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# COMPLIMENTARY AND ALTERNATIVE MEDICINE: A SYSTEMATIC REVIEW OF THE EFFECTS OF KAVA ON ANXIETY

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# CHAPTER 1 INTRODUCTION

Many adults world-wide are afflicted by various anxiety disorders and currently there is a lack of emphasis on nonpharmacological interventions offered to help alleviate symptoms associated with their anxiety disorder. According to the Anxiety and Depression Association of America (2016), 40 million American adults are affected by an anxiety disorder, however only about one-third of those suffering receive treatment even though anxiety disorders are highly treatable. Anxiety disorders are the most common and pervasive mental illness in the United States, affecting multiple aspects of life, including daily activities, work performance, and relationships (Anxiety and Depression Association of America, 2016). The symptoms of nervousness, restlessness, sense of impending danger, increased heart rate, fatigue, difficulty concentrating, social isolation all interfere with daily activities, are difficult to control, are out of proportion to the actual danger and can last a long time (Anxiety and Depression Association of America, 2016). Many people being treated for an anxiety disorders are currently prescribed various medications; however, many of the prescribed medication have serious side effects. It is necessary that alternative, personalized forms of treatment and complementary forms of medicine are explored as part of the treatment plan for individuals.

Researchers have reported that one in six Americans take some kind of psychiatric drug during their lifetime and over eighty percent of these people are taking a psychiatric drug for long-term use (Moore & Mattison, 2017). The most common forms of treatment include medications combined with a variation of therapy. Current methods to treat anxiety disorders include benzodiazepines and antidepressants, however these medications produce severe side effects. Side effects include tolerance, dependence, and withdraw, central nervous system depression, drowsiness, dizziness, nausea, headache, fatigue, nightmares, hypotension,

paradoxical reactions, confusion, ataxia, reduced sexual functioning, insomnia, and weight gain/loss (Vallerand, Sanoski, Deglin, & Mansell, 2015). Considering the adverse effects associated with anxiety medications, other methods to treat anxiety that are not associated with as many side effects should be explored before resorting to medicating a patient.

There are a variety of alternative forms of therapy that can be used to help treat symptoms associated with anxiety disorders that can be personalized to fit the needs of the individual. Some nonpharmacological methods to treat anxiety include life style modifications, psychotherapy, mindfulness, aromatherapy, exercise, and the use of herbals (Kessler et al., 2001). Typically, the use of herbals are not a first line measure to treat anxiety, however previous studies have shown various herbals reduce anxiety in adults diagnosed with an anxiety disorder (Ernst, 2006; Lakhan & Vieira, 2010). Kava root, piper Methysticum, an herbal supplement native to the South Pacific islands, has been used for thousands of years by natives for various purposes (Musser, 2005). In westernized cultures, kava is used as a dietary supplement for anxiety, insomnia, restlessness, stress, muscle spasms and pain (Musser, 2005). In the 1990s and early 2000s multiple countries in Europe imposed bans on the herb based on reports of liver toxicity, however in recent years bans have been lifted and laws have been rewritten as the reports of liver toxicity have contradictory (Kuchta, Schmidt, & Nahrstedt, 2015). Acting on various receptors in the brain, kava inhibits the reuptake of norepinephrine and binds on the Cannabinoid-1 receptor which is reported to have a calming effect (Musser, 2005). This calming effect has the potential to reduce anxiety symptoms associated with anxiety disorders. Kava is not recommended to be taken in conjunction with other psychiatric medications considering studies have indicated increased central nervous system depressant effects when kava and psychiatric medications are combined (Biloba, 1999).

There is a crucial need to understand the effects of this herbal supplement on anxiety disorders as popularity grows in the United States and beyond as bans are lifted in multiple countries and reports of liver toxicity are discredited. The purpose of this thesis is to conduct a systematic review of the literature published since 2000 on the impacts of kava on people diagnosed with an anxiety disorder. By reviewing literature, recommendations can be made regarding patient education, health care practices, and future research.

Definitions

| | |
|---|---|
| Anxiety Disorders | Disorders that exhibit excessive fear and anxiety and related behavioral disturbances. Examples include generalized anxiety disorder, panic disorder, and social anxiety disorder (American Psychiatric Association, 2013) |
| Kava | The dried rhizome and roots of the kava plant used as a dietary supplement chiefly to relieve stress and anxiety (Musser, 2005) |
| Herbal supplement | A supplement to the diet intended to be taken by mouth in various forms and contains one or more dietary ingredients or their constituents and is labeled as a dietary supplement (National Center for Complementary and Integrative Health, 2018) |
| Alternative therapy | Various systems of healing or treating disease, such as chiropractic, homeopathy, or faith healing, not included in the traditional medical practice (National Center for Complementary and Integrative Health, 2016) |
| Complimentary Therapy | A group of diagnostic and therapeutic disciplines that are used together with conventional medicine (National Center for Complementary and Integrative Health, 2016) |
| Integrative Medicine | Healing-oriented practice that takes account of the whole person, including all aspects of lifestyle, to determine best course of treatment (National Center for Complementary and Integrative Health, 2016) |
| Over-the-counter | Medications or related products that can be purchased by the public through ordinary retail, with no need for a prescription or license (U.S. Food and Drug Administration, 2018) |
| Prescription | An instruction written by a medical practitioner that authorizes a patient to be provided a medicine or treatment (U.S. Food and Drug Administration, 2017) |

# CHAPTER 2 LITERATURE REVIEW

## Anxiety Background

Anxiety disorders are the most prevalent mental disorders and are closely tied to other health complications, high health care costs, and high burden (Anxiety and Depression Association of America, 2016). Over one third of the American population is reported to have been affected by an anxiety disorder at least once during their life time (Kessler et al., 1994). The prevalence of anxiety disorders is rising, and first line treatment typically includes medication and therapy. Anxiety affects all aspects of life, including mental and physical health, family life, careers, and social life.

While anxiety is a normal part of life, chronic anxiety can greatly impact one's quality of life. Short term anxiety consists of increased breathing and heart rate, increasing blood flow to the brain, feelings of apprehension or dread, restlessness or irritability, excessive sweating, tremors and twitches, headache, fatigue and weakness, insomnia, and nausea (The National Institute of Mental Health, 2017). Those who are chronically anxious must meet certain criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) to be diagnosed with an anxiety disorder (Anxiety and Depression Association of America, 2016). According to the DSM-5, anxiety disorders consist of disorders that share characteristics of excessive fear, anxiety, and related behavioral disturbances (American Psychiatric Association, 2013). Anxiety disorders include generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder (Anxiety and Depression Association of America, 2016). An excessive or persistent state of these anxiety symptoms have a devastating effect on physical and mental health. Anxiety is linked to developing a weakened immune system, chronic respiratory disease, irritable bowel syndrome,

loss of appetite, lack of interest in sexual activity, and other mental health problems, such as depression (The National Institute of Mental Health, 2017). Chronic anxiety also increases the risk of developing diabetes, high blood pressure and cardiovascular disorders (The National Institute of Mental Health, 2017). Various types of treatment are offered to help reduce symptoms associate with this extremely prevalent mental health condition.

## Treatments of Anxiety

The two major types of treatment for anxiety disorders include pharmacological and non-pharmacological interventions, or a combination of the two. Often these treatments are used in conjunction with alternative treatments including exercise, breathing techniques, and diet alterations.

### Non-Pharmacological Interventions

Behavioral and cognitive psychotherapies are the most commonly used non-pharmacological interventions for treatment of anxiety disorders (Deacon & Abramowitz, 2004). Cognitive behavioral therapy (CBT), a type of psychotherapy, has been shown to be effective in treating anxiety related disorders (Bystritsky, Khalsa, Cameron, & Schiffman, 2013). CBT includes various skills and techniques to identify and replace negative thinking patterns and behaviors with positive ones (Bystritsky et al., 2013). For many patients, one drawback of CBT is that benefits are usually seen 12-16 weeks after treatment has started (Anxiety Disorders Association of America, 2018). CBT requires commitment from the patient, regular attendance, and compliance with assigned work, which can be time consuming for many patients (Anxiety Disorders Association of America, 2018). Exposure therapy, a form of CBT, uses a process to reduce fear and anxiety responses by gradually exposing the feared situation or object till the patient becomes desensitized over time (Anxiety Disorders Association of America, 2018). Some

limitations to exposure therapy include exacerbation of post-traumatic stress disorder symptoms and limited number of therapists who implement this treatment (Kaplan & Tolin, 2011) Other types of therapy that have been proven effective include acceptance and commitment therapy (ACT) and dialectical behavioral therapy (DBT) (Baer, 2015). ACT uses strategies of acceptance and mindfulness as means to cope with unwanted thoughts, feelings, and sensations while DBT centers around taking responsibility for one's problems and sheds light on how participants deal with conflict and negative emotions (Baer, 2015). Interpersonal therapy (IPT) has been used as a short term supportive psychotherapy that addresses interpersonal issues (Anxiety Disorders Association of America, 2018). Yoga and yoga-based exercises have been found to significantly improve anxiety symptoms when compared with placebo, however the few controlled studies evaluating the effectiveness have methodological limitations and/or poor methodology reporting (Antonacci, Davis, Bloch, Manuel, & Saeed, 2010). Literature examining the relationship between exercise and depression is extensive, however less has been published studying exercise in patients with anxiety disorders. From initial trials, exercise is suggested to help improve anxiety symptoms, however more research is needed (Antonacci et al., 2010). Limited evidence supports the use of meditation, relaxation training and/or breathing retraining, and mindfulness-based stress reduction for anxiety (Antonacci et al., 2010). Typically, the different types of therapy are used in conjunction with prescription medications to help control anxiety.

