



Centrum für Therapiesicherheit in der Chinesischen Arzneitherapie

Center for Safety of Chinese Herbal Medicine

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C T C A l e t t e r A p r i l 2 0 1 9

Judicial ruling following prolonged litigation concerning Kava Kava

In 2002, the German Federal Institute for Drugs and Medical Devices (BfArM) ordered the suspension of the marketing authorizations for Kava-Kava preparations because of concerns regarding hepatotoxicity. The assessment was based on a series of case reports that were never comprehensively evaluated in detail; instead, only an ad hoc assessment was conducted. Researchers subsequently demonstrated that a causal relationship between Kava-kava and the reported cases of liver injury could be substantiated in only a minority of cases.

Using the argument that the clinical studies supporting the efficacy of Kava-Kava did not meet current regulatory standards, the authorities concluded that efficacy had not been sufficiently demonstrated, and therefore even a minimal risk would be unacceptable. Kava-Kava was furthermore classified as a novel and insufficiently characterized active substance, for which complete preclinical documentation would be required for approval. Benzodiazepines(!) were suggested as therapeutic alternatives.

The manufacturers appealed against this decision. However, the authority delayed processing the appeal for several years and did not issue a formal rejection until 2012, but actually only under pressure from an action for failure to act. Only then were the marketing authorization holders able to initiate legal proceedings against the decision.

In 2014, the court held that doubts regarding the efficacy of an already authorized medicinal product could not justify a negative benefit–risk assessment on the grounds of lack of efficacy alone. Given the prescription volume, the risk of hepatotoxicity was considered to be at most “rare” to “very rare.” The suspension of the marketing authorizations was lifted, and the court referred to the possibility of risk mitigation through regulatory restrictions and conditions imposed on use — a substantial institutional embarrassment for the BfArM.

The authority subsequently exercised its power to impose regulatory conditions in a manner that, in practice, would have amounted to economic elimination of the products from the market. Kava-Kava preparations were made prescription-only, and the duration of use was restricted to one month, or exceptionally two months. In addition, liver function tests were required prior to initiation of treatment and thereafter on a weekly basis.

The package insert was furthermore required to contain a specific warning directed at patients concerning isolated cases of liver injury “up to and including liver failure with life-threatening outcomes (including fatalities),” and to include an appointment card for liver function monitoring.

In response, the marketing authorization holders filed legal action against these measures. A verdict was passed with the written grounds published in February. The court only moderately relaxed the measures, ruling that liver function tests need to be performed every two weeks rather than weekly, and eliminated the requirement for the appointment card.

This judgment is not entirely satisfactory when the wording used is compared with that used for other medicinal products that are among the most frequent causes of severe liver injury. For example, the package insert for amoxicillin/clavulanic acid lists under adverse effects: “inflammation of the liver (hepatitis), jaundice caused by increased bilirubin levels in the blood, which may cause yellow discoloration of the skin and the whites of the eyes.” No specific warning regarding liver failure or fatal outcomes is included. The European EudraVigilance database contains more than 3,800 reports of hepatobiliary adverse reactions associated with this substance, including 115 cases of liver failure. The example of Kava-Kava gives rise to fears that the BfArM is straying from rational evaluation measures when it comes to other natural remedies as well.

Source: Administrative Court of Cologne, case 7 K 7369/15

No lobeline in *Lobeliae chinensis* Herba (*ban bian lian*)

Lobeline is a toxic alkaloid known from the Western species *Lobelia inflata*. This plant is highly poisonous; according to Lewin (1897), ingestion of as little as 4 g of the leaves may be fatal. *Lobelia inflata* was formerly used medicinally in Europe and is still employed to some extent in other countries, with a maximum daily dose of approximately 0.3 g. The Chinese herbal medicine *Lobeliae chinensis* Herba (*ban bian lian*) must be distinguished from *Lobelia inflata*. The presence of lobeline had also been attributed to this species. However, a recent study contradicted this assumption and was unable to detect lobeline in the herb.

Lobeliae chinensis Herba (*ban bian lian*) belongs to the category of dampness-draining medicinal herbs in Traditional Chinese Medicine. The recommended daily dose ranges from 9 to 15 g. In the *Ben Cao Gang Mu*, the herb is classified as “non-toxic.” A deficiency (*xu*) syndrome is considered a contraindication. According to Wang et al., higher doses may cause abdominal pain and diarrhea. No drug interactions are currently known.

Wang H, Li Y, Huang Y, Zhao C, Cheung HY. *Chemical profiling of Lobelia chinensis with High-Performance Liquid Chromatography/Quadrupole Time-of-Flight Mass Spectrometry (HPLC/Q-TOF MS) reveals absence of lobeline in the herb*. *Molecules*. 2018;23(12):3258

Frequency of liver injury in China associated with Chinese Herbal Medicine, herbal products, and dietary supplements

A new retrospective study compiled 25,927 cases of drug-induced liver injury (DILI) that newly occurred during hospitalization in 308 medical institutions across China. Acute infections with hepatitis A, B, C, E, CMV, EBV, and HPV, as well as Wilson’s disease and autoimmune hepatitis, were excluded. The likelihood of a causal relationship between the suspected drug and the hepatic reaction was assessed using the internationally established RUCAM (Roussel Uclaf Causality Assessment Method) score. Only patients with a score of at least 6, corresponding to a “probable” or “highly probable” causal relationship, or patients for whom at least two out of three hepatologists independently judged causality as “probable,” were included in the analysis.

