Medicon Medical Sciences
Volume 5 Issue 2 August 2023
Article Type: Research Article
ISSN: 2972-2721

Systemic Review of the Use of Kava Kava for the Reduction of Anxiety Disorder

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Received: June 21, 2023; **Published:** July 14, 2023

Abstract

Herbal medicine has been around since the start of humanity, but the advancement of modern medicine has pushed these ancient remedies to the side until recently. Recently, there has been a rise in the interest of herbal medicine and how it can be integrated with modern medicine. A prime example is Kava Kava which has been examined for its anti-anxiety properties. This systemic review aims to evaluate fourty-three current sources on the effectiveness of Kava Kava for Anxiety Disorder as well as its potential impact as a possible substitute for anxiety medicine if it is effective. Sources used in this review were gathered from four databases: Google Scholar, ScienceDirect, PubMed, and USF Library. The sources were then filtered through and selected using the PRIMSA method with the assist of Endnote, Rayyan, and manual evaluation. The general conclusion of the sources is that Kava Kava appears to be a decently effective short-term medication for generalized anxiety disorder. However, more studies will need to be conducted on its potential side effects and the mechanisms behind the herb.

Keywords: Kava Kava; Piper Methysticum; traditional medicine; anxiety; stress; menstrual disorderspain; muscle spasm; systemic review

Introduction

The aim of this systematic review is to collect current data on the impact of Kava Kava on generalized anxiety disorder (GAD) as a possible substitute for medication in terms of efficacy and safety. Generalized anxiety disorder is characterized as “excessive anxiety and worry about a variety of events… that occurs most days… for at least 6 months.” (National Institute of Mental Health, 2010).

According to the Anxiety and Depression Association of America, approximately 40 million adults in the US experience an anxiety disorder, yet only 36.9% are being treated. (*Facts & Statistics: Anxiety and Depression*) This can be due to a variety of factors such as cost, location, stigma, transportation, and etc. Therefore, if Kava Kava can prove to be a reasonable substitute, it could help limit those barriers for mental health resources.

Kava Kava, also known as Kava and Piper Methysticum, originates from the South Pacific and Oceania with an important cultural and historical significance as a ceremonial beverage (Bian et al., 2020)(Lebot et al., 2014). But, Kava Kava has also been used in traditional medicine to treat anxiety, stress, menstrual disorders, pain, and muscle spasms (Savage et al., 2015). Kavalactones, lactones found only in Kava, is hyposythenzied to be the cause behind the benefits of Kava Kava. (Bian et al., 2020) Two of the six kavalactones in kava kava, kawain and dihydrokavain, have an anxiety-reducing effect on the neurobiological activity of the limbic system, the behavioral and emotional part, in the brain. This, in turn, causes an enhanced relaxed state while maintaining cognition unlike other substances such as alcohol. (Savage et al., 2015).

There have been older studies that have indicated that Kava Kava can be useful for treatment in mild-to-moderate anxiety, but the conflication between the studies has led to instances such as the banning of Kava Kava in some European countries during the early 2000s due to 1999/2000 case reports of liver toxicity. (A;, 2015) Some countries, like Germany, are now retracting their ban on Kava Kava due to recent studies disproving this conclusion, but it could be hypothesized that the ban could have prevented research on the herb. As a result, as more research comes out to disprove Kava Kava's connection to liver toxicity, the herb can now be researched as a medical resource for people with GAD on a larger scale.

Methods and Materials

This systematic review was conducted following the PRISMA guidelines. The studies used in this review were gathered from four search databases: Google Scholar, USF Libraries, PubMed, and ScienceDirect. The articles were accessed on February 26th, 2023 using the following keywords: Kava Kava and anxiety, Kava, and Kava in the treatment of "anxiety disorders". This resulted in an initial result of 1780 articles. The obtained articles were then filtered through Endnote for duplicates. There were 379 duplicates identified in Endnote resulting in 1401 articles. The remaining articles were then transferred to Rayyan for manual assessment using specific criteria. Content criteria for inclusion was that the participants of the study had no history of substance abuse, the paper was a clinical study on the efficiency of Kava Kava and related herbs for GAD, or that the paper was a review on multiple results of Kava Kava use from previous trials. This resulted in the inclusion of forty-three articles in the systemic review. Figure one is a visual representation of the PRISMA method used to select the included articles.

