Centrum für Therapiesicherheit in der Chinesischen Arzneitherapie
Center for Safety of Chinese Herbal Medicine
www.ctca.center info@ctca.center

CTCA letter - March 2022

Dear friends of Chinese Medicine,

After a longer pause during which the CTCA underwent restructuring, we are pleased to return with several current topics. Our website is also undergoing a relaunch and will soon feature a new online reporting form, which will make it even easier for you to submit suspected adverse drug reactions associated with Chinese herbal therapy. The CTCA will handle your report collegially, assess the causal relationship with the Chinese herbal medicine, and provide an expert evaluation. Your report is important so that we can all learn from it and further improve the safety of Chinese herbal medicine. At the same time, I hope that, through your careful and conscientious practice, you will rarely have reason to submit such reports.

With best regards,
Axel Wiebrecht

Highly toxic extract unscathed in market for months

Through a patient who was under the care of a colleague at the CTCA, we became aware that a highly toxic extract derived from a Chinese medicinal plant is being marketed in Germany as a "dietary supplement." The product concerned is a full extract of Tripterygii wilfordii Radix (*lei gong teng*). Due to its well-documented toxicity profile, this plant material is considered obsolete for therapeutic use. Reported adverse reactions include clinically significant immunosuppression, hepatotoxicity, nephrotoxicity, male infertility, amenorrhea and other hematological toxicities. In the People's Republic of China, there is an ethanolic extract of *Tripterygium wilfordii* approved as a medicinal product; however, its clinical use is subject to strict regulatory controls. These include limitation of treatment duration, mandatory medical supervision with regular laboratory monitoring including ECG assessment, as well as clearly defined contraindications – most notably pregnancy, due to teratogenic risks demonstrated in animal studies.

In contrast, the above-mentioned full extract has been marketed and distributed via numerous German and international online pharmacies (e.g. Doc Morris). A letter to the editor outlining the pharmacological, regulatory and toxicological concerns, was submitted from our

group to the journal *Zeitschrift für Phytotherapie*[1], and the case was reported on June 25, 2021, to the competent regulatory authority in Baden-Württemberg. It is hence difficult to comprehend that, as of today, March 10, 2022, entering the German term “Dreiflügelfrucht” into an internet search engine still yields numerous vendors offering this “full extract”. The responsible authority appears unable to effectively prevent this acute risk to consumers.

We are currently facing a paradoxical regulatory situation in Germany. On the one hand, within the medicinal product sector, it has become increasingly difficult – if not practically impossible – to import granulated preparations from China or Taiwan that have been manufactured and quality-tested in accordance with established pharmaceutical standards. On the other hand, highly toxic substances – some of which are no longer used in clinical practice within Traditional Chinese Medicine due to well-recognized safety concerns – continue to be marketed and distributed without apparent restriction as dietary supplements.

Probable hepatotoxicity of Psoraleae Fructus (*bu gu zhi*)

Psoraleae Fructus (*bu gu zhi*), derived from *Psoralea corylifolia*, has for some time been under scrutiny for potential hepatotoxicity. During the past two years, the number of reports addressing this issue has increased substantially. A literature search reveals approximately 20 publications indexed in PubMed from 2020 and 2021 alone, as well as around 15 publications in the Chinese database CNKI. In these articles, hepatotoxicity is generally treated as an established fact rather than as a hypothesis requiring further verification.

However, this apparent “certainty” is based predominantly on experimental animal studies, which cannot be directly extrapolated to the clinical setting. The pattern of liver injury under discussion is consistent with an idiosyncratic form of hepatotoxicity. Such reactions are typically not observed in the general population but occur only in susceptible individuals, presumably on the basis of immunological mechanisms or individual metabolic characteristics. By definition, idiosyncratic hepatotoxic reactions are not reliably reproducible in animal models.

Although these adverse reactions are rare and unpredictable, they may, in some cases, follow a severe clinical course. A growing number of well-documented clinical cases have been reported in which liver injury occurred following administration of *bu gu zhi*, either as a single substance or as part of compound prescriptions that did not contain other ingredients with known hepatotoxic potential. A systematic compilation of these clinical cases will soon be published in the journal *Chinesische Medizin*[2], providing a more comprehensive overview of the available evidence.

