The efficacy and toxicity of kavalactones

Main research question: Are kavalactones toxic at the efficacious dose?

With a focus on treating panic attacks (panic disorder, agoraphobia) and counteracting hepatoxicity

Intro: Use document tabs to navigate. Document contains a literature review with references. Second section contains the annotated bibliography that was used to write the review.

Note: This is a work in progress.

Literature Review

Toxicity

Intro

Kavalactones are a group of bioactive compounds found in the roots of *Piper methysticum*. They are responsible for kava's psychoactive and therapeutic effects, including relaxation, mild euphoria, and anxiolytic (anxiety-reducing) properties. There are six major kavalactones: Desmethoxyyangonin (DMY), dihydrokavain (DHK), yangonin (Y), kavain (K), dihydromethysticin (DHM), and methysticin (M), which contribute to kava's overall effects by interacting with neurotransmitter systems, particularly GABAergic pathways. Unlike alcohol or benzodiazepines, kavalactones provide calming effects without significant sedation or cognitive impairment when consumed in moderate amounts. However, some studies suggest that variations in preparation methods and kavalactone concentrations may influence kava's safety profile, particularly regarding potential liver toxicity.

Kava has been used in the Pacific Islands for over 1,500 years and is generally considered safe. In the 1990s, a surge of kava-containing medications entered the German market, with over 450 daily doses recorded between 1990 and 2000 (Schmidt, 2024). However, following reports of liver toxicity - including cases requiring liver transplants - kava was banned. This decision was largely influenced by approximately 11 cases in Switzerland (Schmidt, 2024). Since then, kava has been banned and reinstated in various countries. Traditional kava, appears to be safe when consumed in its traditional form. Similarly, kavatone extracts containing a mix of kavalactones - at approximately 200 mg/kg of the most active kavalactones -

are generally considered safe. As of March 2025, kava is legal in Australia, but has been banned again in Germany - this time because of no efficacy for general anxiety disorder, thus the small risk of hepatotoxicity makes the reward:risk ratio negative (Schmidt, 2024).

We propose kava, at higher doses, and as isolates of kavalactones could could be used as a medication for panic disorder with agoraphobia. Isolates may provide a more precise drug action, and would be useful for those unable to tolerate kava consumption at doses required to produce a benefit. Thus further investigation into the mechanisms of hepatotoxicity was conducted to determine the risk of higher doses of kavalactones and of kavalactone isolates.

Determining causality and mechanisms

Epidemiologist Kenneth Rothman introduced a conceptual model to explain how multiple contributing factors, known as component causes, interact to bring about a disease or condition. This model is often illustrated using causal pie charts, where each "pie" represents a sufficient cause - a complete set of factors that together result in the condition. Some factors may appear in multiple pies, but a necessary cause is one that appears in every pie, meaning the condition cannot occur without it (Rothman, 1976). Applying this framework to hepatotoxicity from kava could help understand the essential and contributing factors involved in liver damage.

1. **Organic Solvent Preparation.** Several review articles have reported that cases of liver failure were predominantly associated with kava extracts prepared using acetone or ethanol (ref). In contrast, aqueous preparations, which have been traditionally used for thousands of years, are considered safe. Additionally, the extraction method plays a crucial role in determining the chemical profile of the final product, which may influence both its efficacy and safety. This factor alone may not be sufficient to cause hepatotoxicity.

2. **Flavokawain B (FKB)** is a chalcone found in the kava plant that exhibits hepatotoxic properties. A study has shown that FKB induces oxidative stress and hepatocyte death by depleting glutathione (GSH) and modulating cell signaling pathways such as IKK/NF-κB and MAPK (Zhou et al., 2010). Notably, FKB is less readily extracted into traditional aqueous kava beverages but is present at higher concentrations in organic solvent extracts. This suggests that the increased hepatotoxicity observed with certain kava products may be linked to the presence of FKB in non-traditional extraction methods (Zhou et al., 2010). Furthermore, not all organic solvent extraction methods extract high KFB.

3. **Part of the Plant Used**. Kava (Piper methysticum) extracts can be prepared from various parts of the plant, each differing in chemical composition and potential

toxicity. The roots are rich in kavalactones and flavokavains, which are primarily responsible for kava's psychoactive and therapeutic effects. In contrast, the stems and leaves contain higher concentrations of toxic alkaloids, such as pipermethystine, which have been associated with hepatotoxicity (Soars et al., 2022). For example, an in vitro study found 100 microM pipermethystine caused 90% loss in cell viability within 24 h, while 50 microM caused 65% cell death. However, kavalactones did not affect cell viability for up to 7 days (Nerurkar et al., 2004) Traditional kava preparations utilize peeled roots, minimizing the risk of toxicity associated with these alkaloids. However, some commercial kava products have incorporated aerial parts of the plant, leading to safety concerns (Soars 2022). Therefore, using only peeled roots in kava preparations is recommended to reduce the potential for adverse effects (Soars 2022)

4. **Cultivars of the Kava Plant.** The chemical composition of kava (Piper methysticum) varies significantly among its cultivars, which are generally categorized into four groups: noble, "two-day" (tudei), medicinal, and Piper wichmannii (wild kava). Noble cultivars are traditionally preferred for regular consumption due to their favorable kavalactone profiles, leading to more desirable effects and a lower incidence of adverse reactions. In contrast, tudei kava contains higher concentrations of dihydromethysticin (DHM) and dihydrokavain (DHK), kavalactones associated with less favorable effects. Additionally, tudei varieties have elevated levels of flavokavain B (FKB), a chalcone linked to hepatotoxicity. The Piper wichmannii species is less studied but is also reported to have higher concentrations of flavokavains, including FKB, raising potential safety concerns**.** (https://pmc.ncbi.nlm.nih.gov/articles/PMC9315573/).

