Herbal Extract Series 3.

Kava-Kava-Extract

For the Treatment of
Anxiety
Tension
and
Excitedness
Introduction

EUROMED is a company specialised on botanical extracts and active principles to be used later as phytomedicines in pharmacy. EUROMED deals with the development and production of these therapeutically active raw materials.

For that purpose the botanical raw materials are subject to strict selections and inspections and the products are manufactured according to methods developed by the EUROMED company. They include inspections to guarantee a standard quality from both analyticochemical and therapeutic points of view and take into consideration the state of art in different fields: research and development, analyses, processes and devices, therapeutic applications on a scientific basis.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.
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1. Kava-Kava Extract

General Information

1.1 Description

Kava-kava extract is an absolutely herbal extract of the dried rhizome (*Piper methystici rhizoma*) of the kava-kava plant *Piper methysticum* G. FORSTER. Absolutely herbal

The kava-kava extract has

- anxiolytic,
- tranquillising,
- relaxant and
- anticonvulsive effects.

Herbal anxiolytic agent

Its application, however, does neither lead to any form of addiction nor to psychic or physical dependence (12).

1.2 Indications

Indications for the therapeutic use of kava-kava extract are states of nervous anxiety, tension and excitedness and sleep disturbances resulting from them.

1.3 Extract Specifications

Kava-kava extract is standardised to kava pyrones (or kava lactones) from 20 to 70 per cent in the extract (51). Depending on the way of application kava-kava preparations contain up to 120 mg kava pyrones (as available from Euromed).
1.4 Dosage and Methods of Application

The application of daily doses of the drug and its preparations corresponding to 60–70 per cent of kava pyrones is recommended for a maximum period of time of 3 months (39). The dosages used in studies normally contained between 120 and 240 mg/d (51, 26, 38, 49, 53). The American Herb Research Foundation recommends 100 to 200 mg/d (4).

1.5 Contraindications and Interactions

Kava-kava extract is not qualified for the therapy of endogenous depressions. Since there is no sufficient experience in pregnancy and lactation period kava-kava should not be taken in these periods. The application of kava-kava can lead to the intensification of the effects of narcotics, such as alcohol, barbiturates and psychopharmacological drugs without having any own narcotic effects (33).

1.6 Side Effects

Kava-kava extract is generally well tolerated and hardly associated with unwanted drug effects. If it is taken for a longer period of time or at high dosage aurantiasis, allergic cutaneous reactions as well as in individual cases accommodation disturbances, a dilatation of the pupils and balance disturbances of the eyes may happen to occur (11, 18, 42).
Tab. 1: Drugs containing kava-kava extract.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Content of Kava-Kava Extract [mg]</th>
<th>Content of Kava Pyrones [mg]</th>
<th>Kava Pyrone Dose/Day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aigin</td>
<td>125-145</td>
<td>40</td>
<td>120-240</td>
</tr>
<tr>
<td>Antares 120</td>
<td>400</td>
<td>120</td>
<td>120-240</td>
</tr>
<tr>
<td>Ardeydystin forte</td>
<td>75.2-120.2</td>
<td>50</td>
<td>50-100</td>
</tr>
<tr>
<td>Cefakava 150</td>
<td>150</td>
<td>35</td>
<td>70-140</td>
</tr>
<tr>
<td>Kavasedon</td>
<td>100</td>
<td>50</td>
<td>50-150</td>
</tr>
<tr>
<td>Kavasporal forte</td>
<td>150</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Kavatino Kapseln</td>
<td>80-150</td>
<td>60</td>
<td>60-120</td>
</tr>
<tr>
<td>Laitan</td>
<td>100</td>
<td>70</td>
<td>210</td>
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</table>
2. From Plant to Extract

2.1 Botanical Definition of Kava-Kava

(Piper methysticum G. Forst.)

