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Enhanced cognitive performance and cheerful mood by standardized extracts of *Piper methysticum* (Kava-kava)

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The acute effects of the herbal anxiolytic Kava-kava (*Piper methysticum* G. Forster) on emotional reactivity and cognitive performance were investigated in a double-blind randomized placebo-controlled trial involving healthy volunteers. Subjects' reports of mood change were assessed with the state-trait-cheerfulness-inventory, which measures the three concepts of cheerfulness, seriousness and bad mood as both traits and states. Cognitive performance was examined with the Sperling partial report and the Sternberg item recognition task, which were used as an index for visual attention and short-term memory processing. The intake of a single dose of Kava extract (300 mg; p.o.) led to an increase in state cheerfulness, while the phytopharmacon did not influence state seriousness and bad mood. The mood-elevating effects of Kava were most prominent in trait cheerful subjects, indicating that trait cheerfulness moderated the drug-induced increase in cheerful mood. Furthermore, Kava improved the accuracy and the speed of performing the partial report and the item recognition task, indicative of a beneficial effect of the phytopharmacon on visual attention and short-term memory retrieval, respectively. Thus, unlike conventional benzodiazepine-type anxiolytics, which tend to impair cognitive performance and to increase the occurrence of negative affective states, Kava is a potent anxiolytic agent, which, additionally, can facilitate cognitive functioning and can increase positive affectivity related to exhilaration. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — kavapyrones; attention; short-term memory; exhilaration; mood; phytopharmacology

INTRODUCTION

Kava is a psychoactive beverage prepared from the root of the intoxicating pepper plant (*Piper methysticum* G. Forster) that plays an important role in the traditional medicine and socio-cultural life of the inhabitants of the South Pacific islands (Singh, 1992). The extract contains at least six pharmacologically active compounds, referred to as kavapyrones (Dharmaratne *et al.*, 2002), which mediate the local anaesthetic, sedating, anticonvulsive, muscle-relaxant and sleep stimulating effects of the plant (Bilia *et al.*, 2002; Cairney *et al.*, 2002). In the search for alternatives to benzodiazepines (BZDs), Kava extract is currently being considered for its potential use in the treatment of fear and anxiety-related disorders (Rex *et al.*, 2002; Singh and Singh, 2002). In clinical trials, Kava was found to be superior to placebo and effectively relieved anxiety and tension (Pittler and Ernst, 2000). The phytopharmacon also proved effective in the treatment of stress (Wheatley, 2001) and mood disorders (Volz and Kieser, 1997). In some of the studies, Kava extract at therapeutically effective doses even compared favourably to BZDs and tricyclic antidepressants but without the side effects commonly seen with these drugs (Malsch and Kieser, 2001; Volz and Kieser, 1997). However, very high doses and/or long-term use of the phytopharmacon can produce liver damage, gastrointestinal disturbances, allergic skin reactions, movement disorders, attention deficits and physiological tolerance (Bilia *et al.*, 2002; Cairney *et al.*, 2003).

Systematic experiments investigating the effects of Kava on mood parameters other than anxiety are lacking. This is surprising with regard to the

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anthropological evidence suggesting that Kava can induce pleasant and even cheerful states. Thus, people using Kava typically report feelings of elevated mood and lowered levels of tension; they feel able to communicate openly and generally feel more relaxed (Hänsel and Woelk, 1994). A close relationship between emotion and mnemonic processes has been pointed out (McGaugh, 1990, 2000). Brain structures thought to be involved in emotion and in the modulation of memory overlap extensively (McIntyre *et al.*, 2003; Taylor *et al.*, 1998), while anxiolytic drugs that decrease emotional arousal, like BZDs, can also impair cognitive performance (Buffett-Jerrott and Stewart, 2002). Thus, with regard to the close relationship between the anxiety-reducing and cognition-impairing effects of a drug, it is feasible that Kava could have adverse effects on cognitive performance similar to those observed after BZD intake. On the other hand, the doses of Kava that proved effective in treating anxiety are largely devoid of the depressant side effects on brain functioning typical of BZD anxiolytics (Malsch and Kieser, 2001), suggesting that the phytopharmacon may exert anxiolytic effects without interfering negatively with cognition. However, up to now, only few studies have addressed this issue, with inconsistent results (Cairney *et al.*, 2002; Stevinson *et al.*, 2002).