5. **Enzyme inhibition.** Genetic polymorphisms in CYP enzymes, particularly **CYP2D6** and **CYP2C19**, affect drug metabolism rates. Poor metabolizers are more common in **Caucasians** than in **Pacific Islanders.** These differences can influence drug efficacy and safety across populations (Kanumuri et al., 2022).

6. **Extract WS-1490 and Neuronika.** In Germany, various medicines were sold on the market, prescribed for ‘ anxiety, tension, and restlessness’. WS-1490 show efficacy for this at 300mg/day (ref https://pubmed.ncbi.nlm.nih.gov/14692723/). Kavain was first synthesised in 1950s (nature ref). Kavain (synthetic or extracted), also named Neuronica/Neuronika was sold in the 1970s to 1990s. Each tablet of Neuronika was 200mg (ref https://pubmed.ncbi.nlm.nih.gov/331057, https://pubmed.ncbi.nlm.nih.gov/2179082/). It appears the 11 cases in 1999-2002 that led to the ban did not include Neuronica or WS-1490 (ref https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm), but there was a

wide sweeping ban effecting all kava products. However links to Neuronika to liver toxicity were made (ref https://www.arznei-telegramm.de/html/2002_06/0206510_01.html, translated to English by ChatGPT) however I have yet to find a primary source linking Neuronika to liver damage due to difficulties in accessing primary sources from Germany at the time.

7. **Production of reactive metabolites of the kavalactones**. There are limited studies demonstrating that kavain itself is toxic. One rat cell study suggested high levels of kavain causes an inflammatory response in the liver (https://pmc.ncbi.nlm.nih.gov/articles/PMC2681144/) and another mouse metabolomic study suggests kavain forms some reactive metabolites(ref https://pubmed.ncbi.nlm.nih.gov/31265262/), but these can be detoxified by glutathione. Studies on the hepatoxicity of kavain are limited.

Teschkle in 2011 (ref https://pubmed.ncbi.nlm.nih.gov/21112196/) proposed a 6 point plan to standardise kava to reduce the chance of hepatotoxicity. (1) use of a noble kava cultivar such as Borogu, at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots, (3) aqueous extraction, (4) dosage recommendation of ≤250mg kavalactones per day (for medicinal use), (5) systematic rigorous future research, and (6) a Pan Pacific quality control system enforced by strict policing. (ref: https://pubmed.ncbi.nlm.nih.gov/21112196/)

However the proposed antipanic dose will exceed 250mg kavalactones/day at approximately 600mg kavalactones/day and may require organic extraction due to the lipophilic nature of the kavalactones – further literature search is required. However organic formulations that reduce Flavokavain B content is available and antioxidant glutathione could be added to replenish the plant's supply.

Further research into safe extraction of kavain from non-noble *Piper methysticum* plants as well as parts other than the roots would have great economic benefit in the Pacific.

It is difficult to find information of the hepatotoxicity of kavain isolates, especially at 600mg/day. However if we assume 30% of this is kavain, that would lead to approximately 180 mg/kg of kavain. Due to potential synergistic effects of kavalactones together, a slightly high dose of kavain may be required.

Thus further studies should first investigate efficacy at a safe dose of ~250mg kavain. There has been a single rat study suggesting liver toxicity with plasma levels of 10 µg/mL kavain showing an inflammatory response and damage to liver

sinusoidal endothelial cells. The authors chose this dose based on the literature based on human consumption levels resulting of plasma levels of 0.1 to 10 µg/mL total kavalactone (ref - https://pmc.ncbi.nlm.nih.gov/articles/PMC2681144/) and tested only the upper limit. However, I found that giving to healthy participants 225 mg of total kavalactones (kavain constituting 25.6% of the extract, 57.6 mg), this resulted in a Cmax of 34.5 ng/ml (0.0345 µg/mL) (ref: https://www.sciencedirect.com/science/article/abs/pii/S0378874122005530). Doubling or tripling that leads us no where near the 0.1 to 10 µg/mL total kavalactone reported by (https://pmc.ncbi.nlm.nih.gov/articles/PMC2681144/).

Efficacy

The primary indication for kava is anxiety, but the specific type of anxiety it treats remains a key question. Kava was banned, in part, due to a lack of demonstrated efficacy in generalized anxiety disorder (GAD). “The main argument in the official reasoning is not the risk of liver toxicity, but the supposed lack of efficacy!” (ref: https://drive.google.com/file/d/1KTJgS5rjymMNbK81yw_cHhDG_HkZUgwv/view). But “Generalized anxiety was never the indication for kava!“. “nervous anxiety, stress and restlessness!” To the current day, that’s not a medical condition? We are interested in making kava and/or its kavalactones a medicine.

The current suggestion is that kava or its isolates may be used as a medication for **panic disorder with agoraphobia** (ref: private communication). The proposed use involves taking kava or isolates prior to exposure to a phobic stimulus to reduce the intensity and likelihood of panic attacks and/or alleviate anticipatory anxiety related to the fear of experiencing a panic attack. Given its anxiolytic properties, kava could also have potential applications in treating **specific phobias**, though further research is needed to confirm its efficacy in these conditions.

Panic studies and kava

Research on the efficacy of kava (*Piper methysticum*) or its active compounds, kavalactones, as treatments for panic disorder with agoraphobia is currently limited. A PubMed search yielded nine results for "kava + panic" and three for "kava + agoraphobia," with one overlapping study, totaling 11 studies. Among these, seven were literature reviews or meta-analyses on anxiety disorder treatments that mentioned kava alongside other therapeutic options. However, these sections focused solely on its efficacy for generalized anxiety disorder (GAD) and did not address its potential effects on panic disorder or phobias.

Two studies, published in German, investigated the kava extract WS 1490, which was indicated for "anxiety, tension, and restlessness states of non-psychotic origin." These studies did not specifically examine its effects on panic disorder or agoraphobia. The remaining two studies were unrelated to panic disorder or agoraphobia.

