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## REPORT ON KAVA AND LIVER DAMAGE

February 15, 2002

To: Mr. Michael McGuffin  
President  
American Herbal Products Association  
8484 Georgia Avenue, #370  
Silver Spring, Maryland 20910

This report has been prepared at the request of the American Herbal Products Association, acting in conjunction with other trade associations of the dietary supplement industry. I have been asked to review information regarding the use of kava (*Piper methysticum*) and its relationship to reports of liver damage in some users. This report is based on my training and over 25 years experience as a toxicologist, including experience in evaluating both the physiological activity and potential toxicity of plant and herbal materials. My curriculum vitae is appended to this report.

I have been provided a variety of documents in connection with recent reports and/or investigations in Europe and in the United States into the alleged association between the consumption of the herbal product kava and liver damage.

Specifically, I have been asked to review and evaluate (1) twenty-six Adverse Event Reports to the Food and Drug Administration (FDA) that have been made public by the FDA (these reports do not contain medical records or other non-FDA generated information), (2) summaries prepared by German health authorities and by companies in Germany of approximately 30 adverse event and case reports collected by European agencies over the past eleven years (no medical records or original reports were made available to me on these cases). The latter reports

plant material and its extracts. Any basis for this concern, including reports of serious medical conditions or death, must be tempered by a rational and scientific analysis of the reports alleging liver damage attributable to kava.

Within this context, I have reviewed the written material available to me related to the purported association of kava consumption with liver damage. I understand that I am reviewing the same information, without supporting backup, that is being reviewed by the German and British health authorities and by FDA. As explained in detail below, it is my opinion, based on the data available to me at this time, that there is no clear evidence that the liver damage reported in the U.S. and Europe was caused by the consumption of kava.

### **FDA Adverse Event Reports**

I have reviewed the twenty-six adverse event reports ("AERs") from FDA MedWatch, each of which was assigned an ARMS number (Adverse Reaction Monitoring System) by the agency. Only five of the twenty-six AERs (#13198, #14538 (MedWatch Triage unit sequence # 133143), #14723, #15035, and #15267) identify a liver related symptom or problem in persons who were reported to be consuming kava. Each of these cases will be discussed separately below. As stated above, the analysis of these cases remains limited by the paucity of specific clinical and historical information. In addition, one case that reported a death had no kava exposure (#14747) and so is not included in this review.

#### **ARMS #13198**

ARMS #13198, relates to a 52 year old female hospitalized for congestive heart failure and acute renal failure. This report indicates that the patient was taking no less than 20 different supplement products (over 60 distinct plant derived materials) and several over the counter medications. The patient reported using kava "occasionally." There is no information about when or if kava had been consumed prior to the exacerbation of congestive heart failure and renal failure. The patient also reported daily alcohol use with "binge" drinking on weekends though the duration of such alcohol consumption was not disclosed. The patient had biopsy confirmed cirrhosis, however, it is unclear from the report when or why the patient underwent a liver biopsy.

There is no evidence that this patient had been taking kava at the time the adverse events occurred. Combined with the multitude of products and alcohol consumed by this patient and evidence of chronic liver disease, this report does not indicate kava consumption caused or was even directly associated with this patient's liver disease.

**ARMS #14538** (Because there is some confusion about the accuracy of the ARMS number corresponding to this case due to the difficulty in reading the numbers from the photocopy, the MedWatch Triage unit sequence #133143 is referenced for clarification)

The case identified by MedWatch Triage unit sequence # 133143 involved a 60 year old female who was undergoing radiation therapy and a multi-drug chemotherapy regimen (5-FU, Xeloda, and eniluracil) for metastatic rectal cancer. Xeloda is known to cause hyperbilirubinemia. In

addition, the patient reported taking three drugs, one of which is a combination of two distinct drugs, and three herbal products, including kava at an undisclosed dosage or frequency. Importantly, all four drugs (docusate, Ogen and Percocet (a combination of acetaminophen and oxycodone)) are metabolized by the liver and can be associated with liver damage. No detailed information is provided in the AER about the dose or dates of therapy with these non-chemotherapeutic drugs or for the herbs. The report indicates only that the patient's liver function tests revealed an increase in serum bilirubin and enzymes during the course of her treatment for cancer, but the liver appeared normal by ultrasound. It further indicates that chemotherapy and herbs were stopped and the liver enzymes returned to normal. Although the reported resumption of two of the three chemotherapy drugs resulted in no further increase in LFT's, there is no indication if the dose was adjusted or if other medications were also continued.

