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Review Article

UNVEILING THE PHARMACOLOGICAL SPECTRUM AND APPROVED THERAPEUTIC ACTIVITIES OF *PIPER METHYSTICUM*: AN IN-DEPTH REVIEW

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ABSTRACT

In the plant *Piper methysticum* G. (Forst), Piperaceae, kava has active constituent storage in its roots and rhizomes. Kava root has been conventionally employed by individuals for alleviating anxiety, stress, managing drug withdrawal symptoms, addressing sleep-related concerns, and various other purposes; however, it is noteworthy that there is a lack of robust scientific evidence substantiating these purported therapeutic uses. The examination of existing literature reveals that kava lactones exert biological activity encompassing local anesthesia, antispasmodic effects, muscular relaxation, antimitotic properties, sedative attributes, anticonvulsive actions, analgesic properties, anxiolytic effects, and neuroprotective characteristics, thereby affirming their pharmacological potency. However, the plant's medicinal value as an anti-depressant, anti-anxiety, or antioxidant has yet to be verified. Synthetic medications, on the other hand, are routinely recommended to alleviate stress and stress-related symptoms, but their tendency to induce drowsiness or sleep, the risk of dependence, and withdrawal effects limit their long-term usage. Clinical studies reveal that kava has 1-week efficacy at a modest dose. Evidently, herbal formulations assert enhancement of physical endurance, cognitive capacities, and non-specific resilience to stress without altering physiological functions; hence, imperative investigation into their safety and efficacy for therapeutic applications is warranted.

Keywords: Kava, Herbal medications, Psychotropic drug, Anxiolytic drugs, Classification, Interactions.

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INTRODUCTION

Considerable research efforts in recent years have been directed towards developing synthetic anxiolytic medications characterized by minimal dependency potential, limited sedative effects, and reduced undesirable side effects. However, in the past decade, there has been a growing acknowledgment of the role of herbal drugs in effectively managing various psychiatric conditions [1]. Nature consistently exemplifies the remarkable phenomenon of interdependence. In the context of primary health care, approximately 80% of individuals in non-industrialized nations continue to rely on traditional medicine, predominantly derived from plant and animal sources [2-4]. Numerous herbal medications with psychotropic potential have been described in ancient pharmacopeias from around the world [5,6]. In fact, nearly 25% of today's conventional pharmaceuticals were discovered through the research of traditional remedies. The exploration of traditional medicinal remedies has led to the identification of numerous advantageous psychoactive compounds, among them yohimbine, ephedrine, tubocurarine, and galanthamine [7-9].

For centuries, the South Pacific substance kava-kava has been consumed in Polynesia, Melanesia, and Micronesia to augment psychomotor and physical performance as well as facilitate social interaction, playing a significant role in the region's sociocultural milieu. The root extract of *Piper methysticum* forster, also known as kava-kava, has been standardized and is now available as a new type of non-synthetic anxiety medication. They promote sleep, social connection, and calm. In the treatment of anxiety, stress, and restlessness, standardized extracts derived from kava-kava roots are utilized. The psychoactive effects observed in both humans and animals are generally attributed to the key components of kava-kava, known as kava pyrones [10].

The primary components of kava-kava extracts are 5,6-dihydro-a-pyrone or a-pyrone derivatives that are highly lipophilic. Generally speaking, it is believed that these kava pyrones provide the plant with its pharmacological effects on both humans and animals [12-14]. The pharmacological features of kava-kava extract consist of anxiolytic and anticonvulsant effects, robust muscle relaxant properties, mild sedative activity at higher doses, and a distinct lack of addictive potential [15,16].

PLANT PROFILE

This botanical specimen grows well in the South Pacific Islands. Across the Pacific Islands, kava has been extensively ingested in the context of traditional ceremonial practices, owing to its psychoactive attributes and stress-relieving properties.

Alternate designations include intoxicating pepper, intoxicating long pepper, ava pepper, kava pepper, and tonga.

HABITAT

Terrestrial, preferring a gloomy, wet environment. Although it cultivates best in the mountains of Pohnpei, it is native to numerous Pacific Ocean islands. This plant grows well in regions characterized by abundant rainfall, reaching an annual rainfall level of over 2,000 mm. Optimal growth parameters include temperatures within the range of 20–35°C and relative humidity levels between 70 and 100%. As an understory crop, excessive sunlight during the initial growth phase proves unfavorable. Notably, kava lacks the ability for sexual reproduction. Female flowers are exceptionally occasional and unproductive, even under manual pollination efforts [17].

In current herbal remedies, the rhizomes (underground roots) and lateral roots are employed [19].

