FOOD STANDARDS Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

6 October 2022
216-22

Supporting document 1

Risk and technical assessment

12 month review of Proposal P1057

Executive summary

In late 2021 and early 2022, Food Standards Australia New Zealand (FSANZ) prepared urgent proposal P1057 – Review of kava standard. The purpose of the proposal was to consider whether the kava provisions in the Australia New Zealand Food Standards Code (the Code) needed to be amended following the Australian Government's decision to allow the commercial importation of kava from 1 December 2021 under Phase 2 of the Pacific Step-up Kava Pilot.

In March 2022 the FSANZ Board approved variations to the Code in the Final consideration report of the urgent stage of the P1057 proposal. The *Food Standards Australia New Zealand Act 1991* (the Act) provides that FSANZ must, within 12 months of notification of the approved draft variation, undertake a full assessment of that variation. This risk and technical assessment complements the initial risk and technical assessment prepared for the urgent stage of Proposal P1057, and considers the available evidence on safe kava beverage consumption to inform FSANZ assessment of the draft variation to the Code.

The kava plant (*Piper methysticum* G. Forst) is an integral part of the dynamic and evolving cultural practices of many Pacific peoples. Historically, kava beverage in Pacific communities has been prepared by cold water extraction from fresh or dried roots of the kava plant, to produce a brew in a communal bowl. The available evidence suggests that kava beverage in Australia and New Zealand is consumed in line with this historical method of preparation.

Kava beverage, containing psychotropic substances, is consumed to promote a sense of relaxation, tranquillity and a sociable attitude. Ongoing consumption of high quantities of kava beverage (240 - 440 g/week of dried kava powder or more) is associated with a form of dry scaly skin rash, altered liver function and a decline in general health.

Limited data are available to identify sub-populations that are at a greater risk of adverse effects from kava beverage consumption. Given the pharmacological properties of the substances in kava, FSANZ considers that kava beverage consumption may pose a risk to pregnant women, children and adolescents, or individuals with reduced liver function.

Kava beverage increases the impact of alcohol on cognition, and there is evidence that some consumers consume kava beverage with alcohol. No data are available however to understand the short- or long-term implications of this co-consumption on public health and safety.

There are indications that kava beverage consumption is increasing in both Australia and New Zealand. However, there are limited quantitative data on consumption amounts of kava beverage and consequent exposure to the psychotropic substances in kava.

Consumers report that kava beverage causes drowsiness and lethargy, which is supported by published observational studies. However, limited data are available to quantify the physiological effects.

Kava beverage has a long history of consumption in the South Pacific and plays an integral role in maintaining the cultural continuity and identity of many Pacific peoples. This significant history of use demonstrates that it is possible to safely consume kava beverage in moderation when prepared and consumed in line with historically safe cultural practices. However, in the absence of evidence of safety, and given the pharmacological properties of substances in kava, the consumption of kava beverage by pregnant or lactating women, children, adolescents, or individuals with reduced liver function, is not recommended.

Table of contents

1 Introduction

This risk and technical assessment complements the initial risk and technical assessment prepared for the urgent stage of Proposal P1057, and considers the available evidence on safe kava beverage consumption to inform FSANZ assessment of the draft variation to the Australia New Zealand Food Standards Code (the Code) made during the urgent phase of proposal P1057. FSANZ previous assessment concluded it is possible to safely consume kava beverage in moderation when prepared and consumed in line with historically safe cultural practices.

The kava plant (*Piper methysticum* G. Forst) is an integral part of the dynamic and evolving cultural practices of many Pacific peoples, and kava is often regarded as an icon of national and/or ethno-cultural identity (Lebot et al., 1992; Aporosa, 2019). Believed to originate in Northern Vanuatu, kava was likely carried across Oceania by early maritime explorers and traders (Lebot et al., 1992).

Historically, kava beverage in Pacific communities has been prepared by cold water extraction from fresh or dried roots of the kava plant, to produce a brew in a communal bowl. Kava beverage has been consumed for more than 1000 years (Cairney et al., 2002; Aporosa, 2019; FSANZ, 2022). The evidence available suggests that kava beverage in Australia and New Zealand is consumed in line with this historical method of preparation, and this risk assessment considers the safety of kava beverage prepared in this way (discussed further in Supporting Document 2 [SD2]).

As part of the FSANZ's 12-month review of Proposal P1057, the following risk assessment questions were considered:

1) What level of kava beverage consumption poses a health and safety risk to consumers?

2) Are certain population sub-groups (e.g. pregnant and lactating women, adolescents, children) at increased risk from kava beverage consumption compared to the general population? If so, describe the health risk.

3) What are the kava beverage consumption patterns in Australia and New Zealand?

4) Does the co-consumption of kava beverage with alcohol increase the health and safety risk to consumers compared with the consumption of alcohol? If yes, what are the additional health risks?

5) What is the evidence for kava beverage consumption causing drowsiness?

This risk assessment examines the data available to answer these questions and is an extension of the FSANZ's previous risk assessment undertaken as part of the Urgent Phase of P1057 (FSANZ, 2022).

1.1 Composition and properties of kava beverage

There are more than 200 varieties of kava plant (Singh, 1992). 'Noble' kava varieties have been safely used by Pacific communities for kava beverage production (FAO/WHO, 2016; FSANZ, 2022). These varieties are distinguished by their geographical distribution, physical characteristics and the properties of the kava beverage they produce (Singh, 1992). Non-Noble kava varieties are not suitable for making kava beverage (FAO/WHO, 2016; FSANZ, 2022).

Drinkers of kava beverage report a sense of relaxation and tranquillity, and the drink is taken to promote a sociable attitude (see SD2 for full analysis). The pharmacologically active compounds in kava are kavalactones, which are extracted from the root of the kava plant during the preparation of kava beverage. The total kavalactone content of kava plants varies from 3% to 20% of dry weight, depending on variety, growth conditions and part of the plant (Duve & Prasad, 1983; Lebot & Lèvesque, 1996; Lebot et al., 1997).

Flavokawains and piperidine alkaloids are documented minor compounds found in the kava plant (Achenbach & Karl, 1970; Dragull et al., 2003; Lechtenberg et al., 2008; Lebot et al., 2014). It has been suggested these compounds present a risk of toxicity when consuming kava beverage extracted from leaves, stems or bark of the kava plant, or from non-Noble kava plant varieties, but little toxicological data are available (FSANZ, 2022).

The quantities of kavalactones, piperidine alkaloids and flavokawains removed from kava plant vary depending on:

1) extraction methods (cold water kava beverage preparation, compared with other extraction methods);

2) the kava plant variety (if the kava is of a Noble variety); or

3) specific kava plant organs used for extraction (roots rhizomes or basal stems, compared with aerial portions).

