

SAFETY OF ETHANOLIC KAVA EXTRACT: RESULTS OF A STUDY OF CHRONIC TOXICITY IN RATS



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Abstract

Backgrounds: Recently, potential liver toxicity was discussed with the intake of kava extract preparations (*Piper methysticum*) as anxiolytic drugs. The aim of this study was to test chronic toxicity in rats by oral application of an ethanolic kava full extract.

Methods: Wistar rats of both sexes were fed 7.3 or 73 mg/kg body weight of ethanolic kava extract for three and six months. The animals were examined for changes in body weight, hematological and liver parameters, and macroscopical and microscopical histological changes in the major organs.

Results and Conclusions: The results are in accordance with the medical experience regarding the safe use of kava preparations and the long tradition of kava drinking in the South Pacific island states. Specifically, the results do not back the suspicion of potential liver toxicity.

Introduction

Kava and kava derived products are generally considered as very safe. In 2002, the German health authorities banned kava extract containing products based on the suspicion of a potential liver toxicity, as derived from adverse effect reports (Schmidt et al. 2002). From the case reports and the sales figures of kava extracts, an incidence rate of one potential case in 60 to 125 million patients was deduced (Schmidt et al. 2002; Teschke et al. 2003; Teschke 2003).

Clinical, pre-clinical and toxicological studies have so far failed to show toxicity for kava preparations and their constituents. Kavalactones and kava extracts display a rather low toxicity in toxicological testing in animals (Bone 1994; Hölzl et al. 2003; Hsu et al. 1994; Kretzschmar 1995; Meyer 1965a; Meyer 1965b; Szirmai et al. 1979).

Already in 1989, we had conducted a study in rats to evaluate chronic toxicity of ethanolic kava extract. The questions to be answered within this study were:

- Toxicity after three months of continuous daily ingestion of either 7.3 or 73 mg of kavalactones per kg body weight
- Potential changes in behavior or toxicity related to withdrawal after three months of continuous daily ingestion of 7.3 respectively 73 mg/kg body weight, followed by an observation period of four weeks on standard diet
- Toxicity after six months of continuous daily ingestion of either 7.3 or 73 mg of kavalactones per kg body weight.

The results were presented to the health authorities at a time when potential liver adverse effects of kava were unknown. With the current discussion on toxicological impact of kava intake on the liver we feel that our study is an important contribution to the discussion of kava safety.

Materials and Methods

All examinations were carried out by experienced personnel under GLP conditions. Male and female Wistar rats were fed Altromin pellets (Altromin International, Germany) enriched with kava extract (Kavasedon[®], HARRAS Pharma, Germany) corresponding to 0.01 respectively 0.1 percent of total kavalactones. Based on an average consumption of 7.3 g of diet per 100 g of body weight, this concentration was equivalent to a daily ingestion of an average of either 7.3 or 73 mg of kavalactones per day. The analytical profile of the standardized kavalactone complex is listed in table 1.

Table 1: Analytical profile of kava extract: Quantification of kavalactones by HPLC

Kavalactone	Content (%)
Total kavalactones	41.4%
Kavain	12.4
Dihydrokavain	8.8
Methysticin	11.8
Dihydromethysticin	6.0
Yangonin	5.0
Desmethoxy-yangonin	3.4

Three month toxicity:

48 weanling rats (24 female, 24 male) were allocated to three groups of diets. Each group consisted of 8 male and 8 female randomly allocated animals. The first group (control) obtained standard diet. The 2nd resp. 3rd group obtained diet with 0.01%/0.1% kavalactones (K0.01/K0.1).

After three months, 8 animals (4m, 4f) of each group were sacrificed for toxicity testing. The remaining rats were set to standard diet and observed for additional 4 weeks prior to toxicological examination.

Laboratory parameters were blood glucose, azotemia, total blood protein, ALT, AST and total cholesterol, next to red and white blood cell count. Liver, lungs, kidneys, heart, adrenal glands, and testes respectively ovaries were examined for abnormalities. In addition, liver total fat was determined.

Six month toxicity:

Experiments were carried out on 48 weanling rats (24 female, 24 male), again allocated to three groups of diets (control, K0.01 and K0.1) with 8 male and 8 female rats each.

After six months, all animals were sacrificed for toxicity testing as described above. The parameters used were identical to those examined in the three month study.

Results and Discussion

Major results:

- No mortality in any treatment group
- No relevant difference in body weight development (figure 1)
- No relevant changes in haematological or biochemical parameters and organ weights (table 2) for all groups.
- No macroscopical abnormalities in organs
- Only minor histological findings of inflammatory (mainly respiratory system) or degenerative origin with no difference between groups (table 3).

