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Minireview

# Kava-kava and anxiety: Growing knowledge about the efficacy and safety

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**Abstract**

Kava-kava (*Piper methysticum* G. Forster) has been used in social and ceremonial life in the Pacific islands from ancient times for the soporific and narcotic effects. Today several extracts standardized in the biologically active constituents kavalactones are marketed both as herbal medicinal products for anxiety disorders and as dietary supplements to improve stress disorders, nervous tension and restlessness. Unlike other substances used for these purposes, kava-kava has been shown to have minimal negative effects, and possibly positive effects, on reaction time and cognitive processing. Furthermore, it decreases anxiety without the loss of mental acuity. Although kava-kava has been found to be very effective, well tolerated, and non-addictive at therapeutic dosages, potential side effects can occur when very high doses are taken for extended periods. In addition, in the last two years unexpected high liver toxicity has been reported in two patients. Until now no studies support the liver toxicity of kavalactones and it is unknown which compound could have provoked the liver disease. On the other hand, it should be possible that unknown or unexpected constituents are the responsible or contributed to the liver toxicity. © 2002 Elsevier Science Inc. All rights reserved.

*Keywords:* Kava-kava; *Piper methysticum*; Kavalactones; Anxiety; Stress and restlessness; Efficacy; Safety

## Introduction

Kava-kava is the name given by Pacific islanders to both a shrub belonging to the pepper family and the psychoactive beverage made from the rhizome [1].

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It has been used in the Pacific at traditional social gatherings as a relaxant and in cultural and religious ceremonies to achieve a higher level of consciousness. In addition, the beverage counteracts fatigue, reduces anxiety and generate a state of well being [1].

Kava-kava was first mentioned in scientific records in 1886, and began gaining popularity as soothing the nerves and inducing relaxation and sleep [2]. In 1914 it was listed in the British Pharmacopoeia and in 1950 it appeared in the US Dispensary in the treatment of both gonorrhea (''Gonosan'') and nervous disorders (''Neurocardin'') [3]. In the last decade preparations based on kava-kava extracts have begun to appear on the European market and in the USA, usually standardized in kavalactones to provide a daily dosage in the range of 60–120 mg [4].

Thus, in 1990 in Germany kava-kava was approved for conditions such as anxiety, and nervous disorders such as stress and restlessness. From that date other European countries (e.g. United Kingdom, Switzerland and Austria) have approved kava-kava preparations containing 30–70% of kavalactones with the same indications on the basis of detailed pharmacological data and favorable clinical studies.

In this minireview the growing knowledge about the efficacy and safety of kava-kava in the treatment of anxiety, stress and restlessness is reported. Thus, clinical studies carried out in the last decade have shown that the herb kava-kava is a safe non-addictive, anti-anxiety medicine and is as effective as prescription anxiety agents. In addition, while synthetic anti-anxiety drugs generally promote lethargy and mental impairment, kava-kava has been shown to improve concentration, memory and reaction time for people suffering from anxiety [1,5–9]. However, a case of recurring necrotizing hepatitis has been reported in 1998 in Germany [10] and recently, at the end of 2000 in Switzerland, a patient was subjected to a liver transplant due to an acute hepatitis associated with kava-kava consumption at 210–280 mg kavalactones [11]. In both cases other causes of hepatitis were excluded, hence after the latter case the market of kava-kava in Switzerland was discontinued.

After these two cases, particularly the latter, we can predict that kava-kava will not continue to be marketed freely but will be subjected to rigid controls.

## Historical overview and source

The first white men who saw and made illustrations of the kava-kava plant were two Swedish botanists during the first expedition of Captain James Cook in the South Pacific area (Endeaviour) in 1768–1771. Johann Georg Forster, a botanist on Captain James Cook's second voyage (1772–1775) who named the plant *Piper methysticum* meaning intoxicating pepper, gave the first detailed description of the plant. Thus, ''methysticum'' being the Latin transcription of the Greek ''Methustikos'' and derived from ''Methu'' which means ''intoxicating drink'' [2].

Kava-kava may have first been domesticated less than 3,000 years ago in Vanuatu (nowadays called the New Hebrides), a group of islands in eastern Melanesia. The use of kava-kava seems then to have diffused both westwards to New Guinea and part of Micronesia and eastward into Fiji and then Polynesia and is locally known by a number of common names, including kawa-kawa, ava ava, awa awa, yati, yagona, and yangona. The herbal drug

consists of the rhizome from which roots are mostly removed. Due to its wide cultivation there are several different varieties of this plant based mainly upon different morphological characteristics such as the intensity of the green leaf color, the color of the stems and the quality of the rhizome. The various varieties are classified with several vernacular names by the indigenous populations, i.e. Apu, Makea, Liwa, Mo'i, Papa [2].

