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KE KIA'ĀINA O KA MOKU'ĀINA 'O HAWAI'I

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In reply, please refer to:
File:

Generally Recognized as Safe (GRAS) Determination for ‘Awa
January 23, 2024

The University of Hawai‘i (UH) College of Tropical Agriculture and Human Resources (CTAHR) Department of Tropical Plant and Soil Sciences, through representative experts in the field of indigenous agricultural, medical, and Polynesian cultural practices, observed in a letter to Hawai‘i’s congressional representatives dated October 5, 2023 and subsequently forwarded to the Director of the Hawai‘i State Department of Health (DOH) via email, that the United States Food and Drug Administration (U.S. FDA) erroneously classified the traditionally prepared ‘awa beverage (also known as “kava”) as unsafe for human consumption (See Attachment A). By way of this memorandum, DOH seeks to clarify its position with respect to the sale and distribution of ‘awa in the State of Hawai‘i and, under the conditions detailed herein, hereby recognizes as GRAS ‘awa for its intended use in the preparation of the traditional and customary beverage pursuant to the applicable federal exception.

‘Awa (*Piper methysticum*) is a shrub that grows from about four to eight feet high with heart-shaped, pointed, green leaves and a root that becomes three to five inches thick at maturity. Globally, there are more than two hundred varieties of ‘awa, with the ‘awa beverage being made using the roots of the noble variety.

The ‘awa beverage was traditionally prepared by cutting the root into bite-sized pieces, chewing the pieces to mince the root, and steeping the minced root product in water. However, for at least the past one hundred years, the beverage has been more commonly prepared by grinding or pounding the noble root prior to mixing with water, in lieu of chewing.

The ‘awa plant contains six major kavalactones, which are the active pharmacological components of ‘awa. Extraction of the kavalactones ordinarily occurs when ‘awa is steeped in a liquid. **However, organic extraction (i.e., using acetone, ethanol, or similar solvents for extraction) results in two to ten times the total amount of kavalactones than is extracted via aqueous extraction (i.e., using water). Per the U.S. FDA, the highly concentrated amount of kavalactones extracted via non-traditional methods may pose a significant health hazard due to liver toxicity.**

Regulatory Authority

Title 21 of the Code of Federal Regulations (CFR) regulates food and drugs, with subchapter B, part 170, subpart B specific to food additive safety in food for human consumption. 21 CFR §170.30 details the eligibility for classifying a food additive as GRAS.

Unfortunately, DOH lacks the necessary resources to conduct the quantity and/or quality of scientific procedures necessary to evaluate the safety of the ‘awa beverage as prescribed by federal law under 21 CFR §170.30(a) or (b). 21 CFR §170.30(c)(2) is also inapplicable as Hawai‘i has been a territory of the United States since 1898.

However, 21 CFR §170.30(c)(1) outlines the following exception:

> “General recognition of safety through experience based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive. General recognition of safety through experience based on common use in food prior to January 1, 1958, shall be based solely on food use of the substance prior to January 1, 1958, and shall ordinarily be based upon generally available data and information. An ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures.”

“Common use in food” is defined in 21 CFR §170.3(f) as “a substantial history of consumption of a substance for food use by a significant number of consumers.”

Per §328-1, Hawaii Revised Statutes (HRS), Definitions:

> “‘Food Additive’ means any substance, the intended use of which results or may be reasonably expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if the substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in a food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use, except that the term does not include:
>
> (1) A pesticide chemical in or on a raw agricultural commodity;
> (2) A pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity;
> (3) A color additive; or
> (4) Any substance used in accordance with a sanction or approval granted prior to the enactment of the Food Additives Amendment of 1958, pursuant to the Federal Act, the Poultry Products Inspection Act (21 U.S.C. §§451-470), or the

> Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. §§601-695).”

DOH adopted 21 CFR §170, including the common use exception found in 21 CFR §170(c)(1), via §11-29-8(a), Hawaii Administrative Rules (HAR):

> “The following food regulations of the United States Food and Drug Administration shall be adopted insofar as they do not conflict with the provisions of this chapter or any other rule enforced by the department of health:… 21 CFR Part 170 Food Additives…”

Based upon this regulatory authority, DOH has the discretion to recognize ‘awa in the context of its intended use as GRAS, provided that its history of safe consumption conforms with the exception detailed in 21 CFR §170.30(c)(1).

Common Use of the ‘Awa Beverage in Hawai‘i

In 2016, the United Nations Food and Agriculture Organization (UNFAO) and the World Health Organization (WHO) jointly published “Kava: a review of the safety of traditional and recreational beverage consumption,” a technical report that reviewed existing scientific information on the safety of ‘awa when consumed as a beverage (See Attachment C). The WHO report notes that the ‘awa beverage has a long history of consumption in the South Pacific, as it has been consumed for more than two thousand years and plays an important role in traditional community ceremonies, with little documented evidence of adverse health effects. The WHO report also notes that commercialization and increased recreational use of ‘awa has resulted in preparation methods that did not exist traditionally (like organic extraction described above), use ‘awa varieties other than the noble variety, and lack sufficient history and documentation of the effects on human health.

DOH finds the WHO report’s conclusion that consumption of the traditional ‘awa beverage has a low-level health risk, and that there is a long and documented history of ‘awa consumption throughout the South Pacific, to be persuasive. However, because the WHO report is centered on the South Pacific, DOH has collected additional literature from UH CTAHR to ascertain common use and traditional preparation of the ‘awa beverage, specific to Hawai‘i, prior to January 1, 1958.

The source of ‘awa in Hawai‘i is unclear, however ‘awa was cultivated throughout Polynesia wherever it could be grown and it is likely that it was introduced to Hawai‘i by Polynesian voyagers. In *The Hawaiian Planter Volume 1: His Plants, Methods and Areas of Cultivation* by E.S. Craighill Handy (1940), “Native tradition reports that awa was first planted in the Hawaiian Islands on Kauai by Oilikukaheana (Fornander, 25, vol. 5, pp. 606-608), who brought it from Tahiti (Kahiki).”

Per Handy, “Awa grows well only where there is constant moisture and not too much sun. Formerly, when it was cultivated, the Hawaiians planted it in or just below the borders of the lower forest zone, in clearings within the lower ranges of the forest, along streams, and in pockets along the base of and upon wet escarpments… There are certain localities on each of

the islands which used to be famous for their awa. Kamakau (40) names some of these: Koukou on Kauai, Hena on Oahu, Lanakila on Maui, and Puna on Hawaii.”

Finally, Handy writes: “In historic times [‘awa] has been so used by all classes of people, especially fishermen, farmers, hunters, and the like whose strenuous work left them stiff and taut with fatigue… The distinction between the awa drinking of the alii and commoners was one of manner and purpose of using the drink. The alii class drank for pleasure largely, the kahuna class ceremonially, and the working people for relaxation after labor. There was an abundance of awa for everyone.”

Margaret Titcomb’s article “Kava in Hawaii” published in *The Journal of the Polynesian Society*, Vol. 57, No. 2 (June 1948) states that “The ‘awa custom is of interest in Hawaii because it was a sacred drink of importance in many phases of Hawaiian life. Outside of water and drinking coconut, no other drink was known. Its effect is to relax mind and body and it was used by farmer and fisherman for this purpose. Medical kahunas had many uses for it. It was customary for chiefs to drink it before meals, for commoners also if obtainable.”

In February 1918, the *Hawaii Herald* newspaper published an article that included a recipe for making the ‘awa beverage and reported that Hawaiian ‘awa roots were shipped and sold in San Francisco for $60 to $70 a ton (roughly $1,300 to $1,500 a ton today) for medicinal purposes. Dried ‘awa powder was also available for purchase nationally in the early 1900s from Sears, Roebuck, and Co. shopping catalogs, to be mixed with water and consumed as a non-alcoholic temperance wine.

Other examples documenting the common use of ‘awa in Hawai‘i include:

- *Roughing It* (1866) by Mark Twain describes ‘awa being sold in Hawaiian markets.

- *The Cultivation of Kava* (1869), quoting historian Samuel M. Kamakau, “Kava was one of the choice foods of the planter” in Hawai‘i.

- *Overland Monthly Out West* magazine (1889) published F.L. Clarke’s account of visiting Hawaiian family homes as a dinner guest and describes in detail the making of the ‘awa beverage. All family members consume the beverage before eating dinner.

<u>Traditional Preparation of the ‘Awa Beverage in Hawai‘i</u>
The traditional preparation of the ‘awa beverage is described in Titcomb’s “Kava in Hawaii” journal article. Using fresh ‘awa root that had just been dried was preferable, but fresh roots were not always obtainable. As such, “a supply of roots was often kept in reserve, thoroughly dried by hanging in the sun. Strength was not lost in drying, and soaking brought back something of the crispness… The root was scraped and washed, then reduced to small pieces. This was done by breaking with a sharp-edged stone if the root was large; by cutting into small pieces with a bamboo knife if small, young and fresh. It was then ready to chew and mix with water to make a cold water infusion.”

“In later days, chewing was replaced by grinding or pounding.” Titcomb further elaborates: “In Hawai‘i, the pounding process finally superseded the chewing process, special tools being developed for the new method.” She quotes O.P. Emerson, who wrote in 1903 that: “It is prepared by pulverizing the root in a mortar; if it is the dry article of commerce it is kept sufficiently moist to prevent its scattering and forming dust.” The resulting mash was mixed with water and “thoroughly kneaded with the hands, and stirred, then strained.” Titcomb also mentions that while water was most commonly used to prepare the ‘awa beverage, “For chiefs, and on rare occasions, water from coconuts was used.”

GRAS Determination

The articles and examples cited above are a small sample of the many references that document and describe a substantial history of consumption, by a significant number of consumers, of the ‘awa beverage in Hawai‘i. Notably, the articles referenced in this memorandum specific to Hawai‘i, documenting and describing the common use of ‘awa, were all published prior to January 1, 1958.

DOH concludes that the use of the noble variety of ‘awa root, mixed with water or coconut water to make a beverage through aqueous extraction, as comporting with the substance and intent of the exception detailed in 21 CFR §170.30(c)(1) and determines ‘awa to be GRAS under those specific set of circumstances consistent with §11-29-8(a), HAR. Consequently, ‘awa root of the noble variety as a food additive for use in a beverage prepared in this specific, traditional, and customary manner shall not be deemed a violation of chapter 328, HRS, provided that all other relevant federal and state food safety laws are satisfied.

‘Awa as a Dietary Supplement

Any ‘awa, including the noble variety, in the form of a dietary ingredient in a dietary supplement, falls under the requirements of the federal Dietary Supplement Health Education Act and may only be offered in its packaged form identifying it as a dietary supplement. All dietary supplements can only be manufactured, processed, or packaged (and must be labeled as a dietary supplement) in a facility registered under the U.S. FDA. ‘Awa as a dietary supplement is not permitted to be used as an ingredient or component of a conventional food item, including but not limited to teas, smoothies, or other beverages. A facility that mixes ‘awa as a supplement with a food or beverage may be cited by DOH under chapter 328, HRS.

