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Health policy versus kava (*Piper methysticum*): Anxiolytic efficacy may be instrumental in restoring the reputation of a major South Pacific crop

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ABSTRACT

Ethnopharmacological relevance: Kava (*Piper methysticum* G. Forst. f.) is by far the most important plant used in the islands of Melanesia, Polynesia and Micronesia for its relaxing effects. Kava drinking is a pillar of South Pacific societies and is also the foundation of their economies. Preparations of kava extract as herbal medicinal drugs were banned in Germany in 2002 and again in 2019, with dramatic consequences for the South Pacific economies. In 2002, the major regulatory argument for the ban of kava was safety issues. In 2019, the assessment report of the European Medicines Agency's Herbal Medicinal Product Committee (HMPC) justified a negative benefit-to-risk ratio by a supposed lack of efficacy of ethanolic extracts for an indication of which kava extract preparations never had an approval. In this HMPC report the efficacy in the approved indications 'nervous anxiety, tension and restlessness' was attributed to the extract branded as 'WS 1490', which was assumed to have been prepared with acetone as an extraction solvent. In addition to this change of indication and the attribution of efficacy to acetone kava extract alone, the German health authorities and the HMPC still refuse to discuss quality issues as a likely factor impacting drug safety. The first case reports of liver toxicity were observed with an acetone extract in a timely relationship with the introduction of 'two-day kava' instead of 'noble kava' as used in ethanolic kava extracts.

Aim of the study: The correlation between clinical benefits and the type of extract preparation was examined.

Methods: In order to identify the types of kava material and extracts used in clinical trials, the respective publications were compared with regulatory databases and protocols of a German regulatory advisory board.

Results and conclusions: The comparison reveals inconsistencies in the regulatory decisions. In all studies with WS 1490, the evidence points to the use of an ethanolic extract. The efficacy of kava extract for the approved indication was clearly demonstrated. The HMPC report and the recent renewed German regulatory ban of kava therefore require major revision, which should include the impact of the use of "two-day kava" on drug safety. Such a revision could contribute to restoring the reputation of "noble kava" on the international markets.

1. Introduction

The roots of the Oceanian shrub *Piper methysticum* G. Forst. f. (Piperaceae), known as 'kava', are a pillar of Oceanian societies. The traditional kava drink, a maceration with cold water of the underground plant parts of so-called "noble kava", has relaxant effects and is regularly consumed at social gatherings (Lebot et al., 1992; Siméoni and Lebot, 2014). The kava drink produces sleepiness and distinct muscle relaxation when taken in large quantities, but it is not an intoxicant and not hallucinogenic. The unusual activity of the traditional kava drink sparked the attention of Western pharmacologists and clinicians: kava extract was recognized as a potential remedy for anxiety, with advantages over, for example, benzodiazepines due to the absence of addictive effects. One of the earliest documented recommendations for clinical uses in Germany dates back more than 110 years (Lewin, 1886).

With the fraction of kavalactones (syn. kavapyrones) identified as being responsible for the effects, dozens of pharmaceutical preparations became available in Germany as herbal medicinal products. A monograph published by the German advisory Commission E in 1990 paved the way for marketing authorizations, by accepting the indication "nervous anxiety, tension and restlessness" for preparations standardized to a defined content of total kavalactones (German Commission E, 1990). The creation of the monograph also triggered clinical

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Abbreviations

AMIS	Arzneimittelinformationssystem (Drug information system)
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
BAH	Bundesverband der Arzneimittelhersteller (German federal association of manufacturers of medicinal products)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte, German Federal Institute for Drugs and Medical Devices
BPI	Bundesverband der Pharmazeutischen Industrie (German federal association of the pharmaceutical industry)
CIOMS	Council for International Organizations of Medical Sciences
EU	European Union
FAO	Food and Agricultural Organization of the United Nations
FKB	Flavokavin B
GAD	Generalized anxiety disorder
HMPC	Herbal Medicinal Product Committee of the European Medicines Agency
GGT	gamma-Glutamyl transaminase
ICD	International classification of diseases
IKS	Interkantonale Kontrollstelle (Swiss intercantonal control authority)
RUCAM	Roussel Uclaf causality assessment method
WHO	World Health Organization

investigations to demonstrate the efficacy of kava. The first draft of the German Commission E monograph of 1988 was negative, as the existing clinical evidence was not considered sufficient for a positive claim (German Commission E, 1988). The situation changed with the submission of new clinical data, leading to the positive claim in 1990. Further data was created in the following years, including randomized, double-blind trials (see also the Supplementary Table 1). The available clinical data of products containing kava extract fulfils the conditions for formally classifying kava preparations as herbal medicinal products with "well-established use" according to Annex I, Part II.1 of EU Directive 2001/83/EC for the indication: "nervous anxiety, tension and restlessness".

It therefore came as a surprise when initial case reports of alleged liver toxicity appeared seemingly out of nowhere in 1999, triggering drug-safety protocols that ultimately led to the withdrawal of marketing authorizations, at first in Germany in 2002, and then, based on the German data, in all EU countries. The ban had a serious impact on South Pacific Economies (Schmidt et al., 2012). The South Pacific kava producing countries struggled to find an explanation for kava being suddenly labeled as a dangerous plant, when thousands of tons of kava roots and rhizomes were, and are still, consumed annually as kava traditional drinks without known adverse outcomes (Anon., 2018; Young et al., 2018).