The kava-kava plant belongs to the pepper family or piperaceae. It is a perennial, erect shrub and about 2 to 3 m high. Its branches are knotty and the relatively large leaves are broad-ovate to heart-shaped and poorly hairy to pubescent at the undersurface. The rootstock is heavily branched, has many roots up to 8 cm thick, is juicy and can reach a mass of 2 to 10 kg. The plant is dioecious. The plain male flowers form a 3 to 9 cm long spicate inflorescence. The flowers of the very rare female plants do not fruit. The plant is vegetatively propagated by cuts. Kava-kava grows in its native areas 150 to 300 m above sea level and prefers stony soils.
Kava-kava is supposed to come originally from New Guinea and the New Hebrides. From there the plant is said to have spread across the whole archipelago of Polynesia, Melanesia and Micronesia in the course of the settlement. Today it is cultivated in large areas (43). It takes about 2 to 3 years until a plantation can be harvested for the first time.
The drug to prepare the kava-kava extract is the whole rootstock, *Kava-kava rhizoma*. Usually it consists of the peeled, cut and dried rootstock where the roots were removed in most cases. It smells mildly aromatic and little earthy. The taste is slightly bitter and also somewhat soapy (16). The drug is used as the whole, as cuts and as powder. Sometimes parts of the lateral roots, dried shoots and parts of the root bark are also used to make kava-kava extract.

Fig. 2: *Kava-kava rhizoma*
2.2 Ethnomedical Uses

Before the Europeans came the inhabitants of the smaller and larger islands of Oceania did not know any alcohol, but they had a beverage they called ‘kava’ or likewise and which they used to drink to relax body and mind. Its preparation and its consumption, however, were also the centre of a system of social ceremonies and rituals with important magic-religious aspects (43). This system has united the island communities over all the distances and ethnic differences and has continued to play a very important part in the life of the islanders even today.

Moreover the inhabitants of Oceania believe that the kava-kava plant used as a beverage prepared on a very special way has a series of healing or helpful effects. So it is said to induce and improve the sleep, to calm down the nerves, to reduce weight, to increase urination and to cure asthma, rheumatic complaints, stomach disorder, chronic cystitis, venereal diseases (16). Other sources mention positive effects on the general debility, particularly with children, headache, urination problems, upset stomach, pulmonary and renal problems and as anorectic (46) as well as obstetric agents (44). In other words, the inhabitants of the Pacific island communities regard kava-kava as a universal remedy for body and mind.
2.3 Chemistry of the Plant Substances

The constituents of the drug kava-kava determining its effects are the kava pyrones or kava lactones. They amount to about 5 to 8 per cent of the constituents. The 6 most important of these substances are the enolides kavain, dihydrokavain, methysticin and dihydromethysticin and the dienolides yangonin and desmethoxyyangonin (51). Furthermore tetrahydroyangonin and 8 less important compounds were found. The structural formulas of the 6 main kava pyrones are shown in the figure below:

![Structural formulas of some important constituents of Kava-kava rhizoma](image)

Fig. 3: Structural formulas of some important constituents of Kava-kava rhizoma
Other constituents extracted and isolated in analyses are 1 alcohol, ketones, 1 phytosterol and organic acids (30).

2.4 Preparation of the Extract, Quality Assurance and Standardisation

Only high-quality raw-plant material chosen according to the strictest criteria is selected. The extraction process is carried out using methods which avoid unnecessary damage and with continuous in-process checks in order to guarantee the best quality of the final product.

All the kava pyrones in the drug kava-kava have in common that they are nearly not water-soluble or to a very small extent only. For this reason chloroform, diethyl ether and ethanol or other solvents for lipids are used to extract them from the powdery drug.

Usually the extract (as available from ) contains up to 70 per cent kava pyrones as the total of the six main kava pyrones shown in Fig. 3. Depending on the geographic origin of the drug and according to the fact if exclusively parts of the rhizome are the raw material of the drug or if other parts of the kava-kava plant were used as well, the proportions of the individual constituents may be different in the extract (17).
Fig. 4: HPL-chromatogram of a prototype mixture of kava constituents: 1 - 3,4-dimethoxybenzaldehyde (standard), 2 - desmethoxyarginin (5), 3 - dihydrokavain, 4 - yangonin (6), 5 - kavain (3), 6 - dihydromethysticin (2), 7 - methysticin (4); (17).