Any other preparation of ‘awa, or the use of any other variety of ‘awa, will be considered an adulterated food and/or an unapproved food additive by DOH pursuant to §328-9, HRS, and a violation of chapter 11-29, HAR, and/or chapter 11-50, HAR, unless the elements of 21 CFR §170.30 can be satisfied.

Consumer Advisory

Despite finding ‘awa, as a food additive introduced into water or coconut water and prepared in the traditional and customary manner, to be GRAS pursuant to the applicable regulations, U.S. FDA research suggests a possible toxicological risk associated with its consumption or with its consumption combined with other contributing factors (e.g., alcohol) and there is concern about interference with other medications. There appears to be no scientific consensus at this time, but ‘awa has been linked to liver failure, as summarized in the U.S. FDA memorandum,

“Review of the published literature pertaining to the safety of Kava for use in conventional foods” (See Attachment B).

With the understanding that the concentration of kavalactones can vary depending on preparation methodology, and also recognizing that individuals can react differently to similar concentrations of the same compounds, DOH recommends posting or providing the following consumer advisory statement:

> “Please be advised that ‘awa/kava should not be used by persons under 18 years of age, or by pregnant or breastfeeding women. ‘Awa/kava should not be used with alcoholic beverages. If taking medication, consultation with your doctor prior to ‘awa consumption is strongly advised. Excessive use, or use with products that cause drowsiness, may impair your ability to operate a vehicle or heavy equipment. A potential risk of rare, but severe, liver injury may be associated with ‘awa/kava-containing dietary supplements.”

Disclaimer

DOH’s findings and determination regarding ‘awa herein are not intended to, nor do they in fact, create any right or cause of action for or against any individual or entities nor does this document constitute a warranty or guarantee of quality, or of fitness for consumption, with respect to ‘awa/kawa by DOH or any of its employees.

Kenneth Fink

KENNETH S. FINK, M.D, MGA, MPH
Director of Health

Date: 01/24/2024

College of Tropical Agriculture and Human Resources
Department of Tropical Plant and Soil Sciences

UNIVERSITY of HAWAI'I® MĀNOA

October 5, 2023

U.S. Representative Jill Tokuda (HI-02)
1005 Longworth House Office Building
Washington DC, 20515

Cc: Mitch Heidenreich, Senior Legislative Assistant, U.S. Representative Jill Tokuda
Coti Haia, Chief of Staff, U.S. Senator Mazie Hirono
Arun Revana, Legislative Assistant, U.S. Senator Brian Schatz
Tim Nelson, Legislative Director, U.S. Representative Ed Case

Re: FDA misclassification of traditional Hawaiian food: ʻAwa/Kava

To our congressional representatives of Hawaiʻi:

This Memo, written and signed by several experts, addresses what we see as a grievous error on behalf of the Food and Drug Administration (FDA), which has classified ʻAwa/Kava (noble varieties of *Piper methysticum*)—a traditional beverage of *kanaka maoli* (Native Hawaiians)—as "not safe for human consumption." Through this Memo we aim to (1) bring the issue to the attention of our congressional representatives, (2) formally request that efforts be made to correct the issue, and (3) provide expert testimony and information regarding the issue.

Summary: The FDA guidelines which apply in this case are 21 CFR 170.30 (c) (1) and (c) 2. A beverage made from the simple water extract of ʻAwa/Kava has a long history of use prior to 1958 in Hawaiʻi and throughout the Pacific, where it has been consumed by Native Hawaiians and Pacific Islanders for centuries and is an integral part of the culture. ʻAwa/Kava is consumed as a beverage and FDA regulations include beverages as food. Unfortunately, due to non-traditional applications of the plant, which includes chemical extractions and concentration of active ingredients, the FDA has classified kava as a dietary supplement. Dietary supplements are considered food additives when added to food, which is why at this time FDA does not see kava as food when mixed with water. We see a fundamental error, in which concentrated ʻAwa/Kava extracts, which rightfully should be classified as supplements, are being conflated with the ʻAwa/Kava beverage, which should be classified as a traditional food. This is akin to considering almonds unsafe to eat because cyanide can be extracted and concentrated from the nuts. We seek assistance in the FDA creating separate classifications of ʻAwa/Kava extracts and traditional ʻAwa/Kava consumption as a beverage, as has been done in international standards, the scientific literature, and even individual states. This as an important issue to support Native Hawaiian well-being and cultural identity, and agricultural industry potential in Hawaiʻi and the broader Pacific.

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Attachment A

Background: 21 CFR 170.30 (c) (1) states that foods may be classified as generally recognized as safe (GRAS) "based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive." By this statement alone, ʻAwa/Kava should be granted GRAS status, as it was commonly consumed for centuries by Native Hawaiians and other Pacific Islanders. Without belaboring the point, an abundance of historical references support that ʻAwa/Kava was a recognized safe food in the United States prior to 1958. Hawaiʻi and American Samoa have been utilizing ʻAwa/Kava as a beverage in documented historical events and daily use for at least 1,000 years. Hawaiian historian Samuel Kamakau states that "Kava was one of the **choice foods** of the planter" (Kamakau 1860), with regular consumption remarked upon with meals (Kekahuna 1963), after labor (Handy 1940, Kamakau 1961), and in ceremonies (Handy et al 1972, Malo 1903). The centrality and importance of ʻAwa/Kava to Pacific Islands cultures is well exemplified by the Territory of American Samoa's decision to place an ava (kava) bowl on the 2009 US Quarter.

Mitch Heidenreich has informed us that the FDA's August 11, 2020 Memorandum (see Attachment I) has raised safety concerns regarding ʻAwa/Kava. However, the FDA's August 11, 2020 Memorandum does not address kava as a traditional food/beverage! As clearly stated in the introduction of the memo: "The memorandum discusses kava root extract's chemistry, absorption, distribution, metabolism and excretion (ADME), and its potential mechanism(s) of action; and highlights concerns regarding its hepatotoxic and carcinogenic effects, and other adverse health effects associated with food uses of kava." When looking at the numerous references consulted and cited in the memo, they deal almost entirely with solvent extracts, with no studies conducted with the traditional beverage. **Clearly, the FDA 2O2O report does not address the traditional preparation as a food/beverage**. Indeed, this was not the aim of the FDA, as stated in their introduction.

The FDA Memorandum concludes that "kava is not safe for human consumption." This is a false conclusion that has tremendous ramifications to Native Hawaiians and all Pacific Islanders. The FDA is conflating "kava root extracts," which is what was studied in the report, and "kava," which is a traditional food/beverage that has been consumed by native Pacific peoples for millennia. In essence, the FDA is misusing the word "kava". Vanuatu is the only country in the world with a legal definition for the word "kava" (Kava Act 2002), and the *Codex Alimentarius* standards by the Food and Agricultural Organization of the United Nations (FAO) also give a definition of the word "kava." By these international definitions, **"kava" is specifically defined in terms of** the plant parts utilized, the varieties, and, importantly, **the preparation**. The FDA should be informed that their memo is incorrectly referring to kava as it is defined by these international standards and by cultural practitioners and consumers, and that their memo and its conclusions are instead referring to solvent extracts of kava. As previously mentioned, **the FDA is incorrectly utilizing the term "kava" to conflate extracts with a food product**, which needs to be corrected. They cannot launch a review on particular subject and conclude on another one.

Furthermore, the FDA's August 11, 2020 Memorandum makes no mention of the World Health Organization's 2016 Review of traditional kava beverages (see Attachment II) which concludes, "Kava beverage has been consumed in the South Pacific community for more than 2,000 years and more recently in other nearby communities. During these times, there has been little documented evidence of adverse health effects associated with moderate consumption, indicating that if adverse health effects have occurred, the incidence is likely to be low." Nor does the memo refer to the recent extensive scientific review *Kava as a Clinical Nutrient: Promises and Challenges* by Bian et al. (2020), which, unlike the FDA, makes the distinction between traditional 'Awa/Kava preparation and chemical extracts. Based on the current literature, they conclude that "**Traditional kava use, therefore, is well accepted to be safe, which is in alignment with the recommendation from the WHO in its 2016 report**."

The poor clarity by the FDA has led to confusion on the term "Kava", conflating extracts with the traditional food/beverage. As a result, multiple farmers and vendors are left in limbo as to the legality of their operations. This has led, for example, to individual states to take action in clarifying the terminology to distinguish "Kava" the beverage from extracts. In a Memorandum dated January 11, 2023 from the State of Michigan's Department of Agriculture and Rural Development (MDARD) to All Local Health Departments (see Attachment III), it is stated that "Based on the Technical Report by the WHO, MDARD considers the use of the noble variety of kava root mixed with water to make a tea to be a low risk to public health and Generally Recognized as Safe (GRAS) (21 CFR 170.30). Therefore, noble kava infused in water (tea) from the rhizome or root only is exempt from the definition of Food Additive (21 U.S.C. § 321(s)) based on its GRAS status. The provisions for approval of a food additive under 21 U.S.C. § 348, therefore, do not apply to this specific type and use of noble kava. Noble kava sold in this specific manner is, therefore, not a violation of the Michigan Food Law, MCL 289.1101 *et seq.* If any other preparations or varieties of kava are used, kava is considered a food additive because they do not have GRAS status, according to 21 CFR Part 170.30 or scientific evidence provided." Such state-by-state action can only lead to increased confusion on behalf of consumers and vendors. Clarity and proper action needs to come from the federal level and the FDA.

<u>In conclusion</u>, we present that:

1) There is overwhelming historical precedent for Kava as a traditional beverage to be classified as a GRAS food product due to its long-term usage prior to 1958 per 21 CFR 170.30 (c) (1); and
2) That the FDA is misusing the term "Kava" as clearly defined in international standards to conflate traditional preparation methods with chemical extracts; and
3) That as a core component of the history and culture of Native Hawaiian and other Pacific Islanders, presenting traditional consumption of 'Awa/Kava as unsafe is an unjust discrimination against the indigenous peoples of Hawaii, the US Affiliated Pacific, and Pacific Island partners.

As such, we urge that the FDA be informed of their error and appropriate steps be taken to recognize the traditional beverage of ‘Awa/Kava as GRAS. In this process, the FDA should codify the definition of Kava to align with the FAO’s *Codex Alimentarius* as was done by the State of Michigan and create a separate terminology and definition for kava extracts.

We sign this Memorandum as recognized and published experts on ‘Awa/Kava within the scientific, cultural, and consumer communities.

