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ORIGINAL ARTICLE

Randomized, dose-controlled double-blind trial: Efficacy of an ethanolic kava (*Piper methysticum* rhizome) extract for the treatment of anxiety in elderly patients

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ABSTRACT

Aim: Kava, an aqueous drink from the roots and peeled rootstock of the plant *Piper methysticum* G.Forst., is renowned in Melanesia, Polynesia and Micronesia for its relaxant effect. Modern extract preparations with defined contents of kavalactones – the major active constituents – are well established as herbal medicinal products on the European market. The aim of this trial was to present data on the clinical efficacy of an ethanolic kava extract.

Methods: In the present double-blind clinical trial, the differences in clinical outcome between a low dose of ethanolic kava extract (equivalent to 20 mg kavalactones daily) and a respective high dose (equivalent to 200 mg kavalactones daily) were investigated. Patients with anxiety disorders were randomized into the two groups, resulting in 33 patients in the high-dose group and 36 patients in the low-dose group. The study duration was 4 weeks; the primary parameter was the Hamilton anxiety (HAMA) score. Global efficacy was rated by the physician at the end of the study. Safety of application was based on the documentation of adverse events.

Results: The high-dose group was statistically significantly superior to the low-dose group on HAMA total score and its subscores for psychological and physical manifestations of anxiety ($P < 0.001$), with a total improvement of −41.5% versus −13.6% relative to baseline HAMA total score on day 28. No adverse events occurred.

Conclusion: Kava preparations have a dose-dependent anxiolytic effect.

KEY WORDS: anxiolytic efficacy, double-blind clinical trial, kava, kavalactone, *Piper methysticum* G.Forst., Piperaceae

INTRODUCTION

Kava, the roots and rootstock of the pepper species *Piper methysticum* G.Forst., is an important pillar of the South Pacific culture and economy. Kava has been used for the preparation of a traditional, non-alcoholic relaxing drink for more than 1000 years in the islands of Melanesia, Polynesia and Micronesia. The kava drink has distinct relaxing, stress-relieving and anti-aggressive properties.

These effects of kava extracts are attributed to the presence of kavalactones, namely kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin (Fig. 1), which are readily absorbed and distributed in the human body [1]. Kavalactones are mostly excreted unchanged or partly hydroxylized or methylated via urine [2]. T_{max} for the major kavalactones is approximately 3 h [3], and the effects do not last longer than 8 h [1].

From a pharmaceutical point of view, there are two distinct phytochemical cultivars of kava: the so-called 'two day kavas', which contain a considerably higher percentage of the lipophilic kavalactones (mainly dihydromethystin); and 'noble kava', which has kavain and dihydrokavain as the major constituents. Two day kava has prolonged activity as a result of enterohepatic cycling, and also contains other constituents probably contributing to its poor tolerability [1]. Officially, the regulations in the South Pacific kava-

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†Since the performance of this trial, Professor de Nicola has passed away. This study is dedicated to his memory.
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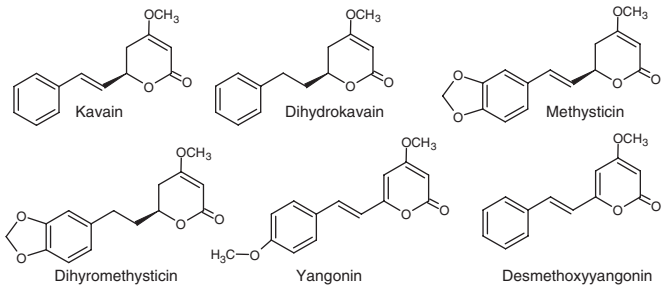

Figure 1 | Major kavalactones in kava and kava extracts.

producing countries (i.e. *Vanuatu Kava Act*) allow the export only of noble kava, to avoid safety-related issues.

Kava reached Europe in colonial times, with medicinal applications described as early as 1886 [4]. With accumulating scientific data, medicinal products containing preparations from kava roots and rootstock were authorized for the treatment of stress-related anxiety, inner tension and restlessness (AMIS, www.dimdi.de). The products were later standardized to a fixed content of kavalactones, typically in the range 50–210 mg per daily dose, depending on the specific preparation. In comparison, the traditional South Pacific kava drink contains approximately 210 mg kavalactones per coconut shell [5], with one to three shells regularly consumed during one session. Currently, regulatory authorities also call for a proof of use of noble kava (German Federal Institute for Drugs and Medical Devices (BfArM), letter to marketing authorization holders, 2017).

