School of International Pharmaceutical Business[1], China Pharmaceutical University, Nanjing; State Key Laboratory of Core Technology in Innovative Chinese Medicine[2], Tasly Pharmaceutical Group Co., Ltd., Tianjin, PR China; Tasly Healthcare Deutschland GmbH[3], Hannover, Germany

Traditional use and safety evaluation of combination Traditional Chinese Medicine in European registration: with XiaoYao Tablets as an example

Qiong Wang[1,2,#], Shenghan Gao[2,#], Wensheng Zhang[2], Yunxia Zhao[2], Yi He[2], Wei Sun[2], Fenglian Zhang[2], Tong Yu[2], Lihong Zhou[2], Zhengliang Ye[2], Jiansen Su[3], Shunnan Zhang[2,*], Yongfa Chen[1,*]

Received November 20, 2021, accepted February 11, 2022

**Corresponding authors: Shunnan Zhang, State Key Laboratory of Core Technology in Innovative Chinese Medicine, Tasly Pharmaceutical Group Co., Ltd., Tianjin, 300410, PR China*
zsn@tasly.com
Yongfa Chen, School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, 211198, PR China
cyf990@163.com
#Co-first authors

Pharmazie 77: 125-130 (2022) *doi: 10.1691/ph.2022.1227*

Mental health disorders such as stress, anxiety, depression and insomnia caused by COVID-19 have attracted worldwide attention. Traditional Chinese medicines (TCMs) have been proven to be a safe and effective option for treating mental health disorders. Recently, after assessing its efficacy and safety fully, the Netherlands Medicines Evaluation Board approved XiaoYao Tablets as a traditional herbal medicinal product (THMP), indicated for an alternative self-care for patients in Europe to relieve the symptoms of mental stress and exhaustion. Despite the fact that TCMs have gradually become one of the therapeutic choices worldwide, to-date, only a few TCMs have been successfully registered in the European Union (EU) as THMPs, and XiaoYao Tablets is the first successfully registered combination TCM from China. In this article, traditional use efficacy and clinical safety of XiaoYao Tablets in the treatment of mental health disorders were summarized and analyzed from the perspective of traditional use registration (TUR). Additionally a safety evolution pathway of combination TCMs was established. This article will not only seek to enhance our understanding about traditional use efficacy and clinical safety of XiaoYao Tablets, but also summarize the experience of XiaoYao Tablets as the first successfully registered combination TCM from China, which could serve as role model for the others to overcome registration difficulties in the EU.

1. Introduction

In 2019, the COVID-19 pandemic took over the world. TCMs played an irreplaceable role as one of the key components of the COVID-19 treatment plan (Wang and Yang 2021). At present, many countries have developed effective vaccines to combat the virus. However, the mental health disorders caused by the pandemic in general population including patients who survived COVID-19, such as stress, anxiety, depression and insomnia, also require attention (Huang and Zhao 2020; Khademi et al. 2021; Serafini et al. 2020). Not only do TCMs have long experience in treating pandemic and endemic diseases for almost thousand years (Wu et al. 2021; Zhao et al. 2021), they have been proven to be an alternatively safe and effective option for treating mental health disorders (Aung et al. 2013; Wu et al. 2020).

Recently, after assessing its efficacy and safety fully, the Netherlands Medicines Evaluation Board (CBG-MEB) approved XiaoYao Tablets (CBG-MEB 2021) as a THMP, indicated for an alternative self-care for patients in Europe to relieve the symptoms of mental stress and exhaustion. Since the simplified registration procedure (traditional use registration, TUR) for THMP was introduced in the EU in 2004 (EC 2004), XiaoYao Tablets is the first combination TCM product from China to be registered in the EU.

Despite the fact that TCMs have a long history and are used widely in China, to-date, only a few TCMs have been successfully marketed in the EU as THMPs. This was mainly due to the limitation of regulatory understanding and registration experience. Therefore, the aim of this article is to summarize and analyze the existing challenges in the registration of TCMs in the EU, and to put forward and discuss the methods to overcome the challenges, on top of the registration experience of XiaoYao Tablets.

Abbreviation: the European Union (EU), Traditional herbal medical products (THMP), Traditional Chinese medicine (TCM), Medicines Evaluation Board (CBG-MEB), Traditional use registration (TUR), European Commission (EC), Committee on Herbal Medicinal Products (HMPC), European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Agency (MHRA), Marketing authorization holder (MAH), Chinese Pharmacopoeia (ChP), Xiaoyao Form (including Xiaoyao San (Powder), Xiaoyao Decoction, Xiaoyao Extract, Xiaoyao Pian (Tablets), Xiaoyao Wan (Pills), Xiaoyao Granules, Xiaoyao Capsules, and other Xiaoyao dosage forms), Summary of product characteristic (SmPC), Cytochrome P450 3A4 (CYP3A4), Pharmacodynamics (PD), Pharmacokinetics (PK), Mechanism of action (MOA), Monoamine oxidase inhibitors (MAOIs).

