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ORIGINAL INVESTIGATION

The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*

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Abstract
Rationale Piper methysticum (Kava) has been withdrawn in European, British, and Canadian markets due to concerns over hepatotoxic reactions. The WHO recently recommended research into "aqueous" extracts of Kava.
Objective The objective of this study was to conduct the first documented human clinical trial assessing the anxiolytic and antidepressant efficacy of an aqueous extract of Kava.
Design and participants The Kava Anxiety Depression Spectrum Study was a 3-week placebo-controlled, double-blind crossover trial that recruited 60 adult participants with 1 month or more of elevated generalized anxiety. Five Kava tablets per day were prescribed containing 250 mg of kavalactones/day.
Results The aqueous extract of Kava reduced participants' Hamilton Anxiety Scale score in the first controlled phase by −9.9 (CI = 7.1, 12.7) vs. −0.8 (CI = −2.7, 4.3) for placebo and in the second controlled phase by −10.3 (CI = 5.8, 14.7) vs. +3.3 (CI = −6.8, 0.2). The pooled effect of Kava vs. placebo across phases was highly significant ($p < 0.0001$), with a substantial effect size ($d = 2.24$, $\eta_p^2 = 0.428$). Pooled analyses also revealed highly significant relative reductions in Beck Anxiety Inventory and Montgomery–Asberg Depression Rating Scale scores. The aqueous extract was found to be safe, with no serious adverse effects and no clinical hepatotoxicity.
Conclusions The aqueous Kava preparation produced significant anxiolytic and antidepressant activity and raised no safety concerns at the dose and duration studied. Kava appears equally effective in cases where anxiety is accompanied by depression. This should encourage further study and consideration of globally reintroducing aqueous rootstock extracts of Kava for the management of anxiety.

Keywords Kava · *Piper methysticum* · Herbal medicine · Aqueous extract · Anxiety · Depression

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Introduction

Anxiety disorders are prevalent and debilitating, and sufferers often exert significant demands on healthcare resources (Wittchen 2002). They are also often unrecognized and are commonly untreated (Lecrubier 2007; Wittchen 2002). Generalized anxiety disorder (GAD) is characterized by persistent and uncontrollable worry (>6 months) and includes symptoms such as restlessness, fatigue, difficulty concentrating, and somatic signs (e.g., heart palpitations, muscular tension, dizziness, respiratory distress, sweating, hyperthermia; American Psychiatric Association 2000). The 12-month prevalence of GAD has been reported as around 3–4%, with a lifetime prevalence

of approximately 5% (Alonso et al. 2004; Kessler et al. 2001).

Orthodox medical treatments of anxiety disorders include synthetic anxiolytic (e.g., benzodiazepines) or somatic agents (e.g., β-blockers), antidepressants, and psychological interventions (e.g., cognitive behavioral therapy; Tyrer and Baldwin 2006). No substantial advances in pharmaceutical treatments of anxiety disorders have occurred in recent decades. As benzodiazepines present dependence and withdrawal issues and synthetic antidepressants may elicit significant side effects, further research into safe and effective anxiolytics is needed (Chouinard 2004; Rickels and Rynn 2002).

Piper methysticum (Kava) has substantial empirical support as an effective anxiolytic agent (Pittler and Ernst 2000; Witte et al. 2005) and has demonstrated equivalent efficacy to buspirone or opipramol in treating GAD (Boerner et al. 2003). However, concerns over hepatotoxicity have led to its withdrawal or restriction in many countries (Clouatre 2004). This withdrawal or restriction has removed an effective anxiolytic from use (Lebot 2006). In evaluating safety concerns, it should be noted that many reported cases have involved concomitant ingestion of other compounds with potential hepatotoxicity (e.g., other medications and/or alcohol). Previous hepatotoxicity of German Kava products may also in part be due to the presence of the aerial parts and root and stem peelings, which while one tenth of the price of peeled root, contain the alkaloid pipermethysticine (Coulter 2007). This alkaloid has demonstrated increased death of human hepatoma cells via an in vitro model (Nerurkar et al. 2004).

In response to these safety concerns, the World Health Organization commissioned a report assessing the risk of Kava products (Coulter 2007). Recommendation 2.1.3 from this report suggested that products from water-based suspensions should be developed and tested in clinical trials and that these preparations should preferentially be used over acetonic and ethanolic extracts. A previous study by Singh and Devkota (2003) using an aqueous extract of Kava in an animal model found no abnormality of liver enzyme markers, and our previous study using the same aqueous extract of Kava as in this trial revealed no significant elevation of liver enzymes over treatment periods of 4 weeks (Sarris et al. 2009).

