

KAVA REPORT 2003

IN-DEPTH INVESTIGATION INTO EU MEMBER STATES MARKET RESTRICTIONS ON KAVA PRODUCTS

PART II A

Expert Report on the Clinical Documentation of Kava Kava (*Piper methysticum*)

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A Profile of Kava kava

a) Qualitative composition

According to the phytotherapeutic definition, the total extract of the rhizome of *Piper methysticum* (Piperaceae) is regarded as the active ingredient.

b) Mode of action

Piperis methystici rhizoma acts anxiolytic. In animal experiments a potentiation of narcosis (sedation), anticonvulsive, antispasmodic, and central muscular relaxant effects were described. An interaction with GABA-receptors and an inhibition of platelet MAO-B is being discussed [8, 39, 75].

The effects of Kava-Kava are not immediate but become apparent after two weeks of treatment.

The main effective components of *Piperis methystici* rhizoma are the kava pyrones. The six major kava pyrones are kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin [3, 14, 15, 24, 26, 27, 28, 47, 66].

c) Preparations used in medicine

Kava is traditionally prepared by grinding and mixing the root or root bark with cold water. This makes an emulsion that is a suspension of the resinous constituents in water. The herb is also prepared as an emulsion in coconut milk. The efficiency of extraction of the active constituents, which is measured by kavalactones extraction into water, varies considerably but is higher from fresh material than from the dried plant. Kava consumed in Vanuatu is reputed to be the strongest anywhere in the South Pacific. The bioavailability of kava constituents varies substantially, depending on the method of extraction. It is thought that the increase in potency is partly the result of preparing the drink from the raw fresh roots, whereas in Fiji and elsewhere, it is made from dried rootstock (Lebot *et al.*, 1997). In Europe kava is predominantly available as a concentrated standardized extract that is designed to maximize the extraction of kavalactones. The extraction is performed either by ethanol or acetone and the content of kavalactones used in kava containing products range from 10 to 70 %. Comparisons of traditional water-based South Pacific kava preparations with those alcoholic extracts used in Europe showed that the European preparations contain considerably lower doses of kavalactones than the traditional forms [46].

d) Indications

In the monograph of *Piper methysticum*, the German Commission E recommended the use of kava kava for conditions of nervous anxiety, stress, and restlessness.

e) Dosage

Kava kava extracts are commonly standardised to its content of kavapyrones, which have been identified as its main active ingredients. In the monograph for kava radix the German Commission E recommends a daily dosage of 60 to 120 mg of kavapyrones for the treatment of conditions of nervous anxiety, stress, and restlessness. In the past, higher dosages of up to 280 mg of kavapyrones were frequently used in medicinal practice.

B Expert Report

Introduction

In June, 2002 the BfArM (German Federal Institute for Drugs and Medical Devices) issued an official letter immediately revoking the marketing authorisation of kava containing products, including homoeopathic preparations up to a concentration of D4. In this letter the BfArM declared that this measure is based upon a revised benefit-risk ratio, mainly resulting from 37 suspected cases of severe adverse effects on liver function. The institute stated that after an evaluation of research data the efficacy of kava kava cannot be regarded as approved, and that a high risk of “severe, life threatening adverse effects on the liver” has to be expected with its intake.

The purpose of this expert report is to critically review and objectively cite or summarize all available published documentation concerning the clinical efficacy and safety of medicines containing *Piperis methystici* rhizoma (kava) extract. This report, carried out by the independent expert, will only summarize and evaluate relevant published data concerning kava and based upon this information draw conclusions and draft recommendations. It will not comment on or judge the decision taken by the officials of the German Federal Institute for Drugs and Medical Devices or other health authorities, nor it will refer to it. In paragraph 4. (conclusions) the expert will briefly summarize the results of the available data, evaluate them, and state his conclusions on the **therapeutic justification** (paragraph 4.1.), **efficacy** (paragraph 4.2.), **safety** (paragraph 4.3.), **dosage** (paragraph 4.4.), **benefit-risk ratio** of kava kava and give a brief statement of his **expert opinion** (paragraph 4.4.) on the use of kava kava in the claimed indication.

This report was based upon published literature relevant to kava kava or kava-containing products. The results of literature searches in the database DIMDI and the private database Phytodok, Berlin, Germany, have been used up to January 2003. Articles in peer review journals have also been used as well as official documents not published in journals, if they were available and of importance. The origin of the data used for the detailed case analysis in paragraph 3.2 (Safety, Case Reports) will be cited separately in the introduction of the case analysis.

1. Problem Statement

Anxiety disorders are probably the most common of the psychiatric disorders. Community surveys, in Great Britain, suggest that at any one time 3 – 5 % of the adult population suffer from generalised anxiety or panic disorder. However, many more suffer lesser degrees of anxiety, usually related to stresses in the environment. At least 15 % of the patients attending general practitioners seek treatment for these symptoms [44]. A German survey suggests a lifetime prevalence of anxiety disorders of approx. 14 % [40]. The U.S. National Co-morbidity Survey suggests a 1-year prevalence of anxiety disorders of 17 % and a lifetime prevalence of almost 25 % [59].

A long list of disorders falls under the rubric of anxiety disorders. The diagnostic criteria for generalised anxiety disorders emphasise that worrying about life situations produces unrealistic or excessive anxiety. This contrasts with stress related anxiety, in which the anxiety is proportional to the adverse circumstances. In panic disorder, the panic attacks are unexpected – that is, not related to a phobic situation [44].

Two different classification systems are commonly used for diagnosis: the “Diagnostic and Statistical Manual of Mental Disorders” (DSM) of the American Psychiatric Association (APA), and the “International Statistical Classification of Diseases and Related Health Problems” (ICD) of the World Health Organisation (WHO). The most current revisions of these classification systems are the DSM-IV (only differing slightly from DSM-III-R) and the ICD-10. They classify anxiety disorders in slightly different ways. According to the DSM-III-R six major categories of anxiety are distinguished: specific and social phobias, panic disorder, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder and generalised anxiety disorder. The ICD-10 distinguishes between phobic disorders (agoraphobia without panic disorder, agoraphobia with panic disorder, social phobia, specific phobia, other phobias, not further described phobias), other anxiety disorders (panic disorder, generalised anxiety disorder, anxiety and depressive disorder - mixed, other mixed anxiety disorders, other further described anxiety disorders, not further described anxiety disorder), and reactions to severe stress and adjustment disorder (combination of adjustment disorder, anxiety and depressive reaction).

According to the therapeutic point of view, a separation of three clinical pictures within the anxiety disorders is useful: generalised anxiety disorder, panic disorder, and phobia. The following are diagnostic criteria for general anxiety disorder according to DSM-III-R: motoric tension (shivering, twitching, or trembling; muscle tension, pain, or hypersensitivity; restlessness; exhaustion), vegetative hyperexcitability (dyspnoea or constriction; palpitation or tachycardia; sweating or cold, wet hands; mouth dryness; obnubilation or vertigo; nausea, diarrhoea, or other abdominal complaints, abdominal and lower abdominal pain; hot flushes or chilliness; pollakisuria), and hyper-vigilance and heightened alertness (being tense or “always about to do something”; excessive nervousness; poor concentration or “blackout”; poor sleep quality; irritability) [40].

90 % of the patients suffering from anxiety disorders call on a general practitioner. 20 % of them are in need of treatment because of psychological disorders. Only 10 % of them are referred to a neurologist, and only 7 % tell their practitioner about their psychological complaints [81]. In the majority of cases anxiety is treated by general practitioners. For many years these benzodiazepines were the stock treatment for anxiety, but in the course of time their side effects and dependence potential have led many physicians to lessen or eschew their use. Instead, a variety of other treatments are being tried [44]. The medical compounds typically used in the therapy now range from antidepressants, such as selective serotonin reuptake inhibitors (SSRI) or monoamine oxidase inhibitors (MAOI), benzodiazepines, buspirone and anticonvulsants to antipsychotics. These compounds are most commonly prescribed by physicians, but are associated with severe adverse effects such as restlessness, insomnia, sexual dysfunction, hyponatremia, increased bleeding, decreased coordination, nervousness, lethargy, seizures, dependence, sedation, and memory impairment [11, 59]. Another limiting factor in the use of these agents is the occurrence of withdrawal reactions after the end of the treatment, especially after long-term treatment.

Recent data from the United States suggest that patients with anxiety disorders, due to the adverse effects of synthetic drugs, more frequently use alternative therapies [59]. Kava kava represents one of the plant-based alternative therapeutic options in the treatment of anxiety disorders [45, 59]. The spectrum of efficacy of kava products is comparable to that of benzodiazepines but without the development of tolerance or withdrawal symptoms/potential for dependence [63]. Kava extract formulations have passed the stage of uncertain efficacy. The clinical data available imply that kava extract is superior to placebo as a symptomatic treatment for anxiety [59].

2. Clinical Pharmacology

2.1 Active Ingredient

Analysis of various kava root extracts has yielded a spectrum of chemical components with pharmacological activities. The leading active substances for identification and standardisation are the kavapyrones. Kavapyrones are considered to be the main active ingredients of *Piperis methystici* rhizoma. So far 18 kavapyrones have been isolated [29], six of which constitute the major and pharmacologically important constituents: kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin. The amount of the single pyrones varies according to the origin of the drug. Chemically, the six major kavapyrones belong to two slightly different categories: kavain, dihydrokavain, methysticin, and dihydromethysticin have only one double bond in the pyrone ring and are therefore called enolids. Yangonin and desmethoxyyangonin have two double bonds in the pyrone ring, which makes them dienolids. This slight difference in chemical structure leads to minor differences in the pharmacodynamical effect of kavain, dihydrokavain, methysticin, and dihydromethysticin on the one hand, and yangonin and desmethoxyyangonin on the other [3, 14, 15, 24, 26, 27, 28, 47, 66].

2.2 Pharmacodynamics

A pharmaceutical special extract from kava rhizomes, standardised to 70 % kavapyrones, WS 1490, has been subjected to comprehensive clinical trials in recent years. Human pharmacological studies confirm its cerebral bioavailability and the pharmacological activity of the active substances in the extract (computer-assisted pharmacological EEG investigations). Studies with voluntary participants show that vigilance, concentration, mental retention, attentiveness and reaction capacity are in no way restricted. On the contrary, there is evidence that WS 1490 increased reaction and concentration faculties in study participants [23].

A single blind pilot study with healthy volunteers (2 male, 4 female, age: 24 – 47) was carried out in order to determine the neurophysiologic efficacy (quantitative EEG, evoked potentials) and the effects of the kava extract WS 1490 on emotional and general variables concerning personality, on the subjective state as well as on various cognitive parameters. After a one-week wash out phase the volunteers received placebo for the first week, WS 1490 300 mg/day for the second week, and WS 1490 600 mg/day plus placebo for the third week. The fourth week was used for follow-up observations. Capsules were given 3 times daily before meals.

Examinations took place on days 0, 7, 14, 21 and 28. The quantitative EEG showed an increase in the β -/ α -index typical for the pharmaco-EEG profile of anxiolytics. The increase in the β -activity was most pronounced in the β_2 -range. Kava extract WS 1490 showed no sedative-hypnotic effects after administration of 600 mg. The results of the evoked potential studies indicate that information processing may be improved in the cortical areas studied, i.e., vigilance is increased. These findings correlate with the results of the psychometric tests, which indicate increased activity and an improvement in emotional stability [38].