Given the current lack of research, the efficacy of kava or kavalactones as antipanic medications, particularly for panic disorder with agoraphobia or specific phobias, remains unsubstantiated. Further studies are necessary to explore kava's potential in these areas.(ref: https://www.sciencedirect.com/science/article/abs/pii/S0165032702002380).

There is one study investigating kavain (EEG ref https://pubmed.ncbi.nlm.nih.gov/1682226/) tested doses of 200, 400 and 600 mg D,L-kawain (racemic kavain) in healthy volunteers to demonstrate EEG changes, and reported it was activating after 200 mg, but mildly sedating after 600 mg.

Conclusion

There is mixed evidence regarding kava's efficacy for generalized anxiety disorder (GAD), though this may be partly due to the low doses typically used in studies, around 100–200 mg of kavalactones per day. Higher doses might yield greater efficacy, as seen in studies on DL-kavain, where 200 mg was found to be activating, while 600 mg produced mild sedation, suggesting a dose-dependent effect.Additionally, research on kava's potential role in panic disorder is extremely limited. While no direct studies were found, there are indications that Neuronika (DL-kavain) may have been used as an antipanic medication. Further investigation into German sources is necessary to clarify its historical use and potential efficacy for panic disorder and phobias.

Annotated bibliography

Panic and kava

To check if this has been considered as separate from anxiety.
Starting from oldest reference to latest.

Drug therapy of panic disorders. Kava-specific extract WS 1490 compared to benzodiazepines

Link:

1994, in German.

Article not available. But this warrants further investigation. A search of WS 1490 reveals 13 results. This article with it is of interest to read later re policy (https://pubmed.ncbi.nlm.nih.gov/33189846/)

[Pharmacotherapy]

Link: https://pubmed.ncbi.nlm.nih.gov/9432751/

Article in German - full text not available.

Abstract:

The high prevalence of anxiety disorders implies the necessity of adequate treatment by GPs. Regarding psychopharmacological treatment benzodiazepines and antidepressants are the drugs of first choice, low potency neuroleptics, beta-blockers as well as the herbal medicine kava-kava may be indicated in special cases (e.g. low degree of anxiety, abuse or tolerability problems). The separation of generalized anxiety disorder from panic disorder seems to be essential due to treatment implications: antidepressants like Imipramine or SSRIs are the drugs of choice in the latter case. Hints regarding handling as well as possible side-effects of the different psychotropics are given, the combination with psychotherapy (relaxation techniques, behaviour therapy) is recommended being the best way of effective treatment.

Effectiveness of complementary and self-help treatments for anxiety disorders

Link: https://pubmed.ncbi.nlm.nih.gov/15462640/

- A systematic review on anxiety disorder treatments. Includes a section on kava
- “A Cochrane review of 11 RCTs concluded that kava is superior to placebo for treating generalised anxiety (ref 41)”. Also reported non addictive at therapeutic doses. Reports of rare liver failure for high doses.
- Kava not linked to panic at all, but is mentioned in other treatments. Doesn’t reveal if it would be efficacious for panic.

Herbal medicines in the treatment of psychiatric disorders: a systematic review

Link: https://pubmed.ncbi.nlm.nih.gov/17562566/

2007

- “Whilst substantial high-quality evidence exists for the use of kava and St John’s wort in the treatment of anxiety and depression respectively, currently there is insufficientrobust clinical evidence for the use of many other herbal medicines in psychiatric disorders”
- Piper methysticum (kava) for phobic, panic and obsessive-compulsive disorder - linking kava to panic.
- Cites Cochrane review - it was kava monopreparations (60–280 mg of kavalactones) - 12 trials included.
- An insufficiency of trials exists regarding the efficacy of kava compared with synthetic agents such as benzo-diazepines or antidepressants.
- There was one and - The results of the study found no significant differences between kava and buspirone or opipramol regarding all efficacy and safety measures, for generalised anxiety. 75% were responders to kava,.
- An animal study using the elevated plus maze test demonstrated anxiolytic activity similar to diazepam,as assessed via the elevated plus maze
- In kava users who were not heavy alcohol users, only those who used kava within the previous 24 h displayed GGT levels higher than nonusers, whereas higher ALP levels occurred only in those who last used kava 1–2 weeks and 24 h previ-ously. Liver function changes in users of aqueous kava extracts at these moderate levels of consumption ap-pear to be reversible and began to return to baseline after 1–2 weeks abstinence from kava. No evidence of irreversible liver damage has been found, although the study indicated that liver function parameters can be altered in humans with moderate kava use
- The risk-benefit ratio is highly favourable towards kava due to respectable clinicalefficacy and relative low risk of potential liver toxicity(1 case/1 million monthly doses (Bauer, 2003). As current synthetic pharmacological treatment involving benzodiazepines possesses far greater adverse effects(Rickels and Rynn 2002; Stevinson et al., 2002), kavastill has an important place in the therapeutic pantheon.
- They suggest making the dose <280mg kavalactones, aqueous root preparations standardized for kavalactones and avoidance of concomitant use with alcohol or in cases of known hepatic insufficiencyor disease. Which may not be ideal for obtaining ~500mg kavalactones.

Herbal and dietary supplements for treatment of anxiety disorders

Link: https://pubmed.ncbi.nlm.nih.gov/17853630/

2007

- Reports mixed efficacy for GAD
- Clues that extract WS1490 was efficacious but have liver concerns
- Kava dramatically inhibits the cytochrome P450 enzyme used by the liver to metabolize many medications, potentially altering the potency of these other medications
- Other side effects reported with long-term use include a reversible skin rash or lesion and a yellow tint to the skin, but these reports have not been routine
- But short term risk do not outweigh benefits
- Again, panic was discussed for the other medications in this review, but not kava

Natural remedies for anxiety disorders: potential use and clinical applications

Link: https://pubmed.ncbi.nlm.nih.gov/19123457/

2009

- A more recent meta analysis was done for Kava on GAD. It suggested efficacy of a specific Kava extract-WS1490 (mean change on HAM-A=5.94, 95% confidence interval −0.86 to 12.8). Because it was linked to liver problems, the authors do not recommend it as a treatment for GAD.
- Another review found 280mg kavalactones/day not efficacious for GAD compared to placebo.
- Panic not mentioned in Kava sections like previous reviews,
- I have noticed inositol discussed for panic (but didn't read). May be interesting later.

Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties

Link: https://pubmed.ncbi.nlm.nih.gov/33008420/

2020

- Zero relevance to Kava , it's a cannabis paper. It hit the keyword because Fiji Kava provided funding.
- Again for GAD, mentioned the two meta-analysis in previous refs. Now there is a third one which suggests insufficient evidence for GAD (here is the reference 2018 review: https://pubmed.ncbi.nlm.nih.gov/29641222/), metaanalysis of 12 articles.
    - Evidence supporting Kava as an effective treatment for GAD was found in two placebo-controlled trials and a reference-controlled trial. One negative trial demonstrated that Kava was not more effective than

placebo. Meta-analyses of the results of three placebo-controlled trials (n = 130) favored Kava for GAD treatment with effect sizes between 0.59 and 0.99 (standard mean difference) without reaching statistical significance.
    - Positive patient experiences and improvement of vagal cardiac control due to Kava treatment were also reported in the literature. Kava is safe and well tolerated for short-term (4-8 weeks) therapeutic use at a dosage of 120-280 mg per day of Kavalactones, regardless of dosage schedule.
    - Lewis suggest dose too low.
    - vagal cardiac control - would that be useful for panic?

Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options

Link: https://pubmed.ncbi.nlm.nih.gov/33424664/

- Kava RCT only GAD, no panic

agoraphobia and kava

3 hits. 1 already in the panic, but this reveals 2 new article.

Kava-kava extract WS 1490 versus placebo in anxiety disorders--a randomized placebo-controlled 25-week outpatient trial

Link: https://pubmed.ncbi.nlm.nih.gov/9065962/

1997

- Again, can't get access to full text, but have abstract.
- 101 outpatients suffering from anxiety of non-psychotic origin (DSM-III-R criteria: agoraphobia, specific phobia, generalized anxiety disorder, and adjustment disorder with anxiety) were included in a 25-week multicenter randomized placebo-controlled double-blind trial with WS 1490, a special extract of kava-kava. In the main outcome criterion, the Hamilton Anxiety Scale (HAMA), there was a significant superiority of the test drug starting from week 8 on. WS 1490 was also found to be superior with respect to the secondary outcome variables. HAMA subscores somatic and psychic anxiety, Clinical Global Impression, Self-Report Symptom Inventory - 90 Items revised, and Adjective Mood Scale. Adverse events were rare and distributed evenly in both groups. These results support WS 1490 as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety disorders, with proven long-term efficacy and none of the tolerance problems associated with tricyclics and benzodiazepines.
- Includes agoraphobia, would need to read full text
- **WS 1490** is a standardized extract of **Piper methysticum** (kava), developed by **Dr. Willmar Schwabe Pharmaceuticals** in German (chatGPT)

Effect of kava extract on vagal cardiac control in generalized anxiety disorder: preliminary findings

Link: https://pubmed.ncbi.nlm.nih.gov/11769822/

2001

Abstract:

Anxiety disorders are associated with low vagal control of heart rate and increased risk of cardiac mortality and sudden cardiac death. This study examined whether the herbal anxiolytic, kava, produces improvement in vagal control in generalized anxiety disorder. Before and after treatment with placebo (n = 7) or kava (n = 6), two indices of vagal control were measured under supine conditions using power spectral analysis: baroreflex control of heart rate (BRC) and respiratory sinus arrhythmia (RSA). Significantly more patients treated with kava showed improved BRC compared to the placebo group ($p < 0.05$). Furthermore, the magnitude of improvement in BRC was significantly correlated with the degree of clinical improvement ($p < 0.05$). RSA did not respond to treatment. These preliminary findings suggest that kava might exert a favourable effect on reflex vagal control of heart rate in generalized anxiety disorder patients. The parallel clinical and BRC responses may reflect an underlying common effect of this herbal anxiolytic.

Included GAD patients only - excluded those with panic disorder!!!

Mixed kavalactones/Kava studies

Evaluation of commercial kava extracts and kavalactone standards for mutagenicity and toxicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells

Link: https://pubmed.ncbi.nlm.nih.gov/17822821/

- Intro (see paper for refs):
    - The root of the plant is macerated, mixed with water and coconut milk and then strained.
    - More recently, kava in tablets, capsules and tinctures prepared from lipophilic extracts
    - It is claimed that kava promotes relaxation, induces restful sleep, relieves headache and migraine pain, and promotes sociability
    - However, with reports of cases of liver damage associated with the use of kava – so there were regulatory actions. This includes 11 cases of

