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The acute effects of kava and oxazepam on anxiety, mood, neurocognition; and genetic correlates: a randomized, placebo-controlled, double-blind study

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Rationale Kava (*Piper methysticum*) is a psychotropic plant medicine with history of cultural and medicinal use. We conducted a study comparing the acute neurocognitive, anxiolytic, and thymoleptic effects of a medicinal dose of kava to a benzodiazepine and explored for the first time specific genetic polymorphisms, which may affect the psychotropic activity of phytomedicines or benzodiazepines.
Methods Twenty-two moderately anxious adults aged between 18 and 65 years were randomized to receive an acute dose of kava (180 mg of kavalactones), oxazepam (30 mg), and placebo 1 week apart in a crossover design trial.
Results After exposure to cognitive tasks, a significant interaction was revealed between conditions on State–Trait Anxiety Inventory-State anxiety ($p = 0.046$, *partial* $\eta^2 = 0.14$). In the oxazepam condition, there was a significant reduction in anxiety ($p = 0.035$), whereas there was no change in anxiety in the kava condition, and there was an increase in anxiety in the placebo condition. An increase in Bond–Lader "calmness" ($p = 0.002$) also occurred for the oxazepam condition. Kava was found to have no negative effect on cognition, whereas a reduction in alertness ($p < 0.001$) occurred in the oxazepam condition. Genetic analyses provide tentative evidence that noradrenaline (SLC6A2) transporter polymorphisms may have an effect on response to kava.
Conclusion Acute "medicinal level" doses of this particular kava cultivar in naive users do not provide anxiolytic activity, although the phytomedicine also appears to have no negative effects on cognition. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—kava; *Piper methysticum*; oxazepam; cognition; pharmacogenetics; polymorphisms

INTRODUCTION

Kava is a perennial shrub of the Piperacea (pepper) family that is native to the ethnogeographic regions of Melanesia, Micronesia, and Polynesia (Singh and Singh, 2002). Kava has traditional and modern clinical use as a relaxant and an anxiolytic. Numerous *in vivo* and *in vitro* models suggest several mechanisms that may mediate a broad spectrum of psychopharmacological actions from its psychoactive constituents, known as kavalactones. These actions include blockade of voltage-gated sodium-ion channels, reduced excitatory neurotransmitter release from blockade of calcium-ion channels, enhanced ligand binding to gamma-aminobutyric acid (GABA) type-A receptors, reversible inhibition of monoamine oxidase B, inhibition of cyclooxygenase, and reduced neuronal reuptake of dopamine and noradrenaline (LaPorte *et al*., 2011). A Cochrane review based on 11 randomized, double-blind, placebo-controlled studies (randomized control trials: RCTS) of rigorous methodology was conducted using kava monopreparations (60–280 mg kavalactones) for the treatment of anxiety (Pittler and Ernst, 2003). All RCTs except for one revealed that the anxiolytic effects favored kava over placebo. Another pooled analysis of six studies of kava versus placebo in the treatment of anxiety found a significant effect in favor of the plant medicine on the Hamilton Anxiety Rating Scale (HAMA), with a Cohen's *d* of 1.1 (Sarris *et al*., 2011a).

Studies have assessed the acute effects of kava on mood and cognitive outcomes. Thompson *et al*. (2004) found that an acute single dose of 300 mg kava extract (90 mg kavalactones) increased state "cheerfulness" and decreased state "seriousness", as measured on the State–Trait Cheerfulness Inventory (STCI). The mood elevating effects of kava have also been observed in patients with chronic generalized anxiety. Sarris *et al*.

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(2009) showed in a placebo-controlled study that an aqueous extract of kava (250 mg kavalactones; Paralasul cultivar; formulation supplied by MediHerb, Warwick, Australia) used for a period of 1 week significantly reduced scores on the Montgomery–Asberg Depression Rating Scale and produced a large effect size ($p = 0.003$, $d = 0.75$). Furthermore, participants' anxiety levels on the HAMA were also reduced ($p < 0.0001$, $d = 2.24$). It should be noted however that these results reflect continued use over the time period and not "acute" use.