As a result of amendments made to the Australia New Zealand Food Standards Code (the Code) in the urgent phase of Proposal P1057, kava food products must only be obtained from the Noble varieties of kava plant that are named in the Codex Regional Standard for Kava (Codex, 2020).

1.2 Other uses of kava

Only kava root, or kava beverage obtained by aqueous suspension of kava root, is currently permitted for sale by the Code.

Commercial herbal extracts of kava are water or organic solvent extracts from kava plant, standardised to contain the maximum yield of kavalactones (WHO, 2007; White, 2018). Kava extracts are used for the treatment of anxiety, insomnia, premenstrual syndrome and stress (White, 2018). Kava extracts are prohibited as an ingredient in food in the Code (Standard 1.1.1)[1], and are a listed prohibited substance for use as an ingredient in supplemented foods in the New Zealand Food (Supplemented Food) Standard 2016 (Part 1.11)[2].

Kava extracts are used in complementary medicines listed on the Australian Register of Therapeutic Goods. Kava (including kavalactone extracts) is currently listed as a Schedule 4 substance in the Australian Poisons Standard[3], except when included in approved products on the Australian Register of Therapeutic Goods[4].

[1] Standard 1.1.1 of the Code is available at: https://www.legislation.gov.au/Details/F2021C00661
[2] The New Zealand Food (Supplemented Food) Standard is available at: https://www.mpi.govt.nz/dmsdocument/11365-New-Zealand-Food-Supplemented-Food-Standard-2016
[3] The Poisons Standard is available at: https://www.legislation.gov.au/Details/F2021L01345
[4] The ARTG is available at: https://www.tga.gov.au/australian-register-therapeutic-goods

2 Toxicological Assessment

FSANZ examined the risks associated with the consumption of kava beverage in the urgent phase of Proposal P1057 (FSANZ, 2022) and concluded, based on the available evidence, that kava beverage can be safely consumed in communities.

In reaching this conclusion FSANZ noted the following aspects as relevant to kava beverage safety:

1) The significant history of consumption in the South Pacific, which demonstrates it is possible to safely consume kava beverage in moderation when prepared and consumed in line with historically safe cultural practices.

2) Ongoing consumption of high quantities of kava beverage (240 - 440 g/week of dried kava powder or more) can have negative health effects, including ichthyosiform skin rash, altered liver function and a decline in general health.

3) Kava beverage prepared using kava plant varieties without a history of safe use, or using aerial parts of the kava plant, are considered to be potentially toxic and not safe for human consumption.

4) In rare cases, hepatotoxicity has been reported following consumption of kava beverage and complementary medicines containing kava. The aetiology of these cases is not well understood but may relate to factors including use of non-historical varieties of kava plants, methods of extraction, drug interactions, or aflatoxin contaminated kava.

5) Given the anxiolytic activity of kavalactones and the potential to inhibit CYP-mediated drug metabolism pathways, care should be taken when consuming kava beverage in combination with medicinal drugs (particularly benzodiazapines, opioids, barbiturates and paracetamol) or other herbal preparations.

6) No information was available to allow an assessment of the safety of kava beverage consumption in pregnant or lactating females, adolescents or children.

No additional toxicological data have been published since FSANZ previous risk assessment.

3 Microbiological Assessment

A qualitative analysis was undertaken by FSANZ of microbiological risks pertinent to the consumption of kava beverages as part of the P1057 final consideration (FSANZ, 2022). The assessment included an analysis of risk factors in the growing and primary processing of kava root, and in the storage distribution and consumption of kava beverages prepared from kava root.

In the absence of data to the contrary, it was concluded the microbiological risk from consumption of kava beverages obtained by aqueous suspension of dried or raw kava root is low when kava is produced and prepared in line with current risk management measures, including the application of Good Agricultural Practices (GAP) and Good Hygienic Practices (GHP).

4 Human Health Assessment

The long history of use, with minimal evidence of adverse health events from consumption, demonstrates that kava beverage can be safely consumed in communities in-line with historical preparation and consumption practices. Kava does not demonstrate the same addictive properties as other substances of abuse, and is seen to be far less harmful to both individual users and the community (FAO/WHO, 2016; Bonomo et al., 2019; FSANZ, 2022).

Nevertheless, some features of kava beverage may pose a potential risk to public health and must be considered appropriately.

4.1 High-level consumers

The consumption of kava beverage may result in kavalactone intakes greater than the recommended maximum daily dose (250 mg kavalactones) for therapeutic goods, and kava beverage has the potential to become a substance of abuse in certain contexts (FSANZ, 2022).

Evidence of negative health outcomes have been observed in communities with established patterns of ongoing high-level consumption of kava beverage. Such ongoing high-level consumption has been associated with a scaly skin rash, altered liver function and other general reductions in overall health (Rychetnik & Madronio, 2011). However, these changes are reversible once kava consumption ceases (FSANZ, 2022).

4.2 Sensitive sub-populations

Children and adolescents

Insufficient data were available to FSANZ to establish if kava beverage can be safely consumed by children and adolescents.

Around 18.5% of New Zealanders who have ever used kava first consumed it before the age of eighteen years, with about 6.5% of kava consumers having first consumed it before the age of fourteen (see SD2 for full analysis). Information on quantity and frequency of kava beverage consumption by these population groups could not be located, thus insufficient data were available to establish a history of safe use.

The biological mechanism of action of kavalactones is poorly understood. Kavalactones are able to cross the blood-brain barrier in mice to elicit their psychotropic effects on the central nervous system (Keledjian et al., 1998; Mathews et al., 2005). Pharmacological data from rats and guinea pigs suggest that kavalactones in the brain can modulate voltage-dependent ion channels and γ-aminobutyric acid receptors, as well as dopamine and serotonin levels (Jussofie et al., 1994; Magura et al., 1997; Walden et al., 1997; Baum et al., 1998). Additional *in vitro* data also suggest that kavalactones may inhibit alpha-glycine receptors and monoamine oxidase enzymes, and weakly interact with cannabinoid receptors (Legresti et al., 2012; Prinsloo et al., 2019, Hegazy et al., 2019). It is unclear if equivalent interactions occur in humans. Given the signalling pathways implicated in kavalactone activity are important for cognitive function, and in the absence of evidence demonstrating kavalactones safety; the potential for kavalactone pharmacology to affect cognitive development cannot be discounted.