Kava in its traditional form was always considered safe: even high doses of five shells and more would lead only to a state of high relaxation and sleepiness for approximately 8 h, with no hangover [1]. It therefore came as a surprise when case reports of liver toxicity were observed in the context of the medicinal use of kava extract preparations in Switzerland and Germany in 1999 and 2000 [6]. Although the causality of the case reports was questioned very early in the debate [7,8], a de facto ban of kava preparations was issued in 2002 for all of Europe. The debate on the potential liver toxicity of kava extracts in Germany continued for many years without new evidence supporting a liver risk, and only recently reached a conclusion when the German Upper Administrative Court ruled that the ban of kava preparations was not justified due to lack of proof of safety issues with noble kava [9]. This may change, however, if two day kava is used in kava extract preparations, given that the acetonic extract of, most likely, today kava, had a high degree of probability of causality [9,10], which is why current German regulations allow noble kava only.

As well as potential risks, considerations on efficacy are also part of the benefit–risk assessment. The efficacy of kava as an anxiolytic active pharmaceutical ingredient is generally accepted by science and corroborated by >20 years of experience of the medicinal use of modern kava extract preparations. None of the clinical trials published to date indicated a risk [8], and the overall efficacy was confirmed in meta-analyses [11,12], as well as in recently published clinical trials with preparations using water as an extraction solvent [13,14].

The specific ethanolic kava extract preparation used in the present study has already been used in previous clinical trials, namely in a study on acute effects in pre-medication for surgery, and in an open, observational trial [15,16]. The present study was mainly inspired by the current debate on the benefits and risks of kava [17].

METHODS

Study design

The study was designed as a single-center, randomized, double-blind parallel group comparison between a high and a low dose of kava extract. The duration of the study was set to 28 days, with one interim visit. Randomization was made in blocks of four.

The study was planned and carried out in accordance with the criteria of Good Clinical Practice (GCP) and the ethics standards defined in the declaration of Helsinki. The study was permitted by the drug regulatory agency. Ethics Committee approval and patient signed informed consent forms were obtained after informing the patients of the study medication, including the risks and potential benefits.

Study medication

Both study groups received the same kava extract (Gehrlicher Pharmazeutische Extrakte, Eurasburg, Germany) in undistinguishable hard gelatin capsules. The high-dose group received two capsules b.i.d. with kava extract standardized to 50 mg kavalactones per capsule, that is, a daily dose of $4 \times 50 = 200$ mg kavalactones, to be taken with liquid at meals in the morning and the evening. In the low-dose group the capsules contained only the equivalent of 5 mg kavalactones per capsule, with a daily total of $4 \times 5 = 20$ mg kavalactones. The weight difference was covered by adding the corresponding quantity of capsule filling matrix. The high-dose medication corresponded to the German authorized medicinal product Kavasedon (Harras Pharma Curarina, Munich, Germany). The plant material used in the study medication extract was identified as a typical noble kava [9] variety from Vanuatu.

Investigator blinding with regard to the preparation and allocation of the individual study medication was guaranteed via labeling provided by the manufacturer of the extract, with the randomization list available only to the manufacturer until unblinding. Physician, patients and the statistician were fully blinded until statistical assessment was completed.

Parameters

The Hamilton Anxiety Score (HAMA) was defined as the primary parameter for the evaluation of efficacy, with subscores for psychological and physical manifestations examined independently [18]. Examinations took place on the day of study entry (V0), after 14 days (V14) and at study termination at day 28 (V28).

Global assessment of efficacy by the physician served as a secondary parameter, and was assessed on a 5-point verbal rating scale with the options 'worse', 'unchanged', 'somewhat better', 'much improved' and 'very much improved'. Safety of application was also analyzed, by documenting tolerance and adverse events at both visits V14 and V28. The final visit also included a physical examination of the patient and a capsule count for compliance testing.

Statistical analysis

The primary parameter (HAMA) was compared between groups using analysis of variance. Group differences in physician assessment and baseline characteristics were calculated using chi-squared test and analysis of variance. Statistical analysis of the secondary parameters was done by comparing the percentages of the different categories. Secondary parameters had no confirmatory value.

