THERAPEUTICS

The primary indication for the use of kava preparations is for the treatment of mild and moderate states of anxiety due to various causes. Several clinical trials have supported the value of kava and its constituents (kavalactones) as natural anxiolytics. There are methodological limitations of most of these studies, especially with regard to the inclusion criteria which often allowed for the inclusion of a heterogeneous patient population. The mode of action of kava has not yet been fully elucidated.

Pharmacokinetics

The modes of action of the different kavalactones are thought to be the same except for quantitative pharmacokinetic differences (Kretzschmar 1995). The bioavailability of mixtures of multiple kavalactones appears to be greater than that of individual kavalactones. Kavalactones are absorbed by the gastrointestinal tract and are cerebrally bioavailable (Klohs and others 1959; Kretzschmar and Teschendorf 1974).

Human Studies

A single oral dose of 200 mg (±)-kavain resulted in a maximum plasma concentration of 18 µg/mL in humans. A distribution half-life of 3-5 hours and an elimination half-life of 9 hours have been determined (Klinge Pharma 1989). The maximum effect of the drug on the encephalogram parallels peak plasma levels of kavain (Saletu and others 1989).

Kavalactones are eliminated unchanged in urine and as metabolites in feces. The main metabolic pathways were hydroxylation of the phenol ring, reduction of the 7,8-double bond, hydroxylation of the lactone ring with subsequent dehydration, and opening of the lactone ring (Köppel 1991; Klinge Pharma 1989; Rasmussen and others 1979). Reduction of the 3,4-double bond and/or demethylation of the 4-methoxyl group of the a-pyrone ring system were also found (Duffield and others 1989a).

Animal Studies

Five minutes after administering single doses (ip) of single kavalactones at 100 mg/kg to mice, the maximum concentration in the brain was 64.7 µg/g for dihydrokavain, 29.3 µg/g for kavain, 10.4 µg/g for desmethoxyyangonin, and 1.2 µg/g for yangonin. After administration of the

extract at 120 mg/kg (containing 23 mg dihydrokavain, 44 mg kavain, 16 mg desmethoxyyangonin, and 18 mg yangonin), cerebral concentrations of 27.8 µg/g for kavain and 4.6 µg/g for yangonin were found. In comparison to single kavalactones, the administration of the extract resulted in a 2- and 20-fold increase in the bioavailability of kavain and yangonin, respectively. The bioavailability of dihydrokavain and desmethoxyyangonin, however, is similar whether administered singly or as part of the rhizome extract (Keledjian and others 1988). This supports an apparent synergistic effect in animal studies of kava extract compared to the individual constituents alone (Klohs and others 1959; Kretzschmar and others 1968).

After oral administration of 100 mg/kg of a kava extract (containing 70 mg kavalactones) to mice, the kavalactone plasma levels reached a maximum of 0.3-2.5 µg/mL after 30 minutes. The change in kavalactone concentration in the brain tissue was parallel to that in the plasma, but reached a maximum of 1.1-2.0 µg/g. The half-life of the kavalactones in mouse plasma and brain tissue was 1 hour (Biber and others 1992).

Pharmacodynamics

Numerous pharmacological studies have been conducted with kava extracts and isolated kavalactones. The most important findings suggest that kava and its preparations possess anxiolytic, anticonvulsive, neuroprotective, sedative, and local anesthetic effects. Various sites or mechanisms of action of kavalactones have been discussed, primarily specific inhibition of voltage-dependent Na^+ and $Ca2^+$ channels, modulatory effects on GABA receptors, bicucullin methochloride binding at $GABA_a$ receptors, specific binding to cortical neurons, stimulation of the amygdalar nucleus of the limbic system, and an ability to antagonize clonic strychnine convulsions. **Need a take-home messagethat is understandable to a typical practitioner.**

Studies on the clinical efficacy of kava often use a variety of tests to assess treatment effects. The assessment criteria used in many of the tests mentioned in the text are given in Table 6

Anxiolytic Effects

Human Clinical Studies

The therapeutic efficacy and tolerability of a commercial kava extract in treating anxiety disorders has been documented in a number of clinical and observational studies. This led to its

receiving a positive monograph from the Commission E (reprinted in Blumenthal and others 1998) for the treatment of anxiety, tension, and agitation. The majority of the studies utilized dry extract from kava rhizome with an herb-to-extract ratio of 11-20:1. An acetone-water mixture was used in extraction and the resulting extract was adjusted to 70% kavalactones. Lipophilic components were removed by a liquid-liquid partitioning of the acetone-water extract with heptane. **We should give drug equivalents here**. **Is this a commercial extract? If so, should say who made it**

In one, 4-week long, placebo-controlled, double-blind study, 58 patients with anxiety, tension, and agitation were treated with either a placebo or 300 mg of kava extract daily (equivalent to 210 mg kavalactones daily) (Kinzler and others 1991). In comparison to those receiving the placebo, the verum group experienced a notable reduction in the total HAMA (Hamilton Anxiety Scale) score ($P < 0.01$) after 1 week of treatment. After 2 and 4 weeks of further treatment this difference remained statistically significant. A comparable baseline score of 25 dropped to 12.6 in the verum group and 21.0 in the placebo group by the end of treatment. The adjunct rating scales implemented in the study, as well as the HAMA subscales for "psychic anxiety" and "somatic anxiety", also displayed statistically significant differences in treatment results ($P < 0.01$). The verum group experienced an increase in the EWL (EWL, Eigenschafts-Wörter-Liste) and the mean value of the self-assessed "performance-dependant activity". There was a clear reduction in the degree of self-assessed "anxiety/depression" in the verum group ($P < 0.05$). The severity of the illness determined by the Clinician's Global Impressions of Change Scale (CGI) showed a not significant reduction in the verum group compared to the placebo group. No unpleasant or adverse side effects caused by the medication were noted during the 4 week administration of the kava extract.