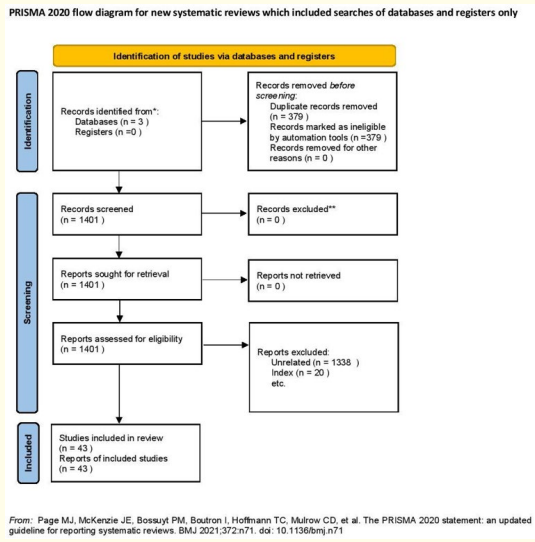


Figure 1

Results

This section of the review will be giving further information on how the studies included were assessed for eligibility, a summary on the kinds of articles that were included in this study, shared characteristics of the included studies, the frequency of adverse to positive effects of Kava Kava on the human body, possible ways to use Kava Kava, and how the articles either combat or support previous conclusions of the efficiency and/or harm caused by Kava Kava.

Further information on included articles

As stated earlier, there was an initial count of 1780 articles that were obtained from four search engine databases: Google Scholar, USF Libraries, PubMed, and ScienceDirect. After the initial gathering, the exclusion process began. The first exclusion criteria was duplicated articles, or articles with a similarity rate equal to or more than ninety percent. This eliminated three hundred and seventy-nine articles before the screening process. This resulted in 1401 articles that were then screened using more specific exclusion criteria. Articles that were mostly unrelated to the topic of the use of Kava Kava for GAD, Articles that were indexed, and/or outdated by three and a half decades or more. Furthermore, articles that did not meet the measures for inclusion were also excluded. These measures are that the participants of the study had no history of substance abuse, the paper was a clinical study on the efficiency of Kava Kava and related herbs for GAD, or that the paper was a review on multiple results of Kava Kava use from previous trials. Both the exclusion and inclusion criteria can be reviewed below in Table 1. This ended up with only forty-three articles being eligible for inclusion in this systematic review. However, articles needed for background information, or reference to previous beliefs and notations about Kava Kava will be used in the article sparsely as a reference point.

Inclusion Criteria	*Exclusion Criteria*
Study participants had no recorded history of substance abuse A clinical study on the efficiency of Kava Kava on General Anxiety Disorder Systematic/Literature Review of Kava Kava Use from previous articles and studies	Duplicates Outdated by 35+ yrs. Unrelated to the Topic Indexes

Table 1

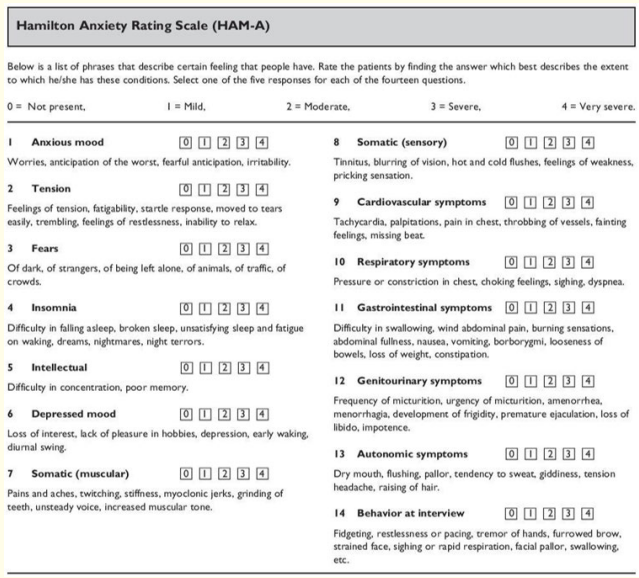
Brief Summary of the Articles Included

There are three different types of articles included in this review. A systematic/meta-analysis reviews of human trials conducted on the efficiency/safety of kava kava for generalized anxiety disorder, systematic/meta-analysis reviews of animal trials conducted on the efficiency/safety of kava kava's anxiolytic properties. Articles reported trials on kava kava to examine its effects on generalized anxiety disorder were studied..