TAXONOMICAL CLASSIFICATION

Kingdom	Plantae- Plants
Subkingdom	Tracheobionta- Vascular plants
Super division	Spermatophyta- Seed plants
Division	Magnoliophyta- Flowering plants
Class	Magnoliopsida- Dicotyledons
Subclass	Magnoliidae
Order	Piperales
Family	Piperaceae- Pepper family
Genus	Piper L. – pepper
Species	*Piper methysticum* G. Frost – kava

Noteworthy information relating to the taxonomy of *P. methysticum* (kava).

Noteworthy information relating to the taxonomy of *P. methysticum* (kava).

DESCRIPTION OF MORPHOLOGY

None

COMPOSITION

The moisture content of freshly harvested kava roots typically registers at approximately 80%. In contrast, desiccated root specimens manifest a composition characterized by approximately 43% starch, 20% dietary fiber, 15% kava lactones, 12% water, 3.2% sugar, 3.6% protein, and 3.2% minerals. It is noteworthy that the roots exhibit the highest concentration of kava lactones [29].

CHEMICAL CONSTITUENTS

Kava lactones present are kavain, demethoxyyangonin, yangonin, dihydrokavain, methysticin, and dihydromethysticin. These six components contribute to approximately 96% of the plant's pharmacological efficacy.

Additional minor constituents encompass three chalcones, namely flavokavain A, flavokavain B, and flavokavain C, along with the presence of the toxic alkaloid pipermethystine in leaves and stem peelings.

MECHANISM INVOLVED [30-32]

- Augmented interactions between the ligand and receptor are exemplified by the amino butyric acid type A receptor.
- Enzyme inhibition (e.g., cyclooxygenase-2).
- Reduced cytokine release (for example, TNF-).
- Kavain and methysticin inhibit the reuptake of norepinephrine.
- Kavain and methysticin inhibit voltage-gated sodium channels and voltage-gated calcium channels.
- All six major kava lactones exhibit reversible inhibition of monoamine oxidase B.

ADVERSE EFFECT OF KAVA

Adverse effects commonly associated with therapeutic doses include gastrointestinal issues, allergic skin reactions, restlessness, drowsiness, tremors, headaches, and fatigue.

Prolonged and excessive consumption of kava, exceeding 300 g/week over several months, may result in kava dermopathy. This syndrome is characterized by facial swelling, bloodshot eyes, yellow discoloration of the skin, and fish-scale-like lesions on various body parts such as the palms, soles, forearms, back, and shins.

Moreover, kava possesses the capacity to potentiate the impacts of central nervous system (CNS) depressants such as ethanol, barbiturates, and benzodiazepines [33-35].

USES OF KAVA

1. Anxiety: Anxiety disorders are currently among the most frequent psychiatric conditions. They are typically treated with either talk therapy, medicines, or both. There are numerous drugs available, but they may have unpleasant side effects and can become habit-forming. This has boosted demand for theoretically safe, natural medicines such as kava.
   In 1997, the first long-term study on the effects of kava extract on people suffering from anxiety was published. The researchers also found no withdrawal or dependency side effects, which are frequent with other medicines commonly used to treat anxiety. Several other researches have shown that kava has anxiety-reducing properties. A meta-analysis of 11 of these researches revealed that kava extract is an effective anxiety therapy [36,37].
2. Insomnia: Sleep deprivation has been related to a variety of medical problems, including high blood pressure, diabetes, depression, obesity, and cancer. As a result, many people seek out sleep drugs to help them sleep better. Sleep medications, like anxiety medictions, can become habit-forming, leading to physical dependence.
   Kava is commonly used as an alternative to these sleep medications due to its calming effects. Anxiety sufferers frequently experience stress-induced sleeplessness. As a result, in cases of insomnia, kava may alleviate anxiety, allowing people to sleep better. It s unknown how KAVA affects sleep in those without anxiety or stress-induced insomnia [38-40].
3. Inflammation: Kava exhibits anti-inflammatory properties, potentially offering efficacy in addressing conditions marked by inflammation. Certain studies propose that modifying kava constituents could enhance these anti-inflammatory effects. Nonetheless, additional research is warranted, as some indications suggest that kava exposure may provoke an inflammatory response [41].
4. Cancer: According to certain studies, kava may help reduce the risk of cancer. Kava has been shown in animal studies to have anti-cancer properties [42]. Other studies have suggested that kava may help prevent prostate cancer, colon cancer, and urothelial cell cancer [43]. Such findings, however, have only been reported in animal studies, and additional research is required to understand the mechanism of action and its implications for humans.
5. For skin disorder: Externally administered for the management of dermatological conditions like leprosy, facilitation of wound healing, and treatment of canker sores, among other applications.
6. Gonorrhea: This herb demonstrates efficacy in managing sub-acute gonorrhea, bladder discharge, nephritis, excessive urination reduction, and alleviation of the burning sensation during micturition. The diuretic attribute is attributed to either kavain or methysticin.
7. Pain relief and muscle spasms: This botanical specimen possesses anti-inflammatory and analgesic characteristics, rendering it suitable for therapeutic applications in conditions such as arthritis or injuries.
8. Headache: Efficacious in alleviating headaches and migraines, this remedy provides prompt relief.
9. For quitting smoking: Kava serves as a potent intervention for abstaining from alcohol, smoking, drugs, etc., as it has the potential to mitigate cravings associated with these substances.
10. Stomach problems: It functions as a bitter stimulant, enhancing appetite without inducing intermittent occurrences of diarrhea or constipation.