Moreover, while the risk assessments undertaken by FAO/WHO and FSANZ concluded that the risk of hepatotoxicity posed by consumption of kava beverage is low, this conclusion may not apply to children or adolescents (FAO/WHO, 2016; FSANZ, 2022). The potential for

drug-induced liver injury differs between children and adults, where substances can have lower or higher hepatotoxicity potential (Shi et al., 2017). In the absence of empirical safety data that account for any age-related variance associated with kava beverage consumption, it is unclear if differences in hepatotoxicity would also occur for kavalactones in children and adolescents.

Given the biologically active properties of kavalactones, and the limited data available to support safety in children and adolescents, kava beverage consumption by this sub-population is not recommended.

Pregnant and lactating women

No data were identified by FSANZ to support the safety of kava beverage consumption in pregnant or lactating women. Nor could any data be identified on the potential for negative developmental consequences to the fetus or infant resulting from exposure to biologically active kavalactones.

It is unclear whether kavalactones can transfer across the placenta or accumulate in human breast milk. However, kavalactones are lipophilic molecules[5] with low molecular weight (less than 500 g/mol), both of which are favourable properties for passive transfer across the placenta or accumulation in human milk (Anderson & Sauberan, 2016; Tetro et al., 2018; FSANZ, 2022).

There were insufficient epidemiological data to establish the degree of kava beverage consumption in pregnant or lactating women in Pacific cultures, nor to establish a history of safe use (see SD2 for full analysis).

In the absence of any reproductive or developmental toxicity data establishing that kavalactone exposure does not pose a safety risk to the fetus or young infant, kava beverage consumption by pregnant or lactating woman is not recommended.

Consumers with reduced liver function

Based on available data in human studies, kavalactone metabolism is complex and involves hydroxylation or demethylation by cytochrome P450 (CYP) monooxygenase enzymes in the liver, before undergoing sulfonation, glucuronidation or glutathione (GSH) conjugation (Tarbah et al., 2003; Wang et al., 2019). This xenobiotic metabolism pathway is shared with other drugs and herbal products, and substances in kava have been shown to inhibit multiple CYP enzymes *in vitro* (Anke & Razman, 2004; Mathews et al., 2005; Lim et al., 2007).

Kava beverage consumption by individuals with reduced liver function is not recommended based on their expected decreased capacity for hepatic metabolism, plus the potential for kava beverage consumption to further inhibit xenobiotic metabolism.

4.3 Co-consumption with alcohol

The co-consumption of kava beverage and alcohol intensifies the effects of alcohol on cognition, although the underlying mechanism of this interaction has not been identified. Kavalactones do not inhibit CYP2E1 or alcohol dehydrogenase *in vitro*, both key metabolic enzymes in alcohol metabolism in humans (Anke et al., 2006; Mathews et al., 2005). Available ethnographic evidence suggests that co-consumption of kava beverage and alcohol occurs in a subset of kava beverage consumers (see SD2 for full analysis).

[5] The average computed *n*-ocatanol/water partition coefficient (XLogP3) is 2.6 for the six major kavalactones (FSANZ, 2022)

A small-scale randomised and blinded study in adults (groups of 5 participants/treatment /sex) observed that an acute dose of kava beverage (1 g kava powder/kg bw) in combination with alcohol (75 mg/kg bw) increased both perceived and measured cognitive impairment, when compared to alcohol alone. Kava beverage alone showed little to no difference compared to alcohol alone (Foo & Lemon, 1997).

Alcohol and kava co-consumption has been proposed as a risk factor in motor vehicle accidents on Fijian roads, however a significant interaction has not been established from available data (Wainiqolo et al., 2016).

4.4 Sedative effects

Kavalactones have been reported to have psychopharmacological effects as well as muscle relaxant, local anaesthetic, anxiolytic and anticonvulsive properties. Observational reports of kava beverage consumption report that a decrease in motor function, slowed speech and hypnotic properties may occur (FAO/WHO, 2016). Moderate to high doses of kavalactones lead to drowsiness and sedation, seemingly without reducing cognitive performance (Cairney et al., 2002; LaPorte et al., 2011).

While the sedative-hypnotic effects of kavalactones in kava beverage are widely accepted, there are limited data available to quantify efficacy in humans or animals. To understand kavalactones' efficacy as a hypnotic, FSANZ considered studies undertaken with kava extracts, recognising the limited value of these studies due to differences between kava extracts and kava beverage (FSANZ, 2022).

An early study on the pharmacological properties of kava beverage demonstrated that kavalactones in kava extract act synergistically with each other to elicit their pharmacological effect in mice, and kavalactones increased sleep duration in mice co-treated with the hypnotic pentobarbital (Klohs et al., 1959).

A single study using an ethanol extract from kava root administered orally (10-300 mg/kg bw) showed a dose-dependent decrease in sleep latency in sleep-deprived mice, compared to controls. The hypnotic effect was not observed in mice that were not sleep-deprived (Shinomiya et al., 2005).

An additional study using high-dose kavain (10-100 mg/kg bw) administered orally showed a dose-dependent decrease in sleep latency in sleep-deprived mice, compared to controls (Tsutsui et al., 2009). This study also showed a slight decrease in awake time in sleep-deprived mice at a high-dose (100 mg/kg bw) of kavain (Tsutsui et al., 2009).

A good laboratory practice (GLP) study in mice showed that oral administration of 100 mg/kg bw kava extract (equivalent to 50 mg/kg bw of kavalactones) reduced amphetamine-induced hyperactivity, and increased barbiturate-induced sleep duration (Capasso & Sorrentino, 2005).

In mice, the hypnotic effects of kavalactones seemingly occur without altering rapid-eye movement (REM) sleep, nor are they inhibited by co-administration of a benzodiazepine antagonists (Shinomiya et al., 2005; Tsutsui et al., 2009). This suggests that the mild-hypnotic effects exhibited by kavalactones are unlikely to share a common mechanism with barbiturate sedatives.

An uncontrolled human clinical trial was conducted on the effect of kava extract as a treatment for stress-induced insomnia (Wheatley, 2001). While the study reported an

improvement in sleep parameters, limitations in study design make these data unsuitable for risk assessment.

Overall, there is evidence that pharmacologically active kavalactones in kava beverage have hypnotic or sedative properties but it was not possible to quantify activity based on the available data.

5 Dietary Exposure assessment

5.1 Consumption of kava

Kava is a traditional beverage and kava drinking has been a significant part of the culture in the Pacific for centuries. Kava beverage is not a widely consumed food in Australia or New Zealand, except in some Pacific communities, or select First Nations communities in Australia (see SD2 for full analysis).