In another placebo-controlled double-blind study lasting 8 weeks (Warneke 1991), 40 female patients with menopausal symptoms were given either a placebo or daily doses of 300 mg kava extract (containing 210 mg kavalactones/daily). Symptoms were evaluated according to the HAMA scale, Depression Status Inventory (DSI), CGI, the Kuppermann scale, the Schneider scale, and the subjective assessment of the patient. The HAMA score mean value in the verum group at the beginning of treatment was 31.1. This declined to 14.65 at week 1 ($P < 0.001$), 4.65 at week 4 ($P < 0.0005$) and 5.50 at week 8 ($P < 0.0005$). In the placebo group, the HAMA score

mean value began at 30.15 and sank to 27.50 at week 1, 22.75 at week 4, and 22.50 at week 8 (statistically non-significant). The DSI score in the verum group was 42.5 falling to 24.8 after 8 weeks. The difference between the verum and placebo groups was statistically significant at the beginning of week 4 and after 8 weeks ($P < 0.01$). The outcomes of the remaining adjunct parameters was similarly significant in favor of the kava extract over placebo. Similar adverse events such as restlessness, gastrointestinal discomfort, and fatigue were observed in both the verum and placebo groups.

In a reference substance-controlled double-blind study, 172 patients with non-psychotic anxiety, tension, and agitation were randomly divided into 3 groups. Over the course of the 6 week treatment, 57 patients received daily dosages of 300 mg kava extract (equivalent to 210 mg kavalactones daily), 59 patients took 15 mg daily of oxazepam, and 56 patients were given 9 mg daily of bromazepam. The main assessment criterion was the HAMA score. Supporting criteria of the study included the CGI, KEPS (Kurzverfahren zur Erfassing der Persönlichkeitsstruktur), EAAS (Erlanger scale for anxiety, aggression, and tension) and EWL60-S (Eigenschaftswörterliste zur Erfassung der Befindlichkeit). In the kava extract group the HAMA score dropped from 27.29 at the beginning of the study to 15.55 at the end of treatment. The score of the bromazepam group was 27.29 at the beginning and fell to 13.40, while that of the oxazepam group dropped from 27.73 to 16.55. No major statistical dissimilarity was detected between groups which can be interpreted to mean that the kava extract effected a reduction in anxiety symptoms comparable to that of the benzodiazepines. The adjunct parameters showed similar results in the testing of all three substances.

In a subsequent open observational study, 158 patients formerly medicated with benzodiazepines were treated for anxiety exclusively with 300 mg daily of kava extract (containing 210 mg kavalactones daily) over the course of 6 weeks, followed by 8 weeks of 150 mg daily of kava extract (containing 105 mg kavalactones daily) (Woelk and others 1993). A decrease in anxiety from week 7-**17,** indicated that these patients may be able to use kava extract as an alternative therapy to benzodiazepines. No adverse events were observed in patients taking the medication. **Does this info come from another study – please check article, seems incongruent. Give product.**

In a randomized, placebo-controlled, multicenter, double-blind study, 100 patients with non-psychotic anxiety, tension, and agitation were treated with a daily dose of 300 mg kava extract (WS1490, containing 210 mg kavalactones daily) over the course of 25 weeks. The inclusion criteria (based upon the revised third edition of the Diagnostic and Statistical Manual [DSM-III-R]) included an age of at least 18 years, the presence of agoraphobia, simple social phobias, and generalized anxiety disorders including adjustment disorders with a MWT-B (Mehrfachwahl-Wortschatz-Test [multiple-choice vocabulary test] version B) score of less than 3 errors, and a HAMA total score greater than 18. The adjunct parameters included the Hopkins Symptom Checklist (SCL-90-R), CGI-Items 1-3, and the von Zerssen mood scale. The HAMA total score in the verum group was 30.7 at the beginning of the trial, decreasing to 9.7 at termination. An intent-to-treat analysis indicated that this change was statistically significant ($P < 0.0015$) compared to the change effected in the placebo group. The disparity between the two treatment groups was visible after 8 weeks ($P < 0.055$). Significant advantages in favor of kava extract were also found in the HAMA subscores (including somatic and psychic anxiety), the SCL-90-R, and CGI-Items 2 and 3. The results in the von Zerssen mood scale and the CGI-Item 1 were borderline significant. Adverse events were rare and distributed evenly in both groups. In the verum group two cases of “stomach upset “ were rated as “possibly related” to the medication. In the placebo group two cases of “vertigo and palpitation“ and of “vertigo“ were rated as “possibly related“ **to what? The placebo?** and one case of “vertigo“ was judged to be “related“ to the medication. The overall tolerability of kava extract was excellent (Volz and Kieser 1997). No changes were observed in clinical blood chemistry, hematological parameters, or vital signs. In contrast to the benzodiazepines and tricyclics, both of which are used to treat anxiety, treatment with kava did not lead to tolerance (Fugh-Berman and Cott 1999).

