LEADING ARTICLE

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Therapeutic Potential of Kava in the Treatment of Anxiety Disorders

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Abstract

Anxiety disorders are among the most common psychiatric disorders that affect all age groups of the general population. Currently, the preferred treatment is with pharmacological drugs that have antidepressant or anti-anxiety properties. However, these agents have numerous and often serious adverse effects, including sedation, impaired cognition, ataxia, aggression, sexual dysfunction, tolerance and dependence. Withdrawal reactions on termination after long-term administration are also a major limiting factor in the use of these agents.

Herbal remedies, including kava (*Piper methysticum*), have been shown to be effective as alternative treatments, at least in mild to moderate cases of anxiety. Kava is a social and ceremonial herb from the South Pacific. It is available in the west as an over-the-counter preparation. Its biological effects, due to a mixture of compounds called kavalactones, are reported to include sedative, anxiolytic, antistress, analgesic, local anaesthetic, anticonvulsant and neuroprotective properties.

The pharmacological properties of kava are postulated to include blockade of voltage-gated sodium ion channels, enhanced ligand binding to γ-aminobutyric acid (GABA) type A receptors, diminished excitatory neurotransmitter release due to calcium ion channel blockade, reduced neuronal reuptake of noradrenaline (norepinephrine), reversible inhibition of monoamine oxidase B and suppression of the synthesis of the eicosanoid thromboxane A_2, which antagonises $GABA_A$ receptor function.

Clinical studies have shown that kava and kavalactones are effective in the treatment of anxiety at subclinical and clinical levels, anxiety associated with menopause and anxiety due to various medical conditions.

Until recently, the adverse effects attributed to kava use were considered mild or negligible, except for the occurrence of a skin lesion. This disorder, called kava dermopathy, occurs only with prolonged use of large amounts of kava and is reversible on reduced intake or cessation. Rare cases of interactions have occurred with pharmaceutical drugs that share one or more mechanisms of action with the kavalactones. In the past few years, about 35 cases of severe liver toxicity associated with kava intake have been reported in Europe and the US. However, a direct causal relationship with kava use has been difficult to establish in the majority of the cases, and there is insufficient evidence to implicate kava as the

responsible agent. Nevertheless, until further research clarifies any causality, kava should be used with caution.

1. Overview of Anxiety

Anxiety disorders are probably the most common of the psychiatric disorders, with a lifetime prevalence of about 15 to 20% in the general population.[1] Anxiety is a very diffuse mental condition characterised by an unpleasant feeling of fear and apprehension with no identifiable source.

Anxiety can be experienced in a number of ways, including behaviourally, affectively, physically and cognitively. Behaviourally, anxiety manifests as fight or flight responses, help seeking and excessive dependence on others. Emotionally, anxiety can produce a dysphoric state of arousal, such as during a panic attack, that is exceedingly unpleasant. Physically, a person may experience cardiac (e.g. chest tightness and palpitations), neurological (e.g. paresthesias and tremulousness), gastrointestinal (e.g. diarrhoea and nausea) or respiratory (e.g. hyperventilation and dyspnoea) symptoms. Cognitively, a person may engage in catastrophic thinking, hypervigilance, apprehension, rumination and worry.[2]

Brief periods of anxiety are common in daily life and do not warrant treatment. Anxiety is diagnosed as a psychiatric disorder when its intensity or duration reaches pathological proportions and its effects are debilitating to the individual. There are six principal categories of anxiety according to the DSM-IV:[2] specific and social phobias, panic disorder, generalised anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder and acute stress disorder. Others include anxiety disorder due to a general medical condition and substance-induced anxiety disorder.[2] In addition, anxiety is often seen in people with other psychiatric disorders such as schizophrenia, affective disorders, borderline states and personality disturbances.

2. Current Treatments

A broad range of nonpharmacological treatments is available for specific anxiety disorders. For example, systematic desensitisation is effective in greatly reducing or eliminating phobias.[3] The use of this technique requires the individual with the phobia to imagine a series of increasingly anxiety-provoking scenes while in a state of relaxation until the individual is able to face the phobic situation *in vivo*. A more general therapeutic approach may be used with someone who has generalised anxiety disorder, because it is difficult to find the specific cause for the anxiety. In such cases, intensive relaxation training is prescribed, because the relaxation response is incompatible with anxiety. The person is taught to relax when he or she begins to feel tense, thus pre-empting the anxiety from spiralling out of control.[4] Other behavioural techniques for treating anxiety disorders include modelling, flooding and social skills training.