In my opinion, this report does not provide information suggestive of an association between elevated liver function tests and kava consumption by this patient.

✓ - **ARMS #14723**

ARMS #14723 involved a 44 year old female with Marfan syndrome complaining of chest and back pain. She was hospitalized in order to rule out an aortic dissection, which is a major cause of morbidity and mortality in patients with Marfan syndrome. Apparently the admission labs revealed a modest neutropenia (low white blood cell count) and elevated liver function tests. The AER indicates chronic kava use in this patient and identified a specific kava product that is advertised to also contain B-vitamins (200% RDI of each of B6, B1 and niacin) There is no information, however, about the specific dose of this or any other kava product taken, the duration of use, or if kava had been taken just prior to her admission. Furthermore, there is no indication in the report that the patient was experiencing symptoms associated with hepatitis. Importantly, this patient was also taking five drugs at unspecified doses or frequencies that are metabolized by the liver and may be associated with liver damage, including an antidepressant (Celexa), an analgesic (oxycontin), an anticoagulant (coumadin), an anti-inflammatory (Celebrex) and estrogen. In addition, without any information regarding dosage it is impossible to evaluate the impact that B-vitamins, and particularly niacin, might have had on this patient's liver function.

Based on all of the above, I do not consider the information conveyed in this AER suggestive of an association between elevated liver function tests and kava consumption.

✓ **ARMS #15035**

ARMS #15035 involved a 45 year old female who was admitted for jaundice and eventually required a liver transplant. This case raises the most concern because of the severity of the reaction. The information provided to me for this case consist of the original AER filed by a physician on 8/17/01, identified as ARMS #15035; label samples and a follow-up report of an interview with the physician by FDA personnel; and an AER filed by the patient on 1/04/02, identified as ARMS #15274.

While the additional follow-up information is available to supplement the AERs of the patient and the reporting physician, this information raises even more questions because of discrepancies

between the physician's original report and information obtained in the follow up, and by inaccurate statements about kava offered by the physician (described further below). In addition, discrepancies between details provided by the patient and the physician further confound any attempt at a conclusion. For example:

- the AER from the patient indicates no preexisting medical conditions; this conflicts with a physician's earlier AER which reported reflux of unknown duration.
- the physician initially reported that the patient was not taking any other medications, however, in his follow-up interview on 10/30/01, the patient was noted to have been taking Aciphex, a gastric acid secretion inhibitor prescribed for treating reflux. Aciphex is metabolized by liver cytochromes and is known to interact with the clearance of other drugs, and jaundice has been recorded as a post-market adverse event, though without any clear causality established.
- the patient reported consuming kava for about eight weeks at half the recommended dosage whereas the follow up report from the physician states that the dosage was twice a day for approximately four months. The product is labeled with a suggested use of one capsule up to three times daily.

Of additional note is that the patient herself stated that "[t]hinking I might have the flu, I went to my PCP (primary care provider) who gave me an antacid. Shortly after that I became visually jaundice" (emphasis supplied). This raises the question about what antacid she began taking just prior to becoming jaundiced. It is also unclear from the physician's AER remarks in the Relevant tests/laboratory data, if autoimmune disease was or was not present and the basis for such judgment.

The patient reported that she was instructed to stop taking the kava containing product. Her symptoms worsened but there is no indication that she was told to stop the treatment for her reflux. There is also no information about prior or concomitant alcohol use, or potential environmental, dietary, or occupational exposures and the herbal product consumed also contained at least four other ingredients in addition to kava. The "complications" recited in the patient's report are consistent with the side effects expected from the immunosuppressive therapy that is required for transplant recipients.

