The Journal of Clinical Pharmacology
2018, 0(0) 1–10

DOI: 10.1002/jcph.1263

The Pharmacology, Pharmacokinetics, Efficacy, and Adverse Events Associated With Kava

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Abstract

Kava is a plant with numerous kavapyrones that can induce pharmacologic effects and drug interactions through the cytochrome P450 and P-glycoprotein systems. Kava is used recreationally and for the treatment of anxiety. Clinical trials verify anxiolytic effects in excess of placebo, but the effects are not seen immediately and the optimal dose and dosing schedule needs to be determined. Clinical trials usually lasting for 4 weeks found generally good tolerability and safety; however, dermatologic, hepatologic, and cognitive adverse effects may occur. Some of these adverse effects are known to occur from the kavapyrones themselves, while others can be caused or exacerbated by use of substandard kava products. There is tremendous variability in the constitution of a kava product based on the parts of the plant that are being extracted and the extraction method. The most commonly studied extract for the treatment of anxiety is the acetone extract.

Keywords

anxiety, herb, kava, kavain, safety

The perennial shrub named kava (meaning bitter plant in Polynesian) and scientifically named *Piper methysticum* (meaning intoxicating pepper), is native to the South Pacific.[1] In the South Pacific, it was traditionally used for religious and ceremonial events, medicinal purposes, and social gatherings. Since the 1990s, kava's recreational and medicinal use has extended around the world, including Australia, New Zealand, Europe, and the United States. After years of general acceptance in these countries, there was a backlash in the early 2000s due to cases of hepatic toxicity in Germany, the United States, and Switzerland.[1–3] In November 2002, the Food and Drug Administration issued a consumer advisory but never banned kava.[3] The Federal Institute of Drugs and Medical Devices in Germany banned kava in 2002.[4] In 2014, a German court ruled that banning kava was an inappropriate action because it did not relate the potential benefits and risks of kava vs those of traditional remedies for anxiety and the harms may be best attributed to lack of quality control, not inherent harm associated with appropriately sourced and manufactured products.[2,4] The German government was given a year to appeal the decision but did not, leading to the final rule ending the ban in 2015.[1,2] Currently, kava can only be used under a prescriber's orders in Germany, not for self-care or for recreational use.[4] Part of the resurgence of kava use in the United States has been predicated on stricter certification and testing processes that improve the quality and consistency of the products that people use.[5] Kava can be purchased in stores, on the Internet, and from kava bars.[5–7] Kava bars are springing up across the United States, and some allow people over 18 years of age drink kava, even though the legal alcohol drinking age is 21 years.[5–7]

This article assesses kava's pharmacology and methods of cultivation and extraction, its efficacy for the treatment of anxiety, its safety profile, and its drug interaction potential.

Pharmacology, Cultivation, and Extraction

Kava derives its pharmacologic effects from the kavapyrones (also known as kavalactones), which are concentrated in the rhizomes, roots, and root stems and progressively diminish the closer you are to the aerial parts of the plant (stem, leaves, peppers).[8] These aerial parts often contain toxic alkaloids like pipermethystine and should not be used. While there are 18 known

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Submitted for publication 15 March 2018; accepted 26 April 2018.

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kavapyrones, 96% of the biologic activity is attributable to 6 of them: kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and demethylxyyangonin.[8]

The amount of plant material incorporated in a product that grows below vs above ground impacts the type and concentration of the various kavapyrones and the total kavapyrone content.[8] In addition, the extraction method can also impact these important variables as well.[9] There are various water extraction techniques, including regular water extraction, boiling water extraction, subcritical water extraction, and Soxhlet apparatus water extraction. There are also alcohol, liquid carbon dioxide, organic solvent (acetone), and coconut milk/oil extraction methods.[9] In the South Pacific, the rhizome and root were historically chewed (masticated) and then expectorated and covered by water and/or coconut milk to extract the kavapyrones.[8] The most commonly studied extract is the WS 1490 dried extract, which uses acetone as a solvent and is standardized to 70% kavapyrone content.[10]

In vitro and in vivo studies have elucidated several biological mechanisms of kava, including enhancement of ligand binding to gamma-aminobutyric acid type A receptors, inhibition of voltage-gated sodium and calcium channels, reduced reuptake of neuronal dopamine and norepinephrine, and acetylcholine enhancement (possibly due to acetylcholinesterase inhibition).[8,11] There may be weak monoamine oxidase inhibitor-B effects as well.[1]

