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Kava Kava in Anxiety Disorders: Current Evidence and Clinical Implications

Aleksandra Muszalska, ORCID https://orcid.org/0009-0007-9162-399X
Email: amuszalska.studia@gmail.com
Greater Poland Regional Hospital (Szpital Wojewódzki w Poznaniu), Juraszów 7/19, 60-479 Poznań, Poland

Brajan Roczyński, ORCID https://orcid.org/0009-0003-9705-4557
Email: brajan.roczynski@wp.pl
Poznan University Clinical Hospital (Uniwersytecki Szpital Kliniczny w Poznaniu), Poznań, Poland

Julia Wiecanowska, ORCID https://orcid.org/0009-0009-1637-2283
Email: julia.wiecanowska@gmail.com
Greater Poland Regional Hospital (Szpital Wojewódzki w Poznaniu), Juraszów 7/19, 60-479 Poznań, Poland

Corresponding Author: Julia Wiecanowska — julia.wiecanowska@gmail.com

Abstract

Piper methysticum, commonly known as kava, has been traditionally used in the South Pacific for centuries due to its calming and anxiolytic properties. Its primary bioactive constituents, kavalactones, are responsible for its pharmacological effects and modulate multiple central nervous system pathways. These compounds exhibit anxiolytic, sedative, and muscle-relaxant activity, which has led to increasing scientific interest in their potential application in anxiety disorders. Generalized anxiety disorder remains one of the most prevalent psychiatric conditions worldwide and is often associated with reduced quality of life and

incomplete response to conventional pharmacotherapy. Consequently, kava is being investigated as a potential complementary therapeutic option. This review summarizes current evidence on *Piper methysticum*, with particular emphasis on the mechanisms of action of kavalactones and their role in anxiety management. A comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar.

Introduction:

Anxiety disorders constitute one of the most prevalent group of psychiatric conditions and are associated with substantial individual burden and socioeconomic costs [1]. They are typically chronic in nature and significantly impair quality of life, as well as occupational and social functioning . Among them, generalized anxiety disorder (GAD) is a particularly disabling condition, characterized by persistent and excessive worry, often following a relapsing course and contributing to long-term functional impairment [2,3]. Although currently available pharmacological treatments, including selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, demonstrate clinical efficacy, their overall effectiveness remains moderate. Importantly, a substantial proportion of patients fail to achieve full remission, and many continue to experience residual symptoms despite multiple treatment attempts, highlighting the need for alternative or adjunctive therapeutic strategies [3]. In this context, increasing attention has been directed toward plant-based and nutraceutical interventions as potential options in anxiety management. One such candidate is *Piper methysticum* (kava), a traditional South Pacific herbal medicine widely used for its anxiolytic and calming properties. Beyond its long-standing ethnopharmacological use, kava has gained popularity in modern settings, prompting growing scientific interest in its efficacy and safety profile in the treatment of anxiety disorders [4]. The aim of this review is to provide a critical appraisal of both clinical and preclinical evidence regarding the effects of *Piper methysticum* on the alleviation of anxiety symptoms. To achieve this, relevant studies were identified through searches of databases including PubMed, Scopus, and Google Scholar.

1.Botanical description

Piper methysticum originates from the South Pacific region and grows best in tropical conditions characterized by high humidity, warm temperatures, and well-drained volcanic soils. It is mainly cultivated in countries such as Vanuatu, Fiji, Samoa, Tonga, Papua New Guinea, and the Solomon Islands, where traditional farming practices are still maintained. Optimal growth requires partial shading, soils rich in organic matter, and regular rainfall. In contrast to other species within the *Piper* genus, kava does not form fertile seeds and is therefore

propagated exclusively through vegetative means, making its cultivation entirely reliant on human involvement [5,6]. Kava usually reaches a height of about 2–3 meters, forming a woody base with many lateral shoots. Its thick, knobby stem is marked by prominent internodes that function as storage sites for water and nutrients necessary for plant development [7]. Leaves of kava are generally broad, ranging from ovate to cordate in shape, and measure approximately 13–28 cm in length and 10–22 cm in width. They exhibit 9–13 clearly visible primary veins that originate at the leaf base. The leaf surface is smooth, with margins that are slightly undulating. Each blade is borne on a short petiole, while large stipules occur at the base, providing both protective and structural support [8]. The inflorescences are composed of small, spike-shaped clusters ranging from 3 to 9 cm long. The flowers are very small, not showy, and do not possess petals. Because kava is dioecious, it seldom forms viable seeds and is propagated almost exclusively by humans through vegetative cuttings [5]. The root system of the plant is well-developed, consisting of dense, fibrous, and extensively branched rhizomes that extend deep into the soil. In mature plants, total weight usually ranges from 2 to 10 kg, with rhizomes accounting for a substantial proportion of the overall biomass. These underground structures are rough in texture, light brown in color, and are rich in bioactive constituents that underlie the plant's pharmacological activity [9]. Kava rhizomes differ in size, usually ranging from 3 to 20 cm long and 1 to 5 cm wide. Their outer part is composed of fibrous tissue, whereas the inner core contains high levels of kavalactones along with other secondary metabolites. Traditionally, the rhizomes are dried and then pulverized into powder, which is used to prepare kava drinks or various extracts [5].

