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Kava Kava: A Boon for Anxiety, Insomnia, and Depression

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D. Jha, I. Vidyarthi, N. Singh, A. Sharma*

Amity Institute of Pharmacy, Amity University Uttar Pradesh, sector 125, Noida, India

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ABSTRACT

Kava kava (*Piper methysticum)* a miraculous ancient herb has given a contemporary approach to medical science. It is native to pacific island but has demarcated world with its medicinal advent. The roots of the herb were earlier used in a drink for Sedative and tranquillizing effects and now with these properties, kava kava has found its place in the treatment of various neurological, psychological diseases like anxiety and depression. The roots of the herb were once used to make a drink that had sedative and tranquilizing effects. Now, with these capabilities, kava kava has found its place in the treatment of many neurological and psychological ailments like anxiety and depression. Kava, a beverage made from *Methysticum piper G. Forst*, promotes a pleasant mental state that makes people feel happy while easing fatigue and anxiety. Its analgesic, anti-inflammatory, anthelmintic, and anti-cancer activities are also demonstrated by the structure-activity relationship. The principal constituents of kava kava are divided into two main categories Kavalactones and Chalcones.

INTRODUCTION

Piper methysticum as Kava Kava which was traditionally served as psychedelic drink in their social assembly was native of Pacific Island. The purpose of the beverage was to serve as relaxant and to halt fatigue (1). The shrub with history of more than 2000 years even gained popularity in western part of the globe where the anxiolytic property of the shrub was used to treat anxiety and anxiety related disorders (2). The shrub gradually gained popularity until 2002 when the cases of toxicity started being reported the use of kava kava was curtailed in various countries (3). Among the adverse reactions were cognitive impairment, dermopathy (4), and hepatotoxicity, the most serious of which was hepatotoxicity **(Figure 1).**

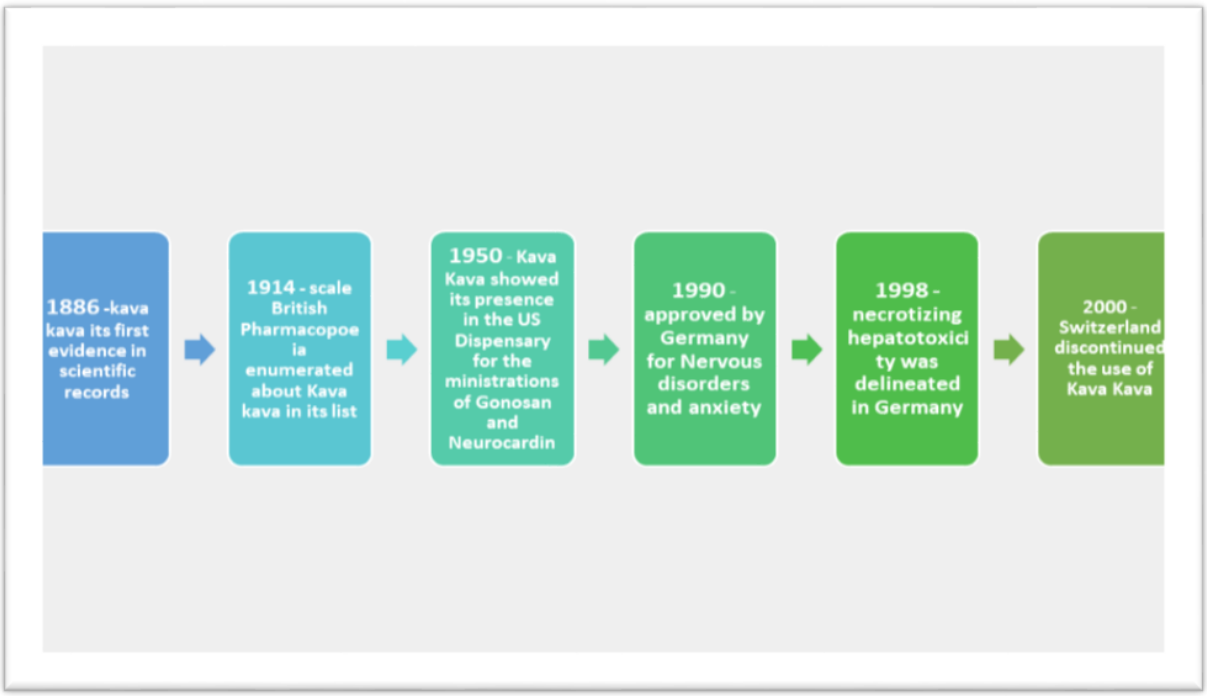


Figure 1: History of Kava Kava

Its first evidence in scientific records was in 1886, following the time scale British Pharmacopoeia enumerated about it in 1914 subsequently in the year 1950. The herb showed its presence in the US Dispensary for the ministrations of Gonosan and Neurocardin which stands for Gonorrhoea and Neurological disorders respectively, followed by approval in Germany in 1990 for nervous disorders and anxiety. As soon as Kava Kava came as boon also turned into ban after necrotizing hepatotoxicity was delineated in 1998 in Germany, where it was granted approval for treatment in 1990. Soon after 10 years in 2000 even Switzerland discontinued the use of Kava Kava because of a reported case of Liver

Transplant due to necrotizing hepatitis which was due to the use of Kava Kava (5). However, after cases of toxicity began to be reported in 2002, the use of kava kava was restricted in many countries.