SIDE EFFECT OF KAVA

The efficacy of kava remains a subject of ongoing debate. While certain individuals contend that kava can be employed safely for short-term anxiety relief, opposing viewpoints suggest that the potential risks outweigh the perceived benefits.

Used for a short period of time, it can cause [44]

- Indigestion
- Mouth numbness
- Rash and headache
- Drowsiness and visual problems.

Used for a long period of time, it can cause

- Liver damage: In March 2002, the Food and Drug Administration in the United States released a cautionary advisory directed at both consumers and healthcare professionals, highlighting the potential risk of liver damage linked to the ingestion of kava. Reports have linked kava to instances of liver toxicity, encompassing conditions such as hepatitis, cirrhosis, liver failure, and, in extreme cases, fatality. ting live.
- Several instances were correlated with pre-existing conditions, elevated kava dosages, and excessive alcohol intake. The causative factor for liver damage remains uncertain, whether attributed to kava lactones, impurities found in substandard extracts, or the organic solvents (such as acetone or ethanol) employed in the production of kava extracts and supplements [45].

Fig. 1: *Piper methysticum* plant

Fig. 2: Leaves of Piper methysticum

Fig. 3: Kava rhizome

Fig. 4: Kava roots

SAFETY MEASURES AND CONTRAINDICATIONS [46]

Before considering the consumption of kava for either recreational or medicinal purposes, it is imperative to deliberate on certain aspects:

- The effect of kava on the nervous system is unknown. As a result, it should not be taken by patients suffering from severe depression, bipolar disorder, or schizophrenia.
- Individuals diagnosed with Parkinson's disease should refrain from the consumption of kava, as it has the potential to exacerbate associated symptoms.
- Kava may inhibit blood coagulation. People with bleeding issues should not use it. To avoid excessive bleeding, you should stop consuming kava at least 2 weeks before surgery.
- The consumption of kava has the potential to induce drowsiness and impede cognitive functions such as judgment, reflexes, and vision. Abstain from kava consumption if the intention is to engage in activities such as driving or operating heavy machinery.
- It is advisable to refrain from the consumption of kava during pregnancy.
- The utilization of kava is not recommended for individuals with a history of alcoholism, liver disease, pulmonary hypertension, low blood pressure (hypotension), or kidney disease.

DRUG INTERACTIONS

A variety of medicines and supplements can interact with kava. In certain instances, it has the potential to enhance the effects of co-administered medication, while in other cases, it may diminish the efficacy of the medication through competition for the same CYP450 liver enzymes responsible for kava metabolism [47].

If kava is being utilized in conjunction with any of the subsequent medications [48], see your doctor:

- Kava interacts with medications metabolized by the liver's CYP450 enzymes.
- Kava exhibits six significant interactions with the following medications: buprenorphine, leflunomide, teriflunomide, lomitapide, mipomersen, and pexidartinib.
- Contraindication is advised for individuals utilizing anticoagulant medications, including warfarin.
- Concurrent administration with alcohol, barbiturates, CNS depressants, or antipsychotic medications such as haldol or mellaril is contraindicated.
- Caution is warranted for individuals concurrently using anti-anxiety medications such as Alprazolam and other sedatives due to the potential for excessive drowsiness.
- Interaction with levodopa is documented, resulting in the diminished efficacy of the latter.

KAVA AND PREGNANCY

- Kava may cause weaken muscle tone in the uterus, so it should not be given in pregnancy.
- Kava may pass into breast milk and may harm the nursing baby, so kava should be avoided during breast feeding.