In Europe, the "kava ban" was considered non-proportional by German courts in 2014 and 2015 (Kraft, 2014; Kuchta et al., 2015), leading to a short revival of the still existing marketing authorizations in Germany. However, the German authorities resumed the ban on 20th of December 2019 (BfArM, 2019a), employing the arguments defined in the year 2017 in an assessment report of the European Medicines Agency's Herbal Medicinal Product Committee (HMPC, 2017).

The kava debate in Europe, which initially had been triggered by safety issues, had now predominantly changed to arguments of a lack of efficacy. The simple logic behind the approach, was that a product without efficacy automatically has a negative benefit-to-risk balance if case reports of adverse events emerge. The rejection of kava efficacy for its authorized indication "nervous anxiety, tension and restlessness" by BfArM during the drug safety protocol had already been refuted by decisions of the Administrative Court of Cologne in 2014 and the Upper Administrative Court of Münster in 2015 (Sträter, 2014, 2015). The new approach differs slightly from the arguments used for the kava ban in 2002: A major argument of the German regulatory authority BfArM (seemingly supported by the HMPC assessment report) is currently that the efficacy in the indication "generalized anxiety" was not proven beyond doubt. However, generalized anxiety never was an authorized indication for medicinal kava extract preparations in Germany. Despite the court decisions of 2014 and 2015, which clearly stated that there was not sufficient evidence for a hepatic risk from use of kava (Sträter, 2014, 2015), the 20-year-old arguments regarding liver toxicity were brought up again in the HMPC assessment report and by BfArM (BfArM, 2019a, b; HMPC, 2017), in order to affirm that the risk aspect of the equation is still present. Additionally, both the German authority and the HMPC's assessment report claim that the efficacy of kava products is mainly proven by an acetone extract, whereas it is insufficiently proven for ethanolic extracts. The battle for kava is therefore currently fought along the new line of a lack of efficacy for an indication not corresponding to the marketing authorizations, and the resurrected line of hepatotoxicity, with South Pacific economies as powerless bystanders.

The major issue is currently therefore not whether kava is in fact toxic, it is regarding the evidence for its anxiolytic effects. Satisfying questions in regard to the nature of the extract used in the various clinical trials and the indication treated should not be challenging, as all clinical studies are published and available in the public domain. However, in the present context, a background check and the comparison of all available sources is worthwhile to detect possible biases.

The questions to be answered in this context are therefore:

1. How many case reports of liver toxicity with a probable causality by kava is the ban based on?
2. Could two-day kava have played a role in the sudden appearance of the case reports?
3. Which kava type was used in clinical trials: Noble or two-day kava?
4. What is the evidence of anxiolytic efficacy for kava extract preparations?
5. What was the indication tested in the clinical trials?
6. What was the safety profile of kava extract preparations in the trials, with an emphasis on hepatotoxicity?
7. Which type of Kava extract was applied in the clinical trials: ethanolic or acetone extract?

2. Methods

The following sources were used as primary sources of information: a) data from published clinical research including the full manuscripts of clinical trials, reviews and meta-analyses; b) data from the German "AMIS" database (hosted at www.DIMDI.de) showing the history and current status of marketing authorizations of German medicinal products including changes to the products; and c) protocols of the German regulatory Commission E meetings in 1988 and 1990 that ultimately led to the creation of the positive kava monograph in 1990 (obtained from BfArM upon request during the court cases). The findings were compared and compiled.

3. Results

3.1. Quantity of case reports of liver toxicity

To date the real number of case reports remains obscure. With the

first hearing letter of 8th of November 2001, BfArM spoke of 24 cases (BfArM, 2001), a number that increased to 38 in the Session of the German Commission E on 27th of February 2002 (BfArM, 2002b), and to 39 in the decision of BfArM to withdraw all marketing authorizations issued on 14th of June 2002 (BfArM, 2002a). A press release of BfArM of 17th of June 2002 spoke of 'more than 40' (BfArM, 2002c) – cases that according to a statement of the German manufacturers of 14th of August 2002 contained duplicate and even triplicate entries (BAH and BPI, 2002). A publication with data obviously received from BfArM mentions more than 100 cases, but discusses only 39 (Stickel et al., 2003), however, with case details in clear contradiction to other sources (Schmidt et al., 2005; Schmidt and Nahrstedt, 2002). The HMPC assessment report of 2017 cites 68 case reports (HMPC, 2017). A collection of 83 case descriptions collected from international sources and from literature publications gave an *ad hoc* assessment with a comparison of assessments of different authorities and other sources (Schmidt et al., 2005). Additional details and *ad hoc* analyses were offered by the working group of Teschke (Teschke, 2002, 2003a,b, 2010; Teschke et al., 2003). Another *ad hoc* analysis was made by the WHO (WHO, 2007). These analyses showed that the case against kava is built on only very few reports with a possible or probable causality by kava. The quantity of case reports is per se, no proof of causality.

The results of the *ad hoc* approach taken mainly in the early analyses were later re-examined using the CIOMS scale (also known as RUCAM scale) for drug-induced liver toxicity recommended by the WHO (Danan and Teschke, 2016; Teschke and Wolff, 2011). Again, the results by the CIOMS approach confirmed that the vast majority of case reports were in fact unrelated or highly unlikely related to kava (Teschke et al., 2008, 2010; Teschke and Wolff, 2009). In most cases the documentation was deplorably poor, and/or there was co-medication suspected of having been responsible for the adverse event.