The treatment of choice for anxiety and anxiety disorders, especially by family physicians, is pharmacological. Drug treatment has been proven effective and is a lot less labour intensive than psychosocial therapies. Many anxiety disorders respond well to antidepressants [especially the selective serotonin reuptake inhibitors (SSRIs), venlafaxine, tricyclic antidepressants and monoamine oxidase (MAO) inhibitors] and anti-anxiety agents (especially benzodiazepines).[5,6] From the early 1960s, the benzodiazepines replaced barbiturates as the most frequently prescribed anti-anxiety agents. Although their popularity peaked in the late 1970s and early 1980s, benzodiazepines are still frequently prescribed to treat anxiety and insomnia as well as for their muscle-relaxant and anticonvulsant properties. For example, in an 8-year period in the 1990s, prescriptions for the benzodiazepine alprazolam alone accounted for 19.7% of 8.4 million physician office visits for the treatment of anxiety.[7] Other benzodiazepines typically prescribed for anxiety disorders include chlorazepate, chlordiazepoxide, clonazepam, diazepam, halazepam, lorazepam, oxazepam and prazepam.

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2.1 Limitations

The common adverse effects of benzodiazepines include sedation, impaired cognition and ataxia. Their behavioural adverse effects include irritability, depression, hyperactivity, aggression and disinhibition.[8,9] Although the data are somewhat mixed, there is evidence to suggest that people taking high-potency benzodiazepines, such as diazepam, chlordiazepoxide and alprazolam, tend to be more hostile in group settings compared with in their nonmedicated state.[10] This effect has been less noticeable with oxazepam.[5] Other limitations include their potential for abuse (because of their rapid absorption and onset of action), tolerance, dependence, rebound after discontinuation and the likelihood of increasing the intoxicating potency of alcohol.

Nonbenzodiazepine anxiolytics, such as buspirone, have an efficacy similar to benzodiazepines but have fewer serious adverse effects and less risk of a fatal consequence due to overdose.[5] Other agents with anxiolytic properties, such as the SSRIs and venlafaxine, may cause some forms of sexual dysfunction, which is the cause of much morbidity and often leads to patient noncompliance.[5]

A major limiting factor has been withdrawal reactions following termination of the drug after prolonged use. For short-acting benzodiazepines (e.g. lorazepam), withdrawal symptoms may begin within just 24 hours, but they may appear as long as 3 to 7 days after stopping a longer-acting drug (e.g. diazepam). It may take several days or months for these symptoms to disappear, depending on the drug, dosage and duration of use. The most frequently reported symptoms following the withdrawal of benzodiazepines include anxiety, insomnia, neuromuscular irritability and depression. Clearly, these withdrawal symptoms overlap substantially with the very conditions that were originally being treated by the drug, and it is difficult to differentiate the re-emergence of pre-existing conditions no longer being treated and the drug withdrawal emergent symptoms. In addition, many of the following symptoms may be related to benzodiazepine withdrawal: headaches, dizziness, loss of appetite, metallic taste, palpitations, tremor, nausea and vomiting, abdominal cramps, blurred vision, diarrhoea, hypotension, hyperthermia, psychosis, seizures and tinnitus.[5,11-13]

3. Alternative Therapies

Long before the advent of modern pharmaceutical agents, several strategies had been employed for the alleviation of mental disorders. With the renewed interest in complementary and alternative therapies, herbs, vitamins, minerals, trace elements, nutraceuticals and homeopathic and other products have found favour with individuals who have become dissatisfied with western therapeutic modalities. Among the natural products that are considered to be efficacious in the management of anxiety and stress are the herbs chamomile, kava (*Piper methysticum*; also known as kava-kava), valerian and St. John's wort, vitamin C, vitamin B complex-25, adrenal extract, magnesium malate, and homeopathic combination formulas containing *Aconitum napellus* (aconite), *Ignatia amara* and phosphoric acid.[14] Although these treatment approaches have not been investigated as rigorously as western pharmaceuticals for effectiveness or adverse effects, they nevertheless appear to have an appreciable clientele, as evidenced by the volume of sales of these products.[15]