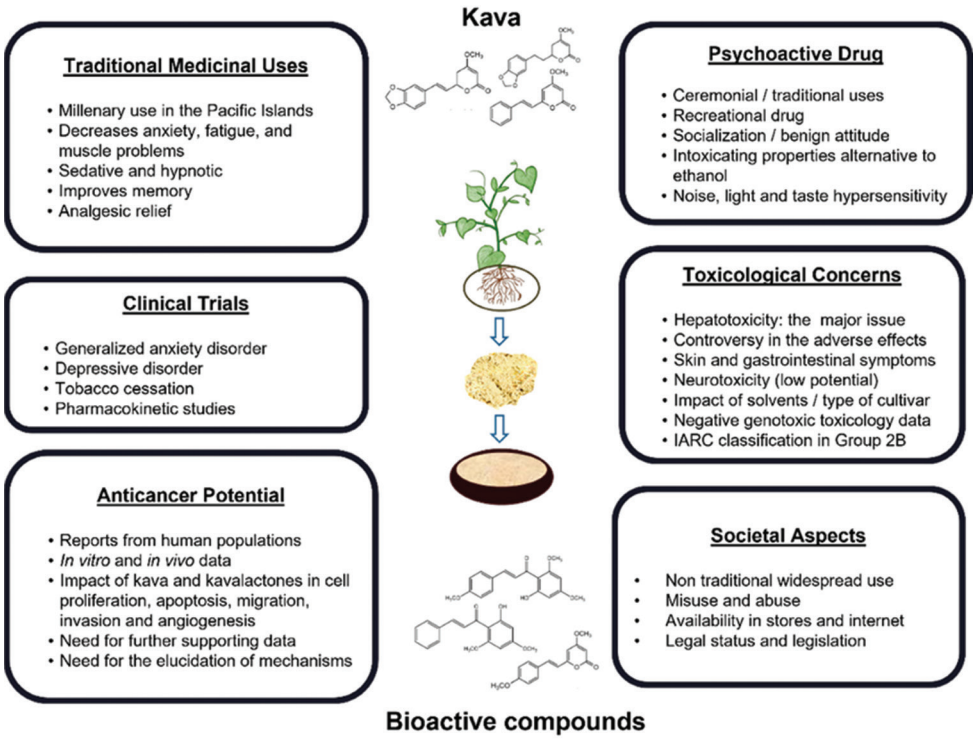


Fig. 5: Uses of *Piper methysticum*

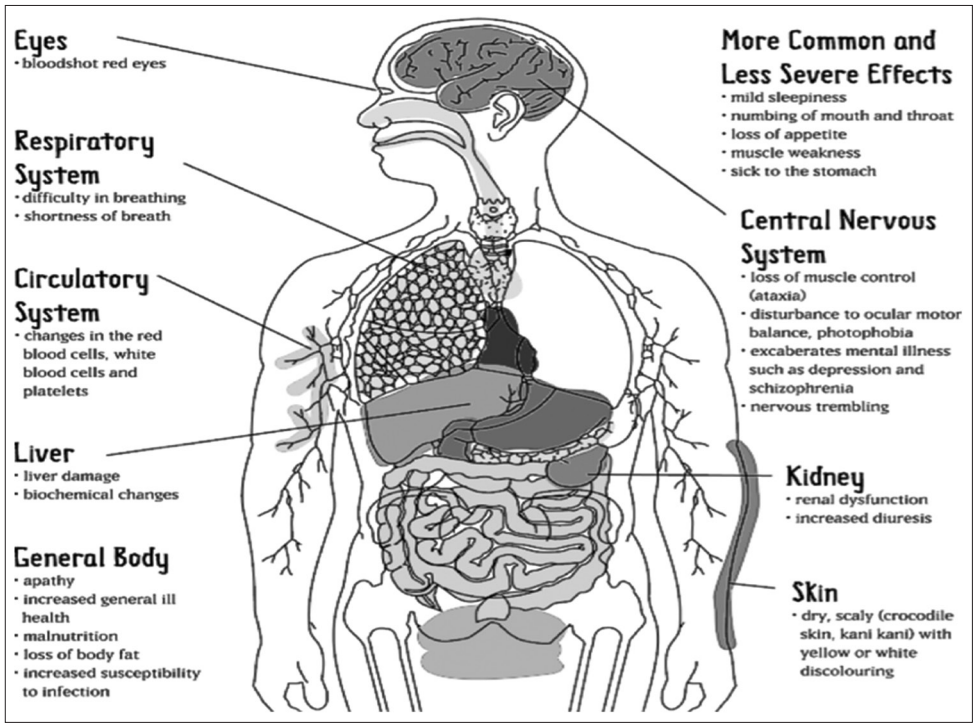


Fig. 6: Side effects of *Piper methysticum*

HERBAL INTERACTIONS

- Avoid the simultaneous use of kava alongside other herbal or health supplements recognized for their potential to cause liver damage, such as niacin (vitamin B3) and red yeast.
- Exercise caution when combining kava with additional herbal or health supplements that have sedative effects, including California poppy, gotu kola, melatonin, St. John's Wort, and Valerian.

