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The effectiveness and safety of Kava Kava for treating anxiety symptoms: A systematic review and analysis of randomized clinical trials

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A B S T R A C T

Background: To determine if Kava Kava is an effective treatment for combating symptoms of anxiety despite warnings of hepatotoxicity from the Centers for Disease Control and Prevention (CDC).

Methods: Databases PubMed, CINAHL, and PsycINFO were utilized to obtain clinical trials on Kava Kava and its effects on anxiety. A total of 11 articles met inclusion/exclusion criteria: 2 for Kava Kava vs. another anti-anxiety medication, 2 detailing additional adverse events, and 7 for Kava Kava vs. placebo. Mantel-Haenszel fixed–effects model was used to analyze the data, with responder rates being pooled to compute weighted risk ratios.

Results: Kava Kava was shown to be more effective than placebo in 3 of the 7 trials. A final risk ratio of 1.50 (95% CI: 1.12, 2.01) from responder rates was calculated in favor of the intervention from 5 clinical trials (n = 330). Adverse events were shown to be the same as placebo (P = 0.574), and laboratory values analyzing hepatotoxicity were no different when compared to baseline except in two studies.

Conclusions: Kava Kava appears to be a short-term treatment for anxiety, but not a replacement for prolonged anti-anxiety use. Although not witnessed in this review, liver toxicity is especially possible if taken longer than 8 weeks.

1. Introduction

The use of complementary and alternative therapies (CAM) has been on the rise in the United States, with an increase in usage from 34% in 1990 to 62% in 2002. The National Health Interview Survey of 2007 estimated a further increase of 14.2% since 2002 [1]. The high cost of healthcare along with convenience [1,2] are cited as major reasons why individuals are turning towards CAM instead of prescription drugs to treat a variety of medical conditions, including psychological diseases. Kava Kava is one such over-the-counter CAM medication.

Kava Kava is a herb extracted from the roots of the plant *Piper methysticum*. Clinical trials have analyzed the effects of the drug on generalized anxiety disorder (GAD) symptoms, including excessive worrying, insomnia [3], headaches, fatigue, muscle strain, and tension [4] due to the anxiolytic and muscle relaxing properties of Kava Kava's kavalactones [2]. The active ingredients found in Kava Kava are kavain (K) and methysticin (M), with dihydrokawaiin (DHK), dihydromethysticin (DHM), yangonin, flavokawain A (FLKA), and flavokawain B (FLKB) occurring in lesser known quantities [5].

Due to Kava Kava's polarity, the utilization of an alcoholic extraction technique leads to a higher kavalactone content [5,6]. The kavalactones K, DHK, M, and DHM were noted to be 1.5 to 5 times higher in the samples extracted with 95% ethanol as compared to samples extracted with 100% water, while FLKA and FLKB were reported at levels 50 times higher in the 95% ethanol extract [5]. These higher quantities—specifically K, DHK, M, and DHM—promote a greater feeling of calmness, thus being potentially more effective in treating excess apprehension found in basic anxiety or anxiety disorders [2,7]. Unfortunately, higher portions of these kavalactones are also associated with Kava Kava induced liver failure [5]. After a series of published case reports, the Centers for Disease Control and Prevention (CDC) issued a statement cautioning against extended and heightened use of the herbal supplement [8]. Currently, there are still no specific dosage or extended user guidelines defined by the Food and Drug Administration for Kava Kava [9]. However, extracts are now made utilizing non-alcoholic extraction techniques to reduce the amount of toxic kavalactones thought to induce adverse events [5,6,10].

The introduction of aqueous and non-polar extraction methods has been shown to decrease the concentration of toxic kavalactones in commercial Kava Kava products. Both M and FLKB are found in lesser quantities in the lipid/aqueous extract as compared to the polar solvent [5]. Methysticin is harmful in that it decreases the viability of human lymphoblastoid cells by 40%, while flavokawain B can induce apoptosis through the use of reactive oxygen species (ROS) as well as causing the rash-like symptoms often associated with Kava Kava [11]. In addition, both FLKA and FLKB in higher quantities were found to decrease cell viability [5,11]. More recent research has also shown genetic

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variability's role in Kava Kava induced hepatotoxicity. In the South Pacific, where Kava Kava is traditionally used, the side effect of liver damage is usually absent [6]. South Pacific islanders are thought to have a genetic advantage that allows them to periodically consume Kava Kava [12,13]. Seventy-nine percent of those from Caucasian descent are estimated to be deficient in CYP2D6, an important enzyme necessary for drug metabolism and prevention of drug-drug interactions [13]. Despite Kava Kava-induced hepatitis being considered a rare event [14], this enzyme is thought to be responsible for the hepatotoxicity in non-South Pacific Islanders because of improper breakdown and clearance of kavalactone metabolites [6]. Toxicity may also arise from using the aerial part of the plant, which contains toxic alkaloids [13].

Other than being classified as an anti-anxiety agent, Kava Kava has also been used to treat insomnia, major depressive disorder (MDD), and other comorbid disorders [2]. Decreased cognitive function (declined visual attention accuracy) and awareness are frequent side effects of benzodiazepines, which are commonly used to treat clinical anxiety [11]. Kava Kava has been shown to have similar negative effects in higher doses, but also has been shown to increase visual processing and working memory [13]. Previous trials have also shown Kava has an absence of severe side effects if the dose remains under 400 mg of kavalactones per day [14], and it has increased effectiveness when taken by females and/or younger adults [15]. Given the increased use of Kava Kava as an alternative therapy for anxiety, this systematic review and meta-analysis will analyze the general effectiveness of Kava Kava as well as address its potential to inflict liver damage in both the short and long-term from more recent studies. Previous reviews have summarized the findings of studies performed prior to the year 2000. The primary goal of this review and meta-analysis is to supplement current findings, make comparisons to previous meta analyses [7,15], and effectively construct recommendations for any further studies conducted to study Kava Kava and its capability in treating anxiety symptoms.

2. Methods

A systematic review and meta-analysis were conducted to evaluate randomized clinical trial research on Kava Kava's effectiveness in treating anxiety among adults 18 years of age and older. Databases PubMed, CINAHL, and PsycInfo were utilized, with the search strategy last repeated on January 23, 2018. Key terms were defined based on pre-existing dictionary items from each database.

Inclusion criteria included: English language, published between January 1, 2000, and December 31, 2017, peer-reviewed, randomized clinical trial, and study population of adults 18 years and older. Reasons behind this inclusion criteria include English being the only language spoken by the researchers, published studies before 2000 have already been covered in previous review articles [7,15], non-peer reviewed articles having lower study quality, randomized clinical trials being highest in clinical evidence, and adults being a more widely accepted study population than children as well as being more likely to purchase over-the-counter Kava Kava products.

Peer-reviewed articles with dictionary items synonymous with Kava Kava and its anxiolytic effects were used. To broaden the research strategy, key terms relating to anxiety as well as anti-anxiety agents were included (Fig. 1). The following formats were used: “Kava"[Mesh] AND (“Anti-Anxiety Agents"[Mesh] OR “Anxiety"[Mesh]) for PubMed, and (MH “Kava Kava”) AND ((MH “Antianxiety Agents+") OR (MH “Anxiety+")) for CINAHL. PsycINFO articles were searched using the phrase “kava and (anti anxiety agents OR anxiety).” A total of 200 articles were retrieved with 121 remaining after excluding duplicates. After applying the previously mentioned inclusion criteria to the title and abstract review, a total of 20 articles remained for full-text evaluation.

The remaining articles were read to exclude articles citing information not related to Kava Kava's effect on anxiety levels or its symptoms/adverse events (AEs). A full-text evaluation was conducted to determine if articles met the aforementioned inclusion criteria as well as the following exclusion criteria: other interfering mental disorders, illnesses, or drug abuse/addictions, not related to anxiety; used additional concurrent interventions with Kava Kava; did not include participants with anxiety or utilized healthy volunteers; and included data sets from other studies as well as their own study participants in the analysis. Due to the limited amount of literature published on the topic of Kava Kava and anxiety, all randomized controlled trials (RCTs) were included regardless of their method of screening for anxiety disorders. A final number of 11 articles were selected for analysis after checking references (Fig. 1) [16-26]. Seven articles provided statistical outcome measures comparing Kava to placebo [16,17,19,20,21,22,23]; two provided additional comments on Kava Kava's side effects and withdrawal symptoms [24,25]; and two provided data on Kava Kava's level of effectiveness against an anxiolytic drug, one with a placebo [18] and one without [26].