In another open, multicenter, observational study of 51 days duration, 52 patients with non-psychotic anxiety received either 200 mg daily of kava extract (containing 100 mg kavalactones daily; n = 15 patients), 300 mg daily of kava extract (containing 150 mg kavalactones daily; n = 28 patients) or 600 mg daily of kava extract (containing 300 mg kavalactones daily; n = 9 patients). Only patients with agoraphobia, other specific phobias, generalized anxiety disorders, as well as adjustment disorders, participated. The DSM-III-R determined the diagnosis criteria. Drug efficacy was evident on measures of a global improvement scale, with 42 patients (80.8%) rating treatment as "very good" or "good". The overall tolerability of kava extract was excellent.

In one patient, the medication was withdrawn because of restlessness rated by the investigator as not drug related. Among patients completing the study, one complained of stomach upset and another of bitter taste; both adverse experiences were judged to be drug related (Scherer 1998).

Human Clinical Studies with Racemic Kavain

Racemic kavain is synthetically produced. This optically inactive material appears to differ little in its pharmacological characteristics from the naturally dextrorotatory (+)-kavain, extracted from the kava rhizome. 3 open studies, 2 comparative studies against an active reference substance, and 7 placebo-controlled studies exist (Krach 1986; Lehmann and others 1989; Lindenberg and others 1990; Möller and Heuberger 1989; Scholing and Clausen 1977; Staedt and others 1991; Volz and Kieser 1997). In doses of 200-600 mg daily the therapeutic results were similar to those found in studies employing the kava extract. Unfortunately, the inclusion criteria in these studies were not very rigorous, resulting in a heterogeneous patient population.

Sedative Effects

Human Clinical Studies

The influence of kava extracts on the quality of sleep was the central focus of a randomized single-blind study with 12 healthy volunteers. Six subjects were given a placebo on day 1, 3, and 4 of the study, followed by either 150 mg kava extract (containing 105 mg kavalactones) or 300 mg kava extract (containing 210 mg kavalactones) on day 2. A polygraphic sleep electroencephalogram (EEG) with electromyographies and an electro-oculography was recorded. In the verum group, 11 of the 12 subjects experienced a 20% increase in sleep spindles density and deep sleep. Rapid eye movement (REM) sleep remained unaffected and sleep stage I and sleep latency showed a tendency towards reduction, while the subjective sleeping quality increased (Emser and Bartylla 1991). While oxazepam predictably impaired function (event-related potentials and recognition memory), kava slightly enhanced both (Fugh-Berman and Cott 1999).

Animal Studies

In rabbits kept in a sleepless condition, a sedative-like increase in the spindle activity in the cortical EEG was observed after they received intravenous (iv) injections of yangonin (5 mg/kg), dihydromethysticin (20 mg/kg), and kavain (20 mg/kg). The reason for the depressed arousal

reaction can be explained by inhibition of the activity of the limbic system (Kretzschmar and Teschendorf 1974).

Analgesic and Anesthetic Effects

Animal Studies

Administration of 150 mg/kg of kava extract ip delayed the pain reaction time of mice in the Tail Immersion Test from 19.7 seconds to 49.7 seconds ($P < 0.001$). Peak analgesia was reached 10 minutes after injection and persisted for approximately 80 minutes. Kavain and methysticin also produced analgesia at doses from 150 to 360 mg/kg. Dihydrokavain (150 mg/kg ip) had the highest analgesic potency, but at 10 minutes the shortest time of action. The yangonins, had no influenza up to doses of 1g/kg ip (Duffield and Jamieson 1988; Jamieson and others 1989).

After po application of 200 mg/kg of kava extract to mice, the results of the Writhing Test (determination of chemical visceral pain sensitivity) showed significant analgesic effects. The amount of pain-dependant reactions was reduced from 22.9 to 11.3 in comparison to the placebo group ($P < 0.001$) (Jamieson and Duffield 1990a).

The topical anesthetic activity of the kavains on the rabbit cornea was more pronounced than that of methysticin, the unreduced ones (kavain, methysticin) being superior to the reduced kavalactones (dihydrokavain and dihydromethysticin). While yangonin in a 1% suspension was ineffective, it was found that a 0.5% solution of kavain had an anesthetic effect equivalent to that of cocaine. The effect of a 3% solution of either compound had a comparable effect on the endurance of total anesthesia, extending it from 5.3 min for kavain and from 6.5 min for cocaine to approximately 31 min for both substances. The kavalactones showed a somewhat weaker infiltration anesthetic effect in comparison to surface anesthetic action (Meyer and May 1964).

The pentobarbital sleeping time in mice was prolonged by 340% after administration of 160 mg/kg po of a chloroform extract (15.6:1 concentration) (Klohs and others 1959). Of individual kavalactones, methysticine (minimal effective dose was 20 mg/kg ip for mice) was the most effective, followed by the kavains and yangonin (Meyer 1966). Hexobarbital-sodium alone produced a maximal period of lateral recumbent position of about 3 hours (200 mg/kg ip). After the animals had been pre-treated with 40 mg/kg ip dihydromethysticin, this same effect was

achieved with 70 mg/kg of barbiturates. With the aid of an EEG, it was shown that kavalactones prolong and deepen anesthesia and consequently bring about an anesthesia potentiation (Meyer 1962).