ALREADY APPROVED ACTIVITY OF *P. METHYSTICUM* IN CERTAIN DISEASES

- Antioxidant and antibacterial properties: Kava beverages bear notable historical and cultural significance in Pacific Island culture, and this study emphasizes the additional therapeutic properties of the herbal plant. The kava root is endowed with abundant bioactive compounds, displaying robust antioxidant activity and potent

Table 1: List of microscopial characterization of kava

Parts	Characteristics	Appearance	Reference [20-28]
Plant	Primarily dioecious, intermittently monoecious, with a basal structure (crown or short rootstock) giving rise to a multitude of shoots.	2–4 m tall, woody perennial shrub, rosette appearance	(Orwa *et al*., 2009; Singh and Blumenthal, 1997).
Stem	Characterized by the presence of lenticels, enlarged nodes, and conspicuous scars resulting from the abscission of leaves and branches.	1–3 cm (diameter), erect, green or red-brown or dark purple.	(Nelson, 2000; Glover, 2007).
Leaves	Evident features include blades with 11–13 alternate veins originating from the base, petioles measuring 2.5 cm (1 in) to 7 cm in length, an entire and undulating margin, an acute apex, and a globular to finely pubescent surface.	Characterized by deciduous, heart-shaped leaves measuring 10–30 cm by 8–23 cm, accompanied by substantial stipules.	(Lebot *et al*., 1984; Singh, 1992).
Roots	Over time, it has the potential to develop into a dense, tangled mass with a width ranging from 8 to 25 cm.	60 cm in length and 8 cm in diameter	(Muller and Komorek, 1999; Douglas, 2007).
Rhizomes	Massive, 2–10 kg, branched and juicy with many roots.	Blackish gray outside, whitish inside.	(PDR for Herbal Medicines, 2000; Broderick *et al*., 2005).
Flowers	Present on a slender spike, exhibiting an inflorescence pattern, these flowers are either axillary or opposite to the leaves, although smaller in size, and are of a little asexual nature.	Sepals or petals (absent) Pendicle (1.5 cm long).	Davis and Brown., 1999; Lebot *et al*., 1999).
Spike	In the male, there are numerous flowers each bearing two brief stamens. In the female, the flower is characterized by a solitary basal ovule situated within a unilocular ovary, surmounted by a stigma.	3–9 cm long.	(Orwa *et al*., 2009; Yarnell., 2007)
Fruit	A berry containing one seed.	-	(Orwa *et al*., 2009; Lebot *et al*., 1984)
Organoleptic property	The flavor is characterized by a pungent and numbing sensation, accompanied by a distinctive odor.	-	(PDR for Herbal Medicines, 2000; Broderick *et al*., 2005).

Table 2: List of chemical constituents and structure of kava plant

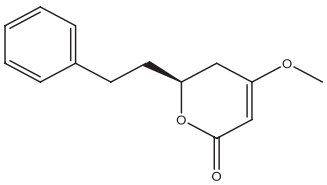
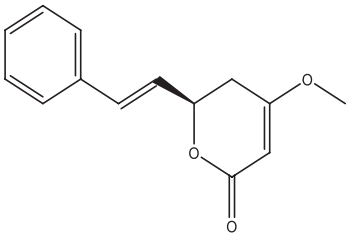
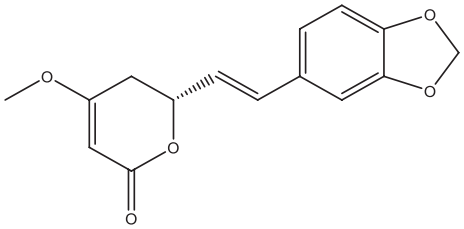
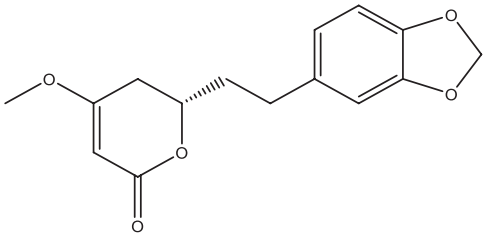
Constituents	Chemical Structure
Resins: Kava lactones Dihydrokawain	
Kawain	
Methysticin	
Dihydromethysticin	