The kava-kava beverage has been compared to the use of wine in western countries and traditionally prepared by fresh rhizome chewed with saliva, usually by virgin girls or boys, and spit into a bowl. This wad of well-masticated rhizome is successively mixed with cold water or the water of the coconut and strained through some natural fiber to give a hot intoxicating juice [1,12]. Besides a social function, kava-kava was, and still is in many regions of the Pacific, an important medicine being used in the treatment of both acute and chronic gonorrhea, vaginitis, leucorrhoea, menstrual problems, venereal disease, nocturnal incontinence and other ailments of the genitourinary tract having an antiseptic effect on the urine [13]. It also has a local anaesthetic effect, relieves pain and is first stimulating on the nerve centers, then depressing, ending with paralysis of the respiratory center. In addition, by putting kava-kava leaves in the vagina, abortions can be provoked [14]. Kava-kava also had great religious significance and was seen to connect the user with the ancestors and the gods [2,13,14].

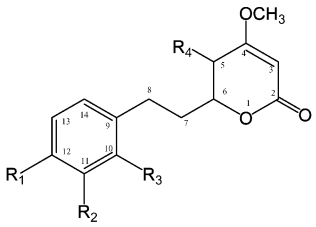
## Active principles

The active constituents of rhizome consist of a group of structurally related lipophilic lactone derivatives with an arylethylene-alpha-pyrone skeleton. They are typically 4-methoxy-2-pyrones with phenyl or styryl sustituents at the 6-position and represent 3–20% of the dried rhizome depending on age of the plant and specific cultivar [15]. The commercial extracts (mainly of them acetone extracts containing 30–70 % active principles) consist of a mixture of more than 18 different $\alpha$-pyrones, collectively known as kavapyrones, or better, kavalactones.

The major constituents are (+)-kavain (1.8%), (+)-methysticin (1.2%), desmethoxyyangonin (1%), yangonin (1%), (+)-dihydrokavain (0.6%), (+)-dihydromethysticin (0.5%) tetrahydroyangonin and their structures are reported in Fig. 1 [16–18]. Minor constituents including other kavalactones and three chalcones are also present (Fig. 1) [16]. Essential oil is also present [17].

## Biochemical mechanisms

The *in vitro* studies carried out on both herbal drug extracts and isolated kavalactones showed a direct activity on central nervous system receptors and on neurotransmitters, which have a fundamental feature in the activity of kavalactones. These behaviors are synthesized in the interaction of kavalactones with GABA-benzodiazepine receptors and in the inhibition of noradrenaline uptake. The modulation of the voltage-dependent $Na^{+}$ and $Ca^{++}$ channels is also reported.




| **Kavalactones** | $R_1$ | $R_2$ | $R_3$ | $R_4$ | C5-C6 | C7-C8 |
|---|---|---|---|---|---|---|
| 11-Hydroxy-12-methoxydihydrokavain | $OCH_3$ | OH | | | | |
| 7,8-Dihydro-5-hydroxykavain | | | | β-OH | | |
| 11,12-Dimethoxydihydrokavain | $OCH_3$ | $OCH_3$ | | | | |
| Methysticin | $OCH_2O$ | | | | | = |
| Dihydromethysticin | $OCH_2O$ | | | | | |
| Kavain | | | | | | = |
| 7,8-Dihydrokavain | | | | | | |
| 5,6-Dehydromethysticin | $OCH_2O$ | | | | = | = |
| 5,6-Dehydrokavain (demethoxyyangonin) | | | | | = | = |
| Yangonin | $OCH_3$ | | | | = | = |
| 5,6,7,8-Tetrahydroyangonin | $OCH_3$ | | | | | |
| 5,6-Dihydroyangonin | $OCH_3$ | | | | | = |
| 7,8-Dihydroyangonin | $OCH_3$ | | | | = | |
| 10-Methoxyyangonin | $OCH_3$ | | $OCH_3$ | | = | = |
| 11-Methoxyyangonin | $OCH_3$ | $OCH_3$ | | | = | = |
| 11-Hydroxyyangonin | $OCH_3$ | OH | | | = | = |
| Hydroxykavain | | | | OH | | = |
| 11-Methoxy-12-hydroxydehydrokavain | OH | $OCH_3$ | | | = | = |

| **Chalcones** | R |
|---|---|
| Flavokavain A | $OCH_3$ |
| Flavokavain B | H |
| Flavokavain C | OH |

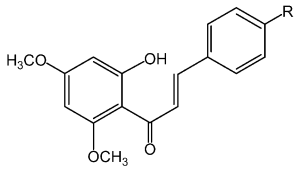



Fig. 1. Kavalactones and chalcones present in kava rhizome.