4. Kava (*Piper Methysticum*)

Kava is a cultural and medicinal herb that is served in island communities of the South Pacific as a social beverage and in ceremonial rituals as a symbol of welcome and respect to important guests and dignitaries.[16,17] Historically, kava was found in the majority of the Pacific islands, but now it is grown mainly in Fiji, Vanuatu, Tonga, Samoa, Wallis and Futuna, and Pohnpei.

A water infusion of kava is prepared from a powder or macerate of the dried root and rhizome, where much of its biological activity is found. The claimed therapeutic effects of the herb have made it in many parts of the world a popular nonprescription treatment for alleviating mild to moderate

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cases of nervous anxiety, stress, insomnia, restlessness and muscle fatigue.[18,19] In some countries – Germany for instance – it is also available by physician's prescription.

4.1 Chemical Constituents

The search for the biologically active constituents that are responsible for the pharmacological activity of kava began about 160 years ago and has resulted in the isolation of a series of novel chemical compounds. About 15 of them, known collectively as kavapyrones or kavalactones, constitute the active components and are concentrated in the roots, rhizomes and root stems, with their distribution decreasing progressively to the aerial parts of the plant.[17] Six of these kavalactones, namely kavain (or kawain), 5,6-dihydrokavain, methysticin, dihydromethysticin, yangonin and desmethoxyyangonin, are responsible for about 95% of the total pharmacological activity. Natural kavalactones occur as the (+)-isomer [e.g. (+)-kavain], whereas synthetic counterparts, which have been used in a number of studies, are racemates [e.g. (±)-kavain].

Kava also contains inactive coloured chalcones (flavokavins A, B and C), minerals (sodium, potassium, calcium, magnesium, iron and aluminium) and amino acids.[18,20,21]

The proportions of the various lactones and the other constituents in kava are dependent on the origin and cultivar of the plant and chemical modification of the various cultivars through ethnobotanical selection, driven by the use and cultural needs of the islanders.[18] Thus, kava from a certain community in Vanuatu may have a completely different chemical profile from that of kava obtained from a locale in Fiji.

4.2 Pharmacology

The majority of the pharmacological studies on kava have been done on fractions obtained by extraction in water or organic solvents such as acetone, ethanol, methanol and chloroform. More recently, natural and synthetic kavain and a few other lactones have also been tested, but the activities obtained are largely independent of the source of the compounds.

However, one of the unresolved problems in considering the effects of kava is the correlation between the pharmacological actions of the kavalactones and their plasma concentrations. In one study, the peak brain tissue concentration of kavalactones after intraperitoneal administration in mice was estimated at about 8 to 20 μmol/L.[22] But since in most of the *in vitro* studies outlined below (sections 4.2.1 to 4.2.5) the 50% inhibitory concentrations (IC_{50}) were in the range of 50 to 150 μmol/L, the question remains whether the postulated mechanisms are indeed responsible for the pharmacological actions. However, Keledjian et al.[22] also found that both pharmacokinetic and pharmacodynamic properties were enhanced synergistically when the kavalactones were given together rather than separately.

Kava has a wide variety of biological activities, including sedative,[23,24] mild local anaesthetic,[18] analgesic,[25-27] anxiolytic and antistress,[28-32] antispasmodic,[33-35] anticonvulsant,[22,36,37] antithrombotic,[38] hypnotic,[39,40] skeletal muscle relaxant,[41] antifungal,[26,42] and neuroprotective[43-45] effects. It also reduces hot flashes associated with menopause[46,47] and produces altered vision (e.g. loss of ability to focus on near objects, blurred images).[48]

Despite the wide spectrum of pharmacological effects associated with the kavalactones and the number of them, the current evidence indicates that there are only slight differences in their mechanisms of action.[18] The major differences between them appear to be in the relative proportions and the pharmacokinetic properties of the individual compounds, namely their rates of absorption, distribution in the body, metabolism and elimination.[22] Based on *in vitro* and *in vivo* scientific data from animals and humans, a number of mechanisms have been proposed that appear to mediate the actions of kava extract and the specific kavalactones, including blockade of ion channels,[24,37,49,50] inhibition of neurotransmitter release[41,49,50] and monoamine reuptake,[51] and reversible inhibition of MAO enzymes.[52]