The best-documented cases had come from the Swiss regulatory authority in 2000 after the announcement of a regulatory revision of kava on 16th of February 2000, with regular updates including case details (IKS, 2000a, b). All but one of the cases were associated with the use of an acetone extract. The single non-ethanolic case had already been published in 1998 (Strahl et al., 1998). After the application of causality assessment using the CIOMS scale for liver toxicity to all case reports as cited above and the exclusion of cases with a high likelihood of having been caused by the co-medication or co-morbidity, only four cases with a possible or probable causality by kava remained:

- One published case of a probable to certain causality with an ethanolic kava extract (Strahl et al., 1998), which was identified as a case of an immuno-allergic reaction to kava and therefore not a case of intrinsic and dose-related liver toxicity (Teschke et al., 2010);
- One published case after kava drinking in New Caledonia (Russmann et al., 2003), with a probable causality by kava (Teschke et al., 2009). No details were given on the quality and quantity of the kava consumed, especially with respect to two-day kava; and
- Two case reports, one signaled by the Swiss regulatory authority in 2000 (IKS case No. 2000–3502) and one by the German regulatory authority BfArM (# 01006939): Both were related to the use of an acetone kava extract. In both cases causality was rated as probable (Teschke et al., 2010), with no co-medication involved.

3.2. Case reports and the use of two-day kava

During the examination of the totality of case reports, it was found that a change in quality of the raw material had taken place shortly before the sudden observation of the events in Switzerland. Whereas prior to this date, all manufacturers had used a rather homogenous selection of kava varieties called "noble" in the South Pacific kava producing countries, a cultivation of so-called "two-day kava" had been established in Vanuatu specifically for the exclusive use in the manufacturing of the acetone extract. The background story is published on page 73 of a kava monograph (Siméoni and Lebot, 2014): Due to huge demand of kava roots and the ever-increasing costs beginning in 1994, the manufacturer of the acetone extract sought a solution to the problems with the purchase of kava plant material, and initiated a screening of varieties. This screening resulted in the finding that the two-day kava variety "Palisi" from Vanuatu showed considerably shorter maturation times, higher kavalactone contents (albeit with low relative quantities of kavain) and higher biomass than the typical noble kava varieties. As a consequence, this two-day kava variety was planted, harvested and exported in large quantities, contrary to regulations of the Ministry of Agriculture of Vanuatu, which opposed exports of two-day kava plant material (Siméoni and Lebot, 2014).

The first harvests of two-day kava coincided with the occurrence of the case reports (Kuchta et al., 2015; Schmidt, 2007; Teschke et al., 2011). Even though two-day kava may thus have been the reason for the sudden change in kava safety, the causative phytochemical ingredient is still not known. Two-day kavas are varieties that are phytochemically very close to the wild form of kava, *Piper wichmanni* (Lebot et al., 1992). They are not traditionally used for recreational kava drinking, as they produce adverse effects such as nausea, headaches and hang-over (Lebot et al., 1992). There is little systematic experience with the local use of two-day kava in the South Pacific islands.

Phytochemically, two-day varieties contain distinctly higher quantities of flavokavin B (FKB) than noble varieties (Lebot et al., 2014, 2019). FKB has in fact been held responsible for toxicity (Jhoo et al., 2006; Narayanapillai et al., 2014; Zhou et al., 2010), but the available data is contradictory (Abu et al., 2015; Johnson et al., 2011; Lin et al., 2009; Tang et al., 2010) and does as yet not allow drawing final conclusions on the implication of FKB. It is possible that FKB is only a surrogate marker for the occurrence of other components in two-day kava. FKB is currently used as a marker for the analytical exclusion of two-day root material in a colorimetric quick test applied in Vanuatu (Lhuissier et al., 2017). Quantification of FKB had been introduced to the quality assessment of German kava products just prior to the most recent ban.

The necessity to distinguish between noble and two-day kava recently resulted in the definition of noble kava as the prescribed quality in a draft regional standard of Codex Alimentarius (FAO, 2019b). The analytical methods were presented for endorsement in the session of the Food and Agricultural Organization (FAO) of the United Nations. Strangely enough, the observation that two-day kava had been used instead of noble kava in German products containing an acetone extract just before the first cases of liver toxicity were reported did not influence the European debate. This change of quality was even used to suspend the finalization of the Codex regional standard, as can be derived from the comments to the draft standard (FAO, 2019a). The debate is still ongoing after meanwhile 20 years, and still has economic consequences for the South Pacific kava producing countries.

3.3. Was two-day kava used in the published clinical studies?

Two-day kava was exclusively planted for the use in the medicinal product "Laitan" (Siméoni and Lebot, 2014). One of the available forms of Laitan was changed from an ethanolic to an acetonic extract in May 1998 (see below), and there is evidence that the two-day variety was in fact introduced in the manufacture of Laitan already in 1997 (Schmidt, 2007). It was, however, never available for the manufacture of ethanolic extracts of other manufacturers. With respect to the clinical studies with Laitan, there may not have been sufficient time for clinical testing of the extract made from two-day-kava, as the first case reports of severe liver adverse events in 1999 coincide with the time of the first harvests in Vanuatu. It is highly unlikely that any of the European clinical trials with Laitan was performed with the use of extracts from two-day-kava.