The objectives of the present study were twofold. With regard to the proposed mood elevating effects of Kava, the subjects' reports of mood change were assessed after a single administration of the compound with the state part (STCI-S) of the state-trait-cheerfulness-inventory (STCI; Ruch *et al.*, 1997), which measures cheerfulness, seriousness and bad mood as transient or actual states. Furthermore, the trait part (STCI-T) was administered to participants as well to assess cheerfulness, seriousness and bad mood as temperaments. The state-trait theory of cheerfulness (Ruch and Köhler, 1998) assumes that trait-cheerfulness can moderate the impact of a (pharmacological) stimulus on the induction of exhilaration. This has already been shown for different pharmacological 'exhilarants' such as alcohol and nitrous oxide ('laughing gas'; Ruch, 1997). Thus, it was hypothesized that trait cheerfulness could also moderate the amount of mood change induced by Kava intake. The effects of Kava on cognitive performance were investigated with a modified version of the Sperling partial report task (Sperling, 1960) and the Sternberg item recognition paradigm (Sternberg, 1966). The tasks provide measures of visual attention and short-term memory retrieval, respectively, and are sensitive for the assessment of both the enhancing as well as disrupting effects of psychoactive drugs on cognitive performance (Houlihan *et al.*, 2001). Furthermore, questionnaire scores and behavioural data were subjected to correlation analysis to examine the relationship between Kava-induced changes in mood and cognitive performance.

MATERIALS AND METHODS

Participants

Twenty Kava-naive healthy volunteers (11 female, 9 male) recruited on the campus of the University of Hertfordshire participated in the study. Their mean age was 24.3 (range: 18 to 53) years. The local Ethics Committee approved the study, and all subjects gave written informed consent. All subjects had normal or corrected-to-normal vision. Exclusion criteria were current illness, use of any type of medication, pregnancy and known adverse/allergic reactions to products containing Kava extract. The participants were informed about the purpose of the study and were asked to refrain from smoking and to avoid eating and drinking caffeinated or alcoholic drinks 3 h beforehand.

Drug schedule

Standardized extract of Kava roots (*Piper methysticum* G. Forster) containing 30% kavapyrones was purchased from Solgar Ltd (UK). The effects of Kava on mood and cognition were investigated in a single-dose, double-blind and placebo-controlled trial. Subjects were assigned randomly to one of the two treatment groups: the Kava group ($n = 10$) received two 150 mg capsules of the Kava extract (equivalent to 90 mg kavapyrones) while placebo controls ($n = 10$) received two identical capsules but without the herb. The cognition tests were performed in succession starting 60 min after drug or placebo intake. Kavapyrones readily cross the blood-brain barrier, attain a maximum concentration in the brain within approximately 45 min and are slowly eliminated from brain tissue (Keledjian *et al.*, 1988).

State-trait-cheerfulness-inventory (STCI)