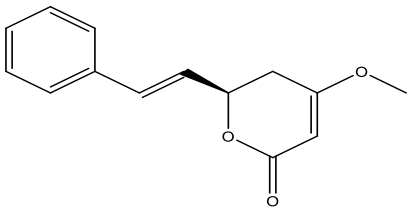
Kava Kava is taken for its sedative effects across the Polynesian civilizations of the Pacific Ocean, including those of Hawaii, Vanuatu, Melanesia, and the Philippines. It is also popular in several regions of Micronesia, especially Pohnpei and Kosrae. In addition to its anxiolytic and antidepressive effects, the roots of the herb were once used to make a drink that had sedative and tranquilizing effects. Its analgesic, anti-inflammatory, anthelmintic, and anti-cancer activities are also demonstrated by the structure-activity relationship. In addition to the medicinal benefits of kava kava, the main components are split into two groups: kavalactones and chalcones.

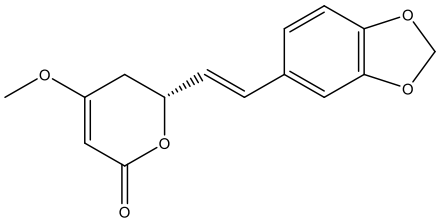
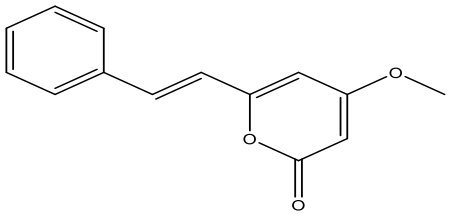
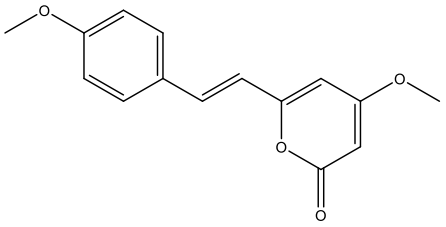
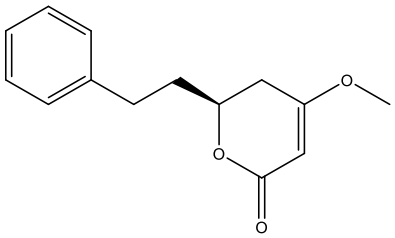
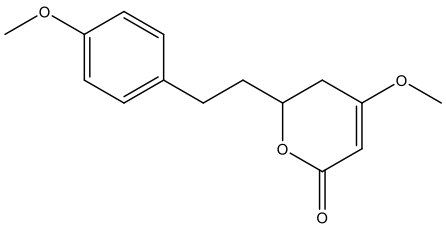
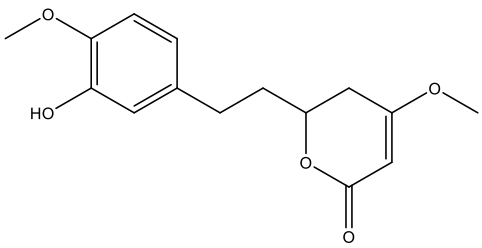
Principle Constituents of Kava Kava