**Pharmacological Interventions**

Current pharmacological interventions to treat anxiety disorders include benzodiazepines and anti-depressants, however these medications produce severe side effects. From a recent study, one in six adults in the United Stated reported taking a psychiatric drug, such as antidepressants and anxiolytics (Moore & Mattison, 2017).

Benzodiazepines work by enhancing the effect of the GABA neurotransmitter, resulting in resulting in sedative, sleep-inducing, anxiolytic, anticonvulsant, and muscle relaxant properties. Benzodiazepines are frequently used as a short-term management for anxiety and promote relaxation by reducing muscular tension and other physical anxiety symptoms (Bystritsky et al., 2013). Long-term use typically requires increased dosages to achieve the same effect, leading to tolerance, dependence, and withdrawal (Bystritsky et al., 2013). Researchers found that over 80% of those taking these medications reported long-term use, which is concerning since some of the drugs are recommended for shorter use and carry a number of serious risks (Moore & Mattison, 2017).

Anti-depressants used to relieve symptoms of anxiety include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and Tricyclic antidepressants. SSRIs and SNRIs block the reabsorption of cells into the brain, leaving more serotonin and norepinephrine available (Vallerand et al., 2015). SNRIs are considered a first line treatment particularly for generalized anxiety disorders considering the effectiveness of reducing anxiety symptoms (Vallerand et al., 2015).

The use of antidepressants and benzodiazepines are associated with severe side effects, including central nervous system depression, drowsiness, dizziness, nausea, headache, fatigue, nightmares, hypotension, paradoxical reactions, confusion, ataxia, reduced sexual functioning, insomnia, and weight gain/loss (Vallerand et al., 2015). It is necessary to investigate alternative and complementary forms of treatment that are effective for anxiety treatment but are not associated with as considerable side effects to help control their anxiety.

**Alternative Treatments**

Studies have shown that adults are very interested in using some types of complementary and alternative medicine (CAM) therapy and over 60% of adults have tried at least one type of CAM therapy during the last year (Barnes, Powell-Griner, McFann, & Nahin, 2004). The data suggest that complementary/alternative therapies are used frequently and increasingly. Americans spent over thirty billion dollars out of pocket on complementary health approaches (National Institutes of Health, 2009). With so many Americans using and spending money on complementary health approaches, it is imperative rigorous research is conducted to know whether the products and practices being used are safe and effective (National Institutes of Health [NIH], 2009).

Types of CAM therapy most frequently used include prayer for one's own health, prayer from others for one's health, natural products, breathing exercises, chiropractic care, yoga, massage, and diet-based therapies (Barnes et al., 2004). There are several limitations to the research on CAM approaches for anxiety disorders. There are a wide range of practices considered to be alternative or complimentary with various ways these practices are implemented across cultures. Generally, there is limited evidence of effectiveness for various CAM based therapies and it is necessary high quality research be conducted to establish effectiveness of many of CAM based therapies. CAM based therapies are used for a variety of conditions, however anxiety is one of the most prevalent reasons a person would use a CAM therapy (Barnes et al., 2004).

Herbal therapy for anxiety is increasing in prevalence, with persons medicating with certain herbs to help reduce anxiety. In 2008, The National Center for Health Statistics reported that almost 20% of children and adults in the United States have used an herbal medicine during

the past year (Barnes, Bloom, & Nahin, 2008). Multiple researchers have studied effectiveness of herbals including passionflower, St. John's wort, lysine, magnesium, valerian, kava, and countless others on decreasing anxiety (Lakhan, & Vieira, 2010). Since the use of herbals as a CAM practice is increasing, more studies have been published on effectiveness and human implications. However, many results of the studies on herbals provide inconsistent results, indicating need for additional research and systematic reviews comparing all current data. Evidence on the synthesis of kava, one of the herbals used in CAM based therapies for anxiety, is limited. Specifically, this systematic review focuses on the herb kava and its effectiveness to reduce anxiety in those diagnosed with an anxiety disorder.

## Use of Kava

### History of Kava

Kava or Kava-kava, Piper Methysticum, is a bitter crop originating in the Pacific islands and is used to produce a drink with sedative, anesthetic, euphoriant, and entheogenic properties (Musser, 2005). Kava has been consumed throughout Pacific Ocean cultures for centuries and holds great cultural significance. Originally, kava was a drink reserved for special ceremonies and royalty (Johnson, Dog, & Kiefer, 2012). Islanders believed drinking kava would provide access to the spirit realm of ancestors and gods (Johnson et al., 2012). The ritual use of kava continues on a number of pacific islands today. In addition to cultural and spiritual use, islanders also employed the herb medicinally. Kava's primary use in these cultures was to relieve nervousness, elevate mood, and induce sleep when taken in larger amounts (Musser, 2005). Additionally, kava was consumed as a restorative measure to promote health, combat fatigue, relieve headaches, alleviate weakness, and treat cold symptoms (Lebot, Merlin, & Lindstrom, 1997). Kava was introduced to Europe during the 18th century, however did not gain popularity

in European and Western countries until late 20th century (Johnson et al., 2012). Today's use of kava in European and Western countries include alternative medicine for treating symptoms associated with anxiety, nervousness, stress, depression, insomnia, and other sleep disorders (Lebot et al., 1997).

Traditionally, kava comes in two strains, noble and non-noble kava. Noble kava strain has been used for regular consumption, while non-noble (Tudei) kava has been produced for rare use in traditional ceremonial form (Lebot et al., 1997). Non-noble can be harvested in shorter time and is a lot less costly to produce than noble kava (Lebot et al., 1997). The Republic of Vanuatu Kava Act in 2002, established that only noble kava cultivars are legal to export and the exporters are required to meet strict quality control standards for storing, harvesting, and processing their kava (Vanuatu Kava Act, 2002). Kava cultivars are differentiated by the effects produced in the human body and by the ratio of kavalactones in the cultivation (Lebot et al., 1997). Noble kava has higher quantities of smaller kavalactone molecules, which metabolize faster, resulting in a shorter onset and duration of their physiological effects (Lebot et al., 1997). Non-noble kava is composed of larger double-bonded kavalactones and take longer to metabolize (Lebot et al., 1997). Non-noble kava is typically associated with more undesirable side effects, such as nausea, dizziness, headache, and drowsiness (Lebot et al., 1997).Prior to legislation that prohibited the sale of non-noble kava, research on kava and anxiety used both noble and non-noble kava. Since the sale of non-noble kava has been prohibited in 2002, all studies since then have only used noble kava to conduct research. The form of kava reviewed in this synthesis refers to noble, aqueous extracted kava. Aqueous extracted kava refers to kavalactones extracted through water, while ethanol/acetone extracted kava refers to

kavalactones extracted through ethanol or acetone which is suggested to lead to liver damage (Musser, 2005).

**Kava Effects on Brain and Body**

Researchers have studied various aspects of noble and non-noble kava, including effectiveness, safety, and interactions, however quality of research and results seem to be ambiguous. Studies conducted on kava and/or its major active constituents, kavalactones, report pharmacological actions on various receptors in the brain and interactions with the body (Lebot et al., 1997). These pharmacological actions include potentiation of gamma-aminobutyric acid$_A$ ($GABA_A$) receptors, inhibition of reuptake of norepinephrine, binding to the cannabinoid type 1 receptor ($CB_{1)}$ receptor, inhibition of voltage-gated sodium channels and voltage-gated calcium channels, and monoamine oxidase B reversible inhibition (Singh, & Singh, 2002; Ligresti, Villano, Allarà, Ujváry, & Di Marzo, 2012). The potentiation of $GABA_A$ receptor activity is suggested to be linked to the anxiolytic effects of kava, while the elevation of dopamine levels underlie the moderately psychotropic effects produced (Ligresti et al., 2012).

Non-noble kava is associated with negative side effects and therefore kava is highly regulated so that this non-noble strain is not regularly marketed (Johnson et al., 2012). Other possible side effects include headaches, dizziness, fatigue, and kava dermopathy (Johnson et al., 2012). Kava dermopathy is associated with long term and heavy kava consumption and is characterized by dry and scaly skin on palms, soles of the feet and back (Lebot et al., 1997). All side effects, possible liver toxicity excluded, are reversible with cessation of kava use and should return to normal state within a couple of weeks.