2.Phytochemicals:

Piper methysticum is characterized by considerable variability in its chemical profile, which directly influences both its pharmacological activity and safety. This variability is associated with factors such as cultivar type, plant part utilized, preparation procedures, and the solvent employed during extraction. The primary bioactive constituents of kava are kavalactones and flavokavains. Although flavokavains A, B, and C share common biosynthetic origins with kavalactones, they typically occur in lower concentrations. Despite their lower abundance, these compounds have demonstrated biological activity, including potential anticancer properties, while also being linked to hepatotoxic effects, making them important from a safety perspective. Kavalactones represent the predominant class of compounds and have therefore received the greatest research attention. The six major kavalactones, kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin, constitute approximately 20–50% of the dry root mass and can account for up to 96% of organic and lipid-

based extracts. Consequently, their relative proportions are considered a key factor in determining the quality of kava preparations [10,11].

Figure 1

Botanical illustration of *Piper methysticum*

2.1 Distribution of kavalactones in plant parts

The concentration of kavalactones within *Piper methysticum* varies depending on the plant tissue, with the highest levels generally observed in peeled crown roots and lateral roots. This distribution aligns with traditional preparation practices, which predominantly utilize these specific root components. Advanced analytical techniques, including GC-MS (gas chromatography-mass spectrometry) and LC-MS (liquid chromatography-mass spectrometry), have confirmed that these tissues contain the greatest concentrations of neuroactive kavalactones. Furthermore, imaging approaches such as IR-MALDESI (infrared matrix-assisted laser desorption electrospray ionization) have demonstrated that individual compounds are localized in a tissue-specific manner. Structural investigations using X-ray micro-computed tomography suggest that the anatomical characteristics of lateral roots may facilitate increased accumulation of kavalactones [12]. Comparative analyses of methanolic extracts obtained from leaves and roots of several Hawaiian cultivars (Mahakea, Nene, Purple Moi, and PNG) have shown that leaf material contains lower concentrations of kavalactones. Nevertheless, leaf extracts exhibit stronger pharmacological effects in receptor binding assays. In particular, inhibition of GABA-A (gamma-aminobutyric acid type A) receptor binding is more pronounced for leaf extracts ($IC_{50} \approx 3$ μg/mL), whereas root-derived extracts demonstrate weaker activity (IC_{50} values ranging from approximately 5 to 87 μg/mL depending on cultivar). These findings indicate that additional bioactive constituents may be present in leaf tissues [13]. In addition to kavalactones and flavokavains, kava contains a wide range of volatile compounds. Elevated levels of β-caryophyllene have been identified in dried root material, while camphene is more prevalent in aqueous extracts. Other detected constituents include alcohols, aldehydes, ketones, terpenes, and related aromatic compounds [14].

3.Mechanisms of the anxiolytic effects of kavalactones

Kavalactones exert anxiolytic effects through modulation of multiple neurotransmitter systems within the central nervous system.

3.1 GABA-A receptor modulation

The anxiolytic properties of kavalactones are partly attributed to their influence on the GABAergic system. Kavain has been demonstrated to potentiate GABA-A receptor function across various receptor subtypes, with more pronounced effects observed in α4β2δ receptors compared to α1β2γ2L receptors. Notably, this modulation does not involve the classical

benzodiazepine binding site, as it remains unaffected by flumazenil. Experimental studies employing recombinant human GABA-A receptors indicate that kavain acts as a positive allosteric modulator irrespective of subunit composition, although the degree of potentiation differs between receptor types. The β3N265M mutation, which reduces sensitivity to certain anesthetics, also diminishes the potentiating effect of kavain, suggesting partial overlap in underlying molecular mechanisms [15]. Gene expression studies conducted in individuals with generalized anxiety disorder have reported reduced expression of GABRR2 (gamma-aminobutyric acid type A receptor rho2 subunit gene) and COMT (catechol-O-methyltransferase) following kava administration. However, these observations were derived from post hoc analyses and did not retain statistical significance after correction for multiple comparisons, highlighting the need for further confirmation [16]. Investigations into genetic polymorphisms of the GABA transporter gene (SLC6A1) initially indicated a possible association with treatment response. Subsequent studies, however, failed to replicate these findings and, in some instances, reported opposing trends. Overall, the contribution of GABA transport mechanisms to variability in response to kava remains unclear [4,17].

