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Review

Contemporary Pacific and Western perspectives on `awa *(Piper methysticum)* toxicology

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ABSTRACT

In 2010, a National Science Foundation project in Hawai`i assembled a collaboration of Pacific indigenous scientists, Hawaiian cultural practitioners and scientists trained in Western pharmacology. The objective of the collaborative project was to study Kava, a culturally significant Pacific beverage, and to address and ultimately transcend, long-standing barriers to communication and collaboration between these groups. Kava is a product of the `awa plant (*Piper methysticum*) that has been used ceremonially and medicinally throughout the history of Pacific Island cultures, and is now in widespread recreational and nutraceutical use in the US. This project, culminating in 2015, has enriched the participants, led to published work that integrates cultural and Western pharmacologic perspectives and established a paradigm for collaboration. This review paper integrates cultural and Western perspectives on efficacy, toxicity and the future cultural and commercial significance of `awa in the Pacific. Here we present a detailed review of traditional and non-traditional kava usage, medicinal efficacy and potential toxicological concerns. Recent mechanistic data on physiological action and potential pathological reactions are evaluated and interpreted.

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1. Background—Kava—historical and geographical perspectives

Piper methysticum Forst. f., meaning, "intoxicating pepper," is a shrub-like plant known predominantly as kava, or `awa to the Native Hawaiians. It is native to Oceania, growing throughout Polynesia, Melanesia, and Micronesia [1]. The plant was domesticated ~3000 years ago in Vanuatu, and spread throughout Oceania via Austronesian colonists [2]. In the Native Hawaiian culture, `awa is described as coming to Hawai`i with the akua (gods) Kāne and Kanaloa. Kāne is believed to have made water appear to nurture the `awa crop.

Traditionally, the consumption of kava as a beverage was sacred in Pacific cultures. Indeed, in the words of Mary Kawena`ulaokalaniahi`iakaikapoliopelekawahine`aihonuainālele ilehuaapele Pukui "*…..`awa was the food of the gods…….no religious ritual was complete without it*" [3]. Offerings of `awa were made to protect the health of the Hawaiian people, in rites of passage, to lift tabus and to both facilitate consensus-building and prepare for war or battle. Margaret Titcomb [4] summarized usages of `awa: "*The `Awa custom is of interest in Hawai`i because it was a sacred drink of importance in many phases of Hawaiian life. … Its effect is to relax mind and body ….. Medical kahunas (learned men) had many uses for it…..It was essential on occasions of hospitality and feasting, and as the drink of pleasure of the chiefs*". A Hawaiian mele illustrating these usages is shown at the left.

He `awaawa no nā kāne
A me nā wahine o ka lani He `awaawa no nā kāne
Me nā wahine o ka lua. Pēlā aku, pēlā mai,
E mū ka waha, e,
E holoi i ka lima.
Elieli kapu, elieli noa, Noa ke kapu, noa ka hele,
Noa kānawaawai a ke akua

`AwaAwa for the men,
And women of the heavens,
`AwaAwa for the men,
And for the women of the pit.
Thus it was, thus it is,
Silence the mouth,
Wash the hands.
Sacred is the taboo, sacred is the freeing,
The taboo is lifted and one can go,
The law is lifted by the gods

Various parts and preparations of `awa were used medicinally in Pacific cultures. From their earliest contact with Pacific islanders, Europeans were therefore interested in kava as a medicine, first as a treatment for venereal diseases [5], and later as a sedative and treatment for anxiety [2]. A major boom in kava popularity occurred in the 1990s linked to both health-related and recreational usage for non-Pacific audiences. The most recent incarnation of the kava story is as a nutraceutical, formulated as pills and liquid extracts, as an analog to anti-anxiety drugs. Products are standardized to a specified concentration of kavalactones, which have been extracted from kava plant material with alcohol, acetone, or water.

2. Contemporary exposures to Kava

In the contemporary Pacific, people still drink kava. The drink is still prepared in a semi-traditional manner as a water extract served from a common bowl into smaller drinking cups (often coconut shells). The drinking protocols and associated social meanings continue to evolve. There is an awareness of the traditions associated with kava, even if little of this knowledge is incorporated into the actual way the beverage is consumed. The purpose of contemporary consumption is largely consonant with less formal consumption of earlier times, but the frequency of consumption, amount consumed, and social context of kava drinking also reflect modern shifts in perspective and social relations. Current exposure is in some cases significantly different from that in the past. As such, a review of kava's safety should examine these shifting and nuanced social dynamics, rather than reiterating past dichotomies of traditional/nontraditional consumption [6].

Contemporary kava use presents two distinct patterns of consumption. Kava drinking is social, involving relatively high doses, and the dosage is not strictly controlled or limited. Kava nutraceutical consumption is of a fixed recommended daily dose for the goal of treating a specific medical condition; it is personal rather than social. Traditionally, kava is mixed with water, is not extracted with another solvent, is strained by hand, and is prepared as a social drink. By contrast, nontraditional nutraceutical forms of kava are solvent-extracted (alcohol or acetone), usually as part of a commercial process, and not consumed socially. A full description of traditional kava drinking and nontraditional consumption is beyond the scope of this paper [2,6], but there are some salient points for comparison when thinking about dosage, effects, and possible risk from these different consumption practices. First, the amount of kava consumed by drinkers is significantly higher than that consumed by those taking supplements. Kava drinkers will normally consume several coconut shells of kava beverage in a typical drinking session. On average, each shell contains as much more than the recommended daily dose of kavalactones used in supplement form for treating anxiety (~200 mg). A

night's dose of kavalactones from drinking kava (5–10 shells) could easily be in the range of 1.0–1.5 g. It should be remembered that these two forms are not identical, as they are prepared by substantially different techniques, and using different solvents. Second, kava drinking is a social activity, whereas supplement consumption is a personal activity with no inherent social dimension. Third, kava beverage is not a standardized product, whereas nutraceuticals supposedly are.