2. Regulatory status and XiaoYao Tablets overview

2.1. Regulatory and application status

In order to protect public health and the free movement of herbal medicinal products in the EU, the European framework of TUR for THMP was established (EC 2004), which allows the registration of THMP with the exemption of full dossier, provided that

the proposed product has a medicinal use throughout a period of at least 30 years (15 years within the EU) without significant safety issues. It is also applicable to herbal medicinal products with "non-European" traditional medicinal use, such as TCM, Ayurvedic medicine, and so on.

The simplified procedure has played an important role in promoting herbal medicinal products harmonization in the EU, and the number of registrations has increased year by year (EMA 2017). Although substantial achievements have been made, only a few THMP from non-European traditions have been registered (Qu et al. 2014). For example, up to now a total of 5 TCM products have been registered in EU: Diao Xin Xue Kang (CBG-MEB 2012), Danshen Capsule (CBG-MEB 2016), Phynova Cold and Flu Relief Powder for Oral Solution (MHRA 2017), YuFeng Ningxin Tablet (CBG-MEB 2019) and XiaoYao Tablets (CBG-MEB 2021).

Furthermore, the proportion of monocomponent products in registered THMPs is about 1.5 times that of combination products (Fig. 1), and XiaoYao Tablets was the first registered combination TCM product from China. Compared with monocomponent THMPs, combination products are facing more complex challenges in the TUR process. Although the directives and guidelines state the scope and general consideration for TUR registration, the applicants have difficulties to put these guidelines into actual practice. Therefore, identifying the obstacles and taking appropriate measures to overcome the challenges of non-European THMPs registration, is essential for TCM products to enter the EU market.

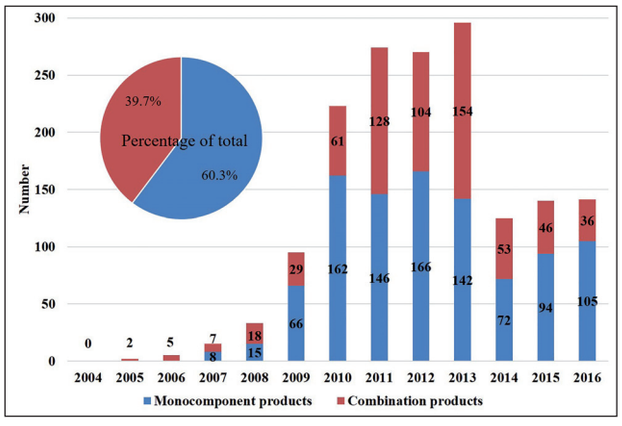

Fig. 1: Number of TUR for THMP in the EU grouped by year of registration for monocomponent and combination products (2004 until December 2016, total 1719).

2.2. *General information of XiaoYao Tablets*

XiaoYao Tablets is used to relieve the symptoms of mental stress and exhaustion, such as low mood and reduced appetite. The marketing authorization holder (MAH) of XiaoYao Tablets is Tasly Healthcare Deutschland GmbH, which is responsible for the marketing authorization, importation, and post-marketing study of herbal medicinal products in EU. XiaoYao Tablets was developed and manufactured by Tasly Pharmaceutical Group Co., Ltd based on the long-standing knowledge of the related products of Xiaoyao Form in the Chinese market. Xiaoyao Form is the corresponding product of XiaoYao Tablets, which has been used more than 900 years in China.

Although EU legislation and Committee on Herbal Medicinal Products (HMPC) provide legal basis and clear reference points for companies to prepare an application for THMP registration, considering the limited practical experiences for combination TCM products registration under the European regulatory framework, two major challenges were identified in the registration process of XiaoYao Tablets. Firstly, the justifications of the traditional use of TCM, and secondly the conducting of safety evaluation. Therefore, this article will discuss the evaluation process of traditional use efficacy and clinical safety for combination TCM products according to the related guidelines and XiaoYao Tablets registration dossier.

3. Justification of traditional use

3.1. *Evidence of traditional use*

As per request by the Directive 2004/24/EC, TUR could be acceptable where the proposed herbal medicinal product had a sufficiently long and coherent use, which stipulates applicants to provide expert evidence or bibliographical to prove that the proposed product has a medicinal use period of at least 30 years (15 years within the EU). Undeniably, evidence of at least 15 years in the EU is a main obstacle for combination TCMs and other non-European herbal products (Qu et al. 2014).

To justify the traditional use of TCMs in and out the EU, apart from gathering different sources and types of authentic and reliable long-standing use evidence, applicants should also scientifically evaluate and discuss on its efficacy.