The gamma-aminobutyric acid related effects of kava may be especially important given the clinical data on anxiety. In one study, the functional properties of kavain at several subtypes of human recombinant gamma-aminobutyric acid type A receptors ($\alpha1\beta2$, $\beta2\gamma2$L, $\alpha x\beta2\gamma2$L, $\alpha1\beta x\gamma2$L, and $\alpha4\beta2\delta$) in *Xenopus* oocytes were assessed using the 2-electrode voltage clamp technique.[12] They found that kavain positively modulated all receptors regardless of the subunit composition. Importantly, kavain's effect was not impeded by the benzodiazepine antagonist flumazenil, indicating that kavain does not work via the classical benzodiazepine binding site.[12] Similarly, naloxone does not impact the biologic action of kava, suggesting that opioid receptors are not involved in kavapyrone pharmacology.[8]

Kava Use in Anxiety

A commonly touted use of kava is in the treatment of anxiety disorders. In a meta-analysis of 7 trials (n = 380) by the Cochrane collaborative in 2003, there was a significant decrease in the Hamilton Anxiety Rating Scale (HAM-A) total score in patients receiving kava extract compared with patients receiving placebo (weighted mean difference: 3.9 [95% confidence interval [CI]: 0.1-7.7]).[13] Kava extract was generally well tolerated and no serious adverse events were found. However, they found the effect sizes for kava extract for HAM-A was small, suggesting that larger future trials of longer duration were needed to establish the role of kava extract in anxiety.[13] The trial by Volz[14] was included in the aforementioned meta-analysis, but since it had the longest follow-up (6 months) and one of the largest sample sizes, it deserves special mention. Volz[14] was a randomized, double-blind, placebo-controlled trial of 100 people with anxiety (baseline HAM-A total scores of ~31). In this 24-week trial, patients were given the WS 1490 extract of kava whereby 100 mg of dry powder contained 70 mg of pure kavapyrones. This was taken 3 times a day for a total daily kavapyrone dose of 210 mg. In this trial, the HAM-A total score decreased 68.4% with kava extract and 51.6% with placebo ($P < .001$) and the Clinical Global Impressions Scale rating of "much" or "very much" improved occurred in 75.5% with kava extract and 51.2% with placebo ($P = .02$). Stomach upset was the most common adverse event with kava, occurring in 2 people. Blood pressure and heart rate were not changed from baseline or different between groups. The authors reported that no clinically relevant changes in aspartate aminotransferase and alanine aminotransferase occurred, but data to substantiate this were not provided.[14]

Table 1 displays the results of 5 recent publications (representing 7 randomized, double-blind, placebo-controlled trials published from 2003 to the present) assessing kava's impact on anxiety.[15–19] Regardless of the trial, the placebo effect was very strong across all trials (like all therapies for mental health disorders like anxiety and depression). With the exception of the publication by Connor et al.,[18] kava-treated patients had greater decreases in the HAM-A total score (showing improved symptoms) than their counterparts receiving placebo, albeit some of the trials achieved significant findings and others did not.[15–19] Connor et al.[18] presented the findings of 3 trials, and the first trial had 35 of the 64 total participants in the pooled results.[18] The last 2 trials used the WS 1490 extract but the first trial did not, although the reported total kavapyrone dose administered was the same as the other two. While there was no significant difference, placebo had a larger qualitative drop in HAM-A scores than was achieved by kava in the first Connor trial. This suggests that perhaps the constituent kavapyrones might have been different than WS 1490 leading to these differential findings. The last 2 trials by Connor were more in line with the Cochrane meta-analysis results and the results of the other newer trials.[18] Kava and placebo therapy were well tolerated in all of these newer trials.[15–19] No clinically relevant alterations in

Table 1. Clinical Trials Assessing the Impact of Kava Extracts on Anxiety From 2003 to the Present[15–21]