Studies with kava-kava extract and pure constituents using a GABA-A receptor agonist (muscimol) showed enhancement of the binding in a concentration-dependent manner [19]. Regional differences in the modulation of [3H]muscimol binding to GABAA receptor

complexes by kavalactones were demonstrated using membrane fractions obtained from hippocampus (HIP), amygdala (AMY) and medulla oblongata (MED), frontal cortex (FC) and cerebellum (CER). The extract enhanced the binding of [3H]muscimol in a concentration-dependent manner with maximal potentiation of 358% over control in HIP followed by AMY and MED (main target brain centers). Minimal stimulation was observed in CER followed by FC. In contrast, apart from CER, the potency of kavalactones was similar in the brain areas investigated with EC50 values ranging between 200 and 300 μM kavalactones. Scatchard analysis revealed that the observed effects of kavalactones were due to an increase in the number of binding sites (Bmax), rather than to a change in affinity. Synergetic effect on [3H] muscimol binding were evidenced between kavalactones and pentobarbital or HPO [19]. Isolated kavalactones showed a weak binding with GABA-A/benzodiazepine receptors but no binding with GABA-B [20,21]. In addition, *in ex vivo* studies, no effects were observed on [3H]diazepam binding to brain membranes prepared from mice in which selected kava-kava constituents were injected intraperitoneally, whereas similarly administered diazepam (5 mg/kg) inhibited [3H]diazepam binding by greater than 95% [20]. Yangonin, (+)-kavain, (+)-dihydrokavain, (+)-methysticin, and (+)-dihydromethysticin at assay concentrations between 100 μM and 10 nM enhanced the specific binding of [3H]bicuculline methochloride ([3H]BMC). (+)-Kavain, (+)-methysticin and (+)-dihydromethysticin showed maximal enhancements of 18% to 28% at a concentration of 0.1 μM, whereas a 100-fold concentration of (+)-dihydrokavain revealed a similar modulatory activity of 22%. In the presence of 1 μM yangonin an increase of about 21% of the specific [3H]BMC binding was observed. Desmethoxyyangonin did not alter the binding behavior of the GABAA-receptor. A structure comparison of desmethoxyyangonin and yangonin indicated that the aromatic methoxy group was of particular importance for the modulatory activity. In contrast, the substitution pattern of the aromatic ring did not influence the modulatory activity of the enolides in a decisive manner. A structure comparison of desmethoxyyangonin and (+)-kavain revealed that an angular lactone ring was an important structure requirement. Both the enolides and the dienolides did not inhibit the specific binding of [3H]flunitrazepan. Thus, the influence on the GABA-A receptor was not based upon an interaction of these kavalactones with the benzodiazepine receptor [22]. Three kavapyrones, the natural compounds (+)-methysticine and (+)-kavain, and the synthetic racemate (±)-kavain, were tested concerning their action on *in vitro* uptake of monoamines in synaptosomes prepared from the cerebral cortex and hippocampus of rats. Both synthetic and isolated kavain potently inhibited the uptake of noradrenaline but none of the kavalactones efficiently blocked the uptake of [3H]-serotonin. Uptake of [3H]-noradrenaline was inhibited in the following order of potency: (±)-kavain = (+)-kavain (up to 70–80% of control)>(+)-methysticine. The results indicate a pyrone-specific non-stereo-selective inhibition of the [3H]-noradrenaline uptake which might be responsible for or, at least, contribute to the psychotropic properties of kavalactones [23].

The *in vitro* effects of kava-kava extract and pure synthetic kavalactones on human platelet MAO-B, in comparison to amitriptyline, imipramine and brofaromine was also investigated. Kava-kava extract was found to be a reversible inhibitor of MAO-B in intact platelets (IC50 24 μM) and disrupted platelet homogenates (IC50 1.2 μM). Structural differences of

kavalactones resulted in a different potency of MAO-B inhibition. The order of potency was desmethoxyyangonin > (±)-methysticin>yangonin > (±)-dihydromethysticin > (±)-dihydrokavain > (±)-kavain. The inhibition of MAO-B by kava pyrone-enriched extracts might be an important mechanism for their psychotropic activity [24].

In addition, both (+)-kavain, and the synthetic racemate (±)-kavain gave rapid and specific inhibition of veratridine-activated voltage-dependent $Na^+$-channels. [25,26]. Veratridine (5 μmol/l) enhanced basal [Na+]i 6.6-fold from 11.3 to 74.1 mmol/l Na+. Incubation of synaptosomes for 100 sec with (±)-kavain was sufficient to reduce dose dependently the stimulated increase of [Na+]i with an IC50 value of 86.0 μmol/l, and almost complete inhibition of Na(+)-channels was attained with 400 μmol/l) reduced veratridine-elevated [Na+]i to 30.4% and 7.9% of control whereas the centrally acting muscle relaxant mephenesin (400 μmol/l) was without any effect. Postapplication of 400 μmol/l (±)-kavain or 10 μmol/l TTX immediately diminished veratridine-elevated [Na+]i to nearly basal levels with a half life time of 69.7 and 41.8 sec, respectively. The presented data indicate a fast and specific inhibition of voltage-dependent Na(+)-channels by (±)-kavain [26].

Effects of (±)-kavain on voltage-activated inward currents were analysed in cultured dorsal root ganglion cells derived from neonatal rats. Voltage-activated Ca2+ and Na+ currents were elicited in the whole-cell configuration of the patch clamp technique. Extracellularly applied (±)-kavain dissolved in hydrous salt solutions reduced voltage-activated Ca2+ and Na+ channel currents within 3–5 min. As the solubility of (±)-kavain in hydrous solutions is low, dimethyl sulfoxide (DMSO) was added to the saline as a solvent for the drug in most experiments. When (±)-kavain was dissolved in DMSO, the drug induced a fast and pronounced reduction of both Ca2+ and Na+ currents, which partly recovered within 2–5 min even in the presence of the drug. The study indicates that (±)-kavain reduces currents through voltage-activated Na+ and Ca2+ channels, thus the anticonvulsive and analgesic effects of (±)-kavain could be partly explained by Na+ and Ca2+ antagonistic action [27].