Seven RCTs (English language) have assessed the acute effects of kava on neurocognition. A systematic review of these studies suggest that kava has nondeleterious effects on cognition during acute administration (LaPorte *et al*., 2011). One study found that kava significantly enhanced visual attention and working memory processes (Thompson *et al*., 2004), whereas another study revealed that kava significantly increased the extent of body sway (similar to that of alcohol intoxication) but had no significant effects on cognition (Prescott *et al*., 1993). Three out of seven acute RCTs found a small positive effect of kava on cognition that was not significant (Saletu *et al*., 1989; Münte *et al*., 1993; Heinze *et al*., 1994). The remaining two studies found that kava produced no significant effects on cognitive domains (Russell *et al*., 1987; Foo and Lemon, 1997).

Although our previous research has found anxiolytic activity of kava from chronic administration, to date, no study has assessed the acute anxiolytic effects of kava in comparison with an established anxiolytic, such as a benzodiazepine. This is surprising as benzodiazepines have well-documented acute anxiolytic activity, whereas the effects of kava have not been studied for this effect. There is traditional knowledge of acute activity (Singh 1992) and established evidence in the longer term treatment of anxiety (Weeks 2009; Sarris *et al*., 2011a). Furthermore, to date, little is known about the impact of genetic polymorphisms in neurobiological targets (e.g., GABA, 5-HTTPR, or BDNF) that potentially are involved in the activity of kava and oxazepam or polymorphisms coding for liver enzymes (CYP P450 3A4 and 2D6) that may affect drug metabolism and subsequently impact efficacy and side-effect profiles of these drugs (Sarris *et al*., 2011b). There are currently no published studies that have explored the relationship of gene polymorphisms with therapeutic effects for any herbal medicine or benzodiazepine (pharmacodynamic effect).

This RCT was designed in response to these gaps in knowledge. It examines and compares the acute effects of kava and the benzodiazepine oxazepam on participants subjected to moderate cognitive demand on validated measures of state anxiety, mood, and neurocognition in mild to moderately anxious individuals. A further aim was to explore potential genetic correlates that may affect any response.

MATERIALS AND METHODS

Study design

In brief, the study was a three-arm, placebo-controlled, double-blind, crossover trial involving the acute administration of kava, oxazepam, and placebo (participants prerandomized to take each a single dose of the intervention 1 week apart over 3 weeks). Adult participants with mild to moderate levels of anxiety were recruited between February 2011 and June 2011at a research laboratory in Hawthorn, Victoria, Australia. To maintain experimenter blinding, group allocation was performed by an independent third party who did not take further part in the study. Allocation to conditions was performed via computer, randomly assigning every participant to a treatment order according to a Latin Squares design. Both the researcher and participants were blinded as to which intervention was being administered. The study was approved by the Swinburne University Human Research Ethics Committee (Ethics Number 0182). The trial was registered on The Australian and New Zealand Clinical Trials Register (number: ACTRN12611000548932).

Participants

Adults (male and female) aged between 18 and 65 years with mild to moderate anxiety (considered as between 14 and 25 years on the HAMA) were recruited. Exclusion criteria included (i) DSM-IV diagnosis of a psychotic or bipolar disorder illness, or Major Depressive Disorder, or any specific anxiety disorder; (ii) significant suicidal ideation in the previous 6 months; (iii) current use of: antidepressants, mood stabilizers, antipsychotics, opioid, analgesics, St John's wort, antiretrovirals, antitumoral/cancer, blood pressure, warfarin, or Parkinson's/epileptic/migraine/antiulcer medications; (iv) diagnosed hepatobiliary disease/inflammation; (v) substance abuse or dependency disorder in the previous 6 months, including alcohol; (vi) previous adverse reaction to kava or benzodiazepines; (vii) regular use of kava or benzodiazepines in the previous 12 months; (viii) more than one occasion of benzodiazepine or kava use each week over the past month; (ix) pregnancy, trying to conceive, or those who could be pregnant; (x) lack of facility in written or spoken English; (xi) a total score below 14 or above

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25 on the HAMA; (xii) regular smokers (more than one cigarette a week); and (xiii) abnormal liver function.