Reference and Design	Length of Treatment and Population	Intervention and Comparator	Outcomes	Adverse Events
WS 1490 Extract				
Gastpar, 2003 R, DB, PC Trial	4 weeks 141 people with anxiety (baseline HAM-A >18)	Single dose: ~50 mg dry powder and ~35 mg pure kavapyrones Frequency: 3 times daily Total daily kavapyrone dose: ~105 mg	ASI total score: Decreased by 8.6 ± 9.1 points with kava and 7.2 ± 9.5 points with placebo ($P < .001$) CGI rating: Rating of much or very much improved; 42% with kava and 32% with placebo (P value not determined)	Kava extract: Eight patients experienced adverse events, but only 1 (tiredness) was said to be due to study medication. Placebo: Five patients experienced adverse events, but none were said to be due to study medication (1 sneezing episode and a left wrist nerve ganglion were specifically mentioned). Liver function tests: No changes from baseline occurred for AST, ALT, gamma-GT, or alkaline phosphatase over the course of the study in either study group.
Geier, 2004 R, DB, PC trial	4 weeks 50 people with nonpsychotic anxiety (baseline HAM-A ~27)	Single dose: ~50 mg dry powder and ~35 mg pure kavapyrones Frequency: 3 times daily Total daily kavapyrone dose: ~105 mg	ITT HAM-A total scores: Decreased 42.2% with kava and 39.1% with placebo ($P = 0.10$) Per-protocol HAM-A total scores: Decreased 53.3% with kava and 42.8% with placebo ($P = .03$)	No adverse events related to the study medication were noted. Kava extract: One patient developed pneumonia. Placebo: One patient developed nausea/retching and restlessness/sleeplessness. Liver function tests: Authors reported no pathologic changes in AST, ALT, gamma-GT, or alkaline phosphatase but no data provided.
Lehrl, 2004 R, DB, PC trial	4 weeks 61 people with anxiety and sleep disturbances (HAM-A >15 points and a rating of >2 on HAM-A insomnia item)	Single dose: ~200 mg dry powder and ~140 mg pure kavapyrones Frequency: Once daily Total daily kavapyrone dose: ~140 mg	HAM-A total scores: Decreased 48.4% with kava and 41.1% with placebo ($P = 0.1$) CGI rating: Rating of improved, much improved, or very much improved; 85.3% with kava extract and 60.9% with placebo ($P = .002$)	Kava extract: No adverse events noted. Placebo: One patient complained of nausea. Liver function tests: The authors state no clinically relevant changes in ALT, gamma-GT, or ketones.
WS 1490 Extract and Unknown Extract Type				
Connor, 2006 Pooled analysis of 3 small R, DB, PC trials (Largest trial used unknown extract type, other 2 used WS-1490)	4 weeks (2 studies) and 8 weeks (1 study) 64 people with generalized anxiety disorder (HAM-A was >16 in 1 study, >18 in another, and between 12 and 20 in the last study)	Single dose: Total powder dose not specified, ~70 mg pure kavapyrones in week 1 and then 140 mg for the next 3 weeks Frequency: Twice daily Total daily kavapyrone dose: ~140 mg in week 1 and ~280 mg for the next 3 weeks	HAM-A total scores: Decreased 34.1% with kava and 44.4% with placebo ($P =$ NS)	Liver function tests: No clinically relevant changes in AST, ALT, alkaline phosphatase, or bilirubin.

(*Continued*)

Table 1. Continued

Reference and Design	Length of Treatment and Population	Intervention and Comparator	Outcomes	Adverse Events
Water Extract Sarris, 2009 R, DB, PC, crossover trial	1 week per phase 41 people with persistent worry or anxiety (Beck anxiety inventory >10) with or without depression	Single dose: 3.2 g dry powder and ~50 mg pure kavapyrones Frequency: 5 times daily Total daily kavapyrone dose: ~250 mg	HAM-A total scores phase 1: In phase 1 HAM-A scores decreased 46.8% with kava and 3.8% with placebo. HAM-A total scores phase 2: In phase 2 HAM-A scores decreased 54.5% with kava and 31.1% with placebo. The benefits in placebo in phase 2 were attributed to the residual effects of kava from phase 1 before with crossover. The difference over both phases was $P <$ .0001 for kava vs placebo	Kava extract: Two patients complained of nausea and another patient complained of dizziness. Placebo: One patient complained of nausea, dizziness, and flulike symptoms, and another patient complained of constipation.

ALT, alanine aminotransferase; ASI, Anxiety Sensitivity Index; AST, aspartate aminotransferase; CGI, Clinical Global Impressions Scale; DB, double-blind; gamma-GT, gamma-glutamyl transferase; HAM-A, Hamilton Anxiety Rating Scale; ITT intention-to-treat analysis; PC, placebo-controlled; R, randomized.

liver function tests were found in the trials that assessed it, but some trials presented liver function test data and others just made a summative statement.[15–19]

As such, the newer trials are supportive of the Cochrane meta-analysis, although some questions remain. Since the total kavapyrone daily dose and the frequency of dosing differed among the trials, do differences in these factors impact its effects? It may be the case with Geir[16] (which had only 105 mg total kavapyrones) and Lehrl[17] (which dosed kava only once daily) failing to find significant differences. Finally, it is unfortunate that these newer trials did not have a duration of follow-up exceeding a month since that is an inherent weakness inherent in the literature base.[13,15–19] The Kava for Generalized Anxiety Disorder (K-GAD) trial is an ongoing multicenter, randomized, double, blind, placebo controlled trial in 210 patients who will receive an aqueous extract of kava standardized to 240 mg of kavapyrones per day or placebo for 18 weeks.[20] The study launched at the end of 2015 but will not conclude until May 31, 2018.

