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A Review on Potential Footprints of *Piper methysticum* for Chronic Disease Management

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Abstract

Background: For centuries, Kava *(Piper methysticum*) has been incorporated as medicine in the Pacific Islands, and modern studies now confirm its therapeutic value on several chronic diseases. **Aim:** This review aims to explore the modes of action of kavalactones and flavokavains in kava to treat neurological disorders, cancer and inflammation. **Methods:** A systematic review was conducted through PubMed, Scopus, Science Direct and Google Scholar databases on articles between 2010 and 2025 by investigating keywords that matched both kava and chronic diseases. **Results:** Kavalactones, including kavain and methysticin, control excessive neuron activity by interacting with GABA receptors and preventing sodium channel activity, which supports kava's historical application for anxiety treatment and its new use in treating epilepsy and providing neuroprotection. Flavokavain A shows strong anti-inflammatory properties because it prevents NF-κB pathway destruction while it activates the protective Nrf2 antioxidant system. Flavokavains induce cancer cell death through various mechanisms, including disrupting the equilibrium between pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins and blocking the blood flow needed by tumours. The therapeutic potential of flavokavain B, which exists in organic solvent extracts, creates a serious risk because it causes damage to the liver. **Conclusion:** kava's kavalactones and flavokavains offer compelling therapeutic benefits for neurological disorders, cancer, and inflammation — calming neural excitability, inducing cancer cell death, and activating antioxidant defences. Moving forward, rigorous clinical studies are needed to fully unlock this ancient botanical's modern medicinal benefits.

Major Findings: Kava's bioactive components kavalactones and flavokavains show remarkable therapeutic potential like neuroprotection, anxiolysis, and anti-inflammatory effects through GABAergic and NF-κB/Nrf2 pathways, while demonstrating potent anticancer activity via apoptosis and angiogenesis inhibition.

Keywords: Anxiety, Cancer, Chronic Disease, Flavokavains, Inflammation, Hepatotoxicity, Kava, Kavalactones, Neuroprotection

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1. Introduction

Herbal remedies have been incorporated for hundreds of years to treat multiple diseases with negligible side effects, hence becoming an essential part of healthcare systems throughout the world. These natural products participate in the therapy of various long-term health disorders such as cancer, diabetes, neurodegenerative diseases and Ulcerative Colitis (UC), Inflammatory Bowel Disease (IBD)[1-3]. Among these medicinal plants, kava (*Piper methysticum*) has received significant attention for its therapeutic properties. Its two main classes of phytochemicals are kavalactones and chalcones (Table 1). Recent studies in preclinical and clinical settings have shown that kavalactone compounds, such as kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, as well as desmethoxyyangonin (Table 2), exhibit neuroprotective and anxiolytic effects[4,5]. Among these compounds, Kavain is predominant due to exhibiting high human body absorption rates, the ability to cross the BBB and long persistence in

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neural tissues for managing many long-term medical conditions[6,7]. Kavain activates the Nrf2 pathway and serves as an antioxidant and anti-inflammatory agent that regulates excitotoxicity in neuronal signalling[8]. It appears to act on $GABA_A$ receptors and also on voltage-gated ion channels together with an enzyme known as monoamine oxidase-B, which is involved in degrading essential neurotransmitters[5,9]. Kavain also reduces the body's inflammatory response, in terms of lowering levels of signalling molecules like TNF-α and IL-6 that drive inflammation when elevated and reduces apoptosis[8]. These mechanisms of kavain protect against progressive neuronal conditions like Alzheimer's and Parkinson's, together with against chronic anxiety and inflammation-based cancers through flavokavain-induced cell death.