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Table 2: ***(Continued)***

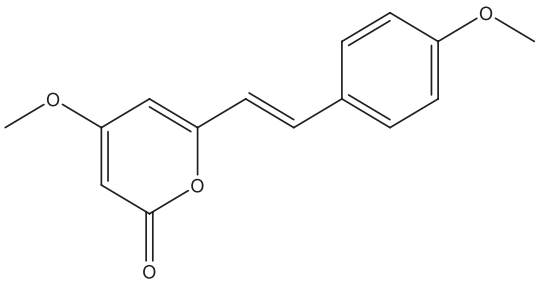
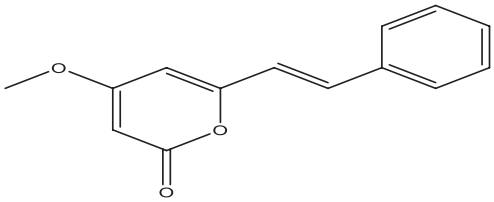
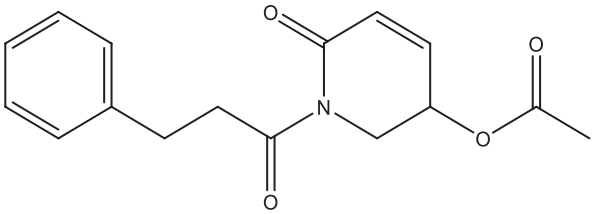
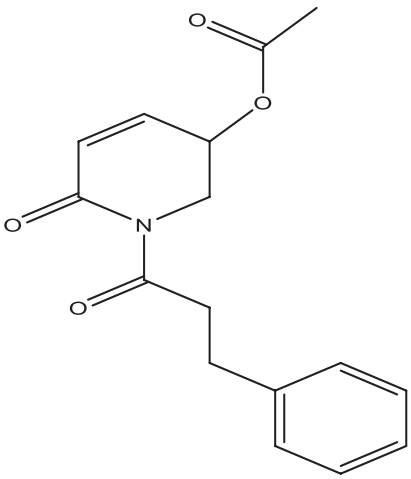
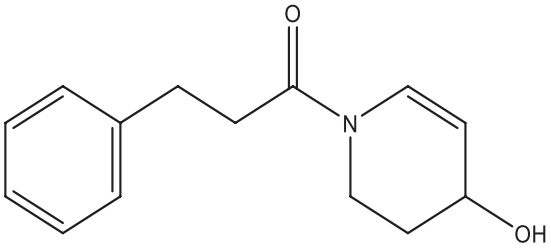
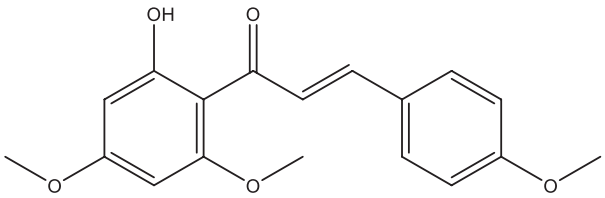
Constituents	Chemical Structure
Resins: Kava lactones Yangonin	
Desmethoxyyangonin	
Alkaloid: Piperidine Pipermethystine	
3α,4α-Epoxy-5β- pipermethystine	
Awaine	
Chalcones: Flavokavain Flavokavain A	

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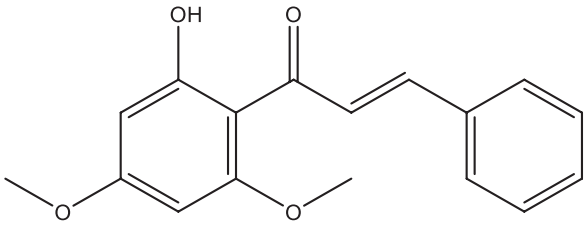
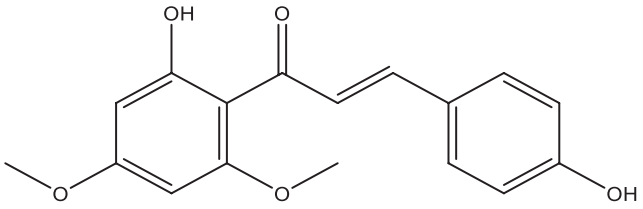
Table 2: ***(Continued)***

Constituents	Chemical Structure
Chalcones: Flavokavain Flavokavain B	
Flavokavain C	

antibacterial properties. Utilizing elution with a combination of hexane and ethyl acetate at ratios of 9:1 and 8:2, the compounds isosakuranetin (C3) and 2′,4′-dihydroxy-6′-methoxydihydrochalcone (MC5) were identified and purified for the 1st time in *P. methysticum* root. Furthermore, antioxidant assays illustrated their superior antioxidant capacity compared to other constituents identified in kava root hitherto. *In vitro* experiments effectively evaluated the antibacterial activity of various extracts and different compounds from this herbal plant. Moreover, bioassay-guided fractionation was instituted to explore the potential natural therapeutic agents of this medicinal plant, with a specific focus on its antioxidant, anti-hyperuricemia, and antibacterial properties [49,50]

- Anxiolytic activity: Among the phytomedicines examined, *P. methysticum* possesses the most substantial evidential foundation for addressing anxiety disorders, with comprehensive support derived from *in vitro*, *in vivo*, and human clinical studies. The accumulation of positive findings from randomized, well-controlled human trials further underscores its efficacy in treating various anxiety disorders and associated symptoms, indicative of its broad clinical applicability. Thus, despite minor concerns related to liver toxicity, *P. methysticum* stands out as the preeminent anxiolytic phytomedicines. It presents compelling evidence, particularly in the context of managing generalized anxiety. Current clinical investigations are actively delving into modifications in GABA metabolites using neuroimaging techniques, as well as examining the potential impact of individual variations in GABA pathway polymorphisms on treatment response [51,52].