In the follow-up notes taken by Nadine Nanko Johnson, CSO, dated 11/09/01, the background statement asserts that the liver transplant resulted from the ingestion of kava. In the same report, second to last paragraph, the treating physician is quoted that "based on his experience, the patient's liver failure is likely the result of overdose of Kava Kava or contaminate [*sic*]," adding that "the contaminate [*sic*] is pyrozoladine [*sic*] alkaloid." Certain pyrrolizidine alkaloids are recognized to be associated with hepatitis, however, pyrrolizidine alkaloids do not exist in kava. I have concern about this mistake because it appears as if the physician's inaccurate belief that these alkaloids are a constituent of kava led him to draw a conclusion that was not based in fact. FDA obtained some of the product taken by the patient and had the sample analyzed for pyrrolizidine alkaloids. Although I have not been provided with the results of the FDA's chemical analysis, it is important to realize that if the sample is found to not contain this contaminant, it does not indicate the kava was responsible for the liver disease.

I do not agree that the available data demonstrates a clear causal relationship between this patient's kava consumption and liver failure. The amount and duration of the exposure is not clear and the ingested material consisted of several plant products. Furthermore there is some confusion about preexisting medical conditions and the medications that were being taken at the time of the incident. Speculation on the presence of a contaminant by the physician raises another point of confusion. Further investigation into this case is needed to enable the evaluation of all the potential factors leading to the liver failure.

#### ARMS #15267

ARMS #15267 involved a 51 year old female with elevated liver function tests that reportedly resolved after stopping three herbal products, including kava. This report offers little meaningful information. Nine products were being taken simultaneously for at least two months, but no dosage is reported for any of these products. Furthermore, there is no information about prior or concomitant alcohol use. This report suggests that some unidentified drugs were resumed and the elevated liver function tests recurred, however, no information is provided about what was taken, how much, or for how long prior to repeating liver function tests. It is difficult to clearly identify any association of kava with the liver alterations reported in this case.

#### Other cases

In reviewing the non-liver related AERs that came out of the FDA system I note that there are two examples of chronic and high dose consumption of kava that were not associated with any significant liver damage. Case #14739 presents a patient consuming four prescription medications plus an exceedingly high dose of kava (reported 10-15 150 mg pills at a time, up to 300 pills (45,000 mg) per day) without liver damage. Similarly, a 13 year old girl consumed 8-10 five hundred milligram kava tablets in an attempt to commit suicide. She was admitted for observation in an intensive care unit, and although no laboratory data is provided, such an admission would have necessarily included extensive blood testing, including a liver panel. She was discharged the following morning with a complete recovery. From a toxicologist perspective, these two cases provide some evidence that kava itself is not a direct hepatotoxin even in extremely high concentrations.

#### Summary of U.S. cases

Based on data available for the incidence of liver disease in the US and the estimated number of kava consumers, it is difficult to make any more than a use-association of liver damage with kava using the FDA adverse event case reports. It is my opinion there is no scientifically supported association of liver disease with the use of kava which can be found using the US FDA adverse reaction case reports. There is always the possibility of an individual hypersensitivity reaction to any food product and such incidents must be expected when large numbers of subjects consume any food or drug product. This type of reaction, termed idiosyncratic, does not generally correlate with ingested dose or duration of use and is not predictable.

#### Swiss and German Cases

A listing of 30 cases was provided by the Swiss and German authorities (hereinafter referred to collectively as BfArM cases) implicating an association of kava with liver damage. I was

provided with a summary spreadsheet identified as "Data provided by BfArM" (appended here), and a report prepared by Mathias Schmidt and translated from German by Lindenmaier and Brinckmann, dated 12/31/01, that examined all of these cases. I was not, however, given any medical records or data that Schmidt relied upon in compiling his report. In formulating my opinions, I have relied on the Schmidt report for providing additional specific information about these cases, however, I am not offering any opinion as to the specific conclusions drawn by Schmidt.

These reports are seriously lacking in details. The summary information available for review did not provide adequate clinical information such as past medical history, weight, diet, allergies, past and concurrent alcohol use, history of viral hepatitis, occupational or environmental exposures, laboratory test results, doses of drugs taken concomitantly with kava products and the like. In fact, these reports are far less detailed than the FDA AER reports. In the absence of more specific information, there is little that can be concluded about most of these cases.

In addition, certain of the data that was available for this group of cases is troubling from the perspective of a toxicological review. At least eight of the cases, for example, involved patients between age 60 and 81; age alone is a significant factor in considering susceptibility from underlying hepatic or cardiovascular insufficiencies and co-morbid conditions. Also, a large percentage of the reported cases are females, but without market data to determine the gender-specific usage pattern of kava, it is impossible to comment on the meaning of this factor.