The South Pacific population has utilised kava to reduce anxiety, treat sleep disorders and chronic pain for generations. A controlled trial of 129 outpatients with generalised anxiety disorder found that kava was effective in reducing anxiety. Additionally, a fourweek randomised controlled trial of 45 patients with nonorganic sleep disturbances reported that kava extract (200 mg daily) was effective for improving sleep[10,11]. Kavalactones demonstrate anxiolytic activity by acting as a $GABA_A$ receptor potentiator and inhibiting the activity of voltage-gated Na^+ channels, preventing excessive neuronal firing. The active ingredient kavain reduced the inflammation of joint arthritic models by activating PPARγ and downregulating iNOS, leading to significant inhibition (45% in rats) in paw oedema. Yangonin enhanced insulin sensitivity in diabetic mice by activating AMPK pathways and reducing hepatic glucose output, thereby treating metabolic syndrome[12-14]. These mechanisms link to chronic disease pathology through their interaction with dihydromethysticin, which shows hepatoprotective effects in alcohol-related liver damage through its Nrf2/HO-1pathway activation and oxidative damage reduction capabilities. However, flavokavain-containing extracts above 300 mg kavalactones per day demonstrated dose-dependent liver toxicity through P450 enzyme inhibition, which shows the necessity for chalcone-depleted product formulations[1,15].

Patients with MDD (Major Depressive Disorder) and anxiety disorders exhibit abnormal levels of monoamine neurotransmitters alongside a somewhat greater capacity for stress upon diagnosis. In clinical trials, kava extracts derived from the root of *Piper methysticum* contain kavalactones and have exhibited anxiolytic and antidepressant properties. It has been shown to increase $GABA_A$ receptor binding as well as its ability to inhibit MAO-B activity and inhibit the neuronal uptake of norepinephrine. These mechanisms have produced positive results in controlling anxiety symptoms and improving mood while cognitive functions remain at standard performance levels[16-19]. Kavalactones show anticonvulsant effects by increasing the seizure thresholds in animal models through their blocking of voltage-gated Na^+ and Ca^{2+} channels, which results in a reduction in the release of excitatory neurotransmitters. The extracts and constituents like methysticin and dihydromethysticin protect against neurodamage by reducing infarct size in cerebral ischemia models, with similar protective effects as memantine[20-22].

2. Materials and Methods

The scientific literature was collected using online search engines and databases, including Science Direct, Scopus, PubMed and Google Scholar. Using keywords "kava", "Piper methysticum", "kavalactones", "flavokavains", "kavain", "methysticin", "dihydromethysticin", "yangonin", "desmethoxyyangonin,", "flavokavain A," "flavokavain B" and "flavokavain C), combined with chronic disease terms ("neurodegenerative disorders", "epilepsy", "anxiety", "inflammatory bowel disease", "cancer" and "hepatotoxicity") We restricted the search to English articles from 2010 to 2025.

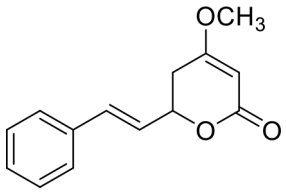
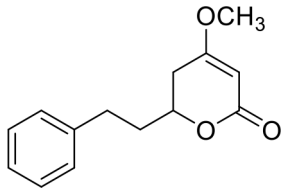
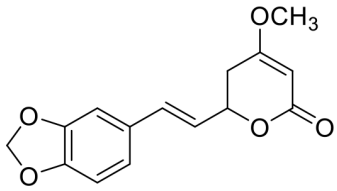
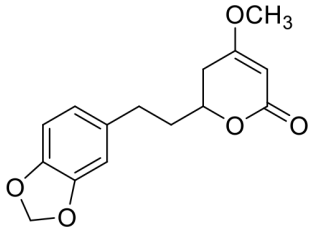
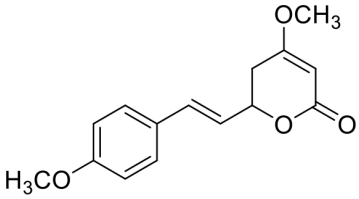
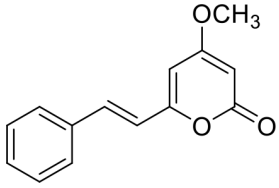
3. Phytochemical Profile of Kava (*Piper methysticum*)

Most of the kava biological studies have been carried out on the six important kavalactones (Table 2), which constituted approximately 20-50% of the dry weight of kava root[23,24]. Due to this significance, it is therefore not surprising that kava quality is primarily determined by the comparative quantity of these six agents (Table 2). Flavokavains A, B and C are considered minor components since they derive from the same anabolic pathways (Table 1). Kava is a mixture of different kavalactones along with other trace elements (Table 1)[25].

