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Kava–Kava administration reduces anxiety in perimenopausal women

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Abstract

Objective: Disturbances of mood, such as anxiety and depression, increase in the perimenopausal period. Hormone replacement therapy or neuroactive drugs represent useful treatments for these disturbances but may be contraindicated or not accepted. Herein it was investigated the efficacy of Kava–Kava, an extract of Piper Methysticum, on mood of perimenopausal women. *Design:* A 3-months randomized prospective open study investigating in perimenopausal women modifications induced by calcium supplementation (control; $n = 34$), calcium plus Kava–Kava at the dose of 100 mg/day ($n = 15$) or calcium plus Kava–Kava at the dose 200 mg/day ($n = 19$). Anxiety was evaluated by the State Trait Anxiety Inventory (STAI); depression by the Zung's scale (SDS), and climacteric symptoms by the Greene's scale. Evaluations were performed at baseline and after 1 and 3 months. *Results:* In the control group during the 3 months, anxiety, depression and climacteric symptoms tended to decline, but not significantly. During Kava–Kava anxiety declined ($P < 0.001$) at 1 (-3.8 ± 1.03) and 3 (-5.03 ± 1.2) months, depression declined at 3 months (-5.03 ± 1.4; $P < 0.002$) and climacteric score declined ($P < 0.0006$) at 1 (-2.87 ± 1.5) and 3 (-5.38 ± 1.3) months. Only the decline of anxiety induced by Kava–Kava was significantly greater than that spontaneously occurring in controls ($P < 0.009$). *Conclusions:* The present data indicate that, in perimenopausal women, administration of Kava–Kava induces an improvement of mood, particularly of anxiety.

Keywords: Kava–Kava; Anxiety; Climacteric; Mood; Menopause

1. Introduction

Along with climacteric symptoms, mood disturbances, particularly anxiety and depression, are frequent around the menopause [1–4]. Although, they are dependent on modifications of central neurotransmitters consequent to rapid modifications of circulating gonadal steroids [5], their manifestation is influenced by individual factors such as education, socio-economic status and the woman capability to cope with daytime stress [1,6–9]. Likely, they spontaneously vanish with time [10], but in the years of their manifestation,

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mood disturbances may greatly impact on the woman quality of life [6,11].

Hormone replacement therapy may ameliorate mood [4] but this pharmacological approach is sometimes contraindicated and frequently non-accepted by the woman. Benzodiazepines, and antidepressants, represent commonly used pharmacological remedies for mood disturbances, but their use is sometimes associated with side effects, that in the case of benzodiazepines are characterized by drowsiness, prolonged time of reaction, and dependence, and in the case of some antidepressants by anticholinergic and cardiotoxic effects [2,3]. Alternative remedies are frequently used [12]. Kava–Kava, an extract from rhizome of Piper Methysticum, has been proposed as a 'natural' remedy for the treatment of anxiety [13,14]. Indeed, Kava–Kava depending on the dose and type of preparation seems to induce variegate effects among which skeletal muscle relaxation, sleepiness and central effects ranging from depression to euphoria [14].

The aim of this study was to evaluate whether the administration of Kava–Kava may exert positive effects on mood, particularly anxiety, of perimenopausal women.

2. Materials and methods

The study was approved by the local ethical committee and Institutional Review Board. Women in perimenopause referring to the Menopause Center of our institute were enrolled and signed an informed consent to enter into the study. Inclusion criteria were the willing to participate to the study and the perimenopausal period. The degree of mood disorders was not considered among the inclusion or exclusion criteria. The study was proposed to all perimenopausal women referring to the center, and requiring a therapy for climacteric symptoms. All women were informed that after the 3-months investigation they may receive established therapies, particularly hormone replacement therapy. Women with organic or neurological pathologies, having used hormones, neuroactive or psychotropic drugs in the 3 preceding months were excluded.

Perimenopause was defined as amenorrhea for 6–24 months, occurring around the menopausal age (47–53 years), associated with the occurrence of hot flushes (at least 3 per day for at least a 1-week evaluation), and a value of FSH higher than 30 IU/l.