Shared Characteristics of the Included Studies

In many of the systemic reviews and meta-analysis studies, the Hamilton Anxiety Rating Scale (HAM-A) is used to analyze the efficiency of Kava Kava (Piper methysticum) for anxiety treatment in people. The HAM-A scale is a fourteen question rating system developed to measure the symptoms of anxiety neurosis, but it has been used in clinical trials to measure the intensity of anxiety symptoms in participants. (HAMILTON, 1959) (*Hamilton Anxiety Rating Scale (HAM-A)*, n.d.) For reference, there are four possible results from the questionnaire: no/minimal, mild, moderate, and severe anxiety. The score range for mild anxiety is a seven or lower. The range for mild anxiety is an eight to an fourteen, and the range for moderate is a fifteen to twenty-three. Lastly, any score equal to, or higher than, a twenty-four is considered severe anxiety. (Matza et al., 2010) Figure two is an example of the Hamilton Anxiety Rating Scale.

Furthermore, all of the articles also either analyze, or conduct a randomly controlled trial on the effect of Piper methysticum on Generalized Anxiety Disorder. Additionally, these studies also include a comparison to a placebo group to compare the results of the Kava Kava to ensure the validity of the results. This adds to the validity of the included studies as well as decreasing the potential risk of bias when it comes to the reporting of the results.



Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present. 1 = Mild. 2 = Moderate. 3 = Severe. 4 = Very severe.

1 **Anxious mood** [0] [1] [2] [3] [4]
Worries, anticipation of the worst, fearful anticipation, irritability.

2 **Tension** [0] [1] [2] [3] [4]
Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3 **Fears** [0] [1] [2] [3] [4]
Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4 **Insomnia** [0] [1] [2] [3] [4]
Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5 **Intellectual** [0] [1] [2] [3] [4]
Difficulty in concentration, poor memory.

6 **Depressed mood** [0] [1] [2] [3] [4]
Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7 **Somatic (muscular)** [0] [1] [2] [3] [4]
Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8 **Somatic (sensory)** [0] [1] [2] [3] [4]
Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9 **Cardiovascular symptoms** [0] [1] [2] [3] [4]
Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10 **Respiratory symptoms** [0] [1] [2] [3] [4]
Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11 **Gastrointestinal symptoms** [0] [1] [2] [3] [4]
Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12 **Genitourinary symptoms** [0] [1] [2] [3] [4]
Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

13 **Autonomic symptoms** [0] [1] [2] [3] [4]
Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14 **Behavior at interview** [0] [1] [2] [3] [4]
Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

Figure 2: (Hamilton Anxiety Rating Scale (HAM-A), n.d.).

Reported Effects of Kava Kava

The Biochemical mechanisms Behind Kava Kava's Antioxlytic Ability.

In animal studies, it was found that when Piper methysticum was extracted to be prepared into tablets, there were two parts to the Kava Kava (*Comparison of the Central Nervous System Activity of the Aqueous and Lipid Extract of Kava (Piper Methysticum*) - PubMed, 1989). There was a water-soluble part and a lipid-soluble part, however the water-soluble part appeared to not have an anxiolytic effect on the mice (*Comparison of the Central Nervous System Activity of the Aqueous and Lipid Extract of Kava (Piper Methysticum)* - PubMed, 1989). However, the lipid-soluble part of the Kava Kava that did have an effect on the mice contained six kavalactones: kawain, dihydrokavain, methysticin, dihydromethysticin, desmethoxyyangonin and yangonin (*Comparison of the Central Nervous System Activity of the Aqueous and Lipid Extract of Kava (Piper Methysticum) - PubMed, 1989) (UNODC - Bulletin on Narcotics - 1973 Issue 2 - 007*, n.d.).

The six kavalactones appear to target the following molecular targets: GABAA R receptors, voltage-dependent Sodium and Calcium channels within the body, opioid receptors, dopamine type 2 receptors, histamine type 1 and 2 receptors, cannabinoid type 1 receptors, and monoamine oxidase type B (Chua et al., 2016)(Cairney et al., 2002).

GABAA R receptors are major inhibitory receptors that are used to facilitate fast inhibition in the basal ganglia system (Goetz et al., n.d.). The basal ganglia system plays a role in the body's decision making processes as well as its chemical reward system which is also why the basal ganglia can have a role in mental illnesses like addiction and anxiety (n.d.). This is relevant because during trial study, it was found that kavain enhances the inhibitory functions of GABAA Rs(Chua et al., 2016).