Table 1. Major phytochemical classes in kava and their relative content

Chemical class	Content	Key representative	References
Kavalactones	4-8% dry root	Kavain, Dihydrokavain, methysticin, Dihydromethysticin, Yangonin, Desmethoxyyangonin	8
Flavokavains	<1% dry root: higher in ethanolic extracts than aqueous extracts	Flavokavains A, B, C	26
Alkaloids	Minor	Canadine and related compounds	8
Terpenes	Volatile fraction	Myrcene, β-caryophyllene, humulene	8
Cinnamic Acid Derivative	Minor	1-Cinnamoylpyrrolidine	8

Table 2. Key kavalactones—Structure and therapeutic applications

Kavalctones	Structure	Relative abundance and uses	References
Kavain		High abundance. Primary Use: Anxiolytic, sedative. Key for CNS effects. Also studied for anti-inflammatory activity.	5,27-29
Dihydrokavain (DHK)		Very High abundance. Primary Use: Anxiety treatment, sedative. One of the most important for CNS effects	5,27
Methysticin		Moderate abundance. Primary Use: Neuroprotective (*e.g.*, reduces brain infarction). Also, a potent inhibitor of cytochrome P450 enzymes.	5,27,30
Dihydromethysticin (DHM)		High to Very High abundance. Primary Use: Neuroprotective (works with methysticin). Also, a potent mechanism-based inhibitor of cytochrome P450 enzymes.	5,27,30
Yangonin		The variable can be High. Primary Use: Potent inhibitor of MAO-B. Suggested hepatoprotective effects. Also binds to CB1 receptors.	5,27,31
Desmethoxyyangonin (DMY)		Moderate abundance. Primary Use: Also, a potent reducer of MAO-B (the locked C5-C6 structure is key for this activity). Inhibits the pro-inflammatory p38 MAPK pathway	27,32

4. Kava and Neurological Disorders

Many neurological conditions are grouped under the label "neurodegeneration." These diseases vary in symptoms, including motor dysfunction, speech difficulties and cognitive impairment. Neurodegenerative disorders are normally distinguished by a functional, gradual decline of the efficient neuronal population in the brain. Neuron death takes place in a specific region of the brain and spinal cord that defines clinical characteristics of an individual neurodegenerative disease[33].

4.1 Epilepsy

People have long appreciated the psychoactive effects of kava usage. Its neurological benefits are one of the most common non-prescription medications for a variety of neurological disorders. Predominantly neuropharmacological effects of kava are ascribed to kavalactones (Table 2), and a plethora of target sites have been proposed[8]. However, proposed mechanisms are still not fully elucidated. Epilepsy is a chronic brain disorder triggered by excessive brain neuronal firing[34]. It is a chronic, paroxysmal and recurrent illness characterised by neurobiological, cognitive, psychological and social factors that collectively contribute to recurrent seizures, alongside enduring risk factors for epileptic episodes[35]. Epilepsy occurs in various clinical presentations, including loss of consciousness, movement difficulties (motor seizures), visual and auditory problems, taste and mood impairments (affective disorders), cognitive capacity impairment or degeneration, bruising, as well as the risk of death[36]. Epilepsy is a medical condition distinguished by two or more seizure episodes, which are hypersynchronous neuronal discharge in the brain[35]. It is a noncommunicable chronic disease, and it influences approximately 50 million people of all ages[37]. Seizures result from inadequate or excessive firing of the neurons, and this culminates in the inability of the brain to coordinate the rest of the human body[34]. It affects processes such as the limbs as well as bowel movements and may take a varying frequency from several seizures per day to less than one per year. Epilepsy can affect one region of the body (focal epilepsy) or the whole body (generalised epilepsy), depending on the location of the affected neurons in the brain[34,36]. Thus, epilepsy accounts for sudden, unexplained deaths of people each year. Around 5 million people around the world have epilepsy[36,38]. The disease is expected to impact 49 out of every 100,000 and 139 per 100,000 individuals in developed and developing countries, respectively. Neuroinflammatory and apoptotic pathways are activated following an epileptogenic event (*e.g.*, traumatic brain injury or status epilepticus) and drive a cascade of neuroplastic changes leading to the development of epilepsy[38-40].