Analysis of results focused on differences in means or medians, responder rates, and percentage/number of adverse events. Changes in scores of Hamilton Anxiety Scale (HAMA), “Befindlichkeits-Skala” subjective well-being scale (Bf-S), Anxiety Status Inventory (ASI), and/or State–Trait Anxiety Inventory-State (STAI-S) were contrasted with one another. All are used by clinicians to measure anxiety levels and symptoms in participants [16-18]. A higher score on the HAMA, Bf-S, STAI-S, or ASI are all directly related to worsening anxiety symptoms [16-18]. Demographics pooled included sample size, age, gender, and baseline HAMA score from the intent-to-treat population. Reported pooled averages were measured according to study weight, which was calculated from the number of participants in each study arm and reported baseline value.

Responder rates were used to create a funnel plot to measure publication bias. Forest plots were created to look at study effectiveness and subgroup analysis was conducted ad hoc. In Kava Kava, if responder criteria were not determined from HAMA scores then the Clinical Global Impressions Scale (CGI) rating was used [17,19]. Data was calculated into relative risk ratios (RR) using RevMan Review Manager, Version 5.3 with a fixed effects and Mantel-Haenszel statistical method. Individual risk ratios in addition to the weighted RR were calculated at the 95% confidence level. A test for overall effect and heterogeneity was performed to help assess sampling error and/or bias using the heterogeneity coefficient (I^2) statistic. Data utilized the intent-to-treat population unless otherwise stated.

3. Results

The 11 articles meeting inclusion/exclusion criteria included 9 studies that were randomized, double-blinded studies with at least two parallel groups [16–23,26] and 2 that detailed more information on adverse events [24,25].

3.1. Demographics and Study Design

Demographics of the 7 clinical trials of Kava Kava vs. Placebo are displayed in Table 1, while study methods are described in Table 2. Sarris et al. (2012) did not provide separate demographic data for Kava Kava or placebo, so it is not included in Table 1 [18]. Of the seven placebo-controlled studies that gave demographic information, weighted averages were calculated from a total sample size of 427. This gave a mean age of 48.8 years and an average HAMA score of 22.7. From the total sample population, 65.5% were female (Table 1).

Malsch and Kieser (2001) had a lower HAMA score than all other studies, with a median score of 13 (IQ range 10–14) for the Kava Kava group [16], while Geier and Konstantinowicz (2004) had a much higher mean HAMA score at 27.6 (SD 3.85) for the placebo group [20]. Sample sizes were generally small throughout studies, under 40 participants. Gastpar and Klimm (2003) was the only study to have upwards of 100

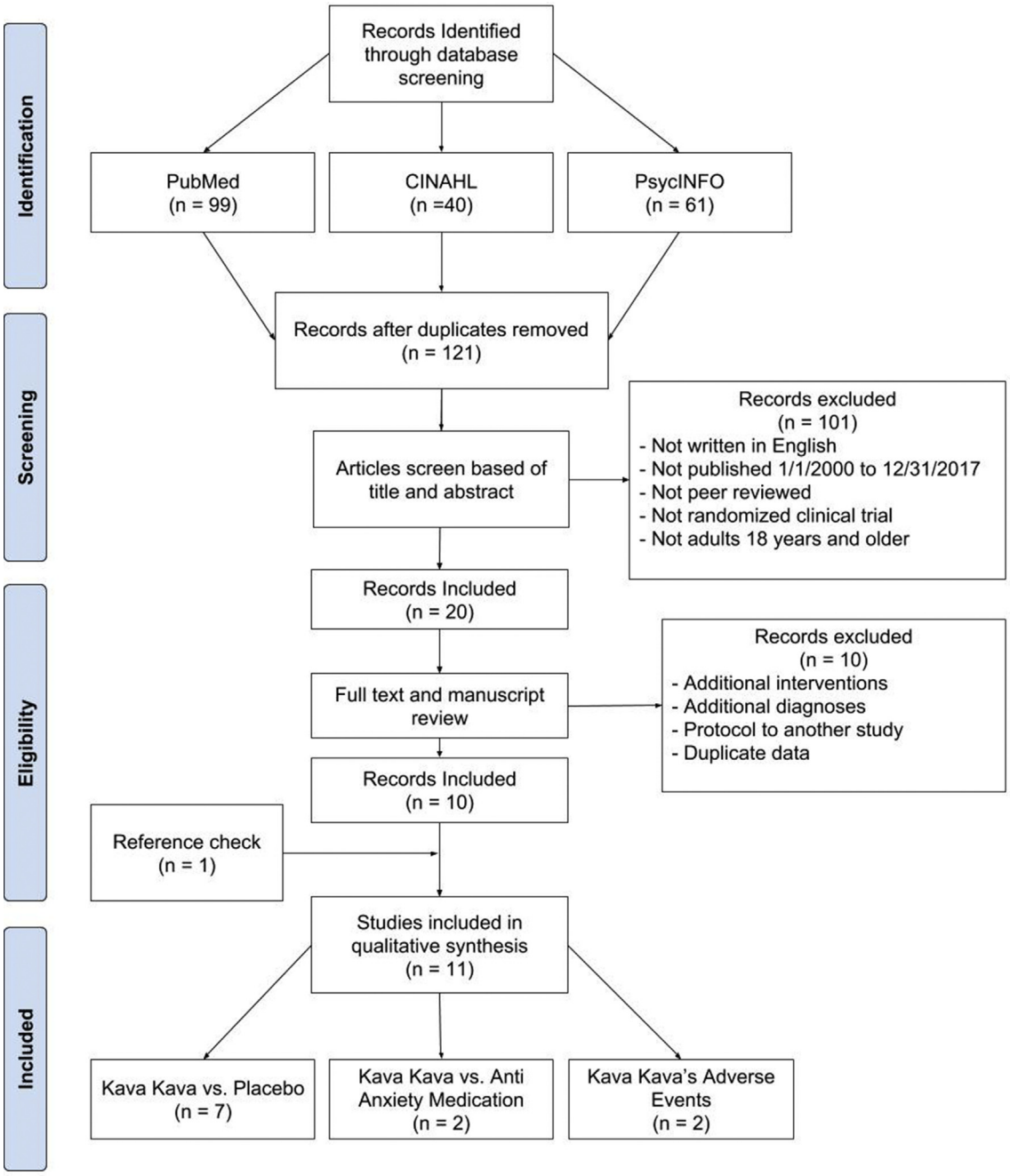

Fig. 1. Method of Search Strategy for Kava Kava and Anxiety Article Selection n = number of articles.

Table 1
Demographics of Kava Kava versus placebo randomized controlled trials.

Kava Kava				Placebo				
Sample Size	Age (mean, or median)	Sex, female (%)	HAMA baseline	Sample Size	Age (mean, or median)	Sex, female (%)	HAMA baseline	
Sarris et al., 2013a [21]	27	29.5 (7.8)	74%	21.63 (4.2)	31	30.6 (9.8)	58%	19.50 (4.4)
Sarris et al., 2009 [23]	19	44.4 (13.1)	56%	24.2 (5.2)	22	43.1 (11.7)	43%	23.6 (5.1)
Lehrl 2004 [19]	34	53	58.80%	22.0 (11–32)	27	51.2	48.20%	22.0 (11–32)
Geier and Konstantinowicz 2004 [20]	25	76 (51–90)	78%	25.6 (3.95)	25	76 (51–90)	78%	27.6 (3.85)
Gastpar and Klimm 2003 [17]	71	48.8 (23–70)	74.50%	25.6 (5.5)	70	48.2 (18–69)	74.50%	25.8 (6.6)
Connor and Davidson 2002 [22]	18	51.7 (11.6)	82%	19.9 (4.1)	18	51.7 (11.6)	82%	18.8 (2.9)
Malsch and Kieser 2001 [16]	20	39.1 (20.8–74.4)	30%	13 (10–14)	20	42.3 (24.8–74.6)	45%	13 (10–14)

Total pooled sample of 427 participants, aged 48.8 years and 65.5% female. Mean HAMA score was 22.7 points [16,17,19,20,21,22,23]. Calculated by study arm weight and reported baseline values. Mean + (Stand Deviation, SD) or Median + (Interquartile Range IQ).