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4.2.1 Effects on Voltage-Gated Sodium Channels

The mechanism by which kava produces CNS depression is by blockade of voltage-gated ion channels.[24,37,50,53,54] Recently, work has been done on the effects of kavalactones on sodium channels in synaptosomes prepared from rat cerebral cortex, anoxic rat brain slices and dorsal root ganglion cells from neonatal rats. Kavain dose-dependently reduced increases in sodium levels in the synaptosomes induced by veratridine and ouabain, in a manner similar to that of the local anaesthetics procaine and tetrodotoxin.[24,37] Kavain also significantly reduced 4-aminopyridine– and KCl-induced elevations in cytosolic sodium ion levels.[24,37]

Using patch clamp techniques in cultured neurons, Schirrmacher et al.[50] showed that (±)-kavain reduced currents through voltage-activated sodium channels within 3 to 5 minutes, while (+)-methysticin was four to five times more potent than (±)-kavain and had a fast and specific inhibitory action on sodium channels.[54] These authors proposed that (+)-methysticin and (±)-kavain bind to the sodium channel in its inactivated state and prolong its inactivation.

In another study, kavain, dihydrokavain and dihydromethysticin were found to be noncompetitive blockers of sodium channels by decreasing the apparent total number of binding sites for [^{3}H]-batrachotoxinin-A.[55] Kavain failed to compete with [^{3}H]-saxitoxin at the sodium ion channel at relatively high concentrations (up to 400 μmol/L), but dose dependently suppressed binding of [^{3}H]-batrachotoxin at these concentrations.[24] These findings suggest an action at receptor site 2 of the sodium channel, a site common to local anaesthetic agents.

4.2.2 Effects on Neurotransmitter Release

Since neurotransmitter release is largely dependent on cytosolic levels of calcium, conditions that depolarise nerve endings will increase the influx of extracellular calcium ions into the nerve terminal and hence promote transmitter release. In synaptosomes depolarised by KCl and 4-aminopyridine, but not by veratridine, (±)-kavain (400 μmol/L) diminished the proportion of glutamate release dependent on extracellular calcium ion levels by about 75% of control.[24,37] The effects of kavain and dihydromethysticin on field potential changes in the hippocampus were found to be additive when both were administered *in vitro*.[56] Furthermore, these effects were consistent with concentrations reached in the brain after peripheral administration. However, neither (±)-kavain nor (+)-dihydromethysticin significantly altered the striatal or cortical tissue levels or the turnover of dopamine or serotonin in rat brain.[57]

On the other hand, using a microdialysis technique, contrasting effects of kava extract and individual kavalactones on transmitter levels in the nucleus accumbens of intact rats were noted.[49,58] Kava extract (120 mg/kg intraperitoneally) increased dopamine levels, whereas (±)-kavain at low doses (30 mg/kg intraperitoneally) decreased dopamine levels and at high doses (120 mg/kg intraperitoneally) increased or did not affect the levels of dopamine or its metabolite homovanillic acid (HVA). At doses of 120 mg/kg, yangonin decreased dopamine levels to below those detectable, and desmethoxyyangonin caused a slight increase in levels; however, the other lactones methysticin, dihydrokavain and dihydromethysticin had no effect on levels of dopamine or HVA. The levels of serotonin and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA) were slightly reduced by (±)-kavain (60 mg/kg intraperitoneally), whereas changes induced by the other kavalactones were inconsistent and greatly variable.[49,58]

Using microelectrode techniques, Singh[41] showed that a kava extract reduced the amplitude of miniature endplate potentials and endplate potential quantal content in isolated mouse diaphragm preparations and depressed generation of muscle action potentials in the frog sartorius muscle. These observations indicate a diminution in transmitter release from motor nerve terminals and a blockade of sodium ion channels leading to skeletal muscle relaxation.

