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*REVIEW ARTICLE*

# Kava for Generalized Anxiety Disorder: A Review of Current Evidence

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**Abstract**

***Background:*** Generalized anxiety disorder (GAD) is a chronic and debilitating condition characterized by persistent and overpowering anxiety. Treatment of GAD with antidepressants and benzodiazepines is only moderately effective and not free from side effects. Kava (*Piper methysticum*) has been explored as a potential phytotherapeutic option for GAD.

***Objectives:*** To perform a systematic review and meta-analysis of the available evidence on Kava as a treatment for GAD.

***Methods:*** Systematic search of English-language publications from major databases for clinical trials reporting the effects of Kava for the treatment of GAD.

***Results:*** Twelve articles were included in this review. Evidence supporting Kava as an effective treatment for GAD was found in two placebo-controlled trials and a reference-controlled trial. One negative trial demonstrated that Kava was not more effective than placebo. Meta-analyses of the results of three placebo-controlled trials ($n = 130$) favored Kava for GAD treatment with effect sizes between 0.59 and 0.99 (standard mean difference) without reaching statistical significance. Kava is an appealing treatment option to GAD patients who are more attune to natural remedies or lifestyle approaches to reduce stress. Positive patient experiences and improvement of vagal cardiac control due to Kava treatment were also reported in the literature. Kava is safe and well tolerated for short-term (4–8 weeks) therapeutic use at a dosage of 120–280 mg per day of Kavalactones, regardless of dosage schedule.

***Conclusions:*** Current evidence, although promising, is insufficient to confirm the effect of Kava for GAD treatment beyond placebo. New evidence is expected from a large, multisite ongoing trial.

**Keywords:** Kava, generalized anxiety disorder, phytomedicine, systematic review, meta-analysis

## Background

Generalized anxiety disorder (GAD) is a common, chronic, and debilitating condition with a lifetime prevalence of 4.3%–5.9%.[1] It is characterized by persistent and overpowering anxiety, with symptoms such as fatigue, restlessness, and difficulty concentrating, as well as somatic signs that include heart palpitations and respiratory distress, severely affecting a patient's quality of life.[1,2] The first line of treatment for GAD typically includes antidepressants like selective serotonin reuptake inhibitors (SSRI, e.g., paroxetine), serotonin-norepinephrine reuptake inhibitors (SNRI, e.g., venlafaxine), tricyclic antidepressants (e.g., opipramol), as well as benzodiazepines (e.g., diazepam).[1,2] Unfortunately, these pharmaceutic drugs have only modest clinical effect.[3] There are also dependence and withdrawal issues with these drugs, as well as the burden of side effects such as drug tolerance, daytime drowsiness, and cognitive impairment.[4,5] Kava (*Piper methysticum*) has been explored as a potential phytotherapeutic option for GAD.[5]

Kava is a perennial shrub, native to the Pacific Ocean societies with historical and cultural significance. Within the Pacific, Kava liquid extracts have been used for thousands of years. They are traditionally prepared from masticated roots

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combined with water or coconut milk.[5] Apart from its use as a recreational beverage, Kava infusion is considered in traditional medicine to have a sedative activity that soothes the nerves, induces sleep, as well as calms the mind and body.[6]

The main active constituent of Kava is the fat-soluble Kavalactones (dihydromethysticin, kavain, dihydrokavain, methysticin, yangonin, and desmethoxyyangonin) found in the resin. Kavalactone content varies with the cultivar, plant part (root, stem, aerial parts), place of origin, and growing conditions. Therefore, Kava extracts are regularly standardized for Kavalactone content.[7] Kavalactones are responsible for the pharmacodynamics of Kava's anxiolytic action; primarily through potentiating gamma-aminobutyric acid (GABA) type A receptors, reducing excitatory neurotransmitter release, as well as limiting neuronal reuptake of dopamine and prefrontal cortex noradrenalin.[8,9] It is the synergistic action of these properties that can potentially inhibit the development and progression of GAD.[5]

Concerns over hepatotoxicity has led to Kava's withdrawal or restriction in many countries since 2002.[9] It has emerged that quality problems, including the use of faster growing varieties (cultivars) and adulteration of the extract with aerial parts of the plant rather than just the peeled rhizomes and roots, potentiated hepatotoxicity in Kava products.[10,11] In addition, the use of ethanol and acetone extraction methods, instead of the traditional water-based extraction method, in commercial preparation in Western countries, further increased the risk of toxicity of non-Kavalactone contents.[10]

A safety assessment of Kava by the World Health Organization (WHO) subsequently established that hepatotoxicity due to Kavalactones was rare, more likely to be caused by background effects of Kava-drug interactions, excessive alcohol intake, metabolic or immune mediated idiosyncrasy, overdosing, or preexisting liver disease, as well as non-Kavalactone constituents from products made from acetonic and ethanolic extracts.[12] WHO recommended the creation of a pharmacopoeia standard for Kava to address the issues of quality, plant parts, dosage, and methods used for preparation.[12] The restriction on Kava has since been lifted in many jurisdictions in Europe, including Germany.[13]

Several reviews have confirmed the efficacy of Kava for treating anxiety. A Cochrane systematic review by Pittler and Ernst of 12 double-blind randomized controlled trials (RCTs, $n=700$) found Kava extract to be a safe and effective symptomatic treatment for anxiety.[14] Meta-analysis of seven of the included trials ($n=380$) showed a significant effect toward a reduction of the Hamilton Anxiety Rating Scale (HAM-A) total score (weighted mean difference [WMD]: 3.9, 95% confidence interval [CI]: 0.1–7.7) in patients receiving Kava extract compared with patients receiving placebo.[14] A meta-analysis of a specific acetonic Kava extract (WS®1490), in patients with nonpsychotic anxiety from six trials ($n=345$), showed that Kava has an effective success rate of odds ratio = 3.3 (95% CI: 2.09–5.22) and a WMD of 5.94 (95% CI: −0.86 to 12.8) points on the HAM-A scale which were better than placebo.[15] A more recent comprehensive review of Kava also found evidence supporting its use in the treatment of anxiety with a significant result occurring in four out of six studies reviewed with effect size of 1.1 (mean Cohen's $d$).[5]