3.2 Monoamine Oxidase (MAO) Inhibition

The potential of kavalactones to inhibit monoamine oxidase enzymes (MAO-A and MAO-B), which are involved in neurotransmitter metabolism, has been explored in several studies. Evidence suggests that multiple kavalactones function as reversible and competitive inhibitors of both isoforms. Among these compounds, yangonin exhibits relatively strong inhibitory activity ($IC_{50} \approx 0.085$ μM for MAO-B and 1.29 μM for MAO-A), whereas kavain demonstrates moderate inhibition of MAO-B ($IC_{50} \approx 5.34$ μM) and weaker activity toward MAO-A ($IC_{50} \approx 19.0$ μM). In general, kavalactones tend to show greater selectivity toward MAO-B, although this may vary depending on experimental conditions [18,19]. Overall, inhibition of MAO by kavalactones is reversible and competitive in nature and may contribute to the pharmacological effects of kava, although it is unlikely to be the sole mechanism responsible for its activity [18,20].

3.3 Dopaminergic and Serotonergic Effects

Kavalactones also modulate monoaminergic neurotransmission, particularly within the mesolimbic dopamine pathway. In vivo studies in rodents have demonstrated dose-dependent alterations in dopamine levels within the nucleus accumbens following administration of kava extract. Lower doses (approximately 20 mg/kg) are associated with modest neurochemical and behavioural effects, whereas higher doses (around 120 mg/kg) result in more substantial

increases in dopamine concentration. Individual kavalactones exhibit distinct pharmacological profiles. D,L-kavain reduces dopamine levels at lower doses but may produce neutral or increased effects at higher doses, while simultaneously decreasing serotonin levels. Yangonin significantly lowers dopamine concentrations, whereas desmethoxyyangonin has the opposite effect, increasing dopamine levels. Other kavalactones appear to exert minimal influence on dopaminergic transmission [21]. Receptor binding studies indicate that kava extracts interact with dopamine D2, opioid, and histamine receptors, although generally with low affinity. Leaf-derived extracts demonstrate stronger inhibitory effects compared to root extracts, despite containing lower concentrations of kavalactones, suggesting the involvement of additional active compounds. In contrast, serotonergic receptors such as 5-HT6 (5-hydroxytryptamine receptor 6) and 5-HT7 (5-hydroxytryptamine receptor 7) are only weakly affected [13]. Kavain and methysticin have also been shown to inhibit noradrenaline reuptake in synaptosomal preparations, while serotonin reuptake appears to remain largely unaffected [22].

3.4 Other mechanisms

Kavalactones have been shown to interact with voltage-gated ion channels. Compounds such as kavain and methysticin inhibit sodium channels in a voltage-dependent manner, with stronger effects observed at depolarized membrane potentials, which may contribute to their anticonvulsant and local anesthetic properties [23–25]. Additionally, these compounds reduce voltage-dependent calcium currents and limit calcium influx, which may result in decreased release of excitatory neurotransmitters [26,27]. Another proposed mechanism involves inhibition of thromboxane A_2 synthesis, which could indirectly enhance GABAergic neurotransmission, although direct experimental evidence supporting this pathway remains limited [25,28].

4.Extracts

Preparations of kava vary substantially depending on extraction methods, solvent systems, and processing conditions, all of which influence both chemical composition and biological activity [29]. Traditional kava beverages are typically produced through aqueous extraction of fresh or dried root material. In contrast, commercial formulations are commonly prepared using organic solvents such as ethanol, acetone, or methanol, resulting in more concentrated extracts that are subsequently formulated into capsules or tablets [30,31]. Organic solvent-based extracts differ from traditional aqueous preparations in both the relative proportions of major kavalactones and the presence of minor constituents. These compositional differences are associated with variations in biological activity. Notably, commercial extracts have been reported to exert

stronger inhibitory effects on cytochrome P450 enzymes, including CYP3A4, CYP1A2, CYP2C9, and CYP2C19, compared to aqueous preparations [30]. Such effects on enzyme activity may have pharmacokinetic consequences, particularly with regard to the metabolism of co-administered drugs. This has been suggested as one factor contributing to differences in safety profiles between traditional and commercial kava products [29,30].