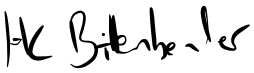
Dr. Vincent Lebot
Scientist, CIRAD, Center for Research and Agricultural Development, Port Vila
Dr. Lebot is widely recognized as one of the world’s leading Kava experts, with dozens of scientific publications on the plant

Michael Louze
Chairman of the Vanuatu Kava Industry Association, Port Vila Vanuatu.
Mr. Louze is a leader within the international kava industry

Edward Johnston
Association for Hawaiian ‘Awa, Pepe‘ekeo, Hawai‘i.
Mr. Johnson has published the authoritative book on noble Hawaiian ‘awa cultivars and is an expert on local kava culture

Dr. Noa Lincoln
Principle Investigator of the Indigenous Cropping Systems Laboratory, University of Hawai‘i at Mānoa, Honolulu, Hawai‘i
Dr. Lincoln is an expert on indigenous Pacific crops and contemporary usage

Dr. Harry C. Bittenbender
Professor Emeritus, College of Tropical Agriculture and Human Resources, Honolulu, Hawai‘i
Dr. Bittenbender specialized in beverage crops, including the kava beverage, for over 4 decades



Dr. Jonathan (JD) Baker
Associate Professor of Biology, Chaminade University, Honolulu, Hawai‘i
Dr. Baker has studied kava from a medical anthropology perspective for over 15 years

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Attachment 1

Food and Drug Administration Memorandum dated August 11, 2020

Attachment B

Memorandum

Date: August 11, 2020

From: [redacted] Ph.D., Toxicologist
Division of Food Ingredients (DFI), HFS-255
Office of Food Additive Safety (OFAS)
Center for Food Safety and Applied Nutrition (CFSAN)

Through: [redacted], Ph.D., Branch Chief, DFI, OFAS, CFSAN

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Through: [redacted], Ph.D., Division Director, DFI, OFAS, CFSAN

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Subject: Review of the published literature pertaining to the safety of Kava for use in conventional foods

I. Introduction

This memorandum summarizes generally available information from the published literature and other informational sources on Kava (*Piper methysticum* G. Forster). The root is the part of the kava plant ordinarily used by consumers. The memorandum discusses kava root extract's chemistry, absorption, distribution, metabolism and excretion (ADME), and its potential mechanism(s) of action; and highlights concerns regarding its hepatotoxic and carcinogenic effects, and other adverse health effects associated with food uses of kava.

II. Literature Searches

The following primary literature databases were searched to retrieve scientific data published on kava: PubMed, ScienceDirect, Embase, ChemIDplus Advanced, Natural Medicines (formerly Natural Standard, and Natural Medicines Comprehensive Database), and Medline. The search terms used were kava, dietary intake of kava, ingestion of kava, kava hepatotoxicity, kava and anxiety, kava and CNS effects, adverse effects of kava, kava pharmacokinetics, metabolism of kava, human exposure of kava, and kava case reports. The entirety of the databases from

all the years available up to July 2020 was searched revealing more than 800 publications. In order to focus on literature most relevant to the use of kava as a "relaxation" beverage and/or as an ingredient in foods, the search was refined to identify studies related to the oral consumption of kava with greater emphasis on potential adverse effects in humans. The literature selected for this review describes some of the effects of kava on the liver, the central nervous system as well as other toxicities.

III. Background

Kava (*Piper methysticum* G. Forster), is a perennial shrub, a member of the pepper family Piperaceae, native to the geographic regions of Polynesia, Micronesia and Melanesia. Some of the common names for kava include intoxicating pepper, ava, ava pepper, awa, kava kava, kava pepper, kava root, kawa, kawa kawa, kew, rauschpfeffer, sakau, tonga, wurzelstock, and yagona.

Kava beverages have been used ceremonially and socially in the South Pacific for many centuries. Kava drinking was introduced to places like New Caledonia, the Solomon Islands, Kiribati, and New Zealand by migrants. Kava became popular in Western society as a recreational drink, a dietary supplement and used for medicinal purposes as an anxiolytic drug for anxiety and insomnia. Traditionally, kava extracts are prepared from macerated rhizome roots combined with cold water or coconut milk. Kava beverages made from fresh or dried roots of *Piper methysticum*, are consumed for their relaxant and psychoactive properties (Bilia et al. 2002). Commercially available kava formulations have been primarily ethanol, methanol or acetone extracts, standardized to specified kavalactone content.

Although there is some scientific evidence for the use of kava to treat anxiety, safety concerns over hepatotoxicity has resulted in withdrawal or ban in several European markets (France, Switzerland, Czech Republic, Spain, UK, Hungary, Portugal and Germany (up to 2015)) and Canada since 2002. FDA also issued a consumer advisory and a letter to health care professionals in 2002 expressing concern about liver damage in individuals who have ingested kava products (CFSAN, March 25, 2002). However, currently, kava is still available for sale in the U.S. as dietary supplements, promoted for relaxation to relieve stress, anxiety, and tension, as well as for sleeplessness and menopausal symptoms and in Australia and New Zealand as herbal medicine in the treatment of generalized anxiety.

In Australia, Kava has a Schedule 4 entry, and there is a regulatory limitation regarding the maximum of 250 mg kavalactones per day derived from water-based extracts of kava rhizomes and roots, with a limit per dosage of 125 mg kavalactones for any individual tablet or capsule (Therapeutic Goods Act (TGA), Oct. 2016).

The Committee on Herbal Medicinal Products (HMPC) of European Medicines Agency (EMA) concluded that based on the available data, a European Union

herbal monograph on kava cannot be established for the treatment of anxiety disorders (EMA Nov. 2017).

IV. Chemistry of Kava

Fresh kava rootstock has been reported to be comprised of about 80% water. Dried rootstock consists of about 43% starch, 20% fibers, 12% water, 3–4% proteins, 3% sugars, 3% minerals, and 3 to 20% kavalactones, depending on the age of the plant and the cultivar (He et al. 1997). More than 40 compounds have been isolated from kava, with the active components present in the lipid-soluble resin (Singh 2005).

There are three chemical classes in the kava resin:
(i) arylethylene-alpha pyrones;
(ii) chalcones and other flavanones; and
(iii) conjugated diene ketones.

The substituted 4-methoxy-5, 6-dihydro-alpha-pyrones or kava pyrones, commonly called kavalactones, possesses the highest purported pharmacological activities.

Kavalactones are concentrated mainly within the rhizomes, roots and root stems of the plant, with the highest concentration in the lateral roots, decreasing gradually towards the aerial plant structures. There are eighteen kavalactones that have been isolated and identified from kava root extract, six of which account for approximately 95–96% of the total kavalactones in the lipid resin, namely, kavain (K), 7, 8-dihydrokavain (DHK) methysticin (M), 7, 8-dihydromethysticin (DHM), yangonin (Y), and desmethoxyyangonin (DMY; 5,6-dehydrokavain) (Fu et al. 2008). In general, kavalactones have low water solubility (Côté et al. 2004). Minor constituents of kava extracts include amino acids, minerals (iron, magnesium, potassium, calcium, sodium and aluminium) and three chalcones (flavokavains A, B and C). Trace amounts of other compounds have been isolated such as alkaloids (pipermethystine, 3α, 4α-epoxy-5β-pipermethystine, and methoxy-cinnamoyl pyrolidine), flavonoids, ketones, phytosterols and aliphatic alcohols.

There are >200 kava varieties or cultivars categorized as noble cultivars, medicinal cultivars, “non-noble” or “two-day” (tudei) cultivars and wild (Wichmannii) species. Kava cultivars are established based on the chemical signature of the six kavalactones obtained from a kava sample. The chemotyping is based on the sequence of the elution of each kavalactone by HPLC and in their decreasing order of quantity. Table 1 shows the chemotype identity and reported “recreational” effects of the six main kavalactones. Hence, variations in chemical composition occur in different cultivars, plant parts, age of the plant, geographic and growth conditions (Singh et al. 2002).

Table 1:

Kavalactone	Chemotype	Reported Effects
Desmethoxyyangonin (DMY)	1	
Dihydrokavain (DHK)	2	Very sedating
Yangonin (Y)	3	
Kavain (K)	4	Euphoria or headiness
Dihydromethysticin (DHM)	5	Very sedating, long lasting
Methysticin (M)	6	

V. Biochemical Aspects of Kava

Absorption, Distribution, Metabolism, and Excretion (ADME)

Mice

Robinson et al. 2009 summarized the absorption of 6 kavalactones—K, DHK, M, DHM, Y, DMY, administered orally in a peanut oil solution to mice. Both K and DHK were rapidly absorbed from the gastrointestinal tract, the peak effect in mice being 10 minutes, as measured by a maximal electric shock test (no details provided about the test). M and DHM had a longer induction period, about 30 to 45 minutes, but also had a longer duration of action. Y and DMY were poorly absorbed from the gut peritoneum, and/or rapidly eliminated.

The pharmacokinetics of four kavalactones, K, DHK, Y, and DMY was studied in the mouse brain. Balb/c mice were administered intraperitoneally (i.p.) each of the kavalactones at a dose of 100 mg/kg, and were sacrificed at specific time intervals (5, 15, 30, and 45 min). The concentrations of these four compounds in brain was determined by GC/MS. After 5 min, DHK and K attained maximum concentrations of 64.7 and 29.3 ng/mg wet brain tissue, respectively, and were rapidly eliminated. In contrast, DMY and Y reached concentrations of 10.4 and 1.2 ng/mg wet brain tissue, respectively, and were more slowly eliminated from brain tissue. However, when crude kava resin (containing 44 mg/kg K and 18 mg/kg Y) was administered i.p. at a dose of 120 mg/kg, the brain concentrations of K and Y markedly increased (2 and 20 times, respectively) relative to the values measured from their individual injection. In contrast, DHK and DMY, after the administration of crude resin, remained similar to their levels obtained after individual i.p. injection suggesting a synergistic effect with kava resin compared with its individual constituents acting alone. The synergism in pharmacological activity appears to be due to potentiation of penetration into the brain when the compounds are administered together rather than separately. However, the mechanism by which this may occur remains unknown. Similarly, it has been reported that Y and DMY when given orally were relatively ineffective. But, in combination with other kava constituents, a marked increase in their potency was observed implying a synergistic action in the absorption of kavalactones from the intestine, when kava constituents are administered together rather than individually (Keledjian et al. 1988).

Rats

The oral pharmacokinetics of Kavain was studied in male Fischer 344 (F344) rats. Kavain (100 mg/kg) was administered either alone or with kava extract (256 mg/kg). The results revealed that K was well absorbed, with >90% of the dose excreted within 72 h, mainly in the urine. When K was co-administered with kava extract, the peak concentration of K (Cmax) in blood plasma was doubled and the area under the plasma drug concentration-time curve was tripled, demonstrating that the presence of other constituents had great impact on the ultimate pharmacokinetics of the whole herb. However, a 7-day pretreatment with kava extract had no effect on the pharmacokinetics of K administered on day 8 (Mathews et al. 2005).

The metabolism of 5 kavalactones (DHK, K, M, DHY and Y) was investigated in Wistar rats. Individual kavalactones were administered by stomach tube at a dose of 400 mg/kg (p.o). The results indicate that ~50% of the dose of DHK was found in the urine within 48 h mostly as hydroxylated metabolites, of which p-hydroxy-DHK was the most abundant and some hippuric acid (9-13% of the dose) was seen. With K, lower amounts of both hydroxylated and ring-opened urinary metabolites were found. M was poorly absorbed with very small amounts of only 2 metabolites seen. In the case of DHY and Y, relatively small amounts of urinary metabolites were formed via O-demethylation. DHK and DHY appear to be better absorbed than other compounds (Rasmussen et al. 1979).