Furthermore, in animal trials with mice and frogs, it was determined that Piper Methysticum's ability to block voltage dependent sodium and calcium channels explains its use as a muscle relaxant and its similar effects to local anesthetics (*Effects of Kava on Neuromuscular Transmission and Muscle Contractility, 2002)((+/-)-Kavain Inhibits Veratridine-activated Voltage-dependent Na(+)-channels in Synaptosomes Prepared From Rat Cerebral Cortex - PubMed, 1995*).

Opioid receptors are a part of the opioid system which can be found throughout the entire brain (MERRER et al., n.d.). The opioid system plays a role in decision making especially when it concerns pain, pleasure, and the brain's reward system (Steenbergen et al., 2019). It has been observed during animal trials that high doses of kava kava binds to the opioid receptors in the brain that are similar to the binding sites of other anxiolytics without affecting cognitive function (*Kavalactones and Dihydrokavain Modulate GABAergic Activity in a Rat Gastric-brainstem Preparation - PubMed, 2002*). This can also provide evidence that kava kava may have some pain-relieving properties from a biochemical perspective (*A Brief Report of Student Research: Mechanism of Analgesic Effect and Efficacy and Anesthesia Interactions of Kava in the Male Sprague-Dawley Rat - PubMed, 2009*).

In animal trials with mice, it was found that Kava had an significant effect on the activity of monoamine oxidase type B (MAO-B) in the cortex and substantia nigra of the brain (Krum et al., 2022). Increased concentrations of Piper methysticum from 30 to 100 micrograms had caused a significant decrease in mono oxidase type B activity in the aforementioned areas of the brain (Krum et al., 2022). This inhibition is mostly caused by three kavalactones: yangonin, kavain, and desmethoxyyangonin (Krum et al., 2022)(Prinsloo et al., 2019)(Mathew et al., n.d.).

From a anatomical perspective during animal trials, kavalactones appear to be most present in the limbic structures like the hippocampus, amygdala complex, and the caudate nucleus (Cairney et al., 2002) (Jussofie et al., 1994)([*the Action Profile of D,L-kavain. Cerebral Sites and Sleep-wakefulness-rhythm in Animals] - PubMed, 1991*).

During the trials, the kavalactones had a sedative effect on the limbic structure areas due to the fact that it increases the likelihood of the binding of muscimol to GABAA receptors (Jussofie et al., 1994). This, once again, is similar to the mechanisms that occur in anesthetic steroids(Jussofie et al., 1994).The limbic structures control the fear and 'fight or flight' emotional responses in the body (Rajmohan & Mohandas, n.d.). The fear response of the limbic structure is due to the activation of the hippocampus and the amygdala complex therefore the sedation of the amygdala leads to the reduction of fear and its effect on the endocrine system (Rajmohan & Mohandas, n.d.). Furthermore, kava kava appears to have no effect on the learning and memory abilities of the hippocampus despite its influence on its behavioral aspects (*The Influence of (+/-)-kavain on Population Spikes and Long-term Potentiation in Guinea Pig Hippocampal Slices - PubMed, 1998*).

The Comparison of Kava Kava to a Placebo

Multiple systematic reviews and meta-analysis studies confirm that Kava Kava has a more significant effect on anxiety than a placebo (Savage et al., 2017) (Bilia et al., 2002). One meta-analysis analyzed the trial done by Malsh in 2001, (Malsch & Kieser, 2001), that showed there was a greater reduction in anxiety with Kava Kava than the placebo (Barić et al., 2018). Three other studies in the meta-analysis also indicated a difference between the placebo and various kava kava concentrations, but there was a lot of variation between the studies' results. Therefore, the review study concluded that due to the inconsistencies with the comparison through numerous studies, it was recognized that although Kava Kava clearly has an impact on anxiety but further research would have to be done. (Barić et al., 2018)

However, the original study done by Malsh tested the efficiency of a special extract that contained 70% of kava-lactones after the use of benzodiazepines, anti-anxiety medication, to see if it could assist in withdrawing patients off of benzodiazepines (Malsch & Kieser, 2001). The original study stated that compared to the placebo group, the extract group appeared to have less withdrawal symptoms and continued to have decreased HAM-A scores unlike the placebo group (Malsch & Kieser, 2001).