Eighty perimenopausal women were enrolled in the study. Women received 1 g/day of calcium and were randomized to receive for 3 months: (1) no other treatment (control; $n = 40$); (2) Kava–Kava, 100 mg/die (1 capsule by mouth, containing 55% of kavaina) (Natural Bradel, Milano, Italy) ($n = 20$); (3) Kava–Kava, 200 mg/die (2 capsules by mouth) ($n = 20$). Because this is a spontaneous study, a Kava–Kava placebo was not available. Accordingly, we choose not to include a placebo group and to compare the effects of Kava–Kava with the spontaneous variations occurring in a control group that was still receiving a treatment (calcium).

In each woman, anxiety, depression and climacteric symptoms were evaluated at the beginning of the study and after 1 and 3 months. At each investigation, women on treatment were requested to return non-used capsule. Subjects having used more than 80% of medicine were considered compliant and entered into the analysis. State of anxiety was evaluated by the State Trait Anxiety Inventory (STAI) [15]. STAI is self-administered, and consists of 20 items. Each item refers to a particular sensation related to anxiety and is rated on a 4-point scale, ranging from 1 (not applicable) to 4 (very much applicable). Sum of scores range from 20 to 80. State of depression was evaluated by the Self-Evaluations Depression Scale (SDS) of Zung [16]. SDS is self-administered and consists of 20 items. Items explore affective, somatic, psychomotor and psychological aspects of depressive mood. Each item is rated on a 4-points scale, ranging from 1 (never or very rarely) to 4 (very frequently or always). Sum of scores range from 20 to 80. Scores below 50 indicate normality, between 50 and 59 slight depression, between 60 and 69 moderate depression, above 70 severe depression. Climacteric symptoms were evaluated by means of the Greene's scale [17]. The scale consists of 29 items investigating vasomotor symptoms, anxiety, depression, somatization, sexuality and urogenital

disturbances. Each item is rated on a 4-points scale ranging from 0 (absent) to 3 (intense). Sum of scores may range from 0 to 87.

Subjective side effects were evaluated after 1 and 3 months, by an interview and clinical examination. Beside the baseline evaluation, no routinary biochemical evaluation was scheduled during the study. Biochemical evaluations were performed in those presenting side effects.

Calculation of scores and statistical analysis were blindly performed by one of us (A.R.). Score obtained at baseline and after 1 and 3 months, were compared by one-factor analysis of variance (ANOVA) for repeated measures. When significant ANOVA was followed by the post hoc test of Scheffe's. Comparisons among the different group of treatments were performed by two-factors ANOVA for repeated measures. When significant ANOVA was followed by the Student's t-test or by one-factor ANOVA, in order to compare single time points of 2 or 3 groups, respectively. Regression analysis was used to evaluate relations among the different scores, and whether variations in each score were dependent on baseline values. Statistical analysis was performed by the StatView SE+ Graphics statistical package for Apple/Macintosh (Abacus Concept, USA, 1991). For all statistical evaluations, the null hypothesis was rejected at a P value lower than 0.05.

3. Results

At baseline, no difference on age, and baseline score of anxiety, depression and climacteric symptoms, was observed among the 3 groups (Table 1).

Twelve women dropped from the study: 6 in the control group, 5 in the group receiving 100 mg of Kava–Kava and 1 in the group receiving 200 mg of Kava–Kava. Reasons for discontinuing were the request of an effective treatment (3 in the control and 1 in the 100 mg group), nausea and gastric pain (1 in the 100 mg and 1 in the 200 mg group), lack of compliance with the medicine (2 in the 100 mg group) or with the follow-up (3 in the control and 1 in the 100 mg group). Accordingly, final analyses were performed on 34 women of the control group, 15 women of the 100-mg and 19 women of the 200-mg Kava–Kava group, respectively.

Table 1
Mean (±S.E.) parameters observed at baseline in three groups of perimenopausal women included in the control group ($n = 34$) in the group receiving Kava–Kava at the dose of 100 mg/day ($n = 15$) and in the group receiving Kava–Kava at the dose of 200 mg/day ($n = 19$)

	Control	Kava 100 mg	Kava 200 mg
Age (Year)	50.2±0.6	51.5±1.1	51.08±0.8
Amenorrhea (months)	9.6±1.8	10.1±1.6	10.4±1.9
Weight (kg)	67.7±1.5	69.7±2.8	68.5±2.4
BMI (kg/m^2)	26.0±0.6	26.9±0.9	26.7±0.8
Anxiety score	48.0±1.6	47.3±2.2	46.6±2.1
Depression score	37.0±1.8	38.2±2.4	38.7±2.0
Climacteric score	25.2±2.3	28.8±2.2	26.4±2.4

A significant relation was observed between baseline score of anxiety and that of depression ($r = 0.65$; $P < 0.0001$), or of climacteric symptoms ($r = 0.50$; $P < 0.0001$). Similarly, a significant relation was observed between the score of depression and that of climacteric symptoms ($r = 0.555$; $P < 0.0001$).