people needing liver transplant, and 78 cases of liver damage in data bases.
    - The active components of kava rootstock are contained primarily in the lipid-soluble resin. The compounds of greatest pharmacological interest are the styryl α-pyrones or kavalactones and represent 3–20% of the dried rhizome depending on age of the plant and specific cultivar. At least 16 lactones have been isolated from kava and six compounds, namely, yangonin, methysticin, dihydromethysticin, kawain, dihydrokawain and desmethoxyyangonin, account for approximately 96% of the lipid resin
- Methods
    - Sources Kaviar and KavaPure. Concentration of each kavalactone given, along with standards.
    - Human S9 liver used, subfraction including p450 enzymes to determine liver toxicity. The doses of each chemical selected for testing were within the range yielding approximately 0–90% cytotoxicity or up to the limit of solubility
    - L5178Y TK+/− 3.7.C mouse lymphoma cells to assess mutagenicity .
- Results
    - The maximum dose level tested for each of the remaining kavalactones was as follows: dihydromethysticin, 300 μg/ml; methysticin, 150 μg/ml; dihydrokawain, 200 μg/ml; dl-kawain, 160 μg/ml, and d-kawain 160 μg/ml. No mutagenic activity was obtained with these standard kavalactones. NOTE mice may metabolise things faster but it depends on the compound.
    - The "+" in the Human S9 column means that metabolic activation (via S9 enzymes) was used during the experiment to assess whether the compound requires metabolism to exert its mutagenic effects
    - Dihydromethysticin appears cytotoxic at higher doses (evidenced by reduced cloning efficiency and total growth) but shows no consistent or strong evidence of mutagenicity within the tested dose range. Under 70% relative growth is considered cytotoxic.
- Discussion
    - There is no evidence of liver damage in kava using populations of the native Pacific Islanders or Australians who have used aqueous kava extracts (Clough et al., 2003).
    - Supports epidemiological evidence that Kava drinkers have a lower incidence of cancers.
    - The traditional aqueous preparations of the kava rhizome produce an extract that contains a balance between the kavalactones and

glutathione that may provide protection against hepatotoxicity (Whitton et al., 2003).
    - Cote et al. (2004) compared the traditional aqueous kava extracts with organic kava extracts and commercial kava caplets and reported differences in the ratio of kavalactones which suggest there could be changes in biological activity. They also compared the extracts for inhibition of the major drug metabolizing P450 enzymes and found that inhibition was more pronounced for the commercial preparation.
    - Kavalactones may influence liver detoxification pathways by inhibition of cytochrome P450 activity and a reduction in liver glutathione
    - Inhibition of cytochrome P450 was strongly suggested for a patient in Switzerland who developed malaise, loss of appetite, and jaundice, with elevated levels of aminotransferases, bilirubin, and alkaline phosphatase after taking 210 mg of kavalactones daily for 3 weeks together with 60 g of alcohol
    - Mechanisms of liver toxicity
        - P450 inhibition
        - Cyclooxygenase inhibition
        - Formation of electrophilic quinoid metabolites
    - The 9 cases of liver damage – included other potentially hepatotoxic medications and the majority used acetone extracts
    - One study found pipermethystine (higher concentrations in the areal or stem parts, not in roots) may play a role in liver toxicity.
    - Another study found it could be flavokavain B, which is found in the hexane faction (from a study showing organic solvent fractions are more hepatotoxic).

An Updated Review on the Psychoactive, Toxic and Anticancer Properties of Kava
Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC9315573/

- In the context of kava ingestion, there are several reports indicating its potential for the development of hepatotoxicity [8], skin rash [10], gastrointestinal problems and headaches [11], among other adverse effects that we address throughout this review.
- In fact, some aspects such as the quality of the plant, mode of extraction, solvents used, and the chemical composition presented are crucial points to consider.
- Kava's liver damaging effects were noticed from recreational use and was banned in Germany 2002.

- Kavalactones are lipophilic, 19 discovered, 6 considered psychoactive. kavain, dihydrokavain and methysticin are considered to be the most important kavalactones for the effects observed in the central nervous system. Yangonin has been suggested to display hepatoprotective effects against cholestatic liver injury
- Contains other constituents. Flavokavains B thought to be anticancer but hepatoxic, creates ROS. Flavokavain A anticancer.

Clinical pharmacokinetics of kavalactones after oral dosing of standardized kava extract in healthy volunteers

https://pubmed.ncbi.nlm.nih.gov/35777607/

- A subsequent safety evaluation by the World Health Organization (WHO) published in 2007 reported that kava-associated hepatotoxicity was rare at lower doses (120–240 mg/day), particularly with proper preparation and reduction or elimination of the non-kavalactone content, following which most of the restrictions for clinical studies were lifted in several parts of the world
- The most recent multi-centered clinical trial in Australia was inconclusive in terms of effectiveness compared to placebo treatment (Sarris et al., 2020).
- These clinical studies were performed using dose ranges from 120 to 280 mg kavalactones per day for multiple days or weeks without any significant adverse effects other than those that were also observed in the placebo arm at similar rates (many refs). Indication GAD.
- No signs of addiction of withdrawal
- Method
- Standardized flavokavain A/B-free kava extract capsules (75 mg total kavalactones/capsule) with the same lot number were obtained from Thorne Research Inc (USA). US FDA Investigation of new drug (IND) (FDA IND Number 142838) and UF-Institutional Review Board (IRB number 201900074) approval were obtained for all aspects of this study. Reference standards for kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, desmethoxyyangonin, flavokavain A, and flavokavain B were isolated and purified in-house

Toxicokinetics of Kava and kavalactones extract

https://pmc.ncbi.nlm.nih.gov/articles/PMC3085297/

Whilst kava extracts are generally well tolerated, toxic doses were determined in vivo using animal studies and in vitro. The LD50 (mg/kg) for kavain, methysticin, dihydrokavain, and dihydromethysticin in mice ranges from 41–69 (intravenous), 325–530 (intraperitoneal), and 920–1130 (oral) [2]. F344 rats treated with 2 g/kg/day kava extracts in corn oil by oral gavage five days a week for fourteen weeks

exhibited elevations in γ-glutamyl transferase (GGT), serum cholesterol, protein, and albumin levels, along with hypoglycaemia, within days of treatment [5]. Cytotoxicity associated with kavalactones was demonstrated for human hepatocytes in vitro (EC50 values approximately 50 μM) [6] and neurones in vivo at ≥300 μM [7], and apoptosis is the mechanism of cell death [8]. Since the highest serum kavain concentration recorded in a human is 17.4 μM [9], these data suggest that for most individuals, kavalactones have a wide therapeutic index.

