Occurrence of Chai Hu (Bupleuri Radix) in Prescriptions of Chinese Herbal Medicine in Switzerland

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Summary

Background: Chai hu (Bupleuri radix), one of the most frequently used herbs in Chinese herbal medicine, has 3 major functions, depending on dosage and combination with other herbs. The aim of this study was to investigate how chai hu is prescribed in everyday practice in Switzerland, and whether these prescription patterns reflect its various applications. **Methods:** A random sample of 1,053 prescriptions was drawn from the database of Lian Chinaherb AG, Wollerau, Switzerland, and analyzed regarding the most frequently used classical formulas containing chai hu, daily dosages and combinations with other herbs. **Results:** 29.0% of all prescriptions contained chai hu, and 98.0% of these were in granular form. The most frequently used classical formulas were xiao yao san ('rambling powder'), jia wei xiao yao san ('augmented rambling powder') and chai hu shu gan san ('Bupleurum powder to spread the liver'). In more than half of the prescriptions, chai hu was combined with bai shao (Paeoniae Radix Alba), dang gui (Angelicae sinensis radix) or fu ling (Poria). 51.8% of the prescriptions contained a low daily dosage of chai hu, 24.9% a medium and 15.1% a high dosage. **Conclusion:** Chai hu was generally prescribed in classic combinations with other herbs and in a medium dosage. Due to the addition of supplementary herbs to classical formulas, its daily dose was often diminished from a high or medium dose to a low dose. This raises the question if chai hu would then still exert its desired function of, e.g., moving liver-qi in these prescriptions.

Zusammenfassung

Hintergrund: Chai Hu (Bupleuri radix) ist eines der am häufigsten verwendeten Heilkräuter in der chinesischen Arzneimitteltherapie und hat, je nach Dosierung und Kombination mit anderen Arzneimitteln, 3 Hauptfunktionen. Das Ziel dieser Studie war zu untersuchen, wie Chai Hu im Praxisalltag in der Schweiz verschrieben wird und ob diese Verschreibungsmuster dessen verschiedene Verwendungsmöglichkeiten widerspiegeln. **Methoden:** Eine zufällige Stichprobe von 1053 Verschreibungen wurde aus der Datenbank der Lian Chinaherb AG, Wollerau, Schweiz, gezogen und auf die am häufigsten verwendeten klassischen Rezepturen, welche Chai Hu enthalten, Tagesdosen und Kombinationen mit anderen Arzneimitteln hin analysiert. **Ergebnisse:** 29,0% aller Verschreibungen enthielten Chai Hu; davon 98,0% in Form von Granulat. Die am häufigsten verwendeten klassischen Rezepturen waren Xiao Yao San («Umherstreifen-Pulver»), Jia Wei Xiao Yao San («Erweitertes Umherstreifen-Pulver») und Chai Hu Shu Gan San («Radix-Bupleuri-Dekokt, das die Leber verteilt»). In mehr als der Hälfte der Verschreibungen war Chai Hu mit Bai Shao (Paeoniae radix alba), Dang Gui (Angelicae sinensis radix) oder Fu Ling (Poria) kombiniert. 51,8% der Verschreibungen enthielten eine niedrige, 24,9% eine mittlere und 15,1% eine hohe Tagesdosis an Chai Hu. **Schlussfolgerungen:** Chai Hu wurde allgemein in klassischen Kombinationen mit anderen Arzneimitteln und in einer mittleren Tagesdosis verschrieben. Durch die Zugabe weiterer Arzneimittel zu klassischen Rezepturen war dessen Tagesdosis häufig von einer hohen oder mittleren Dosis zu einer niedrigen Dosis vermindert. Dies wirft die Frage auf, ob Chai Hu in diesen Dosierungen immer noch die gewünschte Funktion, z.B. die des Bewegens des Leber-Qis, ausübt.