In 2012, the first direct comparison of kava extract and a benzodiazepine was published.[21] Participants (n = 22) with mild to moderate anxiety (HAM-A total scores of 14-25) but without bipolar, major depressive, or psychotic disorders were enrolled. Patients received a single dose of kava extract (180 mg kavapyrones), oxazepam (30 mg), or placebo in a randomized crossover fashion with 1-week washout between study phases. Using the State-Trait Anxiety Inventory-State, oxazepam caused an acute reduction in anxiety ($P = .035$) while kava extract provided no impact ($P = .87$) and placebo tended to increase anxiety ($P = .08$). Using the Bond-Lader "calm" scale, oxazepam provided significant calming ($P = .002$), while kava extract ($P = .88$) and placebo ($P = .20$) did not.[21] The lack of acute anxiety suppression is not a surprising finding, however. In previous placebo-controlled trials, the anxiolytic effects of kava extract are very modest on day 1 but intensify over the next several days and then continue to improve at a slower rate over the next couple of weeks.[14,15]

In a final trial of note, the impact of combination St. John's wort and kava extract in patients with major depressive disorder with comorbid anxiety was assessed.[22] Patients (n = 28) received combination therapy with St. John's wort (990 μg hypericin and 1500 μg flavones 3 times daily) and kava aqueous extract (50 mg total kavapyrones 3 times daily) or placebo in a 4-week crossover trial. Overall, there were no significant effects in intention to treat analyses for either depression or anxiety. It looks as if the lack of washout could have impacted findings for depression with the combination group showing a trend toward improvement vs placebo after the first phase ($P = .094$) but this did not explain the lack of benefit on anxiety. Whether St. John's wort impacted kavapyrone concentrations or half-life, the occurrence of depression impacts kava's ability to treat anxiety, or the mixture of kavapyrones in an aqueous extract of kava is less effective than the WS 1490 extract cannot be determined.[22]

Kava's Safety Profile

As described in Table 1, the safety data derived from kava clinical trials in patients with anxiety suggest generally good tolerability and safety for short-term (1-4 weeks) use.[15–19] However, the doses in these clinical trials were strictly controlled, the duration of therapy

was limited, interacting drugs and severe comorbid diseases were generally avoided, the extraction method in most of the trials was consistent, and patients were closely followed. As such, it provides the idealized situation in which kava can be consumed. These studies did not assess the safety experience of people purchasing kava for recreational use or self-treating anxiety with kava without oversight from a competent health care professional. Patients were not consuming kava with interacting drugs, and it was not used in patients with severely compromising disease states.[15–19]

Kava-Induced Dermopathy

Kava dermopathy has been reported in 45% of regular and 78% of heavy users, defined as those people chronically consuming less than vs more than 310 g of kava dry powder per week, respectively.[23] The condition is characterized by an ichthyosiform eruption that begins as a powdery dryness of the arms and upper back before progressing to a nonerythematous desquamating keratosis with fine polygonal scaling. In Fiji, the skin changes are very common and perceived as a sign of privilege, so treatment is generally not sought. While many hypotheses have been postulated, the prevailing theory comes from the similarity between kava dermopathy and lamellar ichthyosis type 3. Lamellar ichthyosis type 3 is caused by a genetic defect that codes for cytochrome P (CYP) 4F22 on chromosome 19p13. CYP4F22 mediates the conversion of arachidonic acid to oxidized products needed for proper skin hydration. Since CYP4A11 and CYP2C9 are structurally inhibited by kavapyrones and they have a close structural similarity to CYP2F22, it is thought that in high doses or longer kava exposure, reversible CYP2F22 inhibition occurs. The kava dermopathy is generally reversible upon discontinuation with or without emollient therapy.[23]

It is unknown whether the common kava induced skin rash can induce more severe skin and muscle manifestations. However, a patient from New York with bipolar disorder on stable sertraline and valproic acid therapy for 1.5 and 2.0 years, respectively, started taking kava after her dog died.[24] She did not know the amount of kava taken per day but admitted it was excessive. Self-treatment lasted for approximately 2 weeks before the onset of dermatologic symptoms. In addition to the prototypical kava rash that involved the neck, back, upper extremities, and face, she started to have myopathy (pain gauged as 2 out of 5 in shoulders and hips with a creatine kinase concentration of 8,655 μ/L) and a fever to 103°F. Capillaroscopy, muscle and skin biopsy, and electromyogram were interpreted as being consistent with dermatomyositis. They found no known confounders (thyroid, Lyme, *Trichinella,* collagen vascular diseases, or malignancy) after testing. It took 6 weeks of intravenous steroid therapy equivalent to prednisone 1 mg/kg/day for the creatine kinase to return to normal. Maintenance therapy with hydroxychloroquine 400 mg orally per day was then started as prophylaxis. At 1 year of follow-up, she was symptom free and her rash and nail-fold telangiectasia had fully resolved.[24]