Kava consumption was not a feature in the traditions of Aboriginal and Torres Strait Islander peoples until it was introduced into Arnhem land in the 1980s as an alternative to alcohol (Cawte, 1985; Mathews et al., 1988). Kava beverage was not a documented feature in Māori cultural practices after migration to Aotearoa New Zealand, although recent research suggests that consumption within Māori communities may be increasing, in part as a means of reinvigorating ancestral and cultural Māori-Pasifika connections (Aporosa, 2015). In addition, *kawakawa* or *kava* refers to the closely related *Piper excelsum,* which is used as an ingredient in traditional medicine and features in traditional Māori culture. *P. excelsum* does not possess psychotropic properties (Singh, 1992; Butts et al., 2019).

Several kava based products are currently available in Australia, particularly following the recent relaxation of import restrictions, and New Zealand as a commercial food commodity (e.g. dried kava powders). In addition to the ability to purchase kava products online, a number of businesses are already operating in Australia and New Zealand that offer kava beverage as a recreational product for consumption on-site or as a take-away option.

Kava extracts are used in complementary medicines listed on the Australian Register of Therapeutic Goods and are also available in New Zealand in products that are marketed as dietary supplements, even though kava is not permitted to be added to dietary supplements in New Zealand (as noted in SD3). The principal means of exposure of the broader Australian and New Zealand community to kava products would be mainly through kava extracts in such goods.

No information on kava consumption is captured by the 2011-2012 Australian National Nutrition and Physical Activity Survey (ABS, 2014) or the 2012-2013 Australian National Aboriginal and Torres Strait Islander Nutrition and Physical Activity Survey (ABS, 2015). For the 2008 New Zealand Adult Nutrition Survey (Ministry of Health 2011a; Ministry of Health 2011b), there was a small proportion of survey respondents (0.2%) that reported consuming fluid kava at a mean of 1.8 L. However given the very small number of consumers, there is a high degree of uncertainty associated with this value.

In the National Drug Strategy Household Surveys (NDSHS), 1.9%, 2.0% (2.5% men and 1.6% women), 1.8% (2.3% men and 1.3% women) and 1.9% (2.5% men and 1.4% women) of Australians 14 years and older reported being offered or having the opportunity to use kava within the last 12 months in the 2001, 2004, 2007 and 2010 years respectively (AIHW, 2004; AIHW, 2010). This was highest in the 20-29 year old age group at 3.7% in 2010 (AIHW, 2010). In the 2010 NDSHS, 4.2% of Australians 12 years and older expressed their personal approval for the regular use of kava by an adult (AIHW, 2010). This was highest in

the 18-19 year old age group at 7.5% (AIHW, 2010). No specific information on kava has been reported after 2010 because kava has been categorised and reported under 'other psychoactive substances' since the 2013 NDSHS (AIHW, 2013).

In the 2007/08 New Zealand Alcohol and Drug Use Survey (NZADUS), 0.9% of adults (1.4% men and 0.7% women) aged 16-64 years had used kava in the past 12 months (Ministry of Health, 2010). This was highest for men at 3.1% in the 16-17 years age group. Among past-year kava users aged 16-64 years, 12.6% had used it at least weekly and 15.9% at least monthly (Ministry of Health, 2010). The 2007/08 NZADUS also reported that 6.3% (9.2% men and 4.5% women) of the participants aged 16-64 years had ever used kava in their lifetime and 6.5% (7.6% men and 5.4% women) of them had first tried it when they were 14 years or younger (Ministry of Health, 2010).

A survey conducted in 2006 on kava consumption by Tongan men aged between 18 and 70 years and living in Macarthur, Sydney South West (n=73) revealed that 90% of the participants had consumed kava regularly at least twice a week (Maneze et al., 2008). 15% of the participants reported concurrent consumption of alcohol during a kava drinking session. The amount and frequency of kava consumption appeared to be higher among the men at 41 years and older than the younger men (Maneze et al., 2008).

Port (2014) studied changes in kava consumption patterns of Pasifikan males 17 years and older living in South Auckland (n=716) over a ten year period using the data collected from a longitudinal study. It was found that the number of kava users increased by about 15%, and the amount and the frequency of consumption also increased significantly (Port, 2014). There were 3.9% of respondents who were 'once per week' users when first recorded, and after 10 years it was 7.2%. There were 91.1% who did not use at the start compared to a lower 75.7% after ten years.

A 1988 assessment of the health status of Australian kava beverage consumers in a community in Arnhem land categorised kava users into occasional consumers (average 100 g/week dried kava root powder), heavy consumers (average 310 g/week) and very heavy consumers (average 440 g/week) (Mathews et al., 1988). This is consistent with a 1991 assessment in a nearby Arnhem land community, where the average kava drinker consumed an estimated average of 368 g/week of dried kava powder (Clough et al., 2000). Based on these observations, 240 - 440 g/week of dried kava powder has been proposed as the level where negative effects from kava beverage consumption begin to occur (Clough, 2003).

Subsequent observational studies in Australian and Pacific communities show that, while some variances exist, these Australian estimates of high kava beverage consumption largely reflect wider kava beverage consumption patterns (Jowitt & Binihi, 2001; Grace, 2003; Shimoda et al., 2015; Aporosa et al., 2020).

For example, in the 2009 National Population and Housing Census of Vanuatu, 53% of males and 8% of females at 15 years and older reported drinking of kava during the week before the census day (VNSO, 2009). Commonly, the drinking of kava was highest at >70% among 25-49 year old age group (VNSO, 2009). A hospital based survey (n=150, 80 women and 70 men) conducted in Vanuatu including both patients (100) and the hospital staff (50) over 18 years old reported that 35% of the participants had consumed kava and this included 59% men and 15% of women (Grace, 2003). This study further revealed that 85% of the kava consumers drink kava at least weekly and men usually drink more than the women (Grace, 2003).

Notably, studies from the Pacific communities show that the level and the frequency of kava consumption can vary between individuals, between sexes, within the communities and

between the communities, as well depend on the social context where kava is consumed (FAO/WHO, 2016).

5.2 Kavalactone intake from kava beverage

Total kavalactone content of kava plant varies from 3%-20% of dry weight, depending on plant variety, the age of the kava plant when harvested, product storage conditions and post-harvest processing (i.e. fresh or dry) (Duve & Prasad, 1983; Lebot & Lèvesque, 1996; Lebot et al., 1997). Kavalactone concentration in beverages is impacted by the method used for preparation, often heavily influenced by social context and practices (Aporosa, 2019). A survey (n = 24) conducted by Shimoda et al. (2012) across nine Pacific islands revealed that kava beverage was traditionally prepared using ground kava root and stem mixture diluted with water mostly at a ratio of 0.5-1.0% w/v. However, this ratio was higher at 3% w/v in Vanuatu and up to 5% w/v in Kiribati (Shimoda et al., 2012).