Humans

Studies examining the metabolism of kava in humans are described below.

In vitro studies using Caco-2 cells found kavalactones to be potentially bioavailable as they all readily crossed the Caco-2 monolayers, most with more than 70% crossing within 90 min. There are two characteristics that appear to affect the permeability of the kavalactones. The first factor is the presence of the methoxy (OCH3) group at R2 and the absence of an oxygen functionality at R1. The second factor appears to be the other components present in the extract. The study suggests that the extraction method (aqueous or ethanolic) used is able to influence the total concentrations of kavalactones present in a preparation but does not markedly affect the bioavailability of these kavalactones (Matthias et al. 2007).

Duffield et al. (1989) identified human urinary metabolites of kavalactones following ingestion of aqueous kava extract prepared by the traditional method. Nine kavalactone metabolites were identified, including DHK, K, DMY, Y, tetrahydroxyangonin, 11-methoxytetrahydroyangonin, DHM, methylsticin, and dehydromethylsticin. Metabolites formed were due to the reduction of the 3, 4-double bond and /or demethylation of the 4-methoxyl group of the α-pyrone ring system. Demethylation of the 12-methoxy substituent in yangonin was also identified. In contrast to rats, no dihydroxylated or ring opened metabolites were detected. The main metabolic pathways for kavalactones in humans and rats are

hydroxylation of the C-12 in the aromatic ring, breaking and hydroxylation of the lactone ring with subsequent dehydration, reduction of the 7,8-double bond, and demethylation of the 4-methoxyl group.

Zou et al. (2005) analyzed urine samples of two human subjects (one male and one female Caucasian) after ingestion of 10 g of powdered kava root mixed in water. Analysis of the root extract showed that the total kavalactone content was 13%, which is in the typical range of the levels (3-20%) reported. 6-phenyl-3-hexen-2-one (6-PHO) was detected in the urine as a mercapturic adduct confirming the reactivity of 6-PHO with GSH observed in their *in vitro* studies. The authors suggest that 6-PHO could possibly conjugate with other nucleophiles such as protein thiols or DNA bases and potentially alkylate DNA or disrupt enzymatic and metabolic activity resulting in kava-associated hepatotoxicity.

Tarbah et al. 2003 investigated the metabolism of K in humans and found that *p*-hydroxykavain is the major metabolite that was found in blood and urine in its free and conjugate forms (glucuronide and sulfate). *p*-hydroxy-7,8-dihydrokavain was detected only in the urine. O-desmethyl-hydroxy-5,6-dehydrokavain and 5,6-dehydrokavain were the other K metabolites. After a single oral administration of kavain (800 mg), within 1 and 4 h after uptake, the serum concentrations ranged between 40 and 10 ng/ml for kavain, 300 and 125 ng/ml for p-hydroxykavain, 90 and 40 ng/ml for o-desmethyl-hydroxy-5,6-dehydrokavain, and 50 and 30 ng/ml for 5,6-dehydrokavain.

Toxicological studies

Acute toxicity

In an 8-day study, male Sprague-Dawley (SD) rats (6/group) received two different commercial kava products (kava A containing 80% or more kavalactones and kava B-unfiltered juice of the lateral roots) or vehicle by gavage. The results of the treatment with these products containing high doses of kavalactones (equivalent to approximately 380 mg kavalactones/kg/d; 100 times the suggested dose for humans) significantly increased liver weights, markedly enhanced the hepatic CYP1A1 mRNA expression (75-220 fold) as well as ethoxyresorufin O-deethylase (EROD) activities and CYP1A1 immunoreactivities. CYP1A2 mRNA expression was also moderately increased (2.8-7.3 fold) by both the kava products but to a much lesser extent than CYP1A1. The authors considered the NOAEL to be <380 mg/kg/day. The authors suggest that commercial kava products might exert their potencies to induce CYP1A1 in humans and its consequence may possibly be related to hepatotoxicity especially in susceptible individuals (Yamazaki et al. 2008).

A 2-week study was undertaken to mimic a short-term interaction between heavy kavalactones (KL) dosage and incidental consumption of kava alkaloid, pipermethystine (PM) in humans. The toxic effects of PM, abundant in leaves and stem peelings and acetone-water extracts (75:25, v/v) of kava rhizome (KRE) of

Hawaiian cultivar Mahakea were compared in F344 rats. PM and KRE were mixed in corn oil and administered via intragastric gavage daily for 2 weeks. The total content of KL in the acetone-water extract was 62.67%. This study KL dosage (63 mg/kg/day) was 10 times higher than the daily recommended dosage for human consumption (6–7 mg/kg/day) and may be comparable to mimicking the ‘‘heavy kava drinkers.’’ The results indicate that the treatment of F344 rats with PM (10 mg/kg) and KRE (100 mg/kg) for 2 weeks failed to elicit any significant changes in liver function tests or cause severe hepatic toxicity as measured by lipid peroxidation (malondialdehyde formation) and apoptosis markers (Bax, and Bcl-2 mRNA expression). Rats in all experimental groups lost overall body weight; however, KRE caused the most significant weight loss (42 g) compared with the control group. PM-treated rats demonstrated a significant increase in hepatic glutathione, cytosolic superoxide dismutase (Cu/Zn SOD), tumor necrosis factor α mRNA expression, and CYP 1A2, 2E1 and 2D6. The authors suggest that these effects reflect an adaptation to ROS-induced oxidative stress and possible drug-drug interactions. The lack of severe PM toxicity in rats may reflect possible differences in absorption, metabolism, and/or the variety of kava used. (Lim et al. 2007).

Singh and Devkota (2003) demonstrated that SD rats treated with aqueous kava extracts containing 200 or 500 mg KL/kg/d for 2 or 4 weeks did not exhibit any significant adverse effects in the liver function tests. Serum levels of any of the marker enzymes of liver toxicity such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase or lactate dehydrogenase were not elevated. There were no overt signs of clinical toxicity. Similarly, malondialdehyde (indicative of lipid peroxidation) levels in the liver homogenates did not increase suggesting a lack of liver toxicity by aqueous kava extract. The authors note that these kava doses were up to three times higher than the maximum recommended levels in humans.

Hepatotoxicity

The National Toxicology Program (NTP) conducted a comprehensive toxicology rodent study comprising a 2-week, 14-week (3 month), and 2-year toxicity and carcinogenicity studies in F344/N rats and B6C3F1 mice to address kava associated liver toxicity and carcinogenicity concerns. The study revealed clear evidence of carcinogenic activity in male mice with some evidence of carcinogenic activity in female mice, and an equivocal evidence of carcinogenic activity among male rats. In addition, kava extract caused increased incidences of tumor-like lesions in eyes, kidneys, liver, pancreas and forestomach in male and female rats, in the liver of male and female mice, and in the forestomach of female mice.

In the two-week studies, rats and mice were administered orally 0, 0.125, 0.25, 0.5, 1 and 2 g/kg/d kava extract by gavage. Kava-induced toxicity was observed in the livers of both rats and mice. Dose dependent increases in the absolute and relative liver weights were observed in the 1.0 g/kg and 2.0 g/kg males and in $\geq$0.5 g/kg in female rats. This was accompanied by significant increased incidences of minimal

hepatocellular hypertrophy (HP) in the 2.0 g/kg male and in 0.25 g/kg or greater female rats. In mice, liver weights were significantly increased in 2.0 g/kg males and females with accompanying increases in the incidence of hepatocellular hypertrophy in the 2.0 g/kg female mice. No other significant treatment-related effects were noted (Behl et al. 2011).

Subchronic study (NTP study)

Rats and Mice

In the 14-week NTP study, F344 rats and B6C3F1 mice (10/sex/group) were administered kava extract (30% kavalactones) in corn oil by gavage at doses 0, 0.125, 0.25, 0.5, 1.0, and 2.0 g/kg/d, 5 days per week, for 14 weeks. Exposure to kava extract resulted in unscheduled deaths of one female in the 1.0 g/kg group and three male and four female rats in the 2.0 g/kg groups. The authors attribute the cause of death to kava-induced central nervous system (CNS) and/or respiratory depression. Kava induced decreases in the body weights in the high dose groups in both sexes. Clinical chemistry analyses indicated increases in the activities of γ-glutamyl-transpeptidase (GGT) in the 1.0 g/kg females and both sexes of 2.0 g/kg group. Increased serum cholesterol levels were found in 0.5 g/kg and higher dose groups of both sexes. Dose-related increases in the absolute and relative liver weights and the incidence and severity of HP observed in males at 1.0 g/kg and females at 0.5 g/kg and higher were considered to be adaptive in nature by the authors. Immunohistochemical analyses of the protein expression of CYP enzymes in livers of these same rats showed an increased expression of CYP 1A2, 2B1, and 3A1 in both sexes from the 1.0 and 2.0 g/kg dose groups and decreased expression of CYP 2D1 (human 2D6 homolog) in female rats in the 2.0 g/kg group. Based on the neurotoxic and hepatotoxic effects, the authors considered NOAEL to be 0.25 g/kg in both sexes (Clayton et al. 2007). In mice, deaths of four male and three female 2.0 g/kg mice died during week 1 were attributed to kava extract. The mean body weights of the kava-treated groups were not significantly different from the controls. Ataxia and lethargy occurred in males and females of highest dose groups during week 1. The liver weights of 2.0 g/kg males and 1.0 and 2.0 g/kg females were significantly increased compared to those of the control groups. The incidences of centrilobular hypertrophy in the liver of 0.5 g/kg or greater males and 1.0 and 2.0 g/kg females were significantly greater than those in the vehicle controls.

Guo et al. (2009, 2010) analyzed the whole gene expression changes in the livers of male F344 rats and male B6C3F1 mice administered five different doses (0, 0.125, 0.25, 0.5, 1.0, 2.0 g/kg/d) of kava extract (30% kavalactones) in corn oil by gavage, 5 days per week, for 14 weeks. Microarray analyses of the changes in gene expression were also validated by real-time PCR. In rats, in the high dose group (2.0 g/kg), 72 drug metabolizing enzyme associated genes were significantly altered including 19 Phase I metabolizing enzymes genes; 21 Phase II genes; and 32 transporters (Phase III). In all the three higher dose groups, 7 Cyp genes were altered in a dose-dependent manner. While gene expression of Cyp1a1, 1a2, 2c6,

3a1, and 3a3 increased; Cyp 2c23 and 2c40 decreased. The authors point out that Cyp1a1 is primarily expressed in extrahepatic tissues and there is a low amount in the liver. The Cyp1a1 isozyme can metabolize a number of xenobiotics, including those with flat and planar structures, which include the highly toxic and tumorigenic polycyclic aromatic hydrocarbons (PAH). Therefore, the authors suggest that kava induced Cyp 1a1 may enhance the metabolism of PAHs and adversely affect human health.