Table 2
Description of Studies Included in Kava Kava vs. Placebo Review.

Authors	Sample Size	Criteria for Inclusion	Number of Study Arms, Medication and Dosage	Length of Study; Single vs. Multi-center	Kava Drug
Malsch and Kieser 2001 [16]	n = 40	DSM-III-R diagnosed 300.22, 300.29 or so- 300.23, 300.02, or 309.24; ≥12 points on MWT-B; ≥14 on HAMA; Outpatient	2: Kava vs. Placebo 14 days of treatment with benzodiazepines before study inclusion. First Week: 50 mg (50 mg tab: 1 tab qd) Kava vs. Placebo 2nd-5th week: 300 mg (50 mg tabs: 3 tab bid) Kava vs. Placebo	8 weeks total (Single Center) 5 week double blind 3 week withdrawal follow up	WS1490 70% kavalactones per tablet; extract acetonic water
Connor and Davidson 2002 [22]	n = 35	DSM-IV GAD 1 month in duration; GAD diagnosis according to MINI interview; HAMA score > 16; Outpatient	2: Kava vs. Placebo First week: 140 mg/day (70 mg tab:1 tab bid) Kavalactones vs. Placebo 2nd to 4th week: 280 mg/day (70 mg tab: 2 tabs bid) Kavalactones vs. Placebo	5 weeks total (Single Center) 1 week placebo run in 4 week double blind	KavaPure 70 mg kavalactones per tablet
Gastpar and Klimm 2003 [17]	n = 141	DSM-III-R diagnosis of 300.02, 300.22, 300,23, 300,29, or 309.24; Outpatients; HAMA score > 18; MWT-B score of ≥13	2: Kava vs. Placebo 150 mg/day (50 mg tab: 1 tab tib.) Kava vs. Placebo	7 weeks total (Multicenter) 1 week placebo run in 4 week double blind 2 week withdrawal follow up	WS1490 70% kavalactones per tablet; extract acetonic water
Geier and Konstantinowicz 2004 [20]	n = 50	DSM-III-R agoraphobia, specific phobia, generalized anxiety disorder and adjustment disorder with anxiety; HAMA score of > 18; MWT-B score of > 12; Inpatient	2: Kava vs. Placebo 150 mg/day (50 mg tab: 1 tab tib) Kava vs. Placebo	7 weeks total (N/A) 1 week placebo run in 4 week double blind 2 week withdrawal follow up	WS1490 70% kavalactones per tablet; extract acetonic water
Lehrl 2004 [19]	n = 57	> 15 points on HAMA; At least 2 points on HAMA item "insomnia;" < 3 mistakes on MWT-B; DSM-III-R 300.02, 300.22, 300.23, 300.29, 309.24 were considered primarily; Outpatient	2: Kava vs. Placebo 200 mg (100 mg tab: 2 tab qd) Kava vs. Placebo	7 weeks total (Multicenter) 1 week placebo run in 4 week double blind 2 week withdrawal follow up	WS1490 70% kavalactones per tablet; extract acetonic water
Sarris et al., 2009 [23]	n = 60	1 month persistent anxiety; Score > 10 on BAI	2: Crossover Kava and Placebo 250 mg (50 mg tab: 2 tab bid and 1 tab qd) Kavalactones vs. Placebo	3 weeks total (Single Center) 1 week placebo run in 1 week w/Kava 1 week w/placebo Double blinded, Cross-over	50 mg kavalactones per tablet; pressed, dried aqueous extract
Sarris et al., 2012 [18]	n = 22	14–25 years of mild to moderate anxiety according to HAMA; Outpatient; HAMA score between 14 and 25	3: Kava, Oxazepam, Placebo 180 mg (60 mg tab: 3 tab qd) Kavalactones vs 30 mg (1 tab) (qd) Oxazepam vs. Placebo	3 weeks total (Single Center) 1 week oxazepam 1 week w/Kava 1 week w/placebo Double blinded, Cross-over	60 mg kavalactones per tablet; pressed, dried aqueous extract
Sarris et al., 2013a [21]	n = 58	DSM-IV diagnosed GAD; Adult ages 18–65; Outpatient; Less than 17 on MARDS	2: Kava vs. Placebo 120 mg (1 tab, bid) Kavalactones for 3 weeks vs. Placebo If no response then: 240 mg (120 mg tab:1 tab bid) Kavalactones for 3 weeks vs. Placebo	8 weeks total (Single Center) 1 week placebo run in 6 week double blind 1 week single blind	60 mg kavalactones per tablet; pressed, dried aqueous extract

Kava Kava vs. Placebo RCTs; All articles are randomized controlled trials with double-blinded treatment phase. Important information described above includes sample size and criteria for inclusion, length of trial and study design, as well as dosage and type of Kava drug utilized [16-23].

patients, with 70 receiving a placebo and 71 receiving Kava Kava (totaling 141 participants) [17]. Most included participants in the mid-forties to low fifties, but two had much younger or older participants. Sarris et al. (2013a) reported younger mean ages of 29.5 ± 7.8 years for Kava Kava and 30.6 ± 9.8 years for placebo [21], while Geier and Konstantinowicz (2004) detailed an older median age of 76 years in both study arms [20]. The distribution of gender was uneven across studies with most reporting a higher number of female to male participants (Table 1).

Six of the eight trials took advantage of a run-in period to remove false responders [17,19,20,21,22,23] and five out of the six incorporated a double blind phase of 4 weeks or longer duration [17,19,20,21,22]. Malsch and Kieser (2001) included a doubled blind phase of 5 weeks, but did not include a run-in period [16]. Studies before 2009 used an alcoholic extract of Kava Kava [16,17,19,20,22], while studies published in the year 2009 or beyond utilized a dried, pressed Kava root in an aqueous solution [18,21,23]. The majority of the studies were single center trials, with Lehrl (2004) and Gastpar and Klimm (2003) being multi-center RCTs [17,19]. Two studies were crossover trials—Sarris et al. (2009) and Sarris et al. (2012) [18,23]. Sarris et al. (2009) had two study groups (A and B) in which placebo and Kava Kava interventions were switched after one week of treatment [23]. Sarris et al. (2012) was a three arm RCT in which the researchers switched the intervention between placebo, Kava Kava, and Oxazepam after one week of treatment [18]. No washout period was used in-between phases in either of the crossover trials [18,23]. (Table 2).

The majority of trials used the Diagnostic and Statistical Manual of Mental Disorders, either the third or fourth edition (DSM-III or DSM-IV) to classify and diagnose anxiety disorders used for their inclusion criteria (Table 2). The following disorders other than general anxiety were included: agoraphobia without panic disorder (300.22), social phobia (300.23), specific phobia (300.29), generalized anxiety disorder (300.02), or adjustment anxiety disorder (309.24) [16,17,19,20,21,22]. These disorders all include: excessive anxiety in relation to certain events, activities, or situations; symptom onset not due to drugs or underlying medical illnesses; and not characterized by traumatic experiences (such as in post-traumatic stress disorder) or behavioral compulsions (such as in obsessive-compulsive disorder) [27]. Connor and Davidson (2002) and Sarris et al. (2013a) screened specifically for GAD [21,22]. HAMA scores were also used for study inclusion in 6 of the 8 studies. [16-20,22] Malsch and Kieser (2001) was the only RCT that required a baseline HAMA score below 14, equating to mild anxious severity [16,28]. Sarris et al. (2009) required a minimum score of 10 on the Beck Anxiety Scale, which includes patients with mild anxiety levels [23,29]. The rest of the clinical trials focused on recruiting participants with moderate to severe anxiety and eliminating those with mild symptoms (Table 2).