To date, there have been no published studies examining the efficacy of a standardized whole aqueous extract of the peeled root of Kava. As the current pharmacological treatment of anxiety disorders with benzodiazepines has potential health risks and clear dependency issues, a standardized aqueous Kava extract remains a potential therapeutic option (Rickels and Rynn 2002; Stevinson et al. 2002). An aqueous extract of the peeled roots using a "noble" cultivar of Kava holds promise of reducing the likelihood of hepatotoxicity (in accordance with the traditional knowledge of Pacific Islander users and with in vivo studies; Coulter 2007; Singh and Devkota 2003). Noble cultivars are cultivated varieties which can affect positive psychotropic activity with less side effects than cultivars such as tudei, which are much higher in kavalactones such as dihydromethysticin and commonly cause a "hangover" effect, with symptoms such as nausea (Lebot 2006). If an aqueous extract of a noble cultivar were found to be effective and safe, that result may encourage further studies and the eventual reintroduction or endorsement of Kava in European, UK, and North American markets.

A previous clinical trial that we recently completed observed no anxiolytic effect from Kava combined with St. John's wort in a sample of people with major depressive disorder (Sarris et al. 2009). This raised the question whether Kava may be less effective in people with co-occurring anxiety and depression. While Commission E (a European herbal medicine authority) recommends against prescribing Kava in cases of depression, we have located no published data to support that opinion (Blumenthal 2004).

Thus, the aims of the current study were to conduct a human clinical trial using an aqueous extract of Kava, to determine its efficacy and preliminary safety in treating anxiety, to assess the effect of Kava on co-occurring depressive mood, and to observe whether levels of depression at baseline predicted the anxiolytic response to Kava. We report the quantitative data from the Kava Anxiety Depression Spectrum Study (KADSS), the first documented human clinical trial testing effects of an aqueous extract of Kava on anxiety and depression and the first to test whether levels of depressive symptoms affect its anxiolytic impact.

Materials and methods

Study design

The KADSS was a 3-week placebo-controlled, double-blind crossover trial. Sixty adult participants with elevated, stable anxiety were recruited between April and October 2008. The clinical trial was approved by The University of Queensland's Medical Research Ethics Committee (project no. 2008000340) and registered on the Australian and New Zealand Clinical Trial Register (ACTRN12608000536369). Aside from week 1 (a single blinded, placebo run-in phase), the interviewer and the participants were blinded as to the intervention. Only the manufacturer of the tablets (and the medical consultant in cases of potential toxicity) was able to break the blinding code. Participants were assessed at baseline, after an initial week of placebo

(pretreatment), and after each controlled treatment phase (post 1 and post 2).

Participants

Potential participants were adults (18–65 years) reporting at least 1 month of persistent worry or anxiety and scoring >10 on a Beck Anxiety Inventory (BAI; Beck et al. 1988), administered at consent. A diagnosis of generalized anxiety disorder was not required because the shorter period was more consistent with the duration of concerns by many people seeking primary care. Exclusion criteria included a history of psychosis or bipolar disorder, significant suicidal ideation in the previous 6 months, diagnosed hepatobiliary disease or inflammation, presence of a substance use disorder in the previous 6 months, use of conventional antidepressants, regular benzodiazepine or opiate use in the previous month, previous adverse reaction to Kava, concurrent counseling or psychological therapy, and inadequate facility in written or spoken English. Participants who showed a substantial reduction in anxiety during the placebo run-in phase (≥50% on the BAI) were excluded from controlled phases of the trial.

Procedure

Potential participants were recruited via the mass media (radio, newspapers, and Internet) and through advertising in medical and complementary medicine clinics in the greater Brisbane metropolitan area in Queensland, Australia. Referrals from health professionals were also solicited. Initial screening was via a structured telephone interview. If they met inclusion criteria and provided informed consent, participants were assessed on the Composite International Diagnostic Interview (CIDI-Auto; Robins et al. 1989) for the presence of social anxiety disorder, panic disorder, generalized anxiety disorder, major depressive disorder, dysthymia, mania, or psychotic disorder. They were administered a health and medication questionnaire, demographics questionnaire, a drug check form, the Hamilton Anxiety Scale (HAMA; Hamilton 1959), the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979), and the Beck Depression Inventory-II (BDI-II; Beck et al. 1961) and were asked to undergo a liver function test within 3 days.