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4.2.3 Effects on γ-Aminobutyric Acid (GABA) and Benzodiazepine Receptors

In studies designed to elucidate the anxiolytic and sedating properties of kava, purified kavalactones (100 μmol/L to 1 mmol/L) were found to bind weakly to $GABA_A$ receptors and not at all to $GABA_B$ receptors on synaptosomal membranes from rat forebrain and cerebellum.[59] In *ex vivo* studies, no effects were observed on [^{3}H]-diazepam binding to brain membranes prepared from mice that had been administered selected kavalactones, whereas similar treatment with diazepam (5 mg/kg) inhibited [^{3}H]-diazepam binding by >95%.[59] From these studies, it was concluded that the pharmacological activities of kava were not due to direct interactions with the benzodiazepine or $GABA_A$ receptors, but rather that the lipophilic kavalactones were incorporated into the lipid membranes, leading to a nonspecific modification of the $GABA_A$ receptor conformation.[59]

In contrast, low concentrations (0.1 to 1 μmol/L) of the kavalactones (+)-kavain, (+)-dihydrokavain, (+)-methysticin and (+)-dihydromethysticin enhanced the binding of ligands to the $GABA_A$ receptors on freeze-dried rat cortex preparations.[60] Furthermore, regional differences in the binding potency of kavalactones to $GABA_A$ receptors have been shown to exist using membrane fractions from various target brain centres. Kavalactone-enriched kava extracts, with final kavalactone concentrations between 10 μmol/L and 1 mmol/L, augmented binding of the specific $GABA_A$ receptor antagonist [^{3}H]-muscimol to 358% in the hippocampus, 300% in the amygdala and 273% in the medulla oblongata, but had minimal effect in the cerebellum and the frontal cortex. Similar concentrations of the individual lactones were effective in the brain areas tested. Scatchard analysis revealed that the observed effects of kavalactones were due to an increase in the number of drug binding sites rather than to a change in receptor binding affinity.[61] These findings are supported by other observations that limbic structures, particularly the amygdala, were the principal sites of action of kavalactones,[39] which may explain the anxiolytic and sedative effects of kava.

4.2.4 Effects on Monoamines

In view of the ability of kava to reduce anxiety, counteract fatigue and elevate mood, studies have been conducted to determine whether kavalactones could increase CNS levels of monoamines, which are involved in the pathophysiology of depression and anxiety, by blocking their neuronal uptake.[51]

Kavalactones blocked the *in vitro* uptake of noradrenaline into synaptosomes prepared from the cerebral cortex and the hippocampus of the rat with the following order of potency: (±)-kavain ≥ (+)-kavain > (+)-methysticin. Despite their actions on noradrenaline uptake, the tested kavalactones were completely ineffective at concentrations up to 100 μmol/L in blocking serotonin uptake, suggesting different affinities for noradrenaline and serotonin uptake carriers. However, only single lactones were used in the study, thus not allowing the assessment of additive or synergistic actions that are known to occur with combined administration.[51]

Another potential monoamine-related mechanism of kavalactones is inhibition of MAO type B. The compounds reversibly inhibited MAO-B in intact and disrupted human platelets in the micromolar range [IC_{50} = 0.12 to 40 μmol/L; except for (±)-kavain, IC_{50} >400 μmol/L] in the order of potency: desmethoxyyangonin > (±)-methysticin > yangonin > (±)-dihydromethysticin > (±)-dihydrokavain.[52] The IC_{50} values for the antidepressants amitriptyline and imipramine were in the same concentration range.

4.2.5 Effects on Eicosanoids

The proposed antithrombotic effects of (±)-kavain were deduced from its ability in the high micromolar range to suppress arachidonic acid–induced platelet aggregation, exocytosis of adenosine triphosphate and inhibition of cyclooxygenase-2 (COX-2) and thromboxane synthase activity, the latter two actions being deduced from the generation of prostaglandin E_2 and thromboxane A_2.[38] Although these eicosanoids are mainly known for their haemodynamic effects, they are also present in the brain. Their function in the CNS has not been fully delineated, but they are known to antagonise $GABA_A$ receptors. Therefore, inhibition of eico-

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sanoid synthesis would increase $GABA_A$ receptor function.[62] Again, since only one kavalactone was examined, it is uncertain whether a physiologically significant effect would be produced with a kava extract or a combination of kavalactones.