3.1. Anxiety

In the control group, the score of anxiety did not significantly decline in the 3 months of observation ranging from values of 48.06±1.6 at baseline, to 48.0±1.0 at 1 month and to 47.8±1.8 at 3 months (Fig. 1). In comparison to the control group, Kava–Kava (100 mg+200 mg group; $n = 34$) induced a significant decline in anxiety ($P < 0.009$, two-factors ANOVA). Baseline values were similar to those of the control group (46.5±1.5) but significantly declined ($P < 0.0001$) after 1 (43.1±1.3) and 3 (41.9±1.4) months of treatment (Fig. 1). The effect was similar for the 100-mg and the 200-mg dose. In the 100 mg group ($n = 15$) the anxiety score decreased ($P < 0.025$) from baseline values of 47.3±2.2, to 43.2±1.9 after 1 month and to 42.7±2.25 after 3 months of treatment (Fig. 1). In the 200 mg group ($n = 19$) the anxiety score

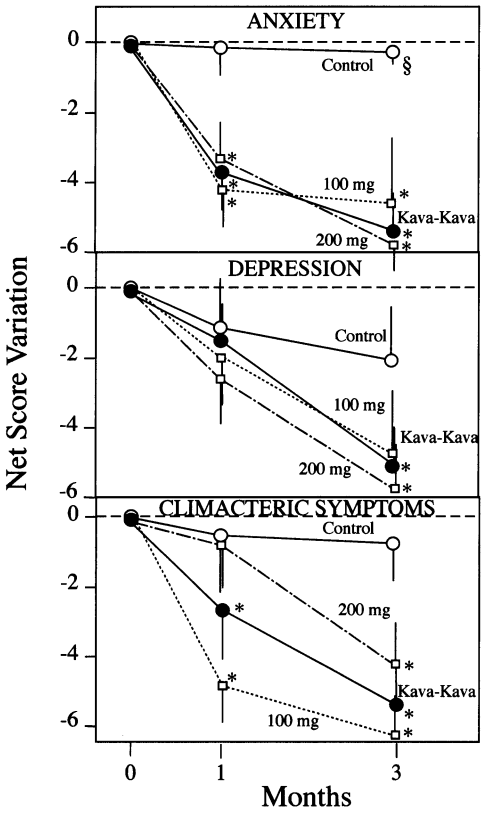

Fig. 1. Mean (±S.E.) net variation of the anxiety (top panel) depression (middle panel) and climacteric (bottom panel) scores observed in perimenopausal women with no therapy (control; empty circles; $n = 34$) and in women receiving Kava–Kava for 3 months. Women receiving Kava–Kava are represented as a whole ($n = 34$; closed circles) or as the two subgroups receiving Kava–Kava in doses of 100 mg/day (open squares dotted line; $n = 15$) or 200 mg/day (open squares continuous line; $n = 19$) *Significant vs. baseline; §significant vs. Kava–Kava.

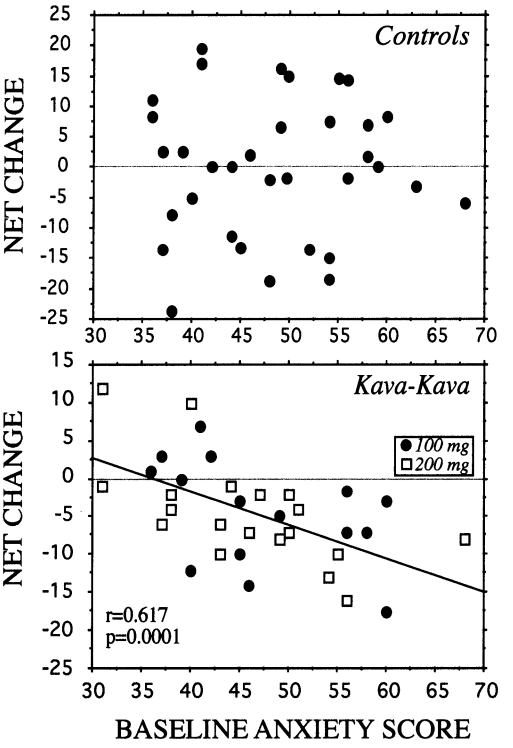

Fig. 2. Linear regression analyses between baseline score of anxiety and its net decline observed in women in perimenopause after 3 months of no treatment (control; $n = 34$) (top panel) or Kava–Kava at the dose of 100 mg/day ($n = 15$; closed circles) or 200 mg/day ($n = 19$; open squares).