3.2. Primary Outcome Measures

HAMA was the primary outcome measure in six of the trials [16,19,20,21,22,23]. The other two forms of measurement were the ASI score in Gastpar and Klimm (2003) and STAI-S in Sarris et al. (2012) [17,18]. Bf-S was a useful secondary measure, as values decreased from baseline in the same matter as HAMA scores, meaning an improvement in anxiety symptoms was witnessed [16,17,19]. Bf-S also provided data that allowed for better comparison of the other trials to Gastpar and Klimm (2003), which originally did not use HAMA as a primary measure and instead used ASI [17]. In relation to Bf-S, both Gastpar and Klimm (2003) and Lehrl (2004) demonstrated no major difference between the intervention and the control, but Kava Kava did have a slight greater decrease in Bf-S score (Table 3) [17,19]. Kava did outperform placebo in Malsch and Kieser (2001), who had a change in Bf-S score of 2.0 (IQ: 0 to 8) for placebo and 18.5 (IQ: 7 to 22) for Kava Kava ($p = 0.002$) (Table 3) [16]. Overall, primary outcome measures showed Kava Kava had a significant advantage over placebo in 3 out of 8 with a p-value of less than 0.05 [16,21,23]. In total, Kava Kava was more beneficial than placebo in 6 out of 8 studies, but results remained non-significant ($p > 0.05$) between parallel groups in Connor and Davidson (2002), Gastpar and Klimm (2003), and Lehrl (2004) (Table 3). In studies where placebo was initially on par or performed better than Kava Kava, post-hoc analyses were performed [20,22].

3.3. Response Rates

Responder rates were reported throughout studies as a primary measure to evaluate whether Kava Kava could treat anxiety symptoms. Responder rates were measured as either a 50% reduction in HAMA score [16,21,22], or a status of “very much improved” on the CGI scale [17,19]. A total of 5 studies were included in the pooling of responder data from Kava vs. placebo RCTs [16,17,19,21,22]. Geier and Konstantinowicz (2004) was not included in the meta-analysis because it utilized the per-protocol population instead of the intent-to-treat population. The per-protocol analysis for Geier and Konstantinowicz (2004) was significant with a p-value of 0.03 [20]. A weighted risk ratio of 1.50 [95% CI: 1.12, 2.01] was otherwise calculated from 330 participants (Fig. 2). Of the 170 participants in the Kava Kava group and 160 in the placebo group, 75 and 47 cases of a responder occurred, respectively. The data revealed that the smaller the sample size of the clinical trial, the higher the risk ratio was in favor of Kava Kava. Gastpar and Klimm (2003) had the largest sample size but the smallest RR at 1.29 [95% CI: 0.84, 1.98]. Malsch and Kieser (2001) had the smallest sample size and highest RR at 3.00 [95% CI: 1.16, 7.73] (Fig. 2). The test for overall effect revealed a significant difference between the intervention and control groups ($p = 0.007$). Additionally, the 5 studies were considered homogeneous. An I^2 statistic of 0% was reported for the pooled sample, suggesting statistical homogeneity (Fig. 2).

3.4. Adverse Events

The number of adverse events (AEs) were pooled from all studies and recorded in Table 4. Overall, there was no major difference in the number of adverse events between Kava Kava and placebo ($p = 0.574$). Kava Kava had a total of 58 while placebo had 43 adverse events (Table 4). The most common AEs were gastrointestinal issues, somatic symptoms (such as fatigue, headaches, muscle aches etc.), and motor problems (trembling and shakiness). Headaches were commented on in Sarris et al. (2013a) (43% in Kava, 23% in placebo; $p = 0.73$) [21]. In Malsch and Kieser (2001) and Lehrl (2004), no major AEs for Kava Kava were reported [16,19]. Withdrawal symptoms were not witnessed for Kava Kava in Malsch and Kieser (2001), Connor and Davidson (2002), Gastpar and Klimm (2003), Geier and Konstantinowicz (2004), Lehrl (2004), Sarris et al. (2009), and Sarris et al. (2013a) [16,17,19,20,21,22,23]. Sarris et al. (2012) expressed continued fatigue throughout the study, with 12 out of 22 participants in the Kava Kava group experiencing it as compared to 10 out of 22 participants in the placebo [18].

A number of additional side effects were reported. In Connor et al. (2001), ASEX scores—which measures sexual satisfaction and performance level—indicated no changes between baseline and treatment end [24], while scores in Sarris et al. (2013b) found a positive correlation ($r = 0.47$; $p = 0.009$) between anxiety reduction and better sexual function when combining scores for both genders [25]. Geier and Konstantinowicz (2004) utilized an inpatient setting and found cholesterol decreased from an unhealthy level down to below 240 mg/dL [20]. In contrast, in an outpatient sample, there was no change in blood pressure from the baseline value [24].

Liver function tests were performed and only reported in a few of the trials [24,25]. Three patients experienced increased levels of alanine aminotransferase (ALT) in Connor et al. (2001), although the results remained statistically non-significant ($p > 0.05$) [24]. In Sarris

Table 3
Outcome measure means and medians, standard deviations and interquartile ranges, and mean differences or change from baseline in Kava Kava randomized controlled trials.

Study	OM	Group	Sample Size	Baseline (SD, or IQ Range)	After treatment (SD, IQ Range)	Difference (SD, or IQ Range)	P for Kava vs. placebo
Malsch and Kieser 2001 [16]	HAMA	Placebo	20	13 (10–14)	14	−1 (-4–0)	0.01
		Kava	20	13 (11–14)	5.5	7.5 (0–8)	
	Bf-S	Placebo	20	42.5 (34–51)	40.5	2 (0–8)	0.002
		Kava	20	41 (33–52)	22.5	18.5 (7–22)	
Connor and Davidson 2002 [22]	HAMA	Placebo	17	18.8 (2.9)	10.3 (4.4)	8.5	NS
		Kava	18	19.9 (4.1)	14.2 (8.3)	5.7	
Gastpar and Klimm 2003 [17]	ASI	Placebo	70	47.8	40.6 (2.30)	7.2 (9.5)	NS
		Kava	71	47.6	39.0 (2.35)	8.6 (9.1)	
	Bf-S	Placebo	70	32 (22–40)	22.5 (13–36)	9.5	NS
		Kava	71	30 (20–40)	16 (8–31)	14	
Geier and Konstantinowicz 2004 [20]	HAMA	Placebo	25	27.6 (3.85)	16.8 (3.55)	10.8	0.1
		Kava	25	25.6 (3.95)	14.8 (4.3)	10.8	
Lehrl 2004 [19]	HAMA	Placebo	23	22.0 (11–31)	14	8.00 (1–18)	0.1
		Kava	34	22.0 (11–32)	11	11.0 (8–14)	
	Bf-S	Placebo	23	33.0 (12–47)	25	8.0 (4–21)	0.11
		Kava	34	29.5 (11–54)	18	11.5 (9–14)	
Sarris et al., 2009 [23]	HAMA	Placebo A	29	21.16 (3.52)	14.58 (5.86)	6.68	0.0001
		Kava A			11.26 (4.47)	9.9	
		Placebo B	18	20.28 (4.78)	19.50 (7.26)	0.78	
		Kava B			9.22 (5.96)	11.06	
Sarris et al., 2012 [18]	STAI-S	Placebo	22	40.50 (9.65)	42.36 (9.02)	−1.86	N/A
		Kava		43.41 (9.05)	43.59 (8.20)	−0.18	
		Oxazepam		44.09 (8.75)	41.50 (9.75)	2.59	
Sarris et al., 2013a [21]	HAMA	Kava	27	21.63 (4.2)	14.03 (7.01)	7.6	$p < 0.05$
		Placebo	31	19.50 (4.2)	15.26 (6.2)	4.2	

Positive value denotes improvement. ITT population was used unless otherwise noted [16-23].
SD = Standard Deviation; IQ = Interquartile Ranges; OM = Outcome Measure.
HAMA = Hamilton Anxiety Scale (Higher Score = Worsening Anxiety Symptoms).
Bf-S = Befindlichkeits-Skal Well-Being Scale (Higher Score = Worsening Anxiety Symptoms).
ASI = Anxiety Status Inventory (Higher Score = Worsening Anxiety Symptoms).
STAI-S = State Trait Anxiety Inventory State (Lower Score = Better Anxiety Symptoms).
NS = Not significant; N/A = Not available.