It is difficult to accurately determine the number of people who are consuming kava, the amount of kava they are taking, and the frequency with which they use it [7]. Global use of kava supplements is certainly substantially lower than it was in 2001, prior to bans instituted by several countries due to concerns about liver toxicity [8–15]. However supplement use in the US continues; consumption of kava as a social beverage seems to be increasing [16–23]. Data on the amount of kava produced and exported are not accurate, sales figures for kava products are not widely available, and it is difficult to estimate number of users since both the production and consumption sides of the commodity chain are fragmented.

Kava is grown in more than 6 different island nations in the Pacific and in the wider Pacific Islander diaspora. It is consumed locally and exported to the United States for manufacture into nutraceuticals. Fiji, Vanuatu, Samoa, and Tonga are primary kava-exporting countries [24]. Export statistics from the producer nations give a partial glimpse of consumption, but they are not widely available or reliable. The decentralized, minimally regulated nature of kava's commodity chain contributes to this uncertainty. With respect to supplement use, several companies produce kava supplements (and other products such as kava skin creams), primarily for the US market. There is the potential for this market to dramatically increase, following a 2014 court decision in Germany that overturned the ban on kava products in that country. Changes such as this to the regulatory frameworks in which kava is embedded could quickly affect the availability of these products.

Kava consumption in the US has expanded through supplement availability and most recently through the proliferation in kava bars. In the Pacific, there have also been changes in the pattern of kava consumption. Migration within the region has brought kava drinking to places where it was not previously a tradition (*e.g.*, Kiribati, New Caledonia, the Solomon Islands, and New Zealand; see [6,25]). In addition, changing social practices in societies for which kava drinking is a tradition may be leading to increased consumption. For example, more women are drinking kava in the Pacific than in previous decades. The aggregate result is more demand for kava for general consumption, and more kava consumed in those drinking sessions, as well as an increase in growing kava [26]. In light of these points, a review of the potential toxicity of kava is timely.

3. Kava pharmacology and targets of action

The known active ingredients in kava are the kavalactones. Eighteen of these have been identified, but only six of them: methysticin, dihydromethysticin, kawain, dihydrokawain, desmethoxyyangonin and yangonin, have been the focus of kava studies as they make up 96% of organic extracts [27]. See Fig. 1 for structures of major kava components. However, kava extractions contain a variety of other non-lactone compounds, which may be responsible for the pharmacological benefits and potential toxicity [27,28]. The activity of kava may be the result of one of these non-lactone compounds or a synergy of several or all components found in kava. In fact, studies on RBL2H3 mast cells (Rat Basophilic Leukemia subtype 2H3, ATCC CRL-2256), showed that traditional aqueous kava extracts elicited strong calcium responses not seen in individual or combined purified kava lactones, specifically methysticin, dihydromethysticin and kawain [29]. Furthermore, traditional aqueous kava extracts demonstrated mast cell degranulation whereas purified lactones did not [29].

A focus on kavalactones may neglect other important compounds in kava that can direct cellular responses. Additional kava components include the dihydrochalcones (flavokawains A, B and C), 5,7-dimethoxyflavanone, cinnamic acid bornyl ester as well as tentatively identified compounds classified as phenolics, flavanones, fatty acids and a chalcone, specifically 2,5,8-trimethyl-1-naphthol, 5-methyl-1phenylhexene-3-yn-5-ol, 8,11-octadecadienoic acid-methyl ester, 5,7-$(OH)_2$-4′-one-6,8-dimethylflavanone, 7-dimethoxyflavanone-5-hydroxy-4′ and pinostrobin chalcone [28]. Cinnamic acid has been shown to activate the mast cell calcium channel TRPA1 and has been associated with contact dermatitis [30–32] while the pinostrobin chalcone can act as a stimulatory or inhibitory molecule on mast cells [33]. Equally important, the type of extraction solvent used has a marked effect on the ratios of these compounds as well as the kavalactones, with some compounds not being extracted at all [28].

Though studies have focused on the kavalactones being the primary components of kava extractions, correctly since they have demonstrated a mechanistic connection to gamma amino butyric acid (GABA) receptors, the chemical complexity of kava extracts suggests that a kavalactone-centric approach may (1) underestimate the complexity of and (2) not provide a mechanism for some of the non-GABA based medicinal effects.

4. Kava side effects

Controversy between the approaches of Western kava use and its traditional counterpart arises when considering its medicinal role and the possible pathological side effects on human physiology [34,35]. The pathophysiological effects of kava include muscle degradation, kava dermopathy presented as scaly skin rashes, urticaria, sebotropic eruption, meningism, depression/suicidal tendencies and hepatotoxicity [11,13,36–44]. Amongst traditional practitioners, chronic use of kava has been associated with exfoliating dermopathy [13,36,37,40] that is acknowledged as common. However, long-term health effects such as hepatotoxicity and carcinogenic activity are generally and historically unknown in these same Pacific cultures. Whether this is the result of underdiagnosis, generally poor health surveillance or genuine protection against adverse affects (via genetics, usage patterns or preparative methods) is a crux of current debate. Conversely, the adverse events reported in the Western scientific literature may reflect preparations, material origins and co-morbidities with alcohol, other supplements or prescription drugs that are not dominant in Pacific cultures.

