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Phytochemical Diversity And Pharmacological Value Of Kava: Neuroprotective Implications Plant Parts

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ABSTRACT

Recent years have seen a growing interest in the therapeutic potential of herbal treatments, particularly in treating disorders affecting the central nervous system (CNS), such as anxiety-related disorders and neurodegenerative diseases. Herbal medicines are generally less likely to cause adverse effects and are often more cost-effective than manufactured drugs. Among these, Kava has garnered attention due to its wide range of bioactive components, including terpenoids, alkaloids, flavokavains, kavalactones, and tannins. A number of components, including sedative, anxiolytic, neuroprotective, and muscle-relaxing properties, contribute significantly to its therapeutic effects. Kava phytochemical composition, pharmacokinetics, mechanisms of action, and potential therapeutic uses in neuropsychiatric disorders are all carefully examined in this investigation. Kava's effects on the body are mostly associated with its interaction with γ-aminobutyric acid (GABA) receptors, inhibition of monoamine oxidase B (MAO-B), modulation of calcium and sodium ion channels, and impact on important neurotransmitters such as dopamine, serotonin, and norepinephrine. Its potential for cancer treatment, anticonvulsant effects, and pain management have also been examined in recent studies. However, concerns regarding the safety features and hepatotoxic effects of different kava formulations necessitate more clinical and toxicological studies.Kava's current understanding is highlighted in this evaluation, which also highlights research gaps and examines the plant's potential as a bioactive agent for illnesses of the central nervous system and other therapeutic applications.

KEYWORDS: kava-kava, kavalactones, phytochemistry, neuroprotection, anxiolytic, bioactive compounds, CNS disorders

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INTRODUCTION

Herbal medicine is gaining popularity because it may be a more accessible and safer alternative to manufactured medications. Numerous bioactive chemicals found in medicinal plants have therapeutic effects, especially in neurological and mental illnesses [1]. Pacific Island civilizations have utilized *kava, also referred to as kava-kava, for generations due to its sedative, muscle-relaxant, and anxiolytic properties* [2]. To encourage calmness, friendliness, and mental clarity, kava has long been used as a beverage made from the plant's roots in ceremonial and social settings [3]." Its pharmacological potential has drawn a lot of research in recent decades, especially for its ability to treat stress, anxiety disorders, and sleeplessness [4]. *Kava* has long played a significant role in Pacific Islander customs, where it is prized for both its alleged therapeutic virtues and its hallucinogenic

qualities [5]. *Kava* has traditionally been used by Indigenous people to cure urinary tract infections, ease menstruation discomfort, lessen exhaustion, and relieve pain [6]. Because of the calming and muscle-relaxing properties of the plant's roots and rhizomes, which are abundant in bioactive chemicals, kava has become a crucial component of both social and therapeutic activities [7]. *Kava* has being investigated as a natural substitute for prescription anxiolytics like benzodiazepines in contemporary medicine. In contrast to these synthetic pharmaceuticals, which frequently lead to dependency and cognitive impairment, kava seems to provide relaxation without causing a great deal of drowsiness or the potential for addiction [8]. *Kava* is a viable option for additional clinical applications because research indicates that its anxiolytic effects are equivalent to those of conventional anxiety therapies [9], [10], and [11]. By altering neurotransmitter activity, especially through their interaction with γ-aminobutyric acid (GABA) receptors, these substances affect the central nervous system (CNS) [12]. By improving inhibitory communication in the brain, this method produces sleepy and anxiolytic effects without the cognitive dulling that comes with traditional sedatives [13]. Kavalactones' anticonvulsant and muscle-relaxant effects are also influenced by voltage-gated sodium and calcium ion channels [14]. Additionally, it has been demonstrated that *kava* inhibits monoamine oxidase B (MAO-B), an enzyme involved in the metabolism of neurotransmitters, which raises dopamine and serotonin levels—neurotransmitters linked to mood regulation [15]. This raises the possibility of using it to treat mood disorders like depression and stress-related illnesses [16]. Kava has anti-inflammatory, analgesic, and antioxidant qualities in addition to its effects on the central nervous system, which may enhance its therapeutic potential [17]. Given that several kavalactones and flavokavains have shown cytotoxic actions against cancer cells, some research has even looked at its potential for usage in cancer prevention and treatment [18]. Concerns about hepatotoxicity have made *kava* controversial despite its potential medical benefits. Several countries, especially in the early 2000s, imposed regulatory restrictions on *kava* use due to reports of liver toxicity [19]. Recent research, however, suggests that rather than a natural toxicity of the plant, liver damage may be caused by variables including the extraction process, the caliber of the raw components, and inappropriate ingestion [20]. Compared to kava products extracted with alcohol or acetone, which may include toxic alkaloids, traditional water-based preparations seem to be safer [21]. The pharmacokinetics, long-term safety, and possible medication interactions of *kava* require more investigation. Determining kava's place in contemporary medicine will require standardization of extracts and clinical studies assessing its effectiveness in various groups [22]. The goal of this review is to present a thorough examination of *Kava*, with an emphasis on its pharmacological characteristics, modes of action, phytochemical composition, and therapeutic uses. It also draws attention to the safety issues with kava usage and points out important directions for further study to maximize its therapeutic benefits.

BOTANICAL DESCRIPTION

Fig. (1). *Kava-Kava*

It is mostly grown in the South Pacific, especially in the Santa Cruz Islands, Vanuatu, Fiji, Tonga, and Samoa, where it has long been used in traditional medicine and cultural rituals [13]. Because female plants hardly ever produce viable seeds, the plant's natural ability to reproduce is limited due to its dioecious nature, which means that individual plants are either male or female. Thus, stem cuttings are used to vegetatively propagate kava [14].

Morphology and Growth Characteristics

Kava typically reaches a height of two to three meters, featuring a woody base and numerous lateral branches. Stout and nodular, the stem has unique internodes that retain nutrients and water necessary for the plant's growth [15]. *Kava* leaves are broadly ovate to heart-shaped (cordate), measuring 13–28 cm in length and 10–22 cm in width. Their surface is smooth with slightly wavy edges, and they have nine to thirteen conspicuous veins extending from the base. A short petiole supports each leaf, while huge stipules at the base provide structural support and protection [16]. The inflorescence consists of tiny clusters of flowers that resemble spikes, measuring 3 to 9 cm in length. The blooms are small, barely noticeable, and have no petals. Because kava is dioecious, it rarely yields fertile seeds and must be propagated only by human culture using cuttings [17].