As another initial matter, there is some confusion about the true number of BfArM reports as some duplication in reporting appears to have occurred. As stated above, the listing from BfArM includes 30 cases but Schmidt identifies two or possibly three of these as redundant, and also provides other (i.e., duplicative) case numbers for 2 cases. I view this detail as of limited importance, however, as I do not believe there is any significance to whether exactly 28 or as many as 32 reports, identified by Schmidt, were actually collected, given the large number of kava doses consumed worldwide. Based on the information available to me I have accepted Schmidt's identification of two duplications and so have reviewed here 28 cases, which I consider to represent all 30 of the cases on the BfArM list.

As an overarching observation, I concur with Schmidt's statement that the classification made by BfArM of causality in each of these cases is largely "incomprehensible and arbitrary." Thus, I will not address all of the BfArM reports on a case by case basis as I have done for the FDA cases that record any liver-associated problems.

Speculation about the cause of liver disease or injury in these several cases is not scientifically supportable in the absence of more complete information. On the other hand, although clear evidence of overt liver toxicity of kava is sorely lacking in any of these cases, it may be possible that rare cases of hypersensitivity or idiosyncratic responses to kava, especially in a person with a previously damaged liver can occur in a small number of consumers considering the widespread use of kava.

Following is a brief synopsis of my opinions regarding the BfArM cases.



### Cases Clearly Not Attributable to Kava

There are four of the BfArM cases that should be set aside as clearly unrelated to use of kava.

The single case reporting a death involved an 81 year old woman with hypertension taking medication with a known, albeit rare, liver toxicity. Information in Schmidt's report indicates this patient (#98004297) had biopsy confirmed alcoholic liver disease. There is no information presented in the BfArM report to even suggest that kava was the actual basis for this patient's death or liver disease.

Two additional cases (#99005139 and the Schwabe case from 1993) indicate respectively that (1) the discontinuation of a co-medication – but not of kava – resulted in the normalization of liver enzymes and (2) that elevated liver function tests had been documented prior to consuming kava and that the abnormality did not get worse while on kava. It is difficult to understand why these last two cases were even included on the BfArM list. In addition, case number IKS #99062501 reports hepatitis (although no laboratory data or physical findings recorded) in a 37 year old female who was taking two medications with documented hepatic toxicity. In fact, diclofenac had been administered intramuscularly and was temporally related to the development and duration of hepatitis. The patient recovered and restarted the two medications and consumption of kava with no recurrence of liver injury.

In the four cases discussed here there is significant evidence to indicate that kava was not responsible for the liver impairment in these patients.

### Cases Involving Concomitant Medication Usage With Known Hepatic Toxicity

Ten of the BfArM cases reviewed here involved the concomitant use of medications with documented hepatic toxicity. No additional information was provided in any of these reports to suggest that kava was primarily or even peripherally responsible for the observed liver toxicity. These cases include: BfArM Nos. 90003882, 93015209, 94901308, 99006005, 00003608, 00005994, 01001228 (duplicates 01001924), 01003951, and IKS Nos. 19992596 and 20002330)

### Other BfArM Cases

The remaining 14 BfArM cases are unified only in that there is insufficient information to either conclusively identify or fully eliminate kava as a potential causal agent in the reported hepatic event. These cases can, however, be organized between most doubtfully and least doubtfully associated, but even this exercise is speculative without additional information.

Six of the cases (BfArM Nos. 92901203, 99003911, 99500453, 01003089, 01004110, and 01006229) are particularly faulted as having inadequate information to assess the cases. Two of these reports lacked any information on concomitant medications, most had very incomplete or apparently inaccurate descriptions of such medications and one did not have adequate follow-up of a reported concomitant exposure to drug known to be associated with liver damage. None of the cases had adequate information on alcohol consumption, supporting laboratory data, or preexisting disease. It is therefore not possible to exclude or to implicate kava in any of these cases.