A **wide therapeutic index (TI)** means that there is a **large margin of safety** between the drug's effective dose and its toxic dose.

An Updated Review on the Psychoactive, Toxic and Anticancer Properties of Kava

Link: https://pubmed.ncbi.nlm.nih.gov/35887801/

2022 paper -recent

Potential Hepatotoxic Compounds:

- **Flavokavain B:** Suggested as the primary compound responsible for hepatotoxicity. It induces apoptosis in liver cells and depletes glutathione (GSH), which may sensitize the liver to damage.
- **Pipermethystine:** A toxic alkaloid found in aerial parts of kava (leaves, stems). While not present in traditional root-based preparations, it may contribute to liver toxicity in improperly processed extracts.
- **Mold toxins (Aflatoxins):** Contaminants from improper storage may contribute to hepatotoxicity, but evidence is weak.

Role of Metabolism:

- Kavalactones, including kavain, are metabolized by **cytochrome P450 (CYP) enzymes**, particularly CYP2D6, CYP1A2, CYP2C19, and CYP3A4.
- Poor CYP2D6 metabolizers (e.g., ~12–21% of Caucasians, vs. ~1% of Pacific Islanders) may be more susceptible to hepatotoxicity.
- Some kava constituents (e.g., methysticin, dihydromethysticin) inhibit CYP enzymes, potentially leading to drug interactions and increased toxicity risk.

Effect of Extraction Methods:

- **Ethanol and acetone extracts** (common in commercial preparations) show a higher association with liver toxicity.

- **Water extracts** (traditional kava preparation) appear to have a lower hepatotoxicity risk.
- **Use of non-root parts (leaves, stems)** can introduce toxic alkaloids not typically found in traditional preparations.

Dosing and Duration:

- Hepatotoxicity has been reported in individuals consuming **twice the recommended dose** over prolonged periods (>3 months).
- Short-term use at moderate doses appears safer.
-

Kava has been linked to liver toxicity, but that may be due to extracts of kava not found in traditional preparations. I'm interested in extracting kavain, one of the kavalactones. Can you do some research - include peer reviewed studies on whether a dose of kavain at 600mg/day (without Flavokavain B) would be toxic to the liver?

Hepatic Toxicity Possibly Associated with Kava-Containing Products --- United States, Germany, and Switzerland, 1999--2002

Link: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm

These are the cases that lead to the banning of Kava in Germany in 2002. Copy pasted the summary:

Eight hepatic transplant cases following hepatic failure associated with the use of kava-containing products have been reported in Europe (six in Germany and two in Switzerland). Two male patients aged 32 and 50 years and six females aged 22--61 years required liver transplants after using kava-containing products. The duration of kava use ranged from 8 weeks to 12 months. The products were used at doses ranging from 60 mg to 240 mg per day. Seven patients used kava prepared either by ethanol or acetone extraction methods; one patient used an unspecified type of kava-containing product. The patients had varying symptoms, including influenza-like symptoms and jaundice. Each patient's condition worsened and progressed to fulminant hepatic failure. Four of these cases have been reported in medical literature (*1--4*). Additional information about these cases is available from the German regulatory authority, the Federal Institute for Drugs and Medical Devices, Bonn, Germany, at http://www.bfarm.de. A ninth European transplant case was

reported directly to FDA's MedWatch System by a U.S. pharmaceutical manufacturer.

Reported by: *Federal Institute for Drugs and Medical Devices, Bonn, Germany. HW McGhee, Children's Hospital of Pittsburgh, Univ of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania. Center for Food Safety and Applied Nutrition, Food and Drug Administration; Div of Environmental Hazards and Health Effects, National Center for Environmental Health, CDC*

Evaluation of the effects of Kava on the Liver

https://d1wqtxts1xzle7.cloudfront.net/79719166/Kava_20article_20DrMalani-libre.pdf?1643474295=&response-content-disposition=inline%3B+filename%3DEvaluation_of_the_effects_of_Kava_on_the.pdf&Expires=1741076835&Signature=IyJEvLFUjwN25Ep3A7PY0Fk0BTXgs4kCogSKLs-6dQUqWNBOC7W7TT2M08TKkdrGOVcuAiv7FwZvuliepxd7p00Jfgs7F8GHmFx3-iVoz0gJ~w0SknDcRDNLE4pWtFGqFsnai2UPPEnWaUOSSNAHm6Ejw~qu3u9O2Ybo8lsj41YsQ3Q3B62uq~ra3zfTJntTTv7H2Wxz7q2zCrgexiM-tfEbcJpUrXBwYn2ebNavYNUr0Ca7Gy5KX2BObdfP2qYNdACyd1w4rxiDtgS58~LbfcjV-ku0D1ma3YtE6RuvA75tsUShZGG2lSyfbUptcP3o13O0VffTfGkr8~z7prqFIQ__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA

Flavokawain B, the hepatotoxic constituent from kava root, induces GSH-sensitive oxidative stress through modulation of IKK/NF-κB and MAPK signaling pathways

https://pmc.ncbi.nlm.nih.gov/articles/PMC2992378/

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

Textbook - https://www.ncbi.nlm.nih.gov/books/NBK548637/

Published 2018

- Confirm it's about Piper methysticum plant
- "Based upon reported cases, the estimated frequency of clinically apparent liver injury due to kava is less than 1:1,000,000 daily doses. However, spontaneous reporting is believed to capture less than 1% of severe adverse events from the use of dietary supplements. Between 50 and 100 cases of clinically apparent liver injury have been published or discussed in the literature."
- Thus the true rate could potentially be **1 in 10,000 daily doses**

- Three cases discussed:
    - **Case 1. Acute liver failure treated with liver transplantation after kava use.**
    - **Case 2. Death from acute liver failure after kava kava use.**
    - **Case 3. Acute hepatitis attributed to kava.**
- "The argument that prescription anxiolytic agents have a similar rate of severe hepatic reactions is not correct. Prescription medications with the number of published instances of severe hepatic injury attributed to kava would be similarly withdrawn from use."
    - No citation given, so this should be fact checked.
    - Furthermore, the rate of traditional kava use should be considered in this value, as in the list of total cases are those attributed to unsafe kava use.

