	Maewo North	Wapil	Tanna Central
Maloglelab	Maleluka North East	Pusan	Tanna South East
Maloglaslas	Maleluka North East	Marangmarang	Tanna South East
Nemleu	Maleluka North East	Kokoffe	Tanna South East
Tafandai	Maleluka North West	Kowariki	Tanna South East
Baan	Maleluka North West	Malamala	Tanna South East
Daou	Maleluka North West	Paama	Tanna South East

Tapoka	Malo	Ewo	Tongoa
Hig	Mere Lava	Metolei	Tongoa
Lab	Mota Lava	Tau	Tongoa
Nagame	Mota Lava	Nimau	Tongoa
Loa	Nguna	Bualap	Tongoariki
Malakesa	Nguna	Buarik	Tongoariki
Pilake	Nguna	Milake	Tongoariki
Nol	Ureparapara	Ngako	Ureparapara
Gemime	Vanua Lava	Ngasien	Ureparapara
Ranranre	Vanua Lava		

Table 3: Two days kava

Variety	**Origin**	**Variety**	**Origin**
Gawoboe	Ambae East	Rongrongwul	Pentecost Central
Ronriki	Ambae East	Abogae	Pentecost Central
Tarivoravora	Ambae East	Fabulakalaka	Pentecost Central
Valeiboe	Ambae East	Lalahk	Pentecost Central
Qoro	Ambae East	Renkaru	Pentecost Central
Sulusulu	Ambae East	Sese	Pentecost North
Ganono	Ambae East	Vabulagaga	Pentecost North
Garaeto	Ambae East	Rara	Pentecost North
makura	Ambae East	Baraeto	Pentecost North
Mologomavute	Ambae East	Rabualeva	Pentecost North
Tarimvute	Ambae East	Kavik	Pentecost North
Taritamaewo	Ambae East	Mangaru	Pentecost North
Memea	Ambae West	Rongrongvula	Pentecost North
Mindo	Ambae West	Sese Iaralara	Pentecost North
Rogorogopula	Ambae West	Tarivarusi	Pentecost North
Tolu	Ambae West	Sese	Pentecost South
Tari	Ambae West	Takere	Pentecost South
Tariporo	Ambae West	Lalahk	Pentecost South
Laklak	Ambrym North	Tarivarusi	Pentecost South
Apeg	Aneityum	Marino	Santo Central
Nisginekrai	Aneityum	Merei	Santo Central
Tchap	Aneityum	Fock	Santo Central
Nidinolai	Aneityum	Malogro	Santo Central
Metche	Aneityum	Thyei	Santo Central
Yag	Aneityum	Tudey	Santo Central
Nakasara	Emae	Yevoet	Santo Central
Meawmelo	Epi	Palavoke	Santo South West
Lo	Epi	Pirimerei	Santo West
Mage	Epi	Aheyoke	Santo South West
Kaviui	Epi	Palisi	Santo West
Mitiptip	Epi	Woko	Santo West
Vila	Epi	Awke	Tanna Central
Wari	Epi	Fare	Tanna Central
Vip	Epi	Kalawas	Tanna Central
Meawlake	Epi South	Tikisikis	Tanna Central
Meawmeia	Epi South	Apin	Tanna Central
Avia	Erromango	Gnare	Tanna Central
Vila	Erromango	Fiji	Tanna Central
Gumaito	Maewo North	Pentecost	Tanna Central
daumangas	Maewo North	Rhowen	Tanna Central
Rairairegi	Maewo North	Tudey	Tanna Central
Tariparaus	Maewo North	Vila	Tanna Central
Tufagi	Maewo North	Apol	Tanna South East
Tumpuinakapmato	Maewo North	Kowarwar	Tanna South East

Tarihani	Maewo North	Ring	Tanna South East
Rongrongvula	Maewo South	Tapuga	Tanna South East
Tarivarusi	Maewo South	Pentecost	Tanna South East
Vabu	Maewo South	Tudey	Tanna South East
Mologubanga	Maewo South and Pentecost North	Vila	Tanna South East
Malokrok	Maleluka North East	Oleikaro	Tongoa
Pade	Maleluka North West	Raro	Tongoa
Malatuwas	Maleluka North West	Nakasara	Tongoa
Nalimliune	Maleluka North West	Maet	Tongoariki
Poua	Maleluka North West	Elot	Tongoariki
Vasa	Malo	Lulu	Tongoariki
Roge	Malo	Hin	Torres
Namtemlao	Mota Lava	Hinyanie	Ureparapara
Nipunstaban	Mota Lava	Ngawo	Ureparapara
Tarivarus	Mota Lava	Tarivarus	Ureparapara
Take	Pentecost Central	Gelava	Vanua Lava
Tabal	Pentecost Central	Nambalao	Vanua Lava
Mologubanano	Maewo South and Pentecost North	Tarvarus	Vanua Lava
Malmalbo	Pentecost Central	Wisabana	Vanua Lava