Participants then commenced the first week of the study, taking five placebo tablets per day (two in the morning, two in the afternoon, one in the evening). One week later, they completed a safety checklist and were questioned regarding their adherence to treatment and the number of tablets remaining (which were retained for safe disposal). If an abnormality was revealed on their liver function test, they were informed that they were taking a placebo and were excluded from the trial. Otherwise, they were assessed again using the HAMA, MADRS, and BAI. If HAMA or BAI showed a reduction of 50% or more from their baseline assessment, the participants were informed that they were taking a placebo, informed about alternative treatment opportunities, and were excluded from further participation.

Randomization Remaining participants were then randomized to order of treatments [Kava-placebo (KP) or placebo-Kava (PK)]. Allocation to treatment groups was undertaken by an independent researcher, using sets of random permutations, in order to ensure approximately equal numbers of participants in each group. Randomization details were provided in an opaque envelope containing the allocation (labeled by group number to retain blinding). To provide approximately matched groups with respect to baseline depression, randomization was stratified by gender and depression level (BDI ≤ or >10).

Interventions Each controlled phase lasted 1 week. Interventions comprised five tablets per day of Kava (each containing 3.2 g, standardized to 50 mg of kavalactones) or placebo. The prescription comprised two tablets in the morning and afternoon and one in the evening (providing a total of 250 mg kavalactones in active treatment, the maximum dose approved in Australia).

Kava tablets used were supplied by MediHerb (Warwick, Australia). Manufacture was conducted under strict pharmaceutical good manufacturing practice (Pharmaceutical GMP). The Kava (organic peeled rootstock from a noble cultivar) was sourced from Vanuatu in accordance with the (2002) Kava Act (Vanuatu Kava 2002). Tablets were formulated from pressed, dried aqueous extract and standardized to contain 50 mg of kavalactones. An independent assay using high-performance liquid chromatographic (HPLC) analysis revealed higher concentrations of the kavalactones dihydrokavain, kavain, and dihydromethysticin, moderate levels of methysticin, and lower levels of yangonin, desmethoxyyangonin, and chalcone methylesters. Placebo tablets were formulated using a color-film coat identical in appearance to the herbal tablets. The excipients were calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycollate, and magnesium stearate.

Posttreatment assessments Participants returned after the first week of controlled treatment and were reassessed using HAMA, MADRS, and BAI. They then received a new packet of tablets for the 1-week crossover phase. At the conclusion of the study, participants were reassessed using the same measures and were compensated with AUS $20 (to cover costs of travel and inconvenience).

Outcome measures and statistical analyses

The HAMA was the primary outcome measure. Secondary outcomes were measured on the BAI and MADRS. Data were analyzed using SPSS 16.0. The primary analyses of outcomes used univariate analyses of variance (ANOVAs) conducted on differences from scores at pretreatment, examining effects of treatment (placebo/Kava), sequence (KP/PK), and time (post 1, post 2). Data from all participants completing post assessments were included in analyses. Results were also examined with the substitution of missing data by the pretreatment score—an extremely conservative data substitution method, given the likely presence of regression to the mean producing some improvements over the course of the study. The dual analysis provided a test of the robustness of the results.

Examination of the predictive effect of depression at baseline on the anxiolytic response to Kava used Pearson's *r* between baseline BDI-II and the degree of reduction in HAMA during the active phase (compared with pretreatment). All statistical tests were two-tailed, and 0.05 was considered to be the critical value of alpha. We calculated the effect size (*d*) of the data by (a) calculating the effect size separately within the active and control groups (taking the difference between means at the start and end of each phase, dividing by the baseline within-group standard deviation of the 41 participants in the controlled trial, and then calculating a mean across phases, weighted for sample size) and (b) subtracting the effect size of the control group from that of the active group (Morris 2008).

Results

Participants

Eligibility screening was conducted on 182 volunteers (Fig. 1). A total of 60 met initial inclusion criteria (30 women, 30 men) and began the study. Potential participants were excluded due to no stabilized anxiety, use of antidepressants or anti-anxiety medication, bipolar depression, liver dysfunction, high alcohol or drug use, or non-provision of consent. After the placebo run-in phase, a further 19 people were excluded because of a placebo response, leaving 41 participants who fulfilled the final eligibility criterion and were randomized to commence the controlled phases of the study. Of these, 37 (90%) completed all three assessment occasions, with no significant difference in completion rates between groups (18/19, 95% in PK; 19/22, 86% in KP). One participant could not be contacted after the first week of treatment with Kava, another receiving Kava withdrew after 2 days due to mild nausea and declined further assessments, one placebo participant broke protocol and did not take any tablets after randomization, and one receiving Kava withdrew from the study due to an infectious illness that carried over from the placebo run-in phase.