decreased ($P < 0.0003$) from baseline values of 46.6±2.1, to 43.1±1.8 after 1 month and to 41.3±1.6 after 3 months of treatment (Fig. 1). Modifications induced by Kava–Kava were inversely related to baseline values ($y = -0.44x \pm 16.08$; $r = 0.617$; $P = 0.0001$) (Fig. 2).

3.2. Depression

In the control group, the score of depression did not significantly decline in the 3 months ranging from values of 37.0±1.8 at baseline, to 36.1±1.7 at 1 month and 34.9±1.7 at 3 months (Fig. 1). During Kava–Kava (100 mg+200 mg group; $n = 34$) the depression score was at baseline 38.5.5±1.5, and after 1 month it was 37.12±1.4. The score was significantly reduced after 3 months of treatment (33.5±1.2; $P < 0.002$) (Fig. 1). In the 100 mg group ($n = 15$) the depression score from baseline values of 38.2±2.4, was 36.5±1.8 after 1 month and 33.7±1.4 after 3 months of treatment (Fig. 1). In the 200 mg group ($n = 19$) the depression score from baseline values of 38.7±2.0, was 36.3±2.1 after 1 month and was significantly lower 33.5±1.9 ($P < 0.01$) after 3 months of treatment (Fig. 1). The decline of the depression score induced by Kava–Kava was not significantly different from that observed in the control group, at ANOVA.

3.3. Climacteric symptoms

In the control group, the Greene's climacteric score did not significantly decline in the 3 months ranging from values of 25.2±2.3 at baseline, to 24.8±2.4 at 1 month and 23.6±2.4 at 3 months (Fig. 1). During Kava–Kava (100 mg+200 mg group; $n=34$) the Greene's score from baseline values of 27.5±1.6 significantly declined ($P<0.006$) to 24.63±1.8 after 1 and to 21.85±1.3 after 3 months of treatment (Fig. 1). In the 100 mg group ($n=15$) the Greene's score from baseline values of 28.8±2.2, significantly declined ($P<0.003$) to 23.6±2.3 after 1 month and 22.1±1.8 after 3 months of treatment (Fig. 1). In the 200 mg group ($n=19$) the Greene's score from baseline values of 26.4±2.4, was 25.5±2.7 after 1 month and was significantly lower (21.6±1.09; $P<0.05$) after 3 months of treatment (Fig. 1). The decline of the Greene's score induced by Kava–Kava was not significantly different from that observed in the control group, at ANOVA.

None of the Greene's subscales significantly declined in the control group. By contrast, a significant decline was observed during Kava–Kava in the subscales of anxiety (6.30±0.61 vs. 5.33±0.49 vs. 4.76±0.47; $P<0.036$) depression (5.36±0.66 vs. 5.0±0.51 vs. 4.09±0.38; $P<0.05$) and somatization (5.18±0.52 vs. 4.48±0.52 vs. 3.96±0.47; $P<0.008$). Scores modifications were similar in the 100 and 200 mg group. Modifications of Greene's subscales that were observed during Kava–Kava were not significantly different from those observed in the control group, at ANOVA.

3.4. Side effects

Side effects as nausea and gastric pain were observed in 1 subject of the control group and 6 subjects receiving Kava–Kava. Intensity of these symptoms was slight. Only in 2 cases, receiving Kava–Kava gastric pain induced the subjects to withdraw from the study. In all women with side effects, the biochemical evaluation did not show any alteration, including those parameters documenting liver toxicity.