3.4. Clinical evidence with kava preparations

Clinical studies of varying quality standards are available with different types of kava preparations and with isolated or synthetic kavain (one of the main kavalactones). Supplementary Table 1 contains a collection of clinical data related to kava, which associates the evidence from the studies with the description of the applied product brands and their composition. Supplementary Table 1 is not meant as an assessment of kava efficacy, it merely shows the overall clinical picture. The composition of the kava preparations is not always mentioned in the publications, but it can be retrieved from regulatory databases (see Section 3.7). Drug-extract ratios (DERs) are typically not mentioned in the publications or in entries of the AMIS database. Kava extract preparations were standardized to a defined quantity of total kavalactones and thus, DERs were not declared.

Overall, 81 studies with kava extract preparations and/or isolated kavalactones were identified. Of these studies,

- Nineteen trials were performed with clearly identifiable ethanolic extract (of which 3 studies were pharmacodynamic studies in healthy volunteers;
- Seventeen trials were performed with a branded extract designated as "WS 1490" and attributed to the product Laitan. Four of these trials were pharmacodynamic studies in healthy volunteers. It will be shown in Section 3.7 that the available evidence allows concluding with a high probability that in all studies with WS 1490 and/or Laitan an ethanolic extract preparation was used;
- Four trials were performed with a combination of an ethanolic extract and racemic kavain;
- Two trials were performed with a combination product containing the same methanolic extract;
- Ten trials were performed with aqueous extracts, five of these trials were pharmacodynamic studies in healthy volunteers;
- Seven trials were performed with unknown extract preparations, where the details published in the study do not allow conclusions on the composition of the preparation (among them one pharmacodynamic study in healthy volunteers); and
- Twenty-two trials with isolated kavalactones (racemic kavain in 21 of these studies), among them nine pharmacodynamic trials in healthy volunteers.

The studies with racemic kavain were added to the Supplementary Table 1 because the efficacy of kava is generally attributed to the fraction of the kavalactones. Higher doses of synthetic (racemic) kavain are obviously required compared to kava extracts containing the sum of extractable kavalactones. In addition, natural extracts contain only the naturally occurring stereoisomer of each kavalactone. Most importantly, the studies confirm that the kavalactones are in fact responsible for the clinical efficacy. The extraction solvent matters less for clinical efficacy than the exposure to kavalactones (to which all preparations were standardized) and the treated condition.

The efficacy of kava preparations has been examined and approved in two meta-analyses (Pittler and Ernst, 2003; Witte et al., 2005) and by an assessment report of the WHO (WHO, 2007). The latter report concluded from 16 randomized and controlled clinical trials that the efficacy of kava preparations for the treatment of anxiety (without a more exact definition of the type of anxiety) was sufficiently documented.

The tension-relieving effects of kava known from traditional kava drinking are reflected in the outcomes of the clinical studies. But do the clinical trials also reflect the use in the treatment of generalized anxiety, as suggested by the HMPC (HMPC, 2017)?

3.5. Indications tested in clinical trials

The variety of indications tested in the clinical trials may seem confusing, as many trials did not explicitly address "nervous anxiety, tension and restlessness" (Supplementary Table 1). The patients in the various trials did, however, show symptoms that may be summarized under this description. Some studies tested patients with generalized, neurotic anxiety (GAD) according to ICD-10 F41.1 or DSM-IV (Boerner et al., 2003; Connor and Davidson, 2002; Connor et al., 2001, 2006; Gastpar and Klimm, 2003; Sarris et al., 2011, 2013a, 2013b; Watkins et al., 2001). The study of De Leo et al. (2000/2001) mentions generalized anxiety (De Leo et al., 2000, 2001), but this diagnosis does not fit to the inclusion of women with menopause-related anxiety, as generalized neurotic anxiety has by definition no identifiable cause.

The studies of Connor et al. did not confirm efficacy in GAD. However, a lack of efficacy of kava in the treatment of GAD cannot be concluded from these studies. They were interrupted at a very early stage due to the start of the safety debate in Germany. The number of included patients was insufficient to allow a statistically valid result. A recent study of Sarris et al. provides more reliable evidence that GAD is no indication for treatment with kava products (Sarris et al., 2019). This is also confirmed by an observational study on the most promising indications of kava extract (Schmidt et al., 2020).

In addition, the treatment of GAD in clinical trials requires long-term studies with a duration of at least six months (EMA, 2005). The HMPC assessment report points out that the majority of the kava trials did not reach this minimum duration for GAD treatment (HMPC, 2017), which contributed to the HMPC's conclusion on the inefficacy of kava. The HMPC used a simple approach: if the indication of kava is GAD and the duration of an individual trial is less than six months, the efficacy cannot have been proven in conformity to the guideline. These studies were then excluded from the assessment of efficacy. In fact, only three clinical trials with a duration of six months were identified (see Supplementary Table 1):

- WS 1490/Laitan was used in a placebo-controlled trial with a duration of 25 weeks. The study was performed by treating patients with anxiety of non-psychotic origin, hence explicitly not GAD (Volz and Kieser, 1997). As will be shown below, there is evidence that the study preparation was, at the time of the study performance, still an ethanolic extract.
- In a case report with a single patient treated with an ethanolic extract, the duration of exposure was stated with six months. The author speaks of GAD, but mentions fear of riding airplanes and fear of speaking in public, which is clearly not GAD (Boerner, 2001).
- A study with six months duration was presented with a treatment of menopausal women undergoing hormone replacement therapy and anxiety defined by the authors as GAD (De Leo et al., 2000, 2001). As already mentioned, the definition of GAD is questionable in this case, as by definition there is no recognizable cause for anxiety in GAD. The kava preparation used in this trial is unknown, the publication merely mentions 100 mg of kava extract with 55 percent of kavain.