The STCI (Ruch *et al.*, 1996, 1997) was used to measure the three constructs of cheerfulness (CH), seriousness (SE) and bad mood (BM) both as traits (STCI-T) and as states (STCI-S). The STCI-T consists of 60 items and the STCI-S is a 30-item scale. Both

parts of the questionnaire have a four-point answer format (strongly disagree to strongly agree). The traits are disposition for the activation of the homologous states. According to Ruch and Köhler (1999), state CH represents positive affectivity related to exhilaration, state SE denotes the readiness to perceive, act, or communicate seriously and state BM refers to sadness/melancholy and ill humour. The STCI-T< 60> was administered to the subjects at the beginning of the experiment to gauge their habitual dispositions; the STCI-S< 30> was administered twice, that is, before (t_1) and 50 min after Kava and placebo intake (t_2) to assess the effects of the pharmacological intervention on the subjects' actual emotional state. In order to determine whether trait-cheerfulness moderates Kava-induced mood changes the subjects were divided into two groups by median split of their trait CH scores. Individuals with scores lower than 68.5 (i.e. STCI-T CH between 60 and 68) were assigned to the low trait CH group (CH^-) and those with scores higher than 68.5 (i.e. STCI-T CH between 69 and 79) to the high trait CH group (CH^+), respectively. This resulted in an equal distribution of the number of high and low trait CH subjects across the two experimental groups ($n = 5$/category). Changes in mood were computed by subtracting the scores for t_1 (pre-drug) from the corresponding t_2 (post-drug) values for each of the three state scales.

Cognition tests

The cognitive performance of the subjects was assessed with modified versions of the Sperling partial report (Sperling, 1960) and the Sternberg item recognition task (Sternberg, 1966). Both paradigms were generated on a standard personal computer equipped to a VGA monitor and keyboard. The device was set up in a sound-attenuating experimental chamber and testing was performed under controlled experimental conditions.

For the Sperling partial report (SPR) test, which measures aspects of visual attention, sets of 12 letters from the English alphabet were assembled in three rows of four letters in a grid. For each trial, one set of letters was displayed on the monitor at a fixed position for a 0.3 s interval. After this time, one of the three rows of letters became masked, the screen was cleared, and the subjects were required to fill in the missing letters from the cued row using the keyboard. The letters used to set up the grid as well as the position of the cued row varied at random from trial to trial. Each subject had five practice trials followed by 30 test trials for which the number of correct and incorrect responses as well as the number of omissions for each position were computed.

Retrieval from short-term memory was assessed with the Sternberg item recognition (SIR) task, which was performed 5 min after completion of the SPR test. A memory set of 5–7 letters was displayed on the monitor for 250 ms. Participants were asked to remember these letters. One second after the onset of the memory set, a single probe letter was displayed for 250 ms and the subject's task was to decide as rapidly as possible whether the probe matched one of the items in the memory set by pressing one of two keys on the keyboard. Each subject had five practice trials followed by 30 test trials. Within these constraints, the order of trials was random with respect to memory-set size and probe type (positive or negative). For the 30 test trials, the percentage of correct responses and the average reaction time (defined as the time from the onset of the probe to the occurrence of the response) were calculated.

Statistics

The data were analysed with single-classification or multivariate ANOVA, where applicable. Correlation analysis was performed with Pearson's correlation coefficient. The level of statistical significance adopted was $\alpha = 0.05$.

RESULTS

STCI-T and STCI-S

The present sample did not differ from the norm scores provided by Ruch and Köhler (1999) with regard to trait cheerfulness (sample: $M = 67.90$, $SD = 5.96$; norm: $M = 64.51$, $SD = 9.70$) although the variance was slightly reduced. In addition, the baseline scores in state cheerfulness (sample: $M = 29.80$, $SD = 2.63$; norm: $M = 28.80$, $SD = 6.36$) were comparable. The two groups (Kava, placebo) did not significantly differ from each other in trait CH, SE and BM scores (p-values 0.290; see Table 1A); furthermore, no significant between-group differences were evident for the corresponding state variables before Kava and placebo intake (p-values 0.183; see Table 1B). A 2×2 ANOVA with condition (Kava vs placebo) and trait CH (low vs high) and the difference scores ($t_2 - t_1$) in state CH, SE and BM was computed. A significant main effect of the condition was obtained for state CH ($F_{1,16} = 55.68$, $p < 0.0001$), suggesting that consumption of Kava led to a higher increase in CH compared with the