Introduction

Chai hu (Bupleuri radix) is commonly used in Chinese herbal medicine. It is described as being bitter, acrid, cool, and entering the liver and gallbladder channels [1]. It has 3 major functions: 1. to harmonize the shaoyang aspect (exterior and interior), 2. to spread the liver and relieve liver-qi stagnation (especially when vinegar-fried), and 3. to raise yang-qi (it would exceed the scope of this article to explain the theory and terminology of Chinese medicine, for an introduction see, e.g., Maciocia [2]). The daily dosage depends on the desired function: treatment of organ prolapse, e.g., requires a small dosage (3 g of crude herbs daily), whereas treatment of shaoyang disorders requires a larger dosage (10–15g, [3, 4]).

Chai hu is included in many classical formulas. It raises qi in bu zhong yi qi tang ('tonify the middle and augment the qi decoction') or pu ji xiao du yin ('universal benefit decoction to eliminate toxins') [5]. It spreads liver-qi or directs the herbs and the action of the prescription to the liver channel in, e.g., long dan xie gan tang ('Gentiana longdancao decoction to drain the liver'), si ni san ('frigid extremities powder'), xiao yao san ('rambling powder'), xue fu zhu yu tang ('drive out stasis in the mansion of blood decoction') or chai hu shu gan san ('Bupleurum powder to spread the liver'). It treats shaoyang syndromes in xiao chai hu tang ('minor Bupleurum decoction'), da chai hu tang ('major Bupleurum decoction') or chai hu jia long gu mu li tang ('Bupleurum plus dragon bone and oyster shell decoction'). It releases the exterior in ren shen bai du san ('ginseng powder to overcome pathogenic influences') or jing fang bai du san ('Schizonepeta and Ledebouriella powder to overcome pathogenic Influences').

In recent years, much research was performed on extracts of chai hu and formulas containing chai hu in vitro and in animal models, and some studies in humans were conducted. Fields of interest were mainly influenza, allergies, cancer and depression: A nasal spray containing essential oil from chai hu was shown to treat fever in rabbits and rats [6]. A Chinese herbal formulation containing chai hu offered symptomatic relief for patients suffering from seasonal allergic rhinitis [7] and inhibited inducible nitric oxide synthase protein expression in Raw 264.7 cells [8]. Bu zhong yi qi tang had radio-protective effects for jejunal crypt cells in mice [9]. An extract of chai hu had an activating effect on the cytotoxic activity of macrophages, natural killer cells and lymphokine activated killer cells against tumor cells [10]. A herbal extract containing chai hu induced apoptosis and production of interleukin 4 and tumor necrosis factor α in liver cancer cells in vitro [11]. Chai hu extract enhanced 5-fluorouracil-induced cytotoxicity in HepG2 cells but protected normal human lymphocytes [12]. Long dan xie gan wan was cytotoxic and induced apoptosis in HL60 and HT29 cancer cell lines, but was only moderately cytotoxic to blood lymphocytes [13]. Chai hu shu gan san extract or chai hu extract showed antidepressant effects in rat models [14], and jia wei xiao yao san ('augmented rambling powder') was effective in patients with post-stroke depression [15].

In everyday practice, many of these studies are hardly relevant for practitioners. Practitioners have to rely on textbook knowledge as well as their experience in order to choose suitable combinations of herbs and dosages for individual patients. Generally, textbooks list dosages for dehydrated crude herbs, while prescriptions are often given as granules. We recently found chai hu to be amongst the most frequently used Chinese herbs and xiao yao san amongst the most frequently used formulas in Switzerland [16]. The aim of this study was to investigate in which concentrations and in combination with which other herbs chai hu is prescribed in everyday practice, and whether these prescription patterns reflect the different textbook applications of chai hu, particularly regarding the different dosing regimens.

Material and Methods

Data

A random sample of 998 orders including 1,053 prescriptions for patients dating between July 2008 and June 2009 was drawn from about 50,000 orders within these 12 months in the database of Lian Chinaherb AG, Wollerau, one of the largest pharmacies for Chinese herbs in Switzerland. Since the data were accessible via the patients' names (and not prescription numbers), every 10th patient was selected. If he/she had orders (prescriptions) within the chosen time period, one of them was included in the sample (alternately 1st, 2nd, 3rd or 4th order, if present, otherwise again the 1st prescription was used).