A further investigation on the action of synthetic kavapyrones, (+)-methysticin and (±)-kavain, on voltage-operated Na+-channels was studied in whole-cell patch-clamped CA1 hippocampal neurons. In doses of 1–400 μM, both compounds exerted a rapid and reversible inhibition of the peak amplitude of Na+-currents. Voltage-dependence of Na+-channel inhibition can be explained by interaction of (+)-methysticin and (±)-kavain with resting closed and inactivated states of Na+-channel [28]. These data evidenced that the observed anticonvulsive and anti-ischaemic effects of kava-kava ingredients may be in part mediated by the blockade of voltage-operated Na+-channels. Considerable voltage-dependence of the observed inhibition of Na+-currents by the studied substances is explained presumably by their interaction with resting closed and inactivated states of Na+-channel [28].

The influences of tetrodotoxin (TTX) and (±)-kavain on anoxic rat brain vesicles were also investigated with respect to lactate synthesis, vesicular ATP content and cytosolic free Na+ and Ca2+ ([Na+]i, [Ca2+]i). The Na+ channel blockers TTX and (±)-kavain, if applied before anoxia, preserved vesicular ATP content, diminished anoxia-induced increases in [Na+]i and [Ca2+]i and prevented both the veratridine-induced increases of [Na+]i and [Ca2+]i and the inhibition of lactate production. The data indicate a considerable Na+ influx via voltage-dependent Na+ channels during anoxia, which speeds up the decline in ATP and provokes an

increase in [Ca2+]i. A massive Na+ and Ca2+ overload induced by veratridine failed to influence lactate synthesis directly, but initiated its inhibition. Thus, anoxia induces a considerable Na+ influx via voltage-dependent Na+ channels in brain vesicles, accompanied by an acceleration of ATP decline and an increase in [Ca2+]i by action of the Na+/Ca2+ exchanger. Prolonged activation of Na+ channels might amplify Ca2+ overload, possibly initiating inhibition of anaerobic glycolysis. (±)-Kavain may be of interest as a lead compound for a new class of unchanged Na+ channel blockers directed against ischaemic insults [29].

The action of (±)-kavain on the veratridine, monensin and KCl-depolarization evoked increase in free cytosolic Ca2+ concentration ([Ca2+]i), and its influence on the release of endogenous glutamate from rat cerebrocortical synaptosomes were investigated. [Ca2+]i was fluorimetrically determined employing Fura as the Ca2+ sensitive fluorophore, and glutamate was detected by a continuous enzyme-linked fluorimetric assay. The incubation of synaptosomes in the presence of (±)-kavain up to a concentration of 500 mumol/l affected neither basal [Ca2+]i nor spontaneous release of glutamate, but dose-dependently reduced both veratridine-elevated [Ca2+]i (IC50 = 63.2 mumol/l) and glutamate-release (IC500 = 116.4 mumol/l). The inhibition of these parameters, attained with 500 mumol/l (±)-kavain, could be overcome by inducing an artificial Na+ influx, using monensin as a Na+ ionophore, An application of (±)-kavain after veratridine caused a decrease in veratridine-elevated [Ca2+]i, which was similar to the action of tetrodotoxin (TTX) with regard to time course, half-life of [Ca2+]i decline and the final steady state level of [Ca2+]i. Concomitantly, veratridine-induced glutamate-release was blocked. The results indicate that specific inhibition of voltage-dependent Na+ channels is a primary target of (±)-kavain, thus preventing a [Na+]i provoked increase in [Ca2+]i and glutamate-release. However, pathways related to the elevation of [Ca2+]i by [Na+]i itself, and the processes involved in normalization of elevated [Ca2+]i and glutamate-release downstream to enhanced [Ca2+]i, seems to be unaffected by (±)-kavain. Using KCl-depolarized synaptosomes, 400 mumol/l (±)-kavain reduced, in analogy to Aga-GI toxin, KCl-evoked [Ca2+]i and diminished the part of glutamate-exocytosis which is related to external Ca2+ to about 75% of control. At a concentration of 150 mumol/l, which is above the IC50 value necessary to block voltage-dependent Na+ channels, (±)-kavain affected neither basal nor the KCl-induced increase in [Ca2+]i. These results might suggest that (±)-kavain at concentrations sufficient to block Na+ channels completely. Moderately inhibits the non-inactivating Ca2+ channels located on mammalian presynaptic nerve endings [30].