However, none of these reviews and meta-analyses is specific to GAD. They included studies with a wide spectrum of anxiety patients ranging from perimenopausal anxiety to preoperative anxiety, to nonpsychotic anxiety (with some GAD participants included). Hence, the specific effect of Kava on GAD is not clear. In addition, an effect size analysis of pharmacologic treatments for GAD by Hidalgo et al. found complementary and alternative medicine, including Kava, to be ineffective (effect size = $-0.31 \pm 0.46$ [standard deviation, SD]).[3] The result was derived from the meta-analysis of a Kava study and a homeopathic study. Therefore, there is a lack of a systematic review and meta-analysis of the evidence supporting Kava for the treatment of GAD.

## Objectives

To perform a systematic review and meta-analysis of the available evidence on the effects and efficacies of Kava for the treatment of GAD.

## Methods

### Literature search

The authors conducted a systematic keyword search on PubMed, Cochrane Library (Issue 5 of 12, May 2017), CINAHL, Embase, and PsycINFO (1967 to June week 1 2017) without any restriction in year of publications. Keywords used were ''Kava,'' ''Piper methysticum,'' ''Generalized Anxiety Disorder,'' ''nonpsychotic anxiety,'' or ''anxiety'' in different combinations. The authors also manually searched the reference lists of current systematic reviews and meta-analyses on Kava and anxiety to identify any relevant clinical studies. The search was conducted during May and June 2017 by two authors (S.L.O. and P.H.) independently.

### Selection criteria

Criteria of inclusion for qualitative analysis were as follows: (1) clinical trial, (2) published in English, (3) Kava extract as the mono therapeutic agent for intervention, (4) a majority or all participants were diagnosed with GAD according to International Classification of Diseases and Related Health Problems version 10 (ICD-10), *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III-R, DSM-IV, or DSM V 300.02. Additional criteria for meta-analysis were as follows: (5) double-blind, randomized placebo-controlled (DBRPC) trial, (6) outcome measures reported in HAM-A score, (7) change from baseline to post-treatment data was reported, (8) study must be completed. The selection was conducted by two authors (S.L.O. and P.H.) and reviewed by the third author (S.C.P.).

### Data extraction and statistical analysis

The authors extracted the following information from the selected clinical studies for qualitative synthesis: type of study, the number of participants and GAD symptom severity, intervention methods and duration, primary outcomes, and adverse events. For meta-analysis, the authors calculated the standardized mean difference (SMD) between Kava and placebo groups using a random effect model. The authors examined the heterogeneity between studies using $I^2$ statistics, with values of 25%, 50%, and 75% reflecting low, moderate, and high heterogeneity, respectively. The authors used only published data for analysis. The sample sizes of

Kava and placebo groups, as well as the mean HAM-A scores with SDs of the Kava and placebo groups at baseline and completion of trials from each selected trial, were extracted for analysis. Review Manager 5.3 was used to calculate and display the results. Data extraction and meta-analysis were performed by S.L.O. and reviewed by S.C.P.

### *Assessment of methodological quality*

The authors assessed the included DBRPC trials for meta-analysis using the Cochrane Collaboration's tool for assessing risk of bias, which was considered to be the best available tool for assessing the methodological quality of RCTs.[16] Criteria of assessment include adequacy in the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.[17] Review Manager 5.3 was used to tabulate and display the results. Risk of bias assessment was performed by S.L.O. and reviewed by S.C.P.

## Results

### *Search results*

The search flow is documented in Figure 1. The systematic search yielded 158 records after duplications were removed. After initial screening, 27 full-text articles were assessed for eligibility. Fifteen articles were excluded with the reasons stated in Table 1. Twelve articles were included in this review.[18–29] Only three DBRPC trials met the inclusion criteria for quantitative synthesis and meta-analysis.[20,24,27]

### *Qualitative synthesis*

Kava versus placebo. Six DBRPC trials that studied the efficacy of Kava for GAD treatment were reported in five of the included articles. Among them include a negative trial, two uncompleted trials, two positive trials, and an ongoing trial. The characteristics of these studies are shown in Table 2.

Connor and Davidson[20] was the first DBRPC trial conducted among patients with GAD according to the DSM-IV, modified with only 1 month of ongoing symptoms. This 4-week trial, with the Kava group treated with a standardized Kava extract (KavaPure®), reported negative results in both primary (changes in HAM-A scores) and secondary measures (changes in Hospital Anxiety and Depression Scale, HADS; changes in Self Assessment of Resilience and Anxiety, SARA), suggesting that Kava was not superior to placebo in the treatment of GAD.[20]

Two additional trials were reported in Connor et al.[22] The first study (Study I) was similar in study design compared to Connor and Davidson,[20] but differed in the entry criteria, accepting patients with milder anxiety symptoms (baseline HAM-A score of 12–20). The second study

