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KAVA (Piper methysticum) - A REVIEW

The Kava plant (Piper methysticum) is a robust, well-branching and erect perennial shrub belonging to the pepper family (Piperaceae). The botanical origin remains unknown, although it is likely that early Polynesian explorers brought the plant with them from island to island. Numerous varieties of Kava exist, and today it is widely cultivated in several Pacific Island countries both for local use as well as the rapidly growing demand for pharmaceutical preparations. The dried rhizomes (roots) are normally used.

The first description to the western world of the ceremonial use of an intoxicating beverage prepared from Kava was made by Captain James Cook following his Pacific voyage in 1768. The drink, prepared as an infusion in an elaborate manner after first chewing the root, is consumed on formal occasions or meetings of village elders and chiefs, as well as in reconciling with enemies and on a more social basis. It remains an important social custom in many Pacific Island countries today.

Most of the islands of the Pacific possessed Kava prior to European contact, particularly those encompassed by Polynesia, Melanesia and Micronesia. After drinking the Kava beverage a pleasantly relaxed and sociable state develops, after which a deep and restful sleep occurs. Early visitors such as the New Zealand clinician Sir Peter Buck described it as “cooling, refreshing, and stimulating without being intoxicating....” (Buck, 1930). While excessive consumption can produce a state of stupefication and intoxication, and Kava abuse is still seen in some communities, the accounts of early missionaries and explorers exaggerated the deleterious effects of Kava drinking. German and American studies have established Kava as a safe, non-addictive anti-anxiety agent with an efficacy comparable to benzodiazepine drugs such as Valium®.

Scientific Studies

Constituents

a) Substituted alpha-pyrones and substituted 5,6-dihydro-alpha-pyrones (kava lactones or kava pyrones) including in particular methysticin, kavain and dihydrokavain (DHK), and smaller amounts of yangonin, dihydromethysticin (DHM).
b) Miscellaneous compounds include substituted chalcone pigments and traces of alkaloids.

Pharmacology

Anxiolytic and Sedative effects

Sedative and sleep-promoting (hypnotic) effects were produced in early studies on animals (Hansel and Beiersdorff, 1959; Keller and Klohs, 1963; Meyer, 1962). While various isolated Kava lactones also showed sedative activity, the extract of the whole root appeared to be more active than these isolated constituents (Klohs et al, 1959).

Human studies have revealed anxiolytic (anti-anxiety) and sleep promoting properties for Kava comparable to those of benzodiazepine drugs (Scholing and Clausen, 1977; Lindenberg and Pitule-Schodel, 1990; Kinzler et al, 1991; Warnecke, 1991; Volz and Kieser, 1997).

While mildly euphoric effects can be produced after large doses, several studies have shown that moderate doses generally do not impair reaction time and in fact may slightly improve it (Munte, 1993; Herberg, 1993). Thus while the benzodiazepine drug oxazepam produced a reduction in reaction time and number of correct answers in a recognition memory task, Kava tended to slightly improve these parameters (Munte et al, 1993).

The mechanism(s) of Kava's anxiolytic and sedative actions remains unknown, although evidence of several likely contributory actions has appeared in recent years. Experiments using Kava extract have demonstrated marked effects on the EEG of cats, as well as activation of the limbic structures of the brain, particularly the amygdala complex (Holm et al, 1991). These structures are thought to be important in modulating emotional processes, and their activation may account for the sleep-promoting and anxiolytic effects of Kava.

Some influence on GABA (gamma amino butyric acid) neurotransmission is probably also involved in these effects. GABA is a neurotransmitter present throughout the brain, and it's release by appropriate nerve stimulation in the cerebral cortex, hippocampus, cerebellum and amygdala is thought to play a crucial role in the pharmacology of stress and anxiety. The well known benzodiazepine group of drugs (eg Valium®) act largely through GABA receptor occupation. While one study using whole brain membranes showed no apparent interaction with GABA or benzodiazepine binding sites (Davies et al, 1992), a subsequent study found marked effects by kavapyrones on GABA-A receptor binding in the main target brain centres, the hippocampus, amygdala and medulla oblongata (Jussofie et al, 1994). The most recent receptor binding studies, however, found modulatory activities by kavapyrones on GABA-A receptors, but these did not appear to be due to direct interaction with these receptors (Boonen and Haberlein, 1998).

Activation of the dopaminergic neurones in the mesolimbic system by Kava pyrones, has been implicated by recent studies on rats, and this is another possible mechanism of the psychotropic actions of Kava (Baum et al, 1998). Effects on serotonin (5-HT)1A and NMDA receptors, as well as calcium channels, may also be relevant (Walden et al, 1997; Baum et al, 1998).

Possible antipsychotic and antidepressant activities

Evidence of possible mild antipsychotic activity has been revealed by experiments showing inhibition of hypermotility induced by amphetamine, and a reduction in the number of conditioned avoidance responses (Duffield et al, 1989; Jamieson et al, 1989). However, these effects were significantly less than those of the standard antipsychotic drugs chlorpromazine and haloperidol.