Muscle-relaxing Effects

Animal Studies

A dose-dependant reduction of muscle tone in mice occurred after administration of more than 120 mg/kg ip of kava resin (Duffield and Jamieson 1988; Jamieson and others 1989). Yangonin at 5-10 mg/kg iv almost totally suppressed impulses in the electromyogram. Two to 3-fold higher dosages were required of kavain, methysticin, and dihydromethysticin to obtain similar results (Kretzschmar and others 1971).

Administration of 120 to 150 mg/kg ip of kava resin (extracted with dichloromethane) hindered the spontaneous motility of mice in a dose-dependent manner. Within 3 hours post application there was a full restitution of agility and muscle tone (Duffield and Jamieson 1988; Jamieson and others 1989). The minimally effective dosage of single kavalactones in a similar motility test was 45 mg/kg for methysticin and yangonin, 60 mg/kg for kavain and dihydromethysticin, 90 mg/kg for dihydrokavain, and 200 mg/kg for desmethoxyyangonin (all ip administered). It could not be clearly determined to what extent psychological sedation is connected to motor inactivation (Meyer 1966). The muscle-relaxing effects of kavalactones can be attributed to a centrally induced attenuation of the a- and g spinal motor systems. These effects, similar to those caused by the muscle relaxant mephenesin, are generated from supraspinal sites of action (Meyer 1966; Meyer and Kretzschmar 1966).

Anti-convulsant Effects

Animal Studies

Many studies have shown that kava extract and the kavalactones present in it have anti-convulsant effects in mice with experimentally induced tonic-extensor convulsions (stimulated by maximal electroshock, strychnine, pentatrazole, bemegride, and picrotoxin) (Klohs and others 1959; Meyer and Kretzschmar 1966; Kretzschmar and others 1969, Kretzschmar and Meyer 1969; Meyer 1964; Meyer and Meyer-Burg 1964). Methysticin and dihydromethysticin proved to be the most effective anticonvulsives. Because kavalactones are poorly absorbed in the gut,

the po administration of unsaturated kavalactones required a dosage that was 10-fold higher than that of iv administration. Mixtures of yangonin or desmethoxyyangonin with 5,6-reduced pyrones (kavain, dihydrokavain, methysticin, dihydromethysticin) applied po led to an synergistic effect. The mean protective dosage against the maximal electroshock was 740 mg/kg for yangonin. This amount decreased to 75 mg/kg when yangonine was administered 1:1 with the kavapyrone mixture (methysticin:dihydromethysticin:kavain:dihydrokavain = 1:1:1:1) instead of the calculated estimate of 115.2 mg/kg (Kretzschmar and Teschendorf 1974) showing a synergism between the two compounds. After po administration, kavain activity peaked at 10 minutes and lasted 40-60 minutes; methysticin activity peaked at 45-60 minutes and lasted 2-4 hours; while yangonin's action peaked at 2 hours and lasted more than 4 hours (Kretzschmar and Meyer 1969).

Neuroprotective Effects

Animal Studies

Administration of 150 mg/kg po of kava extract (adjusted to 70% kavalactones) to mice 1 hour before the occlusion of the middle cerebral artery significantly reduced the cerebral infarct size ($P < 0.05$). Methysticin (10 mg/kg ip) and dihydromethysticin (30 mg/kg ip) displayed approximately the same neuroprotective effects, whereas kavain, dihydrokavain, and yangonin had no effect (Backhauss and Krieglstein 1992).

Effects on Mental Acuity

Human Clinical Studies

In a randomized single-blind study, 6 healthy volunteers were given either 300 or 600 mg daily of kava extract (containing 210 and 420 mg kavalactones) for 14 days. The efficacy of kava was gauged by examining the neurophysiological spectrum of action (quantitative EEG, evoked potential), general personality variables and the subjective state, including a variety of cognitive parameters. An increase in the beta/alpha-index in the quantitative EEG was present, which is typical for the pharmaco-EEG profile of anxiolytics. Delta and theta activity remained uninfluenced, thus a sedative component was not observed. The results of the examination concerning the evoked potential indicated an improvement in attentiveness and information processing in the cortical areas. There was also an increased tendency towards emotional stability (Johnson and others 1991).

In a randomized, double-blind, 3-fold crossover study, 12 healthy volunteers were examined for the effects of a single dose of 400 mg kava extract (containing 120 mg kavalactones) in comparison to a placebo and 10 mg of diazepam (benzodiazepine) as a positive control. Measurements were taken directly before administration as well as at 2 and 6 hours post ingestion. The crossover followed 7 days after the initial testing day. After application of the kava extract, a non-significant increase was noted in the quantitative EEG in the delta/theta intensity in the occipital and frontal areas. A significant reduction of the alpha-wave relative intensity ($P < 0.05$) was also noted. The increase in beta activity typically found with benzodiazepines was not observed. The placebo group witnessed a decline in the relative intensity of the slow delta- and theta-waves and an increase in the alpha-waves ($P < 0.01$). Maximal effects of diazepam were most often observed 2 hours after application, as opposed to the kava extract where even after 6 hours the effects had not lessened. The critical flicker frequency in the psychophysiological tests was found to be lower under the influence of kava extract and diazepam compared to the placebo ($P \leq 0.01$). In contrast, significant increases in performance in the Pauli Test (assessment of concentration under pressure of time) after the administration of kava extract were noted which were not present with the placebo or diazepam ($P < 0.009$) (Gessner and Cnota 1994).

