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Review Article

A Pharmacological and Clinical Reappraisal of Piper methysticum (Kava) for Anxiety: Balancing Traditional Efficacy with Modern Safety

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ABSTRACT

Anxiety disorders represent a major global health burden, yet current pharmacological treatments like SSRIs and benzodiazepines have significant limitations, including delayed onset, side effects, and dependency risks. Kava (Piper methysticum), a traditional Pacific botanical, offers a promising alternative. This review synthesizes evidence on kava's anxiolytic efficacy, safety, and regulatory status. Modern clinical trials demonstrate that standardized, aqueous extracts of noble kava cultivars are effective for mild-to-moderate anxiety with a favorable side-effect profile, primarily causing transient dermopathy or gastrointestinal discomfort. The central safety controversy rare, idiosyncratic hepatotoxicity is now understood as a multifactorial issue linked to poor-quality raw materials (e.g., non-noble varieties, aerial plant parts), specific extraction methods, and individual metabolic susceptibilities, rather than an inherent property of kava itself. Risk mitigation strategies, including the use of noble cultivars, water-based extraction, and adherence to recommended daily doses (≤250 mg kavalactones), are outlined. Despite robust traditional use and evolving scientific understanding, global regulations remain fragmented, ranging from complete bans in parts of Europe to regulated supplement status in the United States and quality-controlled frameworks in the Pacific. This reappraisal concludes that, with stringent quality controls and appropriate patient selection, kava represents a viable, evidence-based phytotherapeutic option for anxiety management.

INTRODUCTION

Globally, mental disorders constitute a major public health challenge, with depressive and anxiety disorders representing the primary drivers of this burden [1]. These conditions are leading causes of disability and are responsible for massive annual economic losses, estimated at

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$925 billion in lost productivity (WHO, 2014). Despite this immense impact, global investment in mental health remains critically insufficient and inequitably distributed, creating a vast treatment gap [2]. The burden of these highly comorbid disorders varies widely across regions, influenced by economic, social, and healthcare factors [3]. As global dynamics evolve including economic development and ongoing societal pressures there is an urgent need for long-term, integrated projections of the burden of depression and anxiety to inform strategic healthcare planning and resource allocation for the coming decade [4]. The current evaluation of antidepressant effectiveness is severely limited by methodological issues with early symptom improvement detection and definition. The variable and late beginning of effect of conventional medicines, including several types of standard antidepressants, is a problem. A significant clinical response usually takes several weeks to manifest. The lack of established definitions for "rapid onset" or "early improvement," since current response and remission criteria were created for longer-term evaluation, exacerbates this delayed treatment window [5,6]. As a result, the majority of the information pertaining to early effects comes from post-hoc analysis of trials that were not adequately powered for such evaluations, which results in inconsistent and untrustworthy estimates of quick efficacy. Additionally, it is possible that traditional depression rating measures and the frequency of their use are not adapted to catch clinically significant improvement that takes place in a matter of hours or days. Leaving a significant gap in the conceptual understanding and assessment of fast antidepressant activity[7] Clinical difficulties with traditional pharmacological treatments for depression and anxiety are substantial. First-line treatments known as selective serotonin reuptake inhibitors (SSRIs) have a delayed onset of therapeutic activity; it frequently takes weeks for them to show clinically significant results. Although benzodiazepines are commonly used for quick symptom alleviation, there is a significant risk of tolerance, dependency, and withdrawal symptoms. Both drug classes have a significant load of adverse effects, including as sedation, weight gain, and sexual dysfunction with SSRIs and cognitive impairment and sleepiness with benzodiazepines, which often result in poor adherence [8]. Additionally, despite sufficient trials of several therapeutic drugs, a sizable percentage of patients have treatment-resistant characteristics, failing to reach remission. Together, these drawbacks highlight the necessity of alternate pharmacological approaches with better efficacy and tolerability [9,10]. Kava, traditionally known as *Piper methysticum* ("intoxicating pepper"), originated as a ceremonial and social beverage deeply embedded in the cultures of the Pacific Islands for millennia. Used to facilitate community bonding, spiritual connection, and conflict resolution, its psychoactive yet non-alcoholic properties fostered a state of calm, focused sociability. In the late 20th century, Western interest transformed this ethnobotanical elixir into a commercial herbal medicine, promoted for its natural anxiolytic properties. This transition from a communal, ritually prepared drink to a standardized, clinically studied extract encapsulates the broader journey of traditional plant medicines into the global phytopharmaceutical market[11,12]