The effects of oxazepam and a standardised extract of kava rhizomes, WS 1490, were investigated for reaction time and event-related potentials (ERPs) in a visual search paradigm on healthy young males ($n = 12$, age: 24 – 37) using a double-blind design. Three types of medication were administered: placebo, WS 1490 3 x 200 mg/day for 5 days, and oxazepam 1 x 15 mg on the day before testing, 75 mg on the morning of the experimental day. Participants took one capsule three times daily for five days prior to the experimental session. For the oxazepam subjects, only the final capsules contained active substances, while the others were identical to placebo. Significant effects were obtained with oxazepam in a number of psychometric tests as well as search time and quality. Several ERP components of different latency, topography and functional significance were affected by the medication. Oxazepam led to a reduction of the amplitude of the parietal N1, frontal N2, posterior contralateral N2, and occipital P3 components. WS 1490 was associated with a greater posterior N1, posterior contralateral N2, and occipital P3. The authors value those findings as evidence of a positive effect of kava extract on the allocation of attention and processing capacity [30].

Twelve healthy volunteers were tested in a double blind, cross-over study to assess the effect of oxazepam and an extract of kava roots, WS 1490, on behaviour and event-related potentials (ERPs) in a recognition memory task. The subject's task was to identify within a list of visually presented words those that were shown for the first time and those that were being repeated. The repeated words were associated with an increased positivity beginning approximately 250 ms post stimulus. Oxazepam led to a reduction of a negative component in the 250 – 500 ms range for both old and new words and to a reduction of the old/new difference in the ERP associated with a significantly worse recognition rate. Kava on the other hand showed a slightly increased recognition rate and a larger ERP difference between old and new words. The authors summarise that hypotheses about the mechanisms of action of the two drugs can be derived from the ERP patterns, suggesting a deficiency in the generation of an internal code for the word stimuli in the case of oxazepam and an influence on later stages possibly related to conscious recollection in the case of kava [56].

In a controlled, double-blind, randomised 3-armed study 12 healthy volunteers received single doses of either one tablet Antares 120 (kava rhizome extract standardised on 120 mg kavapyrones) or one tablet diazepam 10 mg or one placebo tablet. All tests were done immediately before as well as 2 and 6 hours after application of the preparations. The washout period between cross-over was seven days. After application of Antares and diazepam the EEG showed an increase in the relative intensity of α -waves, which was recorded in the occipital area for both preparations, and in the frontal area only for Antares. Maximum effects were often recorded 2 hours after application of diazepam. However, the kava preparation, showed the most distinct effects after 6 hours. A benzodiazepine-specific increase in beta-activity was not recorded for the kava preparation. During the observation period the placebo group showed a time-dependent decrease of the relative intensity in the zone of the α -waves. The marked beta-activity in the diazepam group is the result of frequent significant differences between the two test preparations. In psychophysiological tests the critical flicker frequency was more distinctly reduced by Antares and diazepam than by placebo. As opposed to these results, the volunteers showed significantly better results in the PAULI test ($p < 0.001$), the simple reaction time test and the complex multiple-choice reaction test 2 hours after application of Antares ($p < 0.01$). For diazepam and placebo an improvement of performance could not be statistically proven [21].

In a double-blind, placebo-controlled study the encephalotropic and psychotropic effects of kavain, one of the major pyrone components of kava, as compared with clobazam, were investigated, utilising EEG brain mapping as well as psychometric

and psychophysiological analyses. 15 healthy volunteers received randomised single oral doses of placebo, 200, 400 or 600 mg kavain as well as 30 mg clobazam as reference compound at weekly intervals. EEG recordings, psychometric tests, evaluations of pulse, blood pressure and side effects were carried out at the hours 0, 1, 2, 4, 6, and 8. Brain maps of drug induced pharmaco-EEG changes (pharmaco-EEG maps) demonstrated that kavain exerted a significant action on the human brain function as compared with placebo characterised by a dose-dependent increase of delta, theta and alpha 1 activity, while alpha 2, beta activity and the centroid of the total activity decreased. These findings are indicative of a sedative action, which was, however, in type quite different from that of the 1.5-benzodiazepine. The latter produced a decrease of delta, theta, alpha 1 and alpha 2 and an increase of beta activity while the total centroid was accelerated. Interestingly, 200 mg kavain also induced vigilance promoting effects with a decrease of delta and beta activity and an increase of alpha activity and total power. Psychometric tests also demonstrated clear differences between the two compounds on behaviour.

Kavain improved the noopsyche as compared with placebo at all three dosages as there was a significant improvement in intellectual performance (PAULI test), attention, concentration, reaction time and motor speed (rigidity test), while opposite findings were observed after 30 mg clobazam. In regard to thymopsychic variables such as drive, wakefulness, affectivity, mood, well-being, 200 mg kavain produced an improvement when compared to placebo while 600 mg kavain produced sedation, as did 30 mg clobazam. Psychophysiological tests resulted in only minimal results. Topographically, most encephalotropic effects after administration of kavain were found in the frontal area, after administration of clobazam in the central and parietal areas [61].

A study examined the influence of the kava extract WS 1490 on sleep quality in healthy volunteers versus placebo. Two groups with 6 volunteers each (3 female, 9 male, average age group A: 27.5 ± 2.4 years, group B: 24.5 ± 1.7 years) received a capsule three times daily on four consecutive days. Treatment of group A: placebo on days 1, 3 and 4; 3 x 50 mg WS 1490 on day 2. Treatment of group B: placebo on days 1, 3 and 4; 3 x 100 mg WS 1490 on day 2. A polygraphic sleep-EEG with electromyographies and electro-oculography was recorded on nights 1, 2 and 4. The quality of sleep and the subjective state were recorded daily in a questionnaire. After 3 x 50 mg or 3 x 100 mg kava extract the amount of sleep spindles and the percentage of deep sleep increased, REM-sleep did not change, sleep stage 1 and sleep latency tended to decrease. The subjective sleeping time increased. The authors conclude that the kava extract WS 1490 might have an effect similar to chemical tranquillizers concerning spindle denseness in the sleep-EEG. Furthermore, kava extract positively influences sleep in general, mainly by increasing slow wave sleep (while REM sleep remains unchanged) and decreasing sleep latency [16].

2.3 Pharmacokinetics

According to the “Final Comments and proposal for revision of Part 4 of Annex to Council Directive 75/318/EEC of 20 May 1975 ‘Clinical Documentation’” (EMEA/HPWG/13/99) pharmacokinetical studies are not required for complex mixtures of active substances. However, some studies have been done on urinary metabolites of kava or of one of its major components, kavain.

Methane chemical ionization (CI) gas chromatography-mass spectrometry (GC-MS) has been used to identify some of the human urinary metabolites of the kavapyrones following ingestion of kava prepared by the traditional method of aqueous extraction of *Piper methysticum*. Commercial pulverised kava rhizome (450 g) was immersed in water (3 l) at room temperature and after squeezing (5 min) the beverage was obtained, which was consumed by healthy male subjects in about 100 ml aliquots. Typically 1 litre was consumed over a period of about 1 hour before sleeping and no physiological effects were apparent after consumption of this dosage. Urine samples were collected before sleep and again in the morning. All major, and several minor, kavapyrones were identified in human urine. Observed metabolic transformations include the reduction of the 3,4-double bond and/or demethylation of the 4-methoxyl group of the α -pyrone ring system. Demethylation of the 12-methoxy substituent in yangonin (or alternatively hydroxylation at C-12 of desmethoxyyangonin) was also recognised. This product was isolated by high-performance liquid chromatographic analysis of crude urine extracts and characterised by methane CI GC-MS. No dihydroxylated metabolites of the kavapyrones, or products from ring opening of the 2-pyrone ring system, were identified in human urine [13].

The urinary metabolism of D,L-kavain was studied in humans after oral application. Urine was collected for 24 hours from 5 healthy volunteers after an oral dose of 200 mg of D,L-kavain (Neuronika). The urine samples were stored at -20°C prior to analysis. Ten metabolites of kavain could be identified by gas chromatography-mass spectrometry with electron impact and chemical ionization. The main metabolic pathways were hydroxylation of the phenyl ring, reduction of the 7,8-double bond, hydroxylation of the pyrone ring with subsequent dehydration and opening of the pyrone ring. The metabolites were mainly excreted in the form of their conjugates [43].

The metabolic profile of D,L-kavain and its metabolites has been evaluated in a pilot study with 4 healthy male volunteers. In a cross-over design the volunteers received as a single dose 400 mg (2 x 2 capsules) Neuronika under fasting conditions and 0.5 hours after breakfast, and 400 mg of two experimental formulations. Kavain (M0) and some of the main kavain metabolites in plasma were measured by a new method and tentatively identified as follows: 4'-OH-kavain (M1), 4'-methoxy-kavain (M2) and 4'-OH-kavain-sulfate (M1-s). The metabolites' mean time to peak – 1.6 h (M1), 3.0 h (M2), 2.4 h (M1-s) – showed no or only a slight delay relative to that of M0 (1.5 h) suggesting rapid formation of metabolites. The mean peak concentrations were 277.7 ng/ml (M1), 61.0 ng/ml (M2), 1402.5 ng/ml (M1-s) and 49.5 ng/ml (M0). The mean apparent half-lives of elimination for the identified metabolites M1, M2 and M1–

s were 6.7, 6.2 and 8.1 hours, respectively, that of the parent compound M0 was 4.3 hours.

The metabolic ratios as calculated from the AUC of the metabolites divided by the AUC of kavain were as follows: M1/M0: 8.2, M2/M0: 3.8 and M1-s/Mo: 107.7.

According to the authors the results showed that kavain is extensively metabolized by phase I aromatic hydroxylation at the 4'-position (total metabolic ratio \approx 118) and subsequently converted by phase II reactions to the more water-soluble sulfo-conjugate (metabolic ratio \approx 105) [12].

In yet another study on D,L-kavain, plasma (acetonitrile extract) and urine of subjects receiving up to 600 mg kavain (Neuronika) were screened for metabolites using reversed phase HPLC and photodiode array detection. In human plasma some of the main metabolites were identified as 4'-OH-kavain-sulfate, 4'-OH-kavain and 4'-methoxy-kavain by comparison of the UV-spectra and retention times of the metabolites with that of reference compounds, which were chemically synthesized. Traces of dehydrokavain and other minor metabolites could be detected in human plasma. In human urine only traces of kavain, 4'-OH-kavain and dehydrokavain were found. The main metabolites in urine were 4'-OH-sulfate and other as yet unidentified polar metabolites [36].

2.4 Bioavailability/Bioequivalence

Information on bioavailability/bioequivalence is not available. According to the "Final Comments and proposal for revision of Part 4 of Annex to Council Directive 75/318/EEC of May 20 1975 'Clinical Documentation'" (EMEA/HPWG/13/99) bioavailability/bioequivalence studies are not required for complex mixtures of active substances.

2.5 Interactions

Interactions of kava kava have been reported with CNS-active drugs, caffeine and alcohol. Most of case reports showing interactions are doubtful or discussed controversially. The case reports and referring studies will be analysed in the following paragraph.

Interaction with benzodiazepines

A case report has shown that kava extracts may interact with certain benzodiazepines causing a semicomatose state. A 54 year old man was hospitalised in a lethargic and disoriented state. His regular medication included alprazolam, cimetidine, and terazosin. His vital signs and results of laboratory studies were

normal. His alcohol level was negative, and a drug screen was positive for benzodiazepines.

He became more alert after several hours and stated that he had been taking kava for the past 3 days but denied overdosing on the kava or alprazolam.

Pharmacological studies indicate additional effects between kava α -pyrones, pentobarbital, and pregnane steroids (see Expert Report on the pharmacological-toxicological documentation).

