



For several decades kava products have been used as registered drugs for the treatment of anxiety problems in Europe, especially in Germany and Switzerland. In 1990 the German Commission E issued a positive monograph for dosages of 60-120 mg kava pyrones and limited their use to three months without medical advice. The interactions, specifically with alcohol, barbiturates and psychopharmacological agents, were clearly indicated. We

disclosed its intention to possibly withdraw the market authorization of these products. Companies were given limited time to respond to this notice. This activity was based on adverse event reports concerning possible liver-toxic effects of kava. To our knowledge, at least 30 cases have occurred in Germany so far. Unfortunately, most of these reports have not been published, nor is the data readily accessible for review. Furthermore, most publications do not give the full picture; often, the case history is incomplete. The few available case reports in the literature range from credible to inconclusive. However, one exitus, four liver transplants and several cases of hepatitis and jaundice have been linked to kava use, a matter which cannot be taken lightly and needs thorough investigation.

While the first reports of a possible connection between kava and liver problems are reported in the *PDR for Herbal Medicines* from 1988 (Australia) and 1998 (Germany), recent findings came from Switzerland, followed by Germany. In eight cases, side effects (four serious cases) were recorded that could be related to kava intake at dosages of 140-210 mg kavalactones per day. Most of these patients took acetone extracts. This led to the withdrawal of kava preparations based on acetone extracts in Switzerland, whereas ethanolic extracts were still on the market. The Swiss IKS was the first national authority to prohibit the marketing of certain kava preparations.

The list of available cases in Germany (*Table 1*) suffers from several shortcomings. Of the 30 cases, eight reports (27%) do not state the duration of kava intake until the appearance of the first symptoms. In 11 cases (37%) kava was taken for a longer period than the recommended three months; three people took kava preparations in very high dosages for more than a year. In nine cases (30%), not even the dosage is given. Fourteen patients (47%) took higher dosages than the recommended daily dosage—in some

# Kava: The Present European Situation

A look at the controversy.

By Joerg Gruenwald and Janine Freder

estimate an annual use of over approximately 70 million daily doses in Germany and over 100 million daily doses in Europe based on the sales figures of kava products. In the international context, this usage is only a small percentage compared to the local use of kava in Polynesia, where approximately 70-80% of all consumption is estimated to take place.

Based on these figures, kava belongs to the group of most used herbal medicinal products worldwide that have been regarded for a long time as safe when used as directed. The efficacy is well proven in many properly performed placebo-controlled double-blind studies and the positive effects on mental health problems, especially anxiety, are well documented.

The risk-benefit relationship has been under discussion recently, when producers of kava products and companies that wanted to register new kava products in Germany were informed of possible side effects.

On November 8, 2001 the German Federal Institute of Drugs and Medical Devices issued a letter to all manufacturers of herbal medicinal products containing kava manufactured and marketed in Germany. The Institute

*Dr. Joerg Gruenwald is president and Janine Freder is senior consultant of PhytoPharm Consulting, a specialized business consulting company for herbal medicine, dietary supplements and functional food and author of the PDR for Herbal Medicines. Both authors can be reached at PhytoPharm Consulting, Waldseeveg 6, 13467 Berlin, Germany; 49-30-40008100, Fax: 49-30-40008500; E-mail: jgruenwald@phytopharm.org; www.phytonet.com.*

cases up to four times that of the highest recommended dosage. Furthermore, half of the patients were over 60, which implies a certain susceptibility to multi-morbidity.

The liver is a very sensitive organ that—especially in the Western world—has to deal with a lot of toxins during one's lifetime. A diet rich in fats, the consumption and perhaps misuse of alcohol and nicotine, as well as modern medications and chemical pollutants, have done their share in weakening the detoxification unit of the body. In the case of the patient who died during kava treatment, the liver was probably damaged by alcohol abuse, as stated in the report. One of the patients receiving a liver transplant also reported "mild alcohol use," which leads to one of the problems with case history. People tend to either deliberately withhold information about their alcohol intake or to underestimate it. Furthermore, co-medication was not thoroughly investigated, which leads to a distorted physiological picture.