Overall, there is no reason to define GAD as the translation of the original German Commission E definition of "nervous anxiety, tension and restlessness" into terms of the International Classification of Diseases (ICD-10 F41.1). In contrast, the available studies show good outcomes in the treatment of situational, non-neurotic anxiety, tension and restlessness, which would rather correspond to ICD-10 classifications F40 (context-related phobias), ICD-10 R45.0 (nervous tension) or ICD-10 R45.1 (restlessness and excitation).

3.6. Safety profile of kava

Kava was shown in the clinical trials to be exceptionally safe (Supplementary Table 1). There was no major adverse event, and especially no hint to hepatic adverse events in 14114 patients and healthy subjects exposed to kava preparations. The observation of gamma-glutamyl transaminase (GGT) and alkaline phosphatase (AP) elevations

Table 1
History of 'Laitan' in the AMIS database. MAH = Marketing authorization holder.

Date	'Laitan 100'	'Laitan'
1.1.1978	Entry into the German register of medical specialities under the name of "Geriatrikum". Entry code: 0836112 MAH: Stern-Apotheke Gerd Brinkmann Composition per capsule: 150 mg ginseng extrakt and 100 mg Kava extrakt (extraction solvent ethanol/water)	Entry into the German register of medical specialities under the name of "Plantival". Entry code: 0402081 MAH: Dr. Willmar Schwabe GmbH & Co. KG Composition per film-coated tablet: Valerian root extract, hops extract, passionflower herb extract, and oat herb extract. → No Kava!
22.12.1986	New MAH: Sobripharm Gerd Brinkmann	
18.5.1987	New MAH: Waltraud Ploss-Koschier	
27.8.1987	New MAH: W. Spitzner Arzneimittelfabrik GmbH	
22.2.1988	New MAH: Dr. Willmar Schwabe GmbH & Co. KG, Berlin	
13.9.1988	Submission of data to the German Commission E	
6.10.1988	New product name: "Kavamed" New composition: Per capsule 100 mg kava extract (extraction solvent ethanol/water)	
1989	Negative monograph of the German Commission E	
13.4.1989	Submission of data to the German Commission E	
22.6.1989	Submission of data to the German Commission E	
8.12.1989	New product name: "Laitan" Unchanged composition.	The name is still "Plantival" and the product still does not contain kava.
1.6.1990	Publication of positive monograph of the German Commission E	
12.6.1990	New product name: "Laitan forte" Unchanged composition.	
21.6.1990		New product name: "Laitan" Change of application form from film-coated tablet to capsule. New composition: Capsules with 50 mg of dry extract from kava roots
8.7.1991	New product name: "Laitan 100". Changes to the packaging texts	
5.12.1991	Changes to the packaging texts, probably approval of the introduction of the 70% kavalactone formulation.	Changes to the packaging texts, probably approval of the introduction of the 70% kavalactone formulation.
31.1.1994	Changes to pack sizes and packaging texts	
30.3.1994		Changes to pack sizes and packaging texts including specifications of adverse effects
22.3.1995	Change of extraction solvent and declaration: Kava-Kava rootstock, dry extract with acetone/water, 30–110 mg	No change to extract
24.6.1996	W. Spitzner Arzneimittelfabrik GmbH gets distribution rights	
26.5.1998	Marketing authorization and change of dose per capsule: Kava-Kava rootstock, dry extract with acetone/water, 90–110 mg Marketing authorization number 6836112.00.00	
25.3.1999	Prolongation of shelf-life from 3 to 4 years	
11.5.1999	Changes in adverse effects sections in package leaflet and summary of product characteristics	
29.10.1999	Changes in pack sizes	
20.7.2000	Changes in adverse effects sections in package leaflet and summary of product characteristics	
15.11.2000	New MAH: W. Spitzner Arzneimittelfabrik GmbH	
7.6.2001	New MAH: Dr. Willmar Schwabe GmbH & Co. KG; Spitzner is granted distribution rights.	
14.6.2002	Withdrawal of marketing authorization	Withdrawal of marketing authorization

reported in heavy kava drinkers (Cairney et al., 2003a, 2003b) does not count as hepatotoxicity, as firstly a high percentage of the non-kava drinkers also showed elevations, and secondly the indicators of hepatotoxicity, i.e., the transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were not elevated. Overall, the safety profile deducible from clinical studies is benign and certainly does not confirm a hepatic risk.

3.7. Which type of kava extract was used in clinical studies: ethanol vs. acetone

One might presume that the type of preparation used in a clinical trial can easily be derived from the publication. Unfortunately, this is frequently not the case. Often, only a reference to a brand, and sometimes even only to a branded extract, is provided (Supplementary Table 1). Most studies performed with an ethanolic kava extract refer to a trade name of the medicinal product applied in the trial, which means that the exact composition – if not mentioned in the publication – must be identified by other means. In all studies where the study medication was identified as an acetone extract by the draft version of the HMPC assessment report on kava (HMPC, 2016), the extract WS 1490 was mentioned, and practically always the study referenced to Laitan. With one exception (Gastpar and Klimm, 2003), none of the clinical trials mentioned the extraction solvent. To the contrary, in a review examining the details of four clinical trials with patients exposed to 3 × 100 mg of WS 1490 daily, the extract was reported as ethanolic (Volz and Hänsel, 1994). The same review also gives details on the extraction procedure, which the authors presumably received from the manufacturer. Adding to the confusion, a marketing text of the manufacturer, also published in 1994, described WS 1490 as an acetone extract (Habs and Honold, 1994).