Nevertheless, observations have been made that individuals with psychotic symptoms amongst aboriginal communities of Northern Australia who consume large quantities of Kava appear to show some clinical improvement in these symptoms (Cawte, 1986). While this could be largely due to improved socialisation, the possibility remains that when taken in higher doses than usual, Kava may have distinct antipsychotic effects resembling those of major tranquilisers.

Mild antidepressant properties for Kava, have also been implicated by various *in vitro* and *in vivo* studies. A small trial involving women with menopause-associated psychosomatic dysfunctions, revealed not only a reduction in symptomatology, but also an improvement in depressive mood and

subjective feelings of well-being after only one week's treatment (Warnecke, 1991). Another well-designed trial involving 101 patients with various anxiety disorders, found evidence of an improvement in mood in many patients in addition to anxiolytic effects (Volz and Kieser, 1997).

In animal studies, Kava or its pyrones reduces the effects of the monoamine depleting drug tetrabenazine (Jamieson et al, 1989), and causes a potent inhibition of the neuronal uptake of noradrenaline, but no effect on serotonin reuptake (Seitz et al, 1997). Kava has also exhibited activity recently as a reversible inhibitor of MAO-B (Uebelhack et al, 1998). These activities are also shown by many antidepressant drugs and are thought to contribute to the mechanism of their antidepressant effects.

Clinical trials to determine the existence and extent of any antidepressant and/or antipsychotic activities for Kava, are urgently required.

Muscle Relaxant and Anticonvulsant properties

A muscle relaxant effect was shown for Kava pyrones in early studies on laboratory animals (Meyer 1962; Meyer and Kretzschmar, 1966), and Kava extract demonstrated a direct skeletal muscle relaxing effect *in vitro* (Singh, 1983).

Anticonvulsant effects have also been demonstrated in animal studies. Kava pyrones exhibit a strong protection against strychnine-induced convulsions and experimental tetanus (Kretzschmar et al, 1969; Kretzschmar and Meyer, 1969).

The mechanisms of these muscle relaxant and anticonvulsant properties are unknown, but inhibition of voltage-activated inward currents of both Ca2+ and Na+, as well as modulation of glutamate release, has been observed for Kava pyrones *in vivo* and *in vitro* (Gleitz et al, 1995; Ferger et al, 1998; Schirrmacher et al, 1999).

Local anaesthetic and Analgesic activities

A numbing and astringent effect on the tongue and inner lining of the mouth is the first effect of Kava drinking. Local anaesthetic and analgesic effects were first demonstrated for several Kava pyrones (DHK and DHM) by German workers in the 1960's (Meyer and May, 1964; Bruggemann and Meyer, 1963). This activity was superior to that of aspirin but inferior than that of morphine.

Later work found that both the lactone-free aqueous extract as well as lipid soluble extract (kava resin) showed analgesic and local anaesthetic effects in tests on mice (Jamieson and Duffield, 1989;1990). Analgesia appears to be produced by a non-opiate mechanism.

Other Activities

Kava extract was associated with a significant reduction in the extent of infarction following ischaemia in studies on mice and rats, which is evidence of possible neuroprotective activity (Backhauss and Krieglstein, 1992).

Kava was traditionally used for many medicinal purposes other than as a relaxant, although no research has been conducted into these to date. These conditions included congestion in the urinary tract, urinary retention, chronic cystitis, syphilis and gonorrhoea, as well as general debility, weary muscles, lung disorders, chills and head colds (Deihl, 1932; Titcomb, 1948; Handy and Handy, 1972).

Microbiological studies have detected wide-ranging fungistatic properties by Kava lactones, although not against Candida spp. No particularly pronounced anti-bacterial activity is shown for these compounds however (Hansel, 1966; Hansel et al, 1966).

Pharmacokinetics

While little is known about Kava pharmacokinetics, Kava lactones seem to be relatively well absorbed from oral administration, and are excreted largely in the urine as hydroxylated metabolites (Rasmussen et al, 1979). Absorption of these compounds both from oral as well as intraperitoneal administration was increased when they were given as the whole extract rather than as single compounds (Rasmussen et al, 1979; Biber, 1989; Keledjian et al, 1988). This supports the concept of better bioavailability of Kava lactones when taken in their natural state as part of the whole root, instead of as isolated substances.

Adverse effects and Contraindications

A characteristic skin condition known as Kava dermopathy, is seen in heavy Kava drinkers after long term consumption. This is a reversible, dry and scaly eruption distinguished by discolouration, whose cause is unknown but may relate to interference with cholesterol metabolism (Norton and Ruze, 1994) or the chalcone pigment materials found in Kava (Shulgin, 1973). Adverse haematological and biochemical changes have also been reported following heavy Kava usage in an Australian aboriginal community (Mathews, 1988), although the relationship of these to Kava has been challenged (Singh and Blumenthal, 1997).

In rare cases, allergic skin reactions can also occur (Levine et al, 1988).