1. Rationale for Reappraisal of Kava:

A reappraisal of kava (Piper methysticum) is strongly supported by three key advancements:

I. **Newer, high-quality clinical trials**, particularly from Europe and the Pacific, employing modern diagnostic criteria (e.g., for anxiety disorders), rigorous methodology, and standardized kava extracts, consistently

demonstrate significant anxiolytic efficacy with a favorable side-effect profile, directly addressing historical concerns over trial quality [13].

II. **Advanced phytochemical analyses** now precisely distinguish between traditional water-based extracts (rich in beneficial kavalactones) and potentially hepatotoxic acetone/ethanol extracts or preparations using non-traditional plant parts (stems, leaves), isolating the specific chemotype and ruling out adulterants as primary culprits in past liver issues[14].

III. a **refined safety hypothesis** that shifts focus from inherent kava toxicity to a pharmacogenetic predisposition—specifically, poor metabolizers of CYP2D6 substrates—interacting with specific extraction methods and concomitant medications, effectively exonerating aqueous extracts of noble kava cultivars when used appropriately. This modern evidence framework provides a clear, scientific basis for distinguishing safe, therapeutic use from historically problematic preparations, warranting a formal re-evaluation of its regulatory status[15]

2. Kava Constituents, Chemotypes, and Preparation Methods :

Aspects	Key Details	Key impacts	References
Major Active Constituents	Kavalactones (KLs): A group of ~18 related α-pyrone compounds. The six major KLs are: Kavain, Dihydrokavain, Methysticin, Dihydromethysticin, Yangonin, and Desmethoxyyangonin.	nxiolytic, muscle-relaxant, and analgesic effects are primarily attributed to KLs, which modulate GABAergic, glutamatergic, and monoaminergic systems. KL profile determines the chemotype.	[16,17]
Chemotypes & Cultivars	Defined by the rank order of the 6 major KLs (e.g., "463251"). • Noble Kava: Dominated by Kavain/Dihydrokavain (chemotypes 462531, 426135). • Tudei (Two-Day) Kava: High in Dihydromethysticin/Methysticin (che motypes 246531, 643251)	Noble: Preferred for traditional use; milder, predictable effects, lower risk of adverse effects. Tudei: Associated with stronger, longer-lasting, and less pleasant effects; linked to higher risk of nausea and potential hepatotoxicity. Commercial use is discouraged.	[18]
Other Constituents	Flavokavains A, B, C (chalcones) and trace Piperidine Alkaloids (e.g., pipermethystine).	Flavokavain B (FKB) is implicated in *in vitro* hepatotoxicity, found in higher concentrations in aerial parts and some Tudei cultivars. Alkaloids are present in leaves/stems and are toxic. Safety depends on minimizing these constituents.	[19,20]
Importance of Plant Part	Lateral (Peeled) Roots: Traditionally used; contain high KLs, low FKB. Aerial Parts (Stems, Leaves, Peelings): Contain high concentrations	Use of aerial parts or poor-quality "wild" kava is a major risk factor for hepatotoxicity. Modern safety mandates use of peeled lateral roots/rhizomes only.	[21]

	of FKB and toxic alkaloids; never used in traditional beverage.		
Extraction Methods	1. Traditional Aqueous: Cold water extraction of dried, macerated root**.** 2. Commercial Solvent Extracts: Use of acetone or ethanol (often on whole plant or aerial parts).	Aqueous extract: Yields KLs with minimal FKB; correlates with long history of safe use. Acetonic/Ethanolic extracts: Efficiently co-extract FKB and alkaloid**s**; linked to most hepatotoxic case reports. This is the critical link to safety	[22]
Standardization	Typically standardized to total kavalactone content (e.g., 70% KLs). Debate: Some argue for standardization to a specific KL ratio (e.g., high-kavain chemotype) for efficacy and safety, but this is not yet universally adopted.	Standardization to KL % ensures potency but does not guarantee a safe chemotype or low FKB content. The cultivar (Noble) and plant part (root) remain the most important quality markers.	[23,24]