Consistent quality

However, kava-kava extract is standardised to total kava pyrones, i.e. it is ‘made uniform’ by the addition of constituents or by the dilution of the extract to a defined content of constituents. Also preparations made of kava-kava extract (as available from EUROMED) are subject to a standard corresponding to the monographed daily dose (39, 51).
3 States of Anxiety, Tension and Excitedness

Anxiety is a phenomenon the definition of which is difficult, if it tries to take into consideration all its aspects. In the main it is: ‘...a mood or a feeling of oppression, of constriction and danger, a unpleasant, tense, often agonising emotional state and a negative expectation, respectively, entailing the decrease or leaving-off of the volitional and intellectual control of the own personality.’ (5).

Anxiety is regarded as a many-sided and complex phenomenon always occurring individually and it has to be considered with the biographic, personal and social background of a person (45). It comprises both psychic and physical processes and represents a severe physical and mental stress in most cases. Today every third patient coming to a general practitioner is an anxiety patient (52).

The neurotic anxiety is the anxiety for something indistinct. The causes may be found in the conditions of life of the individual, e.g. excessive demands in working life and private life, anxiety for losses etc.. It is not necessary that there is a real danger. Anxiety is already evoked by the imagination that something bad could happen.
Anxiety may be divided into primary and secondary anxieties. The states of anxiety in the case of psychic and physical basic diseases fall under the primary anxieties. Their manifoldness causes a diversity of states of anxiety. The real anxiety diseases are the primary anxieties (45). There are several diagnostic classifications giving differentiation and descriptions of the individual anxiety diseases, e.g.

- the international diagnostic classification of the World Health Organisation (WHO) ICD¹-10,
- the diagnostic classification of the American Psychiatric Association (APA) DSM²-IV
- and the psychiatric diagnostic manual DSM-III-R.

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¹ ICD: International Classification of Diseases, 10. Überarbeitung, Kapitel V (F), WHO, 1991
² DSM: Diagnostisches und statistisches manual psychischer Störungen
The primary anxieties may be divided into:

- spontaneous anxiety (panic attack, panic disorder and generalised anxiety syndrome),
- phobic anxiety (situational phobia and object phobia, e.g. arachnophobia - the fear of spiders, agoraphobia - the fear of public places, claustrophobia - the fear of narrow rooms and mysophobia - the fear of pollution),
- communication neuroses (social neurosis and sexual neurosis),
- training and job neuroses, characterised by non-attendance at school, examination, success and occupational neuroses and
- fear of losing the psychophysical integrity, among them are the fear of false diagnosis, treatment or injury, the accident neurosis and accident phobia.

Insane anxieties are treated either medicamentously and/or psychotherapeutically. However, the often used benzodiazepines lead to more or less strong side-effects, which are above all potential hazards at work and as road user on wheels and on foot in addition to headache, sleepiness, dizziness, speech and visual disturbances and muscle weakness. Furthermore unwanted interactions may occur with other medicines having an effect upon the central nervous system, such as neuroleptics, tranquillisers, antidepressants, beta-blockers, antihistaminics, sleeping drugs, analgesics or anaesthetics or particularly alcohol.
Kava-kava extract is a herbal alternative to synthetic drugs. Many patients consider that as an unwanted risk. They expect good compatibility and low risk in addition to the effect wanted when they apply the medicine for a longer period of time. The therapy with kava-kava extract (as available from EUROMED, which is a completely phylogenous product represents an alternative, where above all the anxiolytic effect is a marked feature when therapeutic doses are applied (51). It has proved to be well compatible and unwanted side-effects scarcely occurred in investigations only (10, 24, 32).

The monographed field of administration of kava-kava extract (as available from EUROMED) are nervous states of anxiety, tension and excitedness (39).
4 Pharmacology

4.1 Effects of Kava-Kava

Kava-kava is regarded as a true psychopharmacon belonging to the group of the tranquillisers (51). Apart from the ethnomedical applications and expectations in kava-kava in the regions of its traditional consumption some characteristic effects of kava-kava have turned out in several scientific investigations.