**Kava Safety**

In terms of safety, the United Kingdom and several European countries banned all forms of Kava after concerns that it may cause liver damage (Johnson et al., 2012). In a number of cases, participants taking kava extracts had laboratory abnormalities in liver function tests and some developed liver failure (Boon & Wong, 2003) While the numbers were very small given the wide spread use of kava throughout the world, a number of regulatory agencies determined the risk was too high (Johnson et al., 2012). Traditionally, kava is made into tea by adding water to the roots (aqueous extracted), however it is suggested that kava products extracted with ethanol or acetone can lead to liver damage (Musser, 2005). Some researchers believe the alcohol and acetone allowed toxic compounds into the final product (Ernst, 2004). Furthermore, it is possible that manufacturers may have unintentionally used the leaves and stems, which contain potentially toxic compounds, instead of the root (Ernst, 2004). The World Health Organization (WHO) and Food and Agriculture Organization reported moderate consumption of kava as low level of health risk as a result of the long history of use of kava and most recent research findings (World Health Organization, 2007).

Non-noble and noble Kava has been documented to have several adverse interactions with prescription and nonprescription drugs, including anticonvulsants, alcohol, central nervous system (CNS) depressants, antipsychotics, and drugs metabolized by cytochrome P450 (Cairney, Maruff, & Clough, 2002). When combined with alcohol, kava can have additive sedative effects and cognitive impairments (Cairney et al., 2002). If kava is taken with other anxiolytics, benzodiazepines and barbiturates, it may have a potential additive CNS depressant effects (Cairney et al., 2002). It is imperative that those taking prescription medications consult with their primary physician before using kava.

The concerns raised about the safety of kava led to restrictions and regulations in several countries. The United States Food and Drug Administration (FDA) published a report in 2002 about the risk of severe liver injury, which is now archived and outdated (US Food and Drug Administration, 2002). Currently, the FDA website indicates liver damage appears to be rare with kava use, but users should be informed of this potential risk (National Center for Complementary and Integrative Health, 2010). The National Institutes of Health (2018) released a statement explaining that the frequency of liver injury is actually unknown due to the widespread use of kava. Various scientists and medical practitioners criticized the low-quality reports, emphasizing that a majority of the cases of hepatoxicity were in patients with a history of alcohol or prescription drug abuse (Kuchta et al., 2015). Additionally, some studies explain the rare cases of hepatoxicity as rare allergic reactions, or poor quality plant material (Ernst, 2004). There have been a handful of contradictory reports regarding the safety of kava, and various regulations have been put in place to monitor kava use (Boon & Wong, 2003). In recent years, various governmental regulatory bodies and non-profit NGOs have been established to monitor kava quality, certifying vendors selling noble kava, and advising consumers against products containing non-noble kava varieties.

**Liver Toxicity**

Liver toxicity has been a concern when implementing kava for treatment of anxiety. There have been 25 case reports of serious toxic effects on the liver, including cirrhosis, hepatitis, and liver failure, associated with kava use in Germany and Switzerland, along with a case where a woman required a liver transplant in the United States (Boon & Wong, 2003). The type of kava was not specified in these reports. Of the 68 suspected cases of liver hepatoxicity reviewed by Ernst, 14 were assessed as probably being caused by kava, and 14 as possibly being

caused by kava, including 3 severe cases that resulted in a need for liver transplants or death (Wooltorton, 2002). There have been several concerns regarding the evidence for kava hepatoxicity. The data regarding hepatoxicity are from case reports, which are typically considered a weak form of evidence (Boon & Wong, 2003). Some cases may have been reported and counted more than once, and a majority of the patients were taking other potentially hepatotoxic drugs, making it difficult to determine causality (Wooltorton, 2002). Data on concurrent alcohol consumption were often unavailable (Wooltorton, 2002). Liver toxicity typically occurred 2 to 3 months after kava intake, and many of the case reports did not indicate the length of kava use (Boon & Wong, 2003). Before 2002, different types of kava (noble and non-noble) extract were sold, which complicates interpretation of the case reports.

**Regulations of Kava Use Worldwide**

Various countries have different rules and regulations regarding the possession and distribution of kava. Most countries treat kava as a food or dietary supplement (Johnson et al., 2012). The National Code of Kava Management in Australia regulates the supply of kava by permitting commercial import as long as it is under license for medical or scientific purposes. Possession is limited to 2 kilograms per adult in the Northern Territory and can be purchased as an over the counter medication and online (Alcohol and Drug Foundation, 2018). In Western Australia, kava was banned until 2017 when Australia lifted the ban, making kava legal in all states, though closely regulated (Alcohol and Drug Foundation, 2018). Kava sales are also regulated in Switzerland, France, and the Netherlands. In 2014, the German Administrative Court overturned the 2002 ban and reinstated regulatory requirements of 2001 (Kuchta et al., 2015). In Germany personal possession of kava has never been illegal, however when the ban was lifted in 2014, kava was permitted to be sold as a prescription medicine (Kuchta et al.,

2015). The United Kingdom and Poland remains the only European countries with an outright ban on kava, where possession of kava is prohibited (Ernst, 2004). In New Zealand, kava is regulated as a food and as an herbal supplement. New Zealand regulates the type and preparation of Kava so that only noble kava is sold for human consumption (Ernst, 2004). Health Canada, the department of Canadian government with the responsibility for national public health, had prohibited the sale of any kava product; however, this ban was lifted in 2012 (Ostermayer, 2016). In the United States, the FDA had issued a consumer advisory report about the possible implications kava may have on the liver, however the advisory has been archived and no legal action has been taken (Ostermayer, 2016). Kava can be purchased in the United States as an herbal supplement in herbal stores or various online vendors.

It is imperative that a systematic review of literature on the herb kava is conducted to understand the effects of kava on anxiety considering there is an increase in number of people participating in alternative therapy use, the kava ban has been lifted in multiple countries, liver toxicity reports are discredited, and the general ambiguity on the use of herbals as treatment for anxiety disorders.

# CHAPTER 3 METHODS

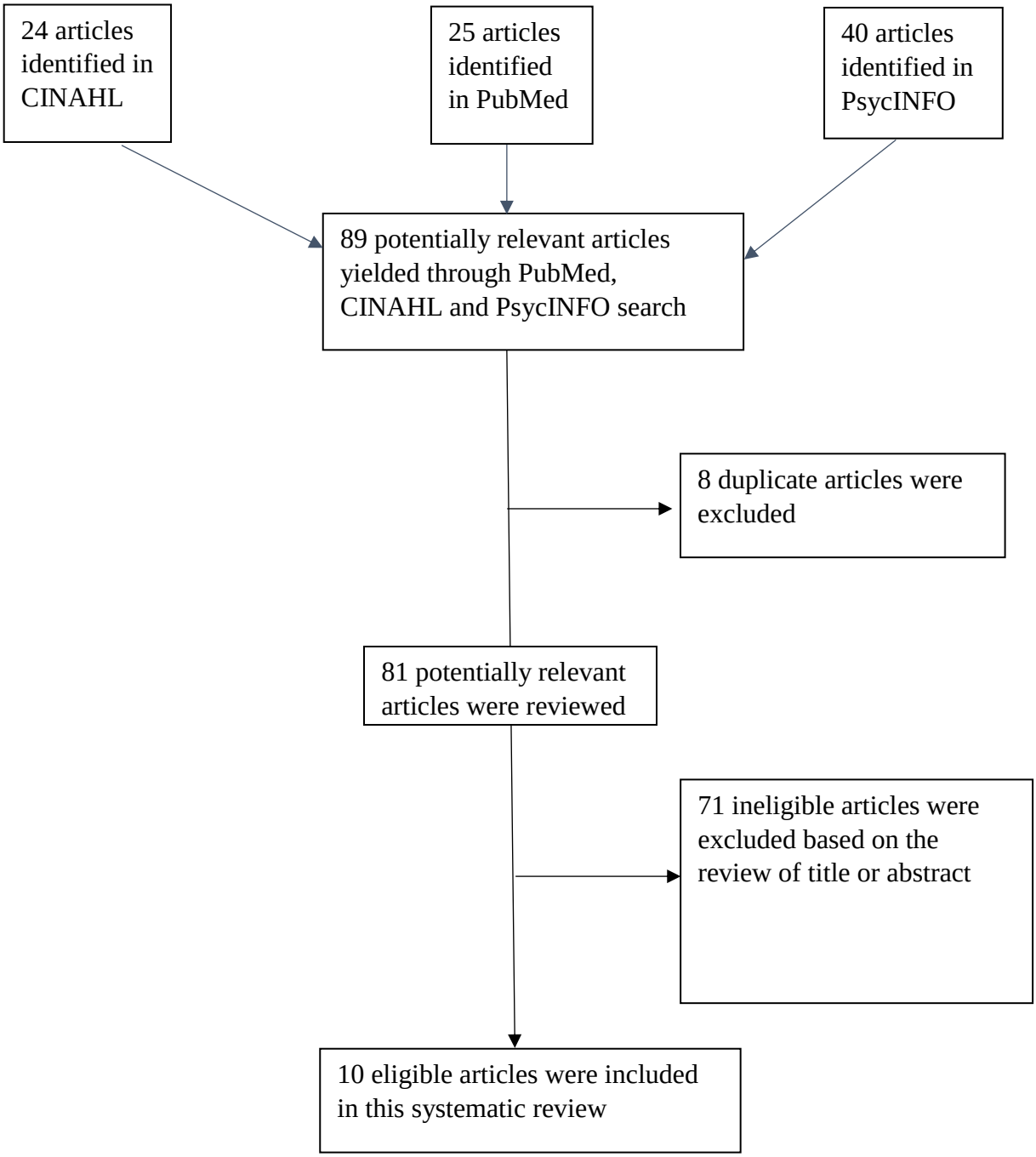
## Literature Search and Selection

The search for literature was conducted using online databases, PubMed, CINAHL, and PsycINFO using mesh terms and medical headings respectively. The key words used were as follows: (“Kava” OR “Piper Methysticum” OR “Kavalactones”) AND (“anxiety” OR “anxiolytic” OR “anti-anxiety”). The terms “kava,” “kavalactones,” or “Piper Methysticum” were required to be in the document title or abstract. The search was limited to articles published between 2000 and 2018 to include most recent studies.