3. Pharmacological Mechanisms of Anxiolytic Action:

- **Multi-Target Neuromodulation: Expanding Beyond the Classical GABA Hypothesis**

Anxiety disorders represent a major global health burden, and pharmacological treatments re Anxiety disorders represent a prevalent class of neuropsychiatric conditions characterized by excessive fear, heightened stress responses, and dysregulated emotional processing. Historically, the pharmacological treatment of anxiety has largely focused on enhancing inhibitory neurotransmission through γ-aminobutyric acid (GABA) receptors, particularly GABAA receptors targeted by benzodiazepines. However, contemporary research emphasizes a multi-target neuromodulation framework that extends beyond the classical GABA-centric view and incorporates glutamatergic modulation, especially involving N-methyl-D-aspartate (NMDA) receptors as part of anxiolytic mechanisms [25].

3.1. Modulation of GABAergic System: Potentiation of GABAA Receptors (Distinct from Benzodiazepine Site)

Classical View and Rationale

The inhibitory neurotransmitter GABA is the primary mediator of inhibitory tone in the central nervous system (CNS). GABAA receptors are ligand-gated chloride channels that, when activated, stabilize neuronal membranes through chloride influx and reduce excitatory firing. Enhancing this inhibition attenuates hyperexcitability underlying anxiety states[26].

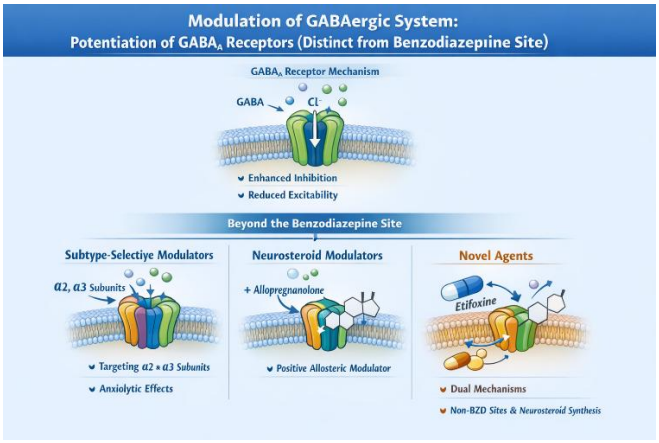
Beyond the Benzodiazepine Site

Unlike classical benzodiazepines that potentiate GABAA receptor function by binding at the canonical benzodiazepine allosteric site, multiple novel anxiolytic compounds modulate GABAA function through distinct receptor subunits or alternative binding sites a mechanism associated with anxiolysis but reduced sedation and dependency risk [27].

a) **Subtype-Selective Modulators**: Compounds that preferentially target α2 and α3 subunit-containing GABAA receptors demonstrate anxiolytic effects with fewer sedative and cognitive side effects, suggesting *anxiolytic selectivity* without the drawbacks of classical benzodiazepines [28].

b) **Neurosteroid Modulators**: Endogenous neurosteroids like allopregnanolone act as positive allosteric modulators of GABAA receptors, contributing to inhibitory balance distinct from benzodiazepine sites, and hold therapeutic anxiolytic potential.

c) **Novel Agents**: Agents such as etifoxine illustrate dual mechanisms binding at non-benzodiazepine sites on GABAA receptors and enhancing neurosteroid synthesis suggesting multi-modal GABAergic modulation as an anxiolytic strategy different from traditional benzodiazepines [29].