The question of how the excitability of neurons is affected was investigated by determining the interaction of (±)-kavain with epitopes (site 1, site 2) of voltage-dependent Na+ channels and the action of (±)-kavain on 4-aminopyridine-stimulated synaptosomes as model of repetitive firing neurons. [3H]Saxitoxin and [3H]batrachotoxin were used for radioligand-binding assays performed with synaptosomal membranes. Glutamate released from 4-amino-pyridine-stimulated cerebrocortical synaptosomes and the cytosolic concentrations of Na+ and Ca2+ ([Na+]i, [Ca2+]i) were detected fluorometrically by using an enzyme-linked assay, sodium-binding benzofuranisophthalate (SBFI) and Fura-2, respectively. (±)-Kavain failed to compete with [3H]saxitoxin up to 400 mol/l but dose-dependently suppressed binding of [3H]batrachotoxin with an IC50 value of 88 mol/l (Ki = 72 mol/l) although displacement of

[3H]batrachotoxin was restricted to 33% of control at 400 mol/l (±)-kavain. In stimulated synaptosomes, 5 mmol/l 4-aminopyridine provoked an increase in [Na+]i and [Ca2+]i by 9 mmol/l Na+ and 235 nmol/l Ca2+. Comparable to the reduction in [3H]batrachotoxin binding, 400 mol/l (±)-kavain suppressed the increase in [Na+]i and [Ca2+]i to 38 and 29% of control, respectively. Consistent with the increase in [Na+]i and [Ca2+]i, 5 mmol/l 4-aminopyridine provoked glutamate release (rate: 38 pmol/s*mg protein) which gas dose-dependently diminished to 60% of control by 400 mol/l (±)-kavain. KCl depolarization (40 mmol/l) provoked an increase in [Ca2+]i and glutamate release almost identical to the responses elicited by 4-aminopyridine but 400 mol/l (±)-kavain suppressed only the rate of glutamate release by 9% of control. The data suggest an interaction of (±)-kavain with voltage-dependent Na+ and Ca2+ channels, thereby suppressing the 4-aminopyridine-induced increase in [Na+]i, [Ca2+]i and the release of endogenous glutamate [31].

Nifedipine and caffeine were used to evidence the $Ca^{2+}$-channel blocking properties of synthetic kavain [32]. In this study, the effect of the synthetic kava pyrone (±)-kavain was investigated on evoked contractile activity of isolated guinea-pig ileum. (±)-Kavain (1 μM-1 mM) dose-dependently reduced contractions of ileum evoked by carbachol (10 μM), by BAY K 8644 (0.3 μM), or by substance P (0.05 μM). (±)-Kavain also inhibited the contractile responses induced by raising the extracellular K+ concentration from 4 to 20 mM and by blocking the K+ channel by barium chloride (1 mM) or 4-aminopyridine (0.3 mM). After pre-incubation with 1 μM nifedipine, carbachol (1 μM) evoked 18.2 +/− 14.3% of contraction at control (i.e. prior pre-incubation with nifedipine). This remaining response was completely abolished by high concentrations of (±)-kavain (400 μM). After treatment of the longitudinal ileum strips with pertussis toxin (PTX), carbachol (1 μM) evoked 27.0 +/− 6.2% of the control response in untreated ileum. These contractions were also blocked by (±)-kavain (400 μM). However, (±)-kavain had no effect on the caffeine-induced (20 mM) contractions of ileum strips, which were permeabilized with digitonin or beta-escin. Moreover, it failed to affect Ca(2+)-evoked contractions of skinned muscles. These results suggest that the kava pyrone (±)-kavain may act in a non-specific musculotropic way on the smooth muscle membrane [32].

The influence of (±)-kavain on population spikes and long-term potentiation (LTP) in guinea pig hippocampal slices in the CA1-region of guinea pig hippocampal slices was also demonstrated. (±)-Kavain reduced the amplitudes of extracellular field potential changes evoked by electrical stimulation in a concentration dependent manner. These effects were reversible. In experiments with LTP no changes were found in the presence of (±)-kavain. In conclusion, our findings suggest (±)-kavain to be an effective drug in modulating excitatory signals in the hippocampus of guinea pigs. Additionally, no alterations on synaptic plasticity in hippocampal neurons for this kavalactone can be presumed. In conclusion, (±)-kavain seems to be an effective drug in modulating excitatory signals in guinea pig hippocampal neurones, but no alterations on synaptic plasticity can be presumed [33].

The effects of kavain and dihydromethysticin on field potential changes (fp) induced by omission of the extracellular Mg2+, recorded from the area CA1 and CA3 of the hippocampal slice preparation of guinea pigs were tested. These fp are generated by an activation of NMDA receptors and voltage dependent calcium channels. Kavain and dihydromethysticin

reduced reversibly the frequency of occurrence of fp in a concentration range from 5 to 40 μmol/l and 10 to 40 μmol/l, respectively.

Reduction of the fp frequency after addition of subthreshold concentrations of 5 μmol/l kavain and 10 μmol/l dihydromethysticin indicated additive actions of both drugs. Since the serotonin-1A agonist ipsapirone also exerts anxiolytic effects, subthreshold concentrations of kavain or dihydromethysticin were combined with a subthreshold concentration of ipsapirone in another set of experiments. Combining kavain and ipsapirone or dihydromethysticin and ipsapirone caused a reduction of the rate of fp to 0.76 and 0.81 of the baseline value, respectively. The findings suggest that (i) single constituents of *Piper methysticum* may have additive actions, (ii) that the two components kavain and dihydromethysticin may enhance the effects of the anxiolytic serotonin-1A agonist ipsapirone and (iii) that activation of NMDA receptors and/or voltage dependent calcium channels may be involved in the elementary mechanism of action of some kavalactones [34].