Kavalactone extraction methods

10. US20160279184 - Kava derived therapeutic compounds and methods of use thereof

https://patentscope.wipo.int/search/en/detail.jsf?docId=US177994188&_cid=P20-M7SY0Y-89884-1

Patent from what appears to be an extraction method you could DIY yourself.

Kavain

dirty drug, has MAO properties as well as GABA potentiation, promising to investigate - also sodium and calcium channel interactions

Pubchem: https://pubchem.ncbi.nlm.nih.gov/compound/5369129

Other names: kawain, neuronica.
DL kawain/kavain means racemic mixture of Levo (L or S) and Dextro (R or D) enantiomers.

Pubmed searches

“Kavain” 149 results 2/1/25.

"Kavain" and "anxiety" 36 results 2/1/25.

"Kavain" and "panic" 1 result: https://pubmed.ncbi.nlm.nih.gov/1682226/

“Kawain” – alternate spelling. 167 results.

Patentscope search for Kavain:
https://patentscope.wipo.int/search/en/result.jsf?_vid=P20-M7SY1T-91165

Patented methods (e.g. of extraction) can be used for research purposes but not comercial.

Kavain Toxicity

Influence of kavain on hepatic ultrastructure

link: https://pmc.ncbi.nlm.nih.gov/articles/PMC2681144/

2008

Study Aim & Methods

- Investigated whether **kavain**, a major kavalactone in *Piper methysticum* (kava), **damages liver structure and function**.
- Isolated rat livers were **perfused with kavain (10 µg/mL or 43.5 µmol/L) for 2 hours**. Human **plasma concentrations of total kavalactones** after kava consumption can range from **0.1 to 10 µg/mL**, depending on the dose. A **fatal case** of liver toxicity had **~33 µg/mL total kavalactones.**
- Liver samples were examined using **light microscopy (LM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM)**.

Key Findings

- **Severe vascular and endothelial damage** was observed in kavain-treated rat livers compared to controls.
- Liver tissue showed **narrowing of blood vessels, loss of endothelial integrity, formation of gaps in endothelium, and vacuolization of hepatocytes**.
- Kupffer cells (liver macrophages) appeared swollen and contained large cytoplasmic vacuoles, indicating **possible activation of inflammatory responses**.

- These changes suggest kavain **directly damages liver sinusoidal endothelial cells** or indirectly triggers an inflammatory response.

Toxicity & Dosing Insights

- **Perfusion concentration:** 10 µg/mL (43.5 µmol/L) **caused significant liver damage** in just 2 hours.
- Dose selected from literature
- **Literature comparisons suggest higher toxicity at higher doses:**
  - **Fatal human case:** ~33 µg/mL total kavalactones detected in plasma (after kava consumption with alcohol and cannabis).
  - **Toxic threshold in rat hepatocytes:** 50 µg/mL.
  - **Toxic threshold in mouse hepatocytes (LDH release):** 125 µg/mL.
- **Normal oral human dose of kava:** 200-300 mg/day (70% kavalactones), linked to liver failure in some cases.
- **Study limitations:** Only one concentration and exposure time tested; effects on humans remain uncertain.

Study only tested a single dose - no dose response given

It is difficult to conclude anything from this study without understanding the equivalent human dose. If it's based on the human fatal dose, that amount seems unlikely, however there may have been metabolic impairment or drug drug interactions.

Enzymes and Pathways of Kavain Bioactivation and Biotransformation

Link: https://pubmed.ncbi.nlm.nih.gov/31265262/

2019 - latest kavain toxicology

Kavain was purchased from Fluka Analytical (St. Louis, MO) (appears to be the expensive reference standard).

Conducted in in the liver, urine, and feces in mice using a metabolomic approach (FVB/NJ mice (2–4 months old, male)). The dose of kavain was set as 50 mg/kg, which was determined by the dose of kavain used in humans and the differences in body surface area between humans and mice. (better justification than the rat study).

Liver samples were harvested after 30 min of kavain treatment

28 kavain metabolites were identified, including 17 new ones.

Kavain undergoes several metabolic pathways:

- Glutathione (GSH) conjugation (indicating formation of reactive metabolites)
- Oxidation & dehydrogenation
- O-demethylation
- Sulfation & glucuronidation

The presence of GSH conjugates in the liver suggests that kavain is bioactivated into reactive metabolites, which may contribute to liver damage.

CYP2C19 was identified as the **main enzyme responsible for kavain metabolism**.

Potential Risk Factors for Kavain-Induced Liver Toxicity

- Formation of reactive metabolites (via CYP2C19) can lead to liver damage.
- Depletion of hepatic GSH (a key antioxidant) could worsen toxicity.
- Comedication risks:
    - Kava use with drugs that induce CYP2C19 could enhance formation of toxic metabolites.
    - Kava use with GSH-depleting drugs (e.g., acetaminophen) could increase liver toxicity.
- Genetic variability in CYP2C19 metabolism may determine individual susceptibility to liver injury.

This study did not find liver damage, as it was a mechanistic study of mouse mtabolomics to determine if liver damage could occur. They found evidence of bioactivation - which means the formation of reactive metabolite that can hurt things. Importantly they found that the reactive metabolites formed by kavain bioactivation were further detoxified by hepatic GSH.