Kava-Induced Hepatotoxicity

Hepatotoxicity is the most concerning adverse effect of kava and led to bans or warnings across the Western world.[1–3] There were 93 cases of presumed hepatotoxicity associated with kava reviewed by the World Health Organization. Seventy-nine percent of the cases involved women, and the mean age was 45 years. The preponderance of women is thought to reflect the distribution of the population using kava for anxiety.[25] In this case series, 7 patients died and 14 had liver transplants. They found that 8 of the cases had probable associations and 53 cases had a possible association between kava use and hepatotoxicity. A causative determination was impossible in many people given substantive missing information. Even when a determination of "possible association" was ascribed to a case, there could have been other information that was not available that could have altered the determination.[25] For example, in 63% of the cases the presence of acute viral infections was not assessed.[26] One case in particular was very strong as the patient had a positive dechallenge upon kava cessation and then a positive rechallenge when kava was reintroduced and liver damage was again detected.[26] However, the number of cases may be overstated because the types of liver damage noted include necrosis, drug-induced hepatitis, and cholestatic hepatitis—a pattern the World Health Organization believes may be more indicative of a range of causes than a single modality.[25]

While included in the World Health Organization assessment, there was an extensive review of the 26 case reports of potential kava hepatotoxicity from Germany and Switzerland performed in 2008.[27] In this case series, 35% of people with hepatotoxicity died ($n = 3$) or survived after liver transplantation ($n = 6$), with the rest of the people resolving their liver issue over time after cessation of kava and supportive care. People with hepatotoxicity all used ethanolic or the acetonic extracts of kava, and in 79% of the cases the dose and/or the duration of therapy was greater than was recommended by regulators in Germany ($\leq$120mg/day kavapyrones for $\leq$3 months).[27] While the investigators found that 88% of patients with liver injury on kava were on other drugs or herbs, my review of these medication lists for drugs commonly associated with hepatotoxicity (>100 case reports of toxicity) found that only 28% of them

were receiving highly implicated hepatotoxic agents (estrogen/progesterone, nonsteroidal anti-inflammatory drugs, and sulfasalazine).[27,28] Thirteen of the cases had strong disease-related confounders including autoimmune hepatitis, primary biliary cirrhosis, hyperthyroid hepatopathy, steatohepatitis, Epstein-Barr or cytomegalovirus infection, and herpetic hepatitis.[27]

While the cases of hepatotoxicity in the German and Swiss experience were with the ethanolic and acetonic extracts, there are observational studies showing that elevated liver function tests or hepatotoxicity also occurs with aqueous extracts.[26,29] It is possible that the ethanolic and acetonic extracts are riskier because they extract a greater percentage of kavapyrones (30% and 70% of the extracted volume, respectively). Similarly, the fact that there is a drug or disease confounder in a case doesn't mean that kava could not be a cofactor for harm.[26,29] For example, in a study of rat hepatocytes, the use of a methanolic kava extract alone or acetaminophen alone led to losses of 50% and 30% of the cells, respectively, but the combination of the 2 eliminated viability in all of the cells. Mechanistically, the investigators of this rat study concluded that kava worsens acetaminophen hepatotoxicity by further depleting glutathione, resulting in oxidative stress and mitochondrial dysfunction.[30] Whether this same effect occurs in humans is not known or whether combining alcohol and kava enhances the liver risk is not known but needs to be considered possible until more data are available.

A hepatologist familiar with kava hepatotoxicity concluded that there are 3 main risks to consider.[26] The first is excessive kava exposure, which can come from consuming too high a dose of kavapyrones or consuming kava for too long a period of time. The second risk comes from adulteration of kava products with synthetic kavain. This was being increasingly done when kava plants of all varieties were scarce and *Piper aduncum* or *Piper auritum* plants (rather than *Piper methyticum*) were being substituted. These plants have much smaller amounts of natural kavalactones and were enriched with synthetic kavain to produce pharmacologic effects. The third risk is using substandard kava cultivars (the precise kava plant used) or using aerial parts of the kava plants for extraction.[26]