4.1.1 Anxiolytic Effects

The German Commission E monograph (of the former Bundesgesundheitsamt) states as fields of administration of the drug made of kava-kava rhizome ‘Nervous states of anxiety, tension and excitedness’. With their variousness and frequency these symptoms seem to be a characteristic feature of our time. Many psychic and somatic complaints or diseases may be both consequences and expressions of these states of anxiety (20). They can manifest themselves as sleep disturbances, muscle tensions, anxiety attacks or other kinds of spontaneous anxiety.
**General relaxation and emotional stability**

Kava-kava extract (as available from EUROMED) and preparations made from it induce a general relaxation and emotional stability so that on the one hand the nervous states of anxiety, tension and excitedness can be relieved and the secondary diseases, such as sleeplessness, overwork syndromes, muscle tensions and climacteric complaints and sexual dysfunctions, can be considerably eased off (20). Nevertheless the vigilance is not only unimpaired (51) but concentration and efficiency are positively influenced (12, 24).

**Gradually developing effect**

Contrary to the application of benzodiazepines which lead to the effect wanted very quickly the anxiolytic effect after the administration of kava-kava develops gradually and the full efficacy is only reached after about one to two weeks. That means that only such states of anxiety, tension and excitedness with psychosomatic and psychovegetative symptoms are treated with kava-kava preparations which have existed for a certain period of time already (20).

**4.1.2 Anticonvulsive and Muscle-Relaxing Effects**

One of the characteristic effects of the kava lactones on the central nervous system is their qualification to effect the relaxation of the skeletal muscles (36).
It was studied whether or not kava lactones a.o. are able to suppress experimentally induced spasms. It was found out that kava lactones at higher doses can inhibit the tonic spasms, i.e. the continuous muscular contraction, but they can intensify the clonic spasms, i.e. the short, successive convulsions of the antagonistic muscles (14).

The anticonvulsive activity of the kava lactones becomes apparent in an evident strychnine antagonism (28). Kava lactones have turned out to be much more effective against the convulsive activity of strychnine than a control (29).

In other investigations a mixture of lactones having the proportions comparable to the proportions in the kava-kava root produced a synergistic effect upon the experimental convulsion (27). The differences in the anticonvulsive effect of the individual lactones were small when injected intravenously, whereas the differences were marked when orally given. That is due to different rates of absorption. The synergistic effect of the mixture of lactones is explained as a result of its enhanced absorption.

The anticonvulsive effect of kava-kava makes it suitable for a remedy against epilepsy, particularly since the strychnine antagonism in experiments already occurs after a smaller dose of kava lactones than e.g. required to induce the muscle-relaxing activities (33).
4.1.3 Sedative and Hypnotic Effects

In addition to the result that kava-kava extracts or purified lactones induced sleep in some test animals in earlier studies (15, 25) also sedative effects were found. Because of the different experimental findings the sedative activities are discussed controversially.

EEG studies show (21) that the limbic brain structures, that means the structures controlling the vegetative processes, and especially the amygdalar complex (Nucleus amygdalae) are the main sites of action for both kavain and the kava-kava extract. This effect on the limbic structures manifests itself in the promotion of sleep without any sedation, since the kava lactones unlike the benzodiazepines and tricyclic antidepressants have no significant interaction with the gamma-aminobutyric acids or benzodiazepine binding sites in the brain (8, 21).

Other investigations (24) with the quantitative EEG, however, showed no influence of kava-kava extract on the delta and theta activities. That leads to the conclusion that kava-kava extract is neither hypnotic nor sedative, because the delta-activity increases after the addition of sedative or hypnotic drugs only.
4.1.4 Local Anaesthetic and Analgesic Effects

Kava pyrones enhance the efficacy of narcotics without being narcotic per se (33). As local anaesthetics they have similar effects as cocain and procain (37) or Benzocain (18), indicating that they act upon the central nervous system. The analgesic activities of kava lactones are proved by a series of investigations (6, 22, 23). They proved superior to aspirin, but inferior to morphine. Combined applications of kava lactones and e.g. aspirin produced synergistic effects, i.e. an enhancement of the non-opiate analgesic effectiveness (22).

4.1.5 Other Effects

The kava pyrones are said to have remarkable fungistatic effects on some pathogenic fungi. However, there is still some uncertainty as to the mode of action (9, 41).