Quite obviously, the characterization of extracts used in clinical trials is not possible using the publications as the sole source of information. Additional sources of information are the databases of the regulatory authorities.

The history and composition of medicinal products originally authorized in Germany were publicly available through the "AMIS" database hosted at www.dimdi.de. The facts retrievable from this database showed, among other details, the exact dates when details of medicinal products such as ownership, composition or packaging texts were changed, and when the products received their marketing authorizations. Frequently, the history of a German herbal medicinal product begins with the entry into the national register of medical formulations in 1978. Based on new legislation, a documentation of quality,

toxicological safety and clinical efficacy had to be submitted subsequently. Until the granting of an official marketing authorization, the products had the status of "fictitiously authorized" medicinal products. All changes to products during and after the authorization process including the approvals were noted in the AMIS database.

For the ethanolic extract preparations the information from the AMIS database is unequivocal, as the extracts have not changed over time. Things are more complicated with the specific product "Laitan", as two different marketing authorizations existed for the same brand name: "Laitan" with 50 mg extract per capsule and "Laitan 100" with 100 mg extract per capsule. For reasons of simplicity, the two marketing authorizations will be called "Laitan 100" and "Laitan 50" in the following considerations, although the name "Laitan 50" never existed. The two marketing authorizations did not merely describe two strengths of the same product, but were independent products. Table 1 shows the history of both products, including a major change in the extract composition of Laitan 100 in 1995, when the manufacturer submitted a variation for changing the extraction solvent from ethanol to acetone. The new solvent was officially approved in 1998. With the background of this change, it becomes important to assess the type of extract used in the individual clinical trials.

Comparing AMIS data with the time of the performance of a study enables us to draw conclusions on the composition of the product used in the trial. EU medicines legislation only allows the marketing of an approved composition. Patients can therefore only be exposed to a defined medicinal product after its official approval – for the acetone form of Laitan 100, this means post May 1998 (Table 1). The focus of this examination therefore went to the identification of the period of study performance and the correlation with the entries in the AMIS database.

3.7.1. Period of study performance

There is no open question with respect to the composition of Laitan 100 in the studies published before 1998, the year of the official approval. Any study performed with Laitan 100 before 1998 must have been performed with an ethanolic extract. In contrast, the situation in studies published after 1998 and in studies performed with Laitan "50" at all times is more complicated, because in these cases the extraction solvent is not openly labelled in the AMIS database (see Section 3.7.3).

The information on the period of time during which patients were exposed, was virtually never provided in the publications of clinical trials with kava preparations. With the withdrawal of marketing authorizations on the 14th of June 2002 (BfArM, 2002a) and the subsequent ban all over Europe, clinical trials could no longer be performed in Europe with European kava extract preparations. Studies with aqueous extracts from Australia were not affected by this limitation, but any study performed in Europe with European extract preparations after the date of the ban was published retrospectively.

A thorough cross-examination of published studies can provide indicators of the time when another study was actually performed. For example, if "study B″ gives a reference to "study A″ as "submitted for publication", as "unpublished study report", or as a poster presentation, study A must have been performed before the publication date of study B, and must therefore necessarily have used the active constituent available and authorized at the time of the study performance. The complete details of the cross-references are collected in the Supplementary Table 2. For example:

- The study of Woelk et al. (1993) cites the study of Herberg (1993) as a poster presentation of 1992. It can therefore be concluded that Herberg (1993) must have been performed in 1992 or before.
- Woelk et al. (1993) also cites the later publication of Heinze et al. (1994) with the statement 'publication in preparation'. Consequently, Heinze must have been performed in 1993 or earlier.
- The data of Woelk et al. (1993) is cited in the review of Jans and Krall (1993) as a study report of 1992. The study of Woelk et al. (1993) must therefore have been performed in 1992 or earlier. Both studies, Woelk et al. (1993) and Heinze et al. (1994) were performed with Laitan 100, which, at the time of the study performance, was registered in the AMIS database as an ethanolic extract (Table 1).
- Similarly, Johnson et al. (1991) cite Emser and Bartylla (1991) and Kinzler et al. (1991) as 'unpublished communications of 1990'. Whereas the publications of Johnson et al. and Emser and Bartylla (1991) used both, Laitan 50 and 100, in the same patients, Kinzler et al. (1991) used Laitan 100 only, and thus unequivocally an ethanolic extract.
- The meta-analysis of Pittler and Ernst (2000) identified the study later published by Malsch and Kieser (2001) with data from a poster presentation in the year 1998.
- According to the meta-analysis of Pittler and Ernst (2003), the trials of Gastpar and Klimm (2003), Geier and Konstantinowicz (2004) and Lehrl (2004) were still unpublished data at the time of the kava ban by BfArM in 2002.

3.7.2. Could a developmental acetone extract have been used in the trials?

Could the study medication "WS 1490" have been a developmental extract later officially authorized? Could a study have been performed with acetone extract before its official regulatory approval? There was a patent published by the company Schwabe in 1992, describing the manufacture of kava extract with organic solvents including ethanol and acetone (Schwabe, 1992). Even though this patent discusses the benefits of an acetone extraction, it contains a graph of clinical effects taken from the publication of Warnecke (1991) – a study performed with Laitan 100, which at the time of the study was labelled as ethanolic in the AMIS database. The patent does therefore not help in clearing the confusion.