Clough et al. (2000) estimated the quantity of kavalactones consumed by kava beverage drinkers in an Arnhem land community with a high level of kava consumption. Assuming a total kavalactone content in kava powder of 12.5% of dry weight, a kavalactone extraction efficiency of 83%, and ingestion of 670 mL of liquid containing 37 g of kava powder per hour, the estimated intake of kavalactones would be 3800 mg per hour by high consumers (Clough et al., 2000).

Aporosa et al. (2020) examined the effects of a six hour kava session on cognitive function of regular kava consumers in New Zealand. The kavalactone content of a single batch of commercially available dried kava powder, originating in Tonga and obtained in Hamilton, New Zealand, was determined to be 9.26% w/w kavalactones. When used to prepare kava beverage reflective of an average ‘strength’, a kava consumer would consume 145 mg kavalactones in a 100 mL serving. Assuming an average consumption rate of 500 mL per hour, the authors concluded that kavalactone intake would equal 725 mg per hour. In a similar study (Aporosa et al., 2022), the dried kava powder, originating in Fiji and purchased from the same locality (Hamilton, New Zealand) was found to contain 5% w/w kavalactones. The kava beverage prepared thus contained 115 mg of kavalactones in a 100 mL serving. In this study the kavalactone intake was determined to be 690 mg per hour based on the assumption that each participant would consume 6 servings per hour (600 mL) (Aporosa et al., 2022).

Bian et al. (2020) have reviewed intake of kavalactones through the traditional kava use in Pacific communities including Vanuatu, Fiji, Tonga and Hawaii and reported that it can range from 750 to 8000 mg of kavalactones per day.

The duration of a single kava drinking session can vary widely based on cultural norms, occasions and user preferences, where individuals have self-reported drinking kava for up to 22 hours in a single session (Jowitt & Binihi, 2001; Cairney et al., 2003). The average duration of a Fijian or Polynesian kava session has been reported to be approximately 6 hours (Aporosa et al., 2020) and in where an attendee would consume about 3.6 L of kava beverage that is referred as a ‘traditionally-influenced’ kava use session for research purposes (Aporosa et al., 2022).

The consumption of kava beverage therefore results in intakes of kavalactones which are far in excess of the recommended maximum daily dose of 250 mg kavalactones for preparations included on the Australian Register of Therapeutic Goods.

5.3 Conclusions

Limited data are available relating to quantitative consumption amounts of kava. There are some data available that describe the proportion of consumers or frequency of consumption. Whilst kava is not widely consumed in the general Australian and New Zealand populations, there are some data, particularly in pacific communities, indicating the proportion of consumers and frequency of consumption may be increasing. Evidence indicates the availability of kava products is also increasing. There are limited data on actual consumption amounts with reports of between 100-440 g dried kava powder consumption per week. From the information gathered, more men consume kava compared to women. There were no consumption data found relevant to the vulnerable sub-populations of pregnant women and children and also specific data on co-consumption of kava beverage with alcohol. The intake of kavalatones from prepared kava beverage can be highly variable depending on the concentration in the powder used, method of preparation and length of kava drinking session, with estimates from 690 mg/hour up to 8000 mg/day.

6 Data limitations

Substantial gaps exist in the data available to assess the safety of aqueous and solvent extracts of kava. These are in addition to the gaps documented in previous FSANZ risk assessment work (FSANZ, 2022).

These additional gaps include:

- Insufficient information on the *in vivo* toxicity of kavalactones, flavokawains, piperidine alkaloids, and their metabolites, to establish health-based guidance values for these substances in kava beverage.
- No data to assess the safety of kava beverage in children or adolescents.
- No data to assess the safety of kava beverage in newborn infants, nor understand potential impacts on fetal development.
- No data to demonstrate whether kava beverage can be safely consumed by pregnant or lactating women without harming the fetus or breastfeeding infant.
- No data to assess the impact of reduced liver function on kava beverage safety.
- Insufficient data to reliably calculate the dietary exposure of Australian and New Zealand consumers to kavalactones from kava beverage consumption.
- No data to assess the risk of adverse events posed by consumption of kava beverage with alcohol.
- Insufficient data to quantify hypnotic and sedative properties of kava beverage for risk assessment, despite these effects being reported in scientific literature and widely recognised by kava consumers.

7 Risk characterisation

The following risk characterisation considers the available evidence on the risk of kava beverage consumption to human health in both Australia and New Zealand, grouped by risk assessment question.

Health and safety risk of kava beverage consumption

Insufficient data were available to establish health-based guidance values for the biologically active substances and their metabolites in kava beverage. However, ongoing consumption of high quantities of kava beverage (240 - 440 g/week of dried kava powder or more) is associated with ichthyosiform skin rash, altered liver function and a decline in general health.

At risk sub-populations

Limited data were available to identify sub-populations that are at a greater risk of adverse effects from kava beverage consumption. However, given the pharmacological properties of kavalactones, FSANZ considers that kava beverage consumption may pose a risk to certain sub-populations. Specifically, pregnant women, children and adolescents, or individuals with reduced liver function.

The biological pathways implicated in kavalactone activity are important for cognitive function and it is not known what impact exposure to kavalactones may have on normal growth and development. As the risk of adverse health effects to children and adolescents cannot be determined, the consumption of kava beverage by this sub-group is not recommended.

Furthermore, fetal and infant development are critical and highly sensitive periods of human growth. Kava beverage consumption by pregnant woman may expose their developing fetus to kavalactones through placental transfer, while kava beverage consumption by lactating woman may expose their infant to kavalactones through breast milk. In both cases, there is also insufficient epidemiological or historical ethnographic evidence to establish a history of safe consumption. Kava beverage consumption by pregnant or lactating woman is therefore not recommended.

Finally, kava beverage consumption in individuals with decreased capacity for hepatic metabolism could increase the risk of adverse effects for this sub-population. This may occur by increasing sensitivity to any hepatotoxic effects of kavalactones directly, or by changing the pharmacokinetics of kavalactones or other concomitant therapeutics. Kava beverage consumption by persons with reduced liver function is not recommended.

Kava beverage consumption in Australia and New Zealand

Limited quantitative data were available on the consumption of kava beverage in Australia and New Zealand. There were some data available describing the proportion of consumers and frequency of consumption. Kava beverage is not widely consumed in the general Australian and New Zealand populations, however there are indications that the proportion of consumers and frequency of consumption is increasing. This coincides with the apparent increase in availability of kava products which appears likely to continue, particularly in Australia following the recent relaxation of import restrictions.