Inclusion criteria included: quantitative research studies testing the effect of Kava as an intervention on adults age 18 and older with anxiety and have outcomes reported. The types of literature searched were limited to intervention research studies, including randomized controlled trials and quasi-experimental studies. Exclusion criteria are literature reviews (e.g., including systematic reviews, integrative reviews, and meta-analysis) editorials or letters, were not available in English, or did not measure anxiety as the outcome. Review articles will be used for ancestry search to identify eligible articles for this review.

The search yielded 89 total articles; PubMed yielded 24 results, CINAHL yielded 25 results, and PsycINFO resulted in 40 results. All studies were published in peer-reviewed, scientific journals. Eight duplicate articles were excluded and 81 articles were screened for relevance. From reviewing titles and abstracts of the results produced from the initial search of 89 articles, 79 articles were excluded. As a result, the search yielded a total of 10 articles to be included in this systematic review (Figure 1).

Figure 1: PRISMA Flowchart of Article Selection



**Data Extraction and Quality Assessment**

These articles were graded for quality and strength of evidence using the Johns Hopkins Nursing Evidence-based Practice Rating Scale (JHNEBP) (Newhouse, Dearholt, Poe, Pugh, & White, 2007). Quality and strength of evidence was conducted by the author by reading the full text of each included study. The author extracted the following information from the selected clinical studies for qualitative synthesis into the matrix: author, year of publication, study design, sample, intervention and control, outcome variables and measures, results, and side effects. According to the JHNEBP evidence rating scales, strength of evidence is rated on a scale of Level I-V. Level I includes experimental study/randomized controlled trials (RCT) or meta-analysis of RCT. Level II consists of quasi-experimental studies. Level III includes non-experimental studies, qualitative studies, or meta-synthesis. Level IV includes opinions of nationally recognized experts based on research evidence or expert consensus panel (systematic review, clinical practice guidelines). Level V consists of opinions of individual expert based on non-research evidence, such as case studies or organizational experiences.

Quality of Evidence is rated on a scale of A (high), B (good), C (low quality or major flaws) (Newhouse et al., 2007). To determine which category a research study belonged to, each study was analyzed by the author for quality of research, summative reviews, organizational, and expert opinion. In the category of research, sample size, controls, conclusions, recommendations, literature review, and scientific evidence were examined. Determining summative reviews consists of analyzing search strategies, results and numbers of studies, scientific strength and quality of included studies, and conclusions. The category of organizational was determined based off of how the methods were defined, consistency of results and sample sizes, and use of

reliable and valid measures. Expert opinion was determined on how credible the expertise seemed to be.

# CHAPTER 4 RESULTS

## Study Design

The data compiled from the analysis of the selected literature are reviewed in this section. The sample characteristics, study designs, inclusion and exclusion criteria, interventions, and results are described within this section. Table 1 summarizes the studies analyzed in this systematic review. Ten studies were included in this review and all were published between 2000 and 2015 (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Jacobs, Bent, Tice, Blackwell, & Cummings, 2005; Malsch & Kieser, 2001; Sarris, Kavanagh, Deed, & Bone, 2009; Sarris et al., 2009; Sarris et al., 2013; Wheatley, 2001).

All studies were randomized, controlled, double blind trials (Boerner et al., 2003, Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Jacobs et al., 2005; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013, Wheatley, 2001). Of the ten studies, two studies randomized participants into different types of intervention groups, including administering different dosage levels of kava and other anti-anxiety medications, as controls and were double-blinded, but did not have a placebo controlled group (Boerner et al., 2003; Wheatley, 2001). Boerner et al.(2003) conducted a double-blind randomized controlled trial comparing the effectiveness of kava compared to parallel groups of buspirone or opipramol. Wheatley (2001) conducted a randomized, crossover controlled trial with intervention groups of kava tablets administered once a day (total 120 mg/day) or kava tablets administered 3 times a day (total 120 mg/day).

## Study Sample

### Sample Size

The sample sizes per studies reviewed ranged from 24 to 391 adults, with an average sample size of 97 participants. Seven of the ten studies had samples sizes under 100 participants.

### Settings and Recruitment

Two of the 10 studies were conducted in the United States (Connor & Davidson, 2002; Jacobs et al., 2005), three were conducted in Australia (Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013), four were conducted in Germany (Boerner et al., 2003; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001), and one was conducted in the United Kingdom (Wheatley, 2001). Four studies recruited participants through mass media (including radio, newspaper, and the internet) and through advertising in medical and complementary medicine clinics (Jacobs et al., 2005; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013); two studies recruited participants through physicians (Boerner et al., 2003; Sarris et al., 2009), and five studies did not address how patients were recruited (Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Wheatley, 2001). All participants in all 10 studies were considered out-patients from the community.

### Participant Demographics

Of the studies that reported ages, ages of participants ranged from 18-90 years old and the average age of participants was approximately 47 years old. Two studies did not report the age range of participants (Jacobs et al., 2005; Wheatley, 2001). In three of the studies, males were the primary participant (Malsch & Kieser, 2001; Sarris et al., 2009; Wheatley, 2001), and in seven of the studies females consisted of the majority of participants (Boerner et al., 2003;

Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Jacobs et al., 2005; Sarris et al., 2009; Sarris et al., 2013). Of the ten studies, three reported the ethnic breakdown of participants. In the three studies that reported ethnicity, a majority of all participants were Caucasian (Connor & Davidson, 2002; Jacobs et al., 2005; Sarris et al., 2013). Three of the ten studies required participants to adequately speak and write English (Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013), however the remaining seven studies did not report a language requirement.

**Participant Anxiety and Other Health Conditions**

Inclusion criteria varied for each study included in this review. A total of 6 out of the 10 studies required a diagnosis of an anxiety disorder by a psychiatrist to be included in the study (Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Sarris et al., 2013; Wheatley, 2001). The remaining four of the 10 studies did not require a diagnosis of an anxiety disorder by a psychiatrist to be included in the study, rather were required to meet other anxiety-related inclusion criteria. Of those that did not require an official diagnosis inclusion criteria included scoring >10 on Beck Anxiety Inventory (Sarris et al., 2009; Sarris et al., 2009) or >40 on the State-Trait Anxiety Inventory State subtest (STAI-State) (Jacobs et al., 2005).

Exclusion criteria for the studies included in this review varied between studies. A total of 8 of the 10 studies excluded those with a history of psychosis or bipolar disorder (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013), or "hepatobiliary disease or inflammation" (Boerner et al., 2003; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Jacobs et al., 2005; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et

al., 2009; Sarris et al., 2013). A total of 7 of the 10 studies excluded people who have substance use disorders (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2013). A total of 6 of the 10 studies excluded participants who had/has "suicidal ideation" (Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013), or use of benzodiazepines or opiates currently or in the previous month (Connor & Davidson, 2002; Geier & Konstantinowicz, 2004; Jacobs et al., 2005; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013). A total of 5 of the 10 studies excluded people who currently use antidepressants currently or have used antidepressants in previous month (Connor & Davidson, 2002; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013), or were pregnant or breastfeeding (Boerner et al., 2003; Jacobs et al., 2005; Malsch & Kieser, 2001; Gastpar & Kilmm, 2003; Sarris et al., 2013).

A total of 4 of the 10 studies excluded people who had an allergic reaction to Kava in the past (Boerner et al., 2003; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2013). A total of 3 of the 10 studies excluded people who were hypotensive (Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001). Two of the 10 studies excluded people who were receiving concurrent counseling or psychological treatment (Sarris et al., 2009; Sarris et al., 2009), or those with lung or cardiovascular disease, neoplasm, or use of barbiturates (Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004), or ataxia, myasthenia gravis, acute sedative or alcohol poisoning, sleep apnea (Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004). Additional exclusion criteria included those who used codeine biweekly or more in the last month (Sarris et al., 2009), or consumed more than two alcoholic beverages per day (Jacobs et al., 2005), or had history of mental health conditions, mood disorders, or mental retardation, the

concurrent use of medicinal herbal substances, unstable medical conditions, or abnormalities upon blood screening (Connor & Davidson, 2002), or had an ocular disorder or lactose intolerance (Gastpar & Kilmm, 2003), or history of seizures (Boerner et al., 2003).