Structure of the Root and Rhizome

Kava has a highly developed root system that produces thick, branched, fibrous rhizomes that delve deeply into the ground. The biomass of a mature plant is primarily composed of its rhizomes, and it usually weighs between 2 and 10 kg. High concentrations of the bioactive substances that give kava its pharmacological effects are found in the tough, light brown rhizomes [18]. The normal dimensions of *kava* rhizomes are 3 to 20 cm in length and 1 to 5 cm in width. The rhizome's interior sections are abundant in kavalactones and other secondary metabolites, whereas its outer layers are composed of fibrous tissues. In order to make *kava* drinks or extracts, the rhizomes are often dried and powdered into a powder [19].

Composition of Phytochemicals

Kavalactones, flavokavains, alkaloids, tannins, and other secondary metabolites are the main bioactive components of *kava*. About 43% starch, 20% fiber, and 3–20% kavalactones—the primary hallucinogenic ingredients—are found in the root and rhizome. 3.6% proteins and 3.2% carbohydrates 3.2% minerals (iron, calcium, magnesium, potassium, sodium, and aluminum) Dihydrochalcones (A, B, and C flavokavains) Alkaloids that may have hepatotoxic effects include pipermethystine.Important Bioactive Substances: The pharmacologically significant of the six primary kavalactones are Yangonin, 5,6,7,8-Tetrahydroyangonin, 5,6-Dihydroyangonin, Kavain, Dihydrokavain, Methysticin, and Dihydromethysticin.Through its interactions with GABA receptors, modulation of dopamine levels, and influence on voltage-gated ion channels, these chemicals contribute to the anxiolytic, sedative, anticonvulsant, and muscle relaxant effects of *kava* [20]. Other Phytochemicals: Apart from kavalactones, *kava* also contains flavonoids, chalcones, and a variety of organic acids, such as Pipermethystine (a minor alkaloid with possible hepatotoxic effects), Dihydrokavain-5-ol, Cuproic acid, Methylenedioxy-3,4-cinnamalketone, Benzoic acid, cinnamic acid, and phenylacetic acid.

Habitat and Geographic Distribution

Originating in the South Pacific, kava grows best in warm, humid regions with volcanic soil that drains well. Traditional growing techniques are still used in Vanuatu, Fiji, Samoa, Tonga, Papua New Guinea, and the Solomon Islands, where it is primarily grown [21]. For kava plants to thrive, they need regular rainfall, a high soil organic matter content, and moderate shade. *Kava* is extremely dependent on human intervention for life since, in contrast to other members of the *Kava* species, it does not produce viable seeds and needs to be propagated manually [22]. *Kava's* pharmacological characteristics are intimately related to its botanical characteristics. The main source of kavalactones, which give *kava* its sedative and anxiolytic properties, is the rhizome and root system. However, the chemical makeup and strength of kava preparations vary depending on the cultivar type, growing environment, and extraction techniques. To maximize kava's therapeutic uses and guarantee its safe ingestion, it is essential to comprehend its botanical properties and phytochemistry.

2.5. Taxonomic classification of *Kava* (*Piper methysticum)*

Kingdom	Plantae
Binomial name *Piper methysticum*	
Class	Dicotyledonae
Order	Piperales G. Forst
Family	Piperaceae
Genus	Piper
Species	*P. Methysticum*

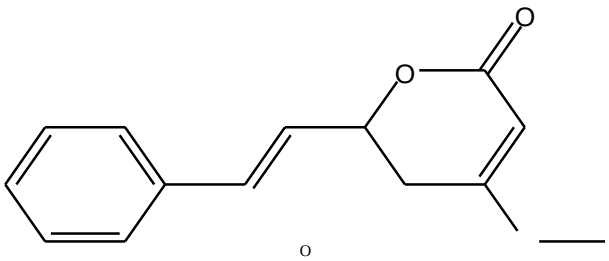
Table 1. Phytochemical Composition of *Kava*by Plant Organ

Plant Organ	Phytochemicals Present	References
Leaves	Alkaloids, which are mostly found in the plant's resin, are found in kava leaves. Although their concentration varies based on the plant species and the section used for extraction, they also include lactones. Chalcones, particularly flavokavains, are abundant in the leaves and support the biological activity of the plant. There are also notable concentrations of flavonoids, terpenoids, and tannins. Along with vital minerals including potassium, calcium, magnesium, iron, and zinc, cardiac glycosides are also present.	[15–17]

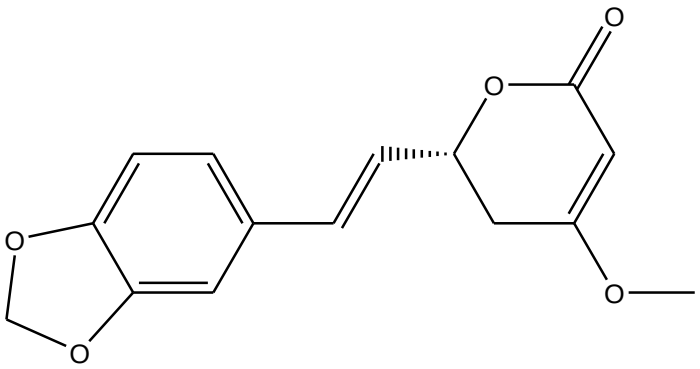
Root	The roots of *kava* are the primary source of kavalactones, a class of bioactive compounds responsible for its anxiolytic, sedative, and anticancer properties. The roots also contain flavokavains, a group of chalcone derivatives known for their cytotoxic and anti-inflammatory effects. Additionally, the root extracts have been found to contain pyrones, sugars, bornyl-cinnamate, stigmasterol, mucilages, benzoic acid, and cinnamic acid, all of which contribute to the plant's diverse pharmacological activities.	[18–22]
Rhizome	With at least eighteen kavalactones found, the rhizome of *kava* is the most abundant section of the plant in terms of bioactive chemicals. These substances are essential to the plant's antibacterial, antioxidant, and hallucinogenic properties.	[49-50]
Stem	Kavalactones are also present in *kava* stems, albeit in smaller amounts than in roots and rhizomes. Kavain, dihydrokavain, methysticin, dihydromethysticin, desmethoxyyangonin, and yangonin are the main kavalactones present in the stem. These substances support the sedative, anxiolytic, and muscle-relaxant actions of the plant on the central nervous system. Higher concentrations of alkaloids, such as pipermethystine, which has been connected to possible hepatotoxic effects, are found in the stem. As a result, compared to the root and rhizome, the stem has a limited value in medicinal formulations.	[51]