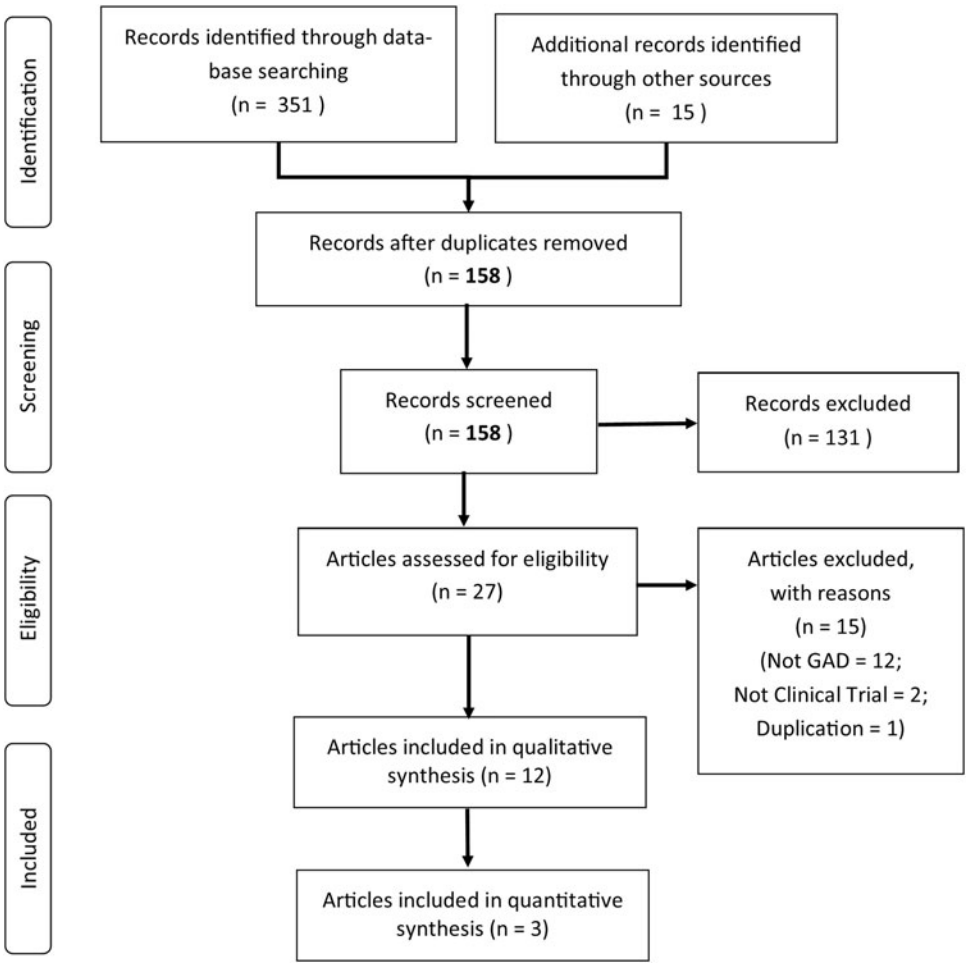


**FIG. 1.** Literature search flow diagram (based on PRISMA 2009). GAD, generalized anxiety disorder.

Table 1. Full Text Articles Excluded with Reasons

| *Full text articles excluded* | *Reasons* |
|---|---|
| Boerner[37] | Not clinical trial (a case report) |
| Cagnacci et al.[38] | Not GAD participants |
| De Leo et al.[39] | Not GAD participants |
| Gastpar and Klimm[40] | Majority were not GAD participants |
| Geier and Konstantinowicz[41] | Majority were not GAD participants |
| Jacobs et al.[42] | Not GAD participants |
| Lehmann et al.[43] | Not GAD participants |
| Lehrl[44] | Majority were not GAD participants |
| Malsch and Kieser[45] | Majority were not GAD participants |
| Pittler[46] | Not clinical trial (a commentary) |
| Sarris et al.[47] | Not GAD participants |
| Sarris et al.[48] | Duplication |
| Sarris et al.[49] | Not GAD participants |
| Singh et al.[50] | Not GAD participants |
| Volz and Kieser[51] | Majority were not GAD participants |

GAD, generalized anxiety disorder.



(Study II) differed from Connor and Davidson[20] in terms of the duration of GAD at study entry (≥6 months), the duration of study (8 weeks), the Kava tablets used (''WS 1490''), and a third arm of active treatment with venlafaxine-XR. Unfortunately, both trials were terminated prematurely due to concerns raised following reports of possible hepatotoxicity with Kava.[22] Data analysis of Study I and II was not reported separately since only results from a small number of participants were available. Instead, data from these uncompleted trials were used in the pooled analysis with Connor and Davidson.[20] This pooled analysis also found no anxiolytic effect of Kava. On the contrary, a significant effect in favor of placebo was observed in participants with higher anxiety at baseline.[22] Hence, the placebo responsivity of GAD was a challenge in investigating this disorder, as noted by the authors.[22]

Sarris et al.[24] was the first clinical trial assessing the efficacy of aqueous extract of Kava in patients with mild-to-moderate anxiety. The inclusion criteria of this trial did not restrict to patients with GAD, although 66% of the participants did satisfy the DSM-IV criteria for GAD diagnosis. This was a crossover trial with 1 week of Kava treatment phase and 1 week of placebo treatment phase without any washout period in between. The weighted mean of the response during each phase was a reduction of 11.4 points over placebo on the HAM-A scale. The results favored Kava over placebo with a substantial effect size ($p < 0.0001$, Cohen's $d = 2.24$).[24]