In mice, in the high dose treatment group, there were some early deaths in the first week of treatment. Mean body weights were about 6% lower and the absolute and relative liver weights were significantly increased when compared to the controls. Gene expression profiles from the livers revealed that there were 95 drug metabolizing enzyme associated genes significantly altered including 28 Phase I metabolizing enzymes genes; 29 Phase II genes; and 38 transporters (Phase III). The expression of 5 genes (Gsta1, Gsta2, Cyp2a5, Cyp2b20, and Cyp2c55) increased in a dose-dependent manner. Significant changes were observed in the gene expression of Cyp 1a1, Cyp1a2, and Cyp3a11. Further, the most prominent changes were observed in the highest dose group, in the genes involved in the detoxification process, with Gsta1, Gsta2 and Nqo1 genes increased by about 50-, 24- and 4-fold, respectively. The authors speculate the enhanced expression to Nrf2 activation, since these genes are target genes controlled by transcription factor, Nrf2. Histopathology results in the male mice administered 0.5 g/kg and higher dosages of kava extract showed minimal to moderate hepatocellular centrilobular hypertrophy (increased severity with increasing dose). Interestingly, no other severe liver toxicities were observed. Based on the gene expression changes in both rats and mice, the authors suggest that kava extract can significantly modulate drug metabolizing enzymes, potentially leading to herb-drug interactions and hepatotoxicity.

Interestingly, in a study investigating the toxicity of an ethanolic kava extract (7.3 or 73 mg/kg/day) in Wistar rats for 3 or 6 months, no signs of toxicity were found, based on changes in body weight, hematological and liver parameters, and macroscopic and microscopic histological changes in the major organs. Although, the authors concluded that their results do not support kava induced liver toxicity, it should be noted that the doses used are significantly lower than those used in NTP study (Sorrentino et al., 2006).

Dog studies

Mongrel dogs received oral exposure to kavain at doses 10-400 mg/kg daily for 3 months. The results revealed the presence of mild toxicity in high dose group dogs and proliferation of small cells of the thyroid epithelium and a multicentric liver necrosis in one dog in high dose group (Hapke et al., 1971).

Chronic toxicity study (NTP study)

In the 2-year toxicity and carcinogenicity studies (Behl et al., 2011), F344 rats and B6C3F1 mice (50/sex/group) were administered kava extract in corn oil by gavage, at concentrations of 0, 0.1, 0.3, 1.0 g/kg (rats) and 0, 0.25, 0.5, 1.0 g/kg (mice), respectively. Chronic administration of kava in rats did not significantly affect survival or body weight in either males or females. In mice, the survival was not affected in either of the sexes. However, there was a slight reduction in the body weight gain in the female mice in the highest dose group. In rats, GGT activity increased several-fold at 18 months in males and at 6, 12, and 18 months in females. Bile salt concentrations were increased in both sexes. Cystic degeneration was observed in all dose groups of male rats. There were dose-related increases in the incidences of hepatocellular hypertrophy in rats and mice administered kava for up to 1 g/kg body weight. This was accompanied by significant increases in incidences of centrilobular fatty change. There were increased incidences of non-neoplastic lesions in the liver, forestomach, kidney, eye, and pancreas of male and female rats. In addition, a unique lesion was noted in the pancreas in the 1.0 g/kg males and females which included incidences of metaplasia of pancreatic acinar cells to a hepatocytic morphology. Microscopically, this lesion was characterized by the presence of small clusters of apparently normal hepatocytes adjacent to islets of Langerhans. The authors state that the etiology of this lesion remains unknown. There was no treatment-related increase in carcinogenic activity in the livers of male or female rats.

Male mice showed significant dose-related increases in the incidences and multiplicities of hepatoblastomas and hepatocellular adenomas as well as an increase in the combined incidences of hepatocellular carcinomas or hepatoblastomas indicating a **clear evidence** of carcinogenic activity in male mice. In female mice, there was a significant increase in the incidence of hepatocellular carcinomas and in the combined incidence of hepatocellular adenomas or carcinomas in the low and mid dose groups but not in the high dose group indicating **some evidence** of carcinogenic activity in female mice, accompanied by non-neoplastic lesions in the liver and forestomach. Based on these findings, NTP included this kava preparation into **group 2B**, meaning sufficient evidence in experimental animals.

In rats, although liver toxicity was observed, kava extract did not induce liver neoplasms suggesting species differences in the sensitivity of induction of liver neoplasms.

Retinal degeneration

In the 2-year NTP bioassay in F344/N rats, the frequency of retinal degeneration was significantly increased in a dose-dependent manner in the 0.3-g/kg and 1.0-g/kg groups in males, and in the 1.0-g/kg group in female rats, compared to the control groups. The proportion of bilateral change was significantly increased in the 1.0-g/kg group compared to the control group in both males and females. In the evaluation of peripheral retinal degeneration, the average severity grade was significantly increased in a dose-dependent manner in the 0.3-g/kg and 1.0-g/kg

groups in males, and in the 1.0-g/kg group in females, compared to the control groups. The degeneration consisted of a thinning and loss of the external retinal layers, such as the photoreceptors and external nuclear layers, with a decreased cellularity and disorganization of the remaining retinal layers. Reduced photoreceptor outer segment disc shedding and subsequent lower number of phagosomes in the retinal pigment epithelium and alterations in the melatonin pathway may have contributed to the increased incidences of retinal degeneration (Yamashita et al. 2016; 2018).

Effect of kava on CYP 450 enzymes

***In vitro* studies**

Rats

Rat hepatocytes treated with the six kavalactones, showed that only DHM and DMY markedly induced CYP3A23 expression (~7-fold) accompanied by increased levels of CYP3A23 mRNA. Interestingly, six kavalactones, mixed at a non-inductive concentration (15 μM for each), caused induction similar to 90 μM DHM or DMY. However, selective removal of both DHM and DMY, completely abolished the inductive activity of the mixtures suggesting that the induction is additively/synergistically enhanced by other kavalactones. DHM and DMY only slightly activated rat and human pregnane X receptor (PXR). The authors suggest that the induction of CYP3A23 by these 2 kavalactones involves transcription activation through a PXR-independent or PXR-involved indirect mechanism (Ma 2004).

The *in vitro* studies suggest that kava supplementation may give rise to significant CYP-mediated herb-drug interactions.

Humans

Côté et al. (2004) compared the kavalactone composition of the traditional aqueous kava root extract (Moi variety), organic kava extracts (acetone, ethanol or methanol) and extracts from commercial caplets which revealed significant differences in the total amount of kavalactones (2-3 fold) and the ratio of the six major KL. The ratio of the 6 major KL was significantly different in aqueous extracts with very low concentration of yangonin whereas the organic extracts were almost identical to one another. The commercial caplets were high in kavain and dihydrokavain. The aqueous kava root extract contains the lowest proportion of KL of all the root extracts, as expected from the reported low water solubility of KL. All the extracts (aqueous, acetone extract and caplet extract) inhibited the activity of the human liver microsomal P450 enzymes, CYPs 1A2, 2C9, 2C19, and 3A4, with the aqueous extract being the least potent. The authors suggest that the variations in the health effects reported for the kava extracts may be due to the differences in the proportion of KL and use of different preparation protocols.

The effect of kava extract and its constituents on human P450 enzyme activity was investigated *in vitro* using human liver microsomes. When hepatic microsomes were incubated with whole kava organic extract (normalized to 100 μM kavalactones), the activities of CYP2C9, CYP2C19, and CYP3A4 were most markedly inhibited (78 to 92%) compared to the control. There were also significant decreases in the activities of CYP1A2 (56%), CYP2D6 (73%), and CYP4A9/11 (65%). In the case of individual kavalactones at a concentration of 10 μM, M, and DHM, were most potent inhibitors followed by DMY. K did not inhibit these enzymes. DHM strongly inhibited CYPs 2C9, 2C19 and 3A4 (54-76%), M inhibited 2C9, 2D6 and 3A4 (27-58%) and DMY inhibited 2C9 and 3A4 (40-42%) (Mathews et al. 2002). *K*i values for the inhibition of CYP2C9 and CYP2C19 activities by M, DHM, and DMY ranged from 5 to 9 μM. K and DMY (<9 μM) modestly stimulated human P-glycoprotein ATPase activities (Mathews 2005).

In another *in vitro* study (Zou et al. 2004) using both cDNA-expressed human enzymes and cryopreserved human hepatocytes, ethanolic extract of dried kava root and three purified kava lactones (M, DMY, and Y) were found to be potent inhibitors of CYPs 1A2, 2C9, 2C19, 2E1, and 3A4 with IC_{50} values <10 μM. The individual KL were also moderately cytotoxic to human hepatocytes (EC_{50} values of approximately 50 μM). Methysticin was the most potent CYP enzyme inhibitor and most cytotoxic affecting hepatocyte viability followed by kava root extract, DMY and Y. These results suggest that kava could potentially reduce the metabolic clearance of a number of co-administered drugs. Moreover, the CYP2C9 and 2C19 being polymorphic, the effects could vary among genetically different individuals.

In vitro studies in human hepatocytes (HepG2) examining the hepatotoxicity of kavain, methysticin and yangonin demonstrated that kavain had minimal cytotoxicity, methysticin showed moderate concentration-dependent toxicity and yangonin (25 μM) displayed marked toxicity with ~ 40% reduction in cell viability unlike it's least toxicity in cryopreserved hepatocytes (Zou et al. 2004). Apoptosis was induced by yangonin and methysticin indicating that the predominant mode of cell death was apoptosis rather than necrosis. No significant changes were observed in glutathione levels suggesting that glutathione depletion may not be involved in the kavalactone induced injury (Tang et al., 2011). The authors note that the discrepancy in yangonin toxicity may be due to the use of cultured hepatocytes versus cryopreserved hepatocytes.

The above *in vitro* studies using cDNA–expressed CYPs, human liver microsomes, or cryopreserved or cultured hepatocytes, kava extracts and specific kavalactones have been shown to inhibit a variety of human CYP isoforms in the low micromolar range.

***In vivo* studies**

Russmann et al. (2005) conducted a small study in 6 healthy volunteers from New Caledonia, who were regular consumers (>6 years) of the traditional aqueous kava

extract (7-27 g kavalactones/week) up to the beginning of the study who agreed to abstain from kava for 30 days. Determination of metabolic ratios after oral administration of 5 probe drugs reflecting CYP enzyme activity during kava drinking and after a 30-day kava abstinence demonstrated the inhibition of CYP 1A2. However, this practice had no effect on the phenotypic markers of CYP2C19, 2D6, 2E1, or 3A4 function.

In contrast, Gurley et al. (2005) observed that 30 days of kava supplementation in healthy volunteers had no effect on the phenotypic markers of CYP1A2, CYP2D6, or CYP3A4 activity; but CYP2E1 activity was significantly inhibited (~40%).

M, DHM, and DMY appear to be the most potent inhibitors of CYP3A4. Inhibition of 3A4 could lead to elevated plasma levels of simultaneously ingested drugs with potential liver toxicity.