These investigational studies suggest that kava might have additive effects with benzodiazepines, given that they act on the same receptor and on the same areas of the central nervous system. The authors believe that these findings may explain the mechanism governing the possible interaction between kava and alprazolam [1].

However, a study conducted to investigate the possibility of interactions of kava with benzodiazepines clearly demonstrated that kava extracts and benzodiazepines do not show additive interactions. The aim of the study was to investigate whether effects on basic performance aspects other than those to be anticipated with the individual substances can be expected when bromazepam (2 x 4.5 mg/d) and a kava extract (2 x 120 mg kavapyrones) are administered simultaneously. These basic performances included accuracy of perception, concentration, reaction speed, vigilance, stress tolerance and motor coordination. These skills were tested in 18 healthy volunteers (6 male, 12 female, mean age 46.6 ± 6.5) in a sequential, balanced, cross-over trial using a computer-assisted test procedure. Assessments were made prior to, and on the second and third and 14th day of treatment. Secondary variables used were parameters of tolerability (well-being scales, adverse reactions). Statistically significant differences (in some cases highly significant) were observed in 3 performance areas after medication. Performance in the fields of stress tolerance, vigilance and motor coordination remained at the baseline level with kava extract, whereas bromazepam as well as the combination impaired stress tolerance and motor coordination over the whole period, and vigilance in the initial phase of treatment (days 2 and 3). Accuracy of perception, concentration and speed of reaction to simple signals remained unchanged throughout. There were no differences between bromazepam treatment and treatment with the combination. The main differences in the well-being scales occurred between kava and the combination, but there were also occasional differences between bromazepam and the combination. The authors state that in principle the least impairment of general health occurred with kava and the relatively greatest impairment was found with the combination. However, as the treatment with the combination was very similar in effect to the treatment with bromazepam, there are no definitive indications of additive interactions between the two substances [33, 34].

Interaction with alcohol

The kava extract WS 1490 (3 x 100 mg/d over a period of 8 days) was tested in a placebo-controlled randomised double-blind study to establish whether it has any adverse effects on safety-related performance when administered simultaneously with ethylalcohol (0.05 % blood alcohol concentration). The study was carried out as a comparison of two independent groups, each containing 10 male and 10 female healthy volunteers between 18 – 60 years of age (mean: 40.45 ± 12.2). Performance tests consisted of seven procedures: accuracy of perception, permanent concentration, reaction to acoustic stimuli, choice-reaction, vigilance, stress tolerance and motor coordination. Secondary variables used were parameters of tolerability (well-being scales, adverse reactions). Assessments were made on days 0, 1, 4, and 8. The results showed that no negative additive or multiplicative effects were caused by the kava extract when simultaneously taken with alcohol. There even was a remarkable advantage of the WS 1490 group on the 4th day of treatment in the concentration test ($p < 0,01$) [32].

Interactions with caffeine

One case report of a 29 year old man who had experienced a rhabdomyolysis after ingesting a herbal combination product consisting of 500 mg guarana, 200 mg of ginkgo and 100 mg of kava was published by Donadio *et al.* (2000). The patient suffered from severe muscle pain, passed a dark urine a few hours after having consumed the preparation. His blood creatine kinase and myoglobin values were considerably elevated without showing signs of an underlying metabolic myopathy. His condition improved within six weeks. Regarding the amount of caffeine ingested with the herbal preparation, a causal relation of the above mentioned symptoms and the concurrent intake of caffeine and kava appears at least doubtful. Estimating a content of 8 % caffeine in guarana, the corresponding dosages of one tablet of the preparation would be about 40 mg, which is equivalent to one to two cups of coffee or tea. On the other hand one of the tables contains about 4 mg of kavalactones, which is a 30 times less than kava preparations dosed according to the monograph of the German Commission E for kava kava. Therefore, if this relation between caffeine and kava preparations is probable many more case reports of interactions should have been published in the past.

3. Clinical Experience

3.1 Efficacy

Kava has been a popular medicinal herb for hundreds of years in the island communities of the Pacific Ocean and can be regarded as a traditional medicine. The relaxant effect of *Piper methysticum* became known to Europeans in the 18th century. Since then extensive research on the pharmacodynamical properties of kava was done, investigating the modes of action of this drug. A multitude of clinical trials has been carried out during the past 20 years to investigate the anxiolytic effect of its extracts. Reliable clinical evaluations do exist and will be quoted later on in this expert report. Most, if not all, scientists investigating kava favour the opinion that it is not one single constituent responsible for the efficacy of kava extract, but the synergy of various constituents, known as the kavapyrones [3, 14, 15, 24, 26, 27, 47, 66].

The efficacy and safety of kava extracts in the treatment of conditions of nervous anxiety, stress, and restlessness was investigated in 11 randomized, placebo-controlled, double-blind trials and one controlled trial with reference therapy (bromazepam, oxazepam) including about 1000 patients. In a systematic review and meta-analysis 7 of these trials were critically reviewed. Furthermore, the results of six non-controlled studies including more than 10 000 patients have been carried out. These controlled and non-controlled studies will be critically reviewed and in the following paragraphs.

3.1.1 Methods

The subjective and objective evidence of the efficacy of kava extract is mainly provided by means of the HAMILTON Anxiety Scale (HAMA) and the Clinical Global Impression Scale (CGI) as well as several other types of questionnaires and self-rating scales.

3.1.2 Meta-Analysis

Pittler et al. (2000) [59] provided a systematic review and meta-analysis aimed at assessing the evidence for or against the efficacy of kava extract as a symptomatic treatment in for anxiety. Only double-blind randomized placebo-controlled trials of oral treatment for the treatment of anxiety, without restrictions referring the language of publication, were included in this meta-analysis. Trials not performed using kava mono-preparations were not included.

Seven [2, 42, 48, 67, 76, 78, 79] trials met the criteria and were included in the review and meta-analysis, six of which [2, 42, 67, 76, 78, 79] scored at least 3 of 5 possible points on the scoring system assessing methodologic quality. Three of these studies (Kinzler *et al.* 1991 [42], Volz & Kieser 1997 [76], Warnecke 1991 [79]), were homogenous in terms of drug quality (210 mg of kavolactones daily), reported the HAMA score as their main outcome measure and include patients only if the total score on the HAMA scale at baseline was 19 or greater and thus could be included in the meta-analysis. All of these trials revealed weighted mean differences that favoured kava extract over placebo. Their 95 % confidence interval did not overlap the zero effect size, indicating a significant difference. The data of these studies show a significant difference in the reduction of the HAM-A total score from baseline in favour of kava extract compared with placebo (weighted mean difference: 9.69; 95 % confidence interval: 3.54-15.83). The studies of Warnecke *et al.* 1990 [79], Singh *et al.* 1997 [67], Bhate *et al.* 1989 [2] and Lehmann *et al.* 1996 [48] that have not been included into the meta-analysis for not being comparable (other inclusion criteria, other main outcome measures or different drug quality) also demonstrated a significant reduction of anxiety in patients treated with kava extract. Three of those (Singh *et al.* 1997 [67], Bhate *et al.* 1989 [2] and Lehmann *et al.* 1996 [48]) reported significant intergroup differences in favour of kava extract and one (Warnecke *et al.* 1990 [79]) stated beneficial effects compared with baseline findings. Adverse effects as stomach complaints, restlessness, drowsiness, tremor, headache and tiredness are reported by patients receiving kava extract in 5 of seven trials. In two of these 7 studies no adverse effects were observed. Evaluating the results of their review and meta-analysis the authors consider kava extract as relatively safe and more efficacious than placebo in the symptomatic treatment of anxiety.

3.1.3 Clinical Trials

Placebo-controlled studies carried out after the review and meta-analysis of Pittler

In a randomized, placebo-controlled, double-blind outpatient trial the efficacy and safety of kava special extract WS[®] 1490 was investigated in 50 patients suffering from non-psychotic anxiety during four weeks. Treatment period as followed by a two-week safety observation period. Inclusion criteria were the presence of non-psychotic anxiety (according to the DSM-III-R criteria agoraphobia, specific phobia, generalized anxiety disorders and adjustment disorder with anxiety), a HAMA total score of at least 18 and a minimum score of 12 in the multiple choice vocabulary test (MWT-B). Main outcome criteria were the HAMA total score which was determined upon inclusion in the one-week run-in phase (without study medication), at the start of the treatment and after 2, 3 and 4 weeks of the treatment.

During the treatment patients received 3 times a day 1 capsule of either 50 mg kava extract (standardized to 70 % of kava lactone) or placebo. For the primary outcome variable and the intention to treat analysis, a tendency of superiority over the course of treatment was observed with WS[®] 1490 ($p = 0.1$). Due to the erroneous inclusion of 5 patients (with a total HAMA score of less than 18) and 3 very early dropouts in verum, a per protocol analysis was performed. In this analysis a statistically and clinically relevant advantage of 4.7 points in favor of the WS[®] 1490 treatment was observed after 4 weeks ($p = 0.03$). For the HAMA subscales “somatic anxiety” and psychic anxiety a statistically significant advantage of verum was also detectable ($p = 0.03$ and 0.04). For the further secondary outcome variables a trend in favor of the kava extract was observed, but none of them reached significance. But on item I (severity of illness) of the Clinical Global Impression (CGI) scale the number of patients graded as “at least markedly ill” was twice as high ($p = 0.08$, chi-square test) in the placebo group (12 out of 21 patients) compared to the verum group (6 out of 22 patients), at the end of the treatment. At the beginning of treatment in both groups 16 out of 25 patients had been rated “at least markedly ill”. No adverse events related to the study medication were observed and none of the patients showed withdrawal symptoms during follow up phase [20].

In a multicenter, randomized, placebo-controlled, double-center trial of Lehl (2002) the efficacy and safety of kava special extract WS[®] 1490 was investigated in 61 patients with sleep disturbances associated with anxiety and restlessness states of non-psychotic origin, for 4 weeks. Included in the trial were patients with diagnoses of generalized anxiety disorder, agoraphobia, social phobia or adaptation disorders (according to the DSM-III-R: 300.02, 300.23, 300.29, 309.24; American Psychiatric Association, 1987), with a total score on the Hamilton Anxiety Rating Scale (HAMA) of not less than 15 points and at least 2 points on HAMA item “insomnia”. Main outcome measures were the SF-B, the Hamilton Anxiety Scale, the Bf-S self-rating scale of well-being and the Clinical Global Impressions scale (CGI). After a single-blind placebo run-in period of seven days, patients (WS[®] 1490: 34; placebo: 23) either took 2 capsules of 100 mg of kava extract (standardized to 70 mg of kava lactones), or placebo once a day for 4 weeks. Double-blind treatment was followed by a 2 weeks of phase without study medication. At the end of the treatment a statistically significant superiority for both primary subscores of the SF-B (subscore 1 (quality of sleep): $p = 0.008$; subscore 2 (recuperative effect after sleep): $p = 0.032$) was observed for verum compared to placebo. For the SF-B subscores 3 to 5, representing the secondary outcome criteria, both treatment groups showed symptom improvement.