EU list entries, monographs and official assessment reports published by the HMPC are most important and reliable sources and references of traditional use. HMPC was committed to establish EU monographs and drafting EU lists since being established. To date, 13 EU lists and 166 monographs were finalized (EMA 2021). However, of the 166 EU monographs, only five are combinations of herbal substances. Although HMPC has given considerable attention to non-European THMP registration, the proportion of non-European traditional herbal substances/preparations in the HMPC assessment work list is still small (Qu et al. 2014). Therefore, the EU lists and herbal monographs play a more important role in showing applicants the ideas and methods to evaluate the traditional use, rather than directly providing the traditional use evidence of herbal substances and/or preparations. The applicant can analyze and evaluate the existing evidence on the basis of available official publications. Furthermore, applicants of TCMs need to pay more attention to collecting and evaluating bibliographical and/or expert evidence from a variety of sources, including medicinal books, pharmacopoeia monograph, literature evidence, etc.

Effective evidence should be able to prove that the proposed indication is consistent with the traditional use, and the indication should also meet the requirements of self-treatment at the same time. The common indications for TUR products included gastrointestinal disorders, mental stress and mood disorders, cough and cold, and others (EMA 2017). In addition, the regulations clearly stipulate that any therapeutic indications which involve diseases, including but not limited to disorders or conditions such as psychiatric disorders; cancer; cardiovascular diseases such as heart failure; metabolic diseases such as diabetes; infectious diseases such as hepatitis or influenza, are not acceptable as THMPs. This requirement also challenges the registration of combination TCMs and limits the types of TCM products that could be registered. On the other hand, the description of indication is based on the traditional TCM principle, which is significantly different from modern medical terms, therefore it needs to be professionally translated.

When providing evidence of traditional use, the applicant should not only focus on the duration and continuity, but also fully consider its support for the consistency of the active ingredients, strength, posology, and administration route of the proposed products with the traditional use. In another words, the applicant must ensure consistency in the herbal substance, the process method of herbal substances, and the style of the herbal preparation, for extracts, the primary solvent.

3.2. *Traditional use evidence of XiaoYao Tablets*

The corresponding product of XiaoYao Tablets is Xiaoyao Form, a classic and widely used combination TCM formula in the treatment of mental disorders (Du 2014; Jin 2018). Xiaoyao Form was first documented in Taiping Huimin Heji Bureau Prescription in the Song Dynasty of China. After that, Xiaoyao Form or its similar formulation and indication were discovered in many other ancient medical books (Table 1). It was also included in the Chinese Pharmacopoeia (ChP) from 1963. To date, numerous TCMs originated from Xiaoyao Form were approved by the National Medical Products Administration and were commercially available in China. In the EU, Xiaoyao Form with medical use first appeared in the Netherlands market in 1987. In 2000, Xiaoyao Form was included

Table 1: Formulas and indications of Xiaoyao Form from 1151 to 2015

Year	Medical book	Formula	Dosage form	Actions
1151	Taiping Huimin Heji Bureau Prescription	Gancao, Danggui, Fuling, Baishao, Baizhu, Chaihu, Bohe, Shengjiang	Decoction	To soothe the liver, invigorate the function of the spleen, nourish the blood, distend pain in the chest and hypochondrium, impair appetite and menstrual disorders
1560	Pharmaceutical Characterization	Gancao, Danggui, Fuling, Baishao, Baizhu, Chaihu, Bohe, Shengjiang	Decoction	To soothe the liver, relieve depressive disorder
1764	Lantai Prescription Collection	Gancao, Danggui, Fuling, Baishao, Baizhu, Chaihu, Bohe	Decoction	To soothe the liver, nourish the blood, distend pain in the chest and hypochondrium, impair appetite and menstrual disorders
1904	Prescription Easy to Read	Gancao, Danggui, Fuling, Baishao, Baizhu, Chaihu, Bohe, Shengjiang	Decoction	To soothe the liver, invigorate the function of the spleen
1963	Chinese Pharmacopoeia (ChP)	Gancao, Danggui, Fuling, Baishao, Baizhu, Chaihu, Bohe	Pills	To soothe the liver, impair menstrual disorders, distend pain in the chest and hypochondrium
2015	ChP	Gancao, Danggui, Fuling, Baishao, Baizhu, Chaihu, Bohe	Pills/ Tablets/ Capsules	To soothe the liver, fortify the spleen, nourish blood and regulate menstruation.

in the list of food supplements in Belgium, and four years later it was included in the list of Chinese medicines in Switzerland. In addition, use estimations, sales data, packing trading lists and data on supply chain also sufficiently demonstrated that Xiaoyao Form was used in Europe for more than 15 years.

As shown in Table 1, the formula and indication of Xiaoyao Form was constantly modified between 1151 and 2015. This is due to the TCM principle of prescriptions corresponding to the different physiques, characterizations and symptoms (Dong et al. 2019). According to "sovereign, minister, assistant and courier" (*Jun-Chen-Zuo-Shi*), in Xiaoyao Form, Chaihu (*Bupleuri Radix*) can soothe the liver and resolve depression as sovereign; Danggui (*Angelicae sinensis Radix*) and Baishao (*Paeoniae Radix Alba*) can nourish blood and emolliate the liver as minister; Bohe (*Menthae haplocalycis Herba*) can disperse *wind-heat* as assistant; Fuling (*Poria*), Baizhu (*Atractylodis macrocephalae Rhizoma*), and Gancao (*Liquiritiae Radix*) can strengthen the spleen and replenish *qi* as assistant; Chaihu with meridian tropism in liver also as courier. The entire formula soothes the liver depression, fortifies the spleen deficiency, nourishes blood and regulates menstruation (Zeng 2011). Therefore, it is named Xiaoyao Form, which is often called "free and easy wanderer" in the EU.