Inclusion and exclusion criteria

Patients with nervous anxiety, tension and restlessness (corresponding approximately to specific and situational anxiety according to item F40.2 of the 10th edition of the International Classification of Diseases (ICD-10)) with HAMA score ≥15 were included. The minimum age for inclusion was 40 years. The clinical definition of anxiety required the presence of the first two main symptoms (Table 1), with at least three more symptoms, all with at least moderate intensity.

Exclusion criteria were severe diseases of the liver and kidney, cardiovascular system, gastrointestinal tract, hematopoietic system or the endocrine system; drug, alcohol, or medication abuse; anxiety due to organic diseases; psychoses or severe behavioral disorders; pre-treatment in the preceding 4 weeks or concomitant treatment with hypnotics, antidepressants, neuroleptics, reserpine, beta-blockers, antihistamines or anti-emetics, or recent changes in the dosing or the medication of antihypertonics; and pregnancy and lactation. Other, concomitant medication was permitted as long as it was well tolerated and there were no changes in dosing and intake intervals.

RESULTS

Demographic data

Seventy patients were screened and admitted to the study. One patient originally assigned to the high-dose group did not return to the follow-up examination. Sixty-nine patients concluded the study and could be evaluated. Thirty-three patients were assigned to the high-dose group, and 36 to the low-dose group (Table 2). There was no deviation from the inclusion parameters. Most of the patients had recurrent anxiety, which had started 3–6 months prior to study start. For the anxiety episodes prior to study start, all patients but one were treated with drugs.

There was no statistically significant difference between the two study groups with respect to gender (chi-squared test), age, height or bodyweight (analysis of variance). The treatment groups were similar with respect to previous episodes of anxiety, duration of complaints and severity of symptoms at baseline.

Primary efficacy parameter: HAMA

Groups were compared using analysis of variance for day 0 versus 14, day 14 versus 28, and day 0 versus 28. The total score and the two subscores for psychological and physical manifestations were independently examined. In no case was a gender effect detected ($P \geq 0.3$).

Table 1 | Symptom list for the diagnosis of anxiety disorder

ID no.	Symptoms
	Subjective symptoms
1	Nervous, shaky, distracted feeling
2	Fearful, timorous, oppressive, panicky feeling
3	Fear of falling over/fainting, of screaming, of losing control of one's self, of large crowds of people, of places, of disaster or of death
4	Avoidance of certain places, things or activities because of anxiety
5	Tense or overexcited feeling, muscular or motor phenomena
6	Tense, painful muscles
7	Shivering, shaking
8	Restlessness, fidgetiness
	Autonomic symptoms
9	Tachycardia or palpitations, breast pain
10	Difficulty in breathing, gasping for breath, feeling of suffocation, lump in the throat, choking
11	Sweating, particularly in the armpits, palms of the hands, soles of the feet
12	Cold, sweaty hands
13	Dry mouth
14	Rotary vertigo, unconsciousness (fainting), dizziness, weakness
15	Tingly sensation in the hands or feet
16	Gastric flatulence, nausea, indigestion
17	Frequent urge or urgency to pass water/stools

Table 2 | Subject characteristics vs kava dose

	High-dose group n = 33 Mean ± SD (range) or n (%)	Low-dose group n = 36 Mean ± SD (range) or n (%)	Total n = 69 Mean ± SD (range) or n (%)
Gender			
Female	17 (51.5)	16 (44.4)	33 (47.8)
Male	16 (48.5)	20 (55.6)	36 (52.2)
Marital status			
Single	4 (12.1)	5 (13.9)	9 (13.0)
Married	22 (66.7)	29 (80.6)	51 (73.9)
Widowed	6 (18.2)	2 (5.6)	8 (11.6)
Missing data	1 (3.0)	0 (0)	1 (1.5)
Age (years)	67.9 ± 4.6 (57–82)	67.6 ± 5.1 (48–76)	67.7 ± 4.8 (48–82)
Height (cm)	166.0 ± 4.7 (154–180)	163.7 ± 18.5 (61–180)	164.8 ± 13.7 (61–180)
Weight (kg)	63.7 ± 5.0 (55–75)	72.7 ± 29.4 (50–176)	68.5 ± 22.0 (50–176)
Status at inclusion			
Deterioration	0 (0)	1 (2.8)	1 (1.4)
Recurrence	32 (97.9)	35 (97.2)	67 (97.1)
Different from earlier	1 (3.0)	0 (0)	1 (1.4)
Start of symptoms			
3–6 months before the trial	32 (97.0)	34 (94.4)	66 (95.7)
6–12 months before the trial	1 (3.0)	2 (5.6)	3 (4.3)