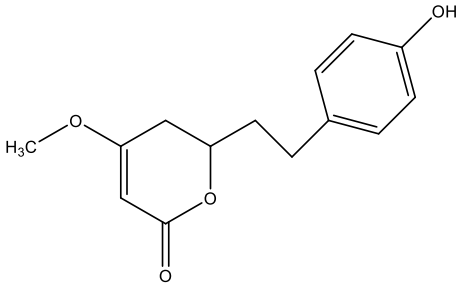
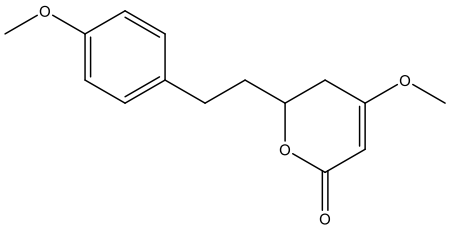
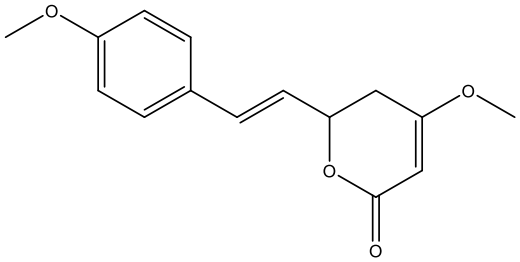
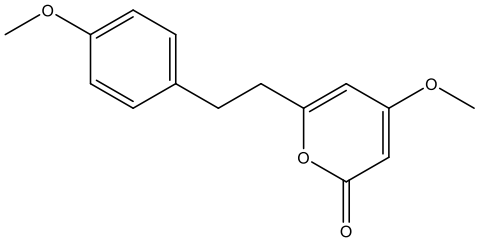
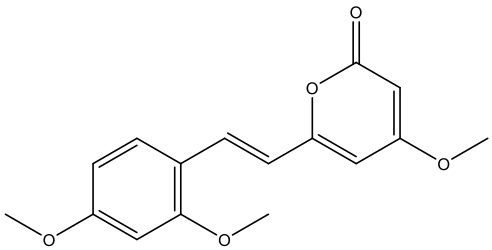
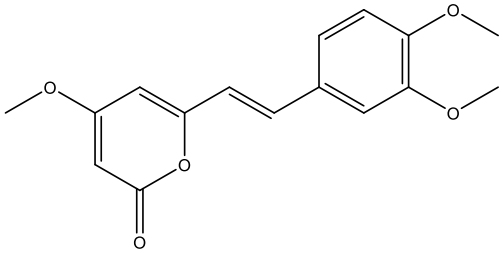
The Active constituents of Kava Kava is broadly classified into minor and major constituents which are mainly present in the rhizoids of *Piper methysticum*. The principal constituents that are present in kava kava are structurally related group of lactone derivatives and it contains a skeleton of aryl ethylene-alpha-pyrone. So, customarily they are 4- methoxy-2-pyrones with phenyl or styryl substituent, substituted at 6^{th} position which constitutes 3 to 20% ratio of the dried rhizome also these ratios may vary depending upon the plant cultivar.

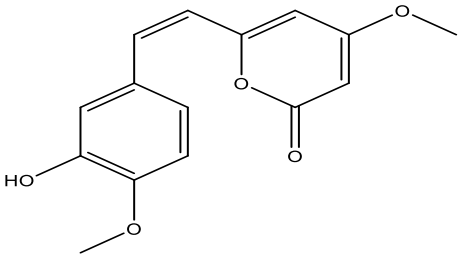
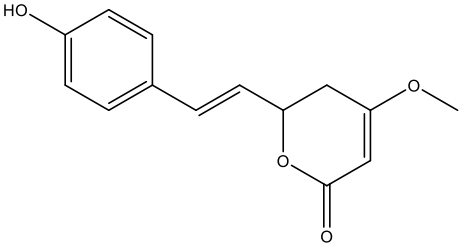
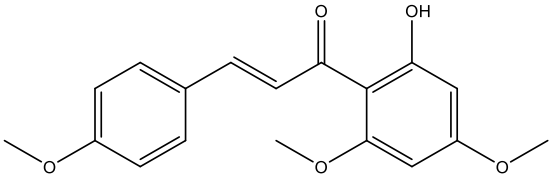
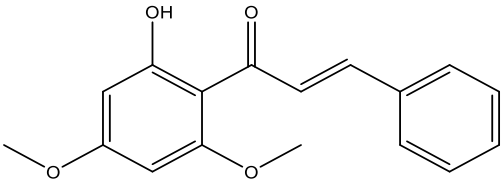
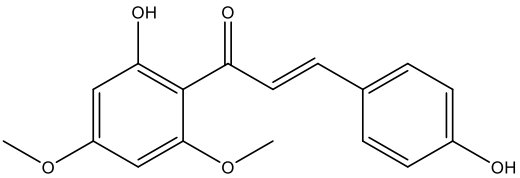
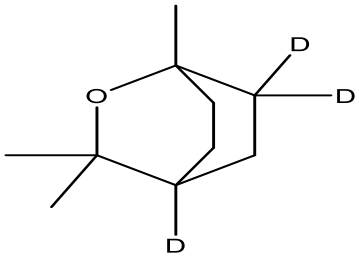
Taking a dig upon Kavalactones or kavapyrones are mixture of 18 or more different pyrones which are mainly found in the commercial acetone extracts which approximately contains around 70% active principles **(Table1**) (5)(6)(7).

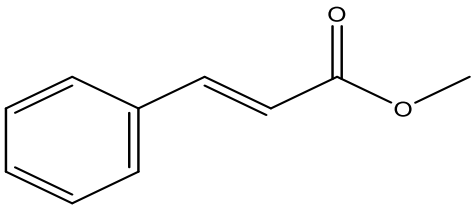
Table 1: Constituents Of Kava Kava

S.No.	Type of constituent	Name of the constituent	Structure
1.	Kava lactone	(+)-kavain	

		(+)-methysticin	
		desmethoxyyangonin	
		yangonin	
		(+)-dihydrokavain	
		tetrahydroyangonin	
		11- Hydroxy-12-methoxydihydrokavain	

		7,8-Dihydro-5-hydroxykavain	
		5,6,7,8 – Tetrahydroyangonin	
		5,6-Dihydroyangonin	
		7,8- Dihydroyangonin	
		10-Methoxyyangonin	
		11 – Methoxyyangonin	

		11 – Hydroxyyangonin	
		Hydroxykavain	
2.	Chalcones	Flavokavain A	
		Flavokavain B	
		Flavokavain C	
3.	Essential Oil	1,8-cineol	

		methyl cinnamate	

Structure Activity Relationship

Every sort of biological activity generated by chemical substances is covered by the idea of the Structure Activity Relationship, which is a key tenet in contemporary pharmacology.