However, according to the regulatory requirements, the formula and indication of XiaoYao Tablets has to be fixed, and the indication of XiaoYao Tablets needed to be transformed from traditional words into modern medical terms. In the principle of TCM, Xiaoyao Form is used in the treatment of *Yu Syndrome*, which is translated into modern medical terms as mental health disorders, including depression (Li et al. 2020; Ma et al. 2020; Shang et al. 2020). The 2015 edition of ChP expounds the indications of fixed Xiaoyao Formula in combination with the principles of TCM and modern medical concepts, which is described as depression and constraint liver *qi*, distending pain in the chest and hypochondrium, dizziness, reduced appetite, and menstrual irregularities due to liver depression and spleen deficiency. In order to adapt XiaoYao Tablets to the EU market, an anti-depression study and a literature review were carried out in the product development stage to analyze the relationship between the formula and indication. After fully evaluating its efficacy and pharmacological effect on relieving mental stress and exhaustion, a more exclusive formula was determined, which reduced Fuling and Bohe, to meet the regulatory rules, quality control requirements, and market demand (Fig. 2).

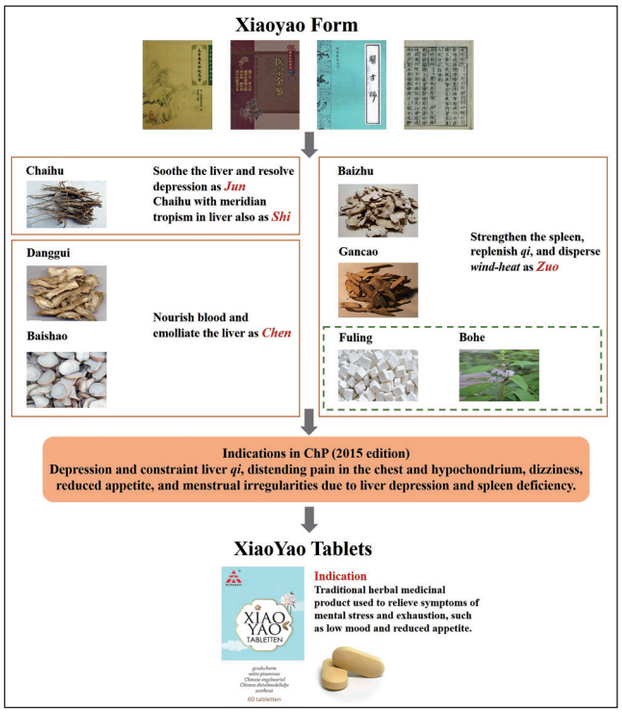

Fig. 2: The transformation process from Xiaoyao Form to XiaoYao Tablets.

4. Safety evaluation

Besides traditional use, safety evaluation and assurance are another challenges for TCMs registration. In order to prove the proposed product is not harmful in the specified conditions of use, it is particularly essential to scientifically assess and evaluate the safety data on traditional use, as well as the information on the types of application, possible side effects and indications (Jütte et al. 2017). According to the Directive 2004/24/EC, a bibliographic review of safety data is needed for the proposed THMP. Taking into account the regulatory requirements, the application experience of XiaoYao Tablets, and the particularities of combination TCM as mixtures of different herbal substances, it is suggested that the clinical safety evaluation of combination TCM products could be carried out from three aspects: combination herbal medicinal product, herbal substances and drug interactions.

4.1. Clinical safety of combination herbal medicinal products

Based on the long-term use experience of specific populations (not only in EU), the plausibility of the clinical safety of combination TCMs can be justified from a holistic perspective. At the

same time, the pharmacological effects of TCMs are reflected in the principle of TCMs, which should also become an important criterion for consideration in clinical safety evaluation.

The prescription in TCM is characterized by the principle of compatibility. The core components of TCM include "sovereign, minister, assistant, and courier" and its formulation was summarized into seven relations of medicinal compatibility. The formulation based on the compatibility provides holistic perspective in the treatment of diseases, enhancing the therapeutic efficacy and antagonizing the toxicity effects (Li and Zhang 2013; Liu 2009; Schwabl and Vennos 2015). Apart from that, the "eighteen antagonistic medicaments" and "nineteen mutual inhibitions" principles suggest that the combination of certain herbal pairs could potentiate the toxic effects or diminish the therapeutic effects. For example, the herbal pair of Wutou (*Aconitum carmichaeli Debx.*) and Banxia (*Pinellia ternata Breit.*) is one of the incompatible pairs as stated in the "eighteen antagonistic medicaments". Banxia inhibits one of the enzymes responsible for metabolism of Wutou, which increases the plasma concentration of the aconitine (the active metabolite of Wutou), and in turn increasing its toxicity (Xv et al. 2019).