Mechanisms of toxicity

Many mechanisms have been postulated to explain the unexpected toxicity, one being pharmacokinetic interactions between kavalactones and co-administered drugs involving cytochrome P450 enzyme system. Alcohol is often co-ingested in kava hepatotoxicity cases.

It has been reported that 7-9% of Caucasians (Poolsup et al., 2000) 5.5% of Western European, almost 1% of Asian are homozygous deficient in CYP2D6, while it is almost 0% in persons of pure Polynesian descent (Wanwimolruk et al., 1998). Similarly, CYP 2C19 (wild type) gene is absent in 2 to 6% of Caucasian populations and in up to 20% of Asian populations (Zou et al 2004). Thus, genetic polymorphism of CYP enzymes may be one of the factors contributing to the differences in the hepatotoxic response between Pacific islanders and Caucasians.

Overall, it can be concluded that these findings indicate that kava has a high potential for causing drug interactions through inhibition of P450 enzymes responsible for the majority of the metabolism of pharmaceutical agents.

Neurological effects:

The major physiological action in humans is consistently reported as a pleasant, mild, centrally acting relaxant property which induces a generalized muscle relaxation and, ultimately, a deep natural sleep. A minor property of kava is its local anesthetic properties which are experienced as numbing of the mucous membranes of the mouth and tongue when the beverage is consumed.

K and DHK are reported to exert the strongest anxiolytic activity. The psychotropic effects of kava are achieved by the modulation of gamma-amino-butyric acid (GABA) receptors. Although the exact mechanisms are not known, studies suggest that the effects are mediated via different mechanisms such as upregulation of GABA-A receptor function, blockade of voltage-gated sodium ion channels,

enhanced ligand binding across GABA-A receptor subtypes, and reduced excitatory neurotransmitter release.

Using an *in vitro* neonatal rat gastric-brainstem preparation, it was shown that kavalactones and DHK significantly inhibited the activity of the neurons in the nucleus tractus solitarius of the brain stem suggesting their role in the modulation of GABAergic neurotransmission (Yuan et al. 2002). Another *in vitro* study examining the functional effects of kavain at 9 different human GABA-A receptor subtypes expressed in xenopus oocytes found that kavain positively modulated all receptors regardless of the subunit composition, but the degree of enhancement varied at certain receptors. Thus, providing evidence for the direct interaction of K with GABA-A receptors. The modulatory effect of kavain was unaffected by flumazenil, indicating that kavain did not enhance GABA-A receptors via the classical benzodiazepine binding site. It is interesting that K and diazepam did not modulate GABA-A receptors in an additive manner (Chua et al. 2016).

Thus, N-methyl-D-aspartate (NMDA) receptors and/or voltage-dependent calcium channels may be also involved in the elementary mechanism of action. Their effect on the brain is different from that of benzodiazepines or tricyclic antidepressants. The anticonvulsive properties are similar to those of local anesthetics, especially procaine. Analgesia produced by kava occurs via non-opiate pathways.

In addition, a synergistic effect is possible for substances acting on the central nervous system, such as alcohol, barbiturates and psychopharmacological agents.

Effects of Alcohol

Kava is often consumed with alcohol, which may potentiate the hepatic injury. Jamieson and Duffield observed the positive interaction of intraperitoneally administered ethanol and orally administered kava resin in male Balb/c mice. The authors stated that kava resin significantly increased alcohol hypnosis and noted that 300 mg/kg kava resin proved to be lethal to 3 of 6 mice treated with 4 g/kg ethanol, indicating that toxicity and hypnosis were increased. (Jamieson and Duffield, 1990).

Genotoxicity test

The mutagenicity of 6 major kavalactones as well as different solvents kava extractions of roots, leaves, and stem peelings were evaluated using the *umu* test (a sensitive test for point mutations). The results indicated that the 6 KL (100-300uM) were not mutagenic. Two C-glycoside flavonoids (2''-O-rhamnosylvitexin and schaftoside) isolated from *n*-butanol fraction of kava leaves displayed mutagenic potential (Jhoo et al. 2007). Bacterial mutagenicity and *in vivo* micronucleus studies also indicate that kava extract is not mutagenic (Whittaker et al. 2008).

VI. Safety Concerns of the Use of kava in Food

Although small doses of kava induce muscle relaxation and/or drowsiness, long-term and excessive use of kava can lead to malnutrition, weight loss, and apathy**.**

Adverse effects of kava consumption

Hepatotoxicity

Case reports

Kava associated hepatotoxicity is the most concerning adverse effect and has led to bans in Germany, Switzerland, France and Canada. Several cases of liver damage have been associated with kava exposure in Europe including hepatitis (Humberston et al., 2003; Stickel et al., 2003), cirrhosis and liver failure (Escher et al., 2001; Kraft et al., 2001), and death (Gow et al., 2003, Russmann 2001).

World Health Organization (WHO) identified and reviewed 93 case reports with presumed kava related hepatotoxicity. 79% cases involved women with an average age of 45 years using kava for anxiety. In this case series, 7 patients died and 14 had liver transplants. 8 cases with probable associations (essential information for standard assessment available) and 53 cases with possible kava use and hepatotoxicity (insufficient data for a full assessment, or there were other potential causes of liver damage). 5 cases with a positive rechallenge. WHO conclusions after the review of these cases are 1. There is a significant concern of a cause and effect relationship between kava products and hepatotoxicity. 2. A nonrandom effect is indicated by a higher rate for the organic extracts than for synthetic products. 3. In organic extracts, components other than kavalactones might be responsible for hepatotoxicity. 4. Kava products have a strong propensity for kava-drug interactions. 5. Risk factors for hepatic reactions appear to be the use of organic extracts, excessive dose, heavy alcohol intake, pre-existing liver disease, and genetic polymorphisms of cytochrome P450 enzymes. Also, co-medication with other potentially hepatotoxic drugs and interacting drugs, particularly other anxiolytics, antipsychotics, and anti-thrombotics might lead to harm (Coulter et al., 2007).

26 cases of suspected kava hepatotoxicity reported from Germany (20) & Switzerland (6), of which 3 died, 6 survived after liver transplantation and the rest liver issues resolved after kava cessation & supportive care. Patients with hepatotoxicity all used ethanolic and acetonic extracts of kava. Teschke et al. (2008) re-analyzed and assessed the causality using the system of the Council for International Organizations of Medical Sciences, for probability scoring. The results of the analysis were as follows indicating that kava when taken as recommended carries a lower risk whereas overdose, prolonged treatment, and co-medication may carry an increased risk.

16-excluded due to lack of temporal association, independent of kava or co-medication
2-low score excluded
8-various degrees of causality

1- Toxic liver injury, probable causality for kava, the patient followed kava usage recommendations (≤120 mg/d kavalactones and ≤3 months)
1- Probable
1- Highly probable (rechallenge)
2- possible co-medicated drugs
3- possible overdose and/or longer duration

78 cases of hepatotoxicity have been reported following ingestion of commercial kava caplets. In several of these cases, hepatic failure required liver transplantation or has been fatal (Clouatre, 2004). Two cases have been attributed to depletion of human CYP2D6, the enzyme responsible for kavalactones metabolism (Anke, J., Ramzan, I. 2004). Most other cases involved concomitant ingestion of drugs known for their potential hepatotoxicity or of other pharmaceuticals, which suggests that herb–drug interactions may be implicated.

Becker et al. 2019 report first detailed case report of liver transplantation in a 45-year old female associated with kava use (100 mg daily) for 52 days in Brazil. The authors thoroughly investigated the case, analyzed the sample used by the patient to exclude contaminants and intrinsic toxicity of the substance. The chemical analysis demonstrated methanolic extraction and all the kavalactones were present with no contaminants or adulterants. Causality was inferred between liver damage & kava usage through the Roussel Uclaf Causality Assessment Method (RUCAM) algorithm.

Several studies show a clear association of increased level of liver enzymes GGT, ALP, and moderate to heavy kava beverage consumption as shown in Table 2.

Table 2

% population w/ Abnormal Liver function test results					
Study	Subjects	GGT	ALP	AST	ALT
Brown et al. 2007	Healthy Tongan (31+31)	65 vs. 26 control	23	Normal	Normal
Cairney et al. 2003	Australian Arboriginal (11)	73	65	NA	Normal
Clough et al. 2003	North Arnhem Aboriginal (98)	48	37	NA	24-29
Clough et al. 2003	East Arnhem Aboriginal (101)	61	50	NA	21-24
Russmann et al. 2003	New Caledonia (27)	85	NA	26-29	19-35
Mathews et al. 1988	Arboriginal	NA	NA	NA	NA

Hepatic injury due to traditional aqueous extracts of kava root was reported in a study of 27 heavy kava drinkers in New Caledonia (Russmann et al. 2003). Kava-induced toxic hepatitis was reported in a tourist after consumption of kava beverages (cumulative volume of 2-3L) in traditional Samoan Kava ceremonies (Christl SU et al. 2009). An outbreak of hepatitis A was associated with kava drinking in Western Australian Goldfields when a hepatitis A infected individual, a day after discharge from the hospital participated in kava drinking. The authors suggest that the source of hepatitis A infection was most likely during preparation of kava and/or via the shared drinking vessel (Parker et al. 2014).

In 2002, the US Centers for Disease Control and Prevention (CDC) issued a report on hepatotoxicity associated with kava-containing products. On March 25, 2002, the FDA warned that kava may be linked to serious liver damage, including hepatitis, cirrhosis, and at least four urgent liver transplants. FDA has issued warnings to consumers and physicians.

Phototoxicity

UVA irradiation of kava extract in the presence of a lipid, methyl linoleate, induced singlet oxygen and carbon-centered free radicals, which mediated lipid peroxidation, caused DNA strand cleavage, and generated 8-hydroxy-2′-deoxyguanosine (8-OHdG) adduct in human HaCaT skin keratinocytes. The results revealed that kava extract, 5,6-dehydrokawain, and yangonin are cytotoxic. The

authors of the study suggest that kava is photocytotoxic, photogenotoxic and human exposure to products that contain kava extract may enhance their sensitivity to skin dermopathy and skin cancer caused by ultraviolet A light or sunlight (Xia et al. 2012).

Dermopathy

Kava dermopathy is the most common side effect of excessive and chronic use of kava >310 g/week) and widely recognized in Fijians (Hannam et al. 2014). Kava dermopathy, a type of reversible icthyosiform dermatitis is presented as scaly skin rashes, urticaria, sebotropic eruption. It has been reported in approximately 45% of "regular" consumers, and up to 78% of heavy kava consumers (Rychetnic et al. 2011). Current and ex-kava users among Aboriginal population in northern Australia, showed a higher rate of kava dermopathy, lower body mass index, lowered blood lymphocytes and, in addition, current kava users showed elevated liver enzymes (Cairney et al. 2003). There are case reports of inflammatory sebotropic eruption with erythematous papules, pruritic eruptions on face and torso (Huynh et al 2014, Guro-Razuman et al. 1999). Recently, in the USA, inflammatory sebotropic eruption was reported in a female in her 30s who drank kava tea presented with notable facial swelling, postauricular lymphadenopathy and erythematous papules coalescing into plaques on the face, arms, thighs, chest, abdomen, and back. Her lab results showed significant elevation of white blood cell, eosinophil and neutrophil counts and liver enzymes (Brown-Joel et al. 2018). In UK, the first report of acute cutaneous toxicity in a 23-year old white woman to kava consumption showed inflammatory sebotropic eruption and urticaria with consistent clinical (pruritic, erythematous plaques with some facial swelling, fever and lymphadenopathy), histological (folliculocentric inflammation, rich in neutrophils lymphocytic) and biochemical (neutrophilia and transaminitis) features. (Steele et al. 2020). The sebotropic eruption is thought to be caused by the lipophilic nature of the kavalactones that accumulate in the lipids of the sebaceous glands which then leads to folliculocentric inflammation.