Concerns about possible toxic effects of kava arose in Western countries when reports from Germany, Switzerland and the United States allegedly linked the use of kava containing products with liver failure [45,46]. From 1999 to 2002, a

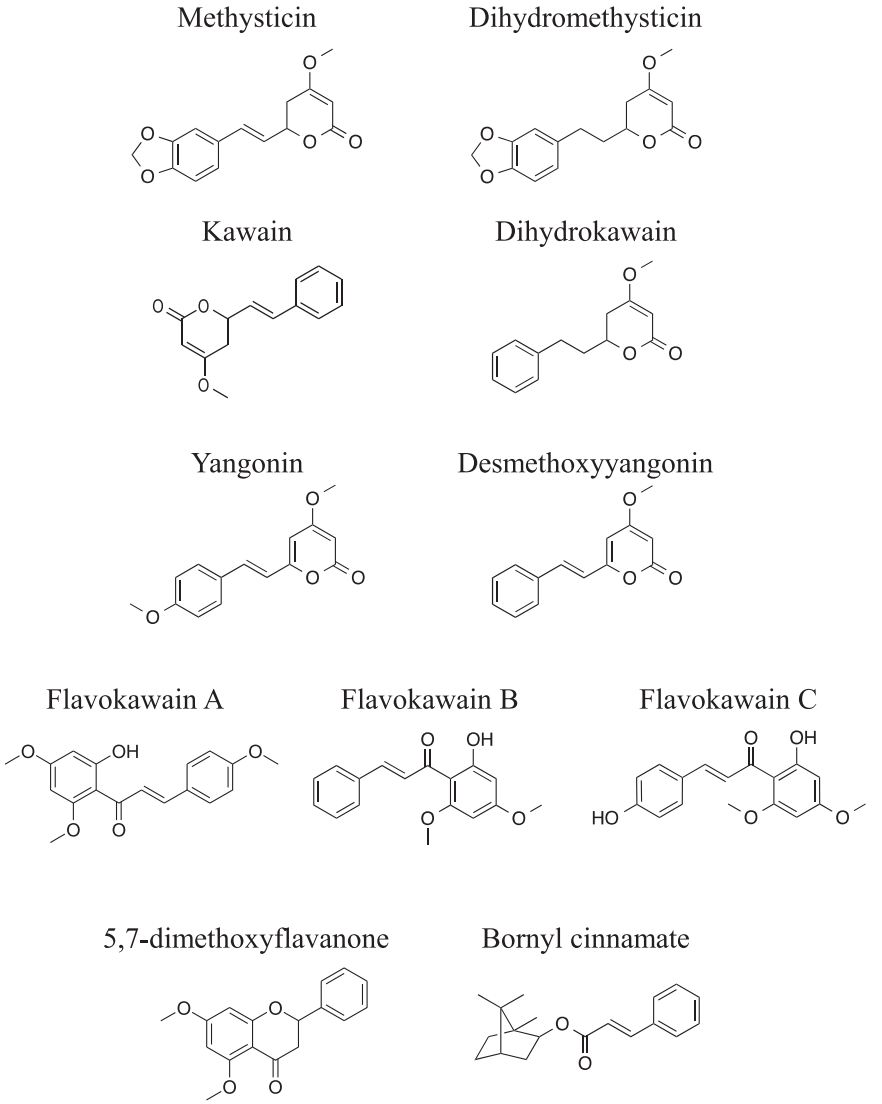

Fig. 1. Kava constituents discussed in the text.

total of 10 patients; six in Germany, two in Switzerland, and two in the U.S. required liver transplants after using products containing kavalactones at doses ranging from 60 mg to 240 mg for as little as 8 weeks to as long as 12 months [9,11,13,41,47,48]. Both patients in the U.S. reported taking kava supplements in capsule form while most European patients reported kava prepared by extraction with either acetone or ethanol [41]. CDC advisories were released in 2002 and 2003 [15,41]. Due to potential toxicity, kava was banned in 2002 by the German Federal Institute for Drugs and Medical Devices (BfArM) and the British Parliament followed suit banning the sale of all products containing kava in 2003 [8–13,49]. However, on June 10, 2014, the German Administrative Court overturned the 2002 ban reinstating the regulatory requirements of 2001. This court stated that risk from kava exposure has not been clearly demonstrated nor appears unusually high, an opinion presumably driven by the very small number of cases of reported toxicity ($n \sim 3$) with even a certain degree of causality linked to kava in a global kava-consuming community that may number in the millions of doses consumed daily.

As we review below, Western science has reported inconsistent information with some studies showing human kava use with hepatotoxicity ranging from cirrhosis, hepatitis and even liver failure [9,11,13,41,47] and some which do not [50–52]. A range of side effects and adverse effect outside the liver are suggested by human cases and animal studies [34,35]. Animal studies demonstrate carcinogenicity of kava, and yet chemopreventive actions, creating a confusing picture for consumers and health professionals. One question which is little addressed in the literature concerns whether under-reporting or diagnosis of health conditions contributes to the perception that kava is not dangerous in the Pacific. This is a clear critique of the work of Steiner which is oft-quoted as an epidemiological basis for the cancer-preventive effects of kava, and by extension as a logic that kava in the Pacific 'does no harm' [53]. The Steiner study draws a correlation between kava use and 'low' cancer rates in Pacific

countries, but fails to address a multitude of confounding factors and alternate explanations, and the high potential for under-reporting/under-diagnosis of cancer rates in Pacific island societies with challenges in health care access and provisions such as pathology services. Absent more evidence, the Steiner study is an exemplar of the *cum hoc ergo propter hoc (Lat., with this, therefore because of this)* class of epidemiological fallacy where association cannot be used to infer causation.