3.2.Effects on Glutamatergic System: NMDA Receptor Antagonism

Why Glutamate Matters in Anxiety

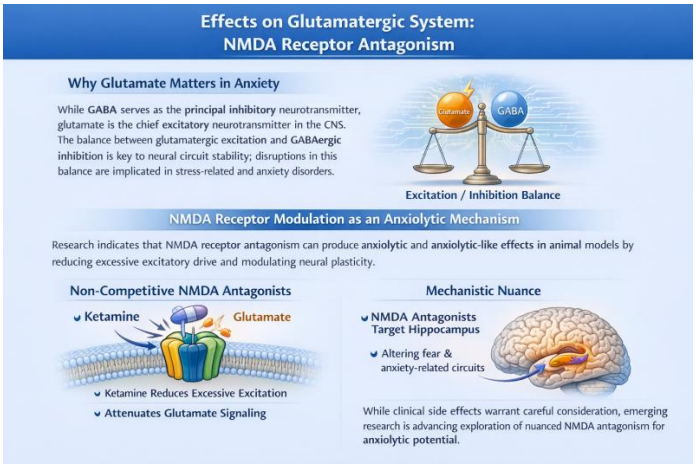
While GABA serves as the principal inhibitory neurotransmitter, glutamate is the chief excitatory neurotransmitter in the CNS. The balance between glutamatergic excitation and GABAergic inhibition is key to neural circuit stability; disruptions in this balance are implicated in stress-related and anxiety disorders[30].

NMDA Receptor Modulation as an Anxiolytic Mechanism

Research indicates that NMDA receptor antagonism can produce anxiolytic and anxiolytic-like effects in animal models by reducing excessive excitatory drive and modulating neural plasticity.

- **Non-Competitive NMDA Antagonists** such as ketamine have been shown in experimental studies to reduce anxiety-like behaviors, likely by attenuating glutamate-mediated excitatory neurotransmission and altering downstream neural circuits related to fear and emotional responses [31].
- **Mechanistic Nuance**: NMDA receptor antagonists reduce excitatory activity in critical regions such as the hippocampus, a structure closely involved in emotion and anxiety regulation, thereby contributing to anxiolytic outcomes.

Although NMDA antagonists carry side-effect considerations in clinical settings, emerging research motivates a deeper exploration of subunit-specific antagonism and nuanced modulation that might maximize anxiolytic benefits while minimizing adverse effects [32].



3.3.Integrating Multi-Target Neuromodulation

The current landscape of anxiolytic pharmacology reflects an evolution from **mono-targeted GABA potentiation** to **multi-target strategies** that integrate inhibitory enhancement with excitatory suppression and neural circuit modulation. This integrative approach acknowledges complexity in neural network dynamics underpinning anxiety and seeks pharmacological interventions that more comprehensively address excitatory–inhibitory imbalance.

- **Rationale**: Anxiety disorders often involve dysregulated interactions between multiple neurotransmitter systems; hence, combining GABAergic potentiation with glutamatergic damping may offer improved clinical profiles and therapeutic outcomes.

- **Clinical Implications**: Such strategies may outperform traditional agents by reducing side effects while engaging multiple neurobiological pathways associated with anxiety [33,34].

3.4.Monoaminergic Systems: Influence on Noradrenaline, Dopamine & Serotonin Reuptake/Transport

Mechanistic Overview Monoamines in Anxiety: The monoaminergic hypothesis posits that serotonin (5-HT), noradrenaline (NE), and dopamine (DA) regulate mood and emotional behavior by modulating synaptic transmission. Anxiolytic interventions often influence these neurotransmitters by inhibiting their reuptake transporters SERT, NET, and DAT or by preventing their enzymatic breakdown, thereby increasing synaptic availability and enhancing signaling within limbic and cortical circuits that regulate fear and stress responses.

a) **Serotonin reuptake inhibition:** Selective serotonin reuptake inhibitors (SSRIs) e.g., escitalopram and sertraline block SERT, increasing 5-HT levels that correlate with anxiolytic efficacy in clinical and preclinical studies [35].

b) **Noradrenergic modulation:** Inhibiting NET (e.g., via norepinephrine reuptake inhibitors or SNRIs) enhances NE transmission in anxiety-

related circuits such as the locus coeruleus and amygdala, impacting arousal and stress-induced hypervigilance [36].

c) **Dopaminergic involvement:** Though less studied, modifications of dopamine signaling (e.g., via DAT modulation or D-receptor interactions) influence exploratory ambivalence and reward components disrupted in anxiety states [37].