For subscore 4 WS[®] 1490 showed a more pronounced reduction of psychotic exhaustion in the evening ($p = 0.07$), while the improvement in the subscore 5 (psychosomatic symptoms during sleep) observed for WS[®] 1490 compared to placebo was statistically significant ($p = 0.001$). The analysis of the five of SF-A subscores showed similar results with p-values ranging from 0.03 to 0.06 in favor of the kava extract. In the HAMA total score both groups showed a comparable monotonic decrease. But at the end of the treatment and follow-up-phase WS[®] 1490 showed better results in the subscale “somatic anxiety” ($p = 0.41$) and statistical significant superiority in the subscale “psychic anxiety” ($p = 0.002$). Recurrence of primary symptoms was less frequent in the kava group (11.8 %) than in the placebo group (26.1 %). Furthermore, neither adverse effects during the treatment, nor withdrawal effects during follow up phase could be observed. All the obtained data of this study indicate kava extract is particularly effective in alleviating anxiety-related sleep disturbances [50].

Malsch & Kieser (2001) conducted a 5-week randomized, placebo-controlled, double-blind trial to investigate the efficacy of kava-kava special extract WS[®] 1490 in non-psychotic nervous anxiety, tension and restlessness states, following pretreatment with benzodiazepines. 40 Patients (25 male, 15 female) suffering from agoraphobia, simple or social phobia, generalized anxiety disorders or adaptation disturbances according to the DSM-III-R had been included in this GCP-conform, well conducted trial. Further inclusion criteria have been a maximum score of 14 in the Hamilton Anxiety Scale (HAMA), and a minimum history of 14 days of uninterrupted treatment with benzodiazepines (lorazepam, bromazepam, alprazolam, or oxazepam) prior to the study inclusion. Study medication was available in capsules filled with either 50 mg of dried kava extract (standardized to 35 mg of kava lactone) or placebo. During the first week the daily dose was increased from 50 mg (1 capsule) up to 300 mg (3x2 capsules). Simultaneously, the preexisting benzodiazepine treatment was tapered off at a steady rate over the first two weeks of double-blind treatment (at least 50 % reduction at day 7). These three weeks of initial treatment were followed by 3 weeks of anxiolytic treatment with the study medication alone. The treatment was followed by a three-week follow-up-phase, at the end of which the patients were reexamined. Primary outcome measures of the trial were the differences in the overall scores of the Hamilton Anxiety Scale (HAMA) and the “Befindlichkeits-Skala” (Bf-S — subjective well-being scale) and the incidence of benzodiazepine withdrawal symptoms during the double-blind treatment phase.

The results of the primary outcome measures showed a clear statistical significant superiority of verum compared to placebo (HAMA: $p=0.01$; Bf-S: $p=0.002$) at the end of the study. In the kava-group the HAMA total score improved with a median of 7.5 points between baseline and treatment end, with a beneficial treatment effect already visible after one week. In contrast, no comparable improvement was found in the placebo-group, in which the median HAMA total score varied around baseline level (maximum improvement: 1 point). Treatment group comparison showed P -values <0.05 (95 % confidence intervals) for the assessment on days 8, 22, 28 and 36 (except day 15: $p=0.07$). Statistical superiority ($P<0.01$) of kava compared to placebo, was also shown for the second mail outcome measure, the Bf-S. Patients treated with verum showed a medium improvement of 18.5 points compared to 3 points in the placebo-group. Treatment group comparison showed a P -value <0.05 (95 % confidence intervals) for the assessment on the days 29 and 36. Regarding the occurrence of withdrawal symptoms no statistically significant differences were observed. Improvements of 7.5 points of the HAMA and 18.5 of the Bf-S have to be regarded as clinically relevant effects. Furthermore, secondary variables measured on the Erlangen Anxiety and Aggression Scale (EAAS) and Clinical Global Impressions Index (CGI) do support the results of the primary outcome measures. Adverse drug reactions have not been reported during the course of the trial. All adverse effects observed were related to the withdrawal of benzodiazepines. The fact that the patients treated with WS[®] 1490, in contrast to the ones treated with placebo showed a clear symptom alleviation in comparison to their condition at the end of benzodiazepine therapy the authors assume in the discussion, that WS[®] 1490 may have an anxiolytic effect beyond the benzodiazepines [54].

As an expansion of earlier research De Leo (2001) investigated his randomized, placebo-controlled trial the efficacy of hormone replacement therapy with combined with a kava extract in the treatment of postmenopausal anxiety. Included in the trial have been 40 women in physiological (22) or surgical (18) menopause from 1 – 12 years who met the diagnostic criteria of DSM IV for generalized anxiety, with a minimum total score on the Hamilton Anxiety Scale (HAMA) of 19. Main outcome criteria have been the HAMA total score as well as the somatic anxiety and the psychic subscores. Patients who were in physiological menopause were treated with 50 µg / day TTS (17β estradiol) plus one tablet / day for 15 days every 3 month progestogen (Lutenyl 50 mg, Schering) and either one capsule of 100 mg kava extract (standardized to 55 mg kavain), or 1 capsule of placebo, each day. The patients in surgical menopause took 50 µg TTS (17β estradiol) and either 1 capsule of 100 mg kava extract (standardized to 55 mg kavain), or 1 capsule of placebo, each day.

The treatments continued for 6 month. After three and six month, in patients in physiological menopause as well as in patients in surgical menopause, the combined therapy with kava led to a significantly greater reduction of HAMA total score than the one with placebo. Similar results were obtained when the subscores of the HAMA of the groups treated with kava were compared to the ones of the placebo-groups ($p \leq 0.05$). In the discussion the authors concluded that the combined therapy with kava extract is effective in hormone replacement therapy with or without progestogen in the treatment of generalized anxiety associated with menopause [9].

Placebo-controlled trials included in the scientific review and meta-analysis of Pittler

Outpatients suffering from anxiety of non-psychotic origin (DSM-III-R criteria: agoraphobia, specific phobia, generalized anxiety disorder, and adjustment disorder with anxiety) were included in a multicenter, randomized, placebo-controlled double-blind trial with the kava extract WS 1490. One capsule containing 70 mg kavapyrones was administered three times a day. 101 patients (average age: 54 years, 74 female, 27 male; 52 on WS 1490, 49 on placebo) were included in 10 centres. The trial duration was 25 weeks after a one-week single-blind placebo washout period. After a 24-week random treatment period, a one-week placebo washout was performed. The following ratings were performed at the beginning of the placebo washout period and at weeks 0, 12, and 24: HAMA scale (main outcome criterion), self-report symptom inventory 90 items - revised (SCL-90-R), CGI, Adjective Mood Scale (Bf-S), and registration of adverse events according to an open, non-leading questionnaire. Additional HAMA ratings and adverse event checks were performed at weeks 4, 8, 16, and 20. The HAMA total score showed a pronounced decrease in both groups. The verum group was superior on all assessment days during the treatment phase. The difference was statistically significant at week 8 ($p = 0.02$) and increased later in the treatment period (week 12: $p = 0.002$, weeks 16, 20, 24: $p < 0.001$).

The HAMA subscores showed a statistically significant advantage for the verum starting at week 8 ($p = 0.02$). The GCI also showed a very clear result; the patients treated with WS 1490 had a statistically significant advantage over those taking placebo ($p = 0.001$ after 12 weeks). For the self-rating scales the results are very similar ($p < 0.05$); in the case of the Bf-S, the result was borderline significant at week 24 ($p = 0.08$). According to the authors, these results support the usage of kava extract as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety disorders, with proven long-term efficacy and none of the tolerance problems associated with tricyclics and benzodiazepines [76].

In a randomized, placebo-controlled, double-blind trial including 58 patients (43 female; 15 male) with anxiety syndrome of non psychotic origin (according to ICD 9) were treated for a period of 4 weeks either with kava extract WS 1490 (Laitan[®]) or placebo. Patients included in the trial showed a minimum total score of 18 on the Hamilton Anxiety Scale (HAMA). After computer randomization the 29 patients of each group received either 3 x 1 capsule kava extract or placebo per day. One capsule of Laitan[®] contained 100 mg of kava dried extract, standardized to 70 mg of kava lactone. Outcome measures were examined at the start of the trial (day 1), day 7, 14 and at the end of the study (day 28). The total score of HAMA served as the main outcome measure to prove the effects of the therapies. From the first week on the WS[®] 1490-group ($x = 16.2/SD = 7.1$) showed significantly better results in the reduction of HAMA total scores than the placebo group ($x = 21.8/SD = 7.8$). The reduction of HAMA total score increased during the treatment up to the end of the trial in the WS[®]-group (mean total score = $12.6/SD = 8.6$) while only a slight reduction of HAMA total score was observed in the placebo-group (mean total score = $21/SD = 10.1$). The superiority of the kava extract compared to placebo was statistically significant on all three-measurement points ($p \leq 0.01$). Similar results have been observed in the secondary outcome measures, as the subscales of the HAMA (somatic anxiety and psychological anxiety) and the Clinical Global Impression Index (CGI). At the end of the trial 6 Patients (10 %), 4 in the verum-group and 2 in the placebo-group, dropped out without further explanation. During the 4-weeks treatment, the patients had reported no adverse effects. Due to the confirmed anxiolytic effect of the kava extract and its good compliance, the authors recommend the use of kava for the treatment anxiety disorders of non-psychotic origin [42].

Within the framework of a randomized, placebo-controlled double-blind study two groups of patients ($n = 20$ per group, 45 – 60 years) with climacteric-related symptomatology were treated with the kava extract WS 1490 (3 x 100 mg/day, resulting in a daily dosage of 210 mg of kavapyrones) or a placebo preparation for a period of 8 weeks. The target variable – the HAMA overall score – revealed a significant difference in the verum group compared to the placebo group already after just one week of treatment ($p < 0.001$). The course of such parameters as depressive mood (DSI), subjective well-being (patient diary), severity of the disease (CGI), and the climacteric symptomatology (KUPPERMANN index and SCHNEIDER scale) over the whole treatment period demonstrated a high level of efficacy of the kava extract in neurovegetative and psychosomatic dysfunction in the climacteric [78].

In a randomized, placebo-controlled double-blind study two groups (n = 29 per group; 43 female, 15 male; 18 – 60 years) containing patients with anxiety syndrome not caused by mental disorders were treated with kava extract WS 1490 (Laitan; 3 x 100 mg/day, resulting in a daily dosage of 210 mg of kavapyrones) or a placebo preparation for a period of 4 weeks. Therapeutic efficacy was assessed by the HAMILTON Anxiety Scale (main target variable), the Adjectives Check List (EWL), and the Clinical Global Impression Scale (CGI; secondary target variables). The HAMA subscales “mental anxiety” and “somatic anxiety” were evaluated descriptively. Assessments were made on days 1, 7, 14 and 28. The HAMA overall score of anxiety symptoms revealed a significant reduction in the verum group after one week of treatment. The difference between the two groups increased during the course of the study ($p < 0.01$). The results of the secondary target variables were in agreement with the HAMA-score and demonstrated the efficacy of WS 1490 in patients with anxiety disorders [48].

Epidural anaesthesia, although safer and of less risk than general anaesthesia, is loaded with more anxiety, fear and stress. Therefore the preoperative treatment of the patient with anxiolytics is justified. By means of a pilot study it was found that 2 x 60 mg kavapyrones (2 x 300 mg kava extract, Kavosporal) were an adequate dosage for regional anaesthesia. The patients received the dose in the evening the night before and the next morning one hour before the operation. A randomised, placebo-controlled double-blind study applying the same dosage regime yielded three remarkable results. Assessments were made on sleep quality, psychological status, blood pressure and pulse rate, evaluation of the course of narcosis, postoperative blood pressure and pulse, and patients' questioning (anxiety scale). By dividing the patients (20 – 70 years, n = 60) into four groups with a planned operation duration of a) less than 40 min, b) 40 – 80 min, c) 80 – 120 min, and d) more than 120 min, verum and placebo turned out to have nearly the same good results in the first group. In the fourth group the results were nearly equally bad.