The withdrawal of the marketing authorization would only be reasonable when it is assumed that kava has no benefit and the side effects are so severe that the benefit-risk-ratio is infinitely negative. The 30 cases listed by the German Federal Institute of Drugs and Medical Devices demonstrate that it is of paramount importance to conduct further investigations on the mechanisms of the assumed hepatotoxic effects of kava. The data at hand is not completely conclusive. Even if, in some cases, liver transplants have been deemed necessary, more than 100 million single daily doses have been sold every year only in Europe.

A recent evaluation reported an incidence of hepatotoxicity with kava use of 0.23 cases per 1 million daily doses. The causality in most cases remains questionable due to co-medication (other drugs including Paracetamol), a history of alcohol abuse or viral infections, all known to possibly interfere with liver function. Other psychotrop-

**Table 1**  
REPORTED CASES OF LIVER PROBLEMS IN PATIENTS  
USING KAVA IN GERMANY  
*(Many different preparations/products are included in these cases;  
please contact PhytoPharm Consulting for further information)*

Mg/Day	Extract	Outcome	Months Uptake	Other Medications
120	ethanol	death	9	3
60	ethanol	transplant	7	4
240	ethanol	transplant	5	3
240	ethanol	transplant?	3	1
480	ethanol	transplant	12	2
280	acetone	transplant	2	2
210	acetone	jaundice	4	3
210	acetone	hepatitis	24	2
210	acetone	hepatitis	2	3
70	acetone	liver insufficiency	0.75	1
70	acetone	jaundice	0.5	—
500	Kavain	liver cell damage	2	4
120	ethanol	hepatitis	3	1
120	ethanol	hepatitis	1	1
400	Kavain	hepatitis	?	3
400	Kavain	hepatitis	?	—
210	acetone	increase in liver enzymes	?	—
210	acetone	hepatitis	?	3
210	acetone	hepatitis	?	?
240	?	liver cell damage	4	1
60?	?	hepatitis	6.5	3
?	acetone	liver cell damage	0.5	1
?	ethanol	increase in liver enzymes	1	1
?	ethanol	hepatitis	3	1
?	ethanol	liver cell damage	?	?
?	ethanol	liver cirrhosis	4	—
?	Kavain/ethanol	hepatitis	?	4
?	?ethanol	hepatitis	6	1
?	?ethanol	hepatitis	24	1
?	?	liver cell damage	?	3

ic agents like benzo-diazepines, neuroleptics or anti-depressants are known to have similar or higher incidents of hepatotoxic adverse effects.

Kava preparations have been demonstrated to be effective anxiolytics. For patients suffering from panic attacks or anxiety, taking kava preparations is often the first step towards a "normal," anxiety-free life. Afterwards, other forms of therapy, such as psychotherapy or autogenic training, are effective. The prescription of

chemico-synthetic medications such as benzodiazepines seems to be a questionable alternative as these medications have side effects and, more importantly, may lead to dependence. Thorough research into kava is necessary to gain information about the pharmacokinetics, distribution, metabolism and hepatic elimination mechanisms as well as the mechanism of liver toxicity itself. Only when the evidence is there can valid statements be made about the safety concerns

regarding kava. Better labeling is clearly required regarding co-medica-

tion, alcohol usage, etc. A physician should be consulted when other drugs

are taken or when the user has severe diseases.

NW

## Perspectives on the Potential Hepatotoxicity of Kava as Reported in Europe

*The following is additional commentary on the kava situation from a North American perspective, by Mark Blumenthal, founder and executive director, American Botanical Council, Austin, TX.*

The American Botanical Council (ABC) has been very interested in the issue surrounding the case reports of hepatotoxicity associated with ingestion of kava since isolated reports began surfacing recently. We have been collecting data on this subject and have been in contact with some of the German regulatory officials and leading scientists at some of the phytomedicine manufacturers.