In clinical practice, combination TCM products and many other non-European THMPs have been used for several decades. The long use period has created an extensive experience published in the literature (Zhang et al. 2016). Taking XiaoYao Tablets for example, an overview of 26 randomized trials (of 1837 patients) proved Xiaoyao Form was superior to antidepressants in terms of the score of Hamilton depression scale with no adverse effects reported (Liu et al. 2012). A meta-analysis with 7 clinical trials (of 607 patients) indicated that Xiaoyao Form had additional benefits in total improvement rates and no serious adverse events were observed (Jin et al. 2018). In order to further assess the proposed THMP, the related literature for the intended indication needs to be summarized and the results of the meta-analysis can be used to evaluate the indications, use period, and adverse reactions (AEs/ADRs). At the same time, the conclusive information will be provided in the section 4.8 "Undesirable effects" of Summary of product characteristic (SmPC) (EMA 2020).

4.2. Clinical safety of herbal substances

Although the TCM products and many other non-European herbal products are plausible within the traditional medicine system, the function of each constituent of the proposed THMP must be clarified, especially the active substance and related dosage should be taken into consideration (EMA 2006).

In order to give enterprises an explicit reference, HMPC publishes scientific opinions on herbal substances/preparations, with safe conditions and usage recommendations. In addition, the pharmacopoeias and monographs on herbal substances established by the EU and its member states also provided a reference for safety use. Therefore, if the herbal substances of a proposed product have been recorded in the official document, including list entries, EU monographs, assessment reports, and/or official pharmacopoeia, the clinical safety analysis could be based on the conclusion of official reports. Not only that the potential clinical safety risks mentioned in the official document need to be paid special attention. Besides the authority released monographs and reports, the clinical literature of a herbal substance is another crucial reference for safety evaluation, which can also be analyzed from the dosage and usage period.

Danggui (*Angelicae sinensis Radix*) in XiaoYao Tablets can serve as an example. According to the HMPC assessment reports (EMA 2013), *Angelica sinensis (Oliv.) Diels* (*A. sinesis*) contains furanocoumarins which can inhibit cytochrome P450 3A4 (CYP3A4) and cause photosensitization. Referring to the official reports, a safety assessment of XiaoYao Tablets was conducted from three aspects: literature research, detection of furanocoumarins in the herbal substance and preparation, and CYP enzyme inhibition test *in vitro*. A literature review showed that *A. sinesis* in XiaoYao Tablets does not contain furanocoumarins; furanocoumarins were not detected in herbal substance and preparation; and CYP enzyme inhibition assay *in vitro* showed that XiaoYao Tablets had no inhibitory effect on CYP3A4. Thus, all the results suggested that oral administration of XiaoYao Tablets would not pose any unacceptable risk caused by furanocoumarins to consumers.

The combination herbal medicinal product and its ingredients are evaluated under comprehensive assessment, this analysis may be sufficient for the justification of the efficacy and safety of the proposed THMP. However, the drug-drug interactions also need to be considered.

4.3. Investigation of drug interactions

It is generally believed that herbal medicines are natural and therefore harmless. However, this is a misconception. Herbal medicines usually consist of a mixture of active ingredients, and with limited experimental data on herbal pharmacokinetics, this will increase the potential adverse herb-drug interactions (Izzo and Ernst 2009). A survey reported that among 122 (15%) patients receiving prescription drugs with herbal medicines, potential drug interactions were identified in 49 (40%) patients (Bush et al. 2007).

When exploring further, the interaction of herbal medicines with prescription drugs is one of the new and serious public health problems with wide implications for clinicians, health authorities and pharmaceutical industries (Parvez and Rishi 2019). As stated in the "Guideline of drug interactions" (EMA 2012), interactions with herbal medicinal products is generally on account of the scientific literature and transformed into common recommendations. However, it is difficult to extrapolate the potential interaction of one specific herbal product to other products with the same raw materials. Therefore, it is recommended that, for new herbal preparations, the potential interactions need to be investigated, and clinically relevant interactions found in humans should be clarified.

Another scenario ought to be considered. Absence of publications does not mean absence of drug interactions. Therefore, the investigation can be analyzed on theoretical grounds (based on the pharmacodynamics (PD) and/or pharmacokinetics (PK) profile), and the scope could be focused on common comorbidity corresponding drugs for proposed population, as well as commonly used western OTC drugs.

PD analysis was performed based on the mechanism of action (MOA). The MOA of common comorbidity typical drugs will be summarized by retrieving databases and the literature, and meanwhile the potential MOA of proposed THMP will be compared and analyzed. For example, with the similar MOA, the combination use might have a synergistic clinical benefit and need further discussion. On the other hand, with the different MOA and there are no published data available on drug-drug interactions, the PD analysis will not continue. As for XiaoYao Tablets, the component of monoamine oxidase inhibitors (MAOIs) works in the brain and affect neurotransmitters, which can cause serious adverse effects. Considering the clinical safety, it is not recommended co-administration with MAOIs.