## Intervention

All 10 studies used an aqueous extracted form of kava. The dosage of kavalactones, the active ingredient in kava, administered to participants ranged from 50 mg to 400 mg per day. Three studies administered 150 mg per day, in 50 mg increments spaced throughout the day (Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Sarris et al., 2009). One study administered 100 mg kavalactones in the morning, 100 mg mid-day, and 50 mg before bed, for a total of 250 mg per day (Sarris et al., 2009). One study administered 300 mg kavalactone per day, spaced in three equal dosages throughout the day (Jacobs et al., 2005), and another administered 400 mg kavalactone per day all in one dose (Boerner et al., 2003). Three studies began the treatment at a lower dosage of kava and increased dosage during the trial (Connor & Davidson, 2002; Malsch & Kieser, 2001; Sarris et al., 2013). One study administered 70 mg kavalactones, twice a day for 1 week (140 mg/day) and increased to 140 mg kavalactones, twice a day, (280 mg/day) for the next 3 weeks (Connor & Davidson, 2002). One study administered 60 mg, twice a day (120 mg/day) for the first three weeks, and increased to 120 mg, twice a day, (240 mg/day) for the next three weeks (Sarris et al., 2013). One study administered 50 mg in the beginning of the study and gradually increased dosage to 300 mg during the first week (Malsch & Kieser, 2001). One study examined the difference between kava administered as one 120 mg kavalactone dose per day compared to three 45 mg dose spaced out equally throughout the day (Wheatley, 2001). Length of the studies reviewed ranged from 3 weeks to 8 weeks, with a mean of 4.6 weeks.

## Control

The majority (9 of the 10) of the studies reported having placebos matching kava tablets as the control group (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2004; Jacobs et al., 2005; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013). The placebos were identical in all aspects of appearance, color, texture, smell, taste, and shape. The study by Wheatley (2001) used a cross-over control to compare different levels of doses of kava.

Five of the ten studies included a run-in trial, or pre-intervention placebo testing (Boerner et al., 2003; Gastpar & Kilmm, 2003; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013). Four of the studies that included a placebo testing lasted one week (Boerner et al., 2003; Gastpar & Kilmm, 2003; Sarris et al., 2009; Sarris et al., 2009), and the fifth study's run-in trial lasted 2 weeks (Sarris et al., 2013). All studies that included a placebo testing phase or a run-in trial phase, required patients to receive placeboes in accordance to the individual study's treatment plan before the intervention phase began. The run-in trial phase was used to determine liver abnormalities, placebo-responders, and additional base-line values for participants before starting the kava intervention (Boerner et al., 2003; Gastpar & Kilmm, 2003; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013).

## Outcome Measures

A total of 7 of the 10 studies used Hamilton Anxiety Scale (HAMA), making it the most commonly used scale to assess anxiety (Boerner et al., 2003; Connor & Davidson, 2002; Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2013; Wheatley, 2001). The HAMA scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety and somatic anxiety. Each item is scored on a scale of 0 (not present) to 4

(severe), with a total score range of 0–56. A higher score on the HAMA scale indicates a higher level of anxiety. Zerssen's Mood-Scale (Bf-S) was the second most used scale by 3 of the 10 studies (Boerner et al., 2003; Gastpar & Kilmm, 2003; Malsch & Kieser, 2001). Beck Anxiety Inventory (BAI) was used by 2 of the 10 studies (Sarris et al., 2009; Sarris et al., 2013). The BAI is a self-reported measure of anxiety included 21 items rated on a scale of 0 (not present) to 3 (severe). A score of 0-21 indicates low anxiety, 22-35 is moderate anxiety, 36 and above indicates potentially concerning levels of anxiety. The HAMA scale, Bf-S scale, and BAI were reported to be valid and reliable (Fydrich, Dowdall, & Chambless, 1992; Heimann, Bobon-Schrod, Schmocker, & Bobon, 1975; Shear et al., 2001).

Hospital Anxiety and Depression Scale (HADS) was used by 1 of the 10 studies (Connor & Davidson, 2002), as well as Self-Assessment of Resilience and Anxiety (SARA) (Connor & Davidson, 2002), Anxiety Sensitivity Index (Gastpar & Kilmm, 2003), Boerner Anxiety scale (BOEAS) (Boerner et al., 2003), and Zung Self-Rating Anxiety Scale (SAS) (Boerner et al., 2003). The HADS is a 14- item scale where 7 of the items relate to anxiety and 7 relate to depression. Each item on the questionnaire is scored from 0 (not present) - 3 (severe) and a higher score indicates higher anxiety or depression. The 8-item SARA assesses the following features: feeling relaxed, calm, confident, free of worries and sociable; focused thoughts; not avoiding things because of fear; and bouncing back after stress. Each item is rated from 0 (not at all) to 10 (extremely), with higher scores reflecting greater resilience or less anxiety. The ASI is a 20-item observer rating scale, which relate to affective and somatic manifestations of anxiety. Each symptom is rated on a four point scale ranging from 1 (not present) - 4 (severe), with a higher score indicating higher anxiety. BOEAS comprises of 11 items; anxiety mood, worry, phobic symptoms, anticipatory anxiety, social anxious symptoms, agoraphobic behavior, panic attacks,

nervousness, irritability, impairment or concentration and catastrophic ideas. Severity can be rated from 0 (not present) – 3 (severe), with a maximum total score of 33. A higher score indicates a higher level of anxiety. The SAS is a 20-item self-report scale to measure anxiety levels, based on scoring in 4 groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. Each question is scored on a Likert-type scale of 1-4 (based on these replies: "a little of the time," "some of the time," "good part of the time," "most of the time"). A higher scale indicates higher levels of anxiety. Both the HADS and SARA scale are reported to be valid and reliable, however there are no reports in English that assesses the BOEAS or SAS scale's validity or reliability (Barnett, Connor, & Davidson, 2001; Bjelland, Dahl, Haug, & Neckelmann, 2002).

## Level and Quality of Evidence

All studies were randomized controlled trials falling into the category of Level I for strength of evidence. Quality of evidence was examined and assigned for each of the studies included in this review. Of the ten studies included in this review, seven were rated as A (high), and three were rated as B (good).

## Research Findings

### Effect of Kava

Among the 10 studies reviewed, 5 studies reviewed reported that kava had a statistically significant reduction in anxiety compared to placebo (Geier & Konstantinowicz, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2013; Wheatley, 2001), while the other 5 studies reported no statistical significance (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Jacobs et al., 2005; Sarris et al., 2009). Of the studies that were statistically significant, kava reduced anxiety an average of 10.8 points on the HAMA scale, while placebo decreased anxiety on average of 2.4 points. Of the studies that showed statistically significant

reduction in anxiety, the quality of evidence was mixed with three rated as A (high) and two rated as B (good).

For the studies that show significant results, the anxiety levels were reduced by 7.5 to 14.2 points on the HAMA scale. Of the studies that reported results to be statistically significant, one study showed greatest reduction in anxiety with 14.2 point reduction on average on HAMA scale ($p=0.03$), while the placebo group had 9.5 point deduction (Geier & Konstantinowicz, 2004). The study design in Wheatley (2001) included a cross over between two intervention groups; kava administered in three separate doses, and kava administered as a single dose. Reductions in symptom severity were significant when comparing weeks 0–2 and 0–4 irrespective of administration order (Wheatley, 2001). Further analysis showed between-group difference was not significant (Wheatley, 2001). A randomized controlled trial conducted by Sarris et al. (2009) compared kava to placebo showed highly significant reduction in anxiety treated group with a reduction of 11.4 points on the HAMA scale over placebo ($p<0.0001$). The results of Sarris et al. (2013) revealed a significant reduction in anxiety for the kava group compared with the placebo group with a moderate effect size ($P = 0.046$). The mean decrease in HAMA score was 7.6 points (Sarris et al., 2013). Malsch and Kieser (2001) reported significant reduction in anxiety compared to placebo in kava treated group by an average decrease of 7.5 points.

Five of the 10 studies did not report significant reduction in anxiety. Four of these studies reported reduction in anxiety, however values were not significant in comparison to placebo (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Sarris et al., 2009). Connor and Davidson (2002) reported no significant difference to placebo, and baseline and endpoint scores were not significantly different; average HAMA score decreased 5.7 points after

kava intervention was implemented. Gastpar and Kilmm (2003) reported average ASI score decreased by 9.8 points after intervention and a favorable trend for effect of Kava on HAMA, however it was not statistically significant in comparison to placebo. Boerner et al.(2003) indicated an average decrease of 14.7 points on HAMA after administration of kava, 13 points on SAS, and 7.2 points on BOEAS, however these were not statistically different compared to the parallel groups (Buspirone or Opipramol). Boerner et al. (2003) reported that kava was shown to be as effective as buspirone or opipramol, but not on a statistically significant level. Sarris et al., 2009, reported that the combination therapy of Hypericum perforatum and kava had not significant effects on anxiety (BAI scale). Jacobs et al. (2005) was the only study that reported the placebo group experienced a greater reduction in anxiety than kava group, however the results are not statistically significant.

The studies that reported a significant reduction in anxiety for the intervention group contained a diverse population. Studies reporting significant reduction in anxiety stated participant average ages from 29 to 76 years old, yet the average age in 3 of the studies was approximately 40 years old. The studies that did not report a statistically significant reduction reported average ages of 30 to 51 years of age, with a majority of studies having a population with approximately 40 years of average age. Of the studies that showed significant reduction in anxiety in the kava treated group, three of the five had a majority of male participants, while the remaining two consisted of a majority of female. All of the studies that did not show a statistically significant reduction consisted of a majority of female participants.