Conventionally, epilepsy is treated symptomatically with synthetic Antiepileptic Drugs (AEDs) available. Nonetheless, the occurrence of a multitude of untoward effects with conventional AEDs represents significant adherence barriers to treatments for epilepsy. Several herbal sedatives — kava, for example — are believed to potentiate the actions of antiepileptic drugs. Kava extract, a commonly used over-the-counter anxiolytic drug, is an anticonvulsant with no effect on attentiveness or memory performance. Kavalactones, which are the main active constituents of kava extract, may have anticonvulsant efficacy[16,21,41,42].

Kava, which possesses antioxidant and anti-inflammatory potential, has shown putative antiepileptic effects. In line with this, kava extract elevated the Maximal Electroshock Seizure Threshold (MEST) in rats, delaying seizure onset by 42-83% acutely and for up to 58% chronically, enhancing diazepam's anticonvulsant effectiveness while reducing its side effects on locomotor activity and liver enzymes[21,43,44]. Kavalactones regulate $GABA_A$ receptors, block voltage-operated Na^+ channels in hippocampal neurons and attenuate p38 MAPK/NF-κB/COX-2 signalling to inhibit neuroinflammation related to epileptogenesis[44,45]. Connexins, a family of 21 protein isoforms (11 expressed in the CNS), form hemichannels (connexons) and gap junctions that enable metabolic coupling between neurons and astrocytes; epileptogenic insults increase astrocytic hemichannel opening, promoting gliotransmitter release and neuronal hypersynchrony in seizure propagation. Although direct kava effects on connexins remain unexplored, its GABAergic potentiation and Na^+ channel blockade may indirectly disrupt epileptiform synchrony, akin to pharmacological Cx43/GJA1 antagonists that confer anti-epileptic benefits[46,47]. In another study, kava (100, 200 mg/kg) alone or combined with low-dose diazepam (5 mg/

kg) provided neuroprotection in electroshock models without motor impairment or hepatotoxicity[43].

4.2 Anxiety Disorders

Anxiety disorders are illnesses in which extreme fear, worry or dread becomes powerful enough to disrupt a person's daily life[48]. They arise from the way in which certain brain systems communicate, becoming disrupted — specifically those involving GABA, monoamine neurotransmitters that are all critical in regulating temperament and emotion within the cerebral limbic regions. The umbrella of anxiety disorders is very broad[49]. The DSM-IV lists a whole range of anxiety disorders — panic disorder, generalised anxiety disorder, various phobias — each with its own distinct identity and origins[50]. What makes them so hard to untangle, though, is that they rarely arrive in isolation. They often co-occur with other psychiatric disorders, especially mood and substance[51,52]. It constitutes the leading manic disorder observed in the United States and many different countries[53].

It is hard to deny the cerebral impact of correct kava use, especially for those who suffer from anxiety and stress[54]. In multiple controlled clinical trials, kava was effective in the recommended range of 20-300 mg kavalactones per day[5,19,55-57]. In clinical studies, GABA is implicated in neuropathology across anxiety conditions, with higher GABA links to anxiety processing in the healthy vmPFC and the medial prefrontal cortex post-traumatic stress disorder[28,58-63].

In PTSD, however, GABA concentrations are lower than those of reference in the LTL and parieto-occipital cortices, but not in the dACC region[64,65]. But the findings of many current studies are mixed. In fact, the latest studies on kava intake by GAD patients (171 participants consuming kava for 16 weeks) revealed no notable differences between kava and placebo groups in reducing anxiety. Anxiolytic properties were evident in a short-term study[66,67].