Analyses of participants' data at randomization revealed no statistically significant difference between KP and PK conditions with regard to age, gender, employment, pretreatment anxiety, or depression (Table 1). By chance, there was a trend for KP to have more participants with a previous diagnosis of major depression than PK ($p = 0.05$; Table 1). GAD was relatively prevalent across the sample (27/41, 66%), as was panic disorder (17/41, 41%).

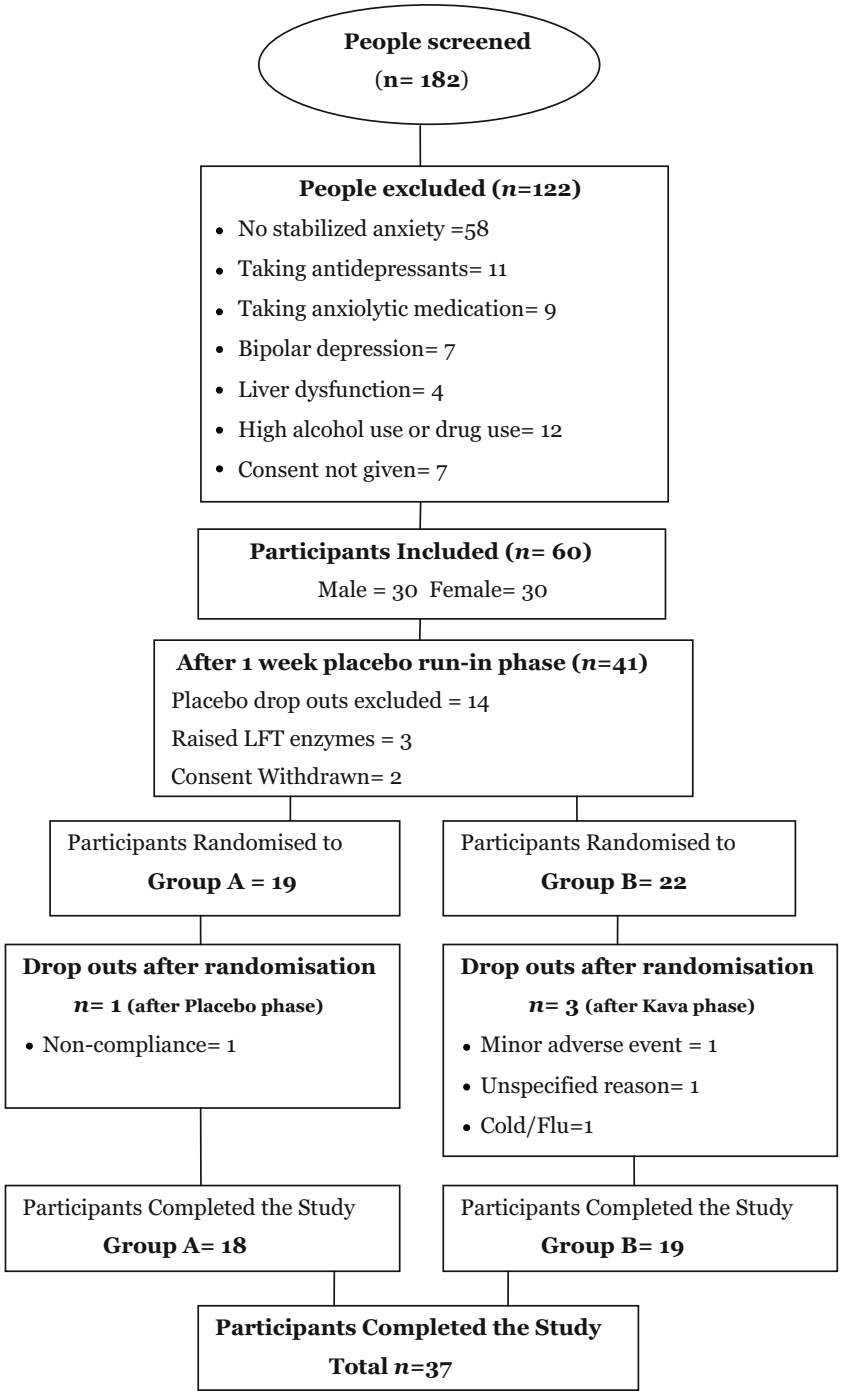
Outcomes on anxiety and depression

Results are displayed in Table 2 and Figs. 2, 3, and 4. On the primary outcome measure (HAMA), anxiety fell an average of −9.9 points (CI = −12.7, −7.1) below pretreatment levels when Kava was received during the first controlled phase compared with −0.8 (CI = −4.3, +2.7) for placebo (Fig. 2). During the second controlled phase, the group that then received Kava had a reduction of −10.3 points (CI = −14.7, −5.8) vs. a rise of +3.3 points (CI = −0.2, +6.8) for the group that then received placebo. The pooled analysis across phases (using differences from pretreatment scores) demonstrated a highly significant effect across phases in favor of Kava [$F(1,35)=26.18$; $p < 0.0001$] and a strong effect size ($d = 2.24$, $\eta_p^2 = 0.428$). There was also a significant improvement over Time across treatments [$F(1,35)=6.87$; $p = 0.01$, $\eta_p^2 = 0.164$], with no significant effect for treatment sequence [$F(1,35)=3.05$; $p = 0.09$, $\eta_p^2 = 0.080$]. The response rate (using ≥50% reduction on HAMA below baseline after treatment with Kava) was 62% (23/37). The remission rate (≤7 on HAMA after Kava treatment) was 35% (13/37).

On the secondary outcome measure for anxiety (BAI), pooled analysis again showed that Kava had a significantly greater effect than placebo [$F(1,35)=12.57$; $p = 0.001$, $\eta_p^2 = 0.264$], producing $d = 1.04$. There was also a significant effect for time across treatments [$F(1,35)=6.16$; $p = 0.02$, $\eta_p^2 = 0.150$] and no effect for sequence [$F(1, 35)=0.42$; $p = 0.52$, $\eta_p^2 = 0.012$]. In phase 1, the reductions for Kava and placebo were −7.2 (CI = −10.8, −3.5) vs. −1.6 (CI = −5.6, +2.5). In phase 2, Kava produced a further reduction of −8.1 (CI = −12.5, −3.6), whereas anxiety rose by +1.4 points (CI = −2.0, +4.9) in placebo.