In the second and third group, however, the kava extract proved to be of doubtless advantage compared to placebo. Anxiety was significantly reduced ($p < 0.05$) [2].

Controlled studies with reference therapies

In a reference-substance-controlled double-blind study over a period of 6 weeks the efficacy of the kava extract WS 1490 (Laitan 100; each capsule contains 100 mg dry extract standardized to 70 mg kavapyrones) on patients with conditions of anxiety, agitation, and tension of non-psychotic origin was compared to that of oxazepam and bromazepam. 172 patients (18 – 65 years; both sexes) from 12 medical practices were assigned randomly to three groups. One group received WS 1490 (100 mg three times daily, n = 57), and the other two groups received either oxazepam (5 mg three times daily, n = 59) or bromazepam (3 mg three times daily, n = 56). The data was objectified by the HAMILTON Anxiety Scale (HAMA). All three types of treatment led to a significant decrease in anxiety. Statistical comparison of the variables of the three groups respectively did not produce a relevant difference between the three types of treatment with respect to a decrease in anxiety and concomitant variables (comparison of HAMA total score bromazepam / WS 1490 after six weeks: p = 0.0925, oxazepam/WS 1490 after six weeks: p = 0.6198). Bromazepam led to a slightly more pronounced decrease in anxiety, but only to a minor extent as compared to the other two groups. The authors conclude that the kava extract is comparable to both oxazepam and bromazepam with regard to its anxiolytic effect [82].

Non-controlled studies

Lehrl & Woelk (2002) conducted an open long-term study with kava extract WS[®] 1490 (Laitan 100; each capsule contains 100 mg dry extract standardized to 70 mg kavapyrones). This long-term study directly followed the above, in the paragraph controlled clinical trials, cited reference-controlled, randomized, double-blind 6-weeks trial of Woelk *et al.* (1993). In this trial 172 patients with conditions of anxiety, agitation, and tension of non-psychotic origin were either treated with 300 mg / day kava extract WS[®] 1490, 15 mg / day oxazepam or 9 mg / day bromazepam. All three treatments were found to be equally effective in lowering anxiety (measured by reduction of HAMA total score). In the directly adjoining long-term study the patients of all three treatment groups continued their therapy with the kava extract, to prove whether the positive results obtained with the bromazepam and oxazepam treatment could be stabilized or even improved by the continuing therapy with kava extract or not. After the premature termination of 8 patients during the double-blind phase and 6 more patients after its termination, 158 patients (57 patients of the kava group, 59 patients of the oxazepam group and 56 patients of the bromazepam group) were included in the non-controlled phase study [49].

In the beginning of the treatment all patients received 3 x daily 1 capsule of 100 mg kava extract for a period of 6 weeks and for further 8 weeks 3 x daily 1 capsule of 50 mg kava extract. The treatment was followed by a two weeks follow-up phase without medication. Like in the controlled phase the main outcome criterion was the HAMA total score. The results showed a further reduction of the mean HAMA total score (former bromazepam group: 5 points; former kava group: 5.25 points; former oxazepam group 4.4 points) was observed for all groups from the first to the 11th week of the treatment. During the following 3 weeks and the follow-up phase mean HAMA total score values stabilized at a constantly low level. Seven patients dropped out of the long-term study for several reasons (successful treatment: 2; unimproved symptoms: 2; nervousness, tremor and sleeplessness, allergic reaction: 3). During the 14 weeks of treatment and the two-week follow-up phase no adverse effects have been reported. During the follow-up phase 14 patients reported re-appearance of single symptoms. Most of these cases were evaluated to be of minor severity and could not be related to withdrawal symptoms. The observed improvement of the HAMA total score and the stability of the patients' conditions, even two weeks after the end of the therapy, can be regarded as a strong indication for the efficacy of kava in the treatment of agoraphobia, specific phobia, social phobia and generalized anxiety disorders [49].

52 outpatients (15 male, 37 female; average age: 49 ± 15) suffering from anxiety of non-psychotic origin were included in an open, observational, multicentric study of a kava preparation. The unit dosage was 100 mg of kava extract. Physicians could lower the dosage, depending on the patient's clinical improvement. All patients had generalized anxiety disorder with ($n = 26$) and without ($n = 26$) concomitant depression. Global improvement was rated on a five-point scale as "slightly worse", "no change", "slightly improved", "much improved" and "very much improved". Target symptoms of "anxiety", "tension", and "restlessness" were rated by physicians on a four-point scale: "not present", "mild", "moderate", and "severe". 25 patients (48.1 %) were already being treated with various drugs for their anxiety. The kava preparation represented the initial treatment for 27 patients (51.9 %). In 24 instances, previous treatment comprised psychotropic drugs, including benzodiazepines, antidepressants, and neuroleptics. All patients discontinued their previous medication when treatment with the kava extract was initiated. More than half of the patients had concomitant illnesses; diseases of the circulatory system were the most common. The physicians prescribed the kava preparation as follows: 15 patients received one capsule twice a day; 28 patients were given one capsule three times a day; and 9 patients were asked to take two capsules three times a day.

The mean treatment duration was 50.75 days. Drug efficacy was evident on measures of a global improvement scale, with 42 patients (80.8 %) rating the treatment as “very good” or “good”.

The target symptoms of anxiety, restlessness, and tension all showed a pronounced decrease from baseline. Before therapy, 22 patients (42.3 %) rated their anxiety as “severe”, 16 (30.8 %) as “moderate”, and 7 patients (13.5 %) as “mild”; in 7 patients (13.5 %), no anxiety was present at baseline. At study end, 6 patients (11.5 %) described “moderate” anxiety and 26 patients (50.0 %) “mild” anxiety symptoms. No patient had “severe” anxiety, and 20 patients (38.5 %) did not report any anxiety at all. Before therapy, tension was rated “severe” in 26 patients (50.0 %), “mild” in 2 patients (3.8 %), and non-existent in 6 patients (11.5 %). By the end of the study, no patients had “severe” tension; 8 patients (15.4 %) had “moderate” tension and 29 patients (55.8 %) “mild” tension. In 15 patients (28.9 %), tension was no longer present. Before being treated, 21 patients (40.4 %) had “severe” restlessness, 18 (34.6 %) “moderate”, and 8 patients (15.4 %) “mild” restlessness; in 5 patients (9.6 %), this symptom was not present. By the end of the study, restlessness was “severe” in no patient, “moderate” in 6 patients (11.6 %), “mild” in 28 patients (54.8 %), and non-existent in 18 patients (34.6 %). The authors conclude that kava extracts are similar in efficacy to benzodiazepines without sharing their disadvantages [63].

In a drug-monitoring trial with a kava extract (1 – 2 tablets Antares 120/day, standardized to 120 mg kavapyrones/tablet) conducted by 972 physicians 3029 patients (73.3 % female, 26.7 % male; 16 – 96 years, average age: 48.4 ± 14.5) were included. Assessments were made on primary (nervous tension and unrest, anxiety) and secondary symptoms (sleep impairment, exhaustion syndrome, climacteric complaints, muscle tension, and sexual impairments; all valued as an expression of generalised anxiety disorder). After approx. 15.5 days an intermediate assessment was made. Even at that early stage a clear improvement could be detected. After an average of 34.5 days, the final assessment followed. In the beginning more than 60 % of the patients suffered strongly or very strongly from nervous tension or unrest. At the end of the study that number was down to 5 %. Anxiety states were totally reduced in 25 % of the patients, more than 50 % had only minor problems after the treatment. Complaints of men suffering from sexual impairments and women suffering from climacteric discomforts clearly improved from “severe or very severe” to “none-existent or mild”. 178 patients (26.1 %) had been treated with benzodiazepines before the trial and were switched over to the kava extract. In this subgroup 71 % of physicians and 82 % of patients evaluated the efficacy of the kava treatment as good or very good.

On the whole, in over 80 % of the cases the evaluation of efficacy was good or very good. Patients tended to evaluate the therapeutical success higher than physicians (86 % and 80 %, respectively) [35].

Another drug-monitoring trial demonstrated that a kava extract (Antares, 133 mg KW 1491/tablet standardised on 40 mg kavapyrones) improves complaints such as anxiety, nervous tension, and restlessness. 1673 patients (average age: 48.84 ± 14.77 ; 1168 female, 503 male) took part in this study. In 94 % of the cases, the recommended dosage of 120 mg kavapyrones/day (i.e., 3 x 1 tablet) was prescribed to, and taken by the patients. After an average of 15.5 days an intermediate assessment was made followed by the final assessment after an average of 34.5 days. Clear improvements could already be seen at the intermediate assessment. After the therapy all primary (anxiety, nervous tension, restlessness) and secondary (sleep impairment, exhaustion syndrome, climacteric complaints, muscle tension) symptoms were clearly improved or eliminated. In the category “nervous tension and restlessness” more than 60 % of the patients were suffering from severe or very severe complaints. By the final assessment, only 5 % of the patients had not improved to “good” or “very good”. Concerning the anxiety states, 25 % of the patients were free of complaints, and more than 50 % suffered from only minor ailments. Full effectivity was reached after an average of 10.98 days, in 38 % of patients it was 5 days, in 22 % 5 – 10 days. In 75 % of the cases, the efficacy of the treatment with the kava extract was good or very good [70].

4049 patients (average age: 49; 72 % female, 28 % male) were included in a 7-week multicenter drug-monitoring trial. 69 % of the patients were suffering from conditions of nervous anxiety, stress, and restlessness for at least 1 – 6 months before onset of therapy with the kava extract. They received 3 x one capsule Laitan daily (one capsule containing 50 mg of the kava extract WS 1490, standardised on 35 mg kavapyrones). The major cause (55 % of the cases) of nervous anxiety, stress, and restlessness was “exhaustion syndrome”, followed by “anxious upset” (31 %), “loss syndrome” (24 %), “climacteric discomforts” (20 %) and others (6 %). The data of 3873 patients could be analysed. In 70 % of the patients only one cause was held responsible for the symptoms, in 25 % it was two causes, and in 5 % it was more than two causes. Assessments were made before the beginning of the treatment, twice during the trial, and at the end. 70 % of the patients continued the medication after the end of the study, 30 % stopped treatment after 7 weeks or earlier. Assessments were made according to the HAMA scale. The symptoms clearly improved within the first two weeks. After the end of the study, symptoms were improved or even non-existent in more than 80 % of the cases.

The majority of patients (87 %) judged their general quality of life improved after the end of the study. 9 % felt unchanged, 1.4 % evaluated their state of health as slightly worse, and 2.7 % did not comment. In about 74 % of the cases, physicians rated the efficacy of the kava extract as “good” or “very good”, and as “satisfying” in about 18 %.

Poor efficacy was seen in only 6 % of the cases. There was no physician’s judgement in 2 % of the patients. According to the authors this drug-monitoring trial supports the opinion that kava extracts are very efficacious in respect to the indications nervous anxiety, stress, and restlessness [65].

3.2 Safety

Traditional use

During its long-term traditional medical use kava has not shown any severe side effects like e.g. hepatotoxicity. ‘There is only evidence in the South Pacific of a characteristic kava-induced skin reaction, a scaly rash that is suggestive of ichthyosis – a condition called “kava dermopathy”. Although the skin becomes yellow, the description does not suggest an underlying hepatic condition in that the patient remains well, the rash is not itchy, and the condition is ameliorated without treatment if heavy use of kava is reduced [10]. Dr. P.A. Cox (director of the National Tropical Botanical Garden, Hawaii), who has been extensively studying the traditional use of herbal medicines for more than 20 years in the Pacific region, where the drug kava is used regularly stated: “ The indigenous people of the Pacific have used kava longer than anyone in Europe, and if there is a liver threat, they should be suffering from it”. Although kava has been found to be associated with a few mild side effects, such as skin rash, when taken at high doses for prolonged periods of time, it has never been found to cause hepatotoxicity. Dr.Cox stated that “... in my nearly three decades of work in Polynesia, I have never heard of a single case of liver toxicity caused by kava consumption” [74].