STRUCTURE OF SOME OF THE PHYTOCONSTITUENTS REPORTED FROM *KAVA*

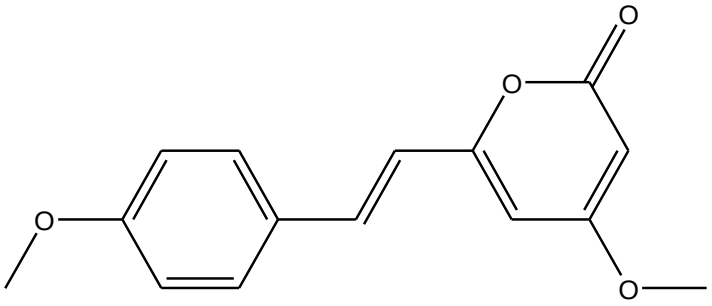
Numerous factors affect *kava's* chemical composition. The parts of the plant used, the types of cultivars that may contain different chemicals, and the extraction solvents are the most important ones. Lipophilic lactones with an aromatic styryl or phenylethyl substituent at position 6 in their αpyrone skeleton are called kavalactones, or kavapyrones. The main ingredients that give *kava* its biological activity are these lactones [23]. Nineteen different kavalactones have been identified as potentially metabolized by cytochrome P450 (CYP450) enzymes in the liver. However, only six kavalactones are thought to be responsible for more than 96% of the chemical action, including kavain, dihydromethysticin, and drokavain [25]. (Figure 2a). Since methylesterin is thought to help with neuroprotection against ischaemia, combining it with dihydromethysticin may reduce brain infarction in mice [26]. Moreover, the main kavalactones believed to be in charge of the effects observed in the central nervous system (CNS) include methysticin, dihydrokavain, and kavain [27]. Yangonin may have hepatoprotective qualities against cholestatic liver injury, according to some theories [28].



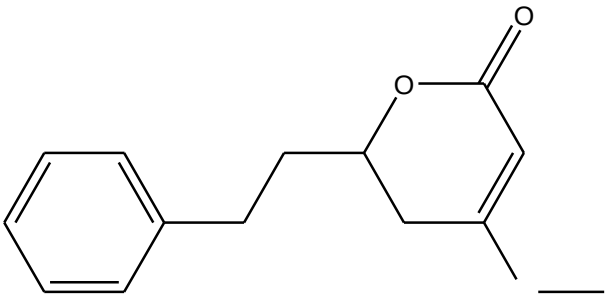
(a) Kavain



(b) Methysticin



(c) Yangonin



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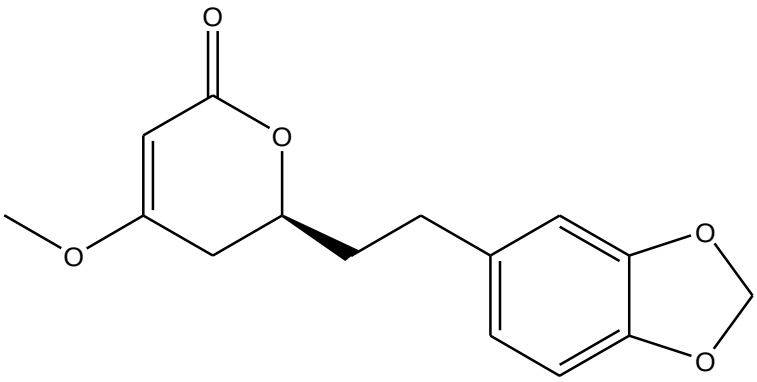
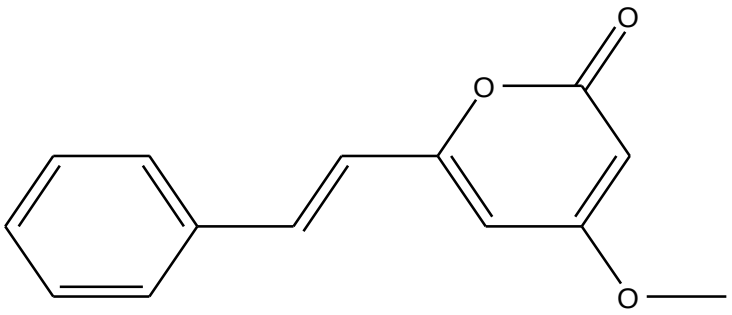
(d) Dihydrokavain