Medicinal products used in Chinese herbal medicine, together with products from Tibetan medicine, Mongolian medicine, natural medicines, and dietary supplements, accounted for 26.81% of all cases. In an additional approximately 7% of cases, Western medications had been taken concomitantly. Among these cases were 44 deaths in which Traditional Chinese Medicine (TCM) products were involved either as primary or contributing factors.

In the vast majority of cases, however, the constituents of the herbal preparations were reported as “unknown.” Among the few identified products were several injectable preparations and highly toxic herbs, such as *Gynura segetum* (*tu san qi*), which would be prohibited in Europe because of its high pyrrolizidine alkaloid content.

Comments

One limitation of the study is that the extent of “liver injury” was not clearly defined, for example by specifying thresholds for ALT elevation. Furthermore, it is striking that the ingredients of the TCM preparations were unknown in the majority of cases. Since these were cases that newly developed during hospitalization, one would assume that the prescribed herbal products should have been identifiable. It appears unlikely that hospitalized patients independently consumed such products to this extent without documentation.

If the ingredients were unknown, establishing causality using the RUCAM score also becomes substantially more difficult. For these reasons, the reliability of the study appears somewhat limited. Nevertheless, the proportion of approximately 26% of liver injuries associated with TCM products — while the contribution of the other grouped products was likely comparatively small — corresponds roughly to the average proportion reported in numerous previous studies.

Overall, liver injury occurred in approximately 1.6 per thousand hospitalized patients. For comparison, the incidence reported by the TCM hospital Kötzing was 1.2 per thousand patients.

Shen T, Liu Y, Shang J, et al. Incidence and etiology of drug-induced liver injury in mainland China. *Gastroenterology*. 2019; 156:2230-2241

Pyrrolizidine alkaloids (PAs) in *Artemisia capillaris* (*yin chen*)

A recent study investigated the concentration of pyrrolizidine alkaloids (PAs) in *Artemisia capillaris* (*yin chen*). Pyrrolizidine alkaloids occur in numerous plant species, including coltsfoot (*Tussilago farfara*) and comfrey (*Symphytum* spp.). They are dose-dependently hepatotoxic and carcinogenic.

Among relevant Chinese medicinal herbs, PAs are known to occur not only in coltsfoot flowers (*kuan dong hua*), but also in *Arnebiae Radix* (*zi cao*) and *Eupatorii Herba* (*pei lan*). As a rule, these herbal drugs are unable to comply with the currently applicable European limits for PA contamination and are therefore not marketable in Europe.

Apparently, the PA concentration in *Artemisia capillaris* (*yin chen*) has now been investigated for the first time. Although the plant part was not explicitly specified, it may reasonably be assumed that the aerial parts (*herba*) were analyzed. Approximately half of the tested samples exceeded the limits established by the European Medicines Agency (EMA) when the maximum recommended dosage was taken into account. Several samples exhibited particularly high PA concentrations.

Comments

*It is noteworthy that the Chinese authors referred to the limits established by the European Medicines Agency (EMA). The German Federal Institute for Risk Assessment (BfR) was also cited. Although medicinal herbs with very high PA concentrations are still used in China, critical voices concerning this issue are increasingly emerging. Consequently, PA determination will likely also become necessary for *Artemisia capillaris* (*yin chen*), which may lead to increased costs of the herbal drug.*

Chen LH, Wang JC, Guo QL, et al. Simultaneous determination and risk assessment of pyrrolizidine alkaloids in *Artemisia capillaris* Thunb. by UPLC-MS/MS together with chemometrics. *Molecules* 2019;24(6):1077. doi:10.3390/molecules24061077.

Chinese authorities take action against illegal practices in traditional medicines

The renowned state-owned company Tong Ren Tang is regarded in China as a benchmark supplier of high-quality traditional medicinal products, and raw materials for clinical studies are frequently sourced from the company.

An investigation conducted by the Beijing Commission for Discipline Inspection of the Communist Party of China found that the company had marketed honey whose expiration date had already passed. The supplier, a company founded in 1669, had delivered the expired honey, while Tong Ren Tang had failed to adequately supervise the supplier. The expiration date labels had reportedly been replaced. The commission identified chaotic internal management practices and concluded that the reputation of Traditional Chinese Medicine had been damaged as a result.

In 2016, another investigation had already determined that Manuka honey imported from New Zealand had been adulterated with syrup by Tong Ren Tang. Five responsible individuals were demoted or dismissed. Tong Ren Tang was fined 4 million yuan (approximately 2.07 million USD). The business license of Beijing Tong Ren Tang Bee Industry was revoked and may not be renewed for a period of five years.

Another major concern is the widespread promotion of unproven indications for Chinese patent medicines. The State Administration of Traditional Chinese Medicine instructed local authorities to strictly monitor products and their marketing practices and to penalize those responsible for “fake advertising.” This directive was prompted by a manufacturer from Tianjin that attracted public attention after disseminating misleading claims about its products through an online platform. One of the company’s products was claimed to have anti-cancer effects. A seven-year-old girl died from cancer in 2015 after discontinuing chemotherapy and switching to the product. Her father had relied on assurances made by the company’s chief executive. Three months after beginning treatment with the product, distant metastases were detected. Online statements issued by the company nevertheless claimed that the child had been cured.

China Daily 2019; <http://global.chinadaily.com.cn/a/201902/13/WS5c635b26a3106c65c34e8fba.html>;
<http://www.chinadaily.com.cn/a/201812/29/WS5c26abc3a310d91214051912.html>;
<http://www.chinadaily.com.cn/a/201812/28/WS5c258238a310d912140516cc.html>



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<http://www.ctca.de/images/files/CTCAMeldebogen.pdf>

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Best wishes,
Axel Wiebrecht

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