Pacific practitioners address the apparent paradox (the toxicity associated with 'Western' use but not in indigenous cultures) through drawing attention to differences in extraction method, uninformed use of particular cultivars or ill-advised production of the kava drink from parts of the plant not in traditional use. This paradox, together with the explosion of relatively uncontrolled mixes and preparations of kava constituents in the nutraceutical market and a concomitant increasing deviation from traditional preparative methods, creates a need to: (1) review the depth and strength of current data on toxicity, (2) reconcile the apparent paradox between the Generally Regarded as Safe (GRAS) status of traditionally prepared beverages in Pacific cultures with studies and clinical experiences that suggest toxicity, and (3) develop recommendations informed by traditional practices that support safe exploitation of the potential medicinal and nutritional benefits of kava and its many bioactive components.

5. Recent progress in kava toxicology

Here, a range of studies is reviewed across *in vitro* and *in vivo* systems that examine the toxicity of kava and kava components in aqueous and organic preparations.

5.1. National Toxicology Program study

A comprehensive toxicology study in rodents was performed the by National Toxicology Program (NTP) and published in 2012. This was a 2-year kava gavage study in F344/N rats and B6C3F1 mice. The study revealed equivocal evidence of carcinogenic activity among male rats, and clear evidence of carcinogenic activity in male mice with some evidence of carcinogenic activity in female mice. In addition, kava extract in male and female rats resulted in an increase of tumor-like lesions in eyes, kidneys, liver, pancreas and rumen. Note that Equivocal Evidence is defined as marginal increases in neoplasms that may be chemical related, and Some Evidence is defined as a chemical-related increase of malignant, benign or a combination of neoplasms with a response in strength less than that defined under the NTP guidelines for Clear Evidence of carcinogenic activity [54].

The bulk powdered kava extract used in the NTP study (Cosmopolitan Trading Co.; Seattle, WA; Lot 9077SDK) was tested for purity, stability, organic constituents, and identity using various chromatographies. Methanol and aqueous extractions tested by HPLC/UV and LC/MS identified six kava lactones present in the powdered extract: methysticin, dihydromethysticin, kavain, yangonin and desmethoxyyangonin. LC/MS tentatively identified seven additional compounds. Cadmium, lead, mercury, organchlorine and organophosphorous pesticide contaminants were below detectable limits. The bulk kava extract contained 1.4 ppb N-nitrosodimethylamine (NDMA) and 31.2 ppb N-nitrosopyrrolidine [54], both of which can be hepatoxic in rodents at 1 mg/kg levels [55].

A three-month study was designed to determine any additive toxic effects to kava exposure and determining best concentrations for a two-year study. Upon terminal sacrifice no gross lesions were observed but both liver weights were increased in all male rat groups and in at some female rat doses. Microscopic visualization showed hepatocellular hypertrophy in female groups. Male mice in some dose groups displayed centrilobular hypertrophy. Absolute liver weights were significantly increased and male rats at week 14 showed a decrease in alkaline phosphatase (ALP), alanine aminotransferase (ALT), and sorbitol dehydrogenase (SDH). Both male and female 2.0 g/kg rats showed a significant increase in cholestasis serum marker γ-glutamyltransferase (GGT); however, all other cholestasis markers were either decreased or unaffected [54].

In the two-year core study, lethargy and lack of muscle control occurred within the first four weeks of the study; these incidences appeared to decrease in the number of rats over time but reappeared periodically through the remainder of the study at this same dosage. Around the first year of the study, some rats experienced seizures. Hematology results in both male and female rats also showed a decrease in ALP, ALT and SDH and increases in cholestasis markers γ-glutamyltransferase and bile salts [54]. Unlike the 3-month study groups, 'statistically significant or biologically noteworthy' tumor and/or tumor-like lesions appeared in the two year study [54]. An increase in the prevalence of hepatocellular hypertrophy and instances of fatty change [54] were observed in liver [56]. Cystic degeneration and significant increases in multiple hepatocellular adenomas were observed. Malignant liver tumors significantly increased in male mice (in the form of hepatoblastomas) and increased in all kava-exposed female mice (in the form of hepatocellular carcinoma). Male and female mice displayed a significant increase in centrilobular hypertrophy and hepatocellular necrosis [54].

Other organs also showed changes after kava exposure. Significant increases in inflammation, formation of ulcers and increased growth in epithelial cells were seen in the forestomach. Increases in kidney damage, transitional epithelial hyperplasia of the renal pelvis, parathyroid gland and in the bone marrow hyperplasia and retinal degeneration were observed. Leydig cell and bilateral interstitial cell adenomas occurred and kava dose correlated with increase in severity of hyperplasia. Microarray data and immunohistochemistry examined any possible mechanisms for the liver toxicity seen in the animal studies. These tests showed that kava alters cytochrome P450 family of drug metabolizing enzymes (specifically CYP1A1) dose-dependently [54].

In summary, evidence from the NTP studies showed that kava exposure impacts liver function and is most likely dose-dependently and chronically toxic as demonstrated by the significant increases in GGT concentrations, hepatocellular hypertrophy and other histological observations in the three-month and two year studies as well as the effects seen on P450 liver enzymes. Liver toxicity did occur in both rats and mice. Despite the differences in tumorigenesis noted between the animal species, the conclusion of the two-year study stated that "*there was equivocal evidence of carcinogenic activity in male F344/N rats based on marginal increases in the incidences of testicular interstitial cell adenoma*", "*clear evidence of carcinogenic activity of kava kava extract in male B6C3F1 mice based on*

increased incidences of hepatoblastoma" and "*some evidence of carcinogenic activity of kava extract in female B6C3F1 mice based on increased incidences of hepatocellular adenoma or carcinoma (combined)*" [54].