Allergy

Delayed hypersensitivity allergic skin reactions have been reported, including systemic/contact-type dermatitis, sebotropic reactions, and generalized erythema with papules following 2 – 3 weeks of use (Schmidt and Boehncke, 2000). Mast cells are key players in delayed hypersensitivity reactions. It is reported that when mast cells are exposed *in vitro* to aqueous extracts of kava prepared by traditional methods of Pacific islanders, highly active, unidentified components of the aqueous extract promoted calcium release, influx and the secretion of pro-inflammatory mediators which may be the causative components of kava-induced skin inflammation. Kavalactones (M, DHM and K) either alone or in combination did not elicit such response in mast cells (Shimoda et al. 2012).

Effect on Motor skills

In a population-based case-control study, the association between driving after consuming kava and serious injury-involved four-wheel motor vehicle crashes was conducted in Fiji. The results of the study showed that driving within 12 hr of consuming kava in recreational settings was associated with a four-fold increase in the odds of crash involvement, after controlling for confounding factors. Frequent use of kava over the previous 12 months (once a month to once a week and several times a week to daily) was also associated with increased odds of injury-involved crashes (Wainiqolo *et al.* 2016). Four experimental studies examining the effect of pharmacological doses of kavalactones (≤300 mg/d) using computer-based driving simulation have shown slowed reaction time, and the visuo-motor performance on driving simulation was significantly impaired when kava was consumed with alcohol (Wainiqolo *et al.* 2015).

If higher doses of kava are used when driving and operating heavy machinery, caution is advised, as visual attention may be possibly impaired under cognitive demand. In addition, caution is also advised when ingesting kava with alcohol or other substances, as deficits in attention, accuracy and concentration may occur (Foo and Lemon, 1997).

In Utah, a 44 yr old was convicted of 'driving under the influence' after ingesting 16 cups of kava beverage as his driving was impaired and was stopped for swerving in and out of traffic lanes (Deseret news, Aug.5, 1996). Similarly, in California, there were two cases of drivers arrested for 'driving under the influence' after ingesting kava tea. Neither of them was prosecuted.

Cardiovascular effect

A cross-sectional study in the Arnhem Land Aboriginal community revealed that kava's health effects include seizures and extreme weight loss in heavy users (up to 20% of body mass), Raised total and low-density lipoprotein (LDL) cholesterol levels may be a risk factor for cardiovascular disease and sudden cardiac deaths. Potential immunosuppressive effects are suggested by relative lymphocytopenia in heavy kava users. It has been associated with increased red blood cell volume, reduced platelet volume, and reduced serum albumin (Clough et al. 2003). In heavy kava users, tachycardia, electrocardiogram abnormalities (tall P waves-sign of right atrial enlargement) and shortness of breath have been reported (Mathews et al. 1988). P wave abnormalities reflect pulmonary hypertension.

Systemic effects associated with excessive kava use are hepatotoxicity, malnutrition, weight loss, renal dysfunction, and depression of plasma proteins, platelet and lymphocyte levels.

Neurological

Intoxicated kava drinkers (who consumed 205g of kava powder (approximately 150-times clinical doses) showed ataxia, tremors, sedation, blepharospasm and elevated liver enzymes (GGT, and alkaline phosphatase), together with saccadic dysmetria, saccadic slowing, and reduced accuracy performing a visual search task. Kava elicits a dose-dependent psychotropic effect. Kava intoxication is characterized by specific abnormalities of movement/motor coordination and visual attention but normal performance of complex cognitive functions. Saccade abnormalities suggest disruption of cerebellar and GABAergic functions (Cairney et al. 2003a).

A double-blind, randomized, placebo-controlled study in participants with generalized anxiety disorder (GAD) (n = 75) treated with either an aqueous extract of kava (120/240 mg kavalactones), for 6 weeks observed moderate effects on reducing anxiety in the kava group (Hamilton Anxiety Rating scale, HAMA) compared to placebo. However, more headaches were reported within the kava group, GABA transporter polymorphisms were associated with HAMA reduction. The authors conclude that standardized kava may be a moderately effective short-term treatment option for GAD (Sarris et al., 2013c).

Kava may also cause adverse neurological effects and cause excessive perioperative sedation. Such a reaction may be due to benzodiazepine and antidepressant activities on noradrenergic and/or serotoninergic pathways that may potentiate benzodiazepine and induction anesthetic potency (Raduege et al. 2004). A review implicates kava use to effect electroconvulsive therapy outcome in patients due to its neurological actions (Patra and Coffey, 2004). Several cases of central dopamine antagonism have been reported after short-term use (1 –4 days), including torticollis, oculogyric crisis and oral dyskinesias in young to middle-aged people, serious exacerbations of Parkinsonian symptoms (Schelosky et al. 1995; Meseguer et al. 2002)

Musculoskeletal effect

A case of rhabdomyolysis was reported in a 29-year old man after ingestion of an herbal product containing guarana (500 mg), ginkgo biloba (200 mg) and kava (100 mg) (Donadio et al. 2000). Another case of rhabdomyolysis associated with ingestion of large amounts of kava was reported where the 34-year old patient developed peak creatine phosphokinase levels in excess of 30,000 U/L but had no significant renal damage. The patient denied any other ingestions, medications, and excessive exertion (Bodkin et al. 2012).

VII. Drug, herb, and dietary supplement interactions

Kava displays a propensity for both pharmacokinetic and/or pharmacodynamic interactions with other drugs and herbs. This is of concern especially with drugs

that are metabolized by CYP1A2, CYP2C19, and CYP3A or those eliminated by P-glycoprotein, or that have sedative or hepatotoxic effects. Use of different kava cultivar varieties, plant parts other than the roots or contamination with mold hepatotoxins may increase toxicity. Co-administration of kava with acetaminophen (APAP) in mice indicated the possibility of kava potentiating APAP-induced hepatotoxicity. Further, the authors identified synergistic action of flavokavains A and B with APAP hepatotoxicity (Narayanapillai et al., 2014)

VIII. Overall Conclusion

After reviewing the available data and information, toxicology concludes that there is enough toxicological data that demonstrates that indiscriminate use of kava either as a "recreational" or "relaxation" beverage is not safe for human consumption. Moreover, there is no food additive regulation in effect that provides for the safe use of kava as an ingredient in conventional foods, and we are not aware of a basis for such use to be considered as generally recognized as safe (GRAS).

A safety determination for a substance that will be used as an ingredient in conventional food must be based on scientific studies appropriate to establish the safety of the substance under the conditions of its intended use. Further, the GRAS exemption requires not only the safety of the intended use of that substance but also that such safety is generally recognized by experts qualified by scientific training and experience to evaluate the safety of substances added to food. As discussed above in the overview of studies regarding the safe use of kava in foods, since the published literature and numerous case reports raise not only the known risk of hepatotoxicity but also several other adverse effects, we believe that the experts cannot come to a consensus regarding the safety of kava. There is sufficient evidence in rodents (NTP studies) for the carcinogenicity of kava extract. The relevance of such findings for humans cannot be ignored, especially when such neoplastic mechanisms were observed in the target organ, liver. The lack of adequate studies on kava preparations to assess any reproductive and developmental toxicities is also a concern. Additionally, kava has been shown to interact with a number of other drugs, herbs, and dietary supplements and co-administration of these substances with kava may lead to serious negative consequences.

In light of the safety concerns as discussed above, there is no basis to conclude that the use of kava as an ingredient in conventional foods is GRAS. Therefore, DFI/OFAS/FDA considers kava an unapproved food additive when used as an ingredient in conventional foods.

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Attachment 2

Food and Agriculture Organization of the United Nations Technical Report: Kava: a review of the safety of traditional and recreational beverage consumption

Attachment C

Food and Agriculture Organization of the United Nations

World Health Organization

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

Technical Report

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

Food and Agriculture Organization of the United Nations
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Summary

Background to this review

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

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

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

Kava varieties and beverage composition

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

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

Data gaps

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

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

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

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

Kava components and their properties

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

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

Data gaps

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

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

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

Human health effects

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

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

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

Data gaps

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

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

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

Consumption

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

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

Data gaps

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

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

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

Harm minimization

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

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

Potential for standard development

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

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

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

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

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

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

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

1 Introduction

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

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

1.1 Background

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

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

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

1.2 Focus of the report

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

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

1.3 Traditional and recreational use of kava beverage

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

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

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

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

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

1.4 Use of kava extracts in medicinal products

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

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

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

2 Kava varieties / beverage preparation

2.1 Kava varieties

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

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

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

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

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

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

2.2 Preparation and composition of kava beverage

2.2.1 Preparation

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

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

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

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

2.2.2 Composition

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

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

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

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

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

2.3 Preparation and composition of medicinal products

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

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

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

- Further information is needed on the source and composition of material used to prepare kava beverage.

- Further information is needed on the composition of kava beverage, both with regard to pharmacologically active and non-active components.

- There is a need for practical and reliable analytical methods for monitoring kava components (kavalactones, alkaloids and flavokavins) and potential contaminants.

3 Kava components and their properties

3.1 Chemistry and pharmacology

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

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

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

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

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

3.2 Pharmacokinetics

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

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

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

3.2.1 Pharmacokinetic drug interactions

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

In *in vitro* studies, there was no difference between IC_{50} values for aqueous (0.9–9.7 µg lactones/mL) and acetonic kava extracts (1.2–15.3 µg lactones/mL) towards inhibiting isoforms 3A4, 1A2, 2C9 and 2C19 (Coté et al 2004). Individual lactones showed varying abilities to inhibit P450 enzymes, although it is unclear if clinically relevant concentrations are reached *in vivo* in humans (Olsen et al 2011).

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

3.3 Toxicity

3.3.1 Kavalactones

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

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

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

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

3.3.2 Alkaloids

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

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

3.3.3 Flavokavins

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

Vergano et al (2012) have used the *in vivo* toxicity information on flavokavin B (Zhou et al 2010) to establish a permitted daily exposure (PDE) of 10.4 mg/day, using the ICH guideline on solvent impurities[1] and a LOEL of 25mg/kg/day. The calculation provided by Vergano et al (2012) indicates that a heavy kava drinker of noble cultivar Borogu would be below the estimated PDE, while the same drinker of the two-day cultivar Palisi would be well above the estimated PDE. While there are many assumptions in this calculation, it provides a route to establish safe levels of exposure for flavokavin B.