The following information was used: product numbers of single herbs and formulas, their respective amount (weight), and dosage instructions. The daily dosage was stated for 92.6% of the granular prescriptions. For further calculations, e.g., to determine the number of herbs per prescription, formulas were split up into their single ingredients.

Data collection was anonymous. The responsible ethics committee appraised a submission of the research protocol as unnecessary.

Prescription of Granules

Granules, the most common form of Chinese herbs employed in Switzerland, are prescribed by practitioners in 3 different ways: a) a combination of single herbs, b) a premixed classical formula, and c) a premixed classical formula with the addition of single herbs (a modified classical formula). In granular form, Lian Chinaherb AG stocks roughly 350 single herbs (granules prepared from decoctions of single herbs) and 150 premixed classical formulas, which are prepared by cooking the crude herbal ingredients of the classical formula together and preparing granular extracts from such decoctions.

Commonly, 4–6 g of granules per day are considered a low dosage, 8–12 g a medium, and 15–20 g a high dosage for prescriptions [17]. Prescriptions contain an average of 12 herbs [16]; therefore, we defined a low dosage of a single herb as <0.6 g, a medium dosage as 0.6–1.0 g, and a high dosage as >1.0 g per day.

Cluster Analysis

Cluster analysis is a multivariate analysis method that is applied to assign similar objects into groups. It is a stepwise procedure, and in every step it is first determined how similar the objects are, and then 2 objects are clustered. For the current analysis, similarity was defined as 2 herbs often occurring together in a prescription. Objects are single herbs in the first

Table 1. Most frequently prescribed premixed granular formulas containing chai hu and the prescription frequency of the three chai hu dosages (low, medium, high) per formula

Formula	Frequency				
	total (%)	low dosage[a]	medium dosage[a]	high dosage[a]	dosage unknown[b]
Xiao yao san (rambling powder)	31 (18.1)	9	12	7	3
Jia wei xiao yao san (augmented rambling powder)	25 (14.6)	10	14	0	1
Chai hu shu gan san (Bupleurum powder to spread the liver)	15 (8.8)	5	6	4	0
Xue fu zhu yu tang (drive out stasis in the mansion of blood decoction)	14 (8.2)	12	1[c]	0	1
Bu zhong yi qi tang (tonify the middle and augment the qi decoction)	14 (8.2)	13	0	1[d]	0
Long dan xie gan tang (Gentiana longdancao decoction to drain the liver)	9 (5.3)	3	2	4	0
Total	108 (100)	52	35	16	5

[a]For granular prescriptions only: low dosage <0.6 g/day chai hu, medium dosage 0.6–1.0 g/day, high dosage >1.0 g/day.
[b]No daily dosage stated.
[c]In combination with jia wei xiao yao san (augmented rambling powder).
[d]With additional chai hu.

steps of the procedure and single herbs or clusters of herbs in later steps of the procedure.

All prescriptions containing chai hu (n = 305) and all herbs occurring in at least 5 of these prescriptions (n = 128) were chosen. The presence or absence of a herb in a prescription was coded as 1 or 0, respectively, resulting in a binary data set. The Jaccard similarity coefficient and average linkage method were used to combine single herbs into clusters [18].

Nomenclature
Herb nomenclature and formula composition follows Bensky [1, 5]. For herbs, the Chinese names (Pinyin) and pharmaceutical names (in Latin) are listed; for formulas the Chinese and English notations. All ingredients are referred to as herbs for reasons of simplicity, although not all products are parts of plants, but some are fungi, minerals, or of animal origin.

Software
For statistical analysis, SPSS Statistics 17.0 (SPSS, Zurich, Switzerland) was used.