5.2. Flavokawain B is a hepatotoxic constituent from kava root

Chalcone kava components have been linked to the hepatotoxic effects seen in kava consumption [51]. HepG2 hepatoma cells exposed to ethanoic extracts of the kavalactones shown to contain kawain, dihydrokawain, methysticin, dihydromethysticin, yangonin and desmethoxyyangonin separately via HPLC showed no toxicity at 150 μM with the exception of yangonin demonstrating an LD_{50} toxicity at 100 μM; whereas, kava root extracts containing Flavokawains A, B and C (FKA, FKB, FKC) showed significant toxicity. FKB showed the highest *in vivo* toxicity with an LD_{50} value of ~15 μM, and inhibited NFκB activity *in vitro*. These results suggest that, for the most part, the kavalactones are not the source of toxicity with only yangonin being weakly toxic [51]. FKB hepatotoxicity was confirmed *in vivo* when male ICR mice were fed 25 mg/kg body weight FKB for one week. FKB fed mice showed substantial liver damage (hepatocellular swelling, vesicles appearing in the cytoplasm, and inflammation in the periportal area). These results strongly suggest that FKB is hepatocellular toxin not only *in vitro*, but also *in vivo* [51].

These studies demonstrate that kava has potential toxicity in both *in vitro* and *in vivo* models, yet understanding of the mechanism involved in kava toxicity is unclear. Several mechanisms have been proposed that may explain not only the toxicity seen in the above models as well as in the few human cases, but also may explain why the toxicity is reserved to a small number of individuals and why this same toxicity is not observed in Polynesian populations.

6. Mechanisms of toxicity

6.1. Importance of the P450 enzymes and the effect of kava on CYP genes

Inhibition or other defect in CYP genes or direct inhibition of the P450 enzymes is of concern when ingesting any chemical. Approximately 1% of Polynesian and nearly 1% of Asian populations have CYP2D6 deficiency; whereas, approximately 6% of Western Europeans and up to 9% of Caucasians are CYP2D6 deficient [54]. Some studies have suggested that kava toxicity in humans is due to a deficiency in the CYP2D6 gene, responsible for coding the cytochrome P450 family of oxidase enzymes [57–59]. *In vitro* experiments have shown inhibition of several CYPs when exposed to kava extracts and kava alkaloids; it is believed that this inhibition increases the possibility of cytotoxicity due to drug interactions when both kava and other chemicals are consumed concurrently [58,60]. Methysticin analogs found in kava contain a methylenedioxyphenol group, which after metabolism, demonstrated inhibition of several P450 enzymes. Kava extracts, normalized to 100 μM kavalactones with NADPH, severely inhibited CYP2C9, CYP2C19 and CYP3A4. Of the individual kavalactones, desmethoxyyangonin showed significant inhibition of CYP2C9 and CYP3A4. Methysticin showed inhibition of CYP2C9, CYP2D6 and CYP3A4; dihydromethysticin inhibited CYP2C9, CYP2C19, and CYP3A4. However, kawain demonstrated no inhibition of these families of P450 enzymes [58,60]. Thus, inhibition of P450 enzymes by kava may be responsible for drug interactions and liver toxicity; and desmethoxyyangonin, methysticin and dihydromethysticin may be competitive inhibitors of P450 enzymes [58].

6.1.1. Influence of extraction method on kava toxicity

The bioavailability of kava components varies with extraction conditions [27,28]. Nutraceutical production of kava products favors organic extraction methods over the traditional water extraction, because they result in higher concentration of kavalactones than aqueous extraction [8]. Analyses comparing water-extracted kava to acetone, ethanol or methanol extractions have demonstrated differences in the kavalactone ratios and representation of polar compounds [27,28]. Despite these differences in extraction methods, it is still unclear if kavalactone overdose *per se* is the root cause of any toxicity. However, the elevated levels of kavalactones in organic extracts (especially those that are over-represented relative to traditional aqueous preparation) are often pointed to as a potential source of toxicity in organic/nutraceutical preparations. It should also be noted that carbon dioxide extraction is used in some nutraceutical preparations, but the chemical profile of extracts from this methodology is not published, and their relative efficacy/toxicity has not been studied comparatively in *in vitro* or *in vivo* systems.

6.1.2. Genetic influences on kava toxicity

CYP2C9, CYP2C19 and CYP2D6 are the most polymorphic CYP [61]. Drug metabolism is either classified as monogenic, or polygenic, or polymorphic (a monogenic trait that has two or more phenotypes and genotypes in a population) variations that result in individual differences in drug metabolism. Individuals are poor, extensive or ultrarapid metabolizers (PM, EM, UM). PMs have a deficiency in drug metabolizing enzymes, which leads them to increased risk of toxicity due to drug accumulation of both the active compound as well as any metabolites [62]. EMs and UMs, though able to quickly metabolize drugs have their own concerns in that therapeutic benefits of such compounds may require higher doses making determination of safe levels of any drug for an entire populous difficult to determine.

CYP2D6 (debrisoquine/sparteine hydroxylase) is believed to metabolize at least 25% of all common drugs [61]. The gene locus is polymorphic with at least 70 allelic variants. Variant D6 alleles (most notably D6*2, D6*4, D6*5, D6*10, D6*17 and D6*41) are responsible for poor, normal and extensive (ultra) metabolizer phenotypes as well as completely annulled activity [61]. Genetic differences in CYP2D6 genes between traditional-kava drinkers of Polynesian decent versus nutraceutical-kava users of non-Polynesian decent, have been hypothesized as a possible cause of the kava toxicity in a few of the previously reported cases [63]. In two cases of toxicity, the patients tested as CYP2D6-deficient [8,11]. Differences in ability to metabolize racemers of drugs may also link to CYP genotype. For example, CYP2C19 metabolism of S-mephenytoin EMs are identified as those able to completely hydroxylate the S-enantiomer with PMs showing a deficiency in the ability to undergo this reaction [62,64].