5. Kava in Inflammatory and Autoimmune Conditions

Inflammation is a key player in the pathology of different disorders, including cancer and progressive neurological disorders. Several phytoconstituents that exist in nature and have anti-inflammatory activities have gained momentum during the last decade. Research on kava and inflammation has been partially inspired by its pain management properties, as anti-inflammatory medicines are commonly used to manage pain. Chronic inflammatory and autoimmune disorders, including rheumatoid arthritis, Inflammatory Bowel Disease (IBD), and pancreatitis, are characterised by dysregulated immune responses, persistent oxidative stress, and elevated pro-inflammatory mediators. In such conditions, patients experience redox imbalance along with increased production of inflammatory mediators. The management of these conditions often requires long-term therapeutic strategies that modulate immune function without causing many off-target effects. Kava-derived phytochemicals, which include Flavokawain A (FKA), flavokawain B and flavokawain C, show potential to target necessary inflammatory pathways according to new scientific research[67-69].

Inflammatory and autoimmune conditions involve chronic immune dysregulation, characterised by excessive cytokine production (*e.g.*, TNF-α, IL-6) and activation of pathways like NF-κB and MAPKs, leading to tissue damage in joints, skin, and systemic sites. Triggers such as infections (*e.g.*, Porphyromonas gingivalis) exacerbate neuroplastic-like changes in immune cells, promoting osteoclast activation and synovial hyperplasia akin to epileptogenesis. Compounds such as kavalactones derived from kava have potent anti-inflammatory and TNF-α-suppressive activities and exhibit therapeutic potential in models of arthritis[38,32,70].

FKA, a predominant chalconoid derived from kava extract, has shown potent anti-inflammatory as well as antioxidant activity through preclinical models[71]. One comprehensive study by Yang *et al.*[71] analysed the molecular mechanisms responsible for the FKA-mediated anti-inflammation effects using BALB/c murine splenic primary cells in lipopolysaccharide (LPS)-induced inflammation. Lipopolysaccharides (LPS), the major structures of gram-negative bacterial endotoxin, are part of the most common sepsis-inducing agents.

LPS administration in laboratory animals mimics an experimental inflammatory process. The MAPKs p38, JNK and ERK drive the induction of proinflammatory genes during the inflammation process. NFκB, an essential factor, exerts substantial

action on the pattern in the genetic regulation of several genes involved in innate and acquired immunity. Active MAPKs drive signal transduction induced by LPS, triggering the activation of NFκB in activated macrophages. Additionally, upon activation of splenocytes by LPS, it induces oxygen consumption to submit immature (LPS-induced) immune cells to an inflammatory state involving oxidative stress, resulting in the production of ROS. Authors find that non-toxic quantities of FKA (2-30 μM) markedly inhibit the release of the major proinflammatory cytokines like TNF-α, IL-1β, IL-6, and IL10. A stunning drop in ratios of pro to anti-inflammatory cytokines provided support for this finding, which describes a consistently aligned direction[71]. To verify that these effects were effective beyond a laboratory environment, the researchers assessed FKA in a murine model of acute pancreatitis and confirmed its anti-inflammatory activity in the biological system (the activation of the digestive enzymes from the pancreas leading to self-inflicted damage), where anti-inflammatory activity was confirmed in a living system. FKA pretreatment reduced plasma lipase levels associated with CCK-8-induced experimental pancreatitis in a murine model, suggesting amelioration of pancreatic exocrine function and a reduction in inflammatory damage[71,72].

The FKA treatment produced its biological effects through two different pathways, which affected redox-dependent signalling systems. FKA pretreatment caused LPS-induced ROS production to decrease, while it prevents NF-κB p65 subunit activation. The inhibition process causes a decrease in all subsequent inflammatory mediators, which include inducible iNOS and COX-2[71]. FKA activated Nrf2, which functions as the main regulatory system for controlling antioxidant defence mechanisms[71,73,74]. FKA then activates the signalling pathway of antioxidant response element, which helps boost the production of key phase II detoxification enzymes [71]. Collectively, these findings give a vivid picture: FKA promoted the nuclear translocation of Nrf2/ARE pathway, a master regulator of antioxidant defense[71,73]. This dual action makes it a compelling new candidate in the race for treatments of inflammation-related diseases[73,74]. In support of these findings, a previous study from Kwon *et al.*[75], FKA blocks iNOS and COX-2 expression in LPS-induced macrophages through blocking NF-κB, AP-1, and JNK/p38 MAPK activation. The current round of research established FKA as a robust anti-inflammatory compound based on its potential to block the creation of both nitric oxide and prostaglandin E2.