Kava pyrones have a neuroprotective effect, that means they inhibit destructive processes which can be induced by oxygen deficiency in the brain. Animal tests were conducted to investigate whether or not kava pyrones have neuroprotective effects similar to those of anticonvulsants and local anaesthetics (1, 2). Methysticin and dihydromethysticin protect the brain tissue against ischaemic damage, whereas kavain, dihydrokavain and yangonin did not show any effects.
4.2. Pharmacokinetics

Kava-kava extract is a mixture of the different kava pyrones as they are obtained from the rhizome of the kava-kava plant. Pharmacological investigations show that kava lactones are more bioactive and more effective when they are administered orally as a complex and not as isolated compounds (4, 13).

On the one side the proportions of the different kava pyrones in the extract have a great influence on their solubility and this way on the other side on their absorption from the intestinal tract as well (7). From there they get to the brain tissue via the blood circulation.
Since kava pyrones are nearly insoluble in water the investigations on the metabolism of the different kava pyrones were conducted with kava pyrones solved or suspended in vegetable oils. Absorption and elimination are different for the individual kava pyrones. Trials showed (28) that kavain and dihydrokavain were absorbed from the digestive tract of the test animals already within 10 to 15 min and eliminated from the organism in 1 hour at the most, whereas both the processes took much more time for methysticin and dihydromethysticin. Obviously there were also differences in the kinetic of the kava pyrones depending on the way of application (35). The elimination from the organism takes place via kidneys and intestinal tract. According to Rasmussen (41) the number of metabolites also increases with increasing absorption, but a part of the kava pyrones is discharged unaltered by urine or faeces. Metabolites cannot be found in the faeces, but in the urine. (41).
5 Toxicology

According to investigations by Warnecke (48, 50) any intoxications could not be observed at daily doses of 60 to 120 mg kava lactones as recommended by the monograph of the German Commission E and an application period not exceeding 3 months. Only when the drug is taken for a longer period or with excessive or chronic abuse of kava-kava dyschromia or allergic cutaneous reactions in the form of skin scales may occur, especially on the back. These phenomena will disappear when the application of kava-kava is stopped. Other studies at doses not exceeding the recommended amount of the drug did not give proof of any chronic toxicity as well (34).
6 Human Pharmacologic Studies

In a single-blind study a group of 6 healthy test persons was given a standardised kava-kava extract and the effects on the general perceptive performance and the emotional condition were investigated against placebo (24). It was found out that kava-kava extract stabilised the perceptive performance and the emotional condition. The EEG changes were comparable to those occurring with other anxiolytic preparations but they did neither indicate any sedation or hypnotic effect at the tested dose nor did they indicate any side effects.

Herberg (19) applied a kava-kava extract standardised to 70 per cent kava lactones in a placebo-controlled double-blind study to assess the effect of the extract given to 20 healthy men and women each between 18 and 60 years on the safety-related performance capability when driving a car or operating machines. The extract was given for 15 days in daily doses of 3 x 100 mg and then a.o. reactivity, concentration, vigilance and motility were tested.

There were no remarkable differences in the tested performance features or in the subjective conditions of the test persons with kava-kava extract or with placebo.
The effects of the benzodiazepine drug oxazepam and of a standardised kava-kava extract on 12 healthy probands were compared in a double-blind crossover study (40). Oxazepam resulted in a significant decrease in the quality and speed of the reactions, whereas no changes were found after kava-kava treatment. On the contrary a memory test using word recognition indicated a tendency for kava-kava to improve reaction time and the number of correct answers. Oxazepam application, however, significantly slowed reaction time and reduced the number of correct answers.

Fig. 4: Comparison of correctly classified old and new words. In the placebo condition the old words are associated with a more positive waveform beginning at about 250 ms. On the basis of the scalp distribution, the old/new effect can be attributed to the modulation of two components. In the oxazepam condition, the reduction of a negative component in the 250 to 450 ms range is the most prominent finding for both old and new words. The kava condition is characterised by a more pronounced positivity to the old words. Straight line = new words; dashed line = old words (40).
7 Proof of Clinical Effectiveness

Two groups of 20 patients each suffering from climacteric syndromes were given 2 capsules daily of a kava-kava preparation or a placebo for 12 weeks in a randomised placebo-controlled double-blind study (50). In addition to the diaries of the patients and other examination criteria the breaking off of the therapy or the possibility to reduce the dosage were important indicators of the success. About half of the patients of the test group could reduce the daily dose to 1 capsule after the sixth week corresponding to a mean dose of 43.5 mg/d total kava lactones. The initial findings in the test group had highly significantly changed already after a third of the test period. 14 of the 20 women of the control group had stopped the therapy due to lack of effectiveness up to the end of the test period, whereas only 2 patients of the test group had left the investigation.