Differences in polymorphic CYP enzymes may affect the functionality or toxicology of Western medicines and nutraceutical alternatives. Moreover, the dominance of these genes in mixed ethnic individuals is not clearly understood, indicating

that the incidences of kava toxicity in these individuals may be higher than previously reported. For example, the incidence of debrisoquine (CYP2D6) PMs in the New Zealand Maori population consisting of mixed racial backgrounds primarily with Caucasian lineage has been reported at 5% and proguanil (CYP2C19) PMs at 7%, suggesting that mixed genetic background is extremely important in the drug metabolism [64]. Due to the origination of South Pacific Polynesians from Southeast Asia, both CYP2D6 and CYP2C19 polymorphisms were studied in unrelated South Pacific Polynesian volunteers and compared to the known polymorphisms in Asians and Caucasians [64]. Volunteer Cook Islanders, Niueans, Samoans and Tongans ranging in ages from 18 to 47 years and of at least 75% Polynesian heritage were given 10 mg of debrisoquine sulfate for the CYP2D6 study after overnight fasting. Of the 78 subjects who classified themselves as 100% Polynesian and the 22 who classified themselves as 75% Polynesian, the incidences of debrisoquine PMs were reported at 0% ± 3.6% with metabolic ratios values from 0.01 to 9.94 [64].

In a proguanil study, 33 females and 26 males from the original group (ranging in ages from 18 to 44) were given 200 mg of proguanil hydrochloride, one week after the debrisoquine study and collected for 8 h and tested using the same protocol above; only the antimode metabolic ratio of proguanil:cycloguanil above 10 ($\log_{10} = 1$) indicated PMs. Of this group, eight subjects (five of 100% Polynesian decent, two of 25% Chinese descent and one of 25% Caucasian decent) were classified as proguanil PMs or 13.6% of the subjects with a 95% confidence interval of 5.9 ± 24.6% with metabolic ratios from 11.1 to 34.4. Compared to EMs, PMs excreted approximate 50% less compared to the amount given orally. The results of these studies showed that Polynesian subjects have a closer resemblance of CYP2D6 and CYP2D16 polymorphisms to that of Southeast Asian populations than to Caucasian populations, which may contribute to differences in kava metabolism and toxicity in Polynesian kava users [64].

The effect of mixed and/or Polynesian ancestry on the rate of CYP polymorphisms within a population has not been studied. Native Hawaiians, for example, have intermixed with many other populations such as Asians and Caucasians, and the prevalence of genes responsible for UM, EM and PM phenotypes is unknown. Diminished CYP2D6 functionality in Mexican American populations may provide a useful analogy that we can use to illustrate the potential for similar polymorphisms in Pacific populations. Mexican Americans (MA) have a diverse American Indian, Spanish, African, Caucasian genetic background and 2.6% of the population was classified as PMs [65]. Within the Native Hawaiian community, the results of an influx of Caucasian and other genes since the late 1700s may have affected the CYP2D6 polymorphisms of this population originating from those of Polynesian decent.

6.2. Drug interactions

Kavalactones inhibit several P450 enzymes, and as a result they could interact with drugs and herbal supplements. In addition to pharmacokinetic interactions, kava may have the potential to cause pharmacodynamic interactions as some of the lactones have exhibit the ability to obstruct gamma-aminobutyric acid (GABA) receptors and both sodium and calcium ion channels [66]. Several drugs and drug categories have been reviewed for their potential interactivity with kava:

> Kava is known for its calming and sedating effects and as such concerns arose to its potential to interact with central nervous system depressants such as alcohol, barbiturates and benzodiazepines [57,66]. Interactions with kava and alcohol have been reported in both mice and human subjects. In humans, the effect of kava (1 g/kg powder in 500 mL water) and alcohol (0.75 g/kg) both alone and together was tested on cognitive performance of 10 subjects. When both kava and alcohol were co-consumed, impairment was noticeably increased [57,66]. Interactions with Levodopa, aspirin and warfarin have also been proposed [57].
>
> Interactions with kava and other herbal products are of potential concern. Several of the cases reviewed for kava toxicity have also indicated that St. John's Wort was co-ingested including one of the CYP2D6 deficient patients and a case involving an approximately 68-year-old woman presenting with cholestatic hepatitis [8]. St. John's Wort has shown inhibition on CYP enzymes, specifically intestinal CYP3A4. Moreover, St. John's Wort extracts in the U.S. must contain at least 3.0% hyperforin, and this compound interferes with the uptake of serotonin, norepinephrine and most importantly, dopamine [22,66]. Consequently, St. John's Wort is a potential inhibitor of any drug that affects these important brain neurotransmitters and since kava has also demonstrated inhibition of dopamine, they may well interact.
>
> Even dietary foods and drinks can have interactions with medications or other supplements. For example, IC_{50} values for kavalactones at CYP1A2, 2C9, 2C19, 2D6, and 3A4 resemble those of the grapefruit components bergamottin, 6,7-dihydroxoybergamottin and naringenin [60,57], and thus there is the potential for interactions of kava even with everyday ingestants.

6.3. Enantiomers of kava components and toxicity

Many biological structures and processes differentiate between chiral compounds. Enzymes, receptors and transporters have enantiomeric specificity. Chiral drugs are processed by biological systems imbued with this enantiomeric propensity and the pharmacokinetics and toxicity of enantiomers differ [67]. Kawain, dihydrokawain, methysticin and dihydromethysticin are chiral compounds [8]. The kava-metabolizing CYP2C19 shows enantiomer (metabolizing S faster than R) preference for mephenytoin, an anticonvulsant [62]. Some commercially available kava treatments add a racemic synthetic kawain, which is thought to increase activity but may instead increase toxicity [27]. Despite concerns that racemic lactones like kawain may be responsible for the toxicity of commercially prepared organic extracts, studies addressing this issue seem to be non-existent (to date). One study examined pharmacokinetics of naturally occurring (+)-

kawain enantiomer as well as the inhibition of P450 enzymes by naturally occurring kavalactones, but did not look at the effects of the other enantiomer [59].