The studies that reported a statistically significant reduction in anxiety measured anxiety on the HAMA, Bf-S, and BAI scales. The significant studies that reported anxiety on the HAMA scale tended to report baseline levels of anxiety of above 20 (intermediate levels of anxiety),

except for Malsch and Kieser (2001) who reported baseline HAMA scale of 13, indicating mild levels of anxiety. Malsch and Kieser (2001) also reported anxiety on the Bf-S scale indicating baseline anxiety was 41, which falls in the category of concerning levels of anxiety. Sarris et al., (2013), also reported anxiety on the BAI scale, 20, indicating lower level anxiety amongst participants. Trends of the level of baseline anxiety that was reported amongst the studies that showed significant reduction in anxiety followed similarly to the studies that did not show statistically significant reduction in anxiety.

The kava dosages do not have major differences between the studies between studies with significant findings and those without. Of the five studies that reported significant reduction in anxiety among kava treated groups, three of the five administered kava in multiple doses during the day. Total milligrams administered per day ranged from 120-300mg in studies with statistically significant results. Two of the studies administered 150mg of kavalactones in 50mg increments throughout the day (Geier & Konstantinowicz, 2004; Sarris et al., 2009). Two studies increased kava dosing during the course of the study from minimum 50mg per day to maximum 300mg (Malsch & Kieser, 2001; Sarris et al., 2013). The last study reporting significant results compared administration of kava in a single dose of 120 mg to three doses of 45 mg throughout the day (Wheatley, 2001). The total milligrams administered in studies that were not statistically significant ranged from 140-400mg. Of the studies that did not report statistically significant results, four of the five administered kava in multiple doses during the day

**Adverse Effects of Kava**

The majority of studies included multiple measures, pre- and post-treatment, to assess safety of kava. All studies provided opportunities for participants to report any adverse effects during and after the kava intervention was implemented, such as self-report.

Among the 10 studies reviewed, 3 reported that no adverse events occurred during the duration of their study (Connor & Davidson, 2002; Geier & Konstantinowicz, 2004; Jacobs et al., 2005), and 6 reported adverse effects (Boerner et al., 2003; Gastpar & Kilmm, 2003; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013; Wheatley, 2001), and 1 attributed the adverse effects that were reported to benzodiazepine tapering that occurred during their study (Malsch & Kieser, 2001).

The most common reported adverse effect was increased daytime tiredness; 11 out of 83 (13%) participants reported daytime tiredness across 2 studies (Gastpar & Kilmm, 2003; Wheatley, 2001). Additional adverse events: five participants reported stomach discomfort (Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013; Wheatley, 2001), five participants reported cold-like symptoms (Boerner et al., 2003; Sarris et al., 2009), four cases of nausea (Boerner et al., 2003; Sarris et al., 2009), three reports of dermatitis (Boerner et al., 2003; Sarris et al., 2013), and three reports tachycardia (Boerner et al., 2003, Wheatley, 2001). Also, each of the following adverse events were reported once: change in urine color/frequency (Sarris et al., 2009), dizziness (Sarris et al., 2009), sleep disturbance (Sarris et al., 2009), emotional oversensitivity/heightened anxiety (Sarris et al., 2009), headache (Sarris et al., 2013), panic attack (Boerner et al., 2003), diarrhea (Boerner et al., 2003), and increased appetite (Boerner et al., 2003). Malsch and Kieser (2001) attributed any adverse effects that arose to the benzodiazepine tapering that occurred during the study. No symptoms were reported in the study by Malsch and Kieser (2001); however, researchers stated benzodiazepine pretreatment was still being tapered off which resulted symptoms associated with benzodiazepine tapering.

**Hepatoxicity of Kava**

Six of the 10 studies specifically mentioned collecting baseline and post intervention blood tests assessing laboratory values associated with liver function and hepatoxicity (Boerner et al., 2003; Connor & Davidson, 2002; Gastpar & Kilmm, 2003; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2009; Sarris et al., 2013). Some examples of liver function values that were monitored include albumin, total protein, bilirubin, alanine aminotransferase, aspartate aminotransferase, ASAT, and ALAT. Blood pressure, heart rate, and other vital signs were assessed and monitored throughout the study for 4 of the 10 studies (Boerner et al., 2003; Connor & Davidson, 2002; Geier & Konstantinowicz, 2004; Jacobs et al., 2005).

Of the ten studies included in this review, five studies reported no signs of hepatoxicity (Gastpar & Kilmm, 2003; Geier & Konstantinowicz, 2001; Jacobs et al., 2005; Sarris et al., 2009; Sarris et al., 2009) three reported slight increase in liver enzymes (Boerner et al, 2003; Connor & Davidson, 2002; Sarris et al, 2013), and two studies did not directly discuss the impact kava had on the liver (Malsch & Kieser, 2001; Wheatley, 2001). Gastpar and Kilmm (2003) and Sarris et al. (2009) reported no signs of hepatoxicity. The laboratory test results from Geier and Konstantinowicz's study (2001) showed no pathological changes in enzyme values (ALT, AST, gamma-GT and alkaline phosphatase). Sarris et al. (2009) had one report of slightly elevated liver enzyme (GGT) compared to baseline, however this event occurred during the placebo run-in phase and not attributed to kava usage. Sarris et al. (2013) revealed no significant differences for any enzyme, reporting the difference between kava and the placebo groups of abnormal liver function tests showed 6 of 25 for kava, versus 4 of 24 for placebo, with the result being nonsignificant ($p=0.73$). Boerner et al. (2003) reported slight increase of transaminases in 2 participants, while Connor and Davidson (2002) reported three subjects experiencing slight

elevations in alanine aminotransferases, however did not report specific values, and determined these results to not be clinically significant. Boerner et al. (2003) did not report specific transaminase values, however reports no significance amongst changes and identified that one subject of the two cases displayed slightly increased transaminase levels upon baseline. All of the studies that reported cases of slight increase in liver enzymes reported no clinical signs of hepatic abnormality. Two studies did not directly discuss the impact kava had on the liver (Malsch & Kieser, 2001; Wheatley, 2001).

Table 1: Matrix Table

| First Author (Year) | Study design | Sample | Intervention and Control | Outcome variables and measures | Results | Research Quality |
|---|---|---|---|---|---|---|
| **Malsch (2001)** | Randomized controlled trial (RCT); double-blind | 40 adult outpatients with non-psychotic anxiety, tension and restlessness impairing multiple aspects of life | Intervention: Pre-treatment with benzodiazepines, tapered off over two weeks, followed 300 mg noble kavalactone aqueous extracted capsule pills for 3 weeks<br><br>Control: Pre-treatment with benzodiazepines, tapered off over 3 weeks, followed by placebo capsules for 3 weeks<br><br>Length of treatment: 5 weeks | Outcome variable: Level of Anxiety<br><br>Measures: HAMA Scale | -Significant reduction in anxiety in kava treated group<br>-HAMA score decreased median 7.5 points in Kava treated group<br>-Kava vs. placebo (P=0.01)<br><br>Side Effects:<br>-No serious adverse events reported<br>-Did not report impact on liver | Level I A-High |
| **Wheatley, (2001)** | RCT, double blind, crossover control | 24 participants diagnosed with GAD (DSM-IV) | Intervention: (1) Noble kava tablet pills once a day 120 mg<br>(2) 45mg x 3 tablet pills noble kava per day<br>Control: Cross over for 2 weeks<br><br>Length of Treatment: 4 weeks | Outcome variable: Level of Anxiety<br><br>Measures: HAMA Scale | -Reduction in symptom severity were significant comparing weeks 0-2 and 0-4 irrespective of administration order (P<0.001)<br>-HAMA score decreased on average 12 points<br><br>Side Effects:<br>-Increased day time tiredness, and stomach discomfort<br>-Did not report impact on liver | Level I B-Good |

| First Author (Year) | Study design | Sample | Intervention and Control | Outcome variables and measures | Results | Research Quality |
|---|---|---|---|---|---|---|
| **Boerner (2003)** | RCT, double-blind | 127 outpatients diagnosed with GAD (ICD-10). HAMA >19 | Intervention: 400 mg/day noble kava extract LI 150 pills standardized to 30% kavapyrones<br><br>Control: (1) 10 mg/day Buspirone or (2) 100 mg/day Opipramol<br><br>Length of Treatment: 8 weeks | Outcome variable: Level of Anxiety<br>Measures: HAMA, SAS, BOEAS Scales | -Kava was shown to be as effective as parallel group treatments<br>-Average HAMA scores decreased 14.7 points in kava treated group (p=0.49)<br>-Average SAS scores decreased 13 points in kava treated group (p=0.29)<br>-Average BOEAS scores decreased 7.2 points in kava treated group (p=0.98)<br><br>Side Effects:<br>-One participant reported panic attack<br>-No liver toxicity reported | Level I A-High |
| **Connor (2002)** | RCT, double-blind | 35 adults diagnosed with GAD (DSM-IV) | Intervention: One week placebo lead in; Aqueous extracted noble kava 140 mg kl/day tablets for one week then increased to 280 mg kl/day tablets for the next 3 weeks<br><br>Control: Placebo<br><br>Length of Treatment: 4 weeks | Outcome variable: Level of Anxiety<br><br>Measures: HAMA Scale | -No significant difference to placebo. Mean baseline and endpoint scores were not significantly different<br>-Average HAMA score decreased 5.7 points in Kava treated group<br><br>Side Effects:<br>-Well tolerated with no evidence of adverse events or negative impact on liver | Level I B-Good |