The use of an acetone extract is hardly conceivable for the published kava studies. In all cases the study product was identified as the branded extract WS 1490, and in all but the duplicate studies of Münte et al. (1993) and Heinze et al. (1994) this branded extract was identified by the trade name "Laitan". Laitan was not a developmental product, it was approved and had an authorized composition. It would be misleading and ethically questionable to refer to an existing product in a publication, whereas in fact the patients were exposed to another composition. The probability that this happened with kava extract seems extremely low.

3.7.3. WS 1490: One extract used in two marketing authorizations

As already mentioned, WS 1490 was marketed as the active constituent of two different medicinal products, which were both called "Laitan" (Table 1). However, the designation as WS 1490 was used for both products in publications. Did the products only differ in their dose?

The AMIS database reveals an eventful history of the two marketing authorizations. Laitan 100 started as a fictitiously authorized combination product with, among other constituents, ethanolic kava extract, which was then transformed into a monopreparation with kava extract. Laitan 50 had the same regulatory status as a fictitiously registered medicinal product and did not even contain kava until the 21st of June 1990 – after that date Laitan 50 was also was a monopreparation with kava extract. For Laitan 100 mg, but not Laitan 50, an application for a switch to acetone extraction was submitted by the marketing authorization holder on the 23rd of May 1995. Laitan 100 received its official marketing authorization three years later, on the 26th of May 1998 (Table 1).

Laitan 50 remained unchanged in the status of a fictitious marketing authorization until the withdrawal of both approvals by the decision of BfArM in the drug safety protocol on the 14th of June 2002.

Overall, the evidence from the regulatory database confirms that WS 1490 and the brand Laitan in its 100 mg form was an ethanolic kava extract, and only from 1998 on Laitan 100 was approved as an acetone extract.

After the switch of Laitan 100 mg to an acetone extract, there were suddenly two different medicinal products on the market using the name 'Laitan'. The clinical studies published after 1998 continue using the

brand name WS 1490. This situation may have contributed to the impression of the HMPC that 'Laitan' and 'WS 1490' were identical – which was obviously correct before 1998 – and that all studies with Laitan/WS 1490 were performed with acetone extract, which was clearly not the case.

3.7.4. If Laitan100 was originally ethanolic, could Laitan 50 form have been an acetone extract all along?

There is of course the improbable possibility that Laitan 50 was always an acetone extract. The AMIS database does not mention the extraction solvent in this case, stating "extract without further details". This possibility is unlikely though: as already shown, the extract designation WS 1490 was used indiscriminately for both, Laitan 50 and 100 (see Supplementary Tables 1 and 2), sometimes even in parallel for dose-effect comparisons in the same patient (Emser and Bartylla, 1991; Johnson et al., 1991). It would be inconceivable if two different extracts had been used in these trials without mentioning this in the publication. It can therefore be assumed that the two forms were identical. This is confirmed by the publication of Geier and Konstantinowicz (2004), who describe their study preparation with 50 mg as "a lower dose of our kava special extract WS 1490".

The extraction solvent acetone was never mentioned in any of the clinical studies published with WS 1490, with the exception of the trial by Gastpar and Klimm (2003). Gastpar and Klimm (2003) state that their test preparation was Laitan, containing 50 mg of the acetonic extract WS 1490 per capsule. This statement cannot have been accurate: WS 1490 was always used to describe the ethanolic extract, and Laitan 50 mg was never switched to acetone (see Supplementary Table 2).

Three studies stating the use of Laitan 100 = WS 1490 were published after 1998 (Boerner and Klement, 2004; Lehrl, 2004; Neto, 1999). Two of these studies were published after the kava ban in 2002. The available data do not allow concluding on the exact time of the study performance. In any case it is inconceivable that the extract designation WS 1490 was used for completely different extracts.

3.7.5. Further evidence from the German Commission E

More details can be derived from the development of the kava monograph of the German Commission E. There was an initial negative monograph issued in 1988 (German Commission E, 1988), which led to a call for data for a new attempt. The protocols of the negative 1988 monograph and the positive 1990 version show that clinical data was submitted to the Commission E. The submitted data can be identified in studies officially published after 1990, and the protocols of the German Commission E mention technical details on the kavalactone concentrations in the extracts. Two of the studies are identifiable as the later published trials of Kinzler et al. (1991) and Warnecke (1991), and both were, according to the protocol of the German Commission E, submitted as studies with an extract containing 20% kavalactones and a daily dose of 60 mg. In the publication of both studies, the tested product is described as "Laitan" at the dose of 100 mg kava extract with 70% kavalactones three times daily (Kinzler et al., 1991; Warnecke, 1991). At the time of the publication this corresponded to the listing of Laitan 100 in the regulatory database AMIS – explicitly as an ethanolic extract until 1998.

An additional indicator that WS 1490 was identical in Laitan 50 and 100 came from marketing events of the marketing authorization holder. As shown in Table 1, the entries in the AMIS database allow for the conclusion that the 70% kavalactone concentration was introduced in parallel for both authorized preparations on the 5th of December 1991. On 7th of December 1991, the marketing authorization holder used this development for a press conference where results of two studies with WS 1490 (Kinzler et al., 1991; Siegers et al., 1992) were presented. Kinzler et al. (1991) had tested Laitan 100, Siegers had applied Laitan 50. The presentation of both forms under the labelling WS 1490 confirms that both extracts were, in fact, identical (Hahn, 1992; Stingl, 1992).