To conduct relevant structure activity relationship studies, obtain meaningful results, and derive reasonable interpretation and rationalization, a realistic and informative description of molecular structure is a necessary precondition. It basically works by differentiating molecular structure and properties in the most practical form (8).

Till now various derivatives of Kava lactones and chalcones have been derived with various substituents. Kavalactones and Flavokavain possess a wide range of pharmacological effects due to the different synthetic and semi synthetic derivatives.

Kavalactones

Through various in vitro testings, it has been observed and concluded that kavalactone analogue apart from having anxiolytic and antidepressant properties, it is also effective against *Haemonchus contortus larvae* which even shows anthelmintic properties of Kava analogues (9). By the modifications at different positions of pendant aryl ring at 2,3 and 4th position two kava lactones namely Yangonin and desmethoxyyangonin and apart from this 17th other analogues were synthesized. The analogues with substitutions 4-difluoromethoxy, 4-tri-fluoromethoxy, 4-N-morpholine and 4-phenoxy showed anthelmintic activities greater than desmethoxyy. Angonin and Yangonin. (6)(10).

Kavain

Kavain analogues were synthesized through various chemical modifications which also highlighted the analgesic and anti-inflammatory activity of kavain among the various kavain analogues. Kava-241 and Kava-001(11) showed promising results on the one hand where Kava-001 exhibited more progressing analgesic activity than kavain whereas on other hand

Kava -241 showed convincing efficacy in the treatment of alveolar bone destruction and advanced periodontal inflammation **(Figure 2)** (2)(12)(6)(13).

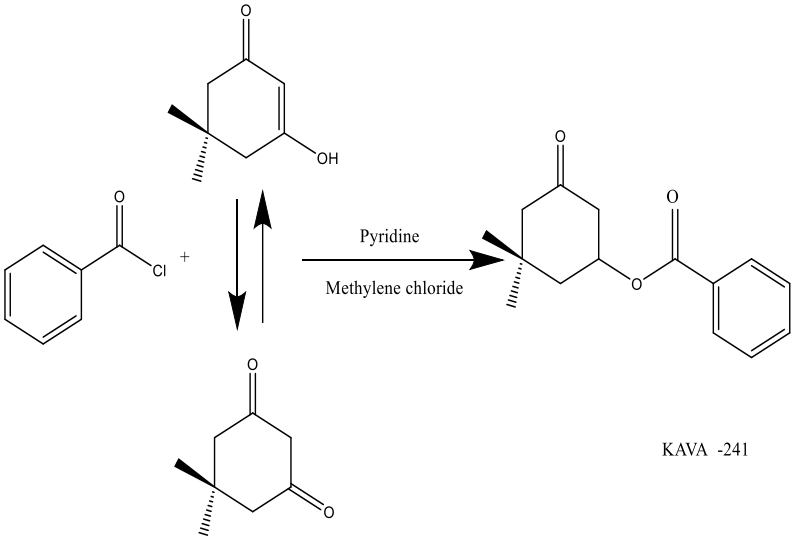


Figure 2: KAVA- 241

Flavokavain

Flavokavain is a kind of Chalcone which naturally occurs in plants in which study was done, on its α, β-unsaturated ketone due to its effortless synthesis, distinctive substituents manifoldness in biological activities and relatively simple chemistry (14).

Through certain structural changes in A and B ring of various flavokavain derivatives were synthesized with characteristic activities like Flavokavain derivatives due to presence of α, β-unsaturated ketone possesses anticancer properties. The change in cytotoxicity can be caused due to the influence of electron donating and electron withdrawing groups which ultimately effects α, β-unsaturated ketone **(Figure 3)** (6)(15)(16).