HAMA total score

Baseline HAMA score was not significantly different between the groups: HAMA total score was 27.55 and 29.25 for the high- and the low-dose group, respectively (Table 3). Score improvement was significantly more pronounced in the high-dose group, with a decrease of 11.43 versus 7.53 score points (41.5% vs 13.6% improvement from starting value; $P < 0.001$ between groups, day 0 vs day 28).

Differences between the high- and the low-dose group were already statistically significant at day 14 ($P < 0.0001$). Additional – but not statistically significant – improvement could be observed in the second half of the trial between day 14 and day 28 (improvement by an additional 2.94 vs 2.58 HAMA score points in the high- and the low-dose groups, respectively; $P = 0.815$, day 14 vs day 28; Fig. 2a).

Psychological manifestations subscore

At the start of the study there was no statistically significant difference between groups. HAMA subscore for psychological manifestations was 16.64 points in the high-dose and 17.33 points in the low-dose group (Table 3). Changes over time were clearly visible in the high-dose, but not in the low-dose group, with overall improvements of the subscore for psychological manifestations of 7.31 points (43.9%) versus 2.41 points (13.9%) in the high-dose versus the low-dose group ($P < 0.0001$ between groups, day 0 vs day 28; Fig. 2b).

The difference between groups was highly significant after 14 days ($P < 0.001$). After these first 2 weeks there was further improvement, with subscore reductions of 2.15 and 1.66 points in the high- and the low-dose group, respectively, between day 14 and day 28. Group comparison of additional score reductions in the second half of the trial did not reach statistical significance ($P = 0.635$).

Physical manifestations subscore

At the start of the study there was no statistically significant difference between groups, with HAMA subscore for physical manifestations of anxiety of 10.91 points in the high-dose and of 11.92 points in the low-dose group (Table 3).

Changes over time were visible in the high-dose, but much less so in the low-dose group, with overall improvements of physical manifestations subscore of 4.12 points (37.8%) versus 1.56 points (13.1%) in the high-dose versus the low-dose group ($P < 0.002$ between groups, day 0 vs day 28; Fig. 2c).

The effect was already fully pronounced after 14 days ($P < 0.0001$ between groups, day 0 vs day 14). No significant changes occurred in the second half of the study period: the

Table 3 | Change in HAMA score during treatment vs kava dose

Examination visit	High-dose group (n = 33) Mean ± SD (% change) (range)	Low-dose group (n = 36) Mean ± SD (% change) (range)	*P*-value
Total HAMA score			<0.001
Study entry	27.55 ± 4.60 16–35	29.25 ± 3.34 22–35	
Day 14	19.06 ± 5.27 (−30.8) 9–34	27.86 ± 5.73 (−4.8) 14–35	
Day 28	16.12 ± 6.38 (−41.5) 8–38	25.28 ± 7.38 (−13.6) 11–34	
HAMA psychological manifestations subscore			<0.001
Study entry	16.64 ± 1.97 13–20	17.33 ± 1.71 13–20	
Day 14	11.48 ± 2.93 (−31.0) 7–19	16.58 ± 3.66 (−4.3) 7–19	
Day 28	9.33 ± 4.38 (−43.9) 6–21	14.92 ± 4.57 (−13.9) 6–19	
HAMA physical manifestations subscore			<0.001
Study entry	10.91 ± 3.19 2–15	11.92 ± 2.59 5–16	
Day 14	7.58 ± 2.94 (−30.5) 1–15	11.28 ± 2.81 (−5.4) 5–16	
Day 28	6.79 ± 3.02 (−37.8) 1–17	10.36 ± 3.38 (−13.1) 3–15	

HAMA, Hamilton anxiety scale.

slight improvements between day 14 and day 28 reached less than 1 additional score point in both groups ($P = 0.837$).