5.Preclinical Trials:

In murine models, administration of an ethanolic root extract resulted in clear anxiolytic-like responses that varied with dose. In BALB/cByJ mice, intraperitoneal treatment reduced avoidance of exposed areas, which was reflected by shorter latencies to enter open spaces and prolonged exploration within them in both the mirrored chamber and elevated plus maze tests. Median effective doses were estimated at approximately 125 mg/kg and 88 mg/kg, respectively. Reductions in locomotor activity, which were used as an indicator of sedation in the open-field test, were observed only at higher doses [ED_{50} (median effective dose) ≈ 172 mg/kg], suggesting a partial dissociation between anxiolytic and sedative effects. Pharmacological validation further indicated that, unlike diazepam, the behavioural effects of kava extract were not significantly altered by flumazenil, which supports a mechanism independent of the benzodiazepine binding site on the GABA-A receptor complex [32]. Comparable behavioural outcomes have been observed in rats following oral administration of a standardized kava preparation (LI 150; 120–240 mg/kg). In the elevated plus maze, treatment increased both the duration of time spent in open arms ($F(3,36) = 4.057$, $p < 0.05$) and the proportion of entries into these arms ($F(3,36) = 2.887$, $p < 0.05$), particularly at intermediate doses of 120 to 180 mg/kg. At the same time, indices of risk assessment were also modified, as indicated by increased head-dipping behaviour ($F(3,36) = 3.974$, $p < 0.05$) and a reduction in return attempts to closed arms ($F(3,36) = 4.564$, $p < 0.01$). Importantly, these behavioural changes occurred without significant alterations in general locomotion, indicating that they cannot be attributed to nonspecific sedative effects [33]. At the cellular level, electrophysiological studies provide mechanistic insight into these behavioural findings. Using recombinant human GABA-A receptor subtypes, including α1β2γ2L and α4β2δ, expressed in Xenopus laevis oocytes, kavain (10–300 µM) was shown to enhance GABA-induced currents in a concentration-dependent manner. At the highest concentration tested, responses increased to approximately 170 ± 23% ($n = 6$). This potentiation was observed across receptor subtypes and was not significantly influenced by flumazenil, which further supports a mechanism distinct from classical benzodiazepine site modulation. The magnitude of this effect depended on receptor composition. In α1β2γ2L receptors, enhancement was limited to submaximal GABA

concentrations and did not affect maximal responses. In contrast, α4β2δ receptors exhibited a significant increase in maximal current amplitude ($p < 0.0001$, paired t-test), which suggests a stronger influence on extrasynaptic receptor populations. Additionally, the β3N265M mutation markedly reduced kavain-induced potentiation ($p < 0.001$), which points to partial overlap with anesthetic-sensitive binding domains [15].

6.Clinical Trials:

One of the earliest clinical trials evaluating the anxiolytic effects of *Piper methysticum* was conducted by J.Sarris et all. This 3-week, randomized, double-blind, placebo-controlled crossover study included 60 adults with at least one month of elevated generalized anxiety. Participants received an aqueous kava extract providing 250 mg of kavalactones daily. Kava treatment led to a marked reduction in anxiety symptoms, with Hamilton Anxiety Rating Scale (HAM-A) scores decreasing by −9.9 and −10.3 across the two study phases, compared to −0.8 and +3.3 with placebo. The overall effect was highly significant ($p < 0.0001$), with a large effect size ($d = 2.24$). Significant improvements were also observed in Beck Anxiety Inventory (BAI) and Montgomery–Asberg Depression Rating Scale (MADRS) scores. The treatment was well tolerated, with no serious adverse events or evidence of hepatotoxicity reported [34]. More disorder-specific evidence for anxiety was provided by a subsequent randomized, double-blind, placebo-controlled trial conducted by the same lead author, J. Sarris et al. This study evaluated a standardized aqueous extract of *Piper methysticum* in patients with generalized anxiety disorder (GAD) without comorbid mood disorders. Over 6 weeks, 75 participants received kava at doses of 120–240 mg kavalactones/day (titrated to response) or placebo. Anxiety severity was assessed using HAM-A, with intention-to-treat analysis performed in 58 participants following a placebo run-in phase. Kava produced a statistically significant reduction in anxiety compared with placebo ($p = 0.046$), with a moderate effect size ($d = 0.62$), indicating it may serve as a moderately effective short-term treatment for GAD. The effect was stronger in individuals with moderate-to-severe symptoms ($p = 0.02$; $d = 0.82$). Remission (HAM-A ≤ 7) was achieved in 26% of the kava group versus 6% in the placebo group ($p = 0.04$). Pharmacogenetic analyses suggested that GABA transporter polymorphisms (rs2601126, rs2697153) were associated with greater symptom improvement. The treatment was well tolerated; apart from a higher incidence of headaches ($p = 0.05$), no significant differences in other adverse events or liver function tests were observed [17]. In contrast to the findings of the previous trials, W. Zhang et al. reported less consistent results. The authors performed a Bayesian network meta-analysis of randomized controlled trials (1987–2021) to compare the efficacy and acceptability of medicinal herbs for anxiety in adults, using data from PubMed,