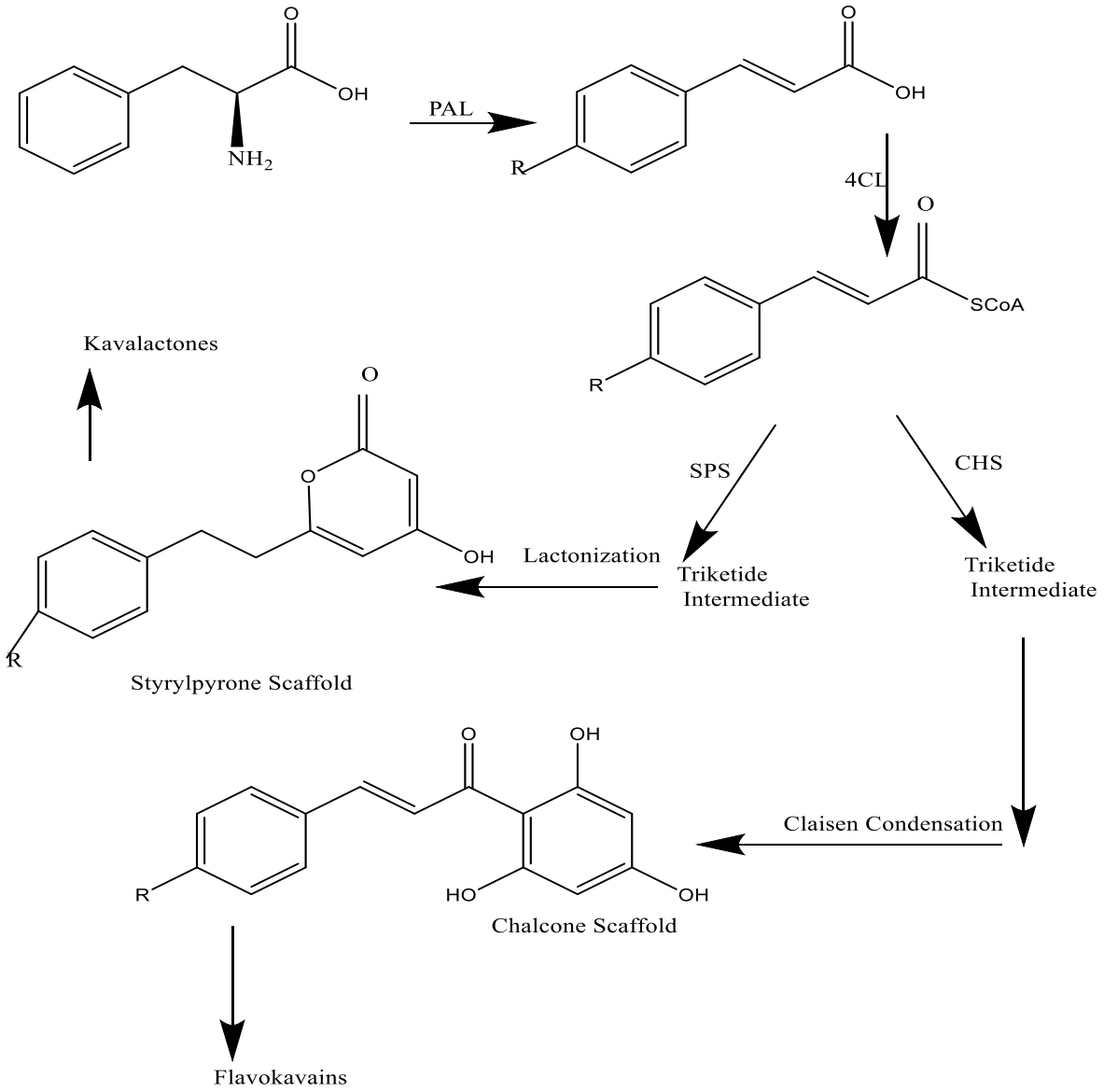


Figure 3: Synthesis of Flavokavain

Mechanism of Action

It blocks the sodium gated ion channel and promotes the binding of ligand with GABA (Gamma Amino Butyric Acid) receptor-A. This leads to the release of depreciated neurotransmitter due to blockage of calcium channel (17)(18). It also causes a decrease in neuronal reuptake of nor-adrenaline and inhibits monoamine oxidase B (reversible). It conquers the synthesis of eicosanoid thromboxane A, which acts as an antagonist of GABA-A receptor (18).

Kavalactone (lipophilic) is the one of the important constituents in kava kava which is responsible for anti-convulsant and muscle relaxant action (19). A study found that standard

extract of kava kava has a remarkable effect in the treatment of anxiety and other neurological disorders within a week. It has been found to have an improvising effect on cognitive performances and moods by using 300mg of kava kava (19).

It has been shown in studies that kava kava gives similar action as that of diazepam (like Valium), shows similar brain activity and reduces cognitive functioning of brain. It is also found to have improvising sleep for patients with sleeplessness disorder (Insomnia) (20).

South Pacific locals used to take kava infusion daily for the action of sedative, sleep and calming effects. The roots and rhizome of kava have been shown to have anti-inflammatory and anti-anxiety activity. Major constituents that are involved in it are kavalactones and flavokavins **(Table 2) (21).**

Table 2: Various Pharmacological Properties of Kava Kava

Pharmacological Activity	**Actions**
1- Anti-inflammatory	Periodontitis & Rheumatoid arthritis
2- Anti-anxiolytic	Induces relaxation and improves sleep quality.
3- Sedative Action	Counteract fatigue
4- Anti-cancer activity	Shows potential against colon, cervical, and lung cancers.
5- Analgesic	Provides significant pain relief.

It has been pharmacodynamically proven that kava have anti-inflammatory and analgesic effects. It is used in advanced periodontal inflammation and bone destruction in alveoli (13).

Kava-S001 is synthetically produced from kavain and has much greater analgesic effects.