## Possible therapeutic applications

### *Preclinical models*

*In vivo* studies conducted on rats and mice evidenced sedative, tranquilizing and muscle relaxing effects of both the extracts and isolated constituents.

Kava-kava extracts reduced both amphetamine- and apomorphine-induced hypermotility in mice and rats [35,36] without effect on conditioned avoidance responses in a "shelf-jump apparatus" [35]. Another investigation with extracts of kava-kava did not alter forced motor activity of mice [37]. Both synthetic kavain and kava-kava extract reduced muscle tone in cats [38] and a central nervous system depression was observed in rodents after their administration [39]. Recently the effect of kava-kava extract and several kavalactones on neurotransmitter levels in the nucleus accumbens of rats was investigated using *in vivo* microdialysis. A small dose of kava-kava extract (20 mg/kg body weight i.p.) caused changes in rat behaviour and concentrations of dopamine in the nucleus accumbens. Higher doses (120 mg/kg i.p.) increased the levels of dopamine. With respect to the individual compounds, D,L-kavain induced in low doses a decrease in dopamine levels and in higher amounts either an increase or no change in dopamine concentrations. Yangonin resulted in a decrease of dopamine levels to below the detection limit and desmethoxyyangonin in an increase of dopamine levels. Dihydrokavain, methysticin and dihydromethysticin did not produce any significant changes of dopamine levels. D,L-kavain caused a decrease in 5-HT concentrations. Some of the other kavapyrones affected 5-HT levels as well. The results suggest that the relaxing and slightly euphoric actions may be caused by the activation of the mesolimbic dopaminergic neurones. Changes of the activity of 5-HT neurones could explain the sleep-inducing action [40].

Isolated kavain, methysticin, dihydromethysticin and yangonin showed strong centrally mediated muscle relaxing activity in rabbits and yangonin was the most potent kavalactone [41]. The *in vivo* effect of a single oral dose of 100 mg (+)-dihydromethysticin/kg body weight on striatal and cortical tissue concentrations of dopamine, serotonin, 3,4-dihydroxyphenyl-

acetic acid and 5-hydroxyindoleacetic acid, as well as the dopamine and serotonin turnover, was tested in rats. Additionally, other rats were fed with a (±)-kavain containing food over a period of 78 days in order to calculate the influence of a chronic treatment with kavapyrones on the neurotransmitters. The results of this *in vivo* study clearly demonstrate that neither (+)-dihydromethysticin in a high single dose, nor (±)-kavain chronically administered, altered the dopaminergic or serotonergic tissue levels in rats significantly [42]. Isolated constituents showed also a marked antagonistic effect to the convulsive and lethal action of strychnine in mice, with an anticonvulsant activity similar to or even better than (in the case of dihydromethysticin) mephenesin [43]. Similar results have been reported in other experiments indicating that methysticin and dihydromethysticin are particularly potent in effecting anticonvulsant activity [44,45] while dihydromethysticin and dihydrokavain strongly inhibited electroshock-induced seizures in rats and mice [46]. Finally, investigations on both kava-kava extract and isolated kavalactones in two models of focal cerebral ischemia in mice and rats showed a decrease of the cerebral infarct area [47,48]. This is the first microdialysis study to address the effects of (±)-kavain on veratridine-induced glutamate release in freely moving rats. (±)-Kavain (100 mg/kg, p.o.) significantly reduced veratridine-induced glutamate release compared with that of vehicle-treated controls. Maximum extracellular glutamate levels were obtained 20–40 min after veratridine stimulation (500 μM, added to the perfusate). In the control group the increase was 301% and in the (±)-kavain group the increase was significantly reduced to 219% (the basal value was 100%). These results demonstrate for the first time that (±)-kavain reduced veratridine-induced glutamate increase in vivo. Perfusion with veratridine led to a maximally stimulated release of extracellular glutamate (to about 300%) in the second intrastriatal dialysate after 20–40 min. In the (±)-kavain-treated group, the peak concentration of extracellular glutamate was obtained during the same collection period (20–40 min after onset of veratridine-stimulation) but was less pronounced, about 220% of basal extracellular glutamate levels [49]. The inhibition of veratridine-stimulated glutamate release, demonstrated by acute administration of (±)-kavain in a high dosage (100 mg/kg) in vivo, seems to be an important extension of previous *in vitro* data [30,31]. A very recent study investigated the potential protective effects of (±)-kavain in the experimental MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease (PD). Male C57BL/6 mice were treated with (±)-kavain (50, 100, or 200 mg/kg i.p.) or vehicle 60 min before and 60 min after a single administration of MPTP (30 mg/kg s.c.) or saline, respectively. Mice were sacrificed after 7 days and the neostriatum was analyzed for dopamine and its metabolites using HPLC with electrochemical detection. Furthermore, nigral sections were processed for tyrosine hydroxylase (TH) immunocytochemistry. To determine the effects of (±)-kavain (200 mg/kg) on MPTP metabolism, HPLC analysis of striatal MPP(+) (1-methyl-4-phenylpyridinium) levels was performed. MPTP treatment alone led to a significant depletion of striatal dopamine levels to 12.61% of saline controls. The lower dosages of (±)-kavain (50 and 100 mg/kg) showed only a nonsignificant attenuation of MPTP-induced dopamine depletion, but a high dosage of (±)-kavain (200 mg/kg) significantly antagonized the dopamine depletion to 58.93% of saline control values. Remarkably, the MPTP-induced decrease of TH-immunoreactivity as well as the loss of nigral neurons was completely prevented by (±)-kavain (200 mg/kg). Striatal MPP(+) levels were not altered by (±)-kavain treatment. In conclusion, we found that MPTP