Effects of Kava were also seen for depression levels, as measured by the MADRS. There were reductions of −5.9 (CI = −11.1, −0.6) for Kava vs. −1.1 (CI = −5.2, +3.1) for placebo in phase 1 and −7.6 (CI = −12.0, −3.2) vs. a rise of +3.3 (CI = −2.3, +9.0) in phase 2. The effect for Kava gave [$F(1,35)=10.03$; $p=0.003$, $\eta_p^2 = 0.223$, $d = 0.75$], with no significant effects for time [$F(1,35)=1.53$; $p = 0.23$, $\eta_p^2 = 0.042$] or treatment sequence [$F(1,35)=0.12$; $p = 0.73$, $\eta_p^2 = 0.003$].

Fig. 1 CONSORT diagram



All of the above effects for Kava remained when missing data of dropouts were substituted by their pretreatment scores [HAMA: $F(1,39)=26.17$; $p < 0.0001$, $\eta_p^2 = 0.402$; BAI: $F(1,39)=13.12$; $p = 0.001$, $\eta_p^2 = 0.252$; MADRS: $F(1,39)=10.26$; $p = 0.003$, $\eta_p^2 = 0.208$].

Prediction of outcomes from baseline depression

BDI scores at baseline did not predict the degree of fall after Kava treatment (relative to pretreatment levels) on any variable: HAMA $r = 0.17$, $p = 0.32$; BAI $r = -0.10$, $p = 0.57$; MAS $r = 0.11$, $p = 0.51$.

Safety and tolerability, retention and blinding

No serious adverse effects from Kava occurred during the trial. As reported above, only one minor adverse effect led to withdrawal in a Kava phase: a mild case of nausea that commenced at the start of the phase and resolved within a day of discontinuation. Four other minor adverse effects

Table 1 Baseline characteristics of participants who were later randomized to groups

Categorical variables	Placebo/Kava *N*/19 (%)	Kava/Placebo *N*/22 (%)	χ^2	*df*	*p*
Male	10 (44%)	13 (57%)	0.17	1	0.678
Employed/studying	17 (90%)	18 (82%)	–	–	0.668[a]
CIDI-Auto diagnosis					
Social phobia[a]	6 (32%)	13 (59%)	–	–	0.118[a]
Panic disorder[a]	9 (47%)	8 (36%)	–	–	0.537[a]
Generalized anxiety disorder[a]	12 (63%)	15 (68%)	–	–	0.754[a]
Major depressive disorder[a]	3 (16%)	4 (18%)	–	–	1.00[a]
Dysthymia	1 (5%)	2 (9%)	–	–	1.00[a]
Depression (previous diagnosis)	1 (5%)	7 (32%)	–	–	0.050[a]
Continuous variables	Placebo/Kava Mean (SD)	Kava/Placebo Mean (SD)	*F*	df	*p*
Age (year)	44.4 (13.1)	43.1 (11.7)	0.11	1,39	0.742
Education (year)	13.7 (2.3)	13.8 (3.1)	0.01	1	0.925
Beck Depression Inventory (BDI)	16.1 (8.0)	21.3 (11.0)	2.94	1,39	0.095
Hamilton Anxiety Scale (HAMA)	24.2 (5.2)	23.6 (5.1)	0.013	1,39	0.724
Beck Anxiety Inventory (BAI)	20.8 (8.3)	21.2 (6.4)	0.03	1,39	0.868
Montgomery–Asberg Depression Rating Scale (MADRS)	21.7 (6.7)	23.3 (7.9)	0.47	1,39	0.497