| First Author (Year) | Study design | Sample | Intervention and Control | Outcome variables and measures | Results | Research Quality |
|---|---|---|---|---|---|---|
| **Gastpar (2003)** | RCT, double-blind | 141 adult outpatients diagnosed with neurotic anxiety, total HAMA score >18 | Intervention: 150 mg/day noble kava special extract WS 1490 tablets standardized to 35 mg kl<br><br>Control: Placebo<br><br>Length of treatment: 4 weeks | Outcome variable: Level of Anxiety<br><br>Measures:<br>ASI scale<br>HAMA scale | -Decrease in ASI score for kava group but not statistically significant overall.<br>-Average ASI score decreased 8.6 points in Kava treated group<br>-Kava vs. placebo ($p>0.05$)<br><br>-HAMA indicated favorable trend for effect of kava but not statistically significant<br><br>Side Effects:<br>-Increased Tiredness<br>-No evidence of liver toxicity reported | Level I A-High |
| **Geier (2004)** | RCT, double-blind | 50 adults with nonpsychotic anxiety (DSM-III-R), total HAMA score of >18 | Intervention: Experimental group received 3 (50mg kavalactone) mono-extract noble kava tablets per day<br><br>Control: placebo<br><br>Length of Treatment: 4 weeks | Outcome variable: Level of Anxiety<br><br>Measures:<br>HAMA scale | -Kava group indicated an average 14.8 point decrease on HAMA scale -Kava vs. placebo ($p=0.03$)<br><br>Side Effects:<br>-No adverse events reported<br>-No evidence of liver toxicity reported | Level I B-Good |

| First Author (Year) | Study design | Sample | Intervention and Control | Outcome variables and measures | Results | Research Quality |
|---|---|---|---|---|---|---|
| **Jacobs (2005)** | RCT, double-blind | 391 healthy volunteers with anxiety and insomnia | Intervention:<br>(1) 100 mg kl/day noble kava tablets (30% total kavalactones in extract) with valerian placebo<br>(2) 6.4 mg/day valerian (1% valerenic acid in extract) with kava placebo tablets<br><br>Control: placebo<br><br>Length of Treatment: 4 weeks | Outcome variable: Level of Anxiety<br><br>Measures: (STAI-State substest) | -Greater reductions in placebo group, but not statistically significant<br><br>-Average STAI-State score reduction 11.8 points in kava treated group<br>-Kava vs. placebo ($p>0.05$)<br><br>Side Effects:<br>-No reports of liver toxicity | Level I A-High |
| **Sarris (2009)** | RCT, double-blind | 37 adult participants with 1 month or more of elevated persistent worry or anxiety | Intervention: One week placebo lead in. 5 noble kava tablets (250 mg/day kavalactones) per day<br><br>Control: Placebo<br><br>Length of Treatment: 3 weeks | Outcome variable: Level of Anxiety<br><br>Measures: HAMA | Highly significant reduction in anxiety in kava-treated group<br><br>HAMA reduction in 11.4 points over placebo ($p<0.0001$)<br><br>Side Effects:<br>-No serious adverse events reported<br>-Mild dizziness, nausea.<br>-No evidence of liver toxicity reported | Level I A-High |

| First Author (Year) | Study design | Sample | Intervention and Control | Outcome variables and measures | Results | Research Quality |
|---|---|---|---|---|---|---|
| **Sarris (2009)** | RCT, double-blind | 28 adults with MDD and co-occurring anxiety | Intervention: (1) Hypericum perforatum (1 × 1.8 g tablet, three times/day)<br>(2) Noble Kava rhizome aqueous extract (1 × 2.66 g tablet, 3 times/day)<br><br>Control: Placebo<br><br>Length of Treatment: 4 weeks | Outcome variable: Level of Anxiety<br><br>Measures: BAI | Combination treatment had no significant effects on anxiety (BAI).<br><br>Side Effects:<br>-No serious adverse events.<br>-Mild gastrointestinal upset.<br>-No evidence of liver toxicity reported | Level I A-High |
| **Sarris (2013)** | RCT, double blind | 58 Adults diagnosed with GAD (DSM-IV) | Intervention: One week placebo lead in. Noble kava tablet twice per day (120 mg kavalactones) for the first 3 weeks. Titrated to 240 mg kavalactones in nonresponsive participants at 3 week mark for the next 3 weeks.<br><br>Control: Placebo<br><br>Length of Treatment: 6 weeks | Outcome variable: Level of Anxiety<br><br>Measures: HAMA, BAI | -Significant reduction in anxiety for the kava treated group compared with the placebo group with a moderate effect size (P = 0.046)<br>-Average HAMA score decreased by 7.6 points in kava treated group<br><br>Side Effects:<br>-No evidence of liver toxicity reported<br>-Increased report of headaches | Level 1 A-High |

# CHAPTER 5 DISCUSSION

## Overall Findings

### Effect of Kava

The overall finding from this systematic review of the effect of kava on anxiety yielded inconsistent results. A total of five studies reported that the use of kava significantly reduced anxiety in participants, while the other five studies reported no statistically significant reduction in kava intervention groups. Notably, of the studies that reported anxiety reduction was not significant, four reported that anxiety levels decreased considerable amounts even though they were not statistically significant in comparison to placebo, suggesting kava as a potential impact on anxiety relief.

For the studies that show significant results, the anxiety levels were reduced by 7.5 to 14.2 points on the HAMA scale. On average a decrease of at least 10 points of the HAMA scale indicates a change in level of anxiety severity. Half of the studies indicate that kava is effective for decreasing anxiety symptoms by nearly a severity category. It is known that studies involving anxiety have a high placebo-response rate that can make it difficult to assess the true effect of a particular treatment in clinical trials (Schweizer & Rickels, 1997). It is significant that in future studies placebo responders are controlled for in order to more correctly assess the effect of kava on anxiety. Considering only half of the studies published in the last two decades report that kava significantly decreases anxiety in comparison to placebo, it is necessary more research is conducted for this potential anxiolytic. With the current amount of data available on kava as an intervention to reduce anxiety, it is not recommended kava is implemented into clinical practice nor for home-remedy purposes until additional research is conducted to identify kava effectiveness.

Before 2018, the latest systematic reviews studying the anxiolytic effects of kava in adults were published by Pittler and Ernst (2003) and Witte, Loew, and Gaus ( 2005), respectively. Since the implementation of laws controlling type of kava exported publication of additional research on kava associated hepatoxicity, and bans being lifted in multiple countries, multiple systematic reviews were published reviewing kava's effect on anxiety (Barić, Đorđević, Cerovečki, & Trkulja, 2018; Ooi, Henderson, & Pak, 2018; Sarris, 2018; Smith & Leiras, 2018; White, 2018). The published literature on the effect of kava on anxiety is ultimately heterogeneous and reports reduction in anxiety symptoms, however effect may not be significant.

Previous reviews of articles published prior to the year 2000 have found similar results confirming kava's clinical effectiveness (Schweizer & Rickels, 1997). Pittler and Ernst (2003) was among the first researchers to compile a systematic review on the effects of kava on anxiety. The systematic review consisted of seven randomized controlled trials before 2003, including studies that administered both ethanol extracted kava and aqueous extracted kava (Pittler & Ernst, 2003). It is unknown if the studies included in Pittler and Ernst (2003) review administered non-noble kava, considering the laws regulating kava have not yet implemented the ban on distribution of non-noble kava. Results from Pittler and Ernst (2003) suggest kava as an effective symptomatic treatment for anxiety compared to placebo, although effect size small. Like Pittler and Ernst (2003) and Witte et al. (2005) suggested kava was associated with significant improvement in anxiety symptoms when compared to placebo treatment. Unlike Pittler and Ernst (2003), Witte et al. (2005) conducted the systematic review analyzing the effect of ethanol extracted kava. Witte et al. (2005) suggests that compared to the studies examined by Pittler and Ernst (2003) using aqueous extracted kava, alcoholic extracts were just as effective in reducing anxiety with no additional adverse events. Witte et al. (2005) previously showed Kava

to also be more effective in younger adults and females. Malsch and Kieser (2001), Sarris et al. (2009), and Sarris et al. (2013) all reported statistically significant results in effectiveness and had a majority of female participants, supporting the conclusion of gender determined in Witte et al. (2005). Although Witte et al. (2005) reported to be more effective in younger adults, this systematic review analysis did not support this conclusion. The average age of participants in both the statistically significant group and not statistically significant group were relatively similar. Further research is needed in order to determine which age kava is most effective.

Reviews published in 2018 reported similar findings as those published nearly two decades previously. All of the studies published in the last year identify that kava is associated with reduction in anxiety symptoms (Barić et al., 2018; Ooi et al., 2018; Sarris, 2018; Smith & Leiras, 2018; White, 2018). Smith and Leiras (2018) and White (2018) conducted systematic reviews on the effectiveness and safety of Kava for treating anxiety symptoms, while Ooi et al. (2018) focused specifically on participants diagnosed with generalized anxiety disorders. The additional studies, by Sarris (2018) and Barić et al. (2018) reviewed kava's effectiveness for treating anxiety symptoms and were published in larger reviews analyzing multiple herbals effect on anxiety. The large scale review conducted by Sarris (2018) identified kava as an effective anxiolytic, while Barić et al. (2018) reported kava has having an modest effect on anxiety however data is scarce on effectiveness and higher quality studies must be conducted in order to determine effectiveness.