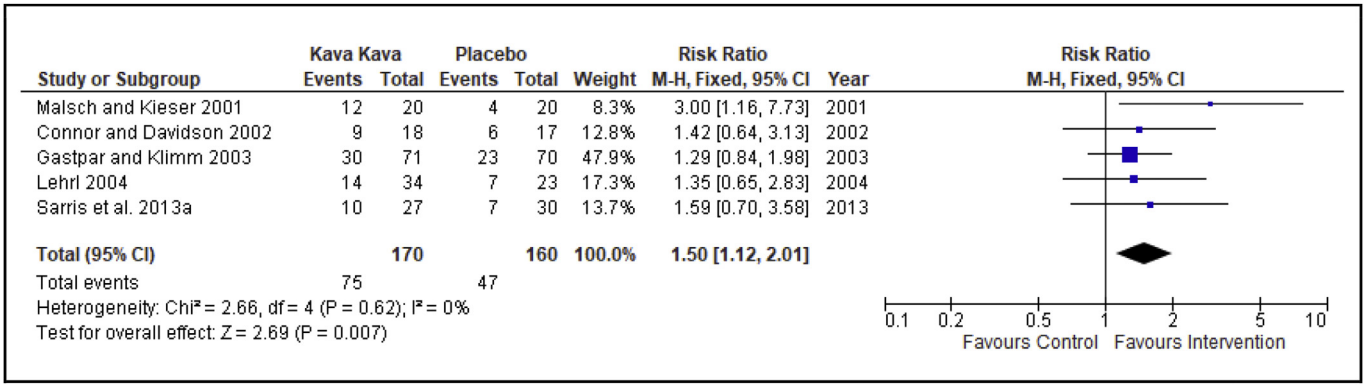

Fig. 2. Forest Plot of Relative Risk Ratios, Calculated from Response Rates Using CGI or HAMA Outcome Measures Data Found in Kava Kava Clinical Trials. Forest plot of comparison: Kava Kava vs. Placebo. CGI = Clinical Global Impression Scale. HAMA = Hamilton Anxiety Scale. Intent-to-treat populations used. A 50% reduction in HAMA score was considered a responder in Malsch and Kieser (2001), Connor and Davidson (2002), and Sarris et al. (2013a). A rating of "very much improved" on the CGI scale was used to classify responders in Gastpar and Klimm (2003) and Lehrl (2004). Geier and Konstantinowicz (2004) was not included in the analysis because values were only given for pre-protocol analysis [16,17,19,20,21,22].

et al. (2013b) higher levels of ALT and gamma-glutamyltransferase (GGT) but lower levels of aspartate aminotransferase (AST) were noted again with p-values greater than 0.05 [25]. Malsch and Kieser (2001), Gastpar and Klimm (2003), Lehrl (2004), Geier and Konstantinowicz (2004), Sarris et al. (2009), and Sarris et al. (2012) all reported results within the normal range. [16-20,23].

3.5. Bias

All of the Kava Kava RCTs utilized a double-blinded method, which greatly decreased the risk of bias in the review. Heterogeneity tests showed no difference in study results ($p = 0.62$) as well as no statistical variation between the studies due to chance ($I^2 = 0\%$), suggesting treatments in each study were equal in effectiveness (Fig. 2). However, the funnel plot was not symmetrical as the studies do not converge into a funnel-shaped distribution (Fig. 3).

3.6. Subgroup Analysis

Responder rates were further broken down into subgroups according to study design and patient demographics. The implementation of a run-in phase was found to decrease the weighted risk ratio (Fig. 4).

Table 4
Number of adverse events found in Kava randomized controlled trials.

Study	Kava Kava	Placebo
Malsch and Kieser 2001 [16]	–	–
Connor and Davidson 2002 [22]	20	18
Gastpar and Klimm 2003 [17]	5	4
Geier and Konstantinowicz 2004 [20]	2	1
Lehrl 2004 [19]	0	1
Sarris et al., 2009 [23]	4	1
Sarris et al., 2012 [18]	12	10
Sarris et al., 2013a [21]	15	8
Total	58	43

Adverse events were reported based on the number of actual events. A two-sided, unpaired T-test used to test for statistical differences revealed a p-value of 0.574 between the intervention and control groups [16-23].

Of the four RCTs that did utilize a run-in period, a risk ratio of 1.36 [95% CI: 1.00, 1.86] was calculated [17,19,21,22]. Malsch and Kieser (2001) did not include a run-in and resulted in a much higher RR at 3.00 [95% CI: 1.16, 7.73] [16]. The length of the double blinded treatment phase may have resulted in different risk ratios, with studies having a treatment length of 4 weeks or less reporting a risk ratio of 1.32 [95% CI: 0.94, 1.85][17,19,22] and those 5 weeks or greater calculating an RR at 2.12 [95% CI: 1.15, 3.90][16,21] (Fig. 5). Tests for subgroup differences revealed both run-in phase and duration of the clinical trial to be non-significant at 0.12 and 0.19, respectively (Figs. 4 and 5). The extraction method used was shown to have no effect on clinical results, as risk ratios of 1.48 [95% CI: 1.08, 2.03] for an alcoholic solvent [16,17,19,22] and 1.59 [95% CI: 0.70, 3.58] for aqueous kava root [21] were calculated with no differences between subgroups (p = 0.88) (Fig. 6). The amount of kavalactones taken may have had an effect, as trials implementing a daily dosage of less than 200 mg of kavalactones [17,19] reported an RR of 1.30 [95% CI: 0.90, 1.89] as opposed to those above [16,21,22] with an RR of 1.86 [95% CI: 1.15, 3.02] (Fig. 7). However, there were no statistically significant subgroup differences due to dosage of kavalactones (p = 0.25) (Fig. 7). Malsch and Kieser (2001) was also the only RCT to specifically use a mildly anxious population in their study sample, with a HAMA score at or below 14 being an inclusion criterion [16]. Separating the trials by anxiety intensity did not change the overall conclusions as noted above (Fig. 4).

An additional analysis was performed looking only at high-intensity anxiety RCTs. The remaining four trials that included participants with moderate to severe anxiety were further broken down to take into account the amount of Kava Kava being consumed daily [17,19,21,22]. Trials at or below 200 mg per day were weighted and averaged and compared with trials among 200 mg per day. Lower doses found in Gasptar and Klimm (2003) and Lehrl (2004) resulted in a RR of 1.30 [95% CI: 0.90, 1.89] while higher doses seen in Connor and Davidson (2002) and Sarris et al. (2013a) showed an RR of 1.51 [95% CI: 0.85, 2.66] (p = 0.68) [17,19,21,22]. Similar subgroup differences calculations were performed in reference to the length of the double-blinded treat phase in addition to the method of extraction used, but no statistically significant subgroup differences were noted (p = 0.68).

3.7. Kava Kava vs. Anxiolytic Drug

Boerner et al. (2003) was the only clinical trial that compared Kava Kava to two anti-anxiety medications [26], while Sarris et al. (2012) include a third arm comparing Oxazepam (a benzodiazepine) to Kava Kava along with placebo [18]. Boerner et al. (2003) was an eight week, double-blinded, multi center RCT with a one week follow-up period to check for withdrawal symptoms [26]. Methodology included 400 mg LI150 (Kava extract standardized to 30% kavalactones, in 96% ethanol in water) (n = 43), verses 10 mg Buspirone (n = 42), verses 100 mg Opipramol (n = 42). Participants were in an outpatient setting between 25 and 65 years of age with a current diagnosis of ICD-10 GAD, a minimum score of 19 on HAMA, and a maximum total score of 12 on HAMD-17. Primary efficacy measure was change in HAMA score and responder rates from baseline to 8 weeks post-treatment intervention [26].

In both trials of Kava Kava vs. Anti-Anxiety Drug, Kava Kava performed with mixed results. In Sarris et al. (2012), there was no change in STAI-S scores from baseline to post-treatment for either placebo, Kava Kava, or Oxazepam (Table 3) [18]. Kava Kava showed effectiveness in treating anxiety in Boerner et al. (2003), as changes in HAMA scores were comparable between all three intervention methods: Kava Kava 6.8 points (27.9% change from baseline), Buspiron 7.1 points (29.7%), and Opipranol 6.7 points (27.9%) [26]. Though Kava Kava