Interventions

Each intervention comprised of three tablets and one capsule that were identical in appearance (kava active group: three kava tablets and one oxazepam placebo capsule; oxazepam active group: three kava placebo tablets and one oxazepam capsule; placebo group: three kava placebo tablets and one oxazepam placebo capsule). The kava tablets were supplied by MediHerb Pty Ltd. (Warwick, Australia) and manufactured under strict pharmaceutical good manufacturing practice (Pharmaceutical GMP). The kava preparation used was a water-soluble extract of the peeled rootstock from a Vanuatu "Noble" cultivar (Palarasul). An independent assay using high-performance liquid chromatographic analysis revealed higher concentrations of the kavalactones dihydrokavain, kavain, and dihydromethysticin, moderate levels of methysticin, and lower levels of yangonin, desmethoxyyangonin, and chalcone methylesters. Tablets were formulated from a pressed, dried aqueous extract and standardized to contain 60 mg of kavalactones per tablet (total acute dose of 180 mg of kavalactones). The benzodiazepine prescribed for the study was also manufactured via Pharmaceutical GMP and contained 30 mg of oxazepam per capsule. Kava placebo tablets and oxazepam placebo capsules were designed to be identical to the active intervention.

Screening measures

The MINI-International Neuropsychiatric Interview (MINI Plus) (Sheehan *et al*., 1998) was used to screen participants for psychiatric disorders for potential exclusion. The HAMA (Hamilton, 1959) was used to assess the severity of anxiety symptomatology, with only participants who scored between 14 and 25 included in the trial (because of ethics committee constraints). Other screening measures included a drug check questionnaire assessing drug/substance use over the past 3 months, an alcohol consumption questionnaire examining alcohol intake over the past month, current health and medications form, and demographics questionnaire, whereas a safety checklist was used to monitor adverse effects of the treatments administered. The State–Trait Anxiety Inventory-State (STAI-S) (Spielberger, 1985) was used as the primary outcome measure to evaluate treatment effects on stress and anxiety. The STCI-Short version (STCI-S) (Ruch *et al*., 1996) was used to measure current moods (cheerfulness, seriousness, and bad mood). Bond–Lader Visual Analogue Scales (VAS) (Bond and Lader, 1974) were used to assess the dimensions of alertness, calmness, and contentment experienced by subjects. The Computerized Mental Performance Assessment battery was employed to assess changes in cognitive performance. The cognitive tasks were presented on a laptop computer with a colored monitor. The total time of the selected tasks included in the battery was approximately 25 min. The tasks included were presented in the following order: Simple Reaction Time (RT), Digit Vigilance Task, Choice RT, Numeric Working Memory, Rapid Visual Information Processing (RVIP), and Corsi Blocks. A detailed account of all the tasks can be found in Scholey *et al*. (2010).

Liver function tests (albumin, total protein, bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, alkaline phosphatase) (Knight, 2005) were undertaken by participants to determine current hepatic function and possible hepatotoxicity or abnormal liver function. An 8-mL venous blood sample was taken to analyze specific genetic polymorphisms that have been associated with (i) increased incidence of anxiety disorders, (ii) response to pharmacotherapies used to treat anxiety or depressive disorders, and (iii) hepatic enzymes responsible for metabolism of kava and oxazepam (see Table 1 for the list) (Horstmann and Binder, 2009; Schosser and Kasper, 2009; Sarris *et al*., 2011b). Polymorphisms were analyzed by Healthscope Pathology (Melbourne, Australia) from DNA extracted from whole blood using Qiagen, QIAmp mini columns according to the manufacturer's instruction. Genotyping was then performed by single base extension assays and analyzed on the Sequenom Massarray (USA).

Table 1. Genetic polymorphisms analyzed

Gene	Polymorphism
GABA transporters (SLC6A1)	rs956053, rs2697153, rs2930152, rs1710879, rs2601126
GABA receptors (GABR)	rs2229940, rs279858, rs279871
Noradrenaline transporters (NET, SLC6A2)	rs3785157, rs11568324, rs998424, rs2242447, rs28386840, rs2242446
Catechol-O-methyltransferase (COMT)	rs737865, rs4680(Val158Met)
Brain derived neurotrophic factor (BDNF)	rs7124442, rs6265(Val66Met)
Serotonin transporter (SLC6A4)	Promoter region variable number tandem repeat
Cytochrome P450 2D6 (CYP2D6)	1 to 70 alleles
Cytochrome P450 3A4 (CYP3A41b)	rs2740574

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Procedure

Participants were required to attend a suite of dedicated laboratories at the Centre for Human Psychopharmacology on three occasions. Each visit was approximately 1 week apart. A structured telephone screening was used to determine whether potential participants satisfied inclusion criteria. Eligible participants met with the researcher to provide informed consent and complete screening assessments. Blood pressure and a liver function blood test were then taken to ensure levels were within normal range. Then, baseline STAI-S, STCI-S, and Bond–Lader questionnaires were administered. Participants were then given a 10-min practice session on the cognitive battery. Participants were then administered their first treatment, followed by a 90-min break in a relaxed environment for treatment absorption. The full cognitive battery was then completed followed by the STAI-S, STCI-S, and Bond–Lader questionnaires. Safety checklists were administered at the conclusion of each visit and at the commencement of the second and third visit to monitor for any possible adverse effects during or between appointments. At visits 2 and 3, the assessment process was repeated. All participants were compensated $A50 per session for travel ($A150 at the conclusion of the trial). At the end of the final trial, they were thanked and debriefed.