4.2.6 Summary of Pharmacological Mechanisms

Of the mechanisms mentioned in sections 4.2.1 to 4.2.5, blockade of voltage-gated cation channels and facilitation of GABAergic transmission would best account for the anti-anxiety and sedative properties of kava. Pharmaceutical agents such as benzodiazepines and barbiturates produce their anxiolytic and sedative effects by facilitating GABAergic transmission, especially in the limbic system, as noted for kava.[61,63,64] Blockade of voltage-gated cation channels depresses neuronal function and can cause sedation. Many antiseizure medications (e.g. barbiturates and hydantoins) share these actions and are known to have sedating adverse effects. On the other hand, blockade of noradrenaline reuptake in the CNS by kava might be expected to produce an increase in alertness by stimulation of central adrenergic mechanisms.[65,66] This may explain why kava, while sharing anxiolytic and sedative actions with the benzodiazepines and barbiturates, differs from them in having no adverse impact on cognitive functioning.[67-69] In fact, there is historical[16-18] and scientific[70,71] evidence to indicate it may enhance memory and have a positive effect on the allocation of attention and processing capacity.

The functional significance of eicosanoid suppression by kava will be resolved when the role of these compounds in the CNS is better understood. But given the blockade of $GABA_A$ receptors by thromboxane A_2, kava-induced suppression of thromboxane A_2 synthesis could conceivably contribute to its anxiolytic and sedative effects.

4.3 Therapeutic Potential

The therapeutic potential of kava in controlling anxiety can be assessed from findings of a fairly small number of clinical trials, mostly from Germany. These studies have been recently reviewed in depth,[31,72] and the details need not be repeated here.

4.3.1 Anxiety at Subclinical and Clinical Levels

Except for two studies[73,74] in which the participants' levels of anxiety were based on DSM-III-R criteria[75] and, therefore, were at clinical levels, the level of anxiety in the trials[29,30,76-85] was subclinical. Of the 12 clinical trials, ten used a double-blind, placebo-controlled methodology,[29,30,73,74,76-79,81,83] and of these ten, three early studies[76-78] used synthetic kavain [(±)-kavain] while the rest used some form of kava extract. The number of patients in the trials ranged from 13 to 766. The trial duration ranged from 2 weeks to 6 months. Benzodiazepines were used as active comparators in one of the studies.[79] Dosages, standardised to the amount of kavalactones in the preparation, ranged from 135 to 240 mg/day for kava extracts and 400 to 600 mg/day for synthetic kava. Although dose-response studies have yet to be reported, dosage did not appear to be differentially related to outcome.

The major finding was that regardless of the nature of the kava preparation, dosage and study methodology, kava in its various forms was effective in significantly reducing anxiety to within the normal levels found in the general population, as assessed on standard rating scales (e.g. Hamilton Anxiety Rating Scale, Zung Self Rating Anxiety Scale, Anxiety Status Inventory, State Trait Anxiety Inventory and Beck Anxiety Inventory). The range of anxiety symptoms treated included the gamut of anxiety disorders, including simple phobia, specific social phobia, generalised anxiety disorder, nonpsychotic anxiety and anxiety due to heightened daily stress. In general, these studies indicated that kava provides effective symptomatic treatment for a range of anxiety symptoms.

4.3.2 Anxiety Associated with Menopause

Data from three double-blind, placebo-controlled studies showed that kava is effective in decreasing anxiety symptoms associated with menopause.[46,47,85] In one study,[46] 300 mg/day of kava extract (equivalent to 210mg of kavalactones) significantly reduced menopausal anxiety in 40 women in a 4-week trial. In a related study,[47] anxiety associated with

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menopause was significantly reduced in 40 peri- and postmenopausal women in an 8-week trial.

In the most recent study,[85] anxiety symptoms associated with menopause were evaluated over 6 months in 40 menopausal women who were taking hormone replacement therapy alone or together with 100 mg/day of kava extract (kavalactones 55 mg/day). Those receiving adjunctive kava therapy showed significant reductions in their anxiety. It should be noted that this study reported a successful outcome with a much lower dosage of kava lactones than that used in previous studies.