Fig. 1. Partial result of the cluster analysis illustrated by a dendrogram. Only the first herbs being grouped with chai hu are shown.

Results

Out of the 1,053 prescriptions, 305 (29.0%) contained chai hu. The majority of these (98.0%) were in granular form and only 2.0% in crude form. 43.9% of the prescriptions containing chai hu were composed of single herbs; 56.1% of the prescriptions were premixed classical formulas to some of which single herbs had been added. 29 prescriptions consisted of 1 classical formula, 13 prescriptions of 2, and 3 prescriptions of 3 formulas without addition of single herbs; single herbs had been added to the remaining 126 premixed formulas. In 3 prescriptions, several classical formulas containing chai hu were mixed; in 1 prescription the single herb chai hu was added to a classical formula already containing chai hu. The average number of herbs per prescription was 12.6. The most frequently used classical formulas containing chai hu are shown in table 1.
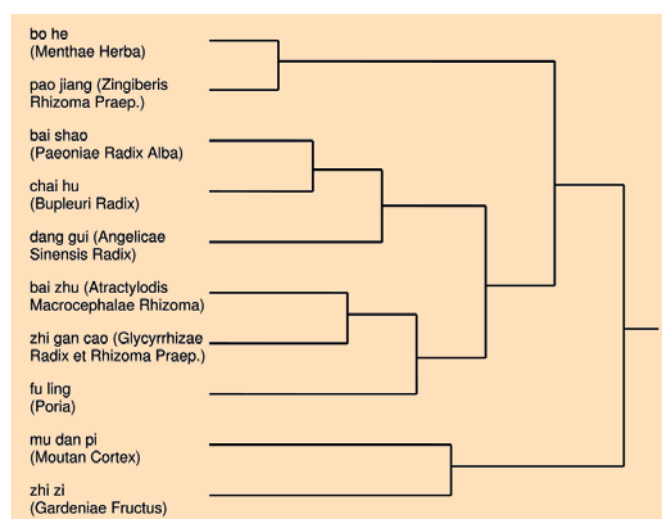
The daily dosage of chai hu depended on the total daily dosage of herbs and the percentage of chai hu in the prescription. The average daily dosage for granule prescriptions was 8.6 g, and the maximal dosage was 18.0 g. 51.8% of the prescriptions contained a low daily dosage of chai hu (<0.6 g of granules), 24.9% a medium (0.6–1.0 g) and 15.1% a high dosage (>1.0 g; for 8.2% the dosage was unknown). There was no significant difference between prescriptions based on single herbs and on premixed classical formulas. The median numbers of days of intake were 13.4, 12.7 and 10.0 for prescriptions with low, medium and high daily dosages, respectively. If taken according to indicated dosing instructions, amounts of granules would last between 3.3 and 42.0 days.

Table 2. Herbs most often combined with chai hu

Herb	Presence in prescriptions containing chai hu (%)
Bai shao (Paeoniae radix alba)	65.2
Dang gui (Angelicae sinensis radix)	63.3
Fu ling (Poria)	51.5
Bai zhu (Atractylodis macrocephalae rhizoma)	44.9
Zhi gan cao (Glycyrrhizae radix et rhizoma praeparata)	43.3
Gan cao (Glycyrrhizae radix et rhizoma)	32.8
Chuan xiong (Chuanxiong rhizoma)	27.5
Bo he (Menthae herba)	26.2
Huang qin (Scutellariae radix)	25.9
Sheng di huang (Rehmanniae radix)	25.9
Sheng jiang (Zingiberis rhizoma recens)	22.3
Chen pi (Citri reticulatae pericarpium)	21.0
Huang qi (Astragali radix)	20.0

Table 2 shows the herbs that were present in at least 20% of the prescriptions containing chai hu. In order to determine which herbs were most commonly combined with chai hu, cluster analysis was applied. This is a stepwise method to group objects (here: herbs within prescriptions). Cluster analysis of all prescriptions containing chai hu resulted first in grouping chai hu with bai shao, and in later steps of the analysis in the composition of the formulas xiao yao san and jia wei xiao yao san. Figure 1 shows the branch of the dendrogram, that includes chai hu (the complete dendrogram contains 128 herbs).