Stereospecificity of enzymes in both the activation and elimination of chiral pharmaceutical drugs is critical in providing safe effective medications. In the absence of explicit kava studies on chirality, we can look to other traditional medicines for analogous studies: Wang and Zeng (2010) reviewed several studies that focused on Traditional Chinese Medicines (TCM) that contain at least one chiral center, which may also give a glimpse into the pharmacokinetics of the chiral components found in kava [67]. The first group, the citrus flavonoids (flavonones), contains a chiral carbon within a ring structure, which can undergo non-enzymatic conversion from one enantiomer to the other or racemization from optically active to inactive. Of these, three flavonones were tested in rats for their pharmacokinetics: hesperetin, naringenin and eridictyol. Hesperetin and naringenin enantiomers were metabolized differently [67,68].

The **L**-(-)-form of an alkaloid, tetrahydropalmatine (THP) from *Cordyalis yanhusuo,* is much more active as a pain reliever than **D**-(+)-THP [67]. Hong *et al.* compared the effects of pharmaceutical grade rac-THP on rats with naturally occurring THP in plant extracts. Stereoselectivity was three times higher for the (-) than (+) THP; interestingly, rats exposed to mixed plant extracts containing THP had significantly higher values for (+)-THP suggesting that stereoselectivity is decreased as the chemical complexity increases [69]. This study underlines that the chemical complexity of herbal remedies has a different effect on pharmacokinetics than the purified known active ingredient. Likewise, the complexity of kava has often been argued, by traditional practitioners, to increase the efficacy and safety of this herbal supplement, and this is the first study to establish a potential mechanism for this hypothesis.

6.4. Kava strains and variability in manufacturing/preparation

Other potential causes, as suggested by traditional practitioners, of kava toxicity in non-traditional preparations are: (1) the use of leaves, stems and other plant parts in manufacturing caplets and tinctures instead of root material, and (2) the use of inappropriate cultivars in a manner uninformed by cultural experience and practice. Variances in the chemical composition between the roots, rhizomes and basal stems of the kava plant have been of concern. The alkaloid pipermethystine, a cytotoxin, has been isolated from aerial parts of the plant [27]. Six different potential products from the plant: roots, stems, basal stems, peelings and chips from the rhizome and residues, each traditionally having a specific definition and designated medicinal uses. It is important that nutraceutical manufacturers and novice kava users understand these differences. Pacific traditional drinkers of kava use only the peeled root, carefully washed and ground. In contrast, commercial kava products are often made from peelings and chips of the dried rhizome contaminated with basal stems in the interests of economy. A code for standardization has been explicitly proposed by Teschke *et al.* [70].

Traditional practitioners also have a sense of the most appropriate cultivars for specific uses. There are 200 known kava cultivars in four classifications: Noble, medicinal, Tu Dei (or Two Days) and Wichmannii cultivars. Noble cultivars are considered by Pacific practitioners as the safest as no incidences of liver toxicity has been linked to their traditional social use. Tu Dei cultivars are known for their extended psychotropic effects lasting "two days," hence their name; these cultivars have been associated with nausea, which is believed to be caused by a high concentration of dihydromethysticin. Finally, *Piper wichmannii*, the wild species from which the domesticated *P. methysticum* is derived, is not used for daily consumption due to its long lasting physical effects and low degree of beneficial effects. Supplement manufacturers and their regulators may not take into account the various cultivar classifications and their different effects. World Health Organization findings alluded to this as a potential cause of liver toxicity and the Secretariat of the Pacific Community expressed the importance of selecting the proper kava cultivar for export and establishing a set of standards to ensure the best possible kava to be used for nutraceuticals [47]. Notably, it may be that kava in Hawai`i is free of toxic effects because it represents the end-point of the cultivar selection process across the whole Pacific, so there are no Wichmannii or two day kavas among the Hawaiian varieties [48,71,72]. Thirteen contemporary cultivars found in Hawai`i are unique to Hawai`i, reflecting a process of selection and strain development that Hawaiian farmers engaged in after bringing cultivars from the Marquesas and through somatic mutation developed/selected the cultivars we have today on the basis of stem color and effect (Fig. 2) [48,71,72].

7. Benefits of kava consumption

Kava has been used in Europe since the 1880s to relieve stress and anxiety and British herbal practitioners have been using it to treat urinary cystitis, rheumatism, urethritis and urinary tract infections since the early 1900s [5,73–75]. Kava has a history of use as a nervine treating dizziness, melancholy and neuralgia [74]. More recently, there has been an increased use of kava to treat disorders such as anxiety, nervous tension, restlessness, insomnia and even mild depression and symptoms of menopause [76–92]. Trials of kava have demonstrated it to be superior in treating anxiety compared to placebos and has even been effective where other medications have not [93]. Additionally, kava does not appear to be addictive like alcohol and many prescription drugs; in addition, there is no association with violent or antisocial behavior and kava use [75,94].