4.3.3 Anxiety Due to Medical Conditions

Three studies have assessed the short-term effects of kava on anxiety related to a medical condition.[86-88] In the first,[86] 59 anxious preoperative patients were given 300mg of kava extract (equivalent to 60mg of kavalactones) the night before and another 300mg of kava an hour before their operation. When compared with the control group, those receiving kava had significantly lower levels of anxiety. In the second study,[87] (±)-kavain 600 mg/day significantly reduced depression associated with anxiety in 60 patients with tuberculosis or who were awaiting a confirmation of its diagnosis. In the third study,[88] kava significantly reduced the anxiety and related depression of 20 patients who were awaiting the results of a biopsy for possible mammary carcinoma. These studies indicate that kava may be a potent short-term anxiolytic for anxiety and depression related to a medical condition.

In summary, current data suggest that kava extracts produce clinically effective and superior control of anxiety symptoms when compared with placebo and possibly benzodiazepines. In these studies, the extracts did not have the serious adverse effects associated with the benzodiazepines (see section 4.4) and thus may offer a viable alternative treatment for anxiety.

4.4 Adverse Effects

Data on adverse effects associated with kava are available from various sources, including historical anecdotal information, case reports, experimental investigations and double-blind, placebo-controlled studies. Few of the well controlled trials described in sections 4.3.1 to 4.3.3 reported any serious adverse effects of kava either at the low or moderate dosages used in these studies.

4.4.1 Cognition

There is no indication from experimental studies that kava has any appreciable adverse impact on cognitive functioning.[67,68] For example, current studies show that kava does not affect alertness,[69] speed of access of information from long-term memory[69] and word recognition tasks.[70,71] When compared with oxazepam, however, kava enhances memory[70] and has a positive effect on the allocation of attention and processing capacity.[71] In comparison, oxazepam produced deficits in automatic feature registration, allocation of attention and the availability of processing capacity.[71]

4.4.2 Psychophysiology

The limited data from psychophysiological studies show either an improvement or no impact with kava. In a double-blind, placebo-controlled study,[89] (±)-kavain had a positive impact on a battery of psychophysiological measures, including memory functions, vigilance, fluency of mental functions, reaction time and circulation functions. Similarly, kava appears to improve performance on simple reaction time and complex multiple choice reaction time tests.[90] Another study reported no significant differences between kava and control groups in heart rate, respiration rate and blood pressure.[67]

4.4.3 Visual Effects

There is scant literature on the visual effects of kava. Anecdotal reports have suggested that drinking kava may cause pupil dilation and reduced light reflexes,[91] but an early experimental investigation did not support these reports.[92] Healthy volunteers were administered an oral dose of 800mg of (±)-dihydromethysticin or (±)-methysticin, two primary ingredients of the kava drink; they experienced no significant changes in pupil size.[92] In a controlled case study,[48] a kava drink reduced near

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point of accommodation, increased pupil diameter, decreased near point convergence and disturbed oculomotor balance.

4.4.4 Physical Effects

Acute effects of kava drink, as traditionally prepared in the South Pacific countries, may occasionally lead to such reversible conditions as anaesthesia of the mouth (especially the tongue), sedation, euphoria, muscle weakness and ataxia.[33,93,94] However, most of the information on physical effects of the kava drink is anecdotal and not derived from controlled studies. Data from a small, controlled study[95] showed a strong but not clinically significant trend that drinking more than socially accepted quantities of kava (i.e. 440 g/week) might lead to 'malnutrition and weight loss, liver and renal dysfunction, a rash, red eyes, shortness of breath and possibly incoordination and pulmonary hypertension, as well as abnormalities in red cells, lymphocytes and platelets'.

That excessive kava drinking may result in skin rash – a reversible ichthyosiform eruption that has been termed 'kava dermopathy' – is unquestioned, as it has been reported for more than a century.[96] As the South Pacific islanders knew by experience, it can be reversed by abstaining from kava drinks until the skin condition clears up, and then drinking at moderate levels. We still do not know what is the exact cause of kava dermopathy, although a number of traditional legends have been invoked to account for it.[97,98] Modern hypotheses about its cause include reduction in glandular secretions,[99] chronic allergic dermatitis,[100] persistent light reaction and pellagra-like dermatosis,[90] accumulation of plant flavopigments such as flavokavins,[101] an accumulation of kavalactones[102] and interference with cholesterol metabolism.[103] However, these hypotheses have yet to be tested empirically in well controlled studies.