3.5.Neuroprotective & Anti-Inflammatory Effects: Mitigating Neuroinflammation Linked to Anxiety

Neuroinflammation in Anxiety:

Emerging evidence indicates that neuroinflammation contributes significantly to the pathophysiology of anxiety disorders. Chronic stress and inflammatory cytokines can alter neurotransmitter synthesis, release, and receptor expression, thereby influencing anxiety-related circuits.

• **Monoamine–Inflammation Interplay:** According to the review *Monoamine Signaling and Neuroinflammation*, monoaminergic systems interact with immune responses pro-inflammatory cytokines can modulate serotonin, norepinephrine, and dopamine metabolism, while monoamines themselves influence microglial activation and cytokine production, creating bidirectional control over neuroinflammatory states implicated in anxiety and other neuropsychiatric conditions[38].

• **Anti-Inflammatory & Neuroprotective Actions:** Agents with anti-inflammatory profiles including some natural flavonoids and phytochemicals show anxiolytic-like effects in preclinical models that are associated with suppressed pro-inflammatory cytokine release, reduced microglial activation, and increased neuronal viability.

Functional Implications:

Neuroprotective mechanisms may facilitate resilience to stress-induced structural and functional brain changes by preserving synaptic integrity, enhancing neurotrophic factors like BDNF, and attenuating oxidative damage processes now recognized as contributing to anxiety symptomatology alongside classical neurotransmitter imbalance [39].

3.6.Preclinical Evidence Summary: Supporting Anxiolytic & Neurobiological Effects in Animal Models

Behavioral Models & Mechanistic Findings:

Preclinical studies using elevated plus maze, open-field tests, and stress paradigms demonstrate that pharmacological agents influencing monoamines, GABAergic function, or inflammatory pathways show anxiolytic-like behavioral effects in rodents [40].

Examples of preclinical findings include:

• Monoaminergic modulation:

Agents that increase extracellular serotonin and norepinephrine via reuptake inhibition or receptor modulation produce reduced anxiety-like behaviors in animal models, consistent with clinical anxiolytic effects seen in humans [41].

• Anti-Inflammatory effects:

Compounds with anti-inflammatory and antioxidant profiles (e.g., certain flavonoids) reduce anxious behaviors in rodents exposed to stress or inflammatory challenges, correlating with

decreased neuroinflammation markers and improved neural health [42].

• **Neuroprotective outcomes:** In various rodent studies, agents that protect neurons from stress-induced damage also mitigate anxiety-like behavior, supporting the notion that neuroprotection is a component of anxiolytic mechanisms when inflammation and excitotoxicity are involved [43].

4. Clinical Efficacy for Anxiety Disorders

4.1. Review of Meta-Analyses & Systematic Reviews (2010-Present)

The body of clinical evidence evaluating kava (Piper methysticum) for anxiety has been synthesized in multiple systematic reviews and meta-analyses. A comprehensive meta-analysis of double-blind randomized controlled trials (RCTs) found that kava extract was associated with greater reductions in Hamilton Anxiety Rating Scale (HAM-A) scores compared with placebo across several studies, though the overall effect size was modest and based on relatively small samples (total n≈700).7 Trials included in this synthesis demonstrated mild, transient adverse effects similar to placebo, suggesting a generally favorable short-term safety profile[44]. Earlier meta-analyses (e.g., Pittler & Ernst, 2000) also reported that kava extract produced significant symptomatic anxiolytic effects vs placebo, with a weighted mean reduction in HAM-A scores in favor of kava, although methodological and sample size limitations reduced the strength of conclusions[45]. A more recent systematic review focused specifically on Generalized Anxiety Disorder (GAD) identified 12 clinical trials. While pooled estimates showed effect sizes favoring kava (standardized mean differences 0.59-0.99), results did not always reach statistical significance, and evidence was considered promising but insufficient to definitively confirm efficacy due to limited trial size and heterogeneity [46].