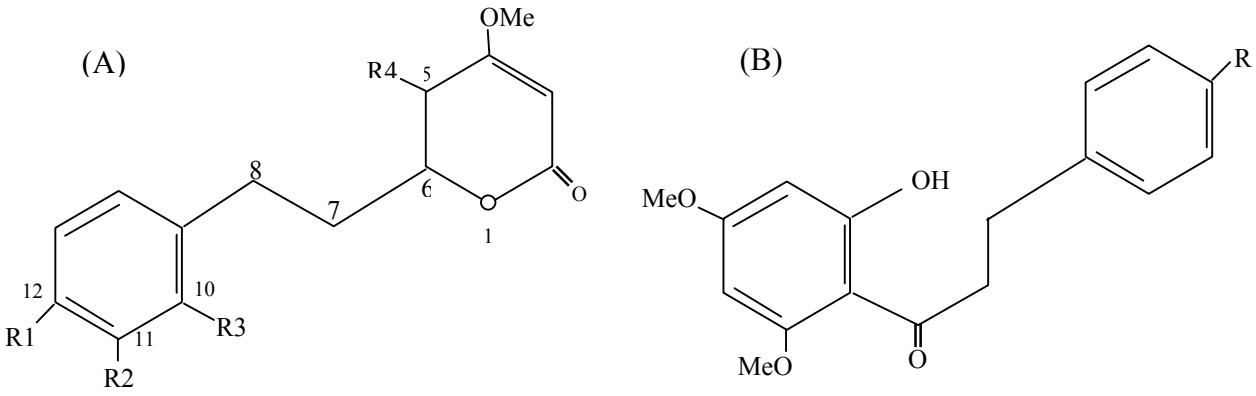
Table 4: Wichmannii kava

Variety	**Origin**	**Variety**	**Origin**
Vambu	Ambae East	Vambu	Vanua Lava
Tchai	Aneityum	Giemonlagakris	Vanua Lava
Bamboo	Maewo North	Bogong	Pentecost Central
Buara	Maewo North	Mele liap	Pentecost Central
Tangurlava	Maewo North	Sini Bo	Pentecost Central
Kau	Tongoa	Bogongo	Pentecost North

Appendix 2

Kavalactone structures

(A) Kavalactones and (B) Chalcones present in Kava root (Xian-guo He *et al*., 1997)



Kavalactone	R1	R2	R3	R4	C5-C6	C7-C8	MW
11-Hydroxy-12-methoxydihydrokavain	OMe	OH	H	H	-	-	278
7,8-Dihydro-5- hydroxykavain			H	βOH	=	-	248
11,12 Dimethoxydihydrokavain	OMe	OMe	H	H	-	-	292
Methysticin	OCH_2O		H	H	-	=	274
Dihydromethysticin	OCH_2O		H	H	-	-	276
Kavain		H	H	H	-	=	230
7,8-Dihydrokavain		H	H	H	-	-	232
5,6-Dehydromethysticin	OCH_2O		H	H	=	=	272
5,6-Dehydrokavain (Demethoxyyangonin)		H	H	H	=	=	228
Yangonin	OMe	H	H	H	=	=	258
5,6,7,8-Tetrahydroyangonin	OMe	H	H	H	-	-	262
5,6-Dihydroyangonin	OMe	H	H	H	-	=	260
7,8-Dihydroyangonin	OMe	H	H	H	=	-	260
10-Methoxyyangonin	OMe	H	OMe	H	=	=	288
11-Methoxyyangonin	OMe	OMe	H	H	=	=	288
11-Hydroxyyangonin	OMe	OH	H	H	=	=	274
Hydroxykavain	H	H	H	OH	-	=	246
11-Methoxy-12-hydroxydehydrokavain	OH	OMe	H	H	=	=	274

Chalcones	R	MW
Flavokavain A	OMe	314
Flavokavain B	H	284
Flavokavain C	OH	300