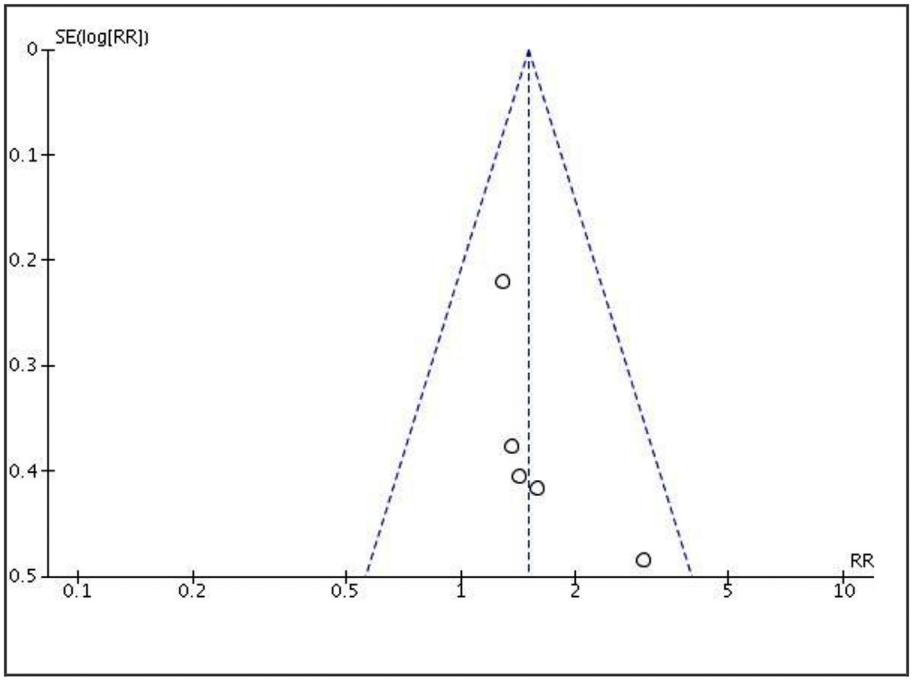

Fig. 3. Funnel plot of comparison of Relative Risk Ratios, Calculated from Response Rates Using CGI or HAMA Outcome Measures Data Found in Kava Kava Clinical Trials. CGI = Clinical Global Impression Scale. HAMA = Hamilton Anxiety Scale. A 50% reduction in HAMA score was considered the definition of a responder for Malsch et al. (2001), Connor and Davidson (2002), and Sarris et al. (2013a). Status of "Very Much Improved" on CGI post treatment was considered the definition of a responder for Gastpar and Klimm (2003) and Lehrl (2004) [16,17,19,21,22].

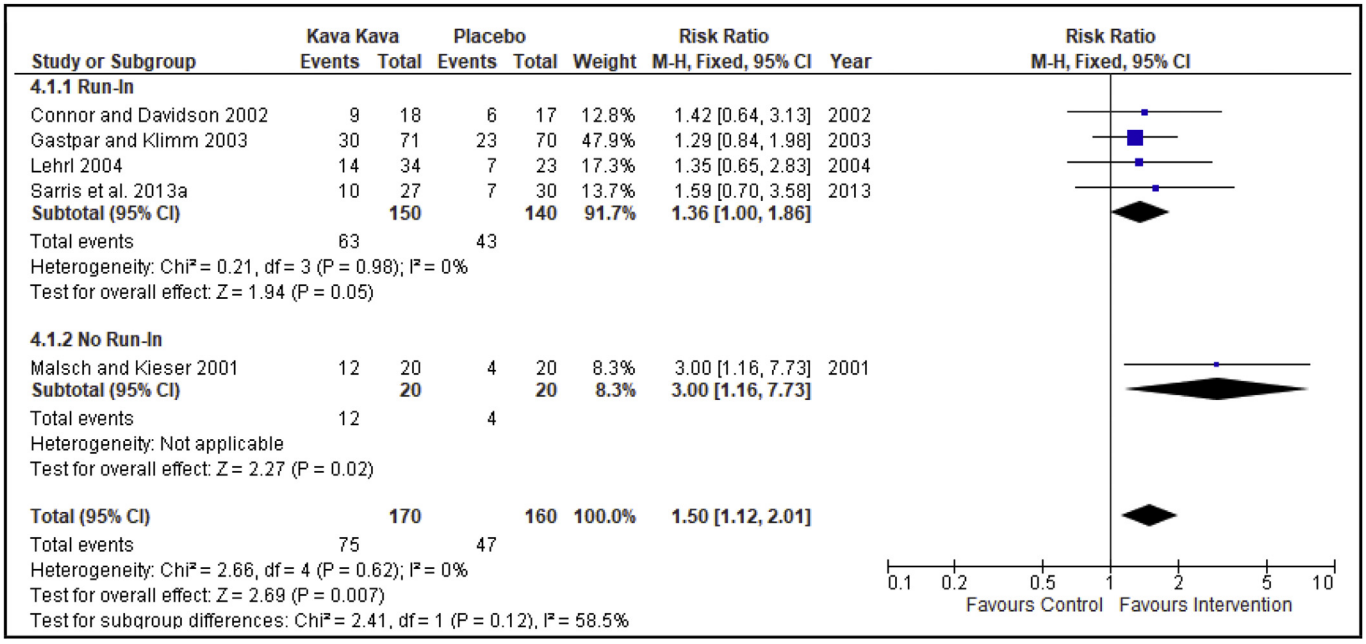

Fig. 4. Sub-Analysis of Kava Kava Randomized Controlled Trials; Analyzing the Effects of a Run-in Phase. Test for subgroup differences revealed a P-value of 0.12 for the utilization of a run-in phase [16,17,19,21,22].

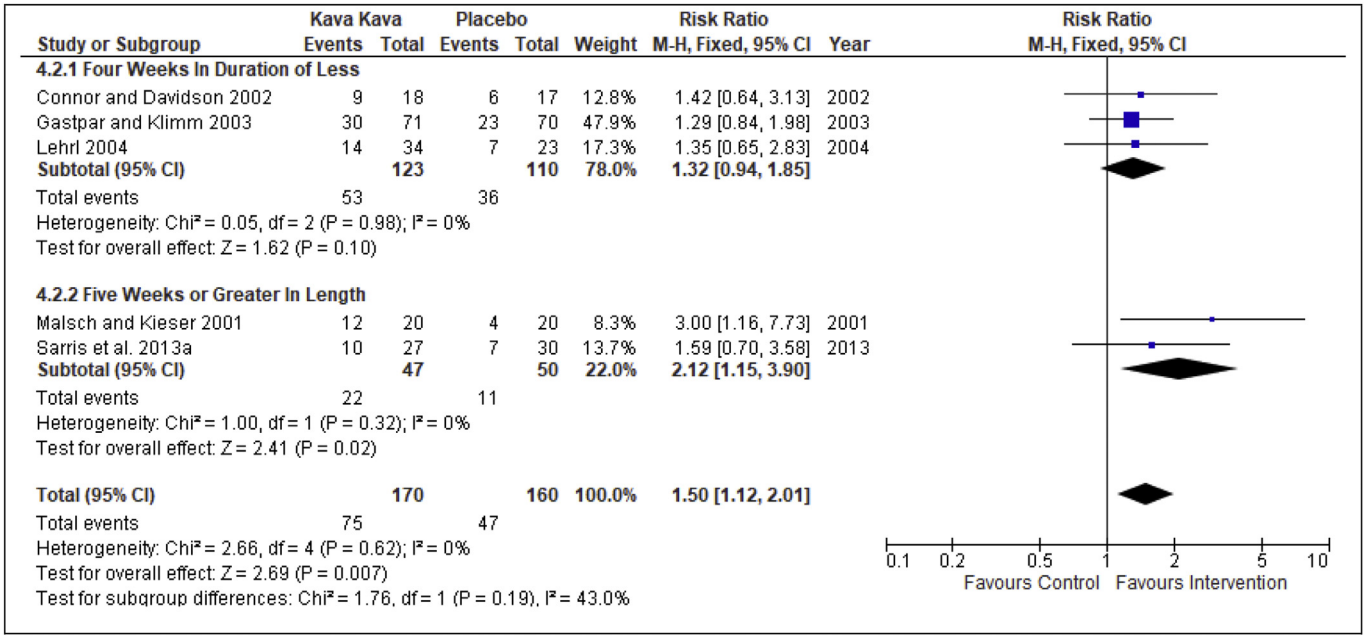

Fig. 5. Sub-Analysis of Kava Kava Randomized Controlled Trial; Analyzing the Effects of the Duration of Double-Blind Treatment Phase. Test for subgroup differences revealed a P-value of 0.19 for the duration of double blinded treatment phase. Treatment phase of double blind was broken into two groups based on being equal to or less than 4 weeks in length [16,17,19,21,22].

was as effective as Buspiron and Opipranol, there was a higher percentage of participants describing side effects in Kava Kava than the other anxiolytic treatments. A total of 27 adverse events were reported in Kava Kava from 14 patients, thus making the percent of people affected 33% (n = 43). Buspiron observed 16 adverse events (AEs) in 10 patients (24% affected, n = 42) while Opipranol identified 14 AEs in 11 patients (26% affected, n = 42) [26]. Opipranol and Buspiron had higher tolerability rates than Kava Kava at 97.6% [26]. Tolerability rates were slightly lower in Kava Kava, with 86.1% of patients remarked as having “good” or “very good” tolerability [26].