Statistical analysis

Data was analyzed using SPSS version 19 (IBM, New York, USA). Power calculations were based on 80% power and an alpha level of 0.05 for presumed anxiety reduction on the STAI-S. An adequate sample size required to confidently detect potential genetic differences was beyond the scope of this pilot study. Individual measures of anxiety, cognition, and mood were assessed by repeated-measures analysis of variance: Treatment (kava, oxazepam and placebo) × Time (pre-treatment, post-treatment). Post-hoc paired samples *t*-tests and pairwise analyses were also performed to determine individual effects of interventions. Correlations between genotypes and changes on STAI-S, STCI-S, and Bond–Lader subdomains were analyzed using Spearman's rho. Significance level was set at $p \leq 0.05$ for mood, anxiety, and neurocognitive outcomes and $p \leq 0.01$ for genetic correlations. For further detail on of the aims and design of the study, cf. Sarris *et al.* (2010).

RESULTS

Participant characteristics

Twenty two participants met inclusion criteria and all completed the study. Average mean age of participants was 33.3 years (±SD 13.0) with a range of 18–39 years old. Fifteen out of 22 participants (68%) were female (seven male), with the difference being statistically significant ($p = 0.026$). Six (27%) had high-school level education, with 16 (73%) having studied at a university or postgraduate level. Eight participants (36%) were in full-time or part-time education, twelve (55%) were currently studying, and two (9%) were unemployed. Genetic data was available from 19 consenting participants. Genetic analysis of serotonin promoter transporter (5-HTTLPR SLC6A4) polymorphisms revealed that the sample had six L/L, six L/S, and seven S/S alleles, whereas analysis of CYP 2D6 revealed that two participants were "poor metabolizers", six were "intermediate metabolizers", and eleven were "extensive metabolizers". All included genetic data were in Hardy–Weinburg equilibrium.

Anxiety and mood

On the primary outcome of STAI-S anxiety, a significant interaction was revealed between conditions ($f(1,21) = 3.36$, $p = 0.046$, *partial* $\eta^2 = 0.14$; see Table 2). Participants with mild to moderate anxiety ($n = 22$) subjected to increased stress from moderate cognitive demand experienced greater anxiety when given placebo compared with oxazepam, with a reduction of 2.6 points for oxazepam on STAI-S ($t(21) = 2.25$, $p = 0.035$). As Figure 1 details, placebo anxiety increased by 1.8 points on STAI-S (trend $p = 0.08$), whereas anxiety levels after kava administration did not change. In the oxazepam condition, a significant increase in self-rated "calmness" was found on the Bond–Lader ($t(20) = 3.57$, $p = 0.002$). Treatment sequence as a between-subjects factor was found to not alter the anxiety results ($f < 1$; *NS*). On Bond–Lader "alertness", a significant Group × Time interaction ($F(20) = 4.17$, $p = 0.032$) was found, with a significant reduction over time for oxazepam ($t(21) = 4.72$, $p < 0.001$), whereas no significant reduction was found in the kava or placebo conditions.

No significant Time × Treatment interaction was found on any other mood measures. Significant individual treatment effects were however found for a reduction on the STCI-S "seriousness" subdomain for the placebo group ($t(21) = 2.09$, $p = 0.047$), whereas a reduction of "bad mood" on STCI-S occurred for oxazepam ($t(21) = 2.86$, $p < 0.01$) and placebo ($t(21) = 2.26$, $p = 0.036$).