In five other of these cases there are additional and confounding factors that would need to be better understood to either fully eliminate or to implicate kava as causing or participating in the observed liver toxicity. BfArM No. 94006568 describes a 68 year old female with jaundice and cholestatic hepatitis. The liver damage was attributed to an immunologically triggered hypersensitivity reaction. However, the time course of the development of symptoms was not consistent with this finding and little other information is available. Case number 97002825 (duplicate of 97003551) describes a 72/75 year old women with jaundice and cholestatic hepatitis who took more than one preparation. Kava was only a small portion of one of the products and it was reported to be taken in compliance with recommendations, thus it is difficult to attribute the events solely on kava. Case 99006200 provides incomplete data on a patient with multiple sclerosis. Although the kava consumption was indicated along with St. John's Wort extract, there was evidently little information on the patient's drug history. Considering the presence of a chronic disease state which frequently requires therapeutic intervention, there is inadequate information to identify kava as the causal agent. A serious case of a 22 year old women which had severe liver disease resulting in liver transplant is described in BfArM case number 00008627. A possible viral cause can not be ruled out in this case and there is inadequate information on concomitant drugs taken. Kava was being taken in substantial amounts for about 4 months prior to the episode. While kava cannot be excluded as a causative agent in this case, there are a number of aspects which need to be further investigated to confirm the lack of any other contributing factors. Finally, in the case identified as IKS #2000-0014, a 33 year old woman who had been taking kava for 2 to 3 months was diagnosed with jaundice and cholestatic hepatitis following an acute alcohol intoxication episode and self medication with paracetamol (acetaminophen) for the resulting hangover symptoms. Acute alcohol intoxication is known to cause alterations in liver function and possible liver damage. The role played by this damage in association with the acetaminophen administration and the presence of kava cannot be determined.

The remaining three cases provide the most plausible incidents of an actual relationship between consumption of kava and an effect on the liver. Full medical records are lacking in each of these cases, however, and should to be evaluated more fully before any meaningful conclusion can be drawn.

- ✓ In one of these cases (Kraft et al., 2001), the subject self-administered excessive doses of kava of up to 1.2 grams of kavactones /day for over one year. This patient had an extensive medical history which included a pulmonary embolism, cardiopulmonary reanimation, cholecystectomy and depression. While kava may have been involved in the liver failure, it is not clear if the medical history included all the potential factors which may have also contributed to the liver damage or what the impact of such high consumption may have been. As noted earlier, however, other cases have been reported where consumption was significantly greater than in this case but where no liver toxicity was observed. If kava was actually a factor in this case its effect would appear to have had a hypersensitivity or idiosyncratic basis.
- ✓ The case described by Strahl et al. (1998) provides the most thorough report of kava consumption associated with an individual who experienced damage to the liver. The pattern



✓ and severity of the recurrence of symptoms following kava exposure provided a positive correlation with kava. However, this patient was found to have a cytochrome P-450 deficiency which may have played an important role in the initiation of the liver response to kava. It is quite possible that both paroxetine and the oral contraceptive, which are primarily metabolized by the cytochrome P-450 metabolizing system, used concomitantly in the early phases may have participated in the initial liver response. Based on the information provided, it appears this response could have been either immunological or idiosyncratic in nature.

✓ Finally, the liver transplant case identified as IKS No. 20003502 is difficult to properly assess since most of the available data relates to events following the initial episode of hepatitis. One detail that needs to be resolved to better understand this case is the discrepancy between the recorded moderate use alcohol, as recorded on the BfArM listing, and a published article of this case (Escher et al., 2001) which stated that this patient "did not consume alcohol." Also, as with all of the cases reviewed here, a much more complete medical record is required in order to provide a conclusion.

### **Summary of BfArM Cases**

In summary, there are only a few of these cases in which kava might be directly associated with liver damage, although speculation about the cause of liver injury in even these few cases is not scientifically supportable in the absence of more complete information. Each of these possible cases appear to have been hypersensitivity or idiosyncratic based responses. There are several other reports which have weak associations with kava consumption and many reports which have inadequate information to make any rational assessments. Clearly, these cases should be revisited where possible, to obtain further information.

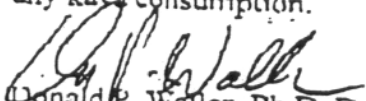
### **Conclusions**

The reaction of the United States natural products industry in initiating a scientific process by engaging toxicologists to critically review and scientifically evaluate the AERs reported by the German and United States health authorities, has been conservative and appropriate. The concern of regulatory agencies for kava toxicity and the public news stories that have reported their actions and reviews has raised the awareness of the general population and may lead to new cases being reported, or not, all of which may help to better define any association that may exist between kava and liver damage.