Table 2: Haematological and laboratory parameters and organ weights (Mean; n=8/group)

Parameter	Control	K0.01	K0.1
3 month study/6-month study (male rats)			
Erythrocytes (10 ⁹ /ml)	7.8/7.6	7.8/7.3	7.7/7.4
Leucocytes (10 ⁹ /ml)	11.2/11.9	12.0/12.5	12.0/11.8
Lymphocytes (%)	74.6/73.9	76.8/73.1	77.8/75.1
Neutrophils (%)	21.4/21.8	20.4/21.6	20.0/21.0
Eosinophils (%)	4.0/4.4	4.1/5.5	3.8/3.9
Haemoglobin (g/100 ml)	13.0/12.5	12.3/11.6	12.1/12.2
Blood glucose (g/l)	0.91/0.90	0.90/0.89	0.85/0.90
Nitrogen (g/l)	0.32/0.26	0.34/0.26	0.34/0.24
Total protein (g/100 ml)	5.6/5.7	5.5/5.8	5.6/6.1
Cholesterol (mg/100 ml)	84.7/84.7	82.4/84.4	83.3/86.3
ALT (U/l)	13.9/14.7	12.4/14.3	12.5/16.2
AST (U/l)	67.5/66.5	63.9/68.2	68.6/73.4
Liver weight (g)	2.71/2.75	2.54/2.72	2.67/2.78
Total liver fat (%)	3.7/3.3	3.3/3.1	3.7/3.4
Lungs, weight (mg)	522/556	550/552	544/544
Kidneys, weight (mg)	443/465	441/455	470/450
Heart, weight (mg)	250/272	269/263	266/267
Adrenal glands (mg)	11.9/11.6	11.4/11.8	11.7/11.7
Testes, weight (mg)	556/562	562/570	545/566
3 month study/6-month study (female rats)			
Erythrocytes (10 ⁹ /ml)	7.4/7.3	7.6/7.7	7.7/7.7
Leucocytes (10 ⁹ /ml)	12.1/11.7	11.8/12.0	11.7/13.0
Lymphocytes (%)	74.0/74.6	76.1/74.6	73.3/75.3
Neutrophils (%)	22.4/21.4	20.6/22.3	22.6/21.1
Eosinophils (%)	4.0/4.0	3.3/4.6	4.1/3.6
Haemoglobin (g/100 ml)	11.8/11.8	11.9/11.5	11.5/12.6
Blood glucose (g/l)	0.86/0.81	0.85/0.80	0.86/0.83
Nitrogen (g/l)	0.23/0.21	0.21/0.23	0.23/0.22
Total protein (g/100 ml)	6.0/5.6	5.7/5.7	6.2/5.8
Cholesterol (mg/100 ml)	86.3/92.1	81.6/91.8	88.2/88.2
ALT (U/l)	11.7/13.1	11.6/13.7	11.4/13.7
AST (U/l)	65.4/69.7	67.3/67.6	68.1/67.7
Liver weight (g)	2.52/2.61	2.52/2.59	2.69/2.67
Total liver fat (%)	3.2/3.5	3.3/3.3	3.4/3.4
Lungs, weight (mg)	554/550	563/543	569/537
Kidneys, weight (mg)	472/466	466/462	464/471
Heart, weight (mg)	265/259	260/260	251/286
Adrenal glands (mg)	22.0/20.9	22.5/23.9	24.7/22.6
Ovaries, weight (mg)	44.2/47.3	44.4/44.2	48.6/46.7

Conclusions

- No harmful effect of the kavalactone complex to the organs.
- No signs of liver toxicity even with high dosage schemes of kavalactones

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Figure 1a: Development of body weight (3 month study, male rats; n=8/group)

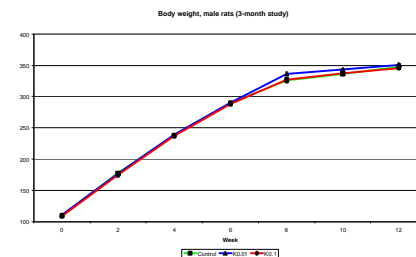


Figure 1b: Development of body weight (6 month study, female rats; n=8/group)

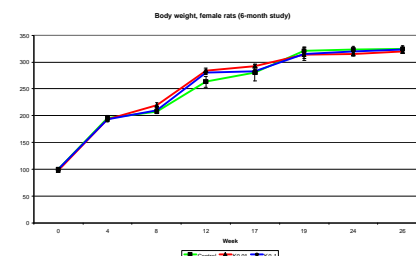


Table 3: Histological changes in lungs, kidneys and liver (n=8/group). I = slight inflammatory infiltrate, B = signs of bronchopneumonia; S = mild turbid swelling; n.c.: no changes

		Lungs	Kidneys	Liver
3 month study				
Control	male	I (n=1)	I (n=1)	S (n=1)
	female	I (n=1)	I (n=1)	I (n=2)
K0.01	male	B (n=1)	I (n=1)	S (n=1)
	female	I (n=1)	I (n=1)	n.c.
K0.1	males	n.c.	n.c.	I (n=1)
	female	B (n=1)	I (n=1)	S (n=1)
6 month study				
Control	male	B (n=1)	n.c.	S (n=1)
	female	B (n=1)	I (n=2)	I (n=1)
K0.01	male	B (n=1)	I (n=1)	S (n=1)
	female	B (n=1)	n.c.	n.c.
K0.1	male	n.c.	I (n=1)	n.c.
	female	I (n=1)	I (n=2)	S (n=1)

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