Cognition

Overall, kava and oxazepam were found to have no impairing effect on the computerized cognitive battery (see Table 3). Significant effects were found on the outcomes of Choice RT Accuracy ($f(2,21) = 7.01$,

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Table 2. Anxiety and mood outcomes

	Kava ($n=22$)			Oxazepam ($n=22$)			Placebo ($n=22$)			Condition interaction (p)
	Pre-treatment	Post-treatment	p	Pre-treatment	Post-treatment	p	Pre-treatment	Post-treatment	p	
STAI-S										
Total anxiety	43.41 (9.05)	43.59 (8.20)	0.87	44.09 (8.75)	41.50 (9.75)*	0.035	40.50 (9.65)	42.36 (9.02)	0.08	0.046*
Bond–Lader VAS										
Alert	61.35 (13.56)	55.75 (15.41)	0.15	62.40 (12.04)	48.95 (14.87)**	<0.001	56.45 (15.64)	57.95 (14.72)	0.65	0.032*
Calm	63.47 (17.47)	61.58 (15.80)	0.88	56.80 (14.57)	67.05 (7.53)**	0.002	59.21 (11.50)	62.16 (12.22)	0.63	0.20
Content	65.19 (11.30)	62.67 (14.14)	0.23	64.24 (12.64)	64.48 (10.14)	0.66	65.19 (11.07)	62.48 (11.35)	0.17	0.15
STCI-S										
Cheerful	13.73 (3.20)	13.77 (3.88)	0.94	12.68 (2.98)	12.64 (3.70)	0.96	13.95 (3.44)	13.32 (3.12)	0.44	0.86
Seriousness	15.14 (3.50)	14.82 (3.94)	0.50	14.95 (3.58)	14.18 (3.30)	0.15	15.73 (3.26)	14.59 (3.17)*	0.05	0.47
Bad mood	11.14 (3.82)	10.82 (3.40)	0.50	10.73 (3.99)	9.23 (3.36)**	<0.01	11.05 (4.03)	9.73 (3.83)*	0.04	0.22

STCI-S, State–Trait Cheerfulness Inventory-Short Version; STAI-S, State-Trait Anxiety Inventory-State; VAS, Visual Analogue Scale.
$n=22$ denotes a total sample of 22 participants receiving each treatment.
*$p<0.05$.
**$p<0.01$.

$p=0.002$, *partial* $\eta^2=.25$); RVIP correct responses ($F(2,21)=7.39$, $p=0.002$, *partial* $\eta^2=.26$); and Digit Vigilance RT ($F(2,21)=3.70$, $p=0.03$, *partial* $\eta^2=.15$). Pairwise analyses showed that Choice RT Percentage Correct was significantly higher in the oxazepam group compared with placebo ($p=0.005$), RVIP Correct Responses was significantly higher after kava administration ($p=0.002$) and oxazepam ($p=0.002$) compared with placebo, whereas Digit Vigilance RT was significantly higher in the placebo group compared with kava ($p=0.016$) (lowest RT) (see Table 3).

Genetic correlates

On mood and anxiety outcomes of participants administered kava, the NET rs3785157-T allele ($rho=-0.48$, $p=0.01$) was associated with declines in Bond–Lader "content" subscale scores, whereas the NET rs2242446-T allele ($rho=0.60$, $p<0.01$) was associated with an increase in STCI-S "seriousness" subscale score. A BDNF polymorphism (rs7124442-T allele) was found to be correlated with a reduction of STCI-S "seriousness"; however, although $p<0.05$, it did not meet the ≤0.01criteria for significance. Within the oxazepam condition, the GABRA4 rs2229940-A allele was associated with a decline on the STCI-S "bad mood" subscale ($rho=0.61$, $p<0.01$), and the NET rs998424 T-allele was associated with an increase on the Bond–Lader "content" subscale ($rho=0.50$, $p=0.008$). On cognitive outcomes, the COMT rs737865-T allele ($rho=0.60$, $p<0.01$) and the SLC6A1 rs2697153-G allele ($rho=0.62$, $p<0.01$) were positively correlated with Digit Vigilance RT in the oxazepam condition. No other significant associations were observed. None of the polymorphic correlations found were associated in both the kava and oxazepam conditions.