Additionally, in another study performed by Sarris, also concluded that kava kava proved to be superior to a placebo, and could be a moderately effective short-term medication for moderate-to-severe GAD (Sarris et al., 2013). In this study, they made tablets from kava extract that were sixty milligrams a piece, and instructed the participants to take twice a day for three weeks, and then switched to two hundred and forty milligrams for another three weeks (Sarris et al., 2013). Although, kava kava appeared to have more of an anxiolytic effect with those that had moderate to severe anxiety, only 37% of the tested participants indicated a response. This is higher

than the placebo which had a 23% response rate. But, the author connects this to the difficulty of treating generalized anxiety disorder, but acknowledges that universal safety and efficiency can not be guaranteed (Sarris et al., 2013).

Possible Side Effects of Kava Kava

In animal trials using mice, it was observed the kava kava was a safe dosage up to two thousand milligrams per kilogram for oral consumption (*Acute Oral Toxicity, Antinociceptive and Antimicrobial Activities of Kava Dried Extracts and Synthetic Kavain, 2022*). Therefore, by definition, this indicates that Piper methysticum is considered a safe/class five by the Globally Harmonised System as an oral drug (*Acute Oral Toxicity, Antinociceptive and Antimicrobial Activities of Kava Dried Extracts and Synthetic Kavain, 2022*)(United Nations, 2018). There were no observed changes in the weight of the mice (*Acute Oral Toxicity, Antinociceptive and Antimicrobial Activities of Kava Dried Extracts and Synthetic Kavain, 2022*). Additionally, the authors found that there were also no observed changes to the kidney or liver of the mice, similar to the results of previous studies (*Acute Oral Toxicity, Antinociceptive and Antimicrobial Activities of Kava Dried Extracts and Synthetic Kavain, 2022*)(Singh & Devkota, 2003) (*Chemical and in Vitro Toxicity Analysis of a Supercritical Fluid Extract of Kava Kava (Piper Methysticum)*, 2019)(Lim et al., 2007).

In a systemic review of eight placebo-controlled trials and one trial comparing kava kava and conventional antioxyltics, six of the nine trials found that kava kava produced the following side effects: Postopertative hangover, tiredness, low energy headache, gastrointestinal symptoms, restlessness, and tremor (Stevinson et al., 2002). However, many of these effects such the restlessness, tiredness, tremor, gastrointestinal symptoms, and postoperative hangover were also observed in the placebo/control group of the trials (Stevinson et al., 2002). Therefore, it can be inferred that while these symptoms may be caused by kava kava, there may also be outside influences that could have caused these reactions.

In the same review, there were also case reports of dermatological reactions, neurological manifestations, liver damage, myoglobinuria, and herb-drug interactions (Stevinson et al., 2002).

All of the dermatological reactions appear to be allergic reactions to kava kava as all of them were resolved with the discontinuation of the drug, and the use of antihistamines and corticosteroids such as prednisone (Stevinson et al., 2002)(*Sebotropic Drug Reaction Resulting From Kava-kava Extract Therapy: A New Entity? - PubMed, 1998*). Furthermore, positive patch testing on the subjects further indicates that it was an allergic reaction to the kava kava extracts (Stevinson et al., 2002)(*Dermatomyositis-like Illness Following Kava-kava Ingestion - PubMed, 1999)(Delayed-type Hypersensitivity Reaction to Kava-kava Extract - PubMed, 2000*)([*Hematogenous Contact Eczema Cause by Phytogenic Drugs Exemplified by Kava Root Extract] - PubMed, 1996*).

There are also four case reports of neurological manifestations reported in the systemic review (Stevinson et al., 2002)(*Kava and Dopamine Antagonism - PubMed, 1995*). This included involuntary movements hours within oral consumption such as: neck extension and twisting, oral and lingual dyskinesias, and various other forms of dyskinesias (Stevinson et al., 2002))(*Kava and Dopamine Antagonism - PubMed, 1995*). Therefore, there is the possibility that one could experience neurological manifestations after orally taking kava kava.