Sarris et al.[27] was the first parallel trial assessing aqueous extract of Kava in the treatment of GAD with all participants restricted to DSM-IV GAD diagnosis. It was conducted with a larger sample size ($n = 58$ vs. $n = 37$) and a longer duration (6 vs. 3 weeks) compared to Sarris et al.[24] The superiority of Kava over placebo was also demonstrated in this trial, although with a more moderate effect size ($p = 0.046$, Cohen's $d = 0.62$). The response rate for the Kava group was only 37% compared to 23% in the placebo group. Hence, not all participants responded to Kava treatment.[27] GABA transporter polymorphisms rs2601126 and rs2697153 were found to be potential pharmacogenetic markers of response to Kava treatment, suggesting a possible association of specific genetic variants that modify the anxiolytic response of Kavalactones in the GABA pathways.[27]

The latest trial, Savage et al.,[28] is an ongoing trial. It is a phase III, multisite, two-arm, 18-week double-blind study using an aqueous extract of Kava versus matching placebo in 210 participants diagnosed with GAD who are nonmedicated.[28] This trial aims to confirm the efficacy and safety of Kava in the treatment of GAD while at the same time exploring potential clinical response patterns through genomic and neuroimaging data. The trial is expected to end in May 2018 as per trial registration information on ClinicalTrials.gov (Identifier: NCT02219880).

Kava versus pharmacologic drugs. Boerner et al.[21] was a double-blind, multicenter RCT that compared the efficacy of Kava (LI 150) to two common pharmacologic drugs (buspirone and opipramol) for the treatment of GAD. The trial characteristics are summarized in Table 3. This trial used ICD-10 as the diagnostic criteria for GAD instead of DSM-VI. It was an 8-week trial. A substantial improvement of the HAM-A total score to the same degree was observed in all three groups of patients starting from the 2nd week. At the end of the trial, the means of HAM-A total scores decreased from about 23 at baseline to about 8 with no significant differences across treatments.[21] In addition, no significant differences between treatments could be observed regarding all other secondary measures, including the percentage of remitted patients, self-rating of anxiety, and sleep impairment. As such, Kava was shown to be as safe and effective as buspirone and opipramol in the treatment of GAD.[21]

Other clinical trials. Two other clinical trials, which evaluated different aspects of Kava treatment on GAD patients, are summarized in Table 3.

Wheatley[18] was a randomized, crossover open trial that compared the effects of different dose schedule of Kava administration for GAD treatment. Kava dosages of 120 mg once a day versus 45 mg thrice daily were studied in 24 GAD diagnosed patients for 4 weeks. Both dosages were found to be equally effective in significantly reducing symptom severity measured in the mean HAM-A scores.[18] However, without a placebo-controlled arm, the true effect of Kava treatment cannot be determined in this trial.

Watkins et al.[19] studied the effect of Kava on vagal cardiac control among a small subgroup of trial participants ($n = 13$) from Connor and Davidson.[20] Two measures of vagal cardiac control were analyzed, with only baroreflex control of heart rate found to be significantly improved by Kava treatment. The other measure, namely the respiratory sinus arrhythmia, did not respond to Kava treatment.[19] Hence, Kava appears to improve vagal cardiac control among GAD patients, but the results need further validation.

Patient beliefs and experiences. Two studies explored patient beliefs and experiences among participants of DBRPC trials that studied the efficacy of Kava for GAD treatment. The characteristics of these trials are shown in Table 3.

The study by Abraham et al.[23] was a *post hoc* analysis of the participants from Connor and Davidson[20] and the Study

Table 2. Double-Blind, Randomized Placebo-Controlled Studies on Kava and Generalized Anxiety Disorder Treatment

| *Study ID* | *Type* | *Participants* | *Methods/interventions* | *Outcomes* | *Adverse events* |
|---|---|---|---|---|---|
| Connor and Davidson[20] | Double-blind, randomized placebo-controlled trial | Presence of GAD (DSM-IV) modified with ongoing GAD symptoms for 1 month. HAM-A ≥16. $N=35$ (Kava = 17, placebo = 18). | One week of placebo lead-in; Kava (KavaPure®) or placebo: 140 mg/day of Kavalactones for 1 week increase to 280 mg/day for next 3 weeks. Total: 4 weeks. | Kava was not superior to placebo. Mean baseline and endpoint scores on HAM-A and all secondary measures were not significantly different. | Adverse event analysis reported in Connor et al.[29] |
| Connor et al[22] Study I | Double-blind, randomized placebo-controlled trial | Presence of GAD (DSM-IV) modified with ongoing symptoms for 1 month. HAM-A: 12–20. $N=13$ (Kava = 6, placebo = 7). | One week of placebo lead-in; Kava (KavaPure) or placebo. One hundred and forty milligrams per day of Kavalactones for 1 week increase to 280 mg/day for next 3 weeks. Total: 4 weeks. | Both studies were discontinued. Pooled analysis with Connor and Davidson[20] did not support the use of Kava in DSM-IV GAD. | No evidence of changes in liver function due to treatments. |
| Study II | Double-blind, randomized placebo-controlled trial | Presence of GAD (DSM-IV) with ongoing symptoms for ≥6 months. HAM-A ≥18. $N=16$ (Kava = 5, venlafaxine = 6, placebo = 5). | One week of placebo lead-in; Kava (WS®1490) 280 mg/day of Kavalactones or venlafaxine 225 mg/day, or placebo. Total: 8 weeks. | | |
| Sarris et al.[24] | Double-blind, randomized, placebo-controlled crossover trial | At least 1 month of persistent worry or anxiety (66% was GAD) and scoring >10 on a Beck Anxiety Inventory. $N=37$ (19/18 in two groups). | One week of placebo lead-in. Five tablets per day of aqueous extract Kava (each containing 3.2 g, standardized to 50 mg of Kavalactones, providing a total of 250 mg Kavalactones in active treatment) or placebo for 1 week. Crossover for another week. Total: 3 weeks. | Kava provided a reduction of 11.4 points over placebo on HAM-A (taking a weighted mean of the response during each phase) with a substantial effect size ($p<0.0001$, Cohen's $d=2.24$). | Cases of mild dizziness and nausea reported. No serious adverse effects from Kava occurred. No clinical signs of hepatotoxicity. |
| Sarris et al.[27] | Double-blind, randomized placebo-controlled trial | Diagnosed with GAD (DSM-IV). No comorbid mood disorders. $N=58$ (Kava = 27, placebo = 31). | One week of placebo lead-in. One aqueous extract Kava tablet twice per day (120 mg Kavalactones) for the first 3 weeks. Titrated to 240 mg of Kavalactones in nonresponse at the 3-week mark for the second 3-week. Total: 6 weeks. | A significant reduction in anxiety for the Kava group compared with the placebo group with a moderate effect size ($p=0.046$, Cohen's $d=0.62$). GABA transporter polymorphisms rs2601126 and rs2697153 were associated with HAM-A reduction. | Adverse event analysis reported in Sarris et al.[26] |
| Savage et al.[28] | Multicenter, double-blind, randomized placebo-controlled trial | Currently anxious participants with GAD (DSM-IV). $N=210$ (Kava = 105, placebo = 105). | Aqueous extract of Kava (240 mg of Kavalactones per day) or matching placebo. Sixteen weeks of controlled phase plus 2-week single-blind, placebo-controlled poststudy observation. | Ongoing trial with measurement of symptoms of GAD with SIGH-A as the primary outcome. | Not currently available. |

