Piper methysticum (Kava): Current Drug regulatory status and international implications

19th Herbal Assembly:
Medicinal plants in the 21st Century
Poznánska, Poland, 14. – 15. June 2024

Dr. rer. nat. Mathias Schmidt
HerbResearch Germany

No culture without kava in Vanuatu, Fiji, Tonga and Samoa

No safety problems for 1500 years

More than 450 mio. daily doses between 1990 and 2000 in Germany

Sudden occurrence of case reports of liver toxicity in 2000 led to the still contested “Kava ban” of 2002

Next due court decision:

June 18, 2024

History of the kava ban in Europe

1996 – 1998: „Boom“ of kava extract products
A German pharmaceutical company starts the cultivation of a two-day variety

1999 – 2000: First case reports of liver toxicity are reported from Switzerland

2001: The German drug regulatory authority (BfArM) questions the safety of kava

History of the kava ban in Europe

June 2002: Germany bans kava-containing medications based on 24 case reports of assumed liver damage, without discrimination of kava quality: The variety and the extraction solvent have to date not been addressed by BfArM!

Consequences of the ban

- **Economic crash in the South Pacific**
- **The South Pacific traders saw the fault in Germany, where one single manufacturer had changed the extraction solvent from ethanol to acetone and simultaneously the raw material quality from noble kava to twoday kava.**

Palarasul (Noble, Vanuatu)

Palisi (Twoday, Vanuatu)

Background information:

Shortly before kava was banned, BfArM was accused of not having reacted in time in the Lipobay disaster. They learned their lesson:

→ Not deciding means to take the heat from the media.

→ Deciding against kava meant „selling“ the decision to the consumer as a measure taken for his best

➔ Once taken, BfArM seems unwilling to correct its actions for fear of losing face.

.

Most crucial for the understanding of the kava ban:

The authority "sold" the kava ban to the consumer as a measure for consumer protection.

But:

The main argument in the official reasoning is not the risk of liver toxicity, but the supposed lack of efficacy!

Efficacy versus safety

Efficacy:

- **To be demonstrated with a specific preparation in a selected indication, e.g., the treatment of stress-related anxiety**
- **Study design must correspond to recent standards and guidelines**

Of note: There were and still are no guidelines for the testing of drugs in acute stress-related anxiety!

Efficacy:

- Kava efficacy against anxiety is generally accepted in the scientific community
- Based on this „well-established use“ marketing authorisations have been granted up the year 2001, well after the start of the safety debate!

Why is kava presumably not efficacious?

- By applying recent standards to older studies BfArM retrospectively discarded all single trials because of flaws in the study design
- The EMA Public Statement of 2017 (called in by BfArM) confirms the lack of efficacy against generalized anxiety.

➔ Generalized anxiety was never the indication for kava!

Overall logic:

→ **BfArM declared kava not to be efficacious**

→ **BfArM detects a risk, even if only minor**

➔ **The benefit to risk ratio becomes negative and kava is banned**

What happened after the ban?

2002 – 2011

- The marketing authorization holders objected to the decision, but could not go to court, as the decision was not final.
- BfArM protracted the final decision until December 2011, when the authority was sued for inactivity.

February 2012

Final decision: Revocation of kava extract marketing authorizations.

This decision finally opens the door to the court.

October 2012 – April 2014

Two rulings in favour of kava by the Administrative Court of Cologne and by the Upper Administrative Court of Münster:

- **The benefit-to-risk ratio of kava is positive!**
- **There is not sufficient evidence for livertoxicity by kava!**

All well then?

No, the manufacturers first had to update their marketing authorisations.

Submission in 2016 with completely new clinical and pharmacological/toxicological dossiers.

→Rejected by BfArM with the arguments

- **Change to the new quality of “noble kava”**
- **No efficacy against generalized anxiety**

Was the quality really changed?

- No, “noble kava” was and is the only accepted quality definition in the South Pacific kava producing countries!
- There is by now a monograph on Codex Alimentarius allowing only noble kava
- “Twoday kava” and especially acetone extracts of twoday kava may have contributed to the case reports und must therefore be avoided!

What about the efficacy against GAD?

- **Clinical studies confirmed that kava is not an option for the treatment of generalized anxiety.**
- **But: The indication never was GAD – it was nervous anxiety, stress and restlessness!**

Piperis methystici rhizoma (Kava-Kava-Wurzelstock).

Erscheinungsdatum Bundesanzeiger: **1.6.1990.**, Heftnummer: **101.**, ATC-Code: **N05BX.**
Monographie BGA/BfArM (Kommission E)

Bezeichnung des Arzneimittels
Piperis methystici rhizoma; Kava-Kava-Wurzelstock.

Bestandteile des Arzneimittels
Kava-Kava-Wurzelstock, bestehend aus dem getrockneten Wurzelstock von Piper methysticum G. FORSTER, sowie dessen Zubereitungen in wirksamer Dosierung.
Die Droge enthält Kava-Pyrone.

Anwendungsgebiete
Nervöse Angst-, Spannungs- und Unruhezustände.

German Commission E 1990

The role of the HMPC

- **In 2017, the HMPC produced a public statement that in large parts reproduces the argumentation of BfArM in the national rejection of the new dossiers. Coincidence? Rather not!**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2017
EMA/HMPC/450588/2016
Committee on Herbal Medicinal Products (HMPC)

Public statement on *Piper methysticum* G. Forst., rhizoma
Final

Current advances

2018:

BfArM uses three different approaches to make sure that kava is and stays banned:

1. **Lack of efficacy as ”proven” by the HMPC**
2. **Repetition of the Drug Safety Protocol of 2001**
3. **Invocation of the sunset timer**

These approaches were discussed at the Administrative Court of Cologne on May 14, 2024.

Lack of efficacy against GAD

The court will take a decision on June 18.

Repetition or the Drug Safety Protocol

Again, the decision will be taken on June 18.

In this case, it is the same judge who already contradicted BfArM in 2012, and BfArm had no new arguments!

Sunset timer

According to the EU drug legislation, the marketing authorization of a medicinal product shell be void if the product was not marketed within a time frame of three years.

But: This rule presumes that market access was possible, which was not the case with the kava products, as BfArM had prevented this from happening

What if…

If the court decides against kava, the product will be gone forever.

If the court decides in favour of kava, the status of 2017/2018 will be reinstalled, with active marketing authorizations. But: expect new initiatives of BfArM to keep the products away from the market!

Summary

The Pacific countries finally took the decision to ban the exports of non-noble kava. This is part of the national legislations of Vanuatu, Fiji, Tonga and Samoa, and has been formalized in a regional standard in Codex Alimentarius,

BfArM has as yet not even acknowledged the existence of a quality issue in one (!) single product back in 2001. Why?

Thank you for your attention

Dr. Mathias Schmidt
HerbResearch Germany
Wartbergweg 15
D-86874 Mattsies
schmidt@herbresearch.de