In the case reports concerning liver damage, all subjects except for one were taking medications with hepatoxic potential concurrently with kava kava, and/or consuming alcohol, or taking an alcoholic extract of kavalactones (Stevinson et al., 2002). These cases, except for the one case, were resolved with discontinuation of all medications including kava kava (Stevinson et al., 2002). The one case that was directly related to the high consumption of kava kava, 300 to 400mg daily, resulted in the subject having to receive a liver transplant (*Hepatitis Associated With Kava, a Herbal Remedy for Anxiety - PubMed, 2001*)(Stevinson et al., 2002).

Lastly, the two case reports of herb-drug interaction and mylogamia both appear to be a result of possible interaction between kava kava and other herbs/drugs that resulted in the hospitalization of the subjects (Stevinson et al., 2002). It is suspected for the herb-drug interaction that there was a negative interaction between the kava extract and a benzaopine taken by the patient (*Coma From the Health Food Store: Interaction Between Kava and Alprazolam - PubMed, 1996*) (Stevinson et al., 2002). For the mylogamia, it is also sus-

pected that there was a negative effect due to the patient taking both guarana and kava kava which both have muscle relaxing effects (Stevinson et al., 2002)(Myoglobinuria After Ingestion of Extracts of Guarana, Ginkgo Biloba and Kava - PubMed, 2000).

Hepatotoxicity and Kava Kava Usage

One study acknowledges that Kava Kava was typically viewed as a safe herb until 2002 (Boon & Wong, n.d.). However, due to twenty-five case reports of serious liver damage in Germany, Switzerland, and the United States of America (Boon & Wong, n.d.) many countries including Canada banned Kava Kava. Canada, as an example, warned against the use of Kava Kava for individuals at risk like those with histories of substance abuse and liver damage (Canada, n.d.). However, the study mentions the several criticisms against the evidence provided for the hepatotoxicity of Kava Kava including the unreliability of case reports, the period of time (typically 2-3 months) between the kava kava usage and the diagnosis, and lastly the difference between the cases compared to the reaction of trial participants who did not experience those side effects (Boon & Wong, n.d.).

Looking further into the criticisms, the original study against the evidence for hepatotoxicity explains that kava hepatotoxicity was not observed when the drink was consumed in the South Pacific for the past few centuries, during the pre-trials before the drink was put onto the market, and that most cases where kava hepatotoxicity was observed, the patient typically had an underlying liver disease and/or issue (Teschke et al., 2003). Additionally, in reference to the nineteen German case reports, only one case seemed directly connected to kava kava with sufficient evidence such as increasing transaminase activity (Teschke et al., 2003). Elevated transaminase activity is associated with both non-alcoholic and fatty liver disease as well as drug-induced liver disease and possibly hepatitis (*Mildly Elevated Liver Transaminase Levels: Causes and Evaluation - PubMed, 2017*). However, it was later found that the patient had many other factors that could have affected this diagnosis such as treatment with medication known to potentially cause hepatotoxicity. The patient had also been known to use St John's Wort which may have caused an enzyme reaction in the liver when they also started to use Kava Kava as well (Teschke et al., 2003).

Overall, the current evidence presented for hepatotoxicity lacks a clear cause and effect relationship to kava kava (Xing et al., 2013). Therefore, it can be concluded that kava kava does not cause liver damage when used in its traditional sense or as a solution in water (*Assessment of the Risk of Hepatotoxicity With Kava Products*, n.d.).

Conclusions

It has been recognized that Kava Kava has great potential as a anti-anxiolytic drug, however there are very few studies comparing the efficiency of kava kava to benzodiazepines and antidepressants (Sarris, 2018). This would greatly improve the reliability of kava kava with both the medical industry and the general public due to the ability to further understand the differences between the two from a biological level. An example of possible further research would be to compare the different mechanisms and pathways the drugs use to reduce anxiety, the side effects of the drugs, and human trials with benzodiazepines, kava kava, and a placebo with the HAM-A scores.

Furthermore, it would be beneficial in the future to require patch testing and an evaluation of the subject's medical history prior to the use of kava kava in patients to reduce the chance of side effects due to herb-drug interactions and allergies. This is because this seems to be a recurring issue in the use of kava kava clinically which could lead to people fearing the herb despite the lack of evidence supporting severe side effects.

Additionally, it would also be beneficial as kava kava becomes more popular in society as an alternative medicine option. Even if it is not used in the medical industry, it should have released guidelines for proper consumption as well as transparency of the possible side effects to limit misuse within the general public due to lack of information.

Conflicts of Interest

All authors declare that they have no conflicts of interest to disclose.

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