Journal of Ethnopharmacology 206 (2017) 363–375

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Review

Recent pharmaceutical evidence on the compatibility rationality of traditional Chinese medicine

Miaomiao Zhou[a,b,1], Yanlong Hong[b,2], Xiao Lin[a,b,3,*], Lan Shen[a,2], Yi Feng[b,3]

[a] College of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, PR China
[b] Engineering Research Center of Modern Preparation Technology of TCM of Ministry of Education, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, PR China

ARTICLE INFO

Keywords:
Traditional Chinese medicine
Compatibility
Herb pair
Pharmaceutics
Pharmacokinetics
Pharmacodynamics

ABSTRACT

Ethnopharmacological relevance: Chinese herbs have been used in China for thousands of years and are also becoming popular in Western medicine. Formulae of traditional Chinese medicine (TCM), which contain two or more herbs, can often obtain better curative efficacies and fewer side effects than single herbs. Though there are many reports on pharmaceutics, pharmacokinetics, and pharmacodynamics of TCM, there remains a serious lack of summarization and systemic analyses of these reported data to help uncover the compatibility rationale of TCM. This review therefore aims to provide such an overview mainly based on the reports published in the last decade. It could be served as an informative reference for researchers interested in compound prescriptions and holistic therapies.

Materials and methods: Relevant information was collected from various resources, including books on Chinese herbs, China Knowledge Resource Integrated (CNKI), and international databases, such as Web of Science, Scopus, and PubMed.

Results: Thirty-six relevant TCM formulae were collected to illustrate the compatibility rationality of TCM from the perspective of pharmaceutics, pharmacokinetics, and/or pharmacodynamics.

Conclusions: Compatibility is a key characteristic of multi-herb prescriptions. It often results in the change of the therapeutic material basis and, thus, produces the effect of reducing toxicity and/or increasing curative efficacy.

Abbreviations: **TCM**, traditional Chinese medicine; **PK**, pharmacokinetics; **PD**, pharmacodynamics; **FA**, ferulic acid; **GA**, glycyrrhetinic acid; **P-gp**, P-glycoprotein; **B**, *Angelica sinensis* (Oliv.) Diels, radix; **C**, *Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao, radix (or *Astragalus membranaceus* (Fisch.) Bunge., radix); **D**, *Carthamus tinctorius* L., flos; **E**, *Ligusticum chuanxiong* Hort., rhizome; **F**, *Rheum palmatum* L., radix and rhizome (or *Rheum tanguticum* Maxim, ex Balf., radix and rhizome, or *Rheum officinale* Baill, radix and rhizome); **G**, *Aconitum carmichaelii* Debx., radix praeparaia; **H**, *Glycyrrhiza uralensis* Fisch., radix and rhizome (or *Glycyrrhiza inflata* Bat., radix and rhizome, or *Glycyrrhiza glabra* L., radix and rhizome); **I**, *Paeonia lactiflora* Pall., radix alba; **J**, *Platycodon grandiflorus* (Jacq.) A. DC., radix; **K**, *Cinnamomum cassia* Presl, ramulus; **L**, *Daphne giraldii* Nitsche, cortex (or *Daphne tangutica* Maxim., cortex, or *Daphne retusa* Hemsl., cortex); **M**, *Sophora flavescens* Ait., radix; **N**, *Cnidium monnieri* (L.) Cuss., fructus; **O**, *Salvia miltiorrhiza* Bge., radix and rhizoma; **P**, *Panax notoginseng* (Burk.) F.H.Chen, radix and rhizoma; **R**, *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. F., radix (or *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f. var. formosana (Boiss.) Shan et Yuan, radix); **S**, *Scutellaria baicalensis* Georgi, radix; **T**, *Typha angustifolia* L., Pollen (or *Typha orientalis* Presl, Pollen); **U**, Faeces Trogopterori; **V**, *Gastrodia elata* Bl., rhizoma; **W**, *Bupleurum chinense* DC., radix (or *Bupleurum scorzonerifolium* Willd., radix); **X**, *Lilium lancifolium* Thunb., bulbus (or *Lilium brownii* F. E. Brown var. viridulum Baker, bulbus, or *Lilium pumilum* D C., bulbus); **Y**, *Anemarrhena asphodeloides* Bge., rhizoma; **Z**, *Zingiber officinale* Rosc., rhizoma; **AA**, *Pueraria lobata* (Willd.) Ohwi, radix; **BB**, *Morus alba* L., cortex; **CC**, *Ephedra sinica* Stapf, herba (or *Ephedra intermedia* Schrenk et C. A. Mey., herba, or *Ephedra equisetina* Bge., herba); **DD**, *Prunus armeniaca* L. var. ansu Maxim., semen (or *Prunus sibirica* L., *Prunus mandshurica* (Maxim.) Koehne, semen, or *Prunus armeniaca* L., semen); **EE**, *Lonicera japonica* Thunb., flos; **FF**, *Forsythia suspensa* (Thunb.) Vahl, fructus; **GG,**, *Bletilla sfriata* (Thunb.)Reiehb.f., tuber; **HH,**, *Panax ginseng* C.A.Mey., radix and rhizoma; **II**, *Atractylodes macrocephala* Koidz., rhizoma; **JJ,**, *Corydalis yanhusuo* W.T.Wang, tuber; **KK**, *Strychnos nux-vomica* L., semen; **LL**, *Aristolochia manshriensis* Kom., caulis; **MM**, *Rehmannia glutinosa* (Gaertn.) DC., radix; **NN**, *Coptis chinensis* Franch., rhizoma; **OO**, *Citrus aurantium* L.,fructus (or *Citrus sinensis* Osbeck, fructus); **PP**, Crotonis Semen Pulveratum; **QQ**, *Magnolia officinalis* Rehd. et Wils., cortex (or *Magnolia officinalis* Rehd. et Wils. var. Biloba Rehd. et W ils, cortex); **RR**, *Gardenia jasminoides* Ellis, fructus