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders IV*; GABA, gamma-aminobutyric acid; GAD, generalized anxiety disorder; HAM-A, The Hamilton Anxiety Rating Scale; SIGH-A, Structured Interview Guide for the Hamilton Anxiety Rating Scale.

Table 3. Other Studies on Kava and Generalized Anxiety Disorder Treatment

| *Study ID* | *Type* | *Participants* | *Methods/interventions* | *Outcomes* | *Adverse events* |
|---|---|---|---|---|---|
| Boerner et al.[21] | Multicenter, double-blind, randomized reference-controlled trial | Diagnosed with GAD (ICD-10). HAM-A ≥19. $N=127$ (Kava = 43, buspirone = 42, opipramol = 42). | 400 mg Kava (LI 150, 30% Kavalactones), or 10 mg buspirone or 100 mg opipramol daily for 8 weeks. | Means of HAM-A total scores decreased from about 23 at baseline to about 8 at week 8 with no significant differences between treatments. | One treatment related panic attack case for Kava. All treatments were well tolerated. |
| Wheatley[18] | Randomized, crossover controlled trial | Diagnosed with GAD (DSM-IV). HAM-A ≥18. $N=24$ (11/13 in 2 groups). | Kava (LI 150) once a day 120 vs. 45 mg × 3 per day for 2 weeks. Crossover for 2 weeks. Total: 4 weeks. | Reductions in symptom severity were significant comparing weeks 0–2 and 0–4 irrespective of administration order. Between-group difference was not significant. | Daytime drowsiness, gastric irritation, increased appetite, tiredness, and palpitations in a small number of participants. |
| Watkins et al.[19] | Double-blind, randomized placebo-controlled trial | Subgroup of Connor and Davidson.[20] $N=13$ (Kava = 6, placebo = 7). | Kava (KavaPure) 280 mg/day (standardized to 30% Kavalactones) or placebo for 4 weeks. | Significantly more patients treated with Kava showed improved baroreflex control of heart rate compared to the placebo group ($p<0.05$). Respiratory sinus arrhythmia did not respond to treatment. | Not reported. |
| Abraham et al.[23] | *Post hoc* study of participants of two RCTs | Participants of Connor and Davidson[20] and the Study I of Connor et al.[22] $N=51$. | Self-rated assessment that evaluated patient beliefs using the EMSQ. | Participants felt more strongly that cognitive patterns, personality, and stress were causative of their GAD and of greatest relevance to recovery. | Not relevant. |
| Sarris et al.[25] | Qualitative research within a clinical trial | Participants of Sarris, et al.[24] Twenty-eight participants provided qualitative data. | A semistructured, open question written form on experiences of taking either Kava or placebo. | Results were consistent with Kava having beneficial effects and being well tolerated. | Well tolerated. No serious adverse reactions. Side effects reported: tiredness, nausea, gastrointestinal discomfort. |

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders IV*; EMSQ, Explanatory Model for Symptoms Questionnaire; GAD, generalized anxiety disorder; HAM-A, The Hamilton Anxiety Rating Scale; ICD-10, International Classification of Diseases and Related Health Problems version 10; RCTs, randomized controlled trials.

I of Connor et al.[22] It was reported that, for patients who sought botanical treatment for GAD, they were most likely to attribute their illnesses to individual personality or temperament, stress and negative experiences, as well as cognitive factors. With respect to the preferred treatment approaches, ability to better deal with stress and negative thoughts was thought to be most likely to help to improve their conditions.[23] Changing lifestyles and natural remedies to correct biologic abnormalities were also relevant. This group of patients did not believe that taking prescription medication could improve their conditions. Treatment response was positively correlated with patient belief that the condition was caused by own experiences. These attributions suggest stronger adherence to an internal locus of control.[23]

Sarris et al.[25] was a qualitative research component incorporated into Sarris et al.[24] It investigated patient experiences in taking Kava during the clinical trial. Participants were asked to answer three questions on any positive effects, negative effects, or external changes occurred from taking the treatment tablets. Key themes identified from the participants' responses were relief of stress and anxiety, elevated mood, improved sleep, and reduction of physical signs of anxiety (such as muscular tensions) after taking Kava. Mild side effects of taking Kava such as nausea, stomach upset, gastrointestinal pain, tiredness, and fatigue were also described.[25] These qualitative findings were consistent with the significant quantitative results reported in Sarris et al.[24]

Adverse events and safety. Among the included studies, the most serious adverse event occurred was a panic attack case that required stationary treatment in Boerner et al.,[21] but the symptoms improved rapidly in the hospital without having to discontinue Kava treatment. Mild side effects commonly reported include tiredness, mild dizziness, nausea, gastrointestinal discomfort, daytime drowsiness, and palpitations. In general, Kava was reported to be well tolerated in these included studies with no major adverse effects.

