



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 - M a r c h 2 0 2 5

Esteemed colleagues and friends of the CTCA,

In this issue of our newsletter, we would like to address further topics relevant to TCM practitioners.

While the study by Peng et al., which attracted considerable attention last year, raised significant concerns, more reassuring perspectives have emerged in this year. Nevertheless, exercising particular caution when administering medicinal and herbal products during pregnancy remains essential. The recently published new edition of the 'Leitfaden Chinesische Medizin' (Guide to Chinese Medicine) provides updated recommendations for Chinese herbal medicine during pregnancy.

Furthermore, this issue discusses adverse effects associated with Indigo naturalis (*qing dai*) as well as the ongoing concerns about donkey-hide gelatin (*ē jiāo*).

As in previous years, the CTCA is your designated contact point for reporting suspected adverse reactions related to Chinese herbal therapy. We encourage you to make use of the reporting form available on our website at www.ctca.center.

All submissions will be handled with strict professional confidentiality. Our interdisciplinary team of specialists will carefully assess the potential causal relationship between the reported reaction and the herbal preparation, and provide an evidence-based evaluation.

Sincerely,

CTCA

Teratogenic risk from Chinese herbal therapy (CHT) not confirmed

Compiled and commented by Axel Wiebrecht

In the February 2024 issue of the CTCA Newsletter, we discussed a study by Peng et al. which purported to demonstrate an increased teratogenic risk associated with exposure to CHT during pregnancy. This publication caused significant concern within the TCM community. However, due to serious methodological flaws, we concluded that the study was inconclusive. A detailed analysis can be found in the journal *Chinesische Medizin* [2]. The Peng study was subsequently retracted by the publishing journal. The CTCA also successfully facilitated the removal of a report on the study from the *Medical Tribune* website.

Recently, a methodologically rigorous and carefully designed Chinese study involving a relatively large sample size was published. This study reported no statistically significant association between CHT use and an increased rate of teratogenic outcomes [3]. The evaluation included 195,824 pregnancies resulting in live births between 2013 and 2018, extracted from the Xiamen database containing records for five million residents. Pregnancies in which exclusively CHT was used in the form of proprietary medicines during the first trimester for miscarriage prevention or pregnancy support were compared with: (a) pregnancies in which no medication was used; and (b) pregnancies in which progesterone monotherapy was used to maintain gestation (active control group). Progesterone is considered safe for use in pregnancy. The newborns were examined for congenital malformations at birth and followed up into adolescence. As this was a non-randomized retrospective observational study, extensive adjustments were made to maximize comparability between groups across a wide range of variables.

In total, 3,024 early pregnancies were managed exclusively with herbal preparations for miscarriage prevention or pregnancy maintenance, 18,977 pregnancies received progesterone monotherapy, and 155,514 pregnancies involved no medication. The most frequently used herbal preparations (not specified for the group receiving exclusively herbal medication) were *Yunkang* granules, *Antai Wan*, *Zishenyutai Wan*, and *Duzhong* granules.

The results showed no statistically significant difference in the overall frequency of congenital malformations between the CHT group and the medication-free group (risk ratio [RR] 1.25; 95% confidence interval [CI] 0.69–2.29), or between the CHT group and the progesterone monotherapy group (RR 1.28; 95% CI 0.57–2.90). No significant differences were observed for any of the 23 individual congenital malformations either. A sensitivity analysis, involving the formation of nine subgroups, did not yield substantially different results.

Comments

This study argues against significant teratogenic risks associated with Chinese proprietary medicines, which are commonly prescribed in China for miscarriage prevention or to support pregnancy. Unlike the Peng study, this study is characterized by a relatively large overall sample size, a reliable data source, and a robust methodology, as it compares pregnancies treated exclusively with CHT with two other groups: one receiving no medication and one receiving progesterone monotherapy.