* Corresponding author at: College of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, PR China.
E-mail address: duotang@163.com (X. Lin).

[1] Contributions to the study: writing the review.
[2] Contributions to the study: collecting and analyzing the literatures.
[3] Contributions to the study: revising the review.

http://dx.doi.org/10.1016/j.jep.2017.06.007
Received 9 February 2017; Received in revised form 1 June 2017; Accepted 5 June 2017
Available online 09 June 2017
0378-8741/

1. Introduction

In recent years, increasing pieces of evidence indicate that therapeutic effects of an active pharmaceutical ingredient or single Chinese herb are often modest and hampered by various side effects or drug resistances, because of the complicated pathogenesis and progression of diseases (Zhao et al., 2010). In contrast, holistic therapies based on compound prescriptions often achieve better curative efficacies and fewer side effects. Such therapies not only have been practiced in traditional Chinese medicine (TCM) for thousands of years, but also are increasingly accepted and becoming popular in Western medicine. TCM formulae, also called TCM recipes (Liang et al., 2008) or TCM prescriptions (Gao et al., 2014a, 2014b), are often composed of multiple herbs. More than 100,000 TCM formulae have been accumulated over the past 2000 years (Qiu, 2007). Note that a TCM formula does not mean a simple quantitative addition of different herbs but reasonable and necessary interactions between herbs with specific functions (Jia et al., 2004). Such interactions include synergism (reinforcing the same effect of each other), assistance (strengthening the effects of other drugs), detoxication, and, if combined incorrectly, antagonism (reducing curative effects of other drugs) and rejection (increasing toxicity of each other) (Jia et al., 2004). It is obvious that among these interactions, the first three should be utilized adequately, while antagonism and rejection must be avoided. In the TCM theory, compatibility plays a significant role. It follows the rule of "monarch, minister, adjuvant, and guide" to maximize the efficacy and minimize the adverse effects. "Monarch" means the main efficacy-contributing herb(s) in a TCM formula; "minister" refers to an adjuvant herb used to enhance curative effects of "monarch" or to target the accompanying symptoms; "adjuvant" is usually used to minimize adverse effects of the formula; and "guide" refers to the herb that guides the bioactive ingredients to reach their target sites and/or to harmonize their effects (Zhou et al., 2016). It is with this rule that TCM becomes a unique treasure, which is quite different from common drug therapies in Western medicine and single herbal therapies across the world.

Theoretically, herb-herb interactions can occur at the levels of pharmaceutics, pharmacokinetics (PK), and pharmacodynamics (PD). In pharmaceutics, the interactions between herbs (e.g., solubilization, salification, complexation, oxidation, hydrolytic decomposition, and reduction) usually happen during the preparation of a formula. They can contribute to changes in the dissolution of active ingredients, the types and levels of ingredients, and the production of new compounds in the final preparation (Yang and Xiao, 2010). In PK, interactions between herbs can happen at one or more stages of the in vivo course (i.e., absorption, distribution, metabolism, and excretion; ADME) of ingredients administered. This can be manifested by significantly changed PK parameters of ingredients and the changed composition of in vivo pharmacodynamic substances (Hao et al., 2009). In PD, the combination of herbs can lead to enhanced efficacy, reduced toxicity, or even emergence of a new pharmacological activity that single herbs don't have (Chen and Zhang, 2016). Therefore, it is crucial to investigate the rationale of herb-herb compatibility at these three levels for understanding and illustrating the essence of TCM.