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

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

- Further data is needed on the potential for formation of reactive metabolites of kavalactones, alkaloids and flavokavins, and their role in kava toxicity.

- Further data is needed on the potential for kavalactones to inhibit P450 enzymes, and to potentially enhance the hepatotoxicity of co-administered medication.

- Further data is needed on the potential *in vitro* and *in vivo* toxicity of kava alkaloids and flavokavins, and their mechanisms of action.

- Further data is needed on the *in vivo* toxicity threshold levels for kava alkaloids and flavokavins.

4 Reported human health effects

4.1 Effects on general health

4.1.1 Traditional kava beverage consumption

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

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

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

4.1.2 Clinical trial outcomes

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

Using kava aqueous extracts

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

Using kava organic extracts

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

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

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

4.1.3 Excessive kava beverage consumption

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

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

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

GGT, gamma-glutamyltransferase.

[a] See Appendix 1.

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

Source: Rychetnik and Madronio (2011).

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

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

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

4.2 Effects on the liver

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

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

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

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

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

4.2.1 Hepatotoxicity and kava beverage consumption

South Pacific island communities

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

Box 4.1 Case study reports of hepatotoxicity from kava beverage consumption

Case 1

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

Source: Russmann et al (2003)

Case 2

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

Source: Russmann et al (2003)

Case 3

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

Source: Christl et al (2009)

Australian Aboriginal communities

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

4.2.2 Liver enzyme changes and kava beverage consumption

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

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

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

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

4.2.3 Human cases of kava-associated hepatotoxicity

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

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

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

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

4.2.4 Mechanisms/risk factors - kava-associated hepatotoxicity

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

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

Specific kavalactones or mixtures of kavalactones

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

Inhibition or induction of major metabolising enzymes

In *in vitro* studies, there was no difference between IC_{50} values for aqueous (0.9–9.7 µg lactones/ml) and acetonic kava extracts (1.2–15.3 µg lactones/ml) towards P450 3A4, 1A2, 2C9 and 2C19 enzymes (Coté et al 2004). Individual kavalactones showed varying ability to inhibit P450 enzymes, although it is unclear if clinically relevant concentrations are reached in humans *in vivo* (Olsen et al 2011). Induction of various P450 enzymes, particularly 1A1, has also been observed *in vivo*, which led Yamazaki et al (2008) to propose a role for P450 1A1 in kava hepatotoxicity based on its role in bioactivation of polycyclic aromatic hydrocarbons.

Cytochrome P450 polymorphisms

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

Formation of reactive kavalactones metabolites

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

Toxicity of minor kava components

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

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

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

Kava mould contaminants

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

4.3 Effects on cognitive function

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

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

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

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

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

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

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

RCT, randomised controlled trial.
a See Appendix 1.

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

4.4 Effects on skin

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

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

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

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

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

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

–, unknown.
a See Appendix 1.
b Individuals were surveyed from Vanuatu, Marshall Islands, Kiribati, Solomon Islands, Hawaii, Samoa, Fiji, Palau and Guam.

4.5 Effects on chronic diseases

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

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

4.6 Limitations of the available data on human health effects

- Further information is needed on the effect of regular kava consumption on general health parameters over time, including weight loss and adverse effects on the liver and skin, and the threshold intake for these effects.

- Further information is needed in order to understand the mechanism of kava-related hepatotoxicity, for both organic and for aqueous extracts.

- Further information is needed to understand the mechanism of the kava-induced increase in GGT and its relationship, if any, with long-term hepatotoxicity, and the intake threshold for this effect.

- Further information is needed to understand the mechanism for kava-induced skin rashes (kava dermopathy) and the intake threshold for this effect.

- Further information is needed to understand the relationship between the pharmacological effects of kavalactones and the observed toxicity in humans.

- Further information is needed to understand the effect of kava beverage consumption on the incidence of chronic diseases, if any.

5 Consumption of kava beverage

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

5.1 Level and frequency of consumption

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

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

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

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

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

5.2 Threshold intake levels for adverse effects

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

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

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

5.1 Limitations of the available data on consumption of kava beverage

- Further comprehensive information is needed on the level and frequency of consumption of kava beverage in South Pacific island communities.

- Further detailed information is needed on the concentration range of active components (kavalactones, alkaloids and flavokavins) and potential contaminants in kava beverage preparations.

- Further information is needed on the extent to which alkaloids and flavokavins are extracted by the aqueous solvent during preparation of kava beverage.

- Further data is needed upon which to estimate the levels of intake of kavalactones, alkaloids and flavokavins, as well as potential contaminants, and to establish a safe level of intake.

6 Conclusions and future directions

6.1 Evidence for harm associated with kava beverage

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

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

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

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

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

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

6.2 Potential harm minimization strategies

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

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

6.3 Further investigations to improve safety

6.3.1 General areas of investigation

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

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

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

6.3.2 Specific areas of investigation to address identified data gaps

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

Kava varieties and beverage composition

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

Kava components and their properties

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

Human health effects

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

Consumption

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

Appendix Levels of evidence

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

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

Source: (NHMRC 1999)

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Attachment 3

Memorandum from the State of Michigan Department of Agriculture and Rural Development dated January 11, 2023

GRETCHEN WHITMER
GOVERNOR

STATE OF MICHIGAN
DEPARTMENT OF AGRICULTURE
AND RURAL DEVELOPMENT

KATHLEEN ANGERER
ACTING DIRECTOR

DATE: January 11, 2023 *****This version supersedes the 3-17-2022 memo issued with the same subject.*****

TO: All Local Health Departments (LHDs)
Attn: Medical Director / Health Officer / Director of Environmental Health

Michigan Department of Agriculture and Rural Development (MDARD)
Attn: Food and Dairy Division Managers

FROM: Tim Slawinski, Division Director
Food and Dairy Division

SUBJECT: Michigan Retail Food Establishments Selling Kava Products

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Kava or kava kava (*Piper methysticum*) is a plant with over 100 varieties and is indigenous to the islands of the South Pacific. A beverage made from kava has a long history of consumption in the South Pacific and serves an important role in traditional community ceremonies. The traditional preparation of this beverage is the grinding or pounding of fresh or dried rhizome/root of the noble variety[1] of kava which is mixed with water to make a tea. The consumption of this kava beverage is known to have a sedative effect.

The World Health Organization (WHO) released a Technical Report in 2016 on kava consumption. According to the report, the traditional preparation method and consumption of kava beverage has a long history of usage with a low-level health risk. However, the commercialization and increased recreational use of kava has resulted in preparation methods extending beyond the historic traditional methods. These alternate preparation methods may include use of varieties of kava that are not of the noble variety and may include the use of the stems or leaves as well as the rhizome/root when mixing with water. The WHO document outlines these non-traditional preparation methods lack sufficient history and documentation of effects on human health and could be correlated to increased health risk. The WHO indicates further research is needed in understanding the effects of kava consumption on human health as it applies to non-traditional preparation methods.

Noble Kava Preparations as Conventional Food[2]: Based on the Technical Report by the WHO, MDARD considers the use of the noble variety of kava root mixed with water to make a tea to be a low risk to public health and Generally Recognized as Safe (GRAS) (21 CFR 170.30). Therefore, noble kava infused in water (tea) from the rhizome or root only is exempt from the definition of Food Additive (21 U.S.C. § 321(s)) based on its GRAS status.[3] The provisions for approval of a food additive under 21 U.S.C. § 348, therefore, do not apply to this specific type and use of noble kava. Noble kava sold in this specific manner is, therefore, not a violation of the Michigan Food Law, MCL 289.1101 *et seq.*[4]

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[1] The noble variety of kava is a cultivar of *Piper methysticum.*
[2] By "conventional food," MDARD means food that is not sold as a dietary supplement.
[3] Food additives are generally deemed unsafe unless they meet the conditions set forth in 21 U.S.C. § 348. See also 21 USC § 342(a)(2)(C) ("A food shall be deemed to be adulterated . . . if it is or if it bears or contains (i) any food additive that is unsafe within the mean of [21 USC § 348.])
[4] As long as all other requirements of the Michigan Food Law are met.

If any other preparations or varieties of kava are used, kava is considered a food additive because they do not have GRAS status, according to 21 CFR Part 170.30 or scientific evidence provided. Additionally, these other preparations or varieties of kava are not listed as approved food additives under 21 CFR part 172 or 21 CFR 181. If a facility sells kava as a conventional food,[5] other than noble kava root mixed with water as described above, this can be cited under the Michigan Food Law as an unapproved additive or adulterated food. Food Law MCL 289.6101 (adopting the Food Code); Food Code § 3-101.11; Food Code § 3-202.12.

Kava as a Dietary Supplement: Any kava, including the noble variety, in the form of a dietary ingredient in a dietary supplement (as opposed to as a conventional food item) falls under the requirements of the federal Dietary Supplement Health Education Act (DSHEA) and may only be offered in its packaged form identifying it as a dietary supplement. 21 U.S.C 321(ff). Further, all dietary supplements can only be manufactured, processed, or packaged, and must be labeled as a dietary supplement, in a facility registered under the Food and Drug Administration (FDA) per 21 CFR Parts 101, 111, 119, and 190. Kava as a dietary supplement is not permitted to be used as an ingredient or component of a conventional food item including but not limited to teas, smoothies, or other beverages. 21 USC 350(c)(1)(B).

If the facility mixes kava as a supplement with a food or beverage this can be cited under the Food Michigan Food Law as adulterated. Food Law MCL 289.6101 (adopting the Food Code); Food Code § 3-101.11; Food Code § 3-202.12.

Summary of Acceptable Uses: Michigan retail food establishments may choose to utilize kava within their establishments in the following ways:

- Kava root of the noble variety mixed with water to make a tea, which is considered GRAS based on the scientific data provided in the WHO Technical Report.
- Customers can purchase kava supplements in their properly labeled packages from the business and the customers can choose to add it to their food or beverage at their discretion. MDARD has not determined that it is safe for customers who choose to add kava to other food items.

MDARD recommends posting or providing a conspicuous consumer advisory statement reading: *"Please be advised kava is not for use by persons under 18 years of age, or by pregnant or breastfeeding women. Not for use with alcoholic beverages. Excessive use, or use with products that cause drowsiness, may impair your ability to operate a vehicle or heavy equipment. A potential risk of rare, but severe, liver injury may be associated with kava-containing dietary supplements."*

Additional Kava resources:

- NIH's information on Kava including what is known about its safety
- FDA's Consumer Advisory: "Kava-Containing Dietary Supplements May be Associated with Severe Liver Injury" March 25, 2002
- CDC's MMWR Cases on "Hepatic Toxicity Possibly Associated with Kava-Containing Products --- United States, Germany, and Switzerland, 1999-2002"
- FDA's website for Dietary Supplements
- Kava: a review of the safety of traditional and recreational beverage consumption World Health Organization, 2016

[5] As opposed to a supplement, as discussed below.