However, it should be noted, that the risk in the CHT group was numerically slightly higher in both comparisons. No definitive conclusions can be drawn from this. If any trend exists, it may be due to the fact that herbal drugs that are considered contraindicated during pregnancy are occasionally prescribed in China – a finding supported by several studies. As the authors emphasize, further research with even larger sample sizes is required to strengthen the evidence regarding the safety of CHT during pregnancy. A study from Japan demonstrated the safety of *Kampo* medicine for treating depression during pregnancy [4]. Although the overall sample size was similar, fewer pregnancies were treated exclusively with herbal preparations than in the present study.

We recommend strictly adhering to the indications for the use of CHT, particularly during the first trimester, and that all contraindications and precautionary measures are rigorously observed. Updated guidelines based on the current state of knowledge are available in the newly published edition of *Leitfaden Chinesische Medizin* (Guide to Chinese Medicine) released this month (Vol. 1, published by Elsevier).

Notable adverse effects of Indigo (*qing dai*)

Compiled by Axel Wiebrecht

A recently published review, which does not cover all cases, summarizes the known risks associated with the use of Indigo naturalis (*Qing dai*). Indigo is a dye that has long been obtained from various plants, including *Isatis indigotica*, in ancient China and other countries. Within the framework of Chinese medicine, it is primarily used for dermatological conditions associated with heat, toxic heat, or blood heat, such as psoriasis. In Japan, it has also been successfully used as a single agent to treat ulcerative colitis, including cases that have not responded to other therapies. However, its efficacy in Crohn's disease has been only moderate. Therapeutic indications generally require prolonged treatment, during which several adverse effects may occur, some of which can be severe.

Mild side effects may include gastrointestinal complaints such as nausea, digestive disturbances, and headaches. Hepatotoxicity is not uncommon but usually not severe. Of greater concern is ischemic colitis, which occurs relatively frequently and must be distinguished from underlying ulcerative colitis. Ischemic colitis presents with abdominal pain and bloody diarrhea. Imaging diagnostics typically reveal bowel wall thickening with edema, and histological examination shows vasculitis of the small intestinal veins. Occasionally, life-threatening intestinal intussusception may occur. Ten such events were reported in Japan within two months of initiating therapy, and 40% of these required surgical intervention. Daily doses were generally 1–2 g, occasionally higher.

Of particular concern is the rare occurrence of pulmonary hypertension, which was first reported in 2016 [6]. Following this report, a previously ongoing randomized trial for ulcerative colitis was terminated [7]. All subsequently reported cases also originated from Japan. The patients developed pulmonary hypertension after at least six months of Indigo therapy presenting with dyspnea, edema, and chest pain. It is unclear whether these cases are always reversible.

Another reported adverse effect occurred in an 11-year-old boy, who developed pancreatitis after receiving two doses of 0.3 g Indigo. A subsequent attempt with 0.15 g Indigo again resulted in pancreatitis after only two doses [8].

When using Indigo naturalis (*qing dai*), the potential therapeutic benefits should be carefully weighed against the associated risks. If therapy is initiated, patients should be diligently monitored for emerging symptoms, and liver function tests are recommended both prior to and throughout treatment.

The Issue of ě jiāo (阿胶, Asini Corii Colla, Donkey-Hide Gelatin)

Researched and compiled by Nina Zhao-Seiler

The use of ě jiāo has increasingly become an ethical concern, as demand for this Chinese medicine has threatened donkey populations, particularly in Africa and Brazil.

Historical Background

The Chinese name ě jiāo literally means “gelatin from Ē.” Ē refers to a location in eastern China (Shandong Province), known for a spring with particularly good water for gelatin production, and does not indicate neither the species of animal from which the gelatin is derived nor the type of hide.

At the time of the earliest documentation of this name in the 5th century BCE, this medicinal gelatin was primarily made from cattle hide, and occasionally from the hides of other domesticated or wild animals of that period. Donkeys imported from West Asia and Africa were not yet widespread in China. Gelatin produced from cattle hide was described as the highest-quality form of ē jiāo. The earliest mention appears in the 5th century BCE in the *Shennong Bencao Jing* (“Materia Medica of the Divine Farmer”) compiled by Táo Hóngjǐng (452–536 CE), who drew on sources from the preceding 300–500 years.