Table 1. Mean (±SEM) scores for the different mood parameters assessed with the trait (A) and the state version (B) of the STCI for subjects administered a single dose of Kava or placebo

	Placebo	Kava 300 mg
A. STCI-T <60>		
CH	67.70 ± 2.38	47.00 ± 2.20
SE	45.80 ± 0.83	59.00 ± 1.35
BM	29.80 ± 1.14	14.00 ± 1.97
B. STCI-S <30>		
CH (t_1)	30.00 ± 0.68	29.60 ± 0.99
CH (t_2)	29.30 ± 0.64	32.40 ± 1.00
CH ($t_2 - t_1$)	−0.70 ± 0.30	2.80 ± 0.47[a]
SE (t_1)	25.00 ± 1.06	21.90 ± 1.97
SE (t_2)	25.10 ± 1.12	20.10 ± 1.95
SE ($t_2 - t_1$)	0.10 ± 0.44	− 1.80 ± 0.95
BM (t_1)	11.90 ± 1.00	10.50 ± 0.27
BM (t_2)	12.00 ± 1.09	10.00 ± 0.00
BM ($t_2 - t_1$)	0.10 ± 0.38	− 0.50 ± 0.27

CH, cheerfulness; SE, seriousness; BM, bad mood; (t_1) before and (t_2) after drug intake; ($t_2 - t_1$) = difference scores calculated by subtracting pre- from corresponding post-drug values; [a]$p < 0.001$ compared with placebo.

control group which remained almost unchanged in their mood (Table 1B). Moreover, there was a significant drug–temperament interaction ($F_{1,16} = 4.59$, $p = 0.027$). Planned comparisons revealed that Kava led to a higher increase in mood compared with controls for both high trait CH ($F_{1,16} = 48.00$, $p = 0.0001$) and low trait CH subjects ($F_{1,16} = 15.36$, $p = 0.0012$; see Figure 1). However, for the Kava condition the increase in state CH was higher for the trait CH individuals than for the individuals scoring low in trait CH ($F_{1,16} = 9.09$, $p = 0.0082$); no such difference was obtained for the placebo condition ($F_{1,16} = 0.91$, ns). Thus, while Kava in general increased state CH it did do so more strongly in individuals with a disposition towards cheerful states, that is, in trait cheerful subjects (see Figure 2). As depicted in Table 1B, subjects in the Kava group also showed a reduction in state SE and BM. However, these changes were not significant (SE: $F_{1,16} = 3.05$, $p = 0.100$; BM: $F_{1,16} = 1.71$, $p = 0.209$) and the respective drug–temperament interaction failed to reach statistical significance (SE: $F_{1,16} = 0.21$, $p = 0.652$; BM: $F_{1,16} = 0.76$, $p = 0.396$).

Cognition tests

The treatment with Kava enhanced the performance of the subjects on the Sperling partial report test, as reflected by a significant increase in the number of correct responses ($F_{1,18} = 9.79$, $p = 0.006$) and by a significant decrease in the number of incorrect responses ($F_{1,18} = 8.53$, $p = 0.009$), respectively. No between-group differences were evident with regard to the number of omissions ($F_{1,18} = 0.25$, $p = 0.625$; Table 2A). In the Sternberg item recognition task, Kava decreased the average reaction time ($F_{1,18} = 27.02$, $p < 0.001$) and increased the percentage of