5.2. Key Randomized Controlled Trials (RCTs)

a. Trials Using Specific Kava Extracts (WS® 1490, LI 150)

WS® 1490 Extract Trials

- A multicenter, randomized, placebo-controlled, double-blind trial of WS® 1490 (200 mg/day) in adults with anxiety and sleep disturbances associated with anxiety showed significant improvements in both anxiety scales (HAM-A psychic sub-score) and sleep outcomes versus placebo over 4 weeks, with excellent tolerability.
- Multiple RCTs with WS1490 demonstrated superior therapeutic efficacy vs placebo across clinician-rated and self-report anxiety measures.
- A long outpatient trial (25 weeks) with WS1490 found significant superiority over placebo starting at week 8 on HAM-A and sustained benefits on secondary anxiety ratings, supporting longer-term anxiolytic efficacy and better tolerability than benzodiazepines and TCAs [47].

LI 150 Extract Trial

- An 8-week, randomized, double-blind, multicenter RCT involving 129 outpatients with *Generalized Anxiety Disorder (ICD-10 F41.1)* compared Kava extract LI 150 (400 mg/day) to Buspirone (10 mg) and Opipramol (100 mg). LI 150 performed as effectively as these standard anxiolytic agents on HAM-A and response rates, with similar tolerability [48].

These trials provide evidence that standardized extracts like **WS® 1490** and **LI 150** exhibit anxiolytic effects in placebo-controlled and active-controlled settings.

b. Efficacy in Generalized Anxiety Disorder (GAD)

RCTs specifically enrolling patients with GAD have shown mixed but promising outcomes. In the LI 150 trial, kava extract yielded anxiolytic effects comparable to buspirone and opipramol over 8 weeks in outpatients diagnosed with GAD. Systematic reviews focusing on GAD noted that while pooled effect sizes often favored kava, statistical significance was not always reached, and existing evidence remains insufficiently robust to establish definitive efficacy beyond placebo due to limited sample sizes and variability in trial design [49].

c. Efficacy in Non-Clinical, Situational, and Perimenopausal Anxiety

Direct RCT evidence in situational anxiety and perimenopausal anxiety is limited:

- Some RCTs using WS1490 reported reductions in anxiety and tension in non-psychotic, non-GAD populations, suggesting benefits for situational or mild anxiety, although these were not always the primary diagnostic groups .
- Preliminary evidence from longer durations and naturalistic studies suggests reductions in anxiety symptoms during perimenopause when combined with other interventions, but rigorous RCT data specifically targeting perimenopausal anxiety is sparse [50].

5.3.Onset of Action and Efficacy Comparison

Kava extracts generally demonstrate anxiolytic effects that emerge gradually over several weeks, as seen in longer randomized trials where significant group differences often were noted after 8 weeks.

In comparison:

- Benzodiazepines typically produce rapid anxiolytic effects within hours to days, making kava appear slower in onset.
- Standard SSRIs (e.g., paroxetine) require 4-6 weeks to demonstrate full anxiolytic effects, similar to or slightly faster than kava's clinical trajectories in RCTs.

Despite a relative *slower onset* compared to benzodiazepines, kava is usually associated with a more favorable side-effect profile (e.g., less sedation, lower risk of dependence) in short-term use [51].

5.4.Limitations of Clinical Data

While existing clinical trials support short-term anxiolytic efficacy and good tolerability of standardized kava extracts, several key limitations constrain the strength of conclusions:

- **Limited long-term data:** Most RCTs are ≤8 weeks; only a few extend beyond this, making conclusions about sustained efficacy and safety over >6 months uncertain.
- **Lack of head-to-head trials:** Few trials have directly compared kava extracts against modern pharmacotherapies (SSRIs, benzodiazepines) in well-powered studies beyond initial small RCTs like the LI 150 trial.
- **Sample size and design variability:** Many studies involve modest sample sizes and

heterogeneous populations, limiting generalizability [52].

Future research with larger, longer, and rigorously controlled designs, including direct comparisons with first-line pharmacotherapies, is needed to clarify the clinical role of kava in anxiety disorders.