Discussion

Everyday use of chai hu corresponds to traditional textbook knowledge. Our analysis revealed that it was used in combinations indicated in textbooks [1, 3] and recommended by experienced practitioners. Thus, in almost two thirds of the prescriptions, chai hu was combined with bai shao (Paeoniae radix alba). Bai shao's sour, nourishing, and astringent qualities are traditionally regarded as counteracting both chai hu's acrid and drying effects as well as its upward and outward direction. Correspondingly, in a cluster analysis, bai shao was the first herb to group with chai hu.

When used to raise the qi, e.g., for organ prolapse or diarrhea, it is traditionally recommended to combine chai hu with huang qi (Astragali radix) and sheng ma (Cimicifugae rhizoma). Although we found sheng ma mostly combined with huang qi, the latter was more often used in the absence rather than in the presence of sheng ma.

In this and in our previous study [16], chai hu was particularly popular for moving liver-qi stagnation, as was shown by the widespread use of xiao yao san, jia wei xiao yao san and chai hu shu gan san. Unfortunately, the diagnoses of the patients were not included in the data set, therefore, no analysis of the frequency of patterns (e.g., liver-qi stagnation with spleen and blood deficiency) could be carried out. Future research could consequently focus on patients and their diagnoses. Outcomes as well as side effects of the herbal remedies could be measured, specific uses of Chinese herbs identified, and changes in prescriptions followed.

Finally, 25.9% of the prescriptions combined huang qin (Scutellariae radix) together with chai hu, a classic combination for harmonizing the shaoyang aspect (exterior and interior) [3].

In Switzerland, approximately 80% of all Chinese herbal medicine prescriptions are applied in granular form [17], and in our sample 98% of the prescriptions consisted of granules. Thus, it is difficult to compare the applied dosages with textbook recommendations for crude herbs. Our results show that prescriptions with higher dosages of chai hu were given for shorter time periods. The maximum duration of intake was 6 weeks. However, we did not follow individual patients, and it may well be possible that antecedent or subsequent prescriptions also contained chai hu. Recent research suggests comparable effectiveness of granules and decoctions in clinical trials in China [19], but given the large percentage of granules used in Switzerland, more studies on their effectiveness are certainly needed.

Prescriptions of Chinese medicinal herbs in Switzerland contain on average 12 herbs, but may contain up to 25 or even more [16]. Since most people experience digestive problems, e.g., nausea or abdominal pain, when taking more than 20 g of herbs in granular form per day [17], the maximum amount of intake is limited, and the addition of more herbs results in lower amounts of each herb in a prescription. According to traditional literature, the function of chai hu changes with increasing dosage from a messenger or uplifting function at a low dose to a harmonizing function at a higher dose. In this regard, the questions to be asked are: 1) What happens when the absolute and relative amount of chai hu is decreased in a

prescription upon the addition of further herbs to, e.g., a classical formula, and 2) is the presence of herbs supporting the desired function sufficient to compensate for this decrease in dosage? Hardly any answers to these questions can be found in the literature, except for a study by Dai et al. [20], showing that higher doses of xiao yao san had larger effects than lower doses in a rat model of chronic unpredictable mild stress, thus indicating that too low doses might be insufficient to achieve the therapeutic goal. Consequently, in general and for chai hu in particular more dosage studies are required.