In contrast to those of FKA, the pharmacological effects of FKB depict a more complex pattern. FKB has been defined among other potent modulators of inflammatory signalling, but with a significant hepatotoxic potential. The anti-inflammatory effect and apoptosis induction of FKB in cell lines have been correlated with the suppression of NF-κB and MAPK signalling cascade[76].

6. Kava and Cancer

Cancer is a complex group of chronic diseases characterised by uncontrolled cell division, resistance to normal apoptotic signals, genomic instability, and the ability to invade surrounding tissues and metastasise to distant sites. Its underpinnings are at the level of genes and cellular signalling pathways, driven by both genetic mutations and epigenetic changes. The characteristics of cancer are continuous cell growth promotion, resisting growth inhibition, evasion of apoptosis, unlimited replicative potential, induction of angiogenesis, and activation of invasion and metastasis, all of which are influenced by the tumour microenvironment and chronic inflammation[77]. Currently, there has been considerable research toward using plant products targeting key nodes of aberrantly activated signalling pathways, to provide important insight into effective cancer therapeutic intervention[78,79]. The anticancer effects of kava (Piper methysticum) are associated with two principal classes of phytochemicals: the kavalactones and the chalconoids, namely FKA, FKB and FKC[80,81]. With both groups playing a role, as related to kava's cancer-fighting ability, research has found that the flavokavains are the strongest. Even at low concentrations, they can induce death in cancer cells and inhibit their divisions [5]. These compounds execute their anti-cancer function by using multiple mechanisms that attack essential characteristics of cancer cells. The main mechanism involves apoptosis induction, which functions as the programmed cell death process. Usually, through this process, cells that are damaged or no longer needed will die, but cancer cells mutate to escape it. Flavokavains revive

this process by targeting proteins within the cell that determine whether it lives or dies. More precisely, FKA alters the equilibrium of proteins that decide a cell's fate of living or dying. It raises the levels of 2 proteins that promote cell death which promote cell death, while decreasing the levels of anti-apoptotic proteins like Bcl-2 and Bcl-xL, which protect the cell[82,83]. When that balance is disrupted, the mitochondria (the structures that provide power to the cell) start to break down and leak their contents. The leaked materials then trigger a cascade of events that activate a group of enzymes known as caspases to implement the cell's destruction. These enzymes eventually break down the cell from the inside, leading to its death[84].

Another mechanism through which Flavokavain B has demonstrated potential is its ability to activate death receptors on the cell surface of cancerous cells, thus initiating another pathway resulting in apoptosis [76]. One of the ways that kava compounds kill cancer cells is by effectively hitting pause on cell division. FKA causes cells to get stuck in the G2/M phase, which is the stage where they are supposed to prepare for and complete division when a cell is preparing to divide into two. When cells become stuck here and cannot move on, division stalls, and the cancer loses one of its most potent advantages: the ability to continue multiplying. It does this by influencing proteins, for example, cyclin B1 and cdc2 (cycle 2), which activate this phase[85].

Flavokavain B, however, arrests cells in the G1 phase, the step before DNA replication. It does so by increasing a protein called p21, which functions as a brake on the cell cycle and by inhibiting daughter proteins such as cyclin D1 and CDK4 that enable the cell to keep moving forward[86]. Kava compounds prevent the formation of cancer by blocking the perfusion to tumours. For the tumour to enlarge and metastasise, it requires novel blood vessels through angiogenesis. They send out signals, like vascular endothelial growth factor, to induce neovascularisation. Flavokavain A, along with B have been shown to reduce VEGF production and to inhibit proliferation and tube formation in endothelial cells (the cells lining blood vessels)[87]. This anti-angiogenic effect does help to inhibit the tumour's growth by starving its oxygen and nutrition. Cancer initiation and progression are associates of chronic inflammation. A major participant in this process is known as the NF-κB pathway, that control activation of numerous genes associated with inflammation, cell viability and cell growth. Flavokavains A and B are potent inhibitors of the NF-κB pathway[71,73]. By blocking this pathway, they lower the concentration of inflammatory molecules, along with proteins that enable cancer cell survival. This not only renders a more hostile environment for tumour growth, but also induces greater apoptosis sensitivity to cancer cells. In addition to their potential in treating existing cancers, some kava components may even prevent cancer before it starts. This is called chemoprevention. Dihydromethysticin and other kavalactones stimulate a pathway called Nrf2, the master regulator of antioxidant defences in the body[24,73].