It is my opinion, based on currently available information, that kava when taken in appropriate doses for reasonable periods of time has no scientifically established potential for causing liver damage. However as with any pharmacologically active agent, there is always the possibility of drug interactions, preexisting disease conditions and idiosyncratic or hypersensitivity reactions, which can exacerbate the toxicity of any such agent. Increased surveillance or reports of adverse effects and judicious use of kava-derived products under the conditions recommended by the natural products industry would be a most prudent approach to confirm its safety and minimize any risk of liver damage.

The medical community and the general public should be made aware that concomitant intake of prescription drugs associated with liver damage, excessive alcohol consumption and preexisting

liver disease or hepatitis with compromised liver function are conditions which may preclude any kava consumption.

  
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Data provided by BfArM (relate. German and Swiss case reports)

Identifier	Patient: Age/Gender <i>f = female</i> <i>m = male</i>	Dose*	Indication	Timeframe (beginning of treatment to first occurrence of symptoms)	Hepatotoxic adverse drug reactions	Concomitant drugs	Notes
1	69/f	2 x 200mg (synthetic Kavain)			Cholestatic hepatitis	ASS, dehydro-sanol, Rentylin	Recovered; Hepatic side-effects are described for the whole concomitant medication Recovery after discontinuation
2	35/m	2 x 200mg (synthetic Kavain)	Anxiety states		Cholestatic hepatitis		
3	68/f	3 x 70mg/d (acetone- extract)			Increased liver enzymes, already before the beginning of the kava-medication		
4	39/f	3 x 70mg/d (acetone- extract)	Depressive neurosis	approx. 4 years	Upper abdominal pressure, nausea, vomiting, icterus	Diazepam, Gravistat, L- Thyroxin	Recovery after discontinuation of the whole medication, hepatotoxicity also known for the concomitant medication
5	68/f	3 x 70mg/d (acetone- extract)	Depressive emotional deterioration	approx. 2 years	Cholestatic hepatitis, icterus	Neuroplant forte, Maaloxan if required	Recovery after 97 days; Sporadic notifications of increased liver parameters under Maaloxan
6	50/f	3 x 70mg/d (acetone- extract)		approx. 2 months	Increased liver enzymes, liver cell impairment, acute hepatitis with icterus	Teldane, Atenolol, Hydrotrix	Hepatic side-effects also described for concomitant medication
7	72/f	Phyto-Geriatrikum (with 25mg dry extract with ethanol)		approx. 6 months	jaundice, cholestatic hepatitis, liver cell impairment	Eunova	No hepatic side effects known for concomitant medication
8	75/f	Phyto-Geriatrikum (with 25mg dry extract with ethanol)		approx. 2 years	Cholestatic hepatitis, hepatitis, liver cell impairment	Eunova	No hepatic side effects known for concomitant medication
9	81/f	2 x 60mg (ethanol- extract)	Anxiety/rest- lessness	approx. 9 months	Toxic hepatitis with liver failure, acute yellow liver dystrophic	Hct-isis 12.5, Cralonin Tr., Bayotensin (bis 1/98)	Exitus, seldomly icterus under HCT, hepatic impairment by alcohol not excluded
10	39/f	60mg/d?		6 months and 14 days after re-exposure	Severe hepatitis with confluent necrosis	Paroxetin, St John's Wort if required, hormonal ovulation inhibitors for 6 years (not by reexposure)	Recovery after 8 resp. 3 weeks; Hepatic side-effects are described for hormonal ovulation inhibitors