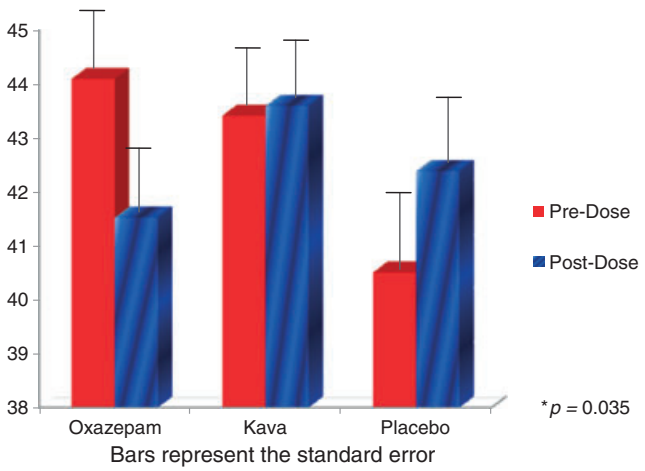

Figure 1. Comparative effects of oxazepam, kava, and placebo on State–Trait Anxiety Inventory-State Anxiety

Adverse reactions

Liver function tests revealed no significant change on any parameter (e.g., gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase, bilirubin) between baseline and after kava or oxazepam administration ($p>0.05$) (see Table 4). In respect to reported adverse effects noted at the conclusion of each session, no significant differences between treatments were found. Of note, in all conditions marked fatigue occurred, 12/22 (kava), 10/22 (oxazepam), and 10/22 (placebo). After oxazepam treatment, 3/22 experienced headaches and 5/22 dizziness, although a similar outcome occurred in the placebo condition: headaches 4/22 and dizziness 2/22.

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Table 3. Cognitive performance outcomes

Cognitive task	Kava ($n = 22$)	Oxazepam ($n = 22$)	Placebo ($n = 22$)	Condition interaction (p)
Simple RT (ms)	322.91 (39.44)	340.10 (71.23)	335.71 (62.41)	0.37
Choice RT (ms)	465.47 (87.83)	463.27 (71.73)	458.97 (87.96)	0.85
Choice RT % correct	95.57 (4.08)	96.14 (3.51)	93.86 (4.41)	<0.01*
Word recognition correct response	24.50 (2.92)	23.91 (3.54)	24.59 (2.26)	0.58
Word recognition RT (ms)	1018.47 (242.77)	1030.58 (241.70)	1014.73 (224.11)	0.95
RVIP RT (ms)	492.92 (61.60)	501.50 (52.20)	514.13 (81.89)	0.51
RVIP correct response	13.64 (9.07)	13.27 (9.49)	10.50 (8.78)	<0.01*
Numeric WM RT (ms)	530.03 (74.71)	514.61 (88.66)	556.97 (91.45)	0.15
Numeric WM accuracy (%)	93.40 (5.34)	94.75 (4.82)	95.06 (3.48)	0.45
Digit vigilance RT (ms)	435.95 (43.13)	442.43 (41.03)	451.83 (37.58)	0.03*
Digit vigilance incorrect response	2.73 (2.76)	2.05 (1.81)	2.18 (1.47)	0.26
Corsi blocks RT (ms)	6452 (1614)	6662 (1782)	6597(1185)	0.90
Corsi blocks (score)	5.22 (1.39)	5.42 (0.92)	5.53 (1.42)	0.34

RT, reaction time; WM, working memory; RVIP, reaction visual information processing; ms, millisecond.
$n = 22$ denotes a total sample of 22 participants receiving each treatment.
*$p < 0.05$.
**$p < 0.01$.

Table 4. Liver function tests

Liver enzyme	Baseline	Post drugs	p value
ALB	42.86 (3.1)	41.76 (2.8)	0.08
ALP	67.48 (18.2)	65.43 (14.3)	0.27
GGT	22.95 (12.4)	21.57 (14.06)	0.21
ALT	26.62 (16.8)	26.19 (19.7)	0.74
AST	22.52 (7.7)	22.43 (7.4)	0.93
BIL	9.48 (4.5)	10.00 (4.8)	0.39

ALB, albumin; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, bilirubin; p value = paired t-tests.

DISCUSSION

This is the first human clinical trial to study the anxiolytic effects of an acute administration of a "medicinal" dose of kava versus a gold standard synthetic anxiolytic. Furthermore, this is the first study to explore the genetic correlates in a human RCT using any herbal medicine or benzodiazepine (pharmacodynamic effect). A primary finding of this study was as hypothesized; the acute administration of oxazepam significantly reduced anxiety when participants were exposed to demanding cognitive testing (which presumably was mildly stressful to this group). Interestingly, although there was a trend showing increased anxiety levels in the placebo condition, this effect did not occur markedly in the kava condition, potentially indicating a mitigating effect on stress-provoked anxiety. However, it should be noted that as the placebo condition had the lowest baseline STAI-S, the rise in anxiety could be due to a "ceiling effect" (although there was no statistically significant difference between baseline scores). Furthermore, self-rated "calmness" was also shown on the Bond–Lader Visual Analogue Scales to be significantly increased over time in the oxazepam condition, whereas the kava condition was statistically unchanged.