When Nrf2 gets activated, it starts the production of genes which create phase II detoxification enzymes, which include quinone reductase. These enzymes help neutralise harmful chemicals and carcinogens, which protect cells from DNA damage that could lead to carcinogenesis[88]. This is an important mechanism, especially for protecting high-risk tissues such as the lungs and liver. Furthermore, some kavalactones can inhibit phase I enzymes (*e.g.*, certain cytochrome P450s) that activate the carcinogen to actively defend against cancer initiation[89]. Many laboratory studies and experiments on animals have provided evidence for these anticancer effects. Celentano *et al.*[88] experimented with kava compounds, flavokavain A (FKA) and Flavokavain B (FKB), in cancer cells from the mouth, namely oral squamous cell carcinoma. They used lab-grown cancer cells (such as H400 and BICR56 lines) alongside healthy mouth cells (OKF6) for their research comparison. In low doses — 2.5 µg/ml for FKB and 10µg/ml for FKA — the compounds inhibited the cancer cells' growth, movement and spread, although they did not harm healthy cells. The way they primarily functioned, however, was by inducing apoptosis or programmed cell death. Liu *et al.*[90] showed that a kava compound, FKA, may slow bladder cancer in an animal model. They worked with genetically altered mice that develop a kind of bladder cancer similar to early-stage non-muscle invasive bladder cancer in people. When these mice were fed FKA in their diet, they had fewer tumours in both the bladder and ureters — and they lived significantly longer than untreated mice. The study also found that FKA didn't just lower the number of tumours — it appeared to make the tumours

less dangerous. FKA-treated mice also had better-differentiated tumours, meaning that their tumours looked less aggressive and were less likely to behave like fast-growing cancer. Another study also supported that FKA attacked cancer cells in multiple ways. It made cells divide more slowly, while at the same time inducing increased programmed cell death in cancer cells. It also reduced levels of "surviving", a protein that keeps cancer cells alive, while increasing levels of "p27", another protein that inhibits excessive cell growth. Altogether, these effects essentially help stop the uncontrolled division of cancer cells. FKA not only directly affected cancer cells, but more importantly, it interfered with certain signalling pathways in the cell that cause the formation of tumours. By inhibiting these pathways, the FKA cuts off the signals for cancer cells to continue growing and surviving. Overall, these findings indicate that dietary intake of FKA alone may be sufficient as a chemopreventive agent against bladder cancer[88].