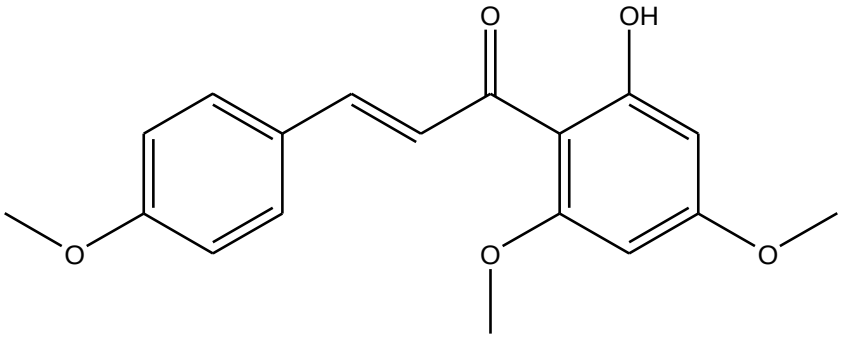


(e)Dihydromethysticin

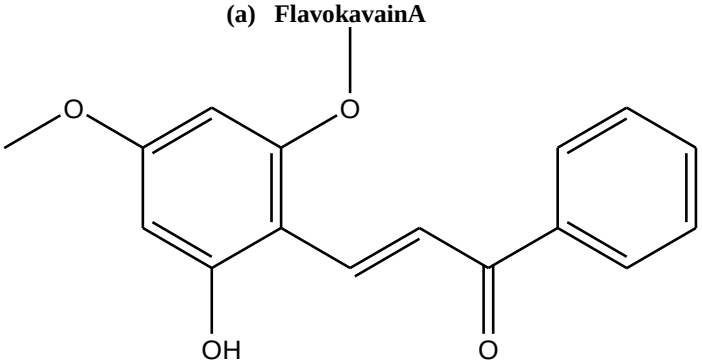


(f) Desmethoxyyangonin

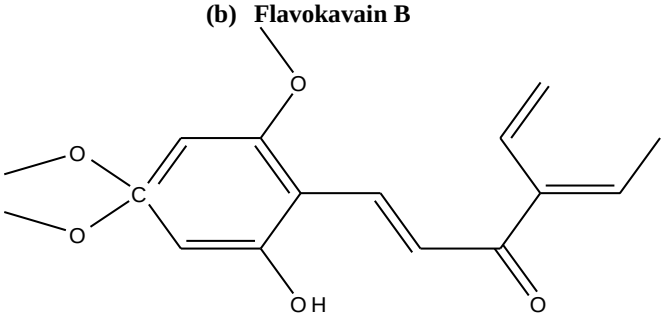
Fig. (2). Chemical compositions of the primary kavalactones.



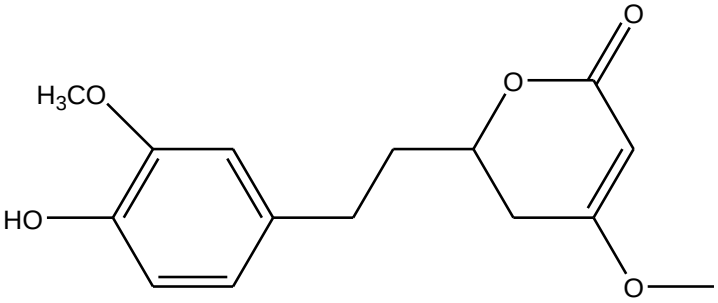
(a) FlavokavainA



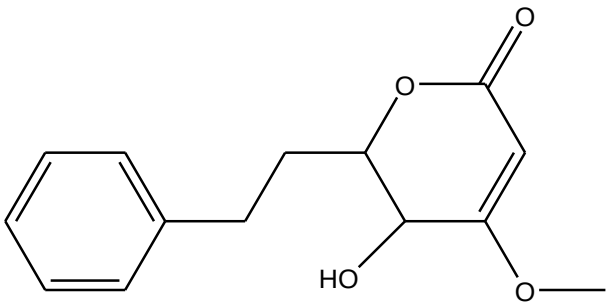
(b) Flavokavain B



(c) Flavokavain C



(d) 11 Hydroxy-12-methoxy dihydrokavain



(e) 7, 8- Dihydro-5-hydroxykavain

Fig. (3). Chemical compositions of the primaryflavokavains

PHYTOCHEMICAL VARIABILITY, CULTIVAR CLASSIFICATION, AND EXTRACTION INFLUENCE IN *KAVA*.

4.1. Influence of Plant Parts on Chemical Composition and Bioactivity

Apart from the widely known kavalactones, kava also includes a number of other small bioactive substances, such as chalcones, vital minerals, and amino acids. Because of their noteworthy biological activities and possible toxicity issues, flavokavains A, B, and C have drawn the most interest among them (Fig. 1b). Despite having lower concentrations than kavalactones, flavokavains—especially Flavokavain B—have strong bioactivity and have been connected to the production of reactive oxygen species (ROS) and the triggering of death in cancer cells [29]. This raises questions regarding Flavokavain B's safe use because it may have a role in anticancer treatment, but it is also thought to be hepatotoxic [30]. Research suggests that cultivars high in flavokavain may be associated with liver damage, particularly when unconventional extraction techniques are used [31]. Flavokavain A has also shown promise as an anticancer agent, especially in chemoprevention [32]. Nevertheless, little is known about the precise pharmacokinetics and processes of these substances, which calls for more research on dose-dependent toxicity and therapeutic effectiveness.The chemical profile of kava extracts is highly dependent on the specific plant organ utilized. Each part of the plant contains different proportions of kavalactones, alkaloids, and other phytochemicals, leading to variability in medicinal properties and safety profiles [33].

4.2.1. Roots and Rhizomes

The favored portion of *kava* for medicinal purposes is its roots and rhizomes because these are the main sources of kavalactones. Because root-derived extracts are abundant in psychoactive kavalactones such kavain, yangonin, and methysticin, which have sedative, neuroprotective, and anxiolytic properties, clinical research has mostly concentrated on these extracts [34]. Though in smaller amounts than in the stems and leaves, flavokavains are also present in these plant sections. Peeling the roots' outer layers prior to extraction has been proposed as a way to minimize liver-related side effects by lowering the content of potentially hepatotoxic alkaloids [35].

Leaves

Compared to the roots, kava leaves have greater concentrations of flavonoids, tannins, and terpenoids. Although these substances have anti-inflammatory and antioxidant qualities, the leaves are not typically utilized in *kava* preparations because of their high alkaloid content, especially pipermethystine, which has been linked in studies to hepatotoxicity [36]. The pharmacological effects of *kava* leaf extracts are still poorly understood because of safety concerns, despite the fact that they have been demonstrated to interact strongly with CNS receptors in vitro [37].

Stems

The stems contain lower concentrations of kavalactones but have higher alkaloid levels, making them less suitable for medicinal use. Some commercial kava preparations include basal stem peelings, but excessive stem content may increase toxicity risks due to the presence of pipermethystine and other potentially harmful alkaloids [38].

Cultivar Influence on Chemical Composition and Therapeutic Effects

The cultivar type of *kava* plays a crucial role in determining the potency, safety, and pharmacological properties of *kava* extracts. The kavalactone-to-flavokavain ratio varies significantly among cultivars, leading to distinct therapeutic and toxicological profiles. In 2002, the Kava Act No. 7 officially categorized *kava* cultivars into four distinct groups based on their phytochemical composition and effects [40]:

4.2.4.1.Noble Cultivars (n = 28)

Considered the highest quality and safest for medicinal use.
Characterized by higher kavain concentrations, which provide anxiolytic effects without excessive sedation [41].
These cultivars are the only legally approved varieties for export and medicinal use in many countries [42].