There are over 200 variant strains of kava, commonly called cultivars. In 2002, the Vanuatu government passed the Kava Act and identified "noble" and "medicinal" cultivars that are safe to cultivate, extract, and distribute.[26] Traditionally, only these "noble" and "medicinal" varieties were used for consumption in the country, but people were allowed to export products of lesser quality. With the Kava Act, they no longer allow the extraction of "Tu Dei" (literally meaning 2-day intoxication) and "Wichmannii" (wild) varieties, as they are believed to have a higher risk of causing harm. The Tu Dei variety has a time from planting to harvesting of 1 to 2 years instead of 4 to 5 years for other varieties and was being increasingly used. The Germans have verified that some of the kava being sold in Germany in the past were of the Tu Dei variety. Similarly, the "Isa" variety is known to have pipermethystine in their roots and rhizomes, whereas noble and other medicinal varieties do not have this toxin. The Isa form may also have high amounts of flavokavain B in their roots, and in vitro evidence has found that this nonkavapyrone constituent is cytotoxic to HepG2 cells in vitro. Even if the plants themselves are of the noble or medicinal varieties, the parts of the plants extracted is important. The aerial parts are not supposed to be used because they contain pipermethystine. It has been verified that the aboveground stems and leaves have been used in products sold in the Western world in the past, with stems selling for one tenth the price of the roots. Even varying the relative proportions of the stumps, rhizomes, and roots below ground can introduce variability in the total kavapyrone content and the individual constituents that are extracted. For example, the German Commission E states that the peeled rhizome and roots should be used, but kava preparations are often extracted from the root peelings themselves, the root stump above the rhizome, and the adventitious roots that come off of the stems and extend down into the soil.[26]

Kava Cognitive Disruption

In a systematic review of 10 clinical trials, the impact of kava on neurocognition was explored.[31] There were 7 small, randomized controlled trials assessing the cognitive impact of acute kava ingestion, while only 1 small, randomized controlled trial and 2 case control studies assessed chronic kava use. The average sample size was only 34 participants per study, and each varied widely in the cognitive measures used, control group, kava dosage and preparation, and the study design. As such, the results were not meta-analyzable. No acute kava ingestion studies found impaired cognitive function and one that found a significant improvement in visual attention and working memory. Kava was found to increase body sway after acute ingestion, an effect that is known to occur during benzodiazepine use as well. In the chronic kava use studies, none of the studies found impairment of cognitive function except in 1 trial in which the accuracy of visual attention was impaired under high-cognitive-demand situations. When assessed without regard for statistical significance, the direction of effect suggested slight positive cognitive effects in some studies and slight negative effects in others.[31]

Several of the studies in the systematic review deserve individual discussion. In 2 of the trials, kava

(600 mg/day of WS 1490) was compared with oxazepam 90 mg/day.[31] While no significant effects were seen with kava, oxazepam impaired functions like automatic feature recognition, attention, processing capability, and word recognition.[31] In 1 of the trials, kavain (200, 400, and 600 mg) was compared against clobazam 30 mg for impact on electroencephalographic recordings, psychometric tests, and adverse effects for 8 hours after ingestion.[32] Kavain exerted a significant action on the human brain function as compared with placebo, characterized by a dose-dependent increase of delta, theta, and alpha 1 activity, while alpha 2 and beta activity and the centroid of the total activity decreased. These findings are indicative of a sedative effect fundamentally different from the benzodiazepine clobazam. Clobazam produced a decrease of delta, theta, alpha 1, and alpha 2 activity and an increase of beta activity, while the total centroid was accelerated. Kavain improved intellectual performance, attention, concentration, reaction time, and motor speed, while clobazam produced the opposite effects. Kavain 200 mg improved drive, wakefulness, affectivity, mood, and well-being compared with placebo, while kavain 600 mg and clobazam produced sedation.[32] In another study included in the systematic review, kava (1 g/kg of body weight) and alcohol (0.75 g/kg of body weight) were administered individually or in combination.[33] Subjective factors of impairment and performance skills on a number of cognitive tests were determined. Kava alone had no negative impact on the 5 subjective measures of impairment, but alcohol produced marked negative effects in each of them. Combining kava and alcohol produced even larger negative changes on these measures. In cognitive tests, kava produced a decrement in performance on Digit Symbol Coding. Alcohol produced a significant decrease in the divided attention test, which was almost entirely driven by the peripheral, discontinuous component of the test. The combination of kava and alcohol produced an even greater decrease in performance on the divided attention test, and again driven by the same component.[33]