Táo Hóngjǐng also authored another *Materia Medica* compilation, the *Mingyi Bielu* (“Commentaries of Notable Physicians”), which provides detailed instructions on the production of ē jiāo. He explicitly noted that it was made from cattle hide and that such ē jiāo produced the best results. The indications he listed are identical to those currently associated with donkey-hide ē jiāo.

With the introduction and spread of donkeys in China, medicinal-grade gelatin from donkey hides started to be produced. During the Tang Dynasty (618–907 CE), both cattle-hide and donkey-hide ē jiāo were approved for medicinal use. During this period, gelatin from cattle hide was first given a distinct name, huáng míng jiāo (黃明膠, “yellow-transparent gelatin”), which remains in use today. Around the year 1000 CE, during the Song Dynasty, the use of donkey-hide became predominant. This shift followed a government-mandated state monopoly on cattle hides, due to prior shortages as cattle hides were extensively used for both military and agricultural purposes. From that time onward, medicinal gelatin from donkey hide was increasingly described as the superior medicinal form.

The Problem

Due to a sharp increase in demand over the past 15 years—particularly driven by the food and wellness industries within China and surrounding East Asian regions—the Chinese donkey population has been severely reduced. Domestic donkey breeding in China is no longer sufficient to meet demand. As a result, traders increasingly purchase donkeys from other countries, especially Brazil and various African nations. In some cases, aggressive and criminal methods, including theft and mistreatment of donkeys, have been employed.

This practice has led to donkey populations being severely decimated in certain regions of Africa and Brazil, placing them at risk of endangerment and causing shortages of these animals in small-scale agricultural settings. In February 2024, the African Union therefore enacted a ban on the export of African donkeys to China.

Possible Solution

Today, China, along with many other countries, maintains a substantial domestic cattle industry. Many cattle hides are available that could theoretically be used to produce high-quality ē jiāo. This approach would constitute a return to the type of ē jiāo used in Zhang Zhongjing’s era, which was regarded as the highest quality. It may be possible to adapt existing processes for producing cattle gelatin in the food industry so that the resulting gelatin contains more blood components and is therefore dark red in color, similar to the donkey-hide gelatin commonly used today.

Altering a long-established traditional medicine in this manner requires a mental shift, both within the industry and among the authorities responsible for the Chinese Pharmacopoeia under the Ministry of Health of the People’s Republic of China.

Animal welfare is an important issue in China, particularly among internet-active generations. Articles regarding the decimation and mistreatment of donkeys are publicly accessible,

though they have not yet been discussed as widely as other controversial TCM topics, such as the use of tiger bone or bear bile, which in recent years have received extensive media attention and sparked highly controversial debates over tradition.

Within parts of the Chinese TCM community, there is awareness that early *Materia Medica* texts described cattle hide as the best raw material for ē jiāo production. However, to date, I am not aware of any initiatives actively promoting a return to cattle-hide ē jiāo. This form of ē jiāo is not listed in the current Pharmacopoeia and is therefore considered a counterfeit product. It is still occasionally used medically, but mainly in cases where financial constraints are an issue, as ē jiāo is expensive.

The aim here is to provide a foundation of information that allows European TCM professionals to engage in informed discussions with responsible parties and potentially help initiate change.

Note from Nina Zhao-Seiler: While researching this article, I found no evidence that donkeys are whipped prior to slaughter to increase blood content in the hide (as I had previously heard), including in detailed reports from the Donkey Sanctuary. According to the Donkey Sanctuary, donkeys purchased or stolen outside of China are slaughtered in their country of origin, with only the hides transported to China. Anyone with additional information is encouraged to contact me, as I am interested in learning as much as possible about the practices involved in the trade and production of donkeys and donkey-hide gelatin.

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Important Notice:

Please report suspected adverse reactions associated with Chinese Herbal Therapy (CHT) directly to the CTCA at www.ctca.center.

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