For PK analysis, *in vitro* studies on the enzyme inhibitory potential are encouraged, on account of available *in vivo* information indicates herbal preparations and/or the constituents may give rise to clinically relevant drug-interactions (EMA 2012). Therefore, *in vitro* enzyme inhibition tests can be conducted from the aspect of PK analysis, and drug transporter-interactions and enzyme induction can also be anticipated.

5. Discussion

Although the European framework for THMP was established in 2004, there is limited experience accumulated in the member states for non-European tradition products (van Galen 2014), and combination TCMs generally involve more ingredients than the fixed-combinations commonly in European phytomedicines (Schwabl and Vennos 2015). Therefore, based on the registration experience of XiaoYao Tablets, combined with traditional use and safety evaluation, a safety evolution pathway of combination TCMs was developed (Fig. 3).

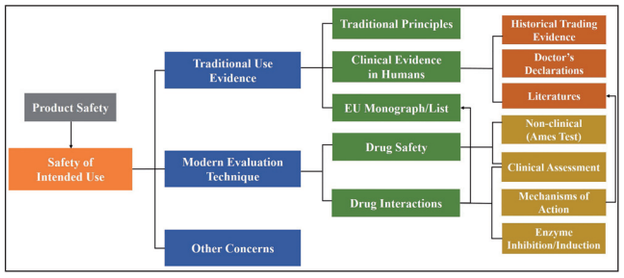

Fig. 3: Safety evolution pathway of combination TCMs.

5.1. Safety evolution pathway of combination TCMs

The safety evolution pathway was established based on the approved XiaoYao Tablets, in which traditional use evidence and modern evaluation technique can be used to demonstrate the product safety of intended use. The safety of traditional use can be justified by historical trading evidence, doctor's declarations, literature, and EU monographs. In addition, product safety can also be evaluated by modern technology, as genotoxicity test, clinical assessment, mechanisms of action, and enzyme inhibition/induction test.

Although the safety evolution pathway has illustrated how to carry out clinical safety control and evaluation, concerns of quality control raised from the herbal substances/preparations need to be observed. This includes the toxicological characteristics arising from starting materials (e.g. furanocoumarins) and extraneous sources (e.g. pesticide residues and pyrrolizidine alkaloids), traditional drying process (e.g. polycyclic aromatic hydrocarbons), and post-marketing pharmacovigilance (Qu et al. 2014). Furthermore, with the increase in mutual communication and understanding, analytical methods and standards are constantly converging between pharmacopoeias of China and the EU. For example, for Chaihu (*Bupleuri radix*), the acceptance criterion for loss of drying is maximum 10.0% in ChP, however, Ph. Eur. stipulated a maximum of 5.0% for the same condition. It is noteworthy that with the strengthening of exchanges between Europe and China on herbal medicines, the acceptance criterion for loss of drying of *Bupleuri radix* in Ph. Eur. has been upgraded to be consistent with that in ChP.

5.2. Considerations for further challenges

In recent years, with changes in medical models and the shifts in public health perception, people worldwide are gradually understanding the importance of TCM, and the influence of TCM is gradually being prominent (Liu et al. 2016; Zhang et al. 2021). However, as things stand at present, only very few TCMs have been registered for medicinal products in the EU regulatory framework (van Galen 2014). Causes of this dilemma not only stems from the challenges faced by TCMs in the European registration process, but also reflects applicants' concerns for sales after approved.

According to the statistics of TCMs being exported to EU, over 96% of the exports are herbal substances/preparations, and only 3% to 4% are Chinese patented medicines (Liu 2016). Not only that, the sales status of the approved TCMs as THMP is not ideal. Through analyzing the underlying reasons for this phenomenon, it may be due to the recognition difference and insufficient promotion. Although China's TCM enterprises have expanded their influence in the mainstream Western market, the cultural difference obstructs the development of TCM in Europe. For example, Western medicine is disease centered, whereas TCM is patient centered under the holistic perspective (Schwabl and Vennos 2015). On the other hand, TCM enterprises do not have wide sales and propaganda channels, and meanwhile, the therapeutic advantages of TCM are not well known by medical practitioners and patients.

Therefore, according to the above status and the prominent advantage of TCM during COVID-19, we propose the following suggestions which may be beneficial for the development of TCMs in the EU market.

First and foremost, domestic enterprises can work together to spur more classical TCMs approved in the EU. China has taken part in the ICH organization as regulatory members. With the drug law reform in recent years, the technological approach and regulatory concepts have progressively being consistent with those in Europe, which is a favorable support for Chinese herbal medicinal enterprises to promote their products into the EU market. Also we can make full use of cultural appeal to facilitate TCM development. It is hoped that relevant regulatory authorities, enterprises, and scholars in China and Europe can effectively promote TCM to the public.