Placebo-controlled, reference-therapy-controlled and non-controlled studies

Apart from the experience of the traditional use several controlled and non-controlled trials can be referred to when evaluating the safety of kava extracts. In all of these trials in general, kava extracts have been very well tolerated and no severe effects have been observed. Only rarely mild side effects or adverse reactions are reported in controlled clinical studies and non-controlled trials. Less than 2 % of the patients complained about such adverse effects; the majority of adverse reactions were gastrointestinal complaints.

In the 11 randomized, placebo-controlled, double-blind trials and the one controlled trial with reference therapy (bromazepam, oxazepam) cited above [2, 9, 20, 42, 48, 50, 54, 66, 76, 78, 79, 82], including about 1000 patients, tolerance of the extracts was evaluated as being very good and gastrointestinal complaints were the only adverse effects reported (equally distributed in the verum and placebo groups). One study that should be mentioned here is the one of Volz & Kieser (1997).

In this randomized, placebo-controlled, double-blind long-term trial, 101 patients were treated with 300 mg kava extract daily (standardised on 70 % kavapyrones) for 24 weeks. Although the treatment period was more than double as long and the dosage nearly triple of the dosage, recommended in the monograph of the German Commission E, only six adverse events in five patients were reported in the kava group. Four of these six adverse events were rated as not being related to the compound under investigation, two (in both cases “stomach upset) were rated as “possibly related”. This strongly argues for the safety of kava [76].

In 5 non-controlled studies [35, 49, 63, 65, 70] on nearly 10 000 patients receiving 100 – 400 mg kava extract or 120 – 240 mg kavapyrones daily, 169 cases of minor adverse effects, mainly were gastrointestinal complaints and allergic reactions, were reported. This also confirms the data on the safety of kava preparations received from the traditional use and the controlled trials.

Case reports hepatotoxicity

In 1998 the first cases of hepatotoxicity have been reported in Germany. On the 8th of November 2001, the BfArM issued a letter to all German manufacturers of medicinal kava or kavaine-containing products proposing to withdraw marketing authorization for all kava-containing products on the basis of 37 cases involving liver toxicity from Switzerland and Germany. Until now a total of 76 international suspected cases of liver toxicity (double and triple entries already excluded) have been reported. During our investigations we compared the results of the evaluations of case reports done by different health authorities. As shown in table 1, the authorities came to very different conclusions after having had evaluated the same cases.

Table 1: Differing evaluations of health authorities

Review section	BfArM case no.	BfArM	MCA	EMA
	98004297	Probable	Unlikely	Unlikely
	94901308	Probable	Unassessable	Possible
	02003010	Possible		Unassessable
	93015209	Probable	Possible	Possible
	99006005	Probable	Unassessable	Possible
	01003950/01003951	Certain	Probable	Probable/ unassessable
	02002090/02002836	Probable		unassessable
	Kraft <i>et al.</i> (2001)	Probable	Possible	Possible
	9400656	Possible	Possible	Possible
	00008627	Probable	Possible	Possible
	01004110/99006200	Probable	Possible	Possible
	01006229	Probable	Unassessable	Probable
	01010536	Probable		Unassessable
	02000370	Probable		Unassessable
	01006939	Probable		Unassessable
	02001414	Probable		Unassessable

Therefore, the expert had to conclude, that the evaluations of health authorities cited above do not provide a reliable source of information, necessary for critical evaluations of case reports. It is to state that more care is required from all parties (patients, physicians and authorities, if a reliable case analysis is to be achieved. Apart from the inclusion of double and triple entries, other failures have been observed.

However, for this report we have reviewed and analysed all of the cases in detail. In our analysis all data available were collected and evaluated critically. Based on the data provided by Dr. Schmidt and our own research we worked out a case data bank, containing all available raw data. On the bases of this data bank we examined all of the 76 cases and commented all of them case by case. The results of this detailed examination are documented in an extensive case analysis that is attached as **Appendix I** in this expert report. The data bank, comprising all the raw data available, on which the analysis is based upon, is copied on two disks going with this report in **Appendix 2**. The data bank consists of 37 case reports from the German Federal Institute for Drugs and Medical Devices (BfArM), plus five duplicate / triplicate entries of otherwise identical reports, five cases from the Swiss SWISSMEDIC (formerly IKS), two cases published in the German public press, three cases from the medicinal literature, 20 cases reported from the Food and Drug Administration (FDA), two cases from the British MCA, one from Australian TGA, three cases from Canada, two cases from the French ADM and finally one reported from the Pharmacovigilance Working Party of the EMA.

In the following we only will summarize the results of our analysis that are explained in detail in the **Appendix I**, in table 2.

Table 2: List of all case reports

Classification	Case No.	Paragraph No.	Number of reports
Double or triple entries	97002825/97003551 01001228/01001924/01001928 01003950/01003951 99006200/01004110	2.1.1 2.1.2 2.1.3 2.1.4	4
No connection to kava	98004297 99005139 93/0351 02003010 Press report FDA 13198 FDA 14810 FDA 15317 FDA 15319 FDA 15465/15476 FDA 15556 MCA (EMEA-id. 1) EMEA id. no. 38	2.7.1 2.7.2 2.7.3 2.7.4 2.7.5 2.7.6 2.7.7 2.7.8 2.7.9 2.7.10 2.7.11 2.7.12 2.7.13	13
Probably connected to concurrent medication	90003882 94901308 93015209 99006005 00003608 00005994 01001228/01001924/01001928 01003950/01003951 IKS 1999-2596 IKS 2000-2330 IKS 99062501 01008989 01010222 02001135/02002378 02001776 02002090/02002836 FDA 14723 FDA 15035/15274 FDA 14538 FDA 10257 FDA 15466 MCA rep. (EMEA id. 2) Kraft <i>et al.</i> 2001	2.6.1 2.6.2 2.6.3 2.6.4 2.6.5 2.6.6 2.6.7 2.6.8 2.6.9 2.6.10 2.6.11 2.6.12 2.6.13 2.6.14 2.6.15 2.6.16 2.6.17 2.6.18 2.6.19 2.6.20 2.6.21 2.6.22 2.6.23	22

Connection to kava doubtful	94006568	2.5.1	6
Connection to kava not assessable due to insufficient documentation	92901203 99003911 99500453 01003089 99006200/01004110 01006229 01009681 01010536 02000370 02002541 02002732 01006939 02003278 02003559 02004364 02005178 02001414 Weekly magazine report FDA 11444 FDA 14951 FDA 14995 FDA 15249 FDA 15250 FDA 15252 FDA 15267 FDA 15320 Canadian rep. (EMEA id. 67) Canadian rep. (EMEA id. 65) French rep. (EMEA id. 64) Australian TGA report Humbertson <i>et al.</i> 2001	2.4.1 2.4.2 2.4.3 2.4.4 2.4.5 2.4.6 2.4.7 2.4.8 2.4.9 2.4.10 2.4.11 2.4.12 2.4.13 2.4.14 2.4.15 2.4.16 2.4.17 2.4.18 2.4.19 2.4.20 2.4.21 2.4.22 2.4.23 2.4.24 2.4.25 2.4.26 2.4.27 2.4.28 2.4.29 2.4.30 2.4.31	31
Possible connection to kava with overdosing	IKS-2000-0014 IKS 2000-3502	2.3.1 2.3.2	2
Possible connection to kava with monograph conform dosage	Strahl <i>et al.</i> 1998	2.2	1
Classification	Case No.	Paragraph No.	Number of reports

Therefore, the 76 cases can be evaluated as follows:

- 14 of these cases obviously cannot be related to the intake of kava.
- In 22 cases a potentially concomitant treatment was identified.
- In 6 cases the causality to kava is considerably doubtful
- In 30 cases the available data are too fragmentary for an assessment
- Only in 4 of the remaining cases there is a high probability of causal relationship to the intake of kava containing products
- In 3 of these 4 cases, kava was taken in doses double or triple as high as recommended by the German Commission E, and exceeding the recommended period of treatment

Other scientists who critically reviewed the reported cases of hepatotoxic adverse effects came to similar results and also confirm the experts' evaluations.

Independently, and on the request of the American Herbal Products Association, the toxicologist expert Prof. Waller from the University of Illinois, Chicago, prepared a report reviewing the 26 case reports in the US and about 30 case reports from Europe. In his introduction Prof. Waller stated that case reports received from modern pharmacovigilance monitoring "must be handled with care and interpreted within the limitations of the information contained in them". He further says that, "reports are often deficient in important information, such as medical histories and information about the actual use and dosage of medications or natural products". Referring to the Swiss and German cases he wrote that "These reports are seriously lacking in details" and that "... information available for review did not provide adequate clinical information such as past medical history weight, diet, allergies, past and current alcohol use, history of viral hepatitis, occupational or environmental exposures, laboratory test results, doses of drugs taken concomitantly ..." and that "there is little that can be concluded about most of the cases." Furthermore, he wrote, "... that, the classification made by the BfArM of causality in each of these cases is largely incomprehensible and arbitrary". In his opinion, based on the currently available information, kava when taken in appropriate doses for reasonable periods of time has no scientifically established potential for causing liver damage [77].

Schmidt & Nahrsted (2002) published a detailed case analysis. Having evaluated the cases they concluded that 3 had no connection with Kava; 11 had probable causal connection to other prescription medication; 4 had an uncertain causal connection to Kava, but could not be excluded; in 6 others the causal connection with Kava could not be determined; in 3 the cause was listed likely due to the excessive dosage and misuse of Kava; and in only 1 where Kava was taken within the recommended dosage range was it listed as the likely cause of liver toxicity [68].

Denham et al. prepared on behalf of the Traditional Medicines Evaluation Committee, a subcommittee of the European Herbal Practitioners Association a detailed review of BfArM's case reports. It was submitted to the U.K. medicines Control Agency and Committee of Safety of Medicines in January 2002. According to the other pharmacological experts the report states that most of the adverse events cited by BfArM should not be attributed to kava [10].

Prof. Dr. Loew, member of the German Expert Commission E, also analyzed the case reports published by the German BfArM. A critical review of 41 cases, led him to similar results [52].

Case reports of extrapyramidal-like dystonic reactions

There are three reports of extrapyramidal-like dystonic reactions and one case of worsening Parkinson's disease. Patient 1, a 28 year old man, had a history of three episodes of acute dystonic reactions and exposure to promethacin (50 mg) and fluspirilen injections (2 x 1.5 mg) for the treatment of anxiety. Each time biperiden (5 mg i.v.) had led to immediate and complete relief of the symptoms. He denied further use of the drugs when admitted to hospital with a recent history of an acute attack of involuntary neck extension with forceful upward deviation of his eyes, which had begun 90 min after the intake of the first dose of 100 mg kava extract (Laitan) and subsided spontaneously within 40 minutes. Patient 2, a 22 year old woman, was prescribed a kava extract (Laitan[®]) for anxiety and nervousness. Four hours after the first morning dose she experienced involuntary oral and lingual dyskinesiae, tonic rotation of the head to the right, and painful twisting movements of the trunk. About 45 minutes later 2.5 mg biperiden was given i.v., and the dystonic reaction immediately subsided. There was no history of any other drug exposure during the preceding months. Patient 3, a 63 year old woman, experienced forceful involuntary oral and lingual dyskinesiae of sudden onset after taking 150 mg of a kava extract per day (Kavosporal forte) for four days because of anxiety. She was seen in the emergency room about one hour later, and 5 mg biperiden given i.v. immediately stopped the dyskinesiae.