4.2.4.2. Two-Day Cultivars (Tudei Kava, n = 128)

Contain higher levels of dihydromethysticin and dihydrokavain, which result in a prolonged intoxicating effect, lasting up to two days [43].
Consumption is associated with hangover-like symptoms, including headaches, nausea, and lethargy [44].

Due to their higher flavokavain B content, these cultivars have been linked to greater hepatotoxicity risks, leading to legal restrictions in multiple countries [45].

4.2.4.3. Medicinal Cultivars (n = 79)

Traditionally used by Pacific herbalists for therapeutic purposes [46].
Unlike noble cultivars, these varieties have only been incorporated into nutritional supplements and experimental formulations, limiting available research data [47].
Some reports suggest potential liver toxicity risks; though further research is needed [48].

4.2.4.4. Wichmannii Cultivar (n = 12)

Considered the wild-type variety, native to the Pacific Islands.
Exhibits intense psychoactive effects, which may be too strong for general consumption [49].
Contains significantly higher concentrations of yangonin and desmethoxyyangonin, as well as flavokavains, making it chemically distinct from cultivated varieties [50].

Extraction Methods and Their Influence on *Kava's* Bioactivity and Safety

In addition to plant part selection and cultivar type, the extraction method plays a critical role in determining the safety and efficacy of *kava* preparations. Different extraction techniques yield varying concentrations of kavalactones, flavokavains, and alkaloids, influencing both therapeutic potency and toxicity risks [51]:
Traditional Water Extracts: Considered the safest preparation method, as harmful alkaloids are not efficiently extracted in water. Traditionally used in Pacific Island cultures, this method has been associated with low toxicity [52].
Ethanol and Acetone Extracts: These commercial extracts yield higher kavalactone concentrations but may co-extract toxic alkaloids such as pipermethystine, increasing hepatotoxicity risks [53].
Supercritical CO_2 Extraction: A modern technique producing high-purity kavalactones while minimizing toxic components. This method is increasingly preferred for pharmaceutical applications due to its improved safety profile [54].
The phytochemical profile of *kava* is highly influenced by plant part selection, cultivar type, and extraction method. Noble cultivars remain the preferred choice for medicinal applications, while two-day cultivars and wild-type varieties present higher risks of hepatotoxicity. Future research should focus on optimizing extraction techniques, refining kavalactone-to-alkaloid ratios, and conducting long-term clinical trials to establish safe dosage guidelines. A standardized approach to *kava* consumption will be essential for maximizing therapeutic benefits while minimizing risks.

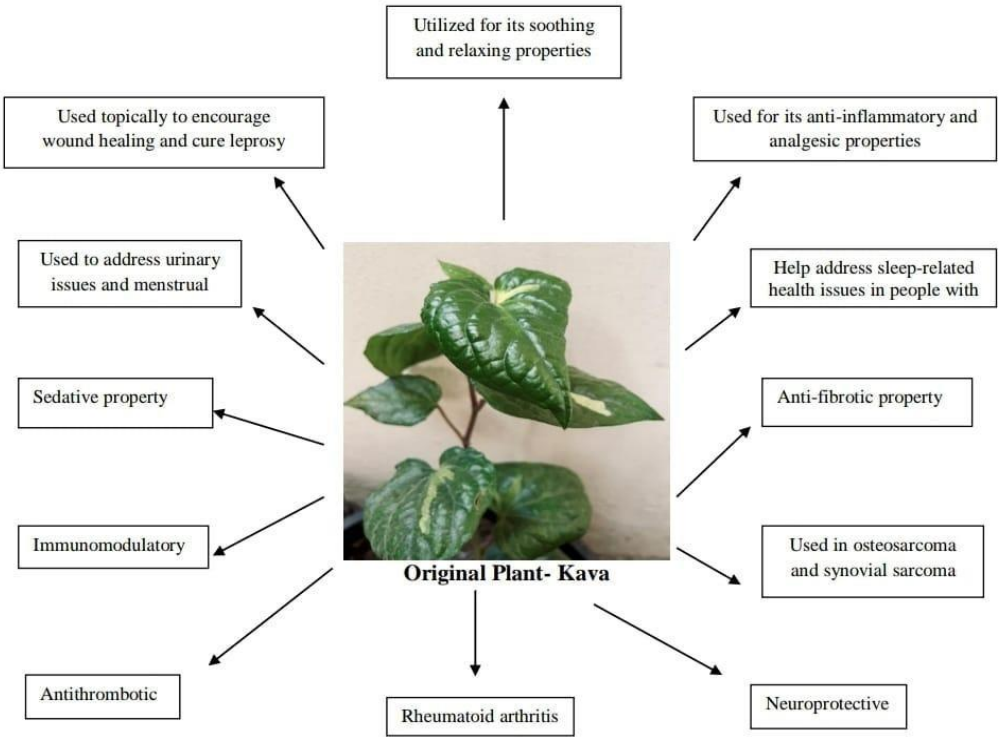
PHARMACOLOGICAL ACTIVITIES OF *KAVA*

5.1. Sedative and Hypnotic Effects of *Kava*

Numerous studies have examined the sedative and hypnotic properties of *kava*, and mounting data indicates that the kavalactones in the plant interact with a variety of neurochemical pathways to produce its soothing effects. In contrast to traditional sedatives like barbiturates, antihistamines, and benzodiazepines (e.g., Halcion, Tranxene), which mainly work by directly altering γ-aminobutyric acid (GABA) receptors, kavalactones seem to function via unconventional pathways, producing a unique sedative profile [1].

5.1.1. Mechanisms of Action Underlying *Kava's* Sedative Properties

It is believed that kavalactones, specifically "kavain, dihydrokavain, methysticin, and dihydromethysticin," alter neurotransmitter function without interacting directly with GABA-A or benzodiazepine receptor sites. However, new data indicates that kavalactones might indirectly improve GABAergic transmission by altering the makeup of receptor subunits or making more GABA binding sites available [2]. Studies demonstrating that kavain and dihydromethysticin enhance the effects of ipsapirone, a serotonin 5-HT1A receptor agonist with sedative and anxiolytic effects, provide credence to this theory, pointing to a potential interaction between the GABAergic and serotonergic systems in *kava's* mode of action [3]."The calming effects of kava may be attributed to its modulation of dopaminergic and glutamatergic signaling pathways in addition to its GABAergic effects. The limbic system's dopaminergic pathways, especially those in the amygdala complex, which is crucial for emotion regulation and anxiety processing, may be the source of some of *kava's* calming effects, according to early dopamine antagonist research [4]. Additionally, kavain and dihydromethysticin have been shown to augment the actions of NMDA receptor antagonists in electrophysiological investigations employing guinea pig hippocampal tissue, indicating that kava may potentially modulate glutamate-mediated excitatory neurotransmission [5].