4. Discussion

Among phytotherapic substances, Kava–Kava has been proposed as an anxiolitic remedy [13,14]. Indeed, in several studies conducted in humans suffering from non-psychotic anxiety, Kava–Kava administered in doses of 300 mg/day (60 mg/day of kavapirones), proved to be more effective than placebo in reducing anxiety, as evaluated by the Hamilton scale for anxiety or STAI [18]. The same was observed in a group of peri-post-menopausal women suffering from non-psychotic anxiety, in which Kava–Kava at the dose of 300 mg/day for 8 weeks proved to be effective, within 1 week of treatment, in reducing anxiety and climacteric symptoms [19], and in another study in which Kava–Kava increased the anxiolitic effect of hormone replacement [20]. We choose not to perform any selection on baseline values and not to choose any cut-off to define anxiety or depression. This is because the perimenopausal period per se induces an increase in mood disturbances [1–4]. The dose of Kava–Kava used, 100 mg/day (55 mg/day of kavapirones) or 200 mg/day (110 mg/day of kavapirones), was in the range of those used in previous studies [18]. The results show that the two doses of Kava–Kava considered as a whole, induced a rapid (within 1 month) decline in anxiety. Effects on depression, and climacteric symptoms were slower, less pronounced and not significant vs. spontaneous modifications observed in control women. Overall these data would be consistent with reported anxiolitic properties of Kava–Kava [13,14,18]. Interestingly, the response to Kava–Kava seemed to depend on baseline values, higher responses to Kava–Kava being more evident with more pronounced disturbances.

All women received a treatment (calcium) but a Kava–Kava placebo was not administered in the control group. Accordingly, the present study was randomized but not controlled with placebo. The decline observed in the control group may thus be spontaneous or the consequence of counseling and medicalization (calcium). By contrast, the modifications observed in the Kava–Kava groups may include a placebo effect. In spite of this, the clear effects of Kava–Kava on anxiety but not on climacteric symptoms seem to argues against a

non-specific placebo effect. A 15% drop-out was observed in the present study. Drop-outs were equally distributed among controls and Kava–Kava users. Lack of efficacy or compliance with the study were the reasons of drop out in the control group and of 3 drop-outs in the 100 mg Kava–Kava group. In the 200 mg Kava–Kava group no drop-outs were observed for lack of compliance or request of a more effective treatment, this further suggesting a certain therapeutic efficacy of Kava–Kava.

The effect of Kava–Kava is documented in the short-term (3 months) and longer clinical trials are necessary to effectively define whether Kava–Kava can be effectively used to treat anxiety in postmenopausal women for long periods. On the other hand it should be considered that 'natural remedies' are not without risk. Mild and reversible side effects have been reported during Kava–Kava, as gastric pain and nausea, restlessness, mydriasis, allergic skin reaction and dermatomyositis. On the other hand, the European Agency for the Evaluation of Medical Products recently reported 30 cases in which the administration of Kava–Kava induced hepatotoxic effects, as severe to induce liver failure in six patients [21]. For this reason, several national authorities are considering to ban Kava–Kava. The only side-effects documented in our study were nausea and gastric pain that were documented in 17% of subjects, and that only in 2 cases were so intense to induce withdrawal from the study. Biochemical evaluation performed in these subjects did not reveal any sign of liver toxicity. Indeed, liver toxicity is likely to be rare, and it is not surprising that it is not documented in small clinical trials, as the present one. While it is necessary to wait for authorities to investigate on the side effects of Kava–Kava and to decide whether or not to ban this molecule, the clinical efficacy of Kava–Kava on anxiety seems to be confirmed by the present investigation.

Several mechanisms have been suggested to explain the anxiolitic properties of Kava–Kava. It has been proposed that kavapirones may exert an action on dopaminergic transmission at the limbic system [22], an effect on serotoninergic neurons [22], an inhibition of central MAO-B [23], a modulating action on GABA-B receptors [24,25] and a modulation of neurons excitability directly exerted at the cellular membrane [26]. Kava–Kava does not activate benzodiazepine receptor [24], and acts differently from benzodiazepines. Indeed, in contrast to benzodiazepines, Kava–Kava does not exert depressive effects on activity of neurons involved in attention or in the response to visual or verbal tasks [27,28]. Furthermore, suspension of Kava–Kava administration is not associated with withdrawal symptoms [29].

In a previous investigation, the capability of Kava–Kava to reduce anxiety resulted similar to that of benzodiazepines [30]. Noteworthy, herein the reduction in anxiety observed with Kava–Kava was of the same extent of that previously observed in postmenopausal women with the use of hormone replacement therapy [4]. Accordingly, present data, in line with previous studies, indicate Kava–Kava as capable to reduce anxiety in the perimenopausal period. More data on its safety are necessary to know whether Kava–Kava can be continued to be used in the clinical practice.

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