The patient denied having taken any other medication during the preceding months. Patient 4, a 76 year old lady, had first developed signs of idiopathic Parkinson's disease at the age of 59. After eight years of levodopa treatment motor fluctuations and dyskinesiae were becoming an increasing problem. When first seen she was taking 500 mg levodopa (plus 125 mg benserazide) per day and was experiencing motor oscillations between Houhn and Yahr stage III when "on" and stage V when "off". 150 mg kava extract (Kavosporal forte) twice daily was prescribed by her general practitioner because of complaints of inner tension. Within 10 days she noted a pronounced increase in the duration and number of her daily "off" periods. She returned to her normal baseline patterns within two days of discontinuing the kava extract. The authors suggest that these effects of kava are due to its dopamine antagonism [62].

Case reports of drug-eruption in sebaceous gland-rich areas

A systemic kava antidepressant therapy over a period of three weeks two patients experienced a drug-eruption in sebaceous gland-rich areas. Case 1: A 70 year old man received multiple drugs during a period of 2–3 weeks: nitrofurantoin, allopurinol, spironolactone, furosemide, yohimbine, mesterolone, and kava extract for anxiety. The patient's history revealed neither skin diseases nor skin reaction after sun exposure and drug therapy. After sunlight exposure for several hours, itching occurred. Later erythematous, infiltrated plaques appeared on the ventral and dorsal thorax and the face. Antinuclear antibody and anti-extractable nuclear antibody titers were negative. A biopsy specimen revealed a lymphocytic infiltrate penetrating and destroying the sebaceous glands and lower infundibula. The infiltrating cells were CD8 positive and CD4 negative. Direct immunofluorescence was negative. Standardized skin testing did not show any immediate or delayed reactions to suspected drugs. Photopatch test was negative. The basophil cellular antigen stimulation test was also negative. Lymphocyte-transformation test with suspected drugs in serial dilution (0.1 – 1000 µg/ml) revealed significant proliferation only with kava extract. Case 2: A 52 year old woman, after 3 weeks of systemic therapy with kava extract, was seen with papules and plaques on the face and later on her dorsal and ventral thorax and arms. Antinuclear antibody and anti-extractable nuclear antibody titers were negative. A biopsy specimen revealed a prominent infiltrate in the reticular dermis. This infiltrate markedly affected sebaceous gland lobules that had become disrupted and necrotic. Direct immunofluorescence was negative. A kava extract patch test was positive in contrast to negative results in a control group of 20 adults. There was no stimulation of basophils in the cellular antigen stimulation test and no stimulation of lymphocyte proliferation in the lymphocyte-transformation test. The authors suppose that the lipophilic kava pyrones become concentrated in

the sebaceous lipids, provoking a lymphocytic attack and resulting clinically in an acute drug eruption.

They conclude that thus the observed kava-induced sebotropic eruption may represent a new entity of an allergic drug reaction reflecting the lipophilic profile of kavapyrones [37].

Other case reports

Further incidents and case-reports of kava-induced dermopathy, eye-irritations or neurological disorders have only been reported after heavy and/or chronic use of the traditional polynesian kava beverage or kava tea [4, 18, 41, 54, 55, 58, 60, 64, 69, 73].

Effects on vigilance

Pharmacodynamical studies on healthy volunteers have demonstrated that kava extracts do not have negative effects on vigilance [21, 56].

A study conducted to investigate the possibility of interactions of kava with benzodiazepines demonstrated that kava extracts do not impair vigilance. The aim of the study was to investigate whether effects on basic performance aspects other than those to be anticipated with the individual substances can be expected when bromazepam (2 x 4.5 mg/d) and a kava extract (2 x 120 mg kavapyrones/d) are administered simultaneously. These basic performances included accuracy of perception, concentration, reaction speed, vigilance, stress tolerance and motor coordination. Performance was tested on 18 healthy volunteers (6 male, 12 female, mean age 46.6 ± 6.5) in a sequential, balanced, cross-over trial using a computer-assisted test procedure. Assessments were made prior to, and on the second and third and 14th day of treatment. Parameters of tolerability (well-being scales, adverse reactions) were used as secondary variables. Statistically significant differences (in some cases highly significant) were observed in 3 performance areas after medication. Performance in the fields of stress tolerance, vigilance and motor coordination remained at the baseline level with kava extract, whereas bromazepam as well as the combination impaired stress tolerance and motor coordination over the whole period, and vigilance in the initial phase of treatment (days 2 and 3). Accuracy of perception, concentration and speed of reaction to simple signals remained unchanged. There were no differences between bromazepam treatment and treatment with the combination. The main differences in the well-being scales occurred between kava and the combination, but there were also occasional differences between bromazepam and the combination. The authors state that in principle the least impairment of general health occurred with kava and the relatively greatest impairment was found with the combination, which is thought to due to its bromazepam content [33, 34].

Potential hazards with respect to driving or operating machines

A randomized, double-blind placebo-controlled study investigated whether the kava extract WS 1490 impaired driving ability or the ability to operate machines. 40 healthy volunteers (20 female, 20 male, 18 – 60 years) received either 100 mg of the kava extract 3 times daily or placebo over a period of 15 days. 7 safety-relevant parameters were assessed: accuracy of perception, concentration, reaction speed, vigilance, stress tolerance and motor coordination. Parameters were assessed by using computer-assisted test procedures. Assessments were made on days 0, 1, 2, and 15. The analysis of the data did not show any relevant differences between volunteers taking the kava extract and those taking placebo concerning performance or well-being. According to the authors, the kava extract did not impair the ability to drive or to operate machines [31].

Overdose

A 47 years old woman presented a rash and proximal muscle weakness 2 weeks after ingestion of kava extract (dosage unknown; according to the patient's statement, it was much more than prescribed). Her creatine kinase level was elevated at 8654 U/l, and an electromyogram showed a myopathic pattern. Skin biopsy and muscle biopsy samples showed changes consistent with dermatomyositis. The patient improved with prednisone and discontinuation of the kava extract. The authors conclude that in this case, the temporal relationship between the ingestion of kava and the onset of dermatomyositis is too close to be ignored, but may well be coincidental. They assume that it may be also possible that the kava extract provided the trigger for myositis, or that this could be an idiosyncratic drug reaction [22].

4. Conclusions

The purpose of the expert report presented was, to re-evaluate the benefit-risk-ratio of drugs containing extracts, derived from the roots of individuals, assigned to the plant species *Piper methysticum* (Piperaceae), better known as kava kava. This has been done on the basis of a critical review of all available data concerning kava kava and an evaluation of their significance and reliability. It was not the mission of the expert report to evaluate whether kava kava is superior or inferior to other medication in the claimed indication. Furthermore it is not the intention of the expert report to evaluate whether kava preparations should be marketed as an OTC or a prescription drug. This is not discussed here.

4.1 Therapeutic Justification

Anxiety disorders are common conditions. Many people in the western world suffer lesser degrees of anxiety, usually related to stress in the environment, so that at least 15 % of patients attending general practitioners seek treatment for this condition [44]. A German survey suggests a lifetime prevalence of anxiety disorders of approx. 14 % [40]. The U.S. National Comorbidity Survey suggests a 1-year prevalence of anxiety disorders of 17 % and a lifetime prevalence of almost 25 %. In the majority of cases, conditions of nervous anxiety, stress, and restlessness are treated by general practitioners. Most patients are afraid of taking the typically prescribed benzodiazepines and tricyclic antidepressants, which are most commonly used, but are associated with serious adverse effects such as dependence, sedation, and memory impairment [59]. For many years benzodiazepines were the stock treatment for anxiety, but eventually the side-effects and dependence potential have led many prescribers to lessen or eschew their use. The spectrum of efficacy of kava products is comparable to that of benzodiazepines but without development of tolerance or withdrawal symptoms/potential for dependence [63]. The clinical studies presented in this expert report support the usage of kava extract as a treatment alternative to tricyclic antidepressants and benzodiazepines in anxiety disorders, with proven long-term efficacy and none of the tolerance problems associated with tricyclics and benzodiazepines.

It is highly appreciated and valued equally within physicians and patients.

4.2 Efficacy

Compared to many other drugs, no matter if synthetic or other herbal remedies, many studies have yet been carried out investigating the efficacy of kava preparations in the treatment of conditions of nervous anxiety, stress, and restlessness. Most of the 11 randomized, placebo-controlled, double-blind trials, and one controlled trial with reference therapy, on more than 1000 patients, follow the actual standards of Good Clinical Practice, and are of high methodological value. In the vast majority of these trials kava extract resulted to be significantly superior compared to placebo. The superiority is more evident in the trials using dosages 2 to 3 fold higher as recommended in the corresponding monograph of the German Commission E, but a significant reduction of symptoms was also observed in the trials using preparations, which conform to the recommended dosage. Although, in most of the trials patients usually were diagnosed according to the ICD 10, DSM-R/III or DSM-IV criteria, the groups included in the studies frequently lacked homogeneity. However, there is clear evidence that Kava preparations are effective in the symptomatic treatment of conditions of nervous anxiety, stress, and restlessness. The results of seven of the clinical trials cited in this report, were confirmed by the systematic review and meta-analysis of Pittler [59] who examined the reliability and methodological quality of these placebo-controlled trials and finally concluded that kava extracts are an effective tool in the symptomatic treatment of anxiety disorders of non psychotic origin.

The German Commission E, an independent commission implemented by the German Health Ministry to advise the Federal Institute for Drugs and Medical Devices (BfArM) in regulatory affairs, concerning plant based medicinal products, stated that after having examined all the available trials and taking into account the post marketing experience regarding kava preparations, they consider kava as an effective drug in the treatment of mild and moderate anxiety disorders of non psychotic origin [5, 6].

Another independent expert commission implemented by the German Federal Ministry of Health, the Institute of Drug Prescription in Public Health Insurances (Institut für die Arzneimittelverordnung in der gesetzlichen Krankenversicherung), also confirmed the efficacy of kava containing mono-preparations. This Institute and its independent commission were established to draft a provisional "Positive List". It should include "all medications that are appropriate for an adequate sufficient and necessary treatment of diseases or major health disorders; precondition for an inclusion in the main part of this list is a more than minor therapeutically benefit, compared to the maximum therapeutic effect achievable".

Furthermore, the evaluation should consider the quality and reliability of scientific data and its therapeutically relevance as well as the prospects of success of the therapeutic measure.

Including kava kava in the main part of this draft this expert commission considered kava kava to conform to the criteria of evidence based medicine, and confirmed its efficacy in the claimed indication.

Critically evaluating all the available information on the efficacy of kava preparations, and statements of independent expert commissions, the efficacy of kava kava in the claimed indication is clearly proven.

4.3 Safety

In this report all available data concerning the safety of kava kava were critically reviewed, analysed and evaluated. This comprises data on the traditional use of kava, all controlled and non-controlled clinical trials, including about 10 000 patients, all documented case reports of adverse effects and reported side effects that could be related to kava intake.

In general, kava extracts are very well tolerated. Side effects or adverse reactions are rare and mild in controlled clinical trials and non-controlled studies. No severe adverse effects have been observed. Less than 1 % of the patients reported unwanted effects; the majority of adverse reactions were gastrointestinal complaints.