CONCLUSION

In conclusion, *P. methysticum* is a botanical substance that exhibits neuropharmacological effects similar to alcohol, inducing sensations of tranquility, relaxation, and euphoria. Additionally, there is a purported analgesic effect, anticonvulsant properties, and muscle relaxant attributes associated with this plant. Optimal outcomes were primarily observed in cases of nervous tension and restlessness, highlighting superior efficacy in individuals with acute rather than chronic conditions.

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AUTHORS CONTRIBUTION

All the authors have contributed equally.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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REFERENCES

1. Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. Phytother Res 2018;32:1147-62.
2. Sharma A, Anchariya R, Dubey C. A review on anti-stress activity of *Piper methysticum*. Asian J Pharm Res Dev 2020;8:130-6.
3. Chopra A, Doiphode VV. Ayurvedic medicine. Core concept, therapeutic principles, and current relevance. Med Clin North Am 2002;86:75-89, vii.
4. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian Medicinal Plants. New Delhi, India: National Institute of Science Communication Council of Scientific and Industrial Research; 1956. p. 207.
5. Bansal N, Yadav S. Stress the stress. Int J Pharm Biol Sci 2010;1:.6.
   Bhattacharya K, Ghosal S. Experimental evaluation of the anti-stress activity of an herbal formulation, zetress. J Nat Remedies 2000;1:1-7.
7. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. Curr Clin Pharmacol 2009;4:198-219.
8. Panossian AG. Adaptogens: Tonic herbs for fatigue and stress. Altern Complement Ther 2003;2003:327-31.
9. Rouse J. Kava: A South Pacific Herb for Anxiety, Tension, and Insomnia. Vol. 6. Clinical Nutrition Insights Inc.; 1998. p. 10.
10. Singh YN. Kava: An overview. J Ethnopharmacol 1992;37:13-45.
11. Kawai S, Nagatsu T. Gas chromatographic and high-pertormance liquid chromatographic determination of monoamine oxidase activity using mixed substrates. In: Kamijo K, Usdin E, Nagatsu T, editors. Monoamine Oxidase. Basic and Clinical Frontiers. Excerpta Medica. Amsterdam, Oxford, Princeton; 1982. p. 52-7.
12. Keledjian J, Duffield PH, Jamieson DD, Lidgard RO, Duffield AM. Uptake into mouse brain of four compounds present in the psychoactive beverage kava. J Pharm Sci 1988;77:1003-6.
13. Kinzler E, Krömer J, Lehmann E. Effect of a special kava extract in patients with anxiety, tension, and excitation states of non-psychotic genesis. Double blind study with placebos over 4 weeks. Arzneimittelforschung 1991;41:584-8.
14. Kretzschmar R, Meyer HJ, Teschendorf HJ. Strychnine antagonistic potency of pyrone compounds of the kavaroot (Piper methysticum Forst.). Experientia 1970;26:283-4.
15. Köppel C, Tenczer J. Mass spectral characterization of urinary metabolites of D, L-kawain. J Chromatogr 1991;562:207-11.
16. Meert TF, Colpaert FC. The shock probe conflict procedure. A new assay responsive to benzodiazepines, barbiturates and related compounds. Psychopharmacology (Berl) 1986;88:445-50.
17. Available from: https://en.wikipedia.org/wiki/kava
18. Available from: https://www.planetayurveda.com/library/kava-piper-methysticum