Four cases have been reported of adverse physical reactions that could be attributed to central dopaminergic antagonism by kava.[104] In each of these cases, variants of dyskinesia (e.g. oral, lingual) were noted after ingestion of kava. They either subsided spontaneously when kava was discontinued or were treated successfully with biperiden. Few adverse effects have been reported in double-blind studies of the effects of kava on anxiety and related problems. Stomach upset[46,74,81,105] and, less frequently, headaches, lack of energy and tiredness, tremor[46,47] and restlessness[47] have been reported.

4.4.5 Drug Interactions

There is a paucity of data on drug interactions with kava. In the only experimental study that has been conducted, when combined with low-dose ethyl alcohol, kava did not have any adverse effects on seven safety-related performance measures.[106]

There was a single case report of a purported interaction between kava and alprazolam that may have caused a semicomatose state in a 54-year-old man.[107] The man was taking alprazolam, cimetidine and terazosin and for 3 days prior to his hospitalisation he self medicated with kava as well. When admitted to the hospital, he was in a lethargic and disoriented state. Tests showed that his vital signs and laboratory studies were normal and he had a negative screen for alcohol, but he had a positive screen for benzodiazepines. Few details, such as dosage of any of the medications or kava, were reported. The authors postulated that kavalactones and alprazolam had additive effects because both act on the same GABA receptors. Whether this man's medical condition was caused by the addition of kava to his prescribed medications is pure speculation given the paucity of information provided.

4.4.6 Hepatotoxicity

In the past few years, about 30 cases of possible hepatotoxicity associated with kava use have been reported from Europe, mostly in Germany, with five additional cases from the US.[108,109] The adverse event reports in these cases included cholestatic hepatitis, icterus (jaundice), increased liver enzyme levels, liver cell impairment, severe hepatitis with confluent necrosis and irreversible liver damage (requiring transplantation in four cases). Although many of the data on these cases are either incomplete or generally unavailable, relatively de-

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tailed information has been published for five of them.[110-114] These reports prompted a number of countries in March 2002 to take regulatory action to either suspend the sale of kava products or issue health advisories on their use.

These incidents of hepatotoxicity are somewhat surprising in light of the experience of South Pacific islanders who have safely consumed kava for hundreds of years. In the South Pacific, only men drink kava, often habitually and in much larger amounts than used in the west, yet their incidence of liver toxicity is low and similar to that of island women who do not take kava (unpublished observations). Reviews of the reports of liver toxicity note that in many cases, other known or suspected hepatotoxic medications had been administered concurrently. In some cases the use of alcohol or microbial infections had not been ruled out.[109,115,116] Furthermore, the commercial preparations were manufactured using organic solvents in contrast to the water infusions drunk by the islanders. And, even if the 35 cited cases are considered to arise from kava hepatotoxicity, they constitute by one estimate less than one case for 10 million daily doses,[115] suggesting that kava is relatively safe even when used in combination with other substances that may themselves be hepatotoxic or interact with kava to produce such a reaction.

5. Conclusion

Kava is a herb that has been used in the treatment of mild and moderate cases of anxiety without the many adverse effects associated with pharmaceutical drugs such as SSRIs, benzodiazepines, barbiturates and tricyclic antidepressants. Its actions are due to six major constituents called kavalactones, which appear to be more effective when used in combination than individually. In addition, kava may be effective in the treatment of some other disorders, such as insomnia, stress, restlessness and muscle fatigue. Its major adverse effect appears to be a scaly skin condition that occurs with long-term use of large amounts. However, there have been recent reports from Europe and the US of several severe cases of hepatotoxicity, which have led to the suspension of kava sales in some countries. Detailed analysis of these reports indicates, for most cases, a lack of direct causal relationship between the toxicity and kava consumption; however, until further research establishes the complete safety of kava, healthcare professionals and the public should use this herb judiciously.

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