HAMA Hamilton Anxiety Scale, *BAI* Beck Anxiety Inventory, *MADRS* Montgomery–Asberg Depression Scale

[a] Probability from Fisher's exact test (two-tailed)

occurred during the trial. One case of dizziness, stomach discomfort, and flu-like symptoms started in the initial placebo phase and worsened during the Kava phase; one case of mild dizziness occurring within the first day of Kava resolved by the second day (the participant continuing with no further problem); one case of constipation in a placebo phase; and one mild case of infrequent nausea in a Kava phase. No clinical signs of hepatotoxicity were apparent in any participant during the trial.

Compliance was rated as good in respect to participants' remaining tablets which were counted weekly. Assessment of blinding revealed that two participants in the Kava group commented that they had a different taste in their mouth, one participant attributing it to Kava and the other not being certain. Three reported changes in urine color or frequency that they attributed to Kava, but two of the three were receiving placebo.

Summary

This paper reports the findings of the first documented human clinical trial using an aqueous extract of Kava on anxiety and depression outcomes. The finding that Kava provided a reduction of 11.4 points over placebo on HAMA (taking a weighted mean of the response during each phase) compares favorably to benzodiazepine efficacy, with a lesser incidence of dropouts (Dundar et al. 2004; Martin et al. 2007). This result also compares very favorably to a Cochrane meta-analysis which revealed a weighted mean of

Table 2 Pooled outcome analysis on univariate ANOVA

Outcome measure		Mean (SD)			Effect for Kava vs. Placebo		Effect size	
		Pretreatment	Post 1	Post 2	*F* (1, 35)	*p*	η_p^2	*d*
HAMA	KP	21.16 (3.52)	11.26 (4.47)	14.58 (5.86)	26.18	<0.0001	0.428	2.24
	PK	20.28 (4.78)	19.50 (7.26)	9.22 (5.96)				
BAI	KP	16.47 (4.90)	9.32 (6.49)	10.74 (6.04)	12.57	0.001	0.264	1.04
	PK	17.94 (5.98)	16.39 (10.16)	8.33 (7.39)				
MADRS	KP	20.32 (9.24)	14.42 (9.81)	17.74 (9.30)	10.03	0.003	0.223	0.75
	PK	17.83 (7.72)	16.77 (7.33)	9.22 (9.00)				

KP: Kava week 1, Placebo week 2; PK: Placebo week 1, Kava week2

HAMA Hamilton Anxiety Scale, *BAI* Beck Anxiety Inventory, *MADRS* Montgomery–Asberg Depression Scale

Effect sizes: η_p^2 = Partial eta squared, *d* = modified Cohen's *d*

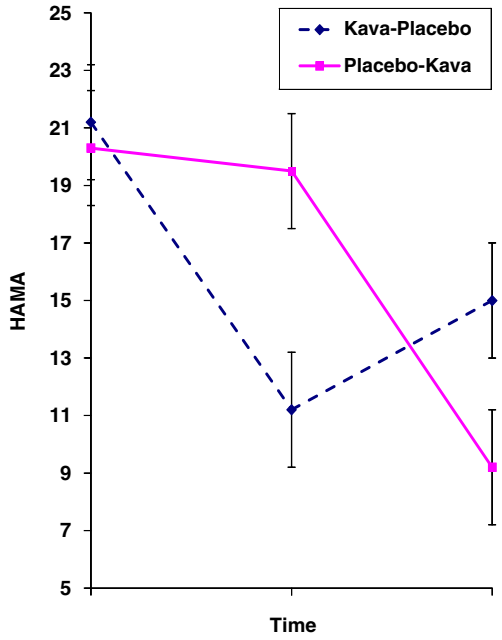


Fig. 2 Results on the Hamilton Anxiety Scale (*HAMA*)