Identifier	Patient: Age/Gender <i>f = female</i> <i>m = male</i>	Dose*	Indication	Timeframe (beginning of treatment to first occurrence of symptoms)	Hepatotoxic adverse drug reactions	Concomitant drugs	Notes
11	59/f	2 x 120mg/d	Anxiety states	approx. 4 months	Liver cell impairment	Buscopan	Sporadic notifications of hepatic side-effects under Buscopan
12	37/f	2 x 70mg/d (acetone-extract)			Hepatitis	Microdiol since 5 years, 2 x Diclofenac 1.m	Recovery after 3 months; Hepatic side-effects also known for concomitant medication
13	62/f	(ethanol-extract)			Liver cell impairment	None denoted	No medical message!
14	33/f	(ethanol-extract)		approx. 4 months	Bilirubinaemia, hepatitis, increased liver enzymes, cirrhosis of the liver	Cisapride	Hepatic side-effects also described for concomitant medication
15	46/f				Severe liver damage with icterus	Propanolol, HCT, Valsartan	Hepatic side-effects also described for concomitant medication
16	33/f	3 x 70mg/d (acetone-extract)			Cholestatic hepatitis with icterus	1 x approx. 60g alcohol	Recovery after 6 weeks
17	60/f	70mg/d (acetone-extract)	Depression		Increased bilirubin and transaminases, indolent icterus	Celecoxib	Recovery after 2 weeks; hepatic side-effects also known for concomitant medication
18	50/m	3-4 x 70mg (acetone-extract)	Nervous tension	approx. 2 months	Acute necrotizing hepatitis, irreversible liver damage	Alcohol moderately, 1- 2 x Paracetamol, Nachtkerzensamenol	Transplantation! Notifications of hepatic side-effects under Paracetamol exist
19	21/f	8-10 x 50mg		approx. 2 months	Increased liver enzymes, jaundice, hepatitis	Paspertin, Pantoprazol, Paracetamol, Basilikum-Tropfen	Side-effects also known for concomitant medication
20	50/f	60mg/d (ethanol-extract)	Stress states	approx. 7 months	Fulminant liver failure	Amaryl, Glucophage S, Gravistat followed by Klimonorm	Transplantation. Hepatic side-effects also known for Amaryl (cholestasis, hepatitis) and Klimonorm as well as Gravistat (tumours of the liver, cholestasis, anicteric hepatitis)
21	22/f	2 x 120mg (ethanol-extract)	Nervosity, anxiety states Endogenous	approx. 5 months	necrosis, complete destruction of the parenchyma, fulminant liver	Maxalat if required, Pramino (beforehand Valette)	Transplantation. Hepatic side-effects also known for Pramino (tumours of the liver, cholestasis,

Identifier	Patient: Age/Gender	Dose*	Indication	Timeframe (beginning of treatment to first occurrence of symptoms)	Hepatotoxic adverse drug reactions	Concomitant drugs	Notes
22	<i>f = female</i> <i>m = male</i> 34/f	120mg/d (dry extract with ethanol)		approx. 3 months	Hepatitis, increased liver enzymes	Jodthrox	Recovery after discontinuation of the Kava medication; Sporadic notifications of hepatic side- effects under Jodthrox
23	34/f	120mg/d (ethanol extract)		approx. 1 month	Increased liver enzymes, jaundice	Paracetamol	Notifications of hepatic side effects under paracetamol Restored to health after discontinuation of the concomitant medication and continuation of the Antares- medication
24	47/f	(Antares 120; ethanol extract)		approx. 1 month	Increased liver enzymes	Fischolkapseln	
25	35/f	(ethanol-extract)		approx. 3 months	Hepatitis, increased liver enzymes	Hypericum aar dragees	Restored to health; <u>No</u> hepatic side-effects known for concomitant medication
26	38/m	(acetone-extract)		approx. 2 weeks	Liver cell impairment	Penicillin-V	<u>No</u> hepatic side effects known for concomitant medication
27	39/m	170mg/d (acetone- extract)		approx. 2 weeks	Liver cell impairment	None	
28	/f	(Kavain)			Hepatitis	L-Thyroxin, Lorzaar plus, Estragel Pflaster, Antra MUPS	Recurrence of the hepatic side- effects; Hepatic side-effects also known for concomitant medication
29	60/f	Up to 480mg/d (ethanol-extract)	Depressive emotional deterioration restlessness	approx. 1 year	Fulminant liver failure	Etilefrin-HCL, Piretanid	<b>Transplantation.</b> Sporadic notifications of hepatic side- effects under Piretanid
30	32/m	Approx. 240mg/d (ethanol-extract)		approx. 3 months	Necrotizing hepatitis with insufficiency of the liver, metabolic-toxic-allergic drug damage	Baldrian (occasionally)	<b>Evaluation of the necessity of a transplantation</b>