Secondly, HMPC and member states in the EU can refine the guidelines in support of TUR registration. Until now, there is still a lack of guidance on the clinical efficacy and safety evaluation of combination TCMs after the reduction of ingredients. Therefore, it is hoped that specialists of HMPC and the member states can put this in the working list, and provide the solutions and methods for applicant.

Last but not least, inter-governmental dialogues will accelerate successful win-win cooperation on TCM. With more communications between Chinese and European enterprises, there is a need to call on the regulatory authorities of the inter-governments to provide policy support for cooperation, and to promote the all-round cooperation ultimately.

6. Conclusion

Although TCMs have gradually become one of the therapeutic choices worldwide, the registration of TCMs in the EU still faces an array of challenges. Thus, the successful experience of XiaoYao Tablets is encouraging, which can serve as role model for combination TCMs and other non-European THMPs. It is hoped that more and more safe, effective, and high-quality TCMs could provide beneficial treatment for medical practitioners and patients in the EU. Therefore, more policies and guidelines should be provided to promote cooperation among governments, enterprises and relevant institutions to facilitate the registration and market authorization of TCMs in the EU.

Author's contribution: Qiong Wang and Shenghan Gao: Conceptualization, Writing – Original Draft, Writing – Review & Editing Wensheng Zhang and Yunxia Zhao: Project administration, Writing – Review Yi He and Zhengliang Ye: Supervision Wei Sun, Fenglian Zhang, Tong Yu, Lihong Zhou, and Jiansen Su: Resources Shunnan Zhang and Yongfa Chen: Supervision, Writing – Review

Conflicts of interest: The authors have no conflicts of interest to declare.

Acknowledgements: Funding: This work was supported by Chinese Thirteenth Five-year Plan of Chinese Ministry of Science and Technology [grant number 2018ZX09303-024].

References

Aung SKH, Fay H, Hobbs RF (2013) Traditional Chinese Medicine as a basis for treating psychiatric disorders: A review of theory with illustrative cases. Med Acupunct 25: 398–406.

Bush TM, Rayburn KS, Holloway SW, Sanchez-Yamamoto DS, Allen BL, Lam T, So BK, Tran DH, Greyber ER, Kantor S, Roth LW (2007) Adverse interactions between herbal and dietary substances and prescription medications: a clinical survey. Altern Ther Health Med 13: 30–35.

CBG-MEB, 2021. XiaoYao Tablets RVG126209. https://www.geneesmiddeleninformatiebank.nl (accessed 9 September 2021).

CBG-MEB, 2019. YuFeng Ningxin Tablet RVG119782. https://www.geneesmiddeleninformatiebank.nl (accessed 9 September 2021).

CBG-MEB, 2016. Danshen Capsule RVG114997. https://www.geneesmiddeleninformatiebank.nl (accessed 9 September 2021).

CBG-MEB, 2012. Diao Xin Xue Kang RVG102142. https://www.geneesmiddeleninformatiebank.nl (accessed 9 September 2021).

Dong Y, Li HZ, Zhu S (2019) Theoretical discussion and clinical application of treating the same syndrome with different methods in treatise on febrile and miscellaneous diseases. China J Chinese Mater Med 44: 3890–3894.

EC, 2004. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off. J. Eur. Union 47, 85–90.

EMA, 2021. Overview of assessment work – Priority list. https://www.ema.europa.eu/en/documents/other/hmpc-overview-assessment-work-priority-list_en.pdf (accessed 9 September 2021).

EMA, 2020. Scientific guidelines with SmPC recommendations.. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137039.pdf (accessed 9 September 2021).

EMA, 2017. Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004 / 24 / EC in EU Member States. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106706.pdf (accessed 9 September 2021).

EMA, 2013. Assessment report on Angelica sinensis (Oliv.) Diels, radix. https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-angelica-sinensis-oliv-diels-radix-first-version_en.pdf (accessed 9 September 2021).

EMA, 2012. Guideline on the investigation of drug interactions. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf (accessed 9 September 2021).

EMA, 2006. GUIDELINE ON THE CLINICAL ASSESSMENT OF FIXED COMBINATIONS OF HERBAL SUBSTANCES / HERBAL PREPARATIONS. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-assessment-fixed-combinations-herbal-substances/herbal-preparations_en.pdf (accessed 9 September 2021).

Huang Y, Zhao N (2020) Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res 288: 112954.

Izzo AA, Ernst E (2009) Interactions between herbal medicines and prescribed drugs. Drugs 69: 1777–1798.

Jin X, Jiang M, Gong D, Chen Y, Fan Y (2018) Efficacy and safety of Xiaoyao formula as an adjuvant treatment for post-stroke depression: a meta-analysis. Explore 14: 224–229.

Jütte R, Heinrich M, Helmstädter A, Langhorst J, Meng G, Niebling W, Pommerening T, Trampisch HJ (2017) Herbal medicinal products – Evidence and tradition from a historical perspective. J Ethnopharmacol 207: 220–225.