A population-based case-control study was undertaken in Fiji from July 1, 2005, to December 31, 2016.[34] The cases were people involved in crashes with serious injuries, while controls were people using the same roads during similar times of the day who did not have an accident. Overall, 24% of drivers involved in crashes and 4% of drivers not involved in crashes consumed kava within 12 hours of the crash, which is associated with a 4-fold increase in the odds of crashing after controlling for confounders (odds ratio, 4.7 [95%CI, 1.9-11.6]). Unfortunately, the investigators did not assess the impact of dose consumed on the risk, although the incredible variation in kavapyrone extraction would make the interpretation of those data difficult. This is the only study that assesses kava use and motor vehicle accidents. While many of the aforementioned studies evaluating cognitive function did not find significant detriments, driving can require high cognitive demand and might be an explanation.[34]

Kava's Drug Interactions

Several in vitro studies have shown that kavapyrones are inhibitors of the CYP enzyme system.[35] Methanol or acetone extracts with ~40% kavapyrones showed 92%, 86%, 78%, 73%, and 56% blockade of CYP2C9, CYP2C19, CYP3A4, CYP2D6, and CYP1A2 at 100 μM concentrations with in vitro human liver microsomes. At 10 μM concentrations, the inhibition of the various CYP isoenzymes were only blocked by 22% to 53%. When individual kavapyrones were assessed at 10 μM concentrations, kavain did not inhibit any of the CYP isoenzymes but desmethoxyyangonin, methysticin, and dihydromethysticin did. In another in vitro assessment using recombinant human CYP isoforms, the concentration needed to inhibit 50% of the enzymatic activity (IC50) was calculated for various kavapyrones. Kavain and dihydrokavain both inhibited CYP2C9 (IC50, 129 μM and 131 μM), CYP2C19 (IC50, 4.86 μM and 10 μM), and CYP3A4 (IC50, 35 μM and 79 μM), while kavain also inhibited CYP1A2 (IC50, 45 μM). However, the IC50 was generally much lower for desmethoxyyangonin, dihydromethysticin, and methysticin for CYP1A2 (IC50, 2 μM, 15 μM, 13 μM), CYP2C19 (IC50, 0.5 μM, 0.4 μM, 0.9 μM), CYP3A4 (IC50, 20 μM, 3 μM, 1 μM), and CYP2C9 (IC50, 50 μM, 13 μM, 16 μM) with both dihydromethysticin and methysticin blocking CYP2D6 (37 μM and 153 μM) as well. The question is whether kavapyrones in normal concentrations would block drug metabolism to a clinically meaningful extent. Grapefruit juice is known to have clinically relevant drug interactions, and bergamottin, an active component, has IC50 concentrations of <0.5 μM for CYP1A2, CYP2C9, CYP2C19, and CYP2D6 and <2 μM for CYP3A4. Another component of grapefruit juice, 6,7-dihydroxybergamottin, has an IC50 <2 μM for CYP2C9, CYP2C19, and CYP2D6. This suggests that CYP1A2, CYP2C19, and CYP3A4 are the most likely isoenzyme systems in which clinically significant interactions with kava may be seen. Kavapyrones might also block the degradation of other kavapyrones.[35]

In a rat study, kavain (100 mg/kg) was administered alone or with kava extract (256 mg/kg). When kavain was administered with kava extract, the peak concentration of drug in blood plasma was doubled and the area under the plasma drug concentration-time curve was tripled.[36] However, after 8 days of continuous

kava extract therapy, there was no impact on kavain pharmacokinetics on the last day.[36]

These in vitro studies are at odds with an in vivo pharmacokinetic drug interaction study.[37] Twelve health volunteers were given kava (Wild Oats Market, Boulder, Colorado) for 28 days, with CYP probes (midazolam, caffeine, chlorzoxazone, and debrisoquine) being administered before and at the end of kava therapy. Serum ratios of 1-hydroxymidazolam/midazolam at 1 hour after dosing was used to probe for CYP3A activity; paraxanthine/caffeine at 6 hours after dosing was used for CYP1A2; 4-hydroxydebrisoquine/(desbrisoquine + 4-hydroxydesbrisoquine) at 8 hours after dosing was used for CYP2D6; and 6-hydroxychlorzoxazone/chlorzoxazone 2 hours after dosing was used for CYP2E1. The geometric means for postsupplementation/presupplementation ratios were 1.00 (95%CI, 0.92-1.10) for CYP3A, 1.03 (95%CI, 0.88-1.06) for CYP1A2, and 1.01 (95%CI, 0.96-1.06) for CYP2D6 but was significantly different for CYP2E1 at 0.59 (95%CI, 0.45-0.77). The daily dose of kava was 138.0 mg, which contained 34.5 mg of total kavapyrones—a very low dose for medicinal purposes, which use kavapyrone doses of 105 to 280 mg, but could be in line with doses used for recreational purposes.[37]