References

1 Bensky D, Clavey S, Stoger E: Materia Medica: Chinese Herbal Medicine, ed 3, revised. Seattle, Eastland Press, 2004.
2 Maciocia G: The Foundations of Chinese Medicine, ed 2. Oxford, Elsevier, 2005.
3 Chen JK, Chen TT: Chinese Medical Herbology and Pharmacology. City of Industry, Art of Medicine Press, 2004.
4 Chen S, Tang D, Yao Y, Yuan Y, Xun J, Zhang W, Jing Z, Yu X: Science of Chinese Materia Medica. Shanghai, Publishing House of Shanghai University of Traditional Chinese Medicine, 2003.
5 Bensky D, Barolet R: Chinese Herbal Medicine: Formulas and Strategies. Seattle, Eastland Press, 1990.
6 Xie Y, Lu W, Cao S, Jiang X, Yin M, Tang W: Preparation of bupleurum nasal spray and evaluation on its safety and efficacy. Chem Pharm Bull 2006;54:48–53.
7 Xue CC, Thien FC, Zhang JJ, Da Costa C, Li CG: Treatment for seasonal allergic rhinitis by Chinese herbal medicine: a randomized placebo controlled trial. Altern Ther Health Med 2003;9:80–87.
8 Lenon GB, Li CG, Xue CC, Thien FC, Story DF: Inhibition of inducible nitric oxide production and iNOS protein expression in lipopolysaccharide-stimulated rat aorta and Raw 264.7 macrophages by ethanol extract of a Chinese herbal medicine formula (RCM-101) for allergic rhinitis. J Ethnopharmacol 2008;116:547–553.

9 Kim SH, Lee SE, Oh H, Kim SR, Yee ST, Yu YB, Byun MW, Jo SK: The radioprotective effects of bu-zhong-yi-qi-tang: a prescription of traditional Chinese medicine. Am J Chin Med 2002;30:127–137.
10 Kok LD, Wong CK, Leung KN, Tsang SF, Fung KP, Choy YM: Activation of the anti-tumor effector cells by Radix bupleuri. Immunopharmacology 1995;30:79–87.
11 Chow LW, Loo WT, Sham JS, Cheung MN: Radix bupleuri containing compound (KY88 liver-livo) induces apoptosis and production of interleukin-4 and tumor necrosis factor-alpha in liver cancer cells in vitro. Am J Chin Med 2004;32:185–193.
12 Kang SJ, Lee YJ, Kim BM, Kim YJ, Woo HD, Jeon HK, Chung HW: Effect of Bupleuri radix extracts on the toxicity of 5-fluorouracil in HepG2 hepatoma cells and normal human lymphocytes. Basic Clin Pharmacol Toxicol 2008;103:305–313.
13 Willimott S, Barker J, Jones LA, Opara EI: An in vitro based investigation of the cytotoxic effect of water extracts of the Chinese herbal remedy LD on cancer cells. Chem Cent J 2009;3:12.
14 Kim SH, Han J, Seog DH, Chung JY, Kim N, Hong Park Y, Lee SK: Antidepressant effect of Chaihu-Shugan-San extract and its constituents in rat models of depression. Life Sci 2005;76:1297–1306.

15 Li LT, Wang SH, Ge HY, Chen J, Yue SW, Yu M: The beneficial effects of the herbal medicine Free and Easy Wanderer Plus (FEWP) and fluoxetine on post-stroke depression. J Altern Complement Med 2008;14:841–846.
16 Klein SD, van der Zypen D, Becker S: Prescription patterns of Chinese medicinal herbs in Switzerland. Schweiz Z Ganzheitsmed 2010;22:226–231.
17 Becker S: Dosierung von Granulaten. Extrakt 2009;1:10–16.
18 Backhaus K, Erichson B, Plinke W, Weiber R: Multivariate Analysemethoden: eine anwendungsorientierte Einführung, ed 13, revised. Berlin, Springer, 2010.
19 Luo H, Flower A, Lewith G, Liu J: Comparison of effectiveness and safety between granules and decoctions of Chinese herbal medicine: a systematic review of randomized clinical trials. J Ethnopharmacol 2012;140:555–567.
20 Dai Y, Li Z, Xue L, Dou C, Zhou Y, Zhang L, Qin X: Metabolomics study on the anti-depression effect of xiaoyaosan on rat model of chronic unpredictable mild stress. J Ethnopharmacol 2010;128:482–489.