There were no cognitive deficits associated with kava administration. This finding is consistent with previous studies that have found that acute or chronic administration of the plant medicine does not impair RT, memory, or attention (LaPorte *et al*., 2011). Although oxazepam was found to reduce alertness, surprisingly, no other cognitive deficits were identified. In previous studies, acute administration of oxazepam significantly decrease RT (Herbert *et al*., 1983; Kerr *et al*., 1992; Buffet-Jerrott *et al*., 1998), allocation of attention (Heinze *et al*., 1994; van Leeuwen *et al*., 1995), implicit and explicit memory (Buffet-Jerrott *et al*., 1998), and recognition rate (Münte *et al*., 1993). Furthermore, no significant difference was found between oxazepam, kava, and placebo on any adverse events. Half of the participants did note pronounced fatigue after the sessions; however, as this occurred across the groups, it is likely that this was due to the demands of the cognitive battery and not a somnolent effect related to either active treatment.

Mood-elevating effects were also apparent for oxazepam with the level of "bad mood" on the STCI-S significantly decreased. These results are consistent with benzodiazepines having a potential acute thymoleptic effect (Tiller and Schweitzer, 1992). No effect, however, was found for kava on any mood measure, which is inconsistent with earlier results of Thompson *et al*. (2004) who found that 300 mg of kava (90 mg of kavalactones) significantly increased state cheerfulness. In their study, they did not subject participants to cognitive demand that evokes stress. It is possible

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that the thymoleptic effects of kava are more apparent when an individual is in a relaxed state and under less cognitive load (such as in the case of traditional recreational use). It is also likely that the anxiolytic and thymoleptic effects from kava may not acutely occur in first-time "kava-naive" people and that repeated administration may be required to reinforce the psychotropic effects. Another consideration is that the dosage of kava used (180 mg of kavalactones) may not be sufficient to provide a strong acute anxiolytic effect, and higher doses may provide a stronger effect. Regardless, considerations regarding safe dosage need to be considered (Teschke *et al*., 2010). Finally, it should be noted that many cultivated kava species (cultivars) exist, and although the particular cultivar used in this study may not exert an acute anxiolytic effect in naive users, other kava cultivars, such as "borogu", which is higher in kavain, may potentially provide this effect (Teschke *et al*., 2010).

No correlations between genetic differences and the primary STAI-S outcome were identified. However, genetic analyses provide preliminary evidence that NET (SLC6A2) transporter polymorphisms may have an effect on response to kava. This result is consistent with the known noradrenergic effects of kava (LaPorte *et al*., 2011). Associations between Digit Vigilance RT and polymorphisms in COMT and GABA transporter genes in the oxazepam arm suggest that these polymorphisms may modulate cognition in the context of oxazepam administration. Despite previously found associations (Tiwari *et al*., 2009), we did not observe effects of the SLC6A4 promoter, CYP3A4, or CYP2D6 polymorphisms for any effect on any outcomes. However, our sample size was relatively small, and consequently, we did not have adequate power to detect small potential associations. Thus, given our sample size, future studies are required to confirm these preliminary findings.

There were limitations of the current study, which may have impeded some analyses from reaching a level of statistical significance. Oxazepam is an intermediate-acting benzodiazepine that is absorbed slowly with plasma concentrations peaking at around 2–3 h (Greenblatt and Koch-Weser, 1975; Buffet-Jerrott *et al*., 1998). Thereby, the time of testing used in the study of approximately 90 min may not have allowed for a full cognitive effect to be observed. General participant fatigue may have also impacted on the quality and reliability of self-report measures, especially on post-treatment self-report questionnaires. Multiple post-hoc statistical corrections were not applied to genetic analyses; however, we did select *a priori* a small and specific sample of genes to test (as described in the Methods section). Finally, baseline cognitive measures were not taken in all three time periods (because of time restrictions).

Although the present findings should be cautiously interpreted, they do provide a foundation upon which future studies of the comparative psychiatric, cognitive, and genomic correlates of the psychopharmacological activity of natural and synthetic psychotropics can build.

CONFLICT OF INTEREST

No conflict of interest declared.

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