Pharmacological Activities of Kava

Electrophysiological and Behavioral Evidence of Sedation

Animal studies have consistently demonstrated *kava* sedative and hypnotic effects across various models. For instance, treatment with *kava* extracts in rabbits induced significant electroencephalographic (EEG) changes that closely resembled those seen with traditional sedative-hypnotic medications [6]. These EEG alterations suggest that *kava* may influence sleep architecture, possibly by increasing slow-wave sleep (SWS) and rapid eye movement (REM) sleep, similar to but distinct from benzodiazepines and barbiturates [7]. Studies in mice and rats have further validated these findings. Dihydrokavain and dihydromethysticin administration resulted in dose-dependent sedation and hypothermia, indicating their potential role as CNS depressants [8]. In a rat model of hypermotility, *kava* resin was shown to reduce spontaneous locomotor activity, an effect comparable to that observed with antipsychotic drugs [9]. Additionally, *kava* extracts have been found to inhibit conditioned avoidance responses, suggesting a possible role in modulating cognitive and emotional reactivity [10].

Human Studies: EEG and Sleep Architecture Modulation

Human clinical trials have further explored kava's potential in enhancing sleep quality without the cognitive impairment typically associated with sedatives. In a 4-day, placebo-controlled study involving 12 healthy participants, subjects were administered either 300 mg (containing 210 mg kavalactones) or 150 mg (containing 105 mg kavalactones) of standardized kava extract, following a 3-day placebo period [11].

Key findings from this study included:

Reduced wakeful periods during sleep cycles.

Shortened light and deep sleep phases, suggesting improved sleep efficiency.

Prolonged REM sleep duration, in contrast to benzodiazepines, which are known to suppress REM sleep.

These results indicate that kava may improve sleep architecture, making it a potentially useful alternative to pharmaceutical sedatives that often disrupt natural sleep cycles [12]. Moreover, increased sleep spindle density, a hallmark of stable sleep states, was observed in kava users, further supporting its role in promoting restful sleep [13].

Cognitive Effects: Preservation of Mental Clarity

One of the most notable distinctions between kava and traditional sedatives is its lack of cognitive impairment. Unlike benzodiazepines, which are known to reduce psychomotor function, impair memory, and induce drowsiness, *kava* may actually enhance cognitive function in some cases. In a double-blind, placebo-controlled, crossover trial, 12 healthy participants were administered either oxazepam (a benzodiazepine) or standardized *kava* extract (600 mg/day for five days). The effects on cognitive function were evaluated using event-related potentials (ERPs) during a word recognition task. The results showed that:

Kava did not impair reaction time or accuracy, while oxazepam significantly reduced both measures.

Kava did not induce excessive drowsiness, in contrast to oxazepam, which caused sedation-related cognitive slowing.

No decline in working memory or attention was observed in *kava* users, whereas benzodiazepine-treated participants exhibited notable deficits in these areas [14].

These findings suggest that *kava's* sedative properties are unique in that they promote relaxation without causing the cognitive dulling commonly associated with pharmaceutical anxiolytics and hypnotics.

Comparison to Standard Sedatives

Kava's unique pharmacological profile makes it a potential alternative to traditional sedativehypnotic medications, particularly in individuals who experience adverse effects with benzodiazepines, barbiturates, or antihistamines.

Table 2. The Most Common Sedative Agents

Sedative Agent	Primary Mechanism	Effects on Sleep	Cognitive Impairment	Risk of Dependence
Benzodiazepines (e.g., Diazepam, Oxazepam)	GABA-A receptor modulation	Suppresses REM sleep	Significant impairment	High
Barbiturates (e.g., Phenobarbital)	GABA-A receptor agonist	Reduces deep sleep	Severe impairment	High
Antihistamines (e.g., Diphenhydramine)	Histamine receptor blockade	Prolongs sleep onset	Moderate impairment	Low to Moderate
Kava (e.g., Kavain, Dihydromethysticin)	GABAergic, serotonergic, and dopaminergic modulation	Enhances REM sleep, promotes sleep stability	Minimal to no impairment	Low

Cognitive Effects, Alcohol Interaction, and Neurophysiological Insights into *Kava's* Sedative Mechanism

In contrast to conventional anxiolytics like benzodiazepines, *kava (Piper methysticum)* has been extensively researched for its distinct sedative effects, which seem to promote relaxation without impairing cognitive function. Numerous clinical studies have examined the effects of *kava* on neurophysiological parameters, mental alertness, and cognitive performance, especially in comparison to conventional prescription sedatives. A growing body of research indicates that kavalactones may modulate neurotransmission through multiple pathways, influencing not only GABAergic activity but also dopaminergic, serotonergic, and limbic system functions [1], even though the exact mechanisms underlying kava's effects are still partially unknown.