At present, the most effective strategy to minimize the risk of serious harm is careful patient education. Individuals receiving herbal drugs with potential hepatotoxicity should be informed about the signs and symptoms of liver injury and explicitly instructed to contact their treating practitioner immediately if such symptoms occur.

Potential interactions with new oral anticoagulants

Interactions with anticoagulant drugs are among the most clinically significant and frequent serious drug–herb interactions. This is particularly true for the class of vitamin K antagonists (e.g., warfarin), which are highly sensitive to such interactions. Similar interactions have been

[1] Wiebrecht A, von Hasselbach Y. Leserbrief. Zschr Phytother 2021;42:213-214
[2] Wiebrecht A. [Beware of possible hepatotoxicity in the use of Psoraleae Fructus (*Buguzhi*)!] (German) Chin Medizin 2022;37:94-105;https://doi.org/10.1007/s00052-022-00052-6

reported with certain Chinese medicinal herbs, such as Lycii Fructus (*gou qi zi*). The newer direct oral anticoagulants (NOACs) are generally considered less prone to interactions; however, they are not entirely exempt from these.

In 2019, two clinical bleeding cases were reported in which an interaction between ginger (*Zingiber officinale*) and dabigatran may have contributed[3,4]. One of these cases resulted in a fatal outcome. Although these individual cases do not provide definitive proof of causality, the mechanism is theoretically plausible. Ginger inhibits P-glycoprotein, a membrane transporter responsible for the efflux of dabigatran from cells. Inhibition of P-glycoprotein may increase systemic exposure to dabigatran and thus potentiate its anticoagulant effect, thereby increasing the risk of bleeding.

Taste disturbances associated with *Andrographis paniculata*

Last year, the Australian Therapeutic Goods Administration (TGA) published safety information indicating that administration of *Andrographis paniculata* may be associated with taste disturbances or loss of taste.[5] Up to July 2020, the TGA had received 226 reports in which Andrographis was considered the probable causative agent. Limited evidence suggests that the active constituent Andrographolide is responsible.

The reported cases primarily involved higher-dosage extracts, particularly those prepared using alcoholic or methanolic solvents. In contrast, aqueous decoctions, as commonly used in Traditional Chinese Medicine, yield lower concentrations of andrographolide. The Chinese Pharmacopoeia monograph for Andrographis Herba (*chuan xin lian*) specifies a minimum content of 0.8% andrographolide in the raw herb. Analytical studies have demonstrated that maximum extraction of andrographolide occurs with 50% ethanol (115 mg/g), whereas aqueous extraction still achieves approximately 25 mg/g.[6] Clinical studies have documented taste disturbances at doses of ≥1200 mg/day of alcoholic extracts of *Andrographis paniculata*.[7] In reported cases, taste alterations persisted for several months. Based on these findings, the TGA has issued a warning recommending that finished product labelling include information on potential taste disturbances or loss of taste.

Whether this adverse effect is clinically relevant for typical use of Andrographis decoctions or granules in Chinese Medicine cannot be determined with certainty, but it cannot be excluded. Considering that taste disturbances also occur in the context of COVID-19 or Long-COVID, clinicians and patients should remain alert to a possible additive effect when using Andrographis-containing products.

Report suspected side effects from Chinese herbal medicine to the CTCA at www.ctca.center.

You can forward this newsletter to anyone who might be interested or, if you haven't already done so, sign up to receive the newsletter regularly at www.ctca.center.

---

[3] Maadarani O, Bitar Z and Mohsen M. Adding herbal products to direct-acting oral anticoagulants can be fatal. Eur J Case Rep Intern Med 2019;6:001190

[4] Gressenberger P, Rief P, Jud P, et al. Increased bleeding risk in a patient with oral anticoagulant therapy and concomitant herbal intake - a case report. J Int Fed Clin Chem Lab Med 2019;30:95-98

[5] https://www.tga.gov.au/outcomes-low-negligible-risk-changes-permissible-ingredients-2020-2021

[6] Rafi M, Devi AF, Syafitri UD, et al. Classification of Andrographis paniculata extracts by solvent extraction using HPLC fingerprint and chemometric analysis. BMC Research Notes 2020;13(1), 56

[7] i.a. Sandborn WJ, Targan SR, Byers VS, et al. Andrographis paniculata extract (HMPL-004) for active ulcerative colitis. Am J Gastroenterol 2013;108:90-98