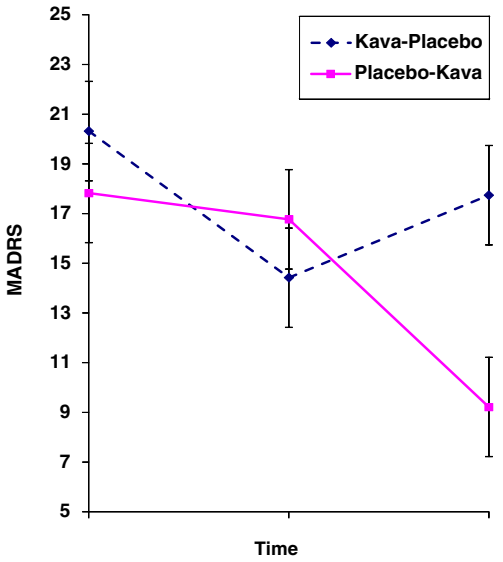


Fig. 4 Results on the Mongomery–Asberg Depression Rating Scale (*MADRS*)

difference of 5.0 points (95% CI = 1.1, 8.8, $p = 0.01$) from Kava over placebo on HAMA (Pittler and Ernst 2006). The effect sizes also reflected a strong clinical outcome, with the effect of Kava treatment (partial eta squared, η_p^2) accounting for 43% of the total variability in the HAMA anxiety scores.

Previous studies with ethanol or acetone extracts of Kava have shown efficacy at 210 and 240 mg of kavalactones (Pittler and Ernst 2006). The dosage of 250 mg of kavalactones used in KADSS was comparable to these studies. It is nevertheless important to recognize that this dosage remains comparatively low compared to traditional use; a bowl of Kava contains approximately 100–200 mg of kavalactones, and Pacific Islanders commonly drink many bowls in a Kava session (Coulter 2007).

A novel aspect of this study was its examination of the effect of Kava on depression levels. The only published study assessing the thymoleptic activity of Kava that was located in our literature search involved acute administration of Kava (90 mg of kavalactones) to healthy human adults (Thompson et al. 2004). The study revealed that Kava improved state cheerfulness on the State-Trait Cheerfulness Inventory. As noted above, Commission E has advised that Kava should not be prescribed in depression (Blumenthal 2004), although no previous study had utilized depression outcome scales to assess Kava's effect on depression. Our results showed that: (a) no depressogenic effect occurred, (b) baseline depression level was not predictive of response on HAMA, and (c) Kava had an antidepressant effect, as measured on the MADRS.

Side effects and safety of the extract appeared comparable (if not superior) to most benzodiazepine studies, with only one dropout due to nausea (Martin et al. 2007). The two cases of nausea in Kava phases may be explained by the amount of dihydromethysticin in the extract. The use of a cultivar with lower dihydromethysticin may lessen the chance of nausea. Importantly, no rebound symptoms occurred after cessation of Kava in the following placebo week, in contrast to those commonly found in abrupt benzodiazepine withdrawal (e.g., insomnia, agitation, digestive disturbance; Chouinard 2004). No clinical signs of hepatotoxicity were apparent. This is consistent with our

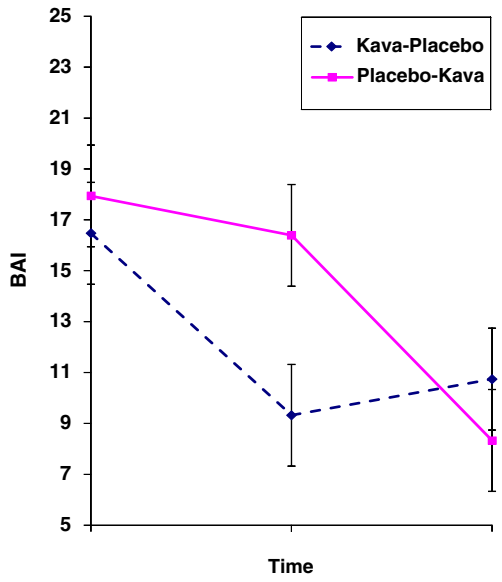


Fig. 3 Results on the Beck Anxiety Inventory (*BAI*)

previous clinical trial using the same aqueous extract of Kava, which had no significant elevations in liver enzymes or clinical signs of hepatotoxicity (Sarris et al. 2009).