With the reports of possible hepatotoxicity with Kava, liver function tests were performed in clinical trials reported in Connor and Davidson,[20] Connor et al.,[22] Sarris et al.,[24] and Sarris et al.[27] Participants were tested before and at the completion of treatment. No evidence of liver function change due to Kava treatment was found. The number of abnormal test results for liver function found in the Kava group was also not significantly different from the placebo group. Furthermore, no clinical signs of hepatotoxicity were observed in these trials.[24,26,29]

In addition, in the analysis of adverse effect of Kava, Connor et al.[29] reported that no differences were found between Kava and placebo on withdrawal symptoms, effect on heart rate, blood pressure, laboratory assessments, and sexual function among participants of Connor and Davidson[20] (Table 4). Analysis of adverse events from Sarris et al.,[27] reported in Sarris et al.[26] (Table 4) also revealed that no differences in withdrawal or addiction were found between groups. Interestingly, Kava was found to significantly increase female's sexual drive compared to placebo. There were no negative sexual effects seen in males. Improved sexual function and performance appeared to correlate with anxiety reduction among the participants.[26]

TABLE 4. SAFETY PROFILE ANALYSIS OF KAVA AMONG CLINICAL TRIAL PARTICIPANTS

| *Study ID* | *Type* | *Participants* | *Methods/interventions* | *Outcomes* | *Adverse events* |
|---|---|---|---|---|---|
| Connor et al.[29] | Safety profile analysis of RCT | Participants of Connor and Davidson.[20] $N=35$. | Occurrence of adverse events, withdrawal symptoms, effect on heart rate, blood pressure, laboratory assessments, and sexual function. | No differences were found between Kava and placebo on any of the parameters evaluated. | Treatments were well tolerated with no major adverse events reported. |
| Sarris et al.[26] | Safety profile analysis of RCT | Participants of Sarris et al.[27] $N=58$. | Liver function blood tests, monitoring of adverse events, withdrawal, and assessment of potential addiction and sexual function (ASEX). | No significant differences across groups for liver function tests, adverse reactions, withdrawal, or addiction. Kava significantly increased female's sexual drive. No negative effects seen in males. | No major adverse reactions occurred. One case of dermatitis and one case of minor stomach upset were related to Kava. |

ASEX, Arizona Sexual Experience Scale; RCT, randomized control trial.

Table 5. Mean Hamilton Anxiety Rating Scale Scores with Standard Deviations of Different Groups in the Included Studies at Different Periods

| | | *Baseline* | | *Midpoint* | | *Endpoint* | |
|---|---|---|---|---|---|---|---|
| *Study ID* | *Group* | n | *Mean ± SD* | n | *Mean ± SD* | n | *Mean ± SD* |
| Connor and Davidson[20] | Kava | 19 | 19.9 ± 4.1 | | | 17 | 14.2 ± 8.3 |
| | Placebo | 18 | 18.8 ± 2.9 | | | 18 | 10.3 ± 4.4 |
| Sarris et al.[24] | Kava-Placebo (KP) | 22 | 21.16 ± 3.52 | 19 | 11.26 ± 4.47 | 19 | 14.58 ± 5.86 |
| | Placebo-Kava (PK) | 19 | 20.28 ± 4.78 | 18 | 19.50 ± 7.26 | 18 | 9.22 ± 5.96 |
| Sarris et al.[27] | Kava | 27 | 21.63 ± 4.2 | | | 27 | 14.03 ± 7.01 |
| | Placebo | 18 | 19.5 ± 4.2 | | | 18 | 15.26 ± 6.2 |

SD, standard deviation.



### *Meta-analysis*

Summary of data. Only three trials fulfilled their selection criteria for meta-analysis, namely, Connor and Davidson[20]; Sarris et al.[24]; and Sarris et al.[27] Outcome measures based on mean HAM-A scores of the different treatment groups of the selected studies are summarized in Table 5. Of the two parallel trials, Connor and Davidson[20] and Sarris et al.,[27] the outcome measure of interest is the difference of the mean HAM-A scores between baseline and endpoint. As for Sarris et al.,[24] which is a crossover trial, there are two periods of data. In the absence of information on the within-individual comparison of treatment from the published data, the authors performed two analyses using the crossover data. Analysis 1 includes only data from the first period and ignores data from the second period due to the potential risk of bias originating from the carryover effect. Analysis 2 ignores the crossover design and uses data from both periods as if they come from two different groups of participants. Both analyses, although not ideal, have been commonly used in practice.[30]

Analyses. The forest plot depicting the combined effect of Kava versus placebo in the treatment of GAD based on Analysis 1 is shown in Figure 2. The combined result ($n = 130$, Kava = 63, Placebo = 67) favored Kava for GAD treatment with an effect size (SMD) of 0.59. However, this effect was not statistically significant (95% CI: 1.75 to −0.57). The effect estimation from Analysis 2 is shown as a forest plot in Figure 3. With a larger sample ($n = 167$, Kava = 81, Placebo = 86), the effect size is larger (SMD = 0.99), but still lag sufficient power to reach statistical significance (95% CI: 2.12 to −0.14). Heterogeneity of data was considered high in both analyses with $I^2 = 89\%$ (Analysis 1) and 91% (Analysis 2), as such, random effect models were used.