6. Safety, Tolerability, and Hepatotoxicity Debat

Aspect	Category	Details	Practical Implications / Risk Mitigation	References
Common Side Effects	Kava Dermopathy	Dry, scaly, discolored skin from prolonged/high-dose use. Reversible upon discontinuation. Common in heavy traditional use (e.g., Fiji).	Usually resolves after stopping kava. Not a sign of systemic toxicity.	[53]
	Gastrointestinal Upset	Nausea, diarrhea, mild digestive discomfort reported in trials and traditional use.	Generally mild and transient.	
	Headache	Mild, often dose-dependent, typically occurs at initiation or with higher intakes	Usually temporary.	
General Tolerability	Conclusion	At recommended anxiolytic doses (≤250 mg kavalactones/day), kava (especially aqueous extracts) is generally well-tolerated with transient, reversible side effect.	Adherence to recommended doses minimizes common adverse events.	[54]
Hepatotoxicity Controversy	Nature of Injury	Idiosyncratic (rare, unpredictable, not dose-dependent). Severe cases (liver failure, transplant) reported in Western countries in the 1990s/2000s	Risk is very low but severe. Cannot be predicted by dose alone	[55,56]
	The "Pacific Paradox"	Traditional Pacific Island populations consume very high doses of water-based kava but do not show proportional liver disease epidemics	Suggested early on that traditional use was safer than Western extracts	
Proposed Causes of Liver Injury	1. Raw Material Quality	Use of non-noble cultivars (e.g., Tudei), aerial parts (leaves/stems), or mold-contaminated (aflatoxin) roots is a major suspect.	Critical Factor: Always use noble cultivar root/rhizome material from reputable sources.	[57,58
	2. Extraction Method	Early cases linked to organic solvents (acetone/ethanol), but causality assessments find injury across all extract types . Solvent alone is not the sole determinant.	Prefer water-based (aqueous) traditional preparations, though not an absolute guarantee of safety	
		Kava inhibits liver enzymes (CYP450), potentially causing interactions with drugs like acetaminophen, increasing toxic load	Avoid concurrent use with medications metabolized by the liver, especially in	

			those on multiple drugs.	
	4. Genetic Predisposition	Individual differences in metabolism may increase susceptibility, fitting the idiosyncratic model. No specific genetic markers confirmed.	Explains rarity but offers no current screening test.	
Safety Recommendations	The "Noble Kava" Doctrine	Use only traditionally accepted, noble kava cultivars. Avoid non-noble (e.g., Tudei) varieties.	Primary Mitigation Strategy: Sourcing noble kava is considered the most important safety measure	[59,60]
	Extraction Preference	Favor traditional water-based extraction methods over organic solvents to avoid concentrating lipophilic compounds	Aligns with traditional practice and regulatory advisories.	
	Dose Adherence	Limit total daily intake to ≤ 250 mg of kavalactones.	Based on clinical trial safety data for anxiolytic effect.	
	Population Avoidance	Contraindicated for individuals with: pre-existing liver disease, heavy alcohol use, or those taking multiple hepatotoxic medications.	Identifies and protects the most at-risk groups.	

7. Regulatory Status and Contemporary Use Guidelines for Kava (*Piper methysticum*):

7.1. Current Global Regulatory Landscape

The regulatory status of kava varies widely between countries and regions, reflecting differing interpretations of its safety profile especially concerns about hepatotoxicity.

a. Europe

In the European Union**,** regulatory bodies such as the Committee on Herbal Medicinal Products (HMPC) determined that the *benefit–risk balance* for oral kava use in anxiety was unfavorable, and thus no EU herbal monograph was established for its medical use. Many EU members (e.g., United Kingdom) classify *kava* as a prohibited medicinal product, making its sale for human consumption illegal, though possession for personal use is sometimes permitted. Other countries like Poland have recently lifted bans on possession and import but still restrict commercial sale. In contrast, the Netherlands continues to prohibit most kava products for human use. These restrictions stem from case reports linking kava extracts to liver injury, particularly during the late 1990s and early 2000s, involving products marketed in Germany**,** Switzerland, and beyond [61].