There are several limitations to the current study. Most obvious was the short length of the intervention phases, which prevents definitive conclusions about its long-term efficacy or safety. Some assurance can be taken from traditional Pacific Islander knowledge that clinically significant hepatotoxicity does not appear to occur in the use of water-based Kava preparations (Currie and Clough 2003), even though an average Fijian Kava user has about 100,000 bowls over a lifetime (Coulter 2007). However, both additional controlled trials and well-controlled epidemiological studies are required. At this stage, prudent advice for the clinical use of Kava should involve the recommendation of only short-term or intermittent use, with the dose titrated to achieve acute anxiolysis as required.

This study did not restrict the sample to people with GAD, and some fulfilled criteria for other anxiety disorders such as panic disorder. Results of the trial may not completely generalize to populations with "pure" GAD, although 66% of participants did satisfy DSM-IV/CIDI-Auto criteria for a diagnosis of GAD.

As a test of Kava as a thymoleptic activity, our study did not specifically select for major depression and did not have sufficient participants to check for the effects of Kava in the subsample that did have major depression. However, the median BDI score was 17 at baseline, and several participants had high scores (e.g., 20% ≥30). Responses from antidepressants typically only emerge after several weeks, rendering our results somewhat surprising. However, a meta-analysis and review by Posternak and Zimmerman (2005) supports the idea that a significant antidepressant response can occur within 1 to 2 weeks (Posternak and Zimmerman 2005). Moreover, the evidence suggests that early improvement is the best predictor of response to an antidepressant medication at endpoint (Posternak and Zimmerman 2005). The current study also did not test the antidepressant effects of Kava in a sample without concomitant anxiety. However, the reduction of MADRS depression in the current study was substantial considering the short period of Kava administration. In summary, results on MADRS indicate that an acute antidepressant effect may occur from taking Kava. This may be due to a halo effect from the reduction in anxiety or may reflect a specific effect on depressive mood.

The use of a placebo washout phase, eliminating placebo responders, was an important design strength of the current trial. Anxious populations are notorious for having high placebo response rates, with around 70% of clinical trials using benzodiazepines having employed placebo run-in periods to address this issue (Mitte et al. 2005). Just under a third of our participants had at least a 50% reduction in baseline HAMA or BAI scores, illustrating the importance of their removal to control for the potential response to placebo.

Another limitation of the study was the absence of a washout period between phases, and some carryover effects were seen. There was, however, a non-significant rise of anxiety in the placebo phase that followed Kava administration. Pharmacokinetic clearance of kavalactones occurs shortly after administration (half-life=approximately 9 h), with a peak plasma level being reached by after 1.8 h after ingestion (Clouatre 2004; Mathews et al. 2005). As no "rebound" anxiogenic effect to pretreatment levels was observed (or was apparent in clinical assessment), there may be a maintenance of initial effects on anxiety, at least over a 1-week period. This is a potentially important finding, as central nervous system withdrawal symptoms commonly occur after the discontinuation of benzodiazepines with short half-lives (Chouinard 2004). The effect in the current study may be due to a sustained modulation of GABAergic pathways or to behavioral–experiential modification.

To confirm the current results, further rigorous studies are advised using a similar aqueous extract of Kava, particularly determining effects over a longer time period. To ensure uniformity of quality, Kava preparations should contain a complementary kavalactone profile which is high in kavain, dihydrokavain, and methysticin and perhaps slightly lower in dihydromethysticin. The Kava extract should be prepared from a peeled rootstock of a noble cultivar of Kava (Coulter 2007; Lebot 2006).

Strict quality controls should also be instituted over extracts to be used for research or medicinal purposes if reintroduction of Kava into European, UK, or Canadian markets can be recommended. Vanuatu has taken steps to institute such a quality control procedure via the establishment of the Vanuatu Kava Act (2002). Similar legislation by other Pacific Island nations would help ensure that the safety and efficacy of Kava can be promoted with confidence.

In summary, our study demonstrated that an aqueous extract of Kava was a safe and efficacious anxiolytic in participants with elevated, stable generalized anxiety and may also have antidepressant effects. In accordance with our results, aqueous preparations of Kava may tentatively be recommended for intermittent or short-term use in people with generalized anxiety. In cases of regular use, liver function tests and clinical examinations should be periodically conducted and dosages should not exceed 250 mg of kavalactones per day. Kava should preferably not be consumed with alcohol, benzodiazepines, or anticonvulsants. This current study—and research that follows—may encourage the reassessment of Kava as a first-line treatment of anxiety. Such a decision would provide a significant expansion of viable treatment options for people with acute anxiety.

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Conflicts of interest Kerry Bone is a consultant to MediHerb Pty Ltd (supplier of the tablets). He was not involved in the conduct of the study or the analysis of the data.

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