Risk of bias assessment. The outcome of the risk of assessment is summarized in Figures 4 and 5.

Randomization and blinding were judged to be adequate in all these studies with the use of accepted randomized technique and matching placebo. All studies were also judged to be low in risk of attrition bias and reporting bias, with the studies sufficiently accounted for all missing data, and all outcomes described were reported. Sarris et al.[24] and Sarris et al.[27] also provided sufficient information to demonstrate low risk in allocation concealment and detection bias. On the contrary, insufficient information was provided in Connor and Davidson[20] to allow us to judge the risk in these items.

The authors assessed Sarris et al.[24] to have a high risk of other bias, particularly the risk of carryover effect in this crossover trial. The risk of other bias was deemed unclear in the other trials. There was no disclosure of source of funding in Sarris et al.[24] and Sarris et al.[27] Funding from industry was declared in Connor and Davidson,[20] but the authors did not disclose the role of the industry partner in the research.

## Discussion

Evidence supporting Kava as an effective treatment for patients with mild-to-moderate GAD comes from two DBRPC trials that favored Kava over placebo for GAD treatment[24,27] and a double-blind, multisite reference-controlled trial that demonstrated the equivocal efficacy of Kava relative to buspirone and opipramol in GAD treatment.[21] However, GAD is a condition known to have a high placebo-response rate that can make it difficult to

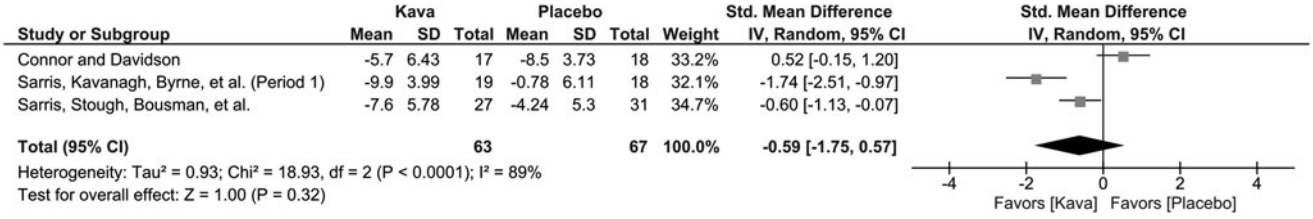


**FIG. 2.** Forest plot showing the effect of Kava versus placebo in the treatment of GAD—Analysis 1. CI, confidence interval; GAD, generalized anxiety disorder; SD, standard deviation. *Squares* show the effect estimates from the single studies; *diamond* shows the pooled result.

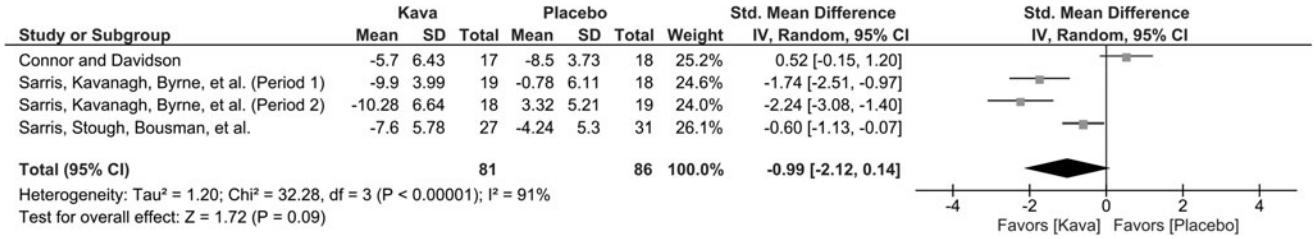


**FIG. 3.** Forest plot showing the effect of Kava versus placebo in the treatment of GAD—Analysis 2. CI, confidence interval; GAD, generalized anxiety disorder; SD, standard deviation. *Squares* show the effect estimates from the single studies; *diamond* shows the pooled result.

assess the true effect of a particular treatment in clinical trials.[31] There is a DBRPC trial showing that Kava is no better than placebo in treating GAD.[20] While their meta-analysis of three trials favored Kava over placebo with effect size of either 0.59 (Analysis 1) or 0.99 (Analysis 2), both results failed to reach statistical significance. Hence, there is still insufficient data to prove the treatment efficacy of Kava beyond doubt. Positive results from the forthcoming trial by Savage et al. are needed to confirm Kava as a viable treatment option for GAD. This review will be updated accordingly upon the availability of published data from this latest trial.

The inclusivity of crossover trials in a meta-analysis is always contentious, especially when the number of included trials is small.[30] The recommended approach is to perform two combined design analyses, with the first using only data from the first crossover period and the second using data from both crossover periods, to investigate simultaneously the statistical significance of both estimators.[32,33] Both analyses have limitations. Analysis 1 is a conservative approach as it decreases the general statistical power and may lead to selection bias.[32] Analysis 2 ignores the fact that the participants appear in both arms and they are not independent.[30] Due to the lack of a washout period between the periods in the crossover trial of Sarris et al.,[24] the potential carryover bias in the second period data is high as apparent in the higher endpoint mean for Kava-Placebo group compared to the mean score at midpoint, with an increase of $3.3 \pm 5.2$ ($p = 0.057$) in mean HAM-A score during the placebo phase (Table 5). This could be caused by symptom rebound due to Kava withdrawal, a negative residual effect that could result in an overestimation of the treatment effect.[32] Thus, incorporating data from the second period in Analysis 2 has the risk of biasing treatment effect in favor of Kava. Hence, the authors postulate that the true effect of Kava treatment over placebo can be between 0.59 and 0.99.