b. North America

In the United States, *kava* is widely marketed as a dietary supplement, not as an approved drug. Under the Dietary Supplement Health and Education Act (DSHEA), products marketed before 1994 may remain on the market without formal safety approval, though labeling must follow Current Good Manufacturing Practices (cGMPs). The U.S. Food and Drug Administration (FDA) issued a consumer advisory in 2002 alerting the public to rare but severe liver injury reports linked to kava products and reiterated in a

2020 memorandum that kava is *not* Generally Recognized as Safe (GRAS) for conventional food use because of potential toxicity and drug interactions [62].

c. Oceania and Pacific Island Nations

In the South Pacific the traditional home of kava consumption export and quality-control legislation exist in countries like Vanuatu, where the Kava Act restricts export and use of non-noble kava varieties or unsuitable plant parts (leaves/stems). In Australia, commercial import and use are regulated through a National Code of Kava Management with import limits and daily kavalactone recommendations; some states previously had bans (e.g., Western Australia) that have since been lifted [63].

d. Other Regions

Various countries in Asia (e.g., Singapore) maintain bans on kava sales, while others such as Japan and South Korea reportedly restrict kava to prescription-only contexts (though official details vary). Global regulation reflects attempts to balance traditional use, public health safety, and commercial freedom amidst lingering concerns about rare hepatotoxicity [64].

7.2. Proposed Clinical Guidelines for Responsible Kava Use

Although formal clinical practice guidelines are limited, several evidence-based recommendations can be distilled from safety reviews and expert opinion to guide clinicians and consumers toward responsible use.

a. Patient Selection

Kava appears most appropriate for adults with mild to moderate anxiety or stress-related symptoms where conventional pharmacotherapy is not preferred or contraindicated. Traditional aqueous kava extracts have shown anxiolytic efficacy in controlled studies, but safety considerations remain paramount. Patients with pre-existing hepatic conditions (e.g., chronic liver disease), a history of alcohol misuse, or concurrent use of hepatotoxic drugs are at higher theoretical risk for adverse hepatic outcomes and should generally avoid kava or use it only under clinical supervision with close monitoring [65].

b. Product Selection Criteria

Quality control is critical in mitigating risk. Recommended criteria for selecting kava products include:

- **Noble cultivars only:** Products derived from traditional, noble kava varieties are associated with a more favorable safety profile compared to non-noble strains (e.g., *Tudei*).
- **Preferred extraction methods:** Use aqueous or supercritical CO_2 extracts rather than non-polar solvent extracts (acetone/ethanol) to minimize potential extraction of lipophilic impurities linked to earlier hepatotoxicity case reports.
- **Standardization:** Choose standardized extracts with reliable kavalactone content labeling to allow accurate dosing.

Experience from traditional use and clinical trials underscores that adherence to these quality parameters helps reduce incidence of adverse effects [66].

c. Dosing and Duration Recommendations

The Therapeutic Goods Administration (TGA) in Australia and similar advisory bodies recommend ≤ 250 mg of kavalactones per day to minimize toxicity risks. This dosing aligns with many

clinical trials and expert reviews suggesting this threshold balances potential benefits with safety. Short- to medium-term use (e.g., up to 8–12 weeks) appears better-studied, with long-term safety data scarce; thus, extended use warrants periodic re-evaluation of benefit and risk [67].

d. Monitoring Advice

To enhance safety when kava is used clinically or as a supplement:

- **Baseline liver function tests (LFTs):** Prior to initiation in *at-risk individuals* (e.g., older adults, those with possible hepatic vulnerabilities), baseline serum aminotransferases (ALT, AST), bilirubin, and other relevant labs can provide a reference.

- **Periodic LFT monitoring:** While not mandatory for healthy adults, regular self-reporting of symptoms (e.g., jaundice, fatigue, abdominal pain) and physician-directed LFTs every 4–8 weeks may be reasonable for prolonged use or in those with intermittent risk exposures.

- **Patient education:** Users should be informed about early signs of liver injury and advised to immediately discontinue kava and seek medical evaluation if symptoms develop.

This structured monitoring approach borrows from recommendations in clinical safety literature and helps detect rare hepatotoxicity early [68].

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