EMBASE, the Cochrane Library, and Web of Science. Outcomes included symptom reduction based on HAM-A and treatment acceptability (discontinuation due to inefficacy, symptom worsening, or adverse events). Overall, kava demonstrated a modest anxiolytic effect (MD: −2.46; 95% CrI: −4.47 to −0.32). However, in the subgroup of patients with GAD, the effect was not significant (MD: −0.17; 95% CrI: −2.55 to 1.97), suggesting limited efficacy specifically in GAD [35]. A further study directly compared kava with a commonly used benzodiazepine, Oxazepam. In a randomized, crossover trial, 22 moderately anxious adults received a single dose of kava (180 mg kavalactones), oxazepam (30 mg), and placebo at weekly intervals. Anxiety was assessed using the State–Trait Anxiety Inventory (STAI) following cognitive task exposure. A significant condition effect was observed ($p = 0.046$). Oxazepam produced a reduction in anxiety ($p = 0.035$) and increased subjective calmness ($p = 0.002$), whereas kava did not significantly alter anxiety levels; placebo was associated with increased anxiety. Importantly, kava showed no detrimental impact on cognitive performance, in contrast to oxazepam, which reduced alertness ($p < 0.001$). Exploratory analyses suggested a possible influence of noradrenaline transporter (SLC6A2) polymorphisms on response to kava. Overall, a single therapeutic dose of kava did not demonstrate acute anxiolytic effects in this model, despite a favorable cognitive profile [36].

Table 1

Review of clinical trials assessing effects of standardized kava products on anxiety disorders.

Type of product	Duration and used dose	Study design	Clinical Tools	Results	References
An aqueous kava extract	3 weeks 250 mg of kavalactones/day	Randomized, double-blind, placebo-controlled crossover trial	HAM-A, BAI, MADRS	Kava significantly reduced anxiety, with a large treatment effect	[28]
An aqueous kava extract	6 weeks 120-240 mg of kavalactones/day	Randomized, double-blind, placebo-controlled trial	HAM-A	Kava modestly reduced anxiety; moderate short-term effect in GAD.	[17]

	(titrated to response)				
Varied across studies included in the analysis	Varied across studies included in the analysis	Bayesian network meta-analysis of randomized controlled trials	HAM-A	Kava: modest overall anxiolysis; no effect in GAD	[29]
Kava tablets by MediHerb (based on a water-soluble extract of the peeled rootstock)	180mg (single acute dose)	Randomized, crossover trial (acute single-dose)	STAI	Oxazepam ↓ anxiety; kava no significant effect; placebo ↑ anxiety	[30]

Conclusion

Kava shows potential anxiolytic effects, with evidence indicating modest to moderate short-term efficacy compared with placebo. However, findings remain inconsistent, particularly in generalized anxiety disorder, where benefits appear limited or non-significant. Current data therefore support a possible role for kava as an adjunct rather than a first-line treatment for anxiety, although further well-designed clinical trials are needed to better establish its efficacy and safety profile. Its pharmacological activity is mainly attributed to kavalactones, with positive modulation of GABA-A receptors appearing to play a central role, while additional mechanisms involving monoaminergic pathways and ion channel interactions may also contribute to its broader anxiolytic effects. Nevertheless, substantial variability in phytochemical composition between cultivars and extract preparations highlights the need for standardization and continued safety assessment.

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Author Contributions:

Conceptualization: Aleksandra Muszalska;

Methodology: Aleksandra Muszalska, Brajan Roczyński, Julia Wiecanowska;

Literature search and literature review: Aleksandra Muszalska, Brajan Roczyński, Julia Wiecanowska;

Writing rough preparation: Aleksandra Muszalska, Brajan Roczyński;
Writing review and editing: Aleksandra Muszalska, Brajan Roczyński, Julia Wiecanowska;
Visualization: Aleksandra Muszalska;
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Project administration: Aleksandra Muszalska;

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