metabolism was not influenced by (±)-kavain and postulate the antiglutamatergic effects of (±)-kavain for its protective effects against MPTP toxicity. (±)-Kavain may be a novel candidate for further preclinical studies in animal models of PD and other disorders with glutamatergic overactivity [50].

Studies on healthy volunteers were performed to investigate sedative effects and sleeping pattern after oral intake of kava-kava extract. The effects on sleeping-pattern after doses of either 150 or 300 mg in comparison with placebo were also tested by the registration of EEG during sleep. Results showed that the phases of deep sleep (III and IV) and period of REM-sleep were clearly prolonged and indicated and an improved quality of sleep during treatment with kava-kava extract. Acute sedative effects were also evaluated by the quantitative EEG analysis using a single oral dose of 600 mg by the increase in both the theta and the slow alpha bands [51,52]. In addition other studies in comparison with placebo and/or classical anxiolityc drugs, showed a good profile on vigilance and cognitive performance of kava-kava extracts [5,7–9].

*Clinical evidence*

The results of five controlled, double-blind clinical trials carried out with a total of more than 400 subjects over periods ranging from 28 to 84 days, using daily doses of kavalactones between 30 and 210 mg, evidenced the efficacy as an anxiolytic drug. All the investigations used the HAMA (Hamilton Anxiety scale), CGI (clinical Global Impressions scale) and other rating scales.

The first study was conducted in 1990 and synthetic kavain was evaluated in comparison with placebo and oxazepam. Patients were affected by anxiety associated with neurotic disturbances. Kavain demonstrated equivalent activity to oxazepam and was superior to placebo [53]. In a second study in 1991, patients with symptoms of anxiety, tension or agitation of non-psychotic origin were treated with standardized kava-kava extract or placebo. The outcome was assessed using the total score on the HAMA rating scale, and other adjunctive rating scales, the Erlanger scale for anxiety, Clinical Global Impressions and the Fischer Somatic Symptoms. After one week of therapy, the patients treated with 210 mg of kavalactones extract per day showed a significant reduction in the HAMA total score as compared with placebo [54]. In 1993 another investigation with the same kavalactone dosages was conducted. Kava-kava extract was evaluated in comparison either 15 mg diazepam or 9 mg bromazepam per day. In all the groups a relevant therapeutic improvement of HAMA (Hamilton Anxiety scale) and CGI (Clinical Global Impressions scale) was revealed after six weeks of treatment. No significant differences between treatment groups were observed [55]. In 1996 a further investigation with the same kavalactone dosage was carried out and HAMA, CGI and Adjectives Checklist assessed therapeutic efficacy. The results demonstrated again efficacy of kava-kava extract in patients with anxiety disorders [56]. The last clinical study was carried out in 1997, with patients suffering from anxiety of non-psychotic origin, and the same kavalactone intake was used and significantly better results where obtained with patients treated with kava-kava rather than those treated with placebo with respect to HAMA-sub-scores somatic and psychic anxiety, CGI, Self-report Symptom Inventory and Adjective Mood Scale [57]. Furthermore,

two clinical studies were carried out in women with climacteric symptoms, i.e. psychosomatic and psychovegetative complaints related to the climacteric period using different rating scales. The results showed that kava-kava extract using standard dosages has a high efficacy and is also suitable for treatment of symptoms related to the climacteric syndrome [58,59].