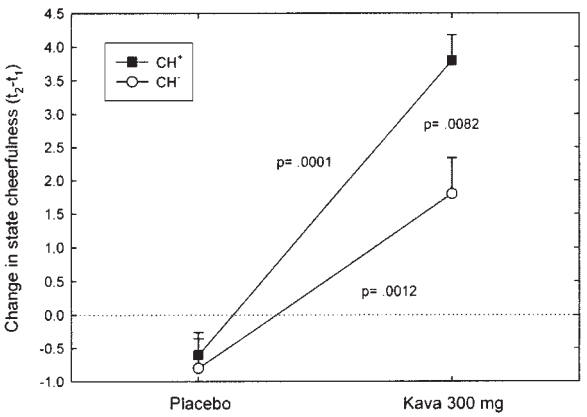

Figure 1. Interactive effect of the treatment (300 mg Kava or placebo) and trait cheerfulness on the change in state cheerfulness. Subjects were divided by median split of trait cheerfulness scores into a low (CH^-) and a high trait cheerful group (CH^+). Changes in cheerful mood were computed by subtracting the scores for t_1 (pre-drug) from the corresponding t_2 (post-drug) values; see Results for explanation of p-values

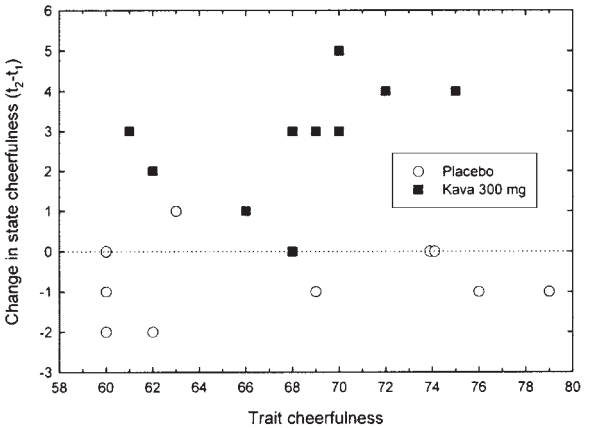

Figure 2. Bivariate scatter plot of the scores in trait cheerfulness and the change in state cheerfulness. Changes in cheerful mood were computed by subtracting the scores for t_1 (pre-drug) from the corresponding t_2 (post-drug) values. High trait cheerful individuals show a higher increase in cheerful mood after Kava consumption compared with low trait cheerful subjects. No such a difference is evident for subjects in the placebo group

Table 2. Mean (±SEM) performance scores on the partial report (A) and the item recognition task (B) for subjects administered a single dose of Kava or placebo

	Placebo	Kava 300 mg
A. Partial report		
Correct	36.60 ± 2.68	47.00 ± 1.97[a]
Incorrect	68.20 ± 2.91	59.00 ± 1.21[a]
Omissions	15.20 ± 1.65	14.00 ± 1.76
B. Item recognition		
%Correct	94.00 ± 1.22	98.22 ± 0.55[a]
Reaction time (ms)	2092.50 ± 141.89	1265.29 ± 72.05[b]

[a]$p < 0.01$; [b]$p < 0.001$ compared with placebo.

correct responses to the probe stimulus ($F_{1,18} = 9.94$, $p = 0.006$; Table 2B), indicative of superior recognition performance.

Correlation analysis

Inter-correlations among and correlations between mood and performance scores were computed for the two treatment groups; only significant correlations are reported. For the subjects in the Kava group, the increase in cheerfulness was accompanied by a decrease in seriousness ($r = -0.62$, $p = 0.029$) and by an increase in the number of incorrect responses on the SPR test ($r = 0.69$, $p = 0.028$). A negative correlation was obtained between the number of correct responses and omissions on this task ($r = -0.80$, $p = 0.006$). In the control condition, higher levels of bad mood were associated with fewer incorrect responses on the SPR task ($r = -0.64$, $p = 0.047$); furthermore, a negative correlation was found between the number of correct and incorrect responses on this task ($r = -0.83$, $p = 0.003$).