Khademi M, Vaziri-Harami R, Shams J (2021) Prevalence of mental health problems and its associated factors among recovered COVID-19 patients during the pandemic: A single-center study. Front Psychiatry 12: 1–6.

Li S, Zhang B (2013) Traditional Chinese medicine network pharmacology: theory, methodology and application. Chin J Nat Med 11: 110–120.

Li XJ, Qiu WQ, Da XL, Hou YJ, Ma QY, Wang TY, Zhou XM, Song M, Bian,QL, Chen JX (2020) A combination of depression and liver Qi stagnation and spleen deficiency syndrome using a rat model. Anat Rec 303: 2154–2167.

Liu J, Zhang Y, Han M, Liu Z, Wang J, He Q (2012) Chinese herbal formula Xiao Yao San for treatment of depression: A systematic review of randomized controlled trials. Evid-based Complement Altern Med 2012: 110810

Liu X (2009) Study of combination methods for formula composition of Chinese herbal medicines and their components. J Chinese Integr Med 7: 601–606.

Liu Y, Yang Z, Cheng J, Fan D (2016) Barriers and countermeasures in developing traditional Chinese medicine in Europe. Front Med 10: 360–376.

Ma K, Wang X, Feng S, Xia X, Zhang H, Rahaman A, Dong Z, Lu Y, Li X, Zhou X, Zhao H, Wang Y, Wang S, Baloch Z (2020) From the perspective of Traditional Chinese Medicine: Treatment of mental disorders in COVID-19 survivors. Biomed Pharmacother 132. https://doi.org/10.1016/j.biopha.2020.110810

MHRA, 2017. Phynova Cold and Flu Relief Powder for Oral Solution THR 44590/0001. https://www.gov.uk/government/publications/herbal-medicines-granted-a-traditional-herbal-registration-thr/herbal-medicines-granted-a-traditional-herbal-registration

Parvez MK, Rishi V (2019) Herb-drug interactions and hepatotoxicity. Curr Drug Metab 20: 275–282.

Qu L, Zou W, Zhou Z, Zhang T, Greef J, Wang M (2014) Non-European traditional herbal medicines in Europe: A community herbal monograph perspective. J Ethnopharmacol 156: 107–114.

Schwabl H, Vennos C (2015) From medical tradition to traditional medicine: A Tibetan formula in the European framework. J Ethnopharmacol 167: 108–114.

Serafini G, Parmigiani B, Amerio A, Aguglia A, Sher L, Amore M (2020) The psychological impact of COVID-19 on the mental health in the general population. QJM 113: 229–235.

Shang B, Zhang H, Lu Y, Zhou X, Wang Y, Ma M, Ma K (2020) Insights from the perspective of traditional Chinese medicine to elucidate association of lily disease and yin deficiency and internal heat of depression. Evid-based Complement Altern Med 2020: 8899079.

van Galen E (2014) Traditional herbal medicines worldwide, from reappraisal to assessment in Europe. J Ethnopharmacol 158: 498–502.

Wang Z, Yang L (2021) Chinese herbal medicine: Fighting SARS-CoV-2 infection on all fronts. J Ethnopharmacol 270: 113869.

Wu X, Lu W, Guo Q, Cao M, Zhang W, Liu C, Qu Y, Peng W, Che J, Fang B, Zhou S (2020) Novel coronavirus pneumonia (COVID-19) combined with Chinese and Western medicine based on "Internal and External Relieving -Truncated Torsion" strategy. Medicine (Baltimore) 99: e23874.

Wu XV, Dong Y, Chi Y, Yu M, Wang W (2021) Traditional Chinese Medicine as a complementary therapy in combat with COVID-19—A review of evidence-based research and clinical practice. J Adv Nurs 77: 1635–1644.

Xv H, Wang N, Li H (2019) Zhong Yao Yao Li Xue, third edit. ed. Shanghai Scientific & Technical Publishers, China.

Zeng N (2011) Modern research and application of Xiaoyao San. People's Medical Publishing House, China.

Zhang H, Ma S, Feng Z, Wang D, Li C, Cao Y, Chen X, Liu A, Zhu Z, Zhang J, Zhang G, Chai Y, Wang L, Xie XQ (2016) Cardiovascular Disease Chemogenomics Knowledgebase-guided target identification and drug synergy mechanism study of an herbal formula. Sci Rep 6: 33963.

Zhang Yukun, Lu P, Qin H, Zhang Yuelin Sun,X, Song X, Liu J. Peng H, Liu Y, Nwafor EO, Li J, Liu Z (2021) Traditional Chinese medicine combined with pulmonary drug delivery system and idiopathic pulmonary fibrosis: Rationale and therapeutic potential. Biomed Pharmacother 133: 111072.

Zhao Z, Li Y, Zhou L, Zhou X, Xie B, Zhang W, Sun J (2021) Prevention and treatment of COVID-19 using Traditional Chinese Medicine: A review. Phytomedicine 85: 153308.