Twelve healthy volunteers were tested in a double-blind crossover study to assess the effects of oxazepam and an extract of kava rhizome on behavior and event-related potentials (ERPs) in a recognition memory task. The verum group (n = 4) received 600 mg kava extract daily in 3 doses (containing 420 mg kavalactones daily) over the course of 5 days. The placebo group (n = 4) received 3 doses daily; while the oxazepam group (n = 4) received the placebo from day 1 to 4 followed by 15 mg oxazepam on the evening of the day 4 and 75 mg oxazepam on day 5. The duration of study was 29 days with a 12 day wash-out days between experiments. The word recognition task, employed as a parameter for memory performance, and psychometric tests were used to examine ERPs. The kava extract resulted in a slight but non-significant increase in the word recognition rate and amplitude of the ERPs. In comparison to the placebo, oxazepam produced a statistically significant attenuation in cerebral information processing and an amplitude increase with corresponding changes in the ERPs, the repeated recognition rate, and psychometric tests (Münte and others 1993).

The influence of kava extract alone or in combination with alcohol and/or bromazepam, on safety-related performance has been investigated in several human pharmacological studies. In a placebo-controlled, double-blind, 15 day study (Herberg 1991), 40 healthy subjects received 3 doses of 100 mg kava extract daily (containing 210 mg kavalactones daily) or a placebo. Seven psychometric testing procedures were used to assess safety-related performance. There were no statistically significant differences detected when comparing the kava group to the placebo group with regard to either vigilance, optic orientation, mental, reaction time, or motor coordination.

In a controlled study with 9 participants, neither the imbibing of 250 mL of a kava beverage, prepared from 30 g of pulverized rhizome, nor the ingestion of a double dose led to impairment of reaction, memory, or motor coordination (Russel and others 1987). In another study (Herberg 1993), 40 healthy individuals were treated with 3 doses of 100 mg kava extract (containing 210 mg kavalactones) daily or a placebo over a period of 8 days. At days 1, 4, and 8, the subjects in each group were also given ethanol (blood alcohol content of 0.5‰ after administration). The combination ethanol and the kava extract showed no significant influence of the reaction ability in comparison to the placebo.

The safety-related performance and basic performance aspects of kava were tested in a randomized, double-blind, crossover study. Eighteen healthy persons were simultaneously given 400 mg kava extract (containing 240 mg kavalactones daily) and 4.5 mg bromazepam twice daily over a period of 14 days. This was compared to the effects of the substances administered individually (Herberg 1996). Performance in stress tolerance ($P = 0.0001$ on day 2), vigilance ($P = 0.0001$ on day 2), and motor coordination ($P = 0.009$ on day 2) under kava extract remained the same as baseline, while the performance of subjects taking bromazepam and the kava-bromazepan combination deteriorated equally. Performance was least effected in those administered kava extract and most effected in those given the combination treatment. There were no clear indications of over-additive interactions when the substances were given in combination.

Central Nervous System Effects

Animal, In Vitro, and Ex Vivo Studies

Effects on Ion Channels

The influence of (±)-kavain on veratridine-stimulated increase in intrasynaptosomal Na^+ concentration of rat cerebrocortical synaptosomes has been studied. Na^+ was measured spectrofluorometrically employing SBFI as Na^+ sensitive fluorescence dye. (±)-kavain dose dependently reduced the stimulated increase of Na^+ (IC_{50} value of 86.0 µM) and almost complete inhibition of Na^+-channels was attained with 400 µM (±)-kavain. Procaine (400 µM) and tetrodotoxin (10 µM) reduced veratridine-elevated Na^+ to 30.4% and 7.9% of control whereas the muscle relaxant mephenesin (400 µM) was without any effect (Gleitz and others 1995).

An interaction of (±)-kavain with receptor site I of Na^+ channels was investigated on synaptosomal membranes by radioligand-binding assays. 4-aminopyridine is known to block K^+ channels, reducing the membrane potential sufficiently to activate voltage-dependent Na^+ channels, an effect correlated with an increase in cytosolic free Na^+, Ca^{2+} and the release of endogenous glutamate. Glutamate release from 4-aminopyridine-stimulated cerebrocortical synaptosomes and the cytosolic free Na^+ and Ca^{2+} were detected fluorometrically by using an enzyme-linked assay, sodium-binding benzofuranisophthalate (SBFI), and Fura-2, respectively. (±)-kavain failed to compete with [^{3}H]saxitoxin up to 400 µM, but dose-dependently suppressed binding of [^{3}H]batrachotoxin with an IC_{50} value of 88 µM, although displacement of

[^{3}H]batrachotoxin was restricted to 33% of control at 400 μM (±)-kavain (Gleitz and others 1996b). 100 μM (±)-kavain, 50 μM (+)-kavain, 70 μM (±)-dihydrokavain, 100 μM (+)-dihydrokavain, and 100 μM (+)-dihydromethysticin decreased ($P \leq 0.01$) the apparent total number of binding sites (B_{max}) for [^{3}H]batrachotoxin, whereas the K_D values were not statistically significant affected for each compound (Friese and others 1998). In synaptosomes stimulated by 4-aminopyridine (5 mM), kavain (400 μM) suppressed the increase in Na^+ and Ca^{2+} to 38 and 29% of control, respectively. The glutamate release was diminished to 60% of control (Gleitz and others 1996a, Gleitz and others 1996b).