Limited data were available on actual consumption quantities of kava beverage and consequent exposure to kavalactones. The intake of kavalactones from prepared kava beverage can be highly variable depending on the concentration in the powder used, method of preparation and length of kava drinking session, with estimates from 690 mg/hour up to 8000 mg/day.

Kava beverage and alcohol

Kava beverage potentiates the effects of alcohol on cognition, although the physiological mechanism is unclear. Ethnographic evidence suggests that co-consumption of kava with alcohol occurs in a subset of kava beverage consumers. A link between kava and alcohol

consumption in motor vehicle accidents has been proposed, but significant interaction has not been established from the available data.

Hypnotic effects of kava beverage

Observational studies of kava beverage consumption report hypnotic properties, which are further supported by the perceptions of kava users. Consumers report that the hypnotic properties of kava beverage can be used for therapeutic purposes to help bring on sleep or are believed to be a key contributor of kava beverage's negative social effects by inducing sleepiness/lethargy in regular users. Notably, kava beverage is considered by both consumers and non-consumers to be relatively safe to consume before driving, despite being recognised by consumers as a substance that promotes sleepiness (see SD2 for analysis).

Despite evidence that pharmacologically active kavalactones in kava beverage have hypnotic or sedative properties, limited data were available to quantify efficacy in either humans or animals.

8 Conclusions

Kava beverage has a long history of consumption in the South Pacific and plays an integral role in maintaining the cultural continuity and identity of many Pacific peoples. This significant history of use demonstrates it is possible to safely consume kava beverage in moderation when prepared and consumed in line with historically safe cultural practices. However, in the absence of evidence of safety, and given the pharmacological properties of kavalactones, the consumption of kava beverage by pregnant or lactating women, children, adolescents, or individuals with reduced liver function, is not recommended.

References

ABS (2014) National Nutrition and Physical Activity Survey, 2011-12, Australian Bureau of Statistics.

ABS (2015) Australian Aboriginal and Torres Strait Islander Health Survey, 2012-13, Australian Bureau of Statistics.

Achenbach, H., Karl, N., (1970) Uber die Isolierung von zwei neuen Pyrrolidinen aus Rauschpfeffer. *Chem. Ber.* 103, 8 : 2535-2540.

Anderson, P.O., Sauberan, J.B. (2016) Modeling drug passage into human milk. *Clin Pharmacol Ther*. 100(1):42-52.

Aporosa, A. S. (2015). The new kava user: Diasporic identity formation in reverse. *New Zealand Sociology*, 30(4): 58-77.

Aporosa, S. A. (2019). Kava and Ethno-cultural Identity in Oceania. In S. Ratuva (Ed.), *The Palgrave Handbook of Ethnicity* (Vol. 17, pp. 1923–1937). Springer Singapore. https://doi.org/10.1007/978-981-13-2898-5_134

Aporosa, A. S., Atkins, M., & Brunton, R. (2020). Kava drinking in traditional settings: Towards understanding effects on cognitive function. *Hum Psychopharmacol*, *35*(2), e2725. https://doi.org/10.1002/hup.2725

Aporosa, A. S., Ballard, H., Pandey, R., & McCarthy, M. J. (2022). The impact of traditional kava (Piper methysticum) use on cognition: Implications for driver fitness. *J. Ethnopharmacol*, *291*, 115080. https://doi.org/10.1016/j.jep.2022.115080

Anke, J., & Ramzan, I. (2004) Pharmacokinetic and pharmacodynamic drug interactions with Kava (Piper methysticum Forst. F.). *J. Ethnopharmacol*, 93(2-3), 153–160. https://doi.org/10.1016/j.jep.2004.04.009

Australian Institute Of Health And Welfare (2004). *National Drug Strategy Household Survey, 2004*. Canberra. https://www.aihw.gov.au/getmedia/111e958c-17a5-4d13-949d-9548f1f43d65/ndshs04.pdf.aspx?inline=true

Australian Institute Of Health And Welfare (2010). *National Drug Strategy Household Survey, 2010*. Canberra. https://www.aihw.gov.au/getmedia/b33ce462-6312-4b59-bef4-35dd30df3927/aihw-phe-145.pdf.aspx?inline=true

Australian Institute Of Health And Welfare (2013). *National Drug Strategy Household Survey, 2013*. Canberra. https://www.aihw.gov.au/getmedia/c2e94ca2-7ce8-496f-a765-94c55c774d2b/16835_1.pdf.aspx?inline=true

Baum, S. S., Hill, R., Rommelspacher, H. (1998) Effect of kava extract and individual kavapyrones on neurotransmitter levels in the nucleus accumbens of rats. *Prog Neuropsychopharmacol Biol Psychiatry* 22(7):1105-20. https://doi.org/10.1016/s0278-5846(98)00062-1

Bian, T., Corral, P., Wang, Y., Botello, J., Kingston, R., Daniels, T., Salloum, R. G., Johnston, E., Huo, Z., Lu, J., Liu, A. C., & Xing, C. (2020). Kava as a Clinical Nutrient: Promises and Challenges. *Nutrients*, *12*(10). https://doi.org/10.3390/nu12103044

Bonomo, Y., Norman, A., Biondo, S., Bruno, R., Daglish, M., Dawe, S., Egerton-Warburton, D., Karro, J., Kim, C., Lenton, S., Lubman, D. I., Pastor, A., Rundle, J., Ryan, J., Gordon, P., Sharry, P., Nutt, D., & Castle, D. (2019). The Australian drug harms ranking study. *J. Psychopharmacol*. 33(7), 759–768. https://doi.org/10.1177/0269881119841569

Butts, C. A., van Klink, J. W., Joyce, N. I., Paturi, G., Hedderley, D. I., Martell, S., & Harvey, D. (2019). Composition and safety evaluation of tea from New Zealand kawakawa (Piper excelsum). *J. Ethnopharmacol*, *232*, 110–118. https://doi.org/10.1016/j.jep.2018.12.029

Cairney, S., Maruff, P., & Clough, A. R. (2002). The neurobehavioural effects of kava. *Aust N Z J Psychiatry*, *36*(5), 657–662. https://doi.org/10.1046/j.1440-1614.2002.01027.x

Cairney, S., Maruff, P., Clough, A. R., Collie, A., Currie, J., & Currie, B. J. (2003). Saccade and cognitive impairment associated with kava intoxication. *Hum Psychopharmacol*, *18*(7), 525–533. https://doi.org/10.1002/hup.532