As Anti-inflammatory

The effects of kavain, dihydrokavain (22) methysticin, and dihydromethysticin on TNF-synthesis in human acute monocytic leukaemia cells and on their reactivity to (lipopolysaccharide) LPS-induced mortality in laboratory mice were studied (6)(23)(24).

The most effective of these kavalactones, kavain, was able to inhibit LPS's induction of TNF- production. Additionally, Kavain shielded C57 mice from deadly LPS dosages (25).

Methysticin (6 mg/kg bodyweight) significantly decreased TNF- and IL-17A release in an Alzheimer's disease model while also easing symptoms of the disorder (26). In the mouse cortex and hippocampus, methylsticin was found to stimulate the Nrf2 pathway, inducing an antioxidant action to preserve cellular redox equilibrium.

A study which demonstrates that in neuronal PC-12 and astroglial C6 cells, methysticin, kava, and yangonin activated the Nrf2 pathway. In C57BL/6 mice, the impact of yangonin on the inflammatory condition known as hepatic cholestasis caused by estrogen was investigated. Through activation of the Farnesoid X receptor (FXR), yangonin therapy (20 mg/kg) has shown to decrease estrogen-induced cholestasis (24).

Desmethoxyyangonin (10 mg/kg) has additionally been shown to be an inhibitor of the inflammation caused by LPS in murine macrophages and LPS/D-galactosamine (LPS/D-GaIN)-induced liver disease in mice (27).

It has been discovered that flavokavains A and B (28) have immunomodulatory properties, including the promotion of splenocyte proliferation.

As Antianxiety and other neurological disorders:

All age groups of the general population are affected by anxiety disorders, which are among the most prevalent psychiatric conditions (29). Currently, pharmaceutical medications with antidepressant or anti-anxiety qualities are the predominant form of treatment. The negative effects of these drugs, however, are numerous and frequently severe, they include sedation, poor cognition, ataxia, hostility, dysfunctional sexual desire, tolerance, and dependence. Another important limiting aspect in the usage of these drugs is withdrawal symptoms after long-term dosing. At least in mild to severe cases of anxiety, herbal therapies, such as kava Kava (Piper methysticum), have been demonstrated to be beneficial as alternative treatments. South Pacific kava is a social and ceremonial herb. In the west, it is a readily available over-the-counter remedy (30)(31), Kava is mostly used to relieve tension and anxiety. According to research, kava may be used to alleviate the signs and symptoms of anxiety disorders (31). In a six-week randomized controlled experiment conducted in 2013, researchers offered 75 individuals with anxiety problems either kava extract or a placebo.

Kava kava's anxiolytic properties may make it easier to fall asleep. People also utilize it as an alternate therapy for sleep issues because of this (32).

Active constituents of kava which shows the pharmacological effects in human and animal population is kavalactones (33). CYP450 based biotransformation of more than 15 different kavalactones by liver. Few of the most important kavalactones are kavain, dihydrokavain, yongonin, methysticin and dihydromethysticin which majorly constitutes for more than 90% of extract obtained (34). Dihydrokavain is the one responsible for anxiolytic action (35).

Acetylcholinesterase (AchE) activity was found to rise after one week of kava treatment (75 mg/kg) in a research study, but it significantly decreased after four weeks of administration in the cortex, hippocampus, and striatum (36).

It has been found that kava extract and particular kavalactones suppress the intracellular calcium influxes that is caused by norepinephrine therapy in carcinoma cells in the lungs. Neurons in Hippocampal showed evidence of methysticin and kavain-induced sodium channel blockage (37). According to a different study, the therapeutic effects of the 5HT1A agonist ipsapirone in the hippocampus of guinea pigs may be improved by kavain and dihydromethysticin.

There were no safety issues connected to anxiolytic and antidepressant activity. It's been reported for sleep-improving and initiating effects, as well as a prolonged sleep time and sleep cycle function. The identical results have been reported in patients using 200 mg/day of kava for non-psychotic anxiety-related insomnia **(Figure 4) (**24).