7.1. Benefits suggested by the traditional Pacific pharmacopeia

Kava, at first glance, has a surprisingly broad indigenous pharmacology. Medicinally, kava has been used for a wide range of both CNS-centered and peripheral effects. The CNS-centered effects of kava are the most highlighted both in traditional practice, recreational use and contemporary nutraceutical marketing campaigns. These are the sedative and calming effects, which, in the world of nutraceuticals are promoted as treatments for stress, anxiety, and depression, often portrayed as "natural" analogs of anxiolytic and antidepressant pharmaceuticals. While the CNS-centered effects are the most widely cited and discussed, much of the broad list of traditional medicinal uses is not related to the CNS-centered effects. Peripherally, `awa is indicated in traditional Pacific medicine for urogenital conditions (gonorrhea infections, chronic cystitis, difficulty urinating), reproductive and women's health

(for menstrual problems and dysmenorrhea, to facilitate delivery, to stimulate milk production, as an abortifacient and contraceptive), gastrointestinal upsets, respiratory ailments (asthma, coughs, and tuberculosis), skin diseases and topical wounds, and as an analgesic, with significant subtlety and nuance attending the precise strain, plant component (leaf, stem, root, etc.) and preparative method to be used [1–4,75]. These data suggest active components in kava that extend beyond the GABA-ergic, CNS-active, kavalactones, and that may be sufficiently varying with strain, component and preparative method to underlie the complexity that is present in the traditional pharmacopeia.

7.2. Potential chemopreventive actions of Kava

In spite of the evidence that suggests that kava consumption is linked to hepatoxicity and tumorigenesis, other studies show kava as a potential chemopreventive. Dosing of a small number of mice with 10 mg/g of kava for 30 weeks showed a reduction in chemically-induced lung adenomas by over 50% [95,96]. These studies saw no liver toxicity due to kava exposure. The flavokawains A, B and C (FKA, FKB, FKC) were tested as possible kava components responsible for the tumor suppression. Flavokawains are chalcones, several of which have exhibited activity against a range of different types of cancers. Of the three, only FKB demonstrated any reduction in lung adenomas (34%) [96]. For example, Wattenberg *et al.* (1994) showed that 2-hydroxychalcone administered at a dose of 5 mg/g reduced lung tumor multiplicity by approximately 30 to 40 percent. Moreover, Zi *et al.* (2005) noted that flavokawain A suppressed tumor growth in bladder cells [52].

Several potential mechanisms of anti-carcinogenic activity were explored in the above studies. First, Proliferating Cell Nuclear Antigen (PCNA) levels were assessed as PCNA overexpression associates with transformation. Substantial increases in PCNA were observed in kava-exposed animals compared to controls [95]. Moreover, data on PCNA and Ki67 expression showed that anti-carcinogenic activity diminishes over time without continued kava treatment [96]. Caspase 3 upregulation and increased cleavage of poly ADP-ribose polymerase (PARP) were also noted in lung tumors from kava-treated mice, suggesting higher levels of apoptosis.

Another possible mechanism for the chemopreventive effect of kava is reduction in induced DNA damage. After normalization of DNA adduct abundance for the time-controlled group experiment, all six NNK-exposed, kava-fed groups exhibited reduction in all four DNA adducts with 7-pobG, O^2-pobdT, and O^6-prodG showing reductions between 30 and 40%; whereas, O^6-mG demonstrated a 70 to 80% reduction. More importantly, the relative abundances of these four DNA adducts showed no differences at different time points after NNK exposure, leading to the idea that kava treatment inhibits DNA damage [97].

8. Conclusions and open questions

A comprehensive understanding of `awa chemistry is of importance in assessing the future of kava exposure in both Pacific and global populations. This generates two key considerations. First, the type of extraction to be characterized has important implications. There is a tension between fidelity to the traditional aqueous extractions of primarily root samples, and the need to analyze organic extracts of

Fig. 2. Hawaiian cultivars of *Piper methysticum* illustrating stem and leaf characteristics used in traditional selection practices. Hawaiian names of cultivars are shown. Photography credits: Mr. Ed Johnston, (upper panels) Mr. Harry Brevoort (lower panels), Association for Hawaiian `Awa, Hilo, Hawai`i.

aerial and root powders that are the major nutraceutical forms of commercialized `awa. There is good evidence that kava toxicity and efficacy are linked to extraction method. Since both traditional and commercial/organic extracts are public health issues, both need to be examined comprehensively.

8.1. Is kava toxic?

Despite the link to kava and liver toxicity demonstrated *in vivo* and *in vitro*, in the history of Western kava use, toxicity is still considered relatively rare. Only a fraction of the handful of cases reviewed for liver toxicity could be, with any certainty, linked to kava consumption and most of those involved the co-ingestion of other medications/supplements [8,57]. That means that the incident rate of liver toxicity due to kava is one in 60-125 million patients [12]. For Pacific traditional users, despite the much higher kavalactone exposure, `awa liver toxicity is either unheard of or unreported. Nevertheless, in rural areas of the Pacific, where hepatitis is endemic, liver disease that may be caused by kava consumption may be masked and reported as other causes [9]. It is difficult to say with any sense of accuracy since there is a shortage of epidemiology and public health data in Pacific populations who habitually use kava.

8.2. Beyond the kavalactones—is there an entourage effect in kava?

Kava plants are likely to contain a diverse secondary metabolome, with hundreds of compounds that can impact the physiological responses of human cells and tissues [27,28,98–100]. The focus of the `awa field upon the kavalactones is linked to the strong likelihood that these compounds' ligation of CNS GABA receptors is responsible for the relaxant and anxiolytic effects of the drink and its supplements [101,102]. However, the physiological (and possibly pathophysiological) effects of kava may be underestimated by a unilateral focus upon the kavalactones. The secondary metabolome of *Cannabis sativa* provides an analogy here. For decades the primary focus of the field, the marijuana growing community, and medicinal marijuana proponents has been on the major cannabinoid compounds Δ9-THC, cannabidiol and cannabinol. These are indeed the main CNS-active components but they and their derivatives comprise ~7 of the >400 known bioactive molecules in *C. sativa*. Indeed, until the so-called 'entourage' of terpenes, alkaloids, etc., was factored into cannabinoid pharmacology [103,104], our understanding of its mechanisms and breadth of effect was severely limited. Similarly, the `awa field may now benefit from examination of the *P. methysticum* 'entourage'.

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