Capasso, A., Sorrentino, L. (2005) Pharmacological studies on the sedative and hypnotic effect of Kava kava and Passiflora extracts combination. *Phytomedicine*. 12(1-2):39-45. https://doi.org/10.1016/j.phymed.2004.03.006

Cawte, J. (1985). Psychoactive substances of the South Seas: Betel, kava and pituri. *Aust N Z J Psychiatry*, *19*(1), 83–87. https://doi.org/10.3109/00048678509158818

Clough, A. (2003). Enough! Or too much. What is 'excessive' kava use in Arnhem Land? *Drug and Alcohol Review*, *22*(1), 43–51. https://doi.org/10.1080/0959523021000059820

Clough, A. R., Burns, C. B., & Mununggurr, N. (2000). Kava in Arnhem Land: a review of consumption and its social correlates. *Drug Alcohol Rev*, *19*(3), 319–328. https://doi.org/10.1080/cdar.19.3.319.328

Codex Alimentarius Commission (2020) CXS 336R-2020 Regional Standard for Kava Products for use as a Beverage When Mixed with Water https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXS%2B336R-2020%252FCXS_336Re.pdf accessed 6 December 2021

Dragull, K., Yoshida, W. Y., & Tang, C.-S. (2003). Piperidine alkaloids from Piper methysticum. *Phytochemistry*, 63(2), 193–198. https://doi.org/10.1016/s0031-9422(03)00111-0

Duve, R. N., & Prasad, J. (1983). Changes in the chemical composition of Yaqona Piper methysticum with time. *Fiji Agric. J*, 45(2), 45–50.

FAO/WHO (2016). Kava: a review of the safety of traditional and recreational beverage consumption.: Technical Report. Rome. http://www.fao.org/3/i5770e/i5770e.pdf

Foo, H., & Lemon, J. (1997). Acute effects of kava, alone or in combination with alcohol, on subjective measures of impairment and intoxication and on cognitive performance. *Drug Alcohol Rev*, 16(2), 147–155. https://doi.org/10.1080/09595239700186441

Food Standards Australia New Zealand (2022) Supporting Document 1 - Risk and technical assessment at approval. *Proposal P1057 - Review of the kava standard*. Canberra https://www.foodstandards.gov.au/code/proposals/Pages/Proposal-P1057--Review-of-the-kava-standard-.aspx. Accessed: 23 March 2022

Grace, R. F. (2003). Kava drinking in Vanuatu—a hospital based survey. *Pacific Health Dialog*, *10*(2), 41–44.

Hegazy, N. H., Breitinger, H. G., Breitinger, U. (2019) Kavalactones from Kava (Piper methysticum) root extract as modulators of recombinant human glycine receptors. *Biol Chem* 27;400(9):1205-1215. https://doi.org/10.1515/hsz-2019-0112

Jowitt, A., & Binihi, J. (2001). The commercialisation of kava in Vanuatu. *Pacific Health Dialog*, *8*(1), 29–37.

Jussofie, A., Schmiz, A., Hiemke, C. (1994) Kavapyrone enriched extract from *Piper methysticum* as modulator of the GABA binding site in different regions of rat brain. *Psychopharmacol* (Berl). 116(4):469-74. https://doi.org/10.1007/BF02247480

Keledjian, J., Duffield, P. H., Jamieson, D. D., Lidgard, R. O., & Duffield, A. M. (1988). Uptake into mouse brain of four compounds present in the psychoactive beverage kava. *J. Pharm Sci*, 77(12), 1003–1006. https://doi.org/10.1002/jps.2600771203

Klohs, M. W., Keller, F., Williams, R. E., Toekes, M. I., Cronheim, G. E., (1959) A chemical and pharmacological investigation of Piper methysticum Forst. *J Med Pharm Chem*. Feb;1(1):95-103. https://doi.org/10.1021/jm50002a007

LaPorte, E., Sarris, J., Stough, C., & Scholey, A. (2011). Neurocognitive effects of kava (Piper methysticum): A systematic review. *Hum Psychopharmacol*, 26(2), 102–111. https://doi.org/10.1002/hup.1180

Lebot, V., & Lèvesque, J. (1996). Genetic control of kavalactone chemotypes in Piper methysticum cultivars. *Phytochemistry*, 43(2), 397–403. https://doi.org/10.1016/0031-9422(96)00209-9

Lebot, V., Merlin, M., & Lindstrom, L. (1992). *Kava: The Pacific Drug*. Yale University Press. https://doi.org/10.2307/j.ctt211qwxb

Lebot, V., Merlin, M. D., & Lindstrom, L. (1997). Kava: The Pacific elixir : the definitive guide to its ethnobotany, history and chemistry / Vincent Lebot, Mark Merlin and Lamont Lindstrom. Healing Arts Press.

Lechtenberg, M., Quandt, B., Schmidt, M., & Nahrstedt, A. (2008). Is the alkaloid pipermethystine connected with the claimed liver toxicity of Kava products? *Die Pharmazie*, 63(1), 71–74.

Ligresti, A., Villano, R., Allarà, M., Ujváry, I., Di Marzo, V. (2012) Kavalactones and the endocannabinoid system: the plant-derived yangonin is a novel CB_1 receptor ligand. *Pharmacol Res*. 66(2):163-9. https://doi.org/10.1016/j.phrs.2012.04.003

Lim, S. T. S., Dragull, K., Tang, C.-S., Bittenbender, H. C., Efird, J. T., & Nerurkar, P. V. (2007). Effects of kava alkaloid, pipermethystine, and kavalactones on oxidative stress and cytochrome P450 in F-344 rats. *Toxicol Sci*, 97(1), 214–221. https://doi.org/10.1093/toxsci/kfm035

Magura, E. I., Kopanitsa, M. V., Gleitz, J., Peters, T., Krishtal, O. A. (1997) Kava extract ingredients, (+)-methysticin and (+/-)-kavain inhibit voltage-operated Na(+)-channels in rat CA1 hippocampal neurons. *Neurosci*. 81(2):345-51. https://doi.org/10.1016/s0306-4522(97)00177-2 Erratum in: *Neurosci* 1998 May;84(1):323.