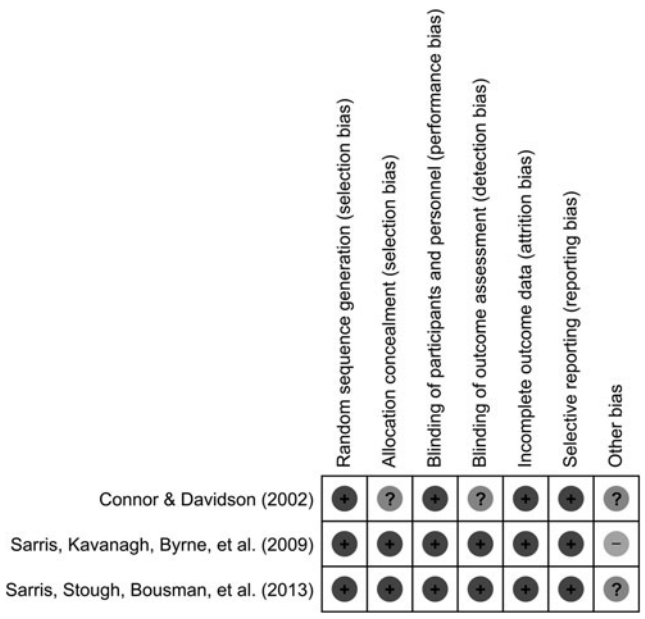


**FIG. 4.** Risk of bias summary: review authors' judgments about each risk of bias item for each included study. +, Indicates low risk of bias; –, high risk of bias; ?, unclear risk of bias.

Kava was well tolerated among the participants in all the included clinical trials with a majority of the reported side effects being mild. The fact that no hepatotoxicity was observed and no change of liver function was detected in the included trials suggests that Kava is safe for therapeutic usage at the dosage of 120–280 mg per day of Kavalactones (regardless of dosage schedule) and for short durations (4–8 weeks). Notwithstanding, Kava may have potential pharmacokinetic interactions with pharmaceutic drugs through inhibition of the CYP450 enzymes responsible for metabolism of most drugs.[34] Potential drug toxicities may still occur, even though it was considered rare in the WHO assessment of Kava safety.[12] As a precaution, it is advisable to avoid co-ingesting Kava with other prescription medications (especially antidepressants such as benzodiazepines), over-the-counter drugs, herbal remedies, and excessive alcohol consumption.[35] In addition, WHO also suggests the preferential use of aqueous extracts of Kava from peeled rhizomes and roots over acetone and ethanol extracts, since aqueous extracts are rich in the hepatoprotective glutathione and have evidence of safety in traditional use.[12] Sarris et al.[24] and Sarris et al.[27] both provided the evidence supporting aqueous extracts of Kava as a potentially safe and effective treatment for GAD.

Taking patient beliefs and experiences into consideration, Kava is an appealing alternative for GAD patients who are more attune to natural remedies or lifestyle approaches to reduce stress and manage their conditions.[23] This group of patients generally do not believe in pharmaceutic drugs. Positive experiences associated with Kava may include relief of stress and anxiety, elevated mood, improved sleep, and reduction of muscular tensions.[25] Physiologically, it appears that Kava may also help to improve the vagal cardiac control through its effects on baroreflex control of heart rate, potentially reducing the risk of major cardiac events due to chronic anxiety.[36] However, not all GAD patients are receptive to

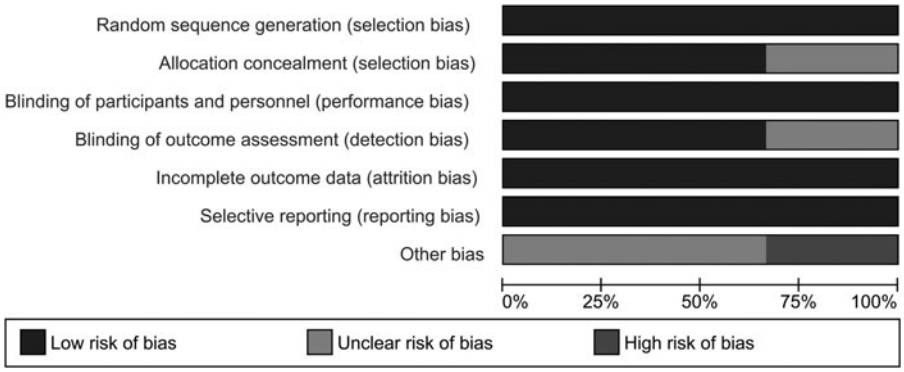


**FIG. 5.** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Kava treatment, and genetics may play a role with specific GABA transporter polymorphisms that determine its responsiveness.[27] Studies in these areas are still in the preliminary stages with much to be learned in the future.

## Conclusion

There is promising evidence from well-designed clinical trials suggesting Kava, particularly the aqueous extracts, to be an effective treatment for GAD. Its efficacy is comparable to commonly prescribed pharmacologic drugs (buspirone and opipramol). Kava is safe for short-term therapeutic use at the dosage of 120–280 mg per day of Kavalactones. Side effects of Kava are mild and well tolerated. Kava can be a potential treatment option for GAD, especially among patients who prefer natural remedies and lifestyle approaches to manage their conditions. Meta-analysis of three DBRPC trials favors Kava over placebo but lack statistical power. A large, multisite, DBRPC trial of Kava for GAD treatment is currently ongoing with new evidence expected soon.

## Author Disclosure Statement

The authors declare that there is no conflict of interest.

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