4. Discussion

Results point to Kava Kava as an all-around treatment for anxiety relief. Individual studies confirm Kava Kava decreases anxiety symptomatology with the absence of liver failure. Previous reviews of articles published prior to the year 2000 have found similar results confirming Kava Kava's clinical effectiveness. Pittler and Ernst (2003) and Witte et al. (2005) also concluded Kava Kava may be more clinically effective in patients who are younger and/or female [7,15]. Individual RCT conclusions found in this analysis seem to confirm these demographic trends found in previous reviews [16,21,23]. This review also

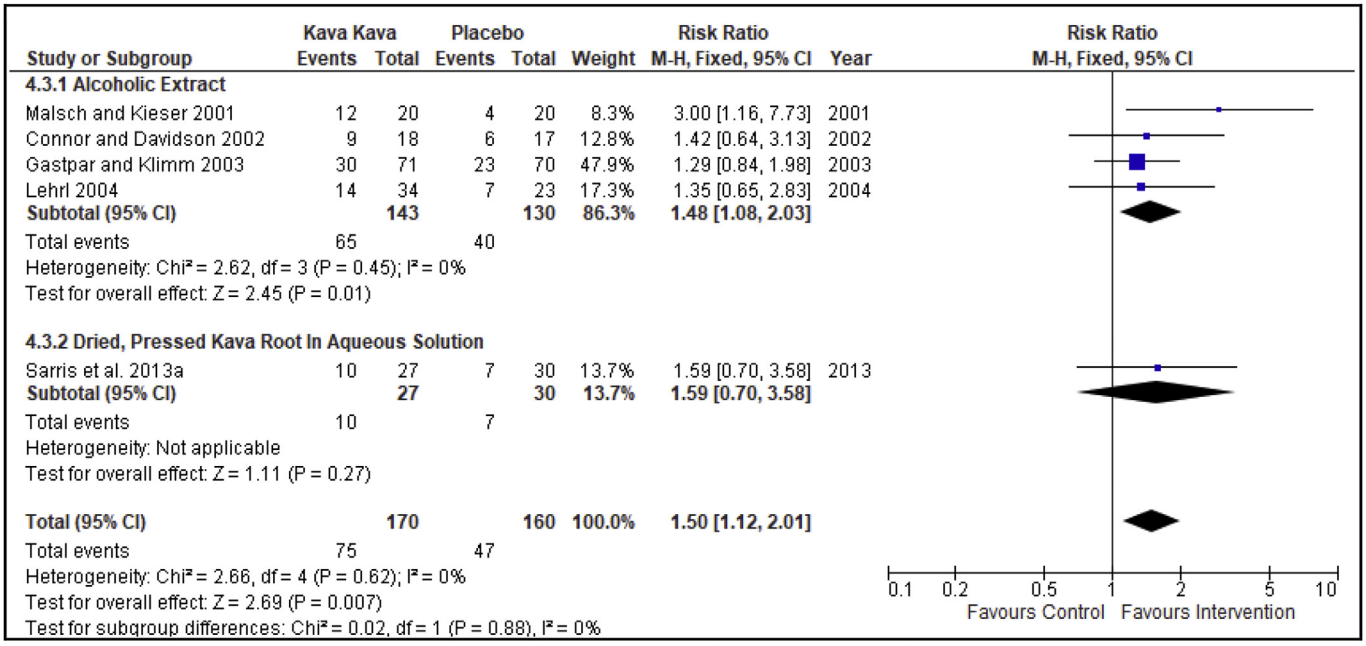

Fig. 6. Sub-Analysis of Kava Kava Randomized Controlled Trials; Analyzing the Effects of Extraction Method Used. Test for subgroup differences revealed a P-value of 0.88 for extraction method. Methods were broken down into alcohol and polar extraction techniques versus dried, pressed kava root in an aqueous extract [16,17,19,21,22].

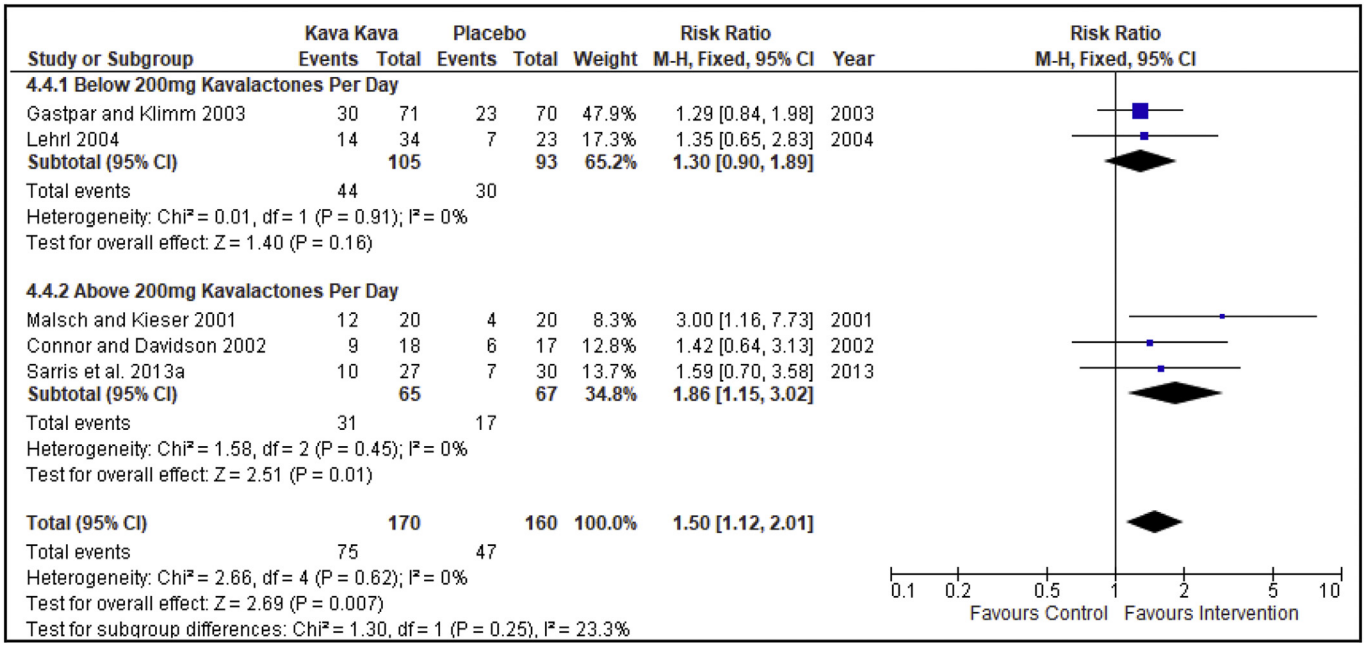

Fig. 7. Subanalysis of Kava Kava Randomized Controlled Trials; Amount of Kavalactones Consumed Per Day. Test for subgroup differences revealed a P-value of 0.25 for the number of kavalactones per daily dose. Dosage was based on taking greater than 200 mg or less than 200 mg of kavalactones in one day. [16,17,19,21,22].

found evidence warranting further research into standardizing: Kava Kava associated liver failure; length of double-blind intervention phase, clinical dosage, and study sample; as well as kavalactone composition and extraction technique.