Maneze, D., Speizer, A., Dalton, N., & Dennis, S. (2008). A descriptive study of kava use among Tongan men in Macarthur, Sydney South West. *Australian and New Zealand journal of public health*, *32*(4), 314-316. https://doi:10.1111/j.1753-6405.2008.00246.x

Mathews, J. D., Riley, M. D., Fejo, L., Munoz, E., Milns, N. R., Gardner, I. D., Powers, J. R., Ganygulpa, E., & Gununuwawuy, B. J. (1988). Effects of the heavy usage of kava on physical health: Summary of a pilot survey in an aboriginal community. *Medl J Aust*, *148*(11), 548–555. https://doi.org/10.5694/j.1326-5377.1988.tb93809.x

Mathews, J. M., Etheridge, A. S., Valentine, J. L., Black, S. R., Coleman, D. P., Patel, P., So, J., & Burka, L. T. (2005). Pharmacokinetics and disposition of the kavalactone kawain: Interaction with kava extract and kavalactones in vivo and in vitro. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, *33*(10), 1555–1563.

Ministry of Health. (2010). *Drug Use in New Zealand: Key results of the 2007/08 New Zealand Alcohol and Drug Use Survey*. Wellington: Ministry of Health. Available at: https://www.health.govt.nz/publication/drug-use-new-zealand-key-results-2007-08-new-zealand-alcohol-and-drug-use-survey.

Ministry of Health (2011a) Methodology report for the 2008/09 New Zealand Adult Nutrition Survey. Ministry of Health, Wellington.

Ministry of Health (2011b) A focus on nutrition: Key findings of the 2008/09 New Zealand Adult Nutrition Survey. Ministry of Health, Wellington.

Port, H. (2014). Kava: A longitudinal study into kava consumption and emerging patterns of kava usage with subsequent effects on Pacific families living in South Auckland. *Auckland, New Zealand: Department of Psychology, Auckland University of Technology*.

Prinsloo, D., van Dyk. S,, Petzer, A., Petzer, J. P. (2019) Monoamine Oxidase Inhibition by Kavalactones from Kava (*Piper Methysticum*). *Planta Med*. 85(14-15):1136-1142. https://doi.org10.1055/a-1008-9491

Rowe, A., Zhang, L. Y., & Ramzan, I. (2011). Toxicokinetics of kava. *Adv Pharmacol Sci*, 326724. https://doi.org/10.1155/2011/326724

Rychetnik, L., & Madronio, C. M. (2011). The health and social effects of drinking water-based infusions of kava: A review of the evidence. *Drug Alcohol Rev*, 30(1), 74–83. https://doi.org/10.1111/j.1465-3362.2010.00184.x

Shi, Q., Yang, X., Greenhaw, J. J., Salminen, A. T., Russotti, G. M., Salminen, W. F. (2017) Drug-Induced Liver Injury in Children: Clinical Observations, Animal Models, and Regulatory Status. *Int J Toxicol*. 36(5):365-379. https://doi.org/10.1177/1091581817721675

Shimoda, L. M. N., Showman, A., Baker, J. D., Lange, I., Koomoa, D. L., Stokes, A. J., Borris, R. P., & Turner, H. (2015). Differential regulation of calcium signalling pathways by components of Piper methysticum (‘Awa). *Phytother Res : PTR*, *29*(4), 582–590. https://doi.org/10.1002/ptr.5291

Shimoda LM, Park C, Stokes AJ, Gomes HH and Turner H (2012). Pacific island 'awa (kava) extracts, but not isolated kavalactones, promote proinflammatory responses in model mast cells. *Phytother Res* 26(12):1934–1941.

Shinomiya, K., Inoue, T., Utsu, Y., Tokunaga, S., Masuoka, T., Ohmori, A., Kamei, C. (2005) Effects of kava-kava extract on the sleep-wake cycle in sleep-disturbed rats. *Psychopharmacol* (Berl). 180(3):564-9. https://doi.org/10.1007/s00213-005-2196-4

Singh, Y. N. (1992). Kava: An overview. *J. Ethnopharmacol*, 37(1), 13–45. https://doi.org/10.1016/0378-8741(92)90003-a

Tarbah, F., Mahler, H., Kardel, B., Weinmann, W., Hafner, D., & Daldrup, T. (2003). Kinetics of kavain and its metabolites after oral application. *J. Chromatogr. B*, 789(1), 115–130. https://doi.org/10.1016/s1570-0232(03)00046-1

Tetro, N., Moushaev, S., Rubinchik-Stern, M., Eyal, S. (2018) The Placental Barrier: the Gate and the Fate in Drug Distribution. *Pharm Res*. 23;35(4):71. https://doi.org/10.1007/s11095-017-2286-0.

Tsutsui, R., Shinomiya, K., Takeda, Y., Obara, Y., Kitamura, Y., Kamei, C. (2009) Hypnotic and sleep quality-enhancing properties of kavain in sleep-disturbed rats. *J Pharmacol Sci*. 111(3):293-8. https://doi.org/10.1254/jphs.09167fp

Vanuatu National Statistics Office (2009), *National Population and Housing Census, Analytical Report Volume 2, 2009*. Republic of Vanuatu. https://vnso.gov.vu/images/Public_Documents/Census_Surveys/Census/2009/2009%20Census%20Analytical%20Report%20-%20Vol2.pdf

Wainiqolo, I., Kafoa, B., Kool, B., Robinson, E., Herman, J., McCaig, E., & Ameratunga, S. (2016). Driving following Kava Use and Road Traffic Injuries: A Population-Based Case-Control Study in Fiji (TRIP 14). *PloS One*, 11(3), e0149719. https://doi.org/10.1371/journal.pone.0149719

Walden, J., von Wegerer, J., Winter, U., Berger, M., Grunze, H. (1997) Effects of kawain and dihydromethysticin on field potential changes in the hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 21(4):697-706. https://doi.org/10.1016/s0278-5846(97)00042-0

Wang, P., Zhu, J., Shehu, A. I., Lu, J., Chen, J., Zhong, X.-B., & Ma, X. (2019). Enzymes and Pathways of Kavain Bioactivation and Biotransformation. *Chem Res Toxicol*, 32(7), 1335–1342. https://doi.org/10.1021/acs.chemrestox.9b00098

Wheatley D. Kava and valerian in the treatment of stress-induced insomnia. (2001) *Phytother Res* 15(6):549-51. https://doi.org/10.1002/ptr.840

White, C. M. (2018). The Pharmacology, Pharmacokinetics, Efficacy, and Adverse Events Associated With Kava. *J. Clinical Pharmacol*, 58(11), 1396–1405. https://doi.org/10.1002/jcph.1263

World Health Organisation (2007) Assessment of the risk of hepatotoxicity with kava products. *WHO Advisory Committee on Safety of Medicinal Products.* Geneva. https://apps.who.int/iris/handle/10665/43630 Accessed: 24 June 2022