The letter sent on November 8 to manufacturers of kava products by the German Federal Institute of Drugs and Medical Devices (BfArM) proposed to withdraw the drug registrations of kava products, pending receipt of data to be submitted by the companies. Those submissions were to be made within four weeks; however, an extension was granted to December 21. As we go to press, the fate of kava in the German market is still unclear.

Based on the case reports of kava hepatotoxicity, Swiss authorities have removed it from the market. Dr. Gruenwald's article points out that this was an acetone solvent-based kava product (highly concentrated and standardized to 70% kavalactones). Ironically, this product has been the subject of most of the clinical trials on kava documenting its safety and efficacy for treatment of symptoms of anxiety. Some readers may incorrectly infer that this would implicate only the acetonic extracts. However, five of the six most serious cases of adverse hepatic effects are associated with ethanolic extracts. While only the acetonic extracts are off the Swiss market at this time, the government has given manufacturers of ethanolic extracts three years to market these products and monitor their safety to see if any liver problems are reported. In addition, all manufacturers of ethanolic extracts in Switzerland have been asked to prove safety and efficacy by conducting new toxicological and clinical trials. (This may pose a significant financial

challenge to these mostly small companies.) It should be no surprise that the initial reports in Switzerland pertain to acetone extracts; they dominate the market there with an approximately 80-85% share, with the ethanolic extracts comprising the balance.

Regarding kava in North America, to date there are no reports of adverse reactions related to hepatic dysfunction associated with the use of kava in the U.S. or Canada. ABC and the American Herbal Products Association (AHPA) have checked the FDA database of AERs related to herbals and found 35 adverse event reports (AERs) *purportedly* associated with kava use. However, a closer inspection of those AERs reveals that 29 of them are based on the infamous "fX" case in which a young man doled out ersatz "kava" doses at a New Years Eve rave in Los Angeles in 1996. The fraudulent products contained 1,4-butanediol and contained no kava whatsoever (or any other herbs or natural products). This case received widespread publicity, the perpetrator's business was closed by federal and state health authorities and he served a prison sentence. Thus, these AERs have nothing to do with kava and should not even be reported as kava AERs in the FDA database. AHPA has contacted FDA and asked the agency to remove these erroneous and highly misleading reports.

The balance of FDA's kava-related AERs contain products that are combinations of numerous herbs and other materials, except one, a single kava product, with the reported adverse effect as "deep somnolence," an intended effect of numerous kava users and a debatable adverse effect. None of the AERs relate to liver function.

There is a question as to whether the potential hepatotoxicity issue is one that pertains to Europe only or if it presents a potential health problem to kava users in the U.S. One discredited allegation is

based on the solvents used in some of the European products, but as noted above, a review of the AERs in Germany and Switzerland shows that ethanolic extracts are also implicated. The argument that acetonic extracts are the culprit thus does not hold up.

The other much more plausible explanation is that the Europeans have a more well developed pharmacovigilance system for catching AERs associated with herbs and phytomedicines and this is possibly the reason that the hepatic AERs are showing up in Europe and not here in the U.S. (This assumes that there are AERs in the U.S. although there is no evidence of any.)

ABC has been in constant contact with representatives of several leading trade associations in the herb and dietary supplement industry. They are taking this issue very seriously. ABC is working with AHPA, the Council for Responsible Nutrition and the National Nutritional Foods Association in an attempt to conduct a proper evaluation of the case reports from Germany, to the extent that adequate information is made available.

A review of the 30 cases reported in Germany and Switzerland is instructive. Of the 29 or 30 cases reported (there may be one duplicate report), 18 appear to be associated with the concomitant use of prescription medications, most of which are known or suspected to be hepatotoxic. Thus, whether some of these AERs are results of the Rx drugs, the interaction of kava and the Rx drugs, or the kava products used still remains to be determined.

There are obviously many more issues to be reviewed and resolved on this matter and by the time this is published, events will probably have progressed quickly. Whatever the outcome, this is clearly one of the most serious challenges ever experienced to the medicinal plant community in recent memory.