***Kava's* Impact on Cognitive Performance and Mental Alertness: Clinical Findings**

The capacity of *kava* to encourage relaxation while maintaining—and in certain situations, even improving—cognitive function is among its most intriguing pharmacological characteristics. An event-related potential (ERP)-based visual search paradigm, which evaluates attention allocation and cognitive processing efficiency, was used in a double-blind, placebo-controlled study with twelve healthy male participants to examine the effects of *kava*. According to the findings, *kava* enhanced information processing speed and attention allocation, while oxazepam, a benzodiazepine, markedly hampered these abilities [2]. This implies that *kava* works in a different way than traditional sedatives, which usually cause sleepiness and cognitive slowness, to provide its soothing effects. Additional studies have looked at how *kava* interacts with alcohol, which is known to affect memory, motor coordination, and reaction time. Standardized *kava* extract and ethanol were administered to 40 healthy individuals in a double-blind, placebo-controlled research, resulting in a blood alcohol content of 0.05%. It's interesting to note that *kava* was found to alleviate some of the negative effects of ethanol alone on mental attention and cognitive performance, suggesting that it may have

a protective role in preserving cognitive function under mild alcohol intoxication [3]. However, *kava's* hypnotic and sedative effects were greatly enhanced when tested at higher ethanol concentrations, which resulted in increased tiredness and motor impairment in an animal model. These results underline the significance of dose-dependent interactions between alcohol and *kava* and the necessity for additional research into the neurochemical underpinnings of these interactions [4]. In a randomized, double-blind, crossover clinical investigation, the sedative and cognitive effects of diazepam (10 mg) and *kava* (120 mg kavalactones) were directly compared to a placebo. To measure mental alertness, reaction speed, and attention span, neurophysiological and psychophysiological tests were performed prior to, two hours after, and six hours following administration. When compared to a placebo, both *kava* and diazepam caused substantial differences, but they had very distinct impacts. Diazepam caused a noticeable deterioration in cognitive function, affecting working memory and reaction time while elevating subjective tiredness. In contrast, *kava* was found to provide a long-lasting soothing effect that lasted for up to six hours after treatment without significantly impairing cognitive function. Furthermore, there was no increase in beta-activity, which is frequently seen with benzodiazepines and linked to cognitive dulling and dependency risk, according to EEG study [5].

The Paradox of Relaxation and Enhanced Performance: How *Kava* Differsfrom Traditional Sedatives

One of the most striking discoveries in kava research is its ability to reduce stress and anxiety while simultaneously improving performance on difficult cognitive tasks. This seemingly counterintuitive effect has been confirmed by numerous psychophysiological studies. In one study, participants who took *kava* performed better on difficult problem-solving tasks than those who took diazepam or a placebo [6]. *Kava* appears to enhance cognitive function while reducing physiological stress reactivity, in contrast to traditional sedatives that impair psychomotor coordination and executive function. Scientists have hypothesized that kava's mode of action involves more than just GABAergic modulation because of its unique profile. Instead, it may involve connections between the dopaminergic and limbic systems, particularly in regions that regulate emotion, motivation, and cognitive flexibility. Numerous investigations have shown that kavalactones produce a calming effect without being too sedative by modifying the activity of limbic regions like the hippocampus and amygdala [7].

Neurophysiological Studies on *Kava*: EEG, Brain Activity, and Limbic Modulation

Studies using electroencephalograms (EEGs) have shed important light on the effects of kava on brainwave activity. *Kava* has a unique neurophysiological profile in contrast to benzodiazepines, which have a tendency to boost slow-wave activity (delta waves) and suppress high-frequency brain waves (beta waves), resulting in mental sluggishness and reduced cognitive function. EEG data from a study with rabbits given *kava* extracts showed changes in brain activity to those brought on by sedative drugs, but with function intact, indicating a special calming effect that doesn't cause excessive drowsiness or lethargy [8]. *Kava* may enhance the quality of sleep by regulating the length of REM and deep sleep stages, according to additional data from sleep studies. *Kava* has been shown to extend REM sleep while preserving deep sleep integrity, resulting in more restorative sleep patterns than benzodiazepines and barbiturates, which interfere with natural sleep architecture [9]. These results suggest that kava may be useful as a sleep aid, especially for people with anxiety-related sleep problems or insomnia brought on by stress.

Interaction Between *Kava* and Other Anxiolytics: Potential Synergistic and Adverse Effects

Given its growing popularity as an alternative to prescription anxiolytics, researchers have also examined how *kava* interacts with pharmaceutical sedatives, particularly benzodiazepines. In a randomized, three-way crossover study, eighteen healthy volunteers were administered bromazepam (4.5 mg twice daily), *kava* (120 mg kavalactones twice daily), or a combination of the two. The study assessed seven cognitive performance measures, including visual orientation, prolonged concentration, auditory reaction time, stress tolerance, vigilance, and motor coordination. While *kava* alone had no adverse effects on vigilance, motor coordination, or cognitive function, the combination of bromazepam and *kava* resulted in significant fatigue and reduced cognitive performance [10]. These findings suggest that kava may not potentiate the sedative effects of benzodiazepines in a linear manner, but rather, the interaction depends on the specific neurochemical pathways involved. While co-administration does not appear to increase major risks, the additive sedative effect observed with bromazepam highlights the importance of careful dosage considerations, particularly in individuals using multiple CNS depressants.

Pharmacological Activities of *Kava* : The Role of Current Bioactive Compounds

The medicinal potential of *kava (Piper methysticum)* has been thoroughly investigated, especially because of its diverse phytochemical profile, which is dominated by flavokavains, kavalactones, and other secondary metabolites. Numerous pharmacological effects, such as analgesic, anxiolytic, anticonvulsant, neuroprotective, ant ischemic, antithrombotic, antifungal, anticancer, and metabolic-modulating properties, are facilitated by these substances. Bioactive chemicals generated from kava influence many molecular pathways, which makes them ideal candidates for drug development and natural therapeutic applications, in contrast to synthetic medications that usually work on single-receptor processes. In the framework of the Current Bioactive Compounds study, the pharmacodynamics, mechanisms of action, and clinical significance of *kava's* bioactive compounds are examined in the sections that follow.

Analgesic and Local Anaesthetic Effects: Non-Opiate Pain Modulation Kavalactones

The kavalactone content of *kava*, specifically kavain, dihydrokavain, and methysticin, is largely responsible for its analgesic effect, one of its most important pharmacological characteristics. *Kava*-derived kavalactones seem to alleviate pain through non-opiate processes, lowering the likelihood of opioid dependency, withdrawal symptoms, and tolerance accumulation, in contrast to traditional opioid analgesics that work by activating μ-opioid receptors. Research has shown that kava-induced analgesia cannot be reversed by the powerful opioid antagonist naloxone, indicating that kavalactones work via other mechanisms, mainly ion channel regulation and cyclooxygenase (COX) inhibition. It has been demonstrated that kavalactones inhibit the activity of the COX-1 and COX-2 enzymes. Because of this mechanism, *kava* has great promise in the treatment of chronic inflammatory

diseases like fibromyalgia, arthritis, and neuropathic pain disorders. According to comparative research, dihydrokavain is more effective than aspirin at relieving pain; however, it is still less potent than morphine. Dihydrokavain and dihydromethysticin, on the other hand, show an additional analgesic effect when taken with aspirin, indicating a possible synergistic interaction with NSAIDs to improve pain relief while lowering NSAID-related side effects. *Kava* has shown topical anaesthetic qualities in addition to its systemic analgesic effects; some kavalactones are as potent as procaine and cocaine. This has raised interest in creating *kava*-based formulations for local pain management, especially for neuropathic pain syndromes, dental operations, and post-operative pain reduction. It's interesting to note that coffee has been shown to shorten the duration of *kava*-induced analgesia without affecting its strength, suggesting that kavalactones and adenosine receptor signalling may interact. The potential effects of these phytochemical interactions on *kava's* analgesic effectiveness in clinical settings should be investigated in future research.