In a further investigation (50) two groups of 20 patients each with neurovegetative symptoms associated with menopause were treated with a standardised kava-kava extract in a randomised placebo-controlled double-blind trial. In general the treatment was well tolerated and resulted in a significant decrease of the states of anxiety and depression and of the severity of the menopausal symptoms as well as to an increase of the subjective well-being of the probands.
In a randomised placebo-controlled double-blind study with 58 patients between 18 and 60 years Kinzler et al. (26) investigated the effects of a treatment with standardised kava-kava extract on states of anxiety, tension and excitedness of non-psychotic origin for four weeks. The criterion of the improvement was the Hamilton-Anxiety-Scale (HAMA). Already one week after the beginning of the investigations a significant improvement has been noticed in the assessments for anxiety and depression. These improvements continuously increased up the end of the test period without being accompanied by any adverse effects.

Fig. 5: Hamilton-Anxiety-Scale, Total Score (mean values), Left column: Kava-Extract, Right column: Placebo (according to 26)
Two groups of 29 patients each with anxiety syndromes were given daily doses of 100 mg kava-kava extract or placebo for 4 weeks in a more recent placebo-controlled double-blind study (31). The patient were very similar in age, height, weight and duration of the disease. The clinical effectiveness of the kava-kava extract and its compatibility were assessed a.o. by the Hamilton-Anxiety-Scale (HAMA) and by the Clinical Global Impression Scale (CGI) after the first, second and fourth weeks. Already after 1 week differences were found in the two groups with respect to the parameters investigated, which increased up to the end of the test period. The HAMA-scores were actually unchanged in the placebo group, whereas the improved significantly in the kava-extract group.

According to the assessment criteria of the CGI the majority of the patients of the kava-extract group could be classified as only ‘slightly ill’ at the end of the investigations. The majority of the placebo group, however, had to be classified as still ‘markedly ill’. There were no unwanted reactions to the kava-kava extract treatment.

The conclusion is that kava-kava extract is well qualified to be taken for the treatment of states of anxiety, tension and excitedness by the general practitioner.
Volz conducted a randomised placebo-controlled double-blind study with kava-kava extract for a period of 6 months (47). He investigated the effectiveness of kava-kava extract at a dosage of 210 mg/d kava lactones with 100 patients suffering from nervous states of anxiety, tension and excitedness. The most important parameter was the difference of the total scores according to the Hamilton-Anxiety-Scale (HAMA) in the course of the investigation period. The result was a significant superiority of the kava-kava treatment in comparison to the placebo group. The kava-kava treatment markedly increased both the somatic anxiety and the panic anxiety and influenced the depression positively as well.

Woelk et al. (53) compared the effect of a daily dose of 210 mg kava pyrones with the effects of 15 mg/d oxazepam or 9 mg/d bromazepam in a double-blind comparative study for more than 6 weeks. The results of all the three groups showed no significant differences with respect to the improvement of the anxiety symptoms treated.
Fig. 6: Course of the Hamilton-Anxiety-Score (HAMA) during a 6-week treatment with a kava extract corresponding to a dose of 210 mg/d kava pyrones compared with 15 mg/d Oxazepam and 9 mg/d Bromazepam (52).

Bhate (3) showed that even higher kava lactone doses can be given in acute states of anxiety, e.g. before operations. He gave 60 mg kava lactones in the evening before the operation. This was repeated 1 hour before the anaesthesia. This way he reached a significant anxiolysis.

The results prove kava-kava extract to be an effective agent to remedy states of anxiety, tension and excitedness. It is most suitable to replace the benzodiazepine tranquillisers.
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