7. Safety Considerations and Hepatotoxicity

Kava use has been associated with liver damage, with over one hundred cases reported between 1990 and 2010; its sale and marketing have therefore been confined to a few countries. Although these reports exist, how kava causes liver toxicity in some people is still poorly characterised, and compound or human variation is presumably involved in the matter[91]. Flavokavains, especially flavokavain B, are a group of compounds implicated as one of the primary contributors to kava-related hepatotoxicity. In mice, high doses of 500 mg/kg of kava alone did not cause any visible damage to the liver. However, when kava was administered to mice prior to acetaminophen (the active ingredient in Tylenol), the combination of the two produced much more severe liver injury, as measured by increased levels of liver enzymes in their blood and greater damage to their liver tissues[92]. Follow-up studies identified flavokawain A and B as the compounds responsible for the heightened liver toxicity, whereas another kava compound, dihydromethysticin, did not have that effect[93]. FKB seems to harm cells by depleting glutathione — a vitamin C-like antioxidant that occurs naturally and is the body's primary barrier against harm — and inducing oxidative stress along the way. In fact, when the researchers restored levels of glutathione in the cells that had been damaged, both the damage and the abnormal signalling reversed, leading them to conclude that glutathione provides critical protection against cellular injury[76]. In addition, kava compounds have been shown to interact with a group of liver enzymes known as cytochrome P450 that the body uses to process many different drugs and toxins — raising further questions about how kava may affect the breakdown of many drugs and toxins within the body. Research suggests that kavalactones target various isoforms of these enzymes[94]. More specifically, methysticin and 7,8-dihydromethysticin have been shown to increase CYP1A1 activity, an action that had raised some concern because this enzyme can dehydroxylate (activate) non-carcinogenic substances into carcinogens, although the significance of this in humans utilising kava is not known[95]. Similarly, kava's ability to affect many drug-metabolising enzymes increases the likelihood of herb-drug interactions[96]. Another significant factor that seems to contribute to the safety of kava is how it is prepared. In Pacific Island cultures, traditional preparations are made using the peeled root of the plant to make water-based extracts, which have a great safety record in populations that have been using them for centuries. By contrast, the majority of liver toxicity case reports are associated with acetonic or ethanolic extracts, which are commonly found in Western herbal products[8,97]. This discrepancy could be due to more potential flavokavains being extracted by organic solvents than through water, or it may relate to mold toxins that contaminate improperly stored raw material[98]. There may be individual differences in people as well. Genetic differences in enzymes such as CYP2D6 can influence the rate at which someone metabolises kava compounds. Studies indicate that those who metabolise these compounds slowly (poor metabolisers) may develop higher levels of toxic constituents in their bodies, thereby giving them an increased risk for liver injury[99,100]. Several approaches can help minimise the risk of liver problems when using kava. In particular, water-based preparations are prepared from kava rhizomes and kava roots of noble cultivars, like those with organic solvent extracts that may pose greater safety concerns. Second, quality must be ensured so that good-quality raw material is used, free from adulterants and impurities, as well as potential mycotoxins such as

aflatoxins; also, one has to know the kavalactone content of the product. Third, individuals with underlying liver problems or individuals on other drugs that interfere with the liver should not use kava at all, because co-medication with synthetic drugs and other dietary supplements has been recognised as an important risk factor. Fourth, it's a good idea to restrict the duration of kava and avoid using very high doses, as both overdose and prolonged treatment have been linked with an increased risk. Lastly, kava should be avoided in combination with alcohol or other substances that modify the same liver enzymes (as comedication should be avoided with all potentially hepatotoxic substances in order to minimise damage[91].

8. Conclusion

Kava (Piper methysticum) exerts multi-target therapeutic effects with implications for chronic disease management. Kavalactones have neuroprotective effects through GABA modulation, ion channels blockade and anti-inflammatory pathways, with evidence supporting the clinical therapeutic efficacies in anxiety and cancer. When it involves cancer, flavokavains could have a multi-faceted mechanism that induces cell death (through modulation of Bax and Bcl-2), cell cycle arrest, anti-angiogenic impact or inhibiting the NF-κB pathway, whereas dihydromethysticin showed chemopreventive properties via Nrf2-mediated activation. Kava appears to target the underlying drivers of disease: chronic inflammation, oxidative stress, neurons that are consuming themselves in hyperactivity and cells too stubborn or cowardly to die when they should. That kind of multi-target action is exactly what researchers are increasingly seeking in modern drug development. However, hepatotoxicity concerns. particularly with the alcohol-based extracts from flavokavain B — are valid and illustrate why using traditionally prepared water-based extracts from noble kava cultivars is still the safer path. For kava to ever live up to its therapeutic promise responsibly, it will need rigorous, well-designed clinical trials and properly standardised extracts moving forward.

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10. References

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Author Contribution

Nidhi Singh: Writing- original draft, review, editing. Avijit Mazumder: Supervision, conceptualisation. Priyanka Bansal: Review, supervision and validation. All authors have read and agreed to the published version of the manuscript.