In vitro, there is also evidence to suggest that kava can modestly inhibit P-glycoprotein.[38] P-glycoprotein–mediated efflux of calcein-acetoxymethylester in cell lines P388/dx and P388 were assessed at various concentrations of raw extract and then for individual kavapyrones. P-glycoprotein was inhibited starting at a concentration of 10^1 μM, while individual kavapyrones (kavain, dihydrokavain, desmethoxyyangonin, dihydromethysticin, yangolin, and methysticin) started inhibiting P-glycoprotein at concentrations ranging from 10^0 to 10^2 μM.[38]

More data are needed to truly determine the impact of kava on drugs like benzodiazepines, barbiturates, and opioids, which have the potential for both pharmacokinetic and pharmacodynamic interactions.[35] In mice, the administration of dihydromethysticin, methysticin, kavain, dihydrokavain, and yangonin prolonged the sleeping time induced by pentobarbital, while dihydrokavain and dihydromethysticin prolonged the sleeping time induced by hexobarbital, pentobarbital, urethane, or glutethimide. Whether this is due to a pharmacokinetic or pharmacodynamic effect (or a combination of both effects) is unknown. Kava also increases sleeping times in mice coadministered alcohol.[35]

In a double-blind crossover trial of 18 subjects, bromazepam 9 mg/day was given with or without kava extract (120 mg lavalactones).[35,39] No significant changes in stress tolerance, vigilance, or motor coordination was found with dual therapy versus bromazepam therapy alone. While not statistically significant, these performance measures were tending to show more impairment with combination therapy, and a larger trial is needed to truly understand the impact. This article was originally in German, and I relied on a review article to provide the salient data.[35,39]

American Kava Association

In the United States, the American Kava Association has created a certification program for kava growers and suppliers to minimize mold, parasite, or bacterial contamination of the product; use of substandard kava cultivars; and the use of aerial parts of the plant.[40] They also subsidize laboratory testing to enhance transparency and consistency in the kava products being sold. It is not a requirement that kava sold in the United States comes from American Kava Association–certified growers and suppliers, but certification is clearly listed and easy to discern during purchase. The disconnect between the favorable liver function test results in clinical trials and the numerous case reports of liver toxicity may stem more from tainted, adulterated, and substandard kava products than the effect of the kavapyrones themselves (although some residual risk might still exist, especially in people combining kava with other hepatotoxic drugs or conditions).[40] Self-regulation is important for both consumers and the future market for kava in the United States, and consumers should have some form of verification of product quality (like the American Kava Association certification) before using it.

Conclusions

Kava is a complex plant composed of kavapyrones with unique pharmacologic effects. It does not provide acute anxiolytic effects like benzodiazepines but does provide significant anxiety attenuating effects over time. How the benefits over several weeks of therapy relate to traditional anxiolytics is not known, and whether benzodiazepines and kava provide more benefits than a benzodiazepine alone needs to be explored. The optimal kavapyrone dose and dosing schedule for anxiety has not been determined, and more work needs to be conducted to determine if different mixes of kavapyrones (from different extraction methods) provide different effects than others. The 3-times-a-day dose used in many kava anxiety trials would be hard to adhere to over time. There are both pharmacokinetic and pharmacodynamic drug interaction concerns with kava, especially with drugs that are metabolized by CYP1A2, CYP2C19, and CYP3A; eliminated by P-glycoprotein; or that have overlapping sedative or hepatotoxic effects. Whether kava suppresses respiratory drive more than opioids alone (or other respiratory depressants) is

unknown but important, especially given the overlapping toxicity between opioids and benzodiazepines. Kava should not be combined with alcohol for recreational or medicinal purposes because there appears to be potentiation of the negative cognitive effects of alcohol. The incidence and intensity of hepatotoxicity seen in the early 2000s may have been accentuated by use of less desirable kava cultivar varieties and the wrong parts of the plant, or by adulteration or contamination of the products that were produced. It is imperative that farms, suppliers, and merchants sell only proper kava products and that good manufacturing practices are being followed. It is possible that concomitant use of kava with acetaminophen and theoretically alcohol could enhance the risk of hepatic damage, but human data are needed to confirm or refute this. Even with quality products, the risk of dermopathy (and possibly concomitant myopathy) with prolonged therapy and the ability to impair people operating a motor vehicle or heavy machinery (especially when consumed with alcohol) still exist.

Declaration of Conflicting Interest

The author declares no conflict of interest.

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