Similar effects of (±)-kavain on voltage-activated Na^+ and Ca^{2+} inward currents were analyzed by patch clamp technique in cultured dorsal root ganglion cells derived from neonatal rats. (±)-Kavain reduced currents through voltage-activated Na^+ and Ca^{2+} channels (Schirrmacher and others 1999). A study of the action of the natural kavapyrone, (+)-kavain, and its synthetic racemate, (±)-kavain, on voltage-dependent Na^+ channels found that both kavalactones were equally effective, suggesting a non-stereospecific inhibition of veratridine-activated Na^+ channels (Gleitz and others 1996a).

(±)-Kavain (100 mg/kg po) significantly reduced veratridine-induced glutamate release compared with that of vehicle-treated controls in a microdialysis study. Maximum extracellular glutamate levels were obtained 20-40 minutes after veratridine stimulation (500 μM, added to the perfusate). In the control group the increase was 301% of basal value and in the (±)-kavain group the increase was reduced to 219% ($P < 0.01$). The coperfusion of veratridine and tetrodotoxin (5 μM) led to an almost complete suppression of veratridine-induced glutamate release after 40 minutes and served as a positive control (Ferger and others 1998).

The action of (+)-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 (shift of V_{hold} to more positive values, shift of h_∞ curves to more negative potentials). (+)-Methysticin was approximately a 4- to 5-fold more potent blocker of peak current amplitude than (±)-kavain at different V_{hold} values. Also, (+)-methysticin caused a larger shift of h_∞ curve than (±)-kavain did. The voltage-dependence of Na^+ channel inhibition can be explained by interaction of (+)-methysticin and (±)-kavain with resting closed and inactivated states of Na^+ channel (Magura and others 1997).

Effects on $GABA_A$- and Benzodiazepine Receptors

Radioreceptor assays using the $GABA_A$-receptor agonist [^{3}H] muscimol and membrane fractions from various target brain centers of rats with kava extract (final kavapyrone concentration ranging between 10 μM and 1 mM) augmented specific [^{3}H]-muscimol binding to about 358% in the hippocampus, 300% in the amygdala, and 273% in the medulla oblongata ($P < 0.01$) over values reported in control animals. Minimal stimulation was observed in the cerebellum followed by the frontal cortex. Similar concentrations of kavalactones were effective in the brain areas investigated, exhibiting EC_{50} values between 200 and 300 μM. Scatchard analysis revealed that the observed effects of kavalactones were due to an increase in the number of binding sites (B_{max}), rather than to a change in receptor-binding affinity (Jussofie and others 1994).

Purified kavalactones (100 μM and 1 mM of each kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and tetrahydroyangonin) had only weak effects on $GABA_A$ and benzodiazepine binding sites in washed synaptosomal membranes prepared from rat brain

(Davies and others 1992). In ex vivo studies, no effects were observed on [^{3}H]diazepam binding to brain membranes prepared from mice in which selected kava constituents were injected intraperitoneally (100 and 1000 mg/kg yangonin, 100 mg/kg of each dihydromethysticin and desmethoxyyangonin, 150 mg/kg dihydrokavain, or 330 mg/kg methysticin). No activity was observed in in vivo binding studies (Davies and others 1992).

Injection of kava resin failed to influence the CNS binding of the benzodiazepine-receptor ligand [^{3}H]Ro15-1788 injected into mice prior to death. The researchers concluded that the pharmacological activities of kava preparations were not due to direct interactions of the kavalactones with the benzodiazepine or $GABA_A$ receptor. Rather it was assumed that the lipophilic kavalactones were bound to the lipid membranes, leading to a non-specific modification of the $GABA_A$ receptor conformation (Davies and others 1992). In contrast, another binding study found an influence of genuine kavalactones enantiomers on the $GABA_A$ binding site (Boonen and Häberlein 1998). Radioreceptor assays were performed using freeze-dried cortex preparations from rats and the radioligand [^{3}H]bicuculline methochloride ([^{3}H]BMC). The radioreceptor assay was verified by an in-process procedure with an increase of specific [^{3}H]BMC binding of about 14% using diazepam (10nM) and an IC_{50} value for bicuculline methoiodide of 50 nM. The kavalactones were examined at assay concentrations between 100 µM and 10 nM. (+)-Kavain, (+)-methysticin, and (+)-dihydromethysticin showed maximal enhancements of the specific [^{3}H]BMC binding of 18% to 28% at a concentration of 0.1 µM, whereas a 100-fold higher concentration of (+)-dihydrokavain revealed a similar modulatory activity of 22% ($P < 0.01$). In the presence of 1 µM yangonin, an increase of about 21% ($P < 0.01$) of the specific [^{3}H]BMC binding was observed. Desmethoxyyangonin did not alter the binding behavior of the $GABA_A$ receptor. Obviously, the aromatic methoxy group is of particular importance for the modulatory activity of the dienolides. The modulatory activity of the kavalactones at assay concentrations between 10 µM and 100 µM and the observed structure

activity relationships seem to indicate specific interactions to a different binding site (Boonen and Häberlein 1998).