DISCUSSION

The present findings show that Kava can enhance positive affectivity related to exhilaration and has beneficial effects on cognitive performance. The acute intake of Kava led to an increase in state cheerfulness while the phytopharmacon did not influence seriousness and bad mood. Furthermore, the hypothesized role of trait cheerfulness as a moderator of the Kava-induced increase in cheerful mood could be confirmed. The state-trait theory of cheerfulness (Ruch and Köhler, 1998) assumes that individuals high and low in trait cheerfulness differ from each other with respect to the threshold for the induction of amusement, smiling, laughter and state-cheerfulness. In line with this assumption, subjects scoring higher in trait cheerfulness yielded a stronger Kava-induced mood increase than those with lower scores. Compared with prior studies the increase in state cheerfulness was lower than when participants were confronted with a clowning experimenter, alcohol, or inhaling laughing gas (Ruch, 1997). However, the present results add further evidence that a cheerful temperament can facilitate the induction of cheerful mood states. Furthermore, for the subjects in the Kava group the increase in state cheerfulness was accompanied by a decrease in state seriousness confirming the proposed reciprocal relationship between the two mood parameters (Ruch, 1993). It remains to be determined whether Kava can influence indicators of exhilaration other than cheerful mood, e.g. smiling, laughter or the perceived funniness of humour, and whether these effects are also moderated by the level of trait cheerfulness. However, the present results provide evidence that the phytopharmacon can act as an 'exhilarant' in normal subjects in addition to its known anxiolytic and mood-elevating action in patients suffering from affective dysfunction (Malsch and Kieser, 2001).

Kava proved to be active in the Sperling partial report (SPR) and in the Sternberg item recognition (SIR) task, which were used to assess drug effects on visual attention and short-term memory retrieval, respectively. In the SPR test, the treatment with Kava significantly enhanced the accuracy in performance reflected by an increase in the number of correct responses to the cued items in the stimulus array. In order to report letters from briefly exposed letter arrays, information from a rapidly decaying trace (iconic memory) has to be transferred to storage that is more durable. This transfer rate appeared to be the product of iconic legibility, which depends on time and retinal location, and attention allocation, which shifts after the cue (Gegenfurtner and Sperling, 1993). Thus, with regard to the specific demands of the task one might speculate that Kava improved the ability to attend selectively to the relevant cues and/or increased the processing speed of the items. Furthermore, it may be that Kava decreased the rate at which items normally decay from the iconic memory and/or increased the speed at which items are transferred to a more permanent memory trace therefore allowing more data to be assimilated. Kava also improved the performance on the Sternberg item recognition task. The facilitatory effect was most prominent for the reaction time measure, which was reduced by about 40% compared with placebo control values. In addition, Kava enhanced the response accuracy, indicating

that the decrease in reaction time cannot be explained simply in terms of a speed/accuracy trade-off but could reflect beneficial effects of the phytopharmacon on short-term (working) memory processes, which in turn lead to a better retrieval performance. Thus, it would be important to know whether Kava enhanced the rate of STM scanning, which is assumed to be directly related to the rate of item recognition/retrieval (Sternberg, 1966). However, in the present experiment a reliable estimate of the STM scanning rate could not be computed because of the small number of memory set presentations employed.

The beneficial action of Kava on cognitive performance concurs with an accumulating body of evidence showing that the phytopharmacon can have positive effects on attention, learning and memory parameters. Thus, in comparison with placebo and/or classical anxiolytic drugs Kava extract improved the performance on a visual search paradigm (Heinze *et al.*, 1994), facilitated word recognition (Münte *et al.*, 1993) and enhanced the speed of access of information from long-term memory (Russel *et al.*, 1987). In the present study, the effective dosage of the Kava extract was 300 mg (containing 90 mg of kavapyrones), which is comparatively lower than the doses that were used to demonstrate cognition enhancement in the cited experiments. Furthermore, the facilitatory effects of Kava were observed after acute drug intake, while the previous studies employed a subchronic drug-administration regimen. The specific kavapyrones, which mediate the beneficial effects of the whole extract on cognition, still have to be determined. Kavain and closely related dihydrokavain seem to be not the active principles since both kavapyrones failed to influence significantly learning and memory parameters (Prescott *et al.*, 1993).