Though there are many reports on the pharmaceutics, PK, and PD of TCM, there remains a serious lack of summarization and systemic analyses of these reported data. So, this review was accomplished, which focused on this area and aimed to provide a comprehensive and relevant overview mainly based on the reports published in the last decade. It can be served as an informative reference for researchers interested in compound prescriptions and holistic therapies. In total, thirty-six relevant TCM formulae were collected. Thirty-four of the formulae were studied in the form of water decoction or aqueous solution, which agrees with the traditional way of preparation and administration of TCM.

2. Compatibility in herb pairs of TCM (Table 1)

In the last decade, numerous investigations on the compatibility of herb pairs have been reported constantly. This is because herb pairs (the specific combinations of two compatible herbs) are the most basic and the simplest form of multi-herb therapies in clinic and, thus, can act as the foundation and a keypoint in exploration of TCM compatibility (Wang et al., 2012).

2.1. *Angelica sinensis (Oliv.) Diels, radix–Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao, radix (or Astragalus membranaceus (Fisch.) Bunge., radix) (B–C)*

The combination of C with B at the ratio of 5:1, i.e., 'Danggui Buxue Decoction (DBD)' in Chinese, has been used for the treatment of blood deficiency syndrome in clinic for thousands of years. DBD can improve female health by raising the "Qi" and nourishing the "Blood". Ferulic acid (FA), a main component of B, was reported to enhance the dissolution behavior of some components from C (Zheng et al., 2014). To mimic the preparation of DBD and investigate this effect, different amounts of FA were added during decocting C. It was found that the dissolution of four chemicals of C (i.e., astragaloside IV, calycosin, formononetin, and total polysaccharide) was enhanced. Compared to decocting C alone, decocting C with 5 mg of FA increased the dissolved amounts of calycosin and formononetin to the levels in DBD. Further increases (50% and 80% for calycosin and formononetin, respectively) were achieved by decocting C with 10 mg of FA. Therefore, FA should be a positive chemical regulator in DBD (Zheng et al., 2014). On the other hand, Gao et al. (2007) speculated that components such as saponins in C also contributed to the enhanced dissolution of components from B (such as FA and ligustilide). For instance, astragaloside could increase the amounts of FA and ligustilide in the decoction. Because both FA and ligustilide are oxidized under heat easily, their amounts will decrease with decocting. However, components in C might block such oxidization processes when C and B were decocted together, thus increasing their contents in DBD (Zhao et al., 2003). The more specific mechanism needs to be further studied.

Wang et al. (2009) studied the compatibility-induced changes in PK parameters of FA and astragaloside IV. Plasma levels of FA were determined by HPLC after rabbits were orally administered with DBD or the decoction of B, while those of astragaloside IV were assayed by HPLC/MS/MS after rats were orally administered with DBD or the decoction of C. Though no obvious PK changes were observed for FA, the C_{max} and $AUC_{0-24\ h}$ values of astragaloside IV in DBD were increased by 1.43-fold and 0.37-fold, respectively, and the T_{max} value was decreased by one-fold (Wang et al., 2009). Namely, components of B in DBD were shown to enhance the activity of astragaloside IV from C (the "monarch" drug) in vivo. This reflects the adjuvant contribution of the "minister" drug B from the perspective of PK.

Evidence also shows that the pharmacological effects are enhanced when B and C are combined. For example, DBD can advance hematopoiesis better (Huang et al., 2017). Mice with significantly decreased peripheral hemogram were administered with the water extracts of B, C, and combinations of B and C with different ratios (10:1 to 1:10), respectively. Single C had no remarkable effects on peripheral hemogram, the hematopoietic growth factor level, the area of bone marrow hematopoietic tissue (HTA), and the nucleated cell count in bone marrow. Meanwhile, single B could only increase HTA and the numbers of white blood cell, red blood cell, and platelet in the peripheral blood. However, the combinations of B and C could effectively increase all of these indexes, while decreasing elevated spleen indexes (Huang et al., 2017). DBD has also shown the excellent functions of boosting immunity of organ systems and anti-fibrosis (Qin, 2012; Tao et al., 2008).

2.2. *B–Carthamus tinctorius L., flos (B–D)*

The herb pair 'B–D (1:1)' has the functions of activating blood circulation and dissipating blood stasis and is commonly used for the