19. Available from: https://kava.com/articles/botany-of-kava
20. Orwa, *et al*. *Piper methysticum Piperaceae* G. Forster. Agroforestry Database 4.0; 2009.
21. Singh YN, Singh NN. Therapeutic potential of kava in the treatment of anxiety disorders. CNS Drugs 2002;16:731-43.
22. Nelson SC. Awa Dieback in Hawaii. Hawaii: University of Hawaiat Mānoa. College of Tropical Agriculture and Human Resources; 2000.
23. Glover DD. Kava. In: Forensic Science and Medicine. United States: Humana Press; 2007. p. 27-40.
24. Davies LP, Drew CA, Duffield P, Johnston GA, Jamieson DD. Kava pyrones and resin: Studies on GABAA, GABAB and benzodiazepine binding sites in rodent brain. Pharmacol Toxicol 1992;71:120-6.
25. Davis RI, Brown JP. Kava (*Piper methysticum*) in the South Pacific: Its Importance, Methods of Cultivation, Cultivars, Diseases and Pests, Australian Centre for International Agricultural Research ACIAR Technical Reports Series No. 46; 1999. p. 32.
26. Lebot V, Sim´eoni P. Is the quality of kava (*Piper methysticum*) responsible for different geographical patterns? Ethnobot Res Appl 2004;2:19-28.
27. Lebot V, Merlin M, Lindstrom L. Kava: The Pacific Elixir. Vol. 10. New Haven, CT: Yale University Press; 1997.
28. Lebot V, McKenna DJ, Johnston E, Zheng QY, McKern QT. Morphological, phytochemical, and genetic variation in Hawaiian cultivars of ‘Awa (Kava, *Piper methysticum*, *piperaceae*). *Econ Bot* 1999;53:407-18.
29. Keller F, Klohs MW. A review of the chemistry and pharmacology of the constituents of *Piper methysticum. Lloydia* 1963;26:1-15.
30. Davies LP, Drew CA, Duffield P, Johnston GA, Jamieson DD. Kava pyrones and resin: Studies on GABAA, GABAB and benzodiazepine binding sites in rodent brain. Pharmacol Toxicol 1992;71:120-6.
31. Anke J, Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.). J Ethnopharmacol 2004;93:153-60.
32. Yarnell E. *Piper methysticum* G Forster (Kava), *Piperaceae* and related species.
33. Volz HP, Kieser M. Kava-kava extract WS 1490 versus placebo in anxiety disorders--a randomized placebo-controlled 25-week outpatient trial. Pharmacopsychiatry 1997;30:1-5.
34. Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: Systematic review and meta-analysis. J Clin Psychopharmacol 2000;20:84-9.
35. Ha¨nsel R, Woelk H, Volz HP, *et al*. Therapie Mit Kava-Kava. Stuttgart: Aesopus Verlag; 1999. p. 1-80.
36. Sarris J, Kavanagh DJ, Byrne G, Bone KM, Adams J, Deed G. The kava anxiety depression spectrum study (KADSS): A randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*. Psychopharmacology (Berl) 2009;205:399-407.
37. Sarris J, Stough C, Bousman CA, Wahid ZT, Murray G, Teschke R, *et al*. Kava in the treatment of generalized anxiety disorder: A double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol 2013;33:643-8.
38. Darker CD, Sweeney BP, Barry JM, Farrell MF, Donnelly-Swift E. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database Syst Rev 2015;5:CD009652.
39. Wheatley D. Stress-induced insomnia treated with kava and valerian: Singly and in combination. Hum Psychopharmacol 2001;16:353-6.
40. Lehrl S. Clinical efficacy of kava extract WS 1490 in sleep disturbances associated with anxiety disorders. Results of a multicenter, randomized, placebo-controlled, double-blind clinical trial. J Affect Disord 2004;78:101-10.
41. Huck O, Han X, Mulhall H, Gumenchuk I, Cai B, Panek J, *et al*. Identification of a Kavain Analog with efficient Anti-inflammatory effects. Sci Rep 2019;9:12940.
42. Shimoda LM, Park C, Stokes AJ, Gomes HH, Turner H. Pacific island ‘Awa (Kava) extracts, but not isolated kavalactones, promote proinflammatory responses in model mast cells. Phytother Res 2012;26:1934-41.
43. Narayanapillai SC, Lin SH, Leitzman P, Upadhyaya P, Baglole CJ, Xing C. Dihydromethysticin (DHM) blocks tobacco carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced O(6)-methylguanine in a manner independent of the aryl hydrocarbon receptor (AhR) pathway in C57BL/6 female mice. Chem Res Toxicol 2016;29:1828-34.
44. Bian T, Corral P, Wang Y, Botello J, Kingston R, Daniels T, *et al*. Kava as a clinical nutrient: Promises and challenges. Nutrients 2020;12:3044.
45. World Health Organization. Food and Agriculture Organization of the United Nations. Kava: A review of the safety of traditional and recreational beverage consumption: Technical Report. Geneva: World Health Organization; .
46. National Center for Complementary and Integrative Health. Kava.
47. Shinde P, Patil P, Bairagi V. Herbs in pregnancy and lactation: A review appraisal. Int J Pharm Sci Res. 2012;3:3001-6.
48. World Health Organization. Food and Agriculture Organization of the United Nations. Kava: A review of the safety of traditional and recreational beverage consumption: Technical Report. Geneva: World Health Organization;
49. Cleveland Clinic. Kava Kava, *Piper mesthystricum* Oral Dosage Forms. Cleveland: Cleveland Clinic;
50. Minh TN, Van TM, Khanh TD, Xuan TD. Isolation and identification of constituents exhibiting antioxidant, antibacterial, and antihyperuricemia activities in piper methysticum root. Foods 2022;11:3889.
51. Savage K, Firth J, Stough C, Sarris J. GABA-modulating phytomedicines for anxiety: A systematic review of preclinical and clinical evidence. Phytother Res 2018;32:3-18.
52. Larzelere MM, Wiseman P. Anxiety, depression, and insomnia. Prim Care 2002;29:339-60, vii.