Furthermore, another aspect should be pointed out. Since Kava was administered 'pre-trial', the observed facilitation of performance on both the SPR as well as the SIR task could be a consequence of various 'secondary' effects of the drug treatment, for example, on visual perception, motor functions, motivation and emotion, which could influence cognitive as well as non-cognitive processes. Several studies have documented that emotional arousal produced by pleasant/fearful situations or by anxiolytic/anxiogenic drugs can modulate associative processes (McGaugh, 1990, 2000). Thus, it was held possible that the cognition-enhancing effects of Kava might be related to its mood-enhancing properties. However, in the present study, the relationship between mood and cognitive performance appeared to be marginal and only evident with regard to the performance scores obtained from the SPR task. Here, the Kava-induced increase in cheerfulness was accompanied by an increase in the number of false responses. The reason for this inverse relationship between mood change and task accuracy is not clear. However, since increased cheerfulness is characterized by a lowered threshold for the induction of laughter and exhilaration/amusement one might speculate that being in a cheerful state can interfere with cognitive processing by increasing the reactivity to task-irrelevant stimuli and/or by decreasing the attentiveness for task-relevant cues.

The neurobiological mechanisms that might account for the effects of Kava on mood and cognition require further investigation. Kavapyrones share several pharmacological properties with the BZDs, but no significant binding to GABA and BZD-receptors was detected (Davies *et al.*, 1992; but see Jussofie *et al.*, 1994). Furthermore, BZDs, like alcohol and barbiturates, are known antagonists at NMDA receptive sites while Kava is not (Walden *et al.*, 1997). These pharmacodynamic differences may explain why kavapyrones, unlike conventional anxiolytics, do not produce sedation or adverse drug reactions such as anterograde amnesia (Buffett-Jerrott and Stewart, 2002), addiction, tolerance and withdrawal symptoms (Volz and Kieser, 1997). Electrophysiological studies in humans revealed that the cognition-enhancing effects of Kava were associated with an increase in event related potentials in frontocentral regions including the prefrontal cortex, which is associated with attention and short-term memory processing (Münte *et al.*, 1993). Animal studies revealed that kavapyrones are most active in limbic structures, including the amygdala, caudate nucleus and hippocampus (Boonen *et al.*, 1998; Holm *et al.*, 1991), which play a role in emotionality and cognitive processes, respectively. Within the hippocampus, synthetic kavain modulated excitatory field potentials (Langosch *et al.*, 1998); however, the compound did not affect long-term potentiation, which is a widely accepted model for learning and synaptic plasticity (Bliss and Collingridge, 1993). Furthermore, it is feasible that the mood-enhancing action of Kava may be caused by a direct activation of the mesolimbic dopamine (DA) reward system. Thus, a recent *in vivo* microdialysis study demonstrated that the systemic administration of Kava extract could increase DA concentrations in the nucleus accumbens, while the opposite effect was obtained for the kavapyrone yangonin, which strongly inhibited accumbal DA activity (Baum *et al.*, 1998). Moreover, it appears that Kava has properties similar to those found for serotonergic agents. For example, synthetic as well as herbal 5-HT_3 antagonists like

Zingiber officinale can also exert anxiolytic effects without interfering with the performance on learning tasks (Buhot *et al.*, 2000; Hasenöhrl *et al.*, 1998). This is interesting in the light of recent evidence showing that kavapyrones can directly interact with central 5-HT receptive sites (Dinh *et al.*, 2001; Grunze *et al.*, 2001), which are considered to play a crucial role in the neural control of emotion and associative processes (Meneses, 1999).

Taken together, the present study provides evidence that a single dose of Kava can enhance cognitive performance in normal volunteers and can increase positive affect related to exhilaration depending on the subjects' disposition for cheerful mood. Further dose-response studies with Kava extract and specific kavapyrones are on the way to characterize more fully these putative beneficial effects of the phytopharmacon.

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