Pharmacodynamical studies on healthy volunteers have demonstrated that kava extracts do not have negative effects on vigilance. Furthermore, kava extracts do not appear to impair the ability to drive or to operate machinery.

A total of 76 cases of severe adverse effects after treatment with kava preparations have been reported during between 1990 and 2002. After an extensive review of each single case, mainly based on all original data available and data provided by Dr. Schmidt and Prof. Nahrstedt, and others, **there only remain four cases in which the causality to the intake of kava is probable**. Only in one of these four cases kava was taken according to the dosage recommended by the German Commission E in its monograph on kava kava.

According to the sales figures of the German Institute of Medical Statistics, approximately 250 million daily doses of kava were sold during the last 10 years in German speaking countries. Correlated to this estimation, the 4 cases that can probably be related to kava intake, lead to an incidence for hepatic adverse effects of 0.0125 in one million daily doses.

All other scientists who critically reviewed the reported cases of hepatotoxic adverse effects came to similar results and also confirm the expert's evaluations.

The American toxicologist Prof. Waller, after having examined 26 cases reported in the US and 30 cases reported in Europe, confirmed our results, writing in his Expert Report "... that **based on the data available to me at this time, there is no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava**". He even says that, "kava taken in appropriate doses for reasonable periods of time has no scientifically established potential for causing liver damage" [77].

Denham et al. prepared on behalf of the Traditional Medicines Evaluation Committee, a subcommittee of the European Herbal Practitioners Association a detailed review of BfArM's case reports. It was submitted to the U.K. medicines Control Agency and Committee of Safety of Medicines in January 2002. According to the other pharmacological experts the report states that most of the adverse events cited by BfArM should not be attributed to kava [10].

4.4 Dosage

In 1990 the German commission E recommended kava preparations within the dosage range of 60 – 120 mg kavapyrones for short-term use of not more than 12 weeks [5]. After case reports of liver diseases, which at this time, were related to the intake of kava preparations, the Commission E revised its recommendations. In a public statement the Commission E now recommended that kava preparations should be taken at a daily doses of 120 mg for 4 weeks. Treatment with a daily doses ranging from 120 mg to 240 mg up to a maximum period of 8 weeks, should always go together with regular pharmacological, toxicological and clinical controls of liver function.

The clinical studies cited in this expert report used daily doses of 60 – 280 mg kavapyrones. Although the results of clinical trials suggest that kava kava seems to be more effective in doses ranging from 120 to 280 mg of kavapyrones, a proven efficacy in the treatment of conditions of nervous anxiety, stress, and restlessness has also been documented at a daily dosage up to 120 mg kavapyrones. Taking into account that in most of the controlled trials and non-controlled studies, kava was applied for four weeks, it seems to be appropriate to the expert that kava usually should be used for 4 weeks and at the dosage recommended by the Commission E. However, there are some controlled clinical trials and non-controlled studies, exceeding a four weeks treatment (Volz & Kieser 1997 [76]: 24 weeks; De Leo, 2002 [9]: 24 weeks; Lehl & Woelk, 2002 [49]: 14 weeks; Warnecke, 1991 [78]: 8 weeks) without observing severe adverse effects. Therefore, the expert agrees with the Commission E and considers an extension of treatment up to 8 weeks as favourable when the patients liver function is regularly controlled during treatment.

4.5 Benefit-Risk-Ratio

Regarding the results of paragraphs 2.2. (Pharmacodynamic), 3.1. (Efficacy) and the conclusions stated in paragraph 4.2.(Efficacy) of this report, the high benefit, for patients who suffer from conditions of nervous anxiety, stress, and restlessness, resulting from a treatment with kava kava is proven.

Regarding the results of paragraphs 3.2. (Safety) and the conclusion stated in paragraph 4.3. (Safety), the risks of possible severe adverse reactions related to the intake of kava preparations is to estimate as relatively low. However there seems to be a very low risk, of potential severe liver diseases.

A benefit-risk-ratio should not evaluate weather there is a potential risk related to the intake of a certain drug or not. The ratio should take into account the severity of the disease the medication is indicated for, the alternatives being available and the consequences for the patients resulting from a positive or negative evaluation. On this bases and regardless the modalities or regulations under which kava preparations should be presented to the patient, **the benefit-risk-ratio of kava kava is clearly in favour of benefit.**

Our result of the benefit-risk-assessment are confirmed by several experts and health authorities, amongst them the Food and Drug Administration (FDA) [17], the German Commission E [5, 6], the Bundesverband der Arzneimittelhersteller (BAH) und der Bundesverband der Pharmazeutischen Industrie (BPI), Prof. Dr. Loew [52] and Prof. Nahrsted & Dr. Schmidt [68].

4.6 Expert Opinion

The purpose of the expert report presented was, to evaluate the benefits and risks resulting from the intake of kava preparations. This has been done on the basis of a critical review of all available data concerning kava kava and an evaluation of their significance and reliability.

Evaluating all the available data, the expert considers the drug under review in this report, kava kava, an effective and safe drug in the treatment of diseases of the claimed indication. It fulfils all the criteria for evidence based medicine, and thus should be available for therapy. The Expert considers kava kava as a powerful alternative to synthetic drugs that are approved for the same indications.

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6. Expert's CV

Curriculum vitae

Dr. Joerg Gruenwald

Personal Data

Date of birth: November 19, 1950
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Education

- Goethe Gymnasium, Neu Isenburg
- University Heidelberg, Diplom Biology, 1975
- University Heidelberg Ph. D. Botany, 1978

Postgraduate Training

- 2nd Pathological Institute, Semmelweis Medical University, Budapest, Hungary, Jan.-Apr. 1980
- Pathological Institute, University of Groningen, Netherlands, Jan. – Mar. 1981

Professional Appointments

- Research Associate, Biologische Bundesanstalt Dossenheim, FRG, 1975-1978
- Research Associate, Institute for Arteriosclerosis Research at the University of Muenster, FRG, 1978-1982
- Research Associate, Mallory Institute of Pathology, Boston University, School of Medicine, USA, 1982-1984
- Head Lab. for Cytopathology, Institute for Arteriosclerosis Research at the University of Muenster, FRG, 1984-May 1988
- Director of Clinical Research, Lichtwer Pharma GmbH, Berlin, FRG 1988-1990
- Medical Director, Lichtwer Pharma GmbH, Berlin, FRG, 1990-end of 1995
- Foundation of PhytoPharm Consulting beginning of 1996, President and CEO of PhytoPharm Consulting
- Foundation of Herbalist & Doc Gesundheitsgesellschaft mbH, beginning of 1997
- Associate Partner of Background Consultancy, beginning of 1997

Professional Societies

- United States Pharmacopoeia Dietary Supplements Advisory Panel on Botanicals
- German Society for Phytotherapy
- European Scientific Cooperative on Phytotherapy (ESCOP)
- International Atherosclerosis Society

- European Atherosclerosis Society
- American Heart Association, Fellow of the Council of Arteriosclerosis
- German Society for Atherosclerosis Research
- Lipid Liga

Publications

Over 180 scientific publications in the area of phytotherapy, dietary supplements, heart disease and arteriosclerosis

- Gruenwald J, Brendler T, Jaenicke C, Scientific Editors: The PDR Family Guide to Natural Medicines & Healing Therapies, Medical Economics Company, 1999
- Gruenwald J, Brendler T, Jaenicke C, Scientific Editors: Physicians Desk Reference for Herbal Medicines, Medical Economics Company, 1998
- Blumenthal M, Busse W R, Goldberg A, Gruenwald J, Hall T, Riggins C W, Rister R S: Editors, The Complete German Commission E Monographs, American Botanical Council, 1998
- Gruenwald J, Brendler T, Jaenicke C, Editors: CD-ROM Heilpflanzen - Herbal Remedies, 1st through 3rd edition, on disk, 1996-1999
- Gruenwald J, Natürlich durch die Wechseljahre, Kabel, 1997
- over 180 scientific publications

Editor of international publications:

- Advances In Natural Therapy, (Editor in Chief)
- Nutrition Business Journal (European Editor)
- AHPA Report (European Correspondent)
- Nutraceuticals World (Contributing Editor)
- Journal of Medicinal Food (Member of the Editorial Board)

Presentations

- Speaker at over 120 scientific presentations worldwide
- Chairman or Secretary of scientific congresses, e.g. DIA Annual Meeting, Green Pharmaceuticals '98, Nutracon '99

Honors

- Organizing Committee: Second Muenster International Arteriosclerosis Symposium, 1981
- Secretary: German study group on arteriosclerosis research, 1984-1987
- Organizing Committee: European Artery Club
- Secretary: 4th Muenster International Arteriosclerosis Symposium, 1985
- Co-Chairman: Poster session of the 7th International Symposium on Atherosclerosis, 1985
- Organizing Committee: 7th European Conference on Vascular Biology, 1986
- Co-Chairman: 7th European Conference on Vascular Biology, 1986
- Organizing Committee: 8th European Conference on Vascular Biology, 1987
- Secretary: German Society for Arteriosclerosis Research, 1987-1988
- Co-Chairman: Poster session of the Conference of the German Society for Arteriosclerosis Research, 1988
- Organizing Committee: 9th European Atherosclerosis Society, 15th Anniversary Meeting, 1989
- Member of the Board: German Society for Arteriosclerosis Research, 1988-1992
- Secretary: Second International Garlic Symposium, 1991
- Member of the International Committee BAH (German Federation of Proprietary Medicine Manufacturers), since 1991

- Member of the "Grenzgebiet Arzneimittel" (Dietary Supplements) Committee BAH (German Federation of Proprietary Medicine Manufacturers), since 1995
- Member of the Drug Research and Drug Development Committee BPI (German Federation of Pharmaceutical Industries), since 1993
- Member of Publications Committee: European Scientific Cooperative on Phytotherapy (ESCOP), since 1991
- Chairman: Seventh Muenster International Arteriosclerosis Symposium, 1993
- Chairman: "International Garlic Research" Symposium at the Congress of the German Society for Phytomedicines in cooperation with ESCOP, Berlin 1996
- Session Chairman: "Opportunities and Challenges for Heterogeneous Botanical Products", 3rd Drug Information Association Workshop on Botanicals: "Botanical Testing: Developing the Scientific Evidence to Support the Medical Use of Heterogeneous Botanical Products " in Cooperation with NIH and FDA, Washington DC, 1997
- Session Chairman: "Advantages/Disadvantages of Heterogeneous Botanicals vs Single Compounds. Drug Information Association, 33rd Annual Meeting, Montréal, Canada 1997
- Workshop Chairperson: "The Role of Botanical Supplements in Health: Research Advances and Directions" 16th International Congress of Nutrition, Montréal, Canada 1997
- Session Chairman: "The Regulation and Classification of Hypericum in Europe", First International Symposium of St. John's Wort, Anaheim, California 1998
- Session Chairman: "Hypericum as Anti-Depressant", Drug Information Association, 34th Annual Meeting, Boston 1998
- Session Chairman: "Green Pharmaceuticals '98 Conference", Vancouver, Canada, 1998
- Chairman: "Herbal Extracts As Food Ingredients, Medicines & Supplements", London, 1999
- Chairman: "Utilizing and Capitalizing on the Benefits of Herbal Extracts", Frankfurt, Germany, 1999
- Chairman: "Business Opportunities for Botanicals + Dietary Supplements in Europe, Global Business Research, Nutracon '99", Las Vegas, 1999

C Appendices

Appendix I: Detailed Case Analysis

Appendix II: Case Report Data Bank (Disk)