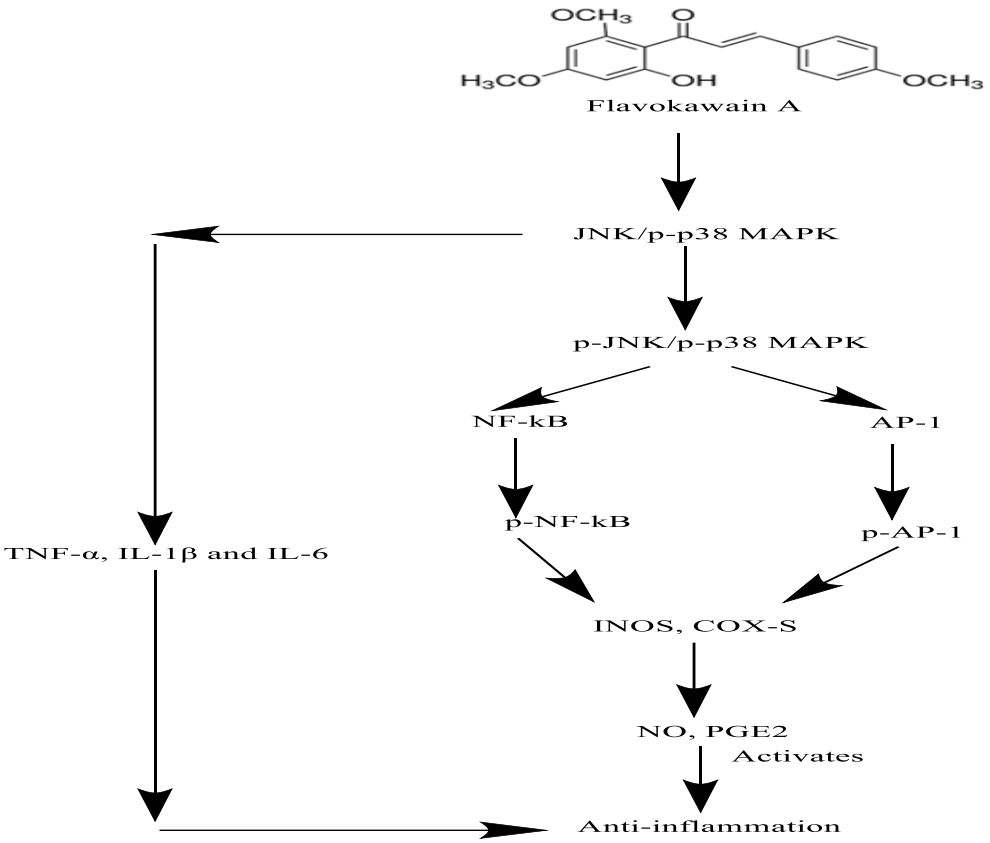


Figure 4: Mechanism of Action as Anti-inflammatory

Most of the studies committed to the usage of kava for insomnia is constrained to animal studies. It is assumed that a particular sort of kavalactone, known as kavain, might also additionally offer the drug's sedative effect. One small takes a look at from Germany concluded that human beings supplied a day by day 200-milligram kava extract skilled giant comfort from insomnia after 14 days. Despite the promising results, the conclusions had been undermined via way of means of the subjective nature of "pleasant of sleep" questionnaire (38)(39)(40).

Kava, a beverage made from *Methysticum piper G. Forst*, promotes a pleasant mental state that makes people feel happy while easing fatigue and anxiety. The study demonstrates that when compared to an aqueous extract, the majority of the pharmacological activity are retained from the lipid-soluble extract. At least seven pyrones, or "kavalactones," are included in the lipid-soluble extract. In general, kavalactones interact with dopaminergic, serotonergic, glutamatergic, and gamma aminobutyric acid (GABA) neurotransmissions. They also inhibit monoamine oxidase B (MOB) and have a variety of effects on ion channels. One of the six main kavalactones found in the kava plant is dihydromethysticin. Dihydromethysticin's

structure consists of an arylethylene-pyrone linked to an indole-like moiety with two oxygens rather than nitrogens. It functions as an antidepressant and aids in anxiolytic activity. Kavalactones have been shown in double-blind, placebo-controlled experiments to have anxiolytic effects that do not impair mental or motor performance while also enhancing sleep. Kavalactones are an alternative to benzodiazepines in the treatment of depression (41)(42).

Toxicity

Despite its mild and negligible side effects, it might show skin lessions (Kava Dermopathy), which is caused by its long-term continuous use and can be reversed by inhibiting its intake (43). There have been many cases of reporting liver toxicity in patients with kava administration.

Kava Kava upon oral administration might shows various side effects such as GI disturbance, headache, drowsiness, hepatitis, cirrhosis, liver failure and death (10)(43)(44). Its action can be worsened by using it along with other CNS depressants causing sedation.

The part primarily focuses on the safety data about kava with respect to human exposure with these difficulties in mind. The analysis of a few lab animal data from the preceding fifteen years aims to cross-inform plausible explanations for these toxicity risks (45).

Kava kava is causing liver damage, several cases have been reported in Europe. The actual root cause for kava kava causing liver damage has not been identified. Whether it is caused by any combination drugs or due to any underlying cause (46)(47).

Food and Drug Administration (FDA) has issued a consumer advisory in the month of March 2002, which includes kava kava causing rare but possibility to have a risk of liver damage (11)(48)(49)(50)(51).

Regarding kava's impact on the liver, not much is known about it. It is possible that the kava pills some individuals received were adulterated with additional drugs that affected the livers of these individuals. It is also likely that some individuals used kava while already having liver issues, or that they combined kava with other drugs or herbs that impacted their livers. It is also likely that different people react differently to the standard kava doses. Therefore, a dose that may be injurious to one individual might not harm the liver in another.

Kava may enhance the risk of adverse effects from phenothiazine drugs, such as chlorpromazine, an antihistamine, and promethazine, which is frequently prescribed for the management of schizophrenia (52)(53)(54).

Levodopa, a drug used in the treatment of Parkinson's disease, may become more ineffective when kava is used, as per at least one study (54). If a person having Parkinson's disease or are on any treatments that contain levodopa, should not use kava (55).