Physician global assessment of efficacy

Physician global assessment of efficacy was likewise positive in favor of the high-dose group. A total of 72.7% of patients in the high-dose group versus 19.4% in the low-dose group were rated as much improved or very much improved, whereas for 24.3% of patients in the high-dose group versus 69.5% in the low-dose group the condition was rated as unchanged or even slightly deteriorated. The difference between groups was statistically significant ($P = 0.00041$; chi-squared test).

Safety

There was no problem with safety of application: no difference in tolerance was found between groups, and no adverse events occurred in either of the study groups.

DISCUSSION

The present study was carried out to demonstrate the efficacy of short-term kava extract use, and to identify an effective dosage. The study duration corresponds to the current definitions of intake of kava preparations in Germany, where the use of kava preparations is restricted to 4 weeks as a safety measure in view of the debate on potential liver toxicity. The results not only demonstrate the efficacy of a typical ethanol-extracted kava preparation during short-term treatment of 4 weeks, but also indicated a dose dependence of the effect and a quick onset of measurable efficacy. The fact that the study used an under-dosed active reference as control group suggests that the statistical superiority of the high-dose group might even be more pronounced had it actually been tested against placebo, but, this must remain speculation given that a calculation against similar placebo-controlled trials was not performed. The effect was already fully manifest after only 2 weeks. These results also demonstrate an advantage of kava over selective serotonin reuptake inhibitors (SSRI), because – in contrast to these chemo-synthetic agents – kava does not require a lengthy build-up of the full effect over many weeks.

The psychological manifestations of anxiety disorders subscore was more strongly improved than the physical manifestations subscore, even though the difference was only minor, at 6.1%. Again, the preferential effect on the psychological manifestations supports the use of kava as an anxiolytic in situational anxiety.

The present study also confirms the results of earlier meta-analyses and reviews on kava extracts [12]. In some of

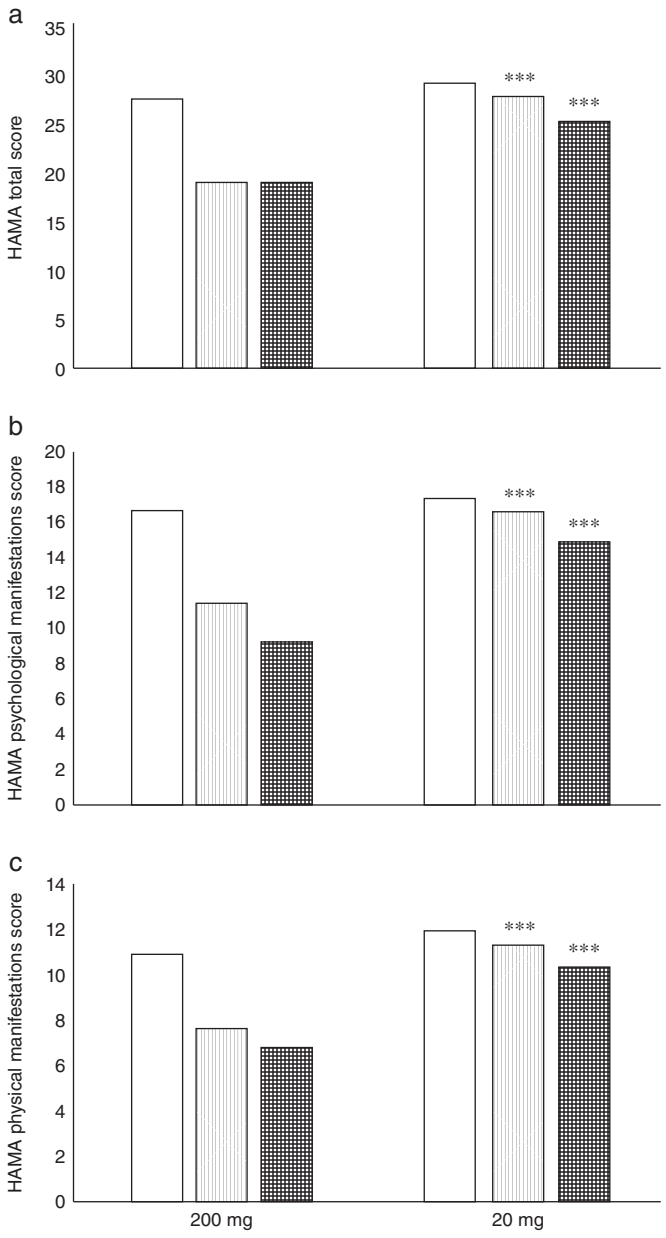

Figure 2 | Change in (a) Hamilton anxiety (HAMA) total score; (b) HAMA psychological manifestations subscore; and (c) HAMA physical manifestations subscore at (□) study entry; (▥) day 14; and (▦) day 28 in the 200 mg vs 20 mg kava groups (***$P < 0.001$ for group differences).