A specific binding to the benzodiazepine receptor of freeze-dried rat cortex preparations, indicated by an inhibition of the [^{3}H]flunitrazepam binding, was not observed for the kavalactones. The radioreceptor assay was verified by an in-process procedure with an IC_{50} value of 9.8 nM for diazepam (Backhauss and Krieglstein 1992).

Specific interactions between a tetramethylrhodamine-labeled kavain derivative and human cortical neurons were found using fluorescence correlation spectroscopy (Boonen and others 2000). Human cortical neurons were incubated with 1 nM of the dye-labeled kavain derivative. A total binding of 0.55 nM was found after an incubation period of 60 minutes. Fifty percent of the total binding was specifically displaced in the presence of 1 µM non-labeled (+)-kavain. Evidence for these specific interactions was verified by a saturation experiment. Both the non-linear Scatchard plot and the n value of 1.58 ± 0.07 in the sigmoid Hill plot indicated binding sites with different binding affinities.

Inhibition of Noradrenaline Uptake

The actions of (+)-methysticin, (+)-kavain and the synthetic racemate (±)-kavain were tested on in vitro uptake of radiolabeled monoamines ([^{3}H]-noradrenaline, [^{3}H]-serotonin) in synaptosomes prepared from the cerebral cortex and the hippocampus of rats. The monoamine uptake assay was verified by an in-process procedure with a K_i value of 0.78 nM for desipramine (specific noradrenaline blocker) and a K_i value of 402 nM for fluoxetine (specific serotonin uptake blocker). (±)-Kavain and (+)-kavain were less potent and significant inhibition of [^{3}H]-noradrenaline uptake was only seen at concentrations above 10 µM. At the maximal concentration of 400 µM, the [^{3}H]-noradrenaline uptake was influenced almost equally by (±)-kavain and (+)-kavain to approximately 70% to 80% of the control. The K_i values were in the same range and amounted to 48.7 µM and 59.6 µM, respectively. (+)-Methysticin was not as

potent as (±)-kavain and (+)-kavain. At the maximal concentration of 400 μM, (+)-methysticin inhibited the [^{3}H]-noradrenaline uptake by only 45% of the control. All tested kavalactones failed to significantly inhibit [^{3}H]-serotonin uptake (Seitz and others 1997).

Effects on Neurotransmitters

The in vivo effect of (+)-dihydromethysticin (100 mg/kg po) on striatal and cortical tissue concentrations of dopamine, serotonin, 3,4-dihydroxyphenylacetic acid, and 5-hydroxyindoleacetic acid, as well as the dopamine and serotonin turnover, was tested in rats. Additionally, rats were fed with a (±)-kavain-containing food (0.48g/kg food) over a period of 78 days in order to calculate the influence of a chronic treatment with kavalactones on the neurotransmitter. The study demonstrated that neither (+)-dihydromethysticin in a high single dose, nor (±)-kavain chronically administered, significantly altered the dopaminergic or serotonergic tissue levels in rats. A smaller gain in weight in the (±)-kavain treated rats compared to the control group was found, even though both groups consumed nearly the same amount of food ($P < 0.05$) (Boonen and others 1998).

Contrasting effects of kava extract and individual kavalactones were found on neurotransmitter levels in the nucleus accumbens of rats. After application of kava extract (120 mg/kg ip), increased levels of dopamine were found by in vivo microdialysis studies. (±)-Kavain administered at low doses (30 mg/kg ip) induced a decrease in dopamine levels ($P < 0.002$), while at higher doses (120 mg/kg ip) it induced either an increase or no change in dopamine and homovanillic acid (HVA) concentrations, but a large increase of 3,4-dihydroxy-phenylacetic acid (DOPAC). Yangonin (120 mg/kg ip) stimulated a decrease of dopamine levels below the detection limit ($P < 0.013$) while desmethoxyyangonin (120 mg/kg ip) caused an increase ($P < 0.034$). Dihydrokavain, methysticin, and dihydromethysticin did not produce any significant change in dopamine, DOPAC, and HVA levels. (±)-Kavain (60 mg/kg ip) induced a decrease in 5-HT concentrations ($P < 0.03$). Some of the other kavalactones affected 5-HT levels as well (Sallström Baum and others 1998).

Other Effects

The influence of tetrodotoxin and (±)-kavain on anoxic rat brain vesicles were investigated with respect to lactate synthesis, vesicular ATP content, and cytosolic free Na^+ and Ca^{2+} ($[Na^+]_i$, $[Ca^{2+}]_i$).The Na^+ channel blocker tetrodotoxin and (±)-kavain, if applied before anoxia, preserved vesicular ATP content, diminished anoxia-induced increase in $[Na^+]_i$ and $[Ca^{2+}]_i$ and prevented both the veratridine-induced increases of $[Na^+]_i$ and $[Ca^{2+}]_i$ and the inhibition of lactate production (Gleitz and others 1996c).