Potentiation of the effects of CNS depressants such as alcohol, barbiturates and sedatives is possible (see next section).

While no specific information exists on the use of Kava during pregnancy, like all drugs and most phytomedicines, it is advisable that it be avoided during pregnancy or when breast-feeding.

Animal studies which specifically investigated the possible development of tolerance to Kava, found it difficult to induce either physiological or learned tolerance even when large doses were given over a 7 week period (Duffield and Jamieson, 1991). The dosages used in clinical trials have failed to produce any significant adverse events or development of tolerance, even when taken over periods of several weeks.

Interactions

As mentioned above, enhancement of the sedative or depressant effects of central acting drugs or alcohol, has been reported for Kava.

Ethanol and Kava resin have been shown to greatly increase each others hypnotic action in mice (Jamieson and Duffield, 1990), and potentiation of barbiturate or benzodiazepine-induced sedation or fatigue is possible (Herberg, 1993; Almeida and Grimsley, 1996). Such interactions are probably less important in clinical practice however, provided moderate dosages are used. This view is supported by a well designed study which failed to detect any potentiation by Kava extract of the negative effects of alcohol in various safety-related performance tests (Herberg, 1993).

Clinical Trials

The efficacy of Kava as a safe, well-tolerated treatment for anxiety has been supported by the results of various clinical trials in recent years.

The first such trials used the purified pyrone compound kavain, which at a dose of 400mg per day was shown to be equivalent to oxazepam for anxiety associated with neurotic disturbances (Scholing and Clausen, 1977; Lindenberg and Pitule-Schodel, 1990).

Subsequent trials have used a whole Kava extract. The first of these was a randomised, double-blind study involving two groups each containing 29 patients with anxiety syndrome not caused by psychotic disorders, who took Kava extract or placebo for 4 weeks. A significant reduction in anxiety symptomatology was revealed within the first week of treatment, and the difference between the treated and placebo groups increased as the trial progressed (Kinzler et al, 1991).

A placebo-controlled, double-blind trial involving 40 women with menopause-related symptoms, demonstrated a high level of efficacy of Kava extract in neurovegetative and psychosomatic dysfunctions over an 8 week treatment period (Warnecke, 1991).

Another double-blind, placebo-controlled clinical trial involved 58 patients with anxiety syndromes not caused by mental disorders, who received Kava extract or placebo three times daily for 4 weeks. Statistically significant improvements were observed for the Kava group in many categories of the outcome measures. These included anxiety symptoms, mental anxiety and somatic anxiety as rated by the Hamilton Anxiety Scale scores, self-assessed performance-oriented activation, and severity of disease (Lehmann et al, 1996).

The most recent and largest trial conducted to date, was a randomised placebo-controlled trial involving 101 outpatients suffering from anxiety of non-psychotic origin, who took Kava or placebo for 25 weeks. Kava was shown to be superior to placebo not only in the Hamilton Anxiety Scale measurements ($p<0.01$), but also with respect to the secondary outcome variables including effects on mood (Volz and Kieser, 1997). The drop out rate was seven patients from the placebo group, and three from the Kava group, of which two were due to improvement of symptoms.

All these trials were associated with very good tolerance of the Kava preparations used.

Actions

Anti-anxiety, sedative, anticonvulsive, antispasmodic, muscle relaxant, local anaesthetic, analgesic

Therapeutic Indications

Anxiety, including that associated with minor forms of depression.
Mild insomnia.
Nervous tension and conditions associated with skeletal muscle spasm and tension (eg headaches due to neck tension)

Dosage and preparations

1.5 to 3g of dried Kava rhizome or 3 to 6ml of a 1:2 strength ethanolic liquid extract per day (20 to 40ml per week), taken in two to three divided doses, or as a single dose before bedtime for hypnotic activity.

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KAVA - CLINICAL SUMMARY

Actions:

- anti-anxiety, sedative, anticonvulsive, antispasmodic, muscle relaxant, local anaesthetic, analgesic.

Therapeutic indications:

- Anxiety, including that associated with mild depression.
- Insomnia.
- Nervous tension, and conditions associated with skeletal muscle spasm and tension (eg headaches due to neck tension).

Dosage & preparations

- Dried Root Liquid Extract, 1 in 2: 3-6ml daily, either in two or three divided doses, or as a single dose at bedtime.
- Dried Root Capsules, 500mg: three to six capsules daily

Suggested combinations

- Liquid extract should be diluted with water or juice before taking
- With 5-15% Liquorice or Peppermint Liquid Extract to improve flavour

Adverse effects

- A generalised scaly rash (kava dermopathy), following use of larger than recommended doses over a prolonged period of time.
- Allergic skin reactions in rare cases.
- Potentiation of the CNS depressant effects of alcohol, barbiturate and benzodiazepine drugs, if larger than recommended doses are taken.

Contraindications and Cautions

- No more than small amounts of alcohol should be taken at the same time as Kava.
- Avoid during pregnancy or breast-feeding.
- Do not exceed the recommended dose, particularly if taking over a prolonged period of time.

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