The reviews by Smith and Leiras (2018) and White (2018) focused on overall relief of anxiety symptoms in multiple anxiety disorders, while Ooi et al. (2018) focused only on people diagnosed with generalized anxiety disorder. Both Smith & Leiras (2018) and White (2018) reported that the studies reviewed confirm reduction of anxiety symptoms when treated with

kava, with the absence of liver failure. White (2018) did not include all of the studies included in this systematic review considering the inclusion/exclusion criteria was more constricted. White (2018) identified benzodiazepines provide more significant acute anxiolytic effects; however kava provided significant reduction in anxiety symptomology over time. A study conducted by Boerner et al. (2003) which was not included in the systematic review by White (2018) identified that kava performed just as well as benzodiazepines in a clinical study. There appears to be a need for further research regarding the effectiveness of kava in comparison to benzodiazepines, in addition to identifying long term anxiolytic effect, and drug interaction between traditional anxiolytics and kava.

**Adverse Effects of Kava**

Kava was reported as being well tolerated among participants in all clinical trials in this systematic review, with a majority of the reported side effects being mild. Common reported side effects included increased daytime tiredness, stomach discomfort, cold-like symptoms, nausea, and dermatitis. While kava was well tolerated in most studies, Boerner et al. (2003) reported higher levels of headaches among participants and had the longest intervention period at 8 weeks, suggesting increased side effects with longer kava use. Current methods to treat anxiety disorders, including benzodiazepines and antidepressants are associated with severe side effects. Side effects include tolerance, dependence, and withdraw, central nervous system depression, drowsiness, dizziness, nausea, headache, fatigue, nightmares, hypotension, paradoxical reactions, confusion, ataxia, reduced sexual functioning, insomnia, and weight gain/loss (Vallerand et al., 2015). From the results of this systematic review, it is evident that kava and benzodiazepines share some similar side effects including fatigue, nausea, and headaches. Reports of side effects associated with kava usage appear to be less severe than side effects typically associated with

benzodiazepines and antidepressants. It is necessary more research is conducted on larger scales to identify all potential side effects of kava usage before implementing kava as an anxiolytic for patient anxiety.

Much research on kava focused on the herbal's role in liver failure. The fact that no clinical signs of hepatotoxicity were observed in the studies that measured liver function and minimal, insignificant, change of liver function was detected in the included trials suggests that Kava is safe for therapeutic usage at the dosage of 50–400mg per day of kavalactones (regardless of dosage schedule) and for short durations (3–8 weeks). Further research is necessary to fully understand the long-term effects of kava and if the amount of kavalactones plays a role in determining the onset of hepatotoxicity. This review indicates need for further research to standardize kava associated liver failure, length of intervention phase, clinical dosage, and study sample.

Previous reviews of articles published prior to the year 2000 have found similar results confirming kava's side effects (Schweizer & Rickels, 1997). As described in Pittler and Ernst (2003) and Witte et al. (2005) kava seemed to reduce anxiety symptoms and was not associated with any adverse events when compared to placebo. Witte et al. (2005) reports no difference in adverse events between ethanol or aqueous extracted kava. Only aqueous extracts of kava have been conducted in recent studies since ethanol extracts contain higher levels of kavalactones which is associated with being more cytotoxic to the liver (Witte et al., 2005). Since 2011, there have been no studies published detailing the effects of kava on cytochrome P450 enzymes and interactions in humans identifying the need for more research considering other laboratory results contradict the outcomes found in the study conducted by Witte et al. (2005). All reviews published in 2018 also noted side effects compared to placebos and other anxiolytics were not

significantly different (Barić et al., 2018; Ooi et al., 2018; Sarris, 2018; Smith & Leiras, 2018; White, 2018). There were no reports of hepatoxicity in any other systematic review (Barić et al., 2018; Ooi et al., 2018; Sarris, 2018; Smith & Leiras, 2018; White, 2018).

The summary of United States and European case studies suggest that consuming kava for extended periods of time (8 weeks to four months) at low doses (60-240mg) may result in jaundice or hepatoxicity (Smith & Leiras, 2018). Boerner et al. (2003) conducted the longest treatment phase in this review (8 weeks), and had reported an increased reports of headaches when compared to other studies in this review. This suggests the risk of hepatoxicity is based more on the duration of consumption rather than amount consumed, since the case studies reported liver failure at lower doses (as low as 60 mg); however there was no evidence in change of liver function in reviewed articles (Smith & Leiras, 2018). It is imperative further research is conducted in order to understand the long term effects of kava and if the amount of kavalactones contribute to the onset of hepatoxicity. Smith and Leiras (2018) identified need for further research analyzing kava-associated hepatoxicity.

**Research Methods of Kava Studies**

The methods of kava administration varied greatly between studies. Some studies administered kava at multiple points during the day while other studies administered kava as a single dose. Additionally, the dosage and administration regimen of kavalactones differed across studies but the difference does not seem to link to the findings of its effect. In the studies that reported kava effectively reduced anxiety, the kavalactones were administered from 150 mg to 300 mg per day while the studies that did not show significant effect administered kavalactones from 120 mg to 400 mg per day. All of the studies that reported statistically significant reduction in anxiety administered kava at multiple points during the day, instead of as a single dose. Upon

closer examination, a majority of studies, except one, that did not report significant reduction in anxiety levels also employed multiple dosages during the day. This suggests that there is no significant difference between single dosages, dosages spread throughout the day, and effectiveness in the studies with significant versus non-significant results. However more research needs to be conducted on kava dosing. The lack of consistency among study samples, designs, and milligrams administered made it difficult to synthesize the overall results and evaluate the true effectiveness of kava on anxiety.

## Limitations

The published literature on the effect of kava on anxiety is ultimately heterogeneous. The studies varied with respect to inclusion and exclusion criteria. Variability in the study population of studies meeting inclusion/exclusion criteria could potentially affect the results obtained. Gender distributions were not consistent across all trials, sample population size varied greatly, and there was a wide variety of anxiety disorders and methods of measurement that were included in this review. Originally, the systematic review wished to limit the study population to generalized anxiety disorder, but due to the insufficient research available, the inclusion criteria had to be adjusted. Some studies suggest kava as a better treatment for low anxious severity. It is necessary that a more thorough, large scale clinical trial is conducted in order to determine overall effectiveness and potency amongst different anxiety levels. Also, whether kava is more effective in certain populations in terms of age, ethnicity, level of anxiety, and dosage of kava needs to be further examined.

## Implications for clinical practice

In current western clinical practice, CAM are not typically implemented or recommended by health care professionals. Alternative medicine use has been increasing in recent years,

however many nurses and other health care professionals have limited knowledge on action, side, effects, and interaction of commonly used CAM agents. It is necessary to for health care professionals to increase knowledge about alternative medicines in order to aide in decision making regarding the use of these agents to treat anxiety. Kava can be a potential treatment option for anxiety, especially among patients who prefer natural remedies and lifestyle approaches to manage their conditions. Based on this review, kava shows great potential to reduce anxiety. However, given that the effect of kava was only evaluated in a relatively small number of randomized controlled trials and showed mixed results, it might be premature to recommend that kava implemented into current practice. It is necessary that further research is conducted on standardize kava associated liver failure, length of intervention phase, clinical dosage, and study sample.

In addition, while kava has been shown to reduce anxiety symptoms, the effect size seems to be modest. The available data from the reviewed studies suggest that kava is relatively safe for short term use (up to 8 weeks), although more information is required before potentially implementing this herbal substance as a viable option to treat anxiety. If kava is being used for anxiety relief, health care providers and users must be aware of duration of consumption until further research establishes liver safety. Currently the amount of existing research included in this review does not currently encourage the prolonged use of kava considering that the effect and adverse effects of kava have not been fully evaluated.

## Implications for further research

Currently there is a lack research regarding multiple aspects of kava. It is necessary future research be aimed at monitoring the long-term effects of kava and potential relation to hepatoxicity. To further understand toxic effects of kava, future research should consider

including the composition of kavalactones to potentially identify combinations of kavalactones with toxic effects or identify the combination that would produce the best clinical results. Longitudinal studies are necessary to establish the effects of prolonged use of kava and if long-term use leads to an increase in adverse events. Large-scale studies must also be conducted in order to account for extraneous events and variability, considering a majority of the studies had under 100 participants. Additionally, there is much variability in dosing and dosing schedule that more studies need to be conducted to determine the most therapeutic dosing and dosing schedule.

## Conclusions

There is promising evidence from multiple well-designed clinical trials suggesting kava may be an effective treatment for anxiety related symptoms. Kava has been shown to be safe for short term therapeutic use at relatively low dose levels. Side effects have been reported as mild and well tolerated. Kava may be a potential treatment option for anxiety symptoms for those who prefer alternative and complementary medicine, however it is necessary further research to be conducted in order to identify safety and proper efficacy before implementation in clinical practice.

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