AVOID combining kava with alcohol. There is a substantial rise in the risk of dysfunction and liver damage. Benzodiazepines, such as alprazolam or Xanax, (55) which are utilised for treating anxiety or sleep problems, as well as barbiturates (such as pentobarbital), which are prescribed to treat seizures and sleep disorders, may also have an increased effect when taken with kava. Included in benzodiazepines are: Both alprazolam (Xanax) and diazepam (Valium) (29).

Benefits And Other Uses

The beverage is being ready through chewing or crushing the plant’s root and is utilized by the Polynesian natives in critical ceremonies and reunions. Currently, capsules, extracts and different merchandise containing kava are additionally available (42).

According to a few authors, kava is historically hired in numerous regions of the South Pacific as an “ice breaker” in marriages, welcoming ceremonies, and different critical events, due to its socializing and calming consequences. This can be as in comparison to using alcohol in western society, however with the principal distinction being that using kava is not always associated with violent acts in comparison to the intake of alcohol. Aside from its enjoyable consequences, kava has been utilized by local peoples of the South Pacific for numerous ailments, starting from venereal disorder to pores and skin infections (56). In outside programs it's far suggested to exert an antimycotic (stops the fungus from reproducing) impact at the pores and skin. Kava has been used efficaciously in Europe for decades for the remedy of numerous disorders, which include urinary tract infections, tension, menopause and as a muscular relaxant. In evaluation to the consequences of pharmaceutical pills with sedating action, kava is suggested to elicit relaxation, however with an alert and comfortable intellectual state. In numerous managed studies, kava has been declared powerful in decreasing tension without displaying a number of the bad aspect

consequences such as “hangover impact” and depressed cognitive characteristic manifested through a number of the traditional sedatives (57).

There is medical proof that kava can be of value, mainly with inside the remedy of non-psychotic tension and depression. Unfortunately, a few human beings have abused kava containing merchandise, using them for “leisure activities” now no longer always associated with the herb’s medicinal programs (58).

According to a preliminary investigation, a group consuming kava experienced a reduction in body fat and skinfold thickness. But there isn't enough proof to support the claim that kava helps lower cholesterol levels. Since kava helps to relax the muscles, it is very useful for bodybuilders. The root removes the symptoms of overwork and calms the muscles.

Some studies show that kava can help treat colds, coughs, flu and other respiratory infections. Drinking kava root tea can help in this regard.

Based on the studies, even human beings supplied a placebo had giant enhancements in sleep. Studies have observed that kava may also have preventative results on lung most cancers in mice (59). Other studies have additionally proven that kava would possibly have preventative results on prostate most cancers, colon most cancers, and urothelial mobileular most cancers (60). However, such consequences have best been discovered in animal studies, and greater studies is wanted to recognize the mechanism of motion and its results in humans.

Studies have shown that sage has the ability to treat bladder cancer. Despite being regular smokers, people living on the South Pacific islands where kava is grown have very low rates of cancer (61). According to Memorial Sloan Kettering Cancer Centre, Kava use has been associated with a reduced risk of cancer (62). Consult your doctor before using kava, as one of its components has been shown to promote melanoma cancer cells.

Conclusion

Kava Kava is undoubtedly an herb with multiple benefits to human population. It is a boon to nearly 30% of adult who are suffering from anxiety. 10-30% of population across globe which accounts roughly 50-70 million people suffering from insomnia and roughly 280 million people suffering from depression**.** Natives of Pacific Islands gave the plant Piper methysticum the name Kava Kava, which was traditionally provided as a hallucinogenic

drink in social gatherings with the aim of relieving stress and preventing weariness. The shrub, which has a history of more than 2000 years, even gained popularity in the western region of the world, where its calming effects were used to treat anxiety and disorders related to anxiety. However, after cases of toxicity began to be reported in 2002, the use of kava kava was banned in many countries. Among the adverse reactions were cognitive impairment, dermopathy, and hepatotoxicity, with hepatotoxicity being the most serious. The Kava's active Ingredients Kava is roughly divided into minor and major components, the majority of which are found in Piper methysticum's rhizoids (63). The main ingredients in kava kava are a structurally similar group of lactone derivatives having arylethylene-alpha-pyrone skeleton.

Additionally, it reduces nor-adrenaline's neuronal reuptake and temporarily inhibits monoamine oxidase B (64).

Structure activity studies state that it is not only acts as drug for neurological benefits but also has anticancer, anti-inflammatory, Anthelmintic properties too (65). Thus it can be concluded that the shrub is not only beneficial for neurology but to other domains of human body as well. Although its harsh drug interactions being a reason for worry hence a physician should always be consulted (66).

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Image **Author -1**	Author Name – Dr. Archana Sharma Author Affiliation-Amity Institute of Pharmacy, Amity university, Uttar Pradesh, Noida Author Address/Institute Address - Amity Institute of Pharmacy, Amity university, Uttar Pradesh, Noida
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