(+)-Kavain was investigated regarding its assumed antithrombotic action on human platelets. Exogenously-applied arachidonic acid (100 µM) provoked a 90% aggregation of platelets, the release of 14 pmol ATP, and the formation of either 220 pg thromboxane A_2 or 43 pg prostaglandin E_2, each parameter being related to 10^6 platelets. If given 5 min before arachidonic acid, (+)-kavain dose-dependently suppressed the aggregation of human platelets (IC_{50} of 78 µM), the release of endogenous ATP (IC_{50} of 115 µM), and the formation of prostaglandin E_2 (IC_{50} of 86 µM) and thromboxane A_2 (IC_{50} of 71 µM) (Gleitz and others 1997).

The effects of kavain and dihydromethysticin were tested on field potential changes induced by omission of the extracellular Mg^{2+}, recorded from the area CA1 and CA3 of the hippocampal slice preparation of guinea pigs. Kavain and dihydromethysticin reversibly reduced the frequency of occurrence of field potentials in a concentration range from 5- 40 µM and 10-40 µM, respectively. Reduction of field potential frequency after addition of subthreshold concentrations of 5 µM kavain and 10 µM dihydromethysticin indicated additive actions of both drugs (Walden and others 1997).

Effects of a kava extract and pure synthetic kavalactones were investigated on human platelet monoamino oxidase type B (MAO-B), in comparison to amitriptyline, imipramine, and brofaromine. The kava extract (67.6% kavalactones) was added to assay mixtures (100 µl of platelet-rich plasma (PRP), 2-phenylethylamine-[ethyl-1-^{14}C]hydrochloride) to achieve final concentrations in the range of 2-225 µM for intact platelets in PRP or 0.25-0.45 µM for disrupted platelets. Synthetic kavalactones were tested at a concentration of 20 µM for intact platelets. The final concentration of (±)-kavain, desmethoxyyangonin, and (±)-methysticin were varied in the range of 0.05-200 µM to determine the IC_{50} values. For kinetic studies, disrupted platelets were incubated with either (±)-methysticin or desmethoxyyangonin (1-16 µM). A much higher concentration of kavalactones was required to inhibit MAO-B activity in intact platelets (IC_{50} 24 µM) than in isolated disrupted platelets (IC_{50} 1.4 µM). The kava extract appeared to be equipotent to amitriptyline and brofaromine in intact platelets and about twice as potent as imipramine. In disrupted platelets the IC_{50} value of the kava extract was about 10 times lower than that of either amitriptyline or brofaromine and 20 times lower than that of imipramine. The sensitivity of MAO activity to pure synthetic kavalactones was very different. The two most potent kavalactones, desmethoxyyangonin (IC_{50} 28.1 µM in intact platelets) and (±)-methysticin (IC_{50} 39.5 µM in intact platelets) displayed a competitive inhibition pattern with mean K_i 0.28 µM and 1.14 µM respectively (Uebelhack and others 1998).

The effects of methysticin on different models of seizure like events were studied in rat hippocampal and entorhinal slices. Methysticin, in concentrations ranging from 10-100 µM, blocked all types of epileptiform discharges induced in all experiments; this included stimulus induced burst discharges in low Mg^{2+}, all types of low Mg^{2+} induced recurrent activities in the entorhinal cortex, and the low Ca^{2+} as well as the high K^{+} induced epileptiform discharges in area CA1 of the hippocampus (Schmitz and others 1995).

Conclusion

Based upon present knowledge, kava extracts are especially well-suited as a primary therapy for patients suffering from non-psychotic anxiety and for those treated in an outpatient or general practice environment. The positive results from the clinical studies show a high therapeutic value and efficacy in the treatment of anxiety disorders. Regrettably, the inclusion criteria employed in the studies were insufficient or at times disregarded and provided for a relatively heterogeneous collective, including patients suffering from depression with various levels of anxiety, panic disorders, and somatic imbalances. Therefore, further well-designed placebo-controlled studies where the inclusion criteria are standardized either by DSM-IV or ICD-10 are required. The latency of kava preparations is between 1 and 2 weeks which is consistent with the latency of antidepressant drugs.

The kavalactones are regarded as the pharmacologically active compounds with anxiolytic, anticonvulsive, and central muscle relaxing actions. Specific inhibition of voltage-dependent Na^+ channels is consistent with local anaesthetic and anticonvulsive actions of kavalactones and may contribute to their neuroprotective properties. Modulatory activities of kavalactones on the binding behaviour of specific ligands at the $GABA_a$ receptor were found by radioreceptor assays. While there is strong evidence suggesting that kava is an effective anxiolytic, the mechanisms of action responsible for this effect has not yet been fully elucidated.

Actions

Analgesic, anesthetic (local), anticonvulsive, anxiolytic, inhibits voltage-dependent Na^+ channels, modulatory activity on $GABA_A$ receptors, muscle relaxant (centrally), neuroprotective, potentiates barbiturate sleeping time.

Medical Indications Supported by Clinical Trials

Based on a review of the available data, kava and its preparations, are effective for the treatment of mild anxiety. The German Commission E describes its use for “states of nervous anxiety, tension, and agitation” (Blumenthal and others 1998).