*Side effects and interactions of kava-kava*

Generally good tolerability with a low incidence of adverse events is reported for preparations based on kava-kava standardized extracts. Observations on 4,049 patients consuming 105 mg of kavalactones daily for seven weeks noted 61 cases (1.5%) of undesired effects. These were mostly mild and reversible gastrointestinal disturbances or allergic skin reactions. A four-week study of 3,029 patients taking 240 mg of kavalactones daily produced a slightly greater incidence (2.3%) of similar side effects. This would be expected because of the larger dosages used [60]. In another drug-monitoring study (120 mg of kavalactones daily) including 1,673 patients, a side effect frequency of 1.73% was reported. In more than 85% of the patients, the therapeutic effect was evaluated as good/very good, and in 93% the tolerability was rated good/very good [61]. Two other recent open studies involving patients with anxiety and using 210 mg kavalactones and 100–300 mg kavalactones daily, respectively are also reported [62,63]. In the first study the efficacy was considered excellent or good by 93.7% of physicians and 86.9% of patients. Tolerability of kava-kava was considered good or very good in 95.8% of patients [62]. In the other trial the treatment resulted very good or good as well [63]. More recently a systematic review and a meta-analysis was also carried out. Superiority of kava-kava extract over placebo as a symptomatic treatment of anxiety was suggested. The meta-analysis suggested a significant reduction of the total score on the Hamilton Rating Scale for Anxiety in favor of kava-kava extract (weighted mean difference, 9.69; 95% confidence interval, 3.54–15.83) [64]. In addition, kava-kava does not produce physiological tolerance or learned tolerance in mice at minimally effective daily doses but higher doses can cause partial physiological tolerance [65]. Despite the very high tolerability in the reported investigations, four cases of patients who developed clinical signs suggesting of dopamine antagonism after taking kava-kava were reported in Germany [66]. In addition, two cases of serious hepatitis associated with the kava-kava consumption at standard doses have been reported. The first one was a woman 39 years old with recurrent acute necrotizing hepatitis in 1998 in Germany. Viral, autoimmune and metabolic causes of the hepatitis were excluded. After the discontinuation of the kava-kava preparation the liver tests quickly became normal [10]. The second case happened at the end of 2000 in Switzerland. 50-year-old man received a liver transplant because he developed stage IV encephalopathy. The relation between ingestion of kava-kava and fulminant hepatic failure was supported by the chronology, histological findings, and exclusion of other causes of hepatitis (negative results for blood tests for hepatitis A, B, C, and E, HIV, cytomegalovirus, and Epstein-Barr virus) [11]. Finally, in an experimental model was demonstrated that high doses of ethanol potentate the sedative and hypnotic activity of kava-kava and markedly increased the toxicity [67] while studies involving aboriginal populations evidenced that the chronic abuse of kava-kava leads to malnutrition and weight loss, liver toxicity, and depression of plasma protein levels, platelets and lymphocytes [68].

## Conclusions

In animal studies kavalactones have been shown to have anxiolytic, sedative, analgesic, anticonvulsant and local anesthetic effects.

Pharmacological properties of kava-kava are comparable to those of benzodiazepines, but a very weak binding of kavalactones to GABA-A and benzodiazepines receptors was detected. Thus, N-methyl-D-aspartate (NMDA) receptors and/or voltage-dependent calcium channels may be also involved in the elementary mechanism of action. Their effect on the brain is different from that of benzodiazepines or tricyclic antidepressants. The anticonvulsive properties are similar to those of local anesthetics, especially procaine. Analgesia produced by kava-kava occurs via non-opiate pathways.

Synergistic actions between kavalactones have also been reported and could partly be explained by the synergism of uptake of these compounds into brain tissue.

Studies on healthy volunteers confirmed the efficacy of standardized extracts, thus the deep sleep phase was lengthened and the duration of REM sleep was not influenced. These effects were viewed as being favorable, in comparison with orthodox sedatives such as benzodiazepines and barbiturates which depress both REM and deep sleep.

Indications supported by clinical trials are anxiety and nervous conditions such as tension, restlessness and menopausal symptoms. Kava-kava may be used by extrapolations from pharmacological studies also to improve cognitive performance, in the treatment of insomnia, to assist in withdrawal from benzodiazepine drugs, pain relief as an analgesic and/or local anaesthetic.

Kava-kava improved cognitive performance and stabilized emotional disposition without causing sedation and anxiolytic activity was produced without sedation or hypnotic effects.

For anxiolytic activity the recommended doses are 50–70 mg kavalactones two to four times per day. For hypnotic activity, 150–210 mg kavalactones in a single dose one hour before bed is suggested.

Adverse effects from ingestion of kava-kava are not generally expected when used within the recommended dosage, although skin reactions and dopamine antagonism have, however been reported. Activation of oppioid and dopamine receptors was excluded, however, kava-kava should be used cautiously in elderly patients, especially those with Parkinson's disease.

Two cases of serious necrotizing hepatitis have also been recently reported and caused the discontinuation of the kava-kava marketing in Switzerland. In addition, a synergistic effect is possible for substances acting on the central nervous system, such as alcohol, barbiturates and psychopharmacological agents. A pigmentation of the skin known as kava dermopathy is a well-known side effect of excessive and chronic use of kava-kava.

All these data pointed out the good profile of efficacy and tolerability of kava-kava, but also the necessity of medical monitoring of products based on this extract. Thus, it is not yet stated if kavalactones are responsible of the liver toxicity or may be other unexpected or unknown compounds have been contributed to the toxicity. Likewise, herbal drugs, their preparations and herbal medicinal products should no longer be considered safe enough for marketing them also as dietary supplements, healthy foods or "over the count" preparations. The majority of them have demonstrated side-effects and contra-indications with similar

profiles to those of other synthetic drugs and their use should be prescribed under the control of physicians.

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