Anxiolytic Effects: Modulation of GABAergic and Monoaminergic Neurotransmission

The anxiolytic (anti-anxiety) benefits of *kava* have drawn a lot of attention and have been confirmed by numerous randomized, double-blind, placebo-controlled research investigations. Kavalactones produce its anxiolytic effects via a more intricate, multi-receptor process that includes GABAergic, dopaminergic, serotonergic, and glutamatergic pathways, in contrast to benzodiazepines, which function as direct agonists of the GABA-A receptor. *Kava's* capacity to inhibit monoamine oxidase B (MAO-B) is one of the main bioactive mechanisms behind its anxiolytic effects. As MAO-B inhibitors, kavalactones like desmethoxyyangonin and methysticin increase the synaptic availability of dopamine and serotonin, two chemicals that are essential for mood control, emotional stability, and cognitive function. This process sets *kava* apart from benzodiazepines since *kava* maintains its anxiolytic effects over time without posing a serious risk of dependence, while benzodiazepines cause tolerance and withdrawal symptoms. Additional data indicates that rather than directly binding to benzodiazepine sites, *kava* indirectly affects GABA-A receptor subunits to alter GABAergic neurotransmission. *Kava* is a great therapeutic choice for people who need to control stress while preserving cognitive function because of this mechanism, which reduces anxiety without causing undue drowsiness. *Kava* improves relaxation without affecting cognitive performance, according to quantitative EEG research conducted in clinical trials. In certain instances, it has also been shown to increase cognitive processing speed and attentional control. According to recent neurophysiological studies, *kava* may also have anxiolytic benefits via regulating glutamate and NMDA receptor activation, which would lessen excitotoxicity and the excitation of neurons brought on by stress. These results shed light on why *kava* works for both acute and long-term anxiety disorders, suggesting that it alters neurotransmitter balance instead of causing widespread central nervous system suppression. *Kava* is being investigated as a possible substitute for benzodiazepines, SSRIs, and other pharmacological anxiolytics in the treatment of generalized anxiety disorder (GAD) and mood disorders associated with stress because of its distinct neuropharmacological profile.

Neuroprotective and Anti-Ischemic Properties: Kavalactones as Potential Stroke Therapeutics

Kava's neuroprotective potential has been emphasized by recent studies, especially in relation to neurodegenerative diseases, ischemic brain injury, and stroke recovery. Kavalactones, including dihydrokavain and methysticin, have been demonstrated to lessen neuronal damage after ischemic stroke by regulating mitochondrial activity, oxidative stress, and glutamate excitotoxicity. Kavalactone pretreatment dramatically lowers infarct size, increases neuronal survival, and improves functional recovery after a stroke, according to research conducted in animal models of localized cerebral ischemia. According to these results, kavalactones may be useful neuroprotective drugs for preventing brain damage following a stroke and maybe lessening the long-term cognitive impairments brought on by cerebrovascular injury. There should be more clinical studies looking into *kava's* potential as an adjuvant neuroprotective therapy because the pharmaceutical choices available for ischemic stroke recovery are still limited. From analgesic and anxiolytic effects to neuroprotection and anti-inflammatory qualities, the bioactive components of *Kava*, including kavalactones, flavokavains, and secondary alkaloids, demonstrate a broad spectrum of pharmacological actions. *Kava* is a versatile therapeutic candidate since it works by modulating many receptors, in contrast to many synthetic medicines that only target one pathway. Its therapeutic promise is highlighted by its capacity to offer neuroprotection in ischemic circumstances, alleviate anxiety without impairing cognitive function, and lessen inflammatory pain without causing opiate dependence. Standardized *kava* formulations may become more significant in integrative medicine as research advances, especially in the areas of neurology, psychiatry, pain treatment, and stroke rehabilitation.

CONCLUSION

The pharmacological significance of *Kava* is based on its diverse mixture of bioactive substances, particularly kavalactones, flavokavains, alkaloids, and phenolic compounds. Because of the anxiolytic, sedative, analgesic, anticonvulsant, neuroprotective, anti-inflammatory, and anticancer properties of its ingredients, *kava* is a promising option for neurological, psychiatric, and pain management applications. Kavalactones, such as kavain, dihydrokavain, methysticin, and dihydromethysticin, interact with GABAergic, dopaminergic, serotonergic, and glutamatergic pathways to improve CNS modulation without producing extreme sleepiness or cognitive impairment. Meanwhile, flavokavains, including flavokavain B, have demonstrated anticancer efficacy by inducing ROS-mediated apoptosis in tumor cells; nevertheless, they may potentially be hepatotoxic. Recent studies demonstrate the importance of cultivar selection and extraction methods in determining the efficacy and safety of kava. Noble cultivars are the preferred choice for medical purposes since they have higher kavain levels and lower flavokavain B concentrations, but "Two-Day" and wild-type cultivars are more hazardous due to their tendency for hepatotoxicity and extended intoxication effects. Furthermore, even though water-based extracts are still the safest preparation, ethanol and acetone extracts may raise the risks of toxicity. Despite its vast therapeutic potential, standardization, toxicological analysis, and clinical validation are necessary for *kava's* safe integration into modern medicine. More research is needed to refine bioactive chemical ratios, assess long-term health effects, and enhance extraction techniques. If handled appropriately, *Kava has* the potential to develop into a strong phototherapeutic agent with safe, natural substitutes for synthetic analgesics, neuroprotective drugs, and anxiolytics.

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