Research has previously indicated Kava Kava's role in liver failure [8-11]. Kava Kava versus placebo suggests there are no additional side effects ($p = 0.574$) (Table 4), while the anti-anxiety drug studies showed more headaches and lower tolerability levels for Kava Kava [18,26]. This discrepancy could potentially be explained from the length of the intervention period. Boerner et al. (2003), despite not including a placebo, had the longest intervention period at 8 weeks and reported higher levels of headaches among participants [26]. Placebo-controlled RCTs had an intervention period of 6 weeks or less [16,17,19,21,22]. The summary of U.S. case studies showed the onset of jaundice from consuming as little as 75 mg of kavalactones for 44 days over the course of a 3.5 month period after it was implemented [8]. The European case reports also detailed Kava Kava use as little as 60–240 mg of kavalactones per day for 8 weeks to 4 months when associated with hepatotoxicity [8]. Due to the length of the 8 week double-blinded treatment phase that was used in Boerner et al. (2003) [26], this suggests the risk of hepatotoxicity is based more on the duration of consumption of Kava Kava rather than the amount taken,

since the case studies reported liver failure at lower doses, ranging once again from 60 to 240 mg [8]. Further research is necessary to fully understand the long-term effects of Kava Kava and if the amount of kavalactones plays a role in determining the onset of hepatotoxicity.

Meta-analysis of responder rates revealed a slight relative risk ratio in favor of Kava Kava. Final weighted RR was 1.50 [95% CI: 1.12, 2.01] (Fig. 2). Pittler and Ernst (2003) conducted a meta-analysis of 6 clinical trials (n = 345) with HAMA scores of Kava Kava versus placebo. The final result was favoring Kava Kava with a weighted mean difference of 5.0 [95% CI: 1.1, 8.8], showing that HAMA scores and anxiety symptoms decreased overall [7]. Unlike Pittler and Ernst (2003), this review included 5 studies in the meta-analysis. A sixth was considered but not used because it only reported per-protocol data [20]. This review showed an increasing RR was inversely proportional to sample size (Figs. 2 and 3) and does support Kava Kava being an effective treatment for anxiety ($p = 0.007$), but only one trial in this meta-analysis used a study population that was above 100 participants [17]. The other trials used a sample size less than 50 [16,19,21,22]. Some studies also point to Kava Kava being a better treatment for low anxious severity [16]. Malsch and Kieser (2001) originally limited their inclusion criteria to a HAMA score less than 14 [16], indicating mild anxiety [25], and reported a RR in favor of Kava Kava at 3.00 [95% CI:1.16, 7.73] (Fig. 2). Therefore, a more thorough and large-scale clinical trial could further support the conclusion that Kava Kava is an overall effective treatment for anxiety and possibly even more potent in low-severity sample populations.

Witte et al. (2005), previously showed Kava Kava to also be more effective in younger adults and females. All three studies—Malsch and Kieser (2001) Sarris et al. (2009), and Sarris et al. (2013a)—that were statistically significant ($p < 0.05$) and in favor of Kava Kava support this conclusion (Tables 1 and 3) [16,21,23]. Compared to the weighted age of all Kava Kava versus placebo trials, which is 48.8 years (n = 427), Malsch and Kieser (2001) had a lower age at 39.1 and 42.3 years for Kava Kava and placebo, respectively [16]. Sarris et al. (2009) followed a similar trend, with ages of 44.4 years for Kava Kava and 43.1 years for placebo being given. Sarris et al. (2013a) reported 29.5 years of age for Kava and 30.6 years for placebo (Table 1) [21]. Malsch and Kieser (2001) and Sarris et al. (2013a) also used a daily dose of kavalactones above 200 mg per day (Table 2), suggesting that despite no significant difference being detected in the subgroup analysis (Fig. 7, $p = 0.25$), a higher clinical dosage in combination with a younger study sample could potentially improve study results [16,21]. Lastly, Sarris et al. (2013a) had a higher percentage of female participants in the treatment group compared to placebo (74% in Kava; 43% in placebo), which could have contributed to better clinical results for Kava Kava [21]. Previous reviews also demonstrated that kavalactones may have better clinical outcomes in younger and female participants [7,15].

The subgroup analysis suggests pressed, dried kava root in an aqueous extract to be as effective as the alcoholic extracts utilized in earlier trials. The risk ratios calculated were 1.59 [95% CI: 0.70, 3.58] and 1.48 [95% CI: 1.08, 2.03], respectively ($p = 0.88$) (Tables 3 and 4; Fig. 6). There was no difference in AEs witnessed between trials using an alcoholic [16,17,20,22,23] or aqueous extract [18,19,21]. This contradicts the claim that higher concentrations of kavalactones methysticin and flavokawain B are likely to cause more harm to the body [5,6,10,11]. Secondly, while alcoholic extracts were found to have higher concentrations of kavalactones [5,11], and thus be more cytotoxic to the liver, as of 2011 no studies have been published detailing the effects of kava on P450 enzymes in humans [11]. This further emphasizes the need for more research, as other laboratory results contradict the outcomes found in this review. A suggestion for future trials would be to include the complete chemical composition of all the kavalactones found in a supplement given in the RCT, as it could provide important information on what combination of kavalactones and extraction technique could produce the best clinical results, or rather prevent the worst cytotoxic effects on liver hepatocytes.

4.1. Limitations

Limitations include not contacting the publishing authors of RCTs included in this review and using a reference check to account for publication bias instead of reaching out to pharmaceutical companies. This may have proven helpful in finding unpublished studies/data. The number of clinical trials included in the meta-analysis was low but consistent with previous reviews which only reported results from 6 RCTs [7,15].

Variability in the study population of studies meeting inclusion/exclusion criteria could potentially affect the results obtained. All RCTs, except Gastpar and Klimm (2003) [17], had a sample population of 40 or less in each study arm [16-23]. Geier and Konstantinowicz (2004) also utilized an inpatient population with a median age of 76 years [20] while the majority of clinical trials used an outpatient sample [16-23]. Gender distributions were not consistent across all trials, with female representation ranging from 30 to 80% (Table 1). There was also a wide variety of anxiety disorders and methods of measurement that were included within this review (Table 2). Originally, the research team wished to limit the study population to either general anxiety or a specific anxiety disorder, but due to the insufficient research available, the inclusion criteria had to be adjusted (Fig. 1).

Other demographics that were reported sporadically in the trials were race, education level, duration of anxiety symptoms, religious affiliation, and sub-classifications of non-psychotic mental disorders (ex. agoraphobia, social phobia, GAD, major depressive disorder, etc.) [16-23,29] but the lack of other evidence found in this review prevents the review team from reaching any definitive conclusions about Kava Kava's effectiveness in GAD patients alone [21,22].

5. Conclusions

Kava Kava appears to alleviate anxiety symptoms as previously described in Pittler and Ernst (2003) and Witte et al. (2005) with no additional AEs as compared to placebo [7,15]. Study samples in this analysis provided a wide range of demographics to examine. Trends previously mentioned in other reviews were noted to be present in this analysis. The research team found Kava Kava to increase anxiety relief in both younger and female samples. There is also some concern over long term Kava Kava use [8-11], but the data extracted in this review seems to support taking Kava Kava for short periods of time, specifically under 8 weeks. It should also be noted that taking as little as 60 mg of kavalactones can induce liver damage [8], while taking a higher dose of 400 kavalactones was previously found safe [14] and could potentially increase clinical results (Fig. 7). Side effects compared to placebo and other anti-anxiety medications were no different (Table 4) [18,29]. Most studies did not report heightened laboratory values for the liver bloodwork, therefore concluding the chances of hepatotoxicity are rare. [16–20,23] The most common AEs in this review for Kava Kava included gastrointestinal and musculoskeletal disorders, headaches, and fatigue. [17-23, 26].

Further research should be aimed at studying the long-term effects of Kava Kava and its possible relation to hepatotoxicity. Including the composition of kavalactones in the study methods would contribute to discovering the combinations of kavalactones with higher toxic effects. A longer running double-blinded trial could also establish if prolonged usage of Kava Kava leads to increased adverse events or if it may be a more effective clinical alternative to other anti-anxiety medications. The amount of existing research from this review and published case studies does not currently encourage the prolonged use of Kava Kava, as the possibility of liver failure is still viable as early as 8 weeks for long-term users. If choosing to consume Kava Kava for anxiety relief, the review team precautions users to consume it for short periods only until further research establishes hepatotoxicity is no longer a valid concern [30]. A clinical trial is currently underway studying the long-term effects of Kava Kava and was last updated on May 15, 2017 [31]. Patients

should continue to be aware of the possible side effects of Kava Kava until long-term safety is verified, as the onset of AEs could indicate the beginnings of liver failure.

Conflicts of Interest

This review did not receive any grant funding from agencies in the public, commercial, or not-for-profit sectors. The authors do not have any conflicts of interest to disclose.

Authorship

All authors participated in the preparation, reading and approval of the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2018.09.003.

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