these, study durations of kava trials ranged up to 6 months [19,20], with no safety-related issues emerging. The present study with no adverse events and an eventless physical examination at the end supports the safe use of kava preparations at least for the currently recommended duration of intake of 4 weeks, and, based on published kava trials, even well beyond this period. With respect to safety, the present results are therefore also in line with all clinical kava trials performed to date.

Hypothetically, the study conditions would not exclude the development of liver toxicity after the cessation of intake. This is, however, unlikely because the current rules for causality assessment of case reports of drug-induced liver toxicity consider an observation of liver symptoms later than 2 weeks after cessation of intake as a strong hint to unrelatedness with the suspected medication [21]. The present patients were still treated for anxiety after the end of the study, and a sudden occurrence of liver symptoms would most likely have been observed and associated with an only-recently terminated participation in a clinical trial. Such severe side-effects, however, were not expected, because the typical exposure to kava from traditional daily kava drinking can easily exceed the present dose by a factor of 5. Although there is still debate on the adverse effects of so-called two day kava with regard to plant material of inferior quality for which there is no traditional experience [9,22], exposure to noble kava has never been related to liver toxicity, in more than 1000 years of experience [1] – therefore it would be extremely surprising if a dose-dependent kava toxicity did exist.

The official indication for kava in Germany, as used in this trial, is the treatment of nervous anxiety, tension and restlessness. This specific indication can be traced back to the monograph on kava of German Commission E, officially accepted and published in 1990 [23]. Both of the most recent diagnostic standards, ICD-10 and *Diagnostic and Statistical Manual of Mental Disorders* (4th edn; DSM-IV), however, do not include 'nervous anxiety, inner tension and restlessness' as a defined illness. The most fitting diagnosis according to ICD-10 would appear to be social anxiety disorder (SAD) or some forms of general anxiety disorder (GAD). 'Nervous anxiety, tension and restlessness' as defined by German Commission E usually involves a relatively short-term intervention, and might be best described as social phobia according to ICD-10F40.1 or specific/situational phobias according to ICD-10F.40.2.

The short-term application does, however, stand in contrast to the current treatment guidelines for SAD and GAD by the European Medicines Agency (CPMP/EWP/3635/03 and CPMP/EWP/4284/02). These guidelines foresee an application of SSRI-type antidepressants, and thus a type of medication that needs to be given long term to allow its effects to develop. There is no European treatment recommendation for shorter applications of anxiolytic drugs. From the physician's point of view, however, there is a medical need to cover acute episodes of anxiety without the requirement of long-term treatment. Examples are situations of stress-related anxiety such as fear of crowds, fear of speaking in front of an audience, fear of taking airplanes or fear of upcoming examinations. Benzodiazepines exert faster effects and can thus be used for the treatment of acute anxiety

situations but, given their addictive properties and their impact on cognitive function [24,25], benzodiazepines would not be recommended for short-term treatment of anxiety over 4 weeks. This is where kava may be useful, given that in contrast to benzodiazepines kava does not carry a risk of addiction. It does not even affect cognitive abilities [26–30]. The present results and all available kava studies confirm this approach for short-term treatment. Kava has both proven effects and – when compared with alternative medications for short-term management of anxiety such as benzodiazepines – a superior safety profile. As a consequence, the current concept of treatment guidelines and the lack of therapeutic recommendations for short-term treatment of anxiety should be re-examined. Whereas the present study alone may not be sufficient to justify a recommendation in treatment guidelines, the combination of all available clinical studies of various kava preparations provide a consistent picture that, with all caveats, ought to ensure the place of kava extracts in the treatment of anxiety.

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CONFLICT OF INTEREST

M.S. received grants from the pharmaceutical industry for consultancy. The other authors declare no conflicts of interest.

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