Kavain and kavalactone pharmacokinetics

Review by Grok 3.0, references checked by KV

A key study by Gleitz et al. (2004), published in Journal of Chromatography B: Biomedical Sciences and Applications, examined kavain metabolism and kinetics, reporting that previous studies showed a maximum plasma concentration of approximately 18 ng/ml (0.018 µg/mL) after an oral dose of 200 mg d,l-kavain, with the peak reached at about 1.8 hours and initial resorption time of 15 minutes (ref: https://www.sciencedirect.com/science/article/abs/pii/S1570023203000461)

To estimate for 120 mg, assuming linear pharmacokinetics, the concentration would be proportional: (120/200)*0.018 µg/mL ≈ 0.0108 µg/mL at peak, and likely lower at 1 hour if not at Tmax. Another study by Mamallapalli et al. (2022), published in Journal of Ethnopharmacology, examined the clinical pharmacokinetics of kavalactones after oral dosing of standardized kava extract, providing data for kavain. They administered doses equivalent to 75 mg and 225 mg of total kavalactones, with kavain constituting 25.6% of the extract. For 75 mg total kavalactones (approximately 19.2 mg kavain), the Cmax was 11.5 ng/ml (0.0115 µg/mL) at 1.5 hours, and for 225 mg total kavalactones (approximately 57.6 mg kavain), Cmax was 34.5 ng/ml (0.0345 µg/mL) at 1.5 hours (ref: https://www.sciencedirect.com/science/article/abs/pii/S0378874122005530)

Dihydrokavain

: promising

Yangonin

: may contribute to anxiolytic effects but seems to be one of the major sources of hepatotoxicity

Methysticin

: same deal as yangonin

Desmethoxyyangonin

: MAO B inhibitor, no GABA effects, worth exploring

possible dopaminergic

may drive compulsion to keep consuming some people experience - may also be stimulating and motivating (important for agoraphobia)

But perhaps removing it might make the medicine have less potential for misuse

Dihydromethysticin

: Maybe liver toxicity but worth exploring

Kavain and dihydrokavain seem like the most promising

Relax-max effervescent powder sachets (berry flavoured), here are the results:

Integration Results													
Chem # Name abv	Rel.Amt %	Spectrum Match	Rtn T. min	Rel.Ar %	Rel.Ht %	R^2 %	HV LoD	Cor.Coef %	Cal. Pts.	Lower Limit	Amount (mg/kg)	Upper Limit	Extracted % of mass
2 DHK	26.26	996.205	13.338	18.69	15.14	99.999	2.2028	100.000	11	9895	9960	10024	1.00
4 K	22.54	990.972	12.716	40.69	30.49	99.634	43.3142	99.817	11	7259	8549	9840	0.85
3 Y	15.67	999.670	14.178	11.76	19.21	100.000	1.4260	100.000	11	5900	5944	5987	0.59
6 M	13.47	997.242	10.856	13.07	9.35	99.992	6.3283	99.996	11	4912	5108	5304	0.51
5 DHM	13.04	991.872	11.176	6.58	7.95	99.993	5.9188	99.997	11	4763	4947	5130	0.49
1 DMY	8.43	994.340	14.543	7.14	12.86	99.984	9.0105	99.992	11	2908	3196	3485	0.32
FKB	0.35	999.842	16.303	0.87	1.90	99.994	0.5752	99.997	11	115	134	153	0.01
FKA	0.25	999.282	15.953	1.19	3.09	99.980	0.8939	99.990	11	94	95		
Total	100			100	100					35847	37933	40019	3.75

It looks like a nice, relaxing, noble kava (chemotype 243651), but it's not very strong - about 4% of the mass of what's in the sachet is kavalactones. Note that this is no longer TGA approved.

This is apparently a pretty typical profile of noble kava, from a defunct aqueous extract.

Lived experience co-production in research

Co-production: Putting principles into practice in mental health contexts

Link:[Coproduction_putting-principles-into-practice.pdf]

“Co-production raises the bar for working with consumers, shifting from seeking involvement or participation after an agenda has already been set, to seeking consumer leadership from the outset so that consumers are engaged in the initial thinking and priority setting processes.”

About power differentials in mental health conditions “While power differentials exist in all areas of life, in no other area of health care is there separate legislation that removes the rights of consumers to refuse medical treatment. This legislation means hospitalisation can be mandated, even if it is against a consumers wishes, and interventions such as seclusion and restraint are able to be authorised.”

A lot of this document has been about power differentials. See page 10 for how to give power to those who have less.

Resources and planning

Databases to use

Pubmed: https://pubmed.ncbi.nlm.nih.gov/

Buying research compounds for academic purposes: https://www.sigmaaldrich.com/ (not recommended for human consumption, too expensive. But useful for information on the compound and to know that a researcher doesn't have to extract or synthesise the compound themselves)

International patent database: https://patentscope.wipo.int/ to search for patents. This is useful if (1) you would like to patent the use

Info on specific chemicals: https://pubchem.ncbi.nlm.nih.gov/ (compounds can have different names, or there may be isomers. An isomer is same molecular formula with a different arrangement of atoms. Think dextro and levo amphetamine which are mirror images of each other and have different efficacies. These are enantiomers. Mirror images. This matters for interacting with biological systems, because the shape of the molecule matters)

To do - things to focus on

Extraction method for high purity kavain (checking studies that use kavain or another kavalactone.

We know aqueous or 'normal use' of kava is safe for your liver. However kavalactone extract (and if we can get it, K and DHK) will involve organic solvents. So (1) Is there a safe extract and (2) are K and DHK toxic *on their own*?

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Definitions

Not official with refs - but for now for purposes of communication by KV

Confusing things about chemical names is confusion with the plural. E.g. kavalactone referring to the singular class and kavalactones refering to different types.

Kava - the root of the piper plant used to make the drink.

Kavalactones extract - an extract with higher concentrations of the 6 kavalactones

Purified kavalactone species (e.g. an isolate of just kavain - but maybe at like 90 percent purity). This is only confusing as I'm not focused on just kavain, but the others as isolates as well.