3.7.6. Conclusions on WS 1490

The comparison of the clinical trial publications with the Commission E protocols and the AMIS database confirms that WS 1490 did not describe an acetone extract. It also reveals that the introduction of the 70% kavalactone concentration probably took place in 1991. This kavalactone concentration is typically reached with ethanol as an extraction solvent. More specifically, the correlation of the available data allows for the conclusion that possibly all of the clinical studies with WS 1490 were performed with an ethanolic extract.

4. Conclusions

The questions raised in this analysis are answered as follows: The authorized and clinically examined indication of kava extract is the treatment of nervous anxiety, tension and restlessness – confirming the long-standing experience with kava drinking in the South Pacific. With a demonstrated benefit and no important evidence of adverse events with noble kava the benefit-to-risk ratio can be rated as positive.

The correlation of the different sources of information on the kava extracts used in the clinical trials confirms that all clinical studies with WS 1490 were performed with ethanolic kava extract. In the case of Gastpar and Klimm (2003), the only study mentioning acetone as the extraction solvent, all study details including the drug-extract ratio, the 50 mg dose and the references to the "same extract" clearly point to an ethanolic extract. More specifically, the frequent automatic equation of the product "Laitan" and the branded extract "WS 1490" with acetone extract seems to be the result of a successful marketing strategy.

As the kava extracts from the studies with WS 1490/Laitan were identified as ethanolic, it becomes clear that all studies examined in the meta-analyses used ethanolic extracts, which supports the positive benefit-to-risk ratio of the ethanolic extract. In addition, the analyzed studies cannot have been performed with two-day kava, which means that the meta-analyses more specifically confirm the efficacy of ethanolic extracts of noble kava in the authorized indication "nervous anxiety, tension and restlessness". There is therefore no doubt with respect to the anxiolytic efficacy of kava as such, but only with respect to the indication GAD. A lack of efficacy for GAD does not justify the deduction of a lack of efficacy in the indication "nervous anxiety, tension and restlessness" as approved by regulatory authorities. The HMPC's assessment report is therefore based on the scientifically unjustified assumptions that GAD is the indication for kava, and that the trials with WS 1490 were performed with an acetone extract. Additionally, the report does not adequately examine the case reports of adverse events by simply accumulating case numbers with no appropriate causality assessment, especially with the background of the use of two-day kava for the acetone extract product just prior to the observation of the severe case reports of liver toxicity with this specific product. The HMPC's assessment requires urgent revision.

The details presented in this analysis are more easily available to regulatory authorities than to scientists. The history of kava extract preparations as medicinal products therefore raises questions with respect to the regulatory decisions taken, decisions that had a severe impact not only on the German marketing authorization holders, but also on the South Pacific kava producing countries:

- What was the base for the officially documented change of the extraction solvent from ethanol to acetone for Laitan 100 in 1998? A variation of this magnitude corresponds to a change of the active pharmaceutical ingredient (API), which requires a detailed documentation of the safety and efficacy of the new form of the API. There is no trace of clinical studies definitively performed with acetone extract, as all published clinical evidence points towards WS 1490 as an ethanolic extract. So how could BfArM approve this variation and at the same time oppose the prolongation of marketing authorizations of other ethanolic extracts?

- How could noble kava be replaced by two-day kava without any trace of an application for a regulatory variation? This substitution can hardly have been undetected by BfArM. Such a change in raw material would today be regarded as a major change of the API by BfArM.
- How could BfArM accept the same trade name "Laitan" for two different extracts after the approval of the switch to acetone extraction for Laitan 100 in 1998? Regulatory experience shows that BfArM usually sees a danger of confounding products even when an API or a manufacturing method varies only slightly.
- Why does BfArM still reject a differential assessment of case reports of kava hepatotoxicity despite regulatory definitions that such a differentiation is required for different types of extracts? Why, in addition to this, do BfArM and the HMPC still rely on the unsuitable methods of adverse event case assessment?

The analysis of the available facts has disclosed evidence of regulatory discrepancies. Some of the assumptions presented herein could be strengthened or confirmed by examining the documentation that led to the regulatory decisions. This would have been the task of the regulatory authority, as they have direct access to the documents. The question is therefore, which steps have been taken by the authority to ensure that the interested parties were correctly informed in the drug safety protocol? The German legal system would even allow the authority to access the sponsors of the clinical trials with requests for more data, especially when there is doubt with respect to the correctness or completeness of the characterization of the preparation to which the patients were exposed in the clinical trials and/or in the case reports of adverse events. There is no indication from the 20 years of debate in the kava safety protocol that this was ever done.

These inexplicable inconsistencies in the long story of the kava debate will perhaps need to be revised in the future. The kava producing South Pacific countries themselves currently have few options to intervene. They are not involved in the running court cases directed against the renewed revocation of marketing authorizations of kava preparations in Germany. The withdrawal of kava-containing medicinal products from the EU market is, from the legal perspective, an internal issue of the system of marketing authorizations of medicinal products in Europe. The withdrawal does not limit the rights of kava producing countries to trade kava roots and rhizomes. In reality, however, the decisions in Germany, subsequently taken over by the EU member states, have been crippling the economies of the South Pacific kava producing countries. Examining the backgrounds of the regulatory activities against kava may in the long run help restore the reputation of noble kava as a major crop of the South Pacific island nations. It may also help restore and expand the potential of noble kava as an active constituent of evidence-based herbal medicinal products. The revision of the HMPC monograph and correction of several errors and false assumptions therein would be an excellent start.

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