DOI: 10.15806/j.issn.2311-8571.2015.0037 World J Tradit Chin Med 2016; 2(1): 10–25

Tonic Herbs and Herbal Mixtures in Chinese Medicine

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ABSTRACT

This review results from a PubMed-based data-mining of scientific literature concerning typical tonic herbs and formulas of Chinese herbal medicine and their application principle under the theory of CM. We have focused on two aspects of tonic activity: body tonification against *qi* 气-, *blood*血-, *yin*阴- and *yang*阳-deficiency, respectively, and organ (*Zang* 脏and *Fu*腑) tonification against heart-, liver-, spleen/stomach-, lung-, and kidney-deficiency, respectively.

Body-tonifying herbs are: *Astragalus Membranaceus Radix* (*Huang-qi*黄芪) and *Panax Ginseng Radix* (*Ren-shen*人参) for *qi*-tonification; *Angelicae Sinensis Radix* (*Dang-gui*当归) and *Rehmannia Glutinosa Radix Preparata* (*Shu-di*熟地) for *blood*-tonification; *Ophiopogon Japonicus Radix* (*Mai-dong*麦冬) and *Scrophularia Ningpoensis Radix* (*Xuan-shen*玄参) for *yin*-deficiency; *Myristica Fragrans Semen* (*Rou-dou-kou*肉豆蔻) and *Psoralea Corylifolia Fructus* (*Bu-gu-zhi*补骨脂) for *yang*-deficiency. The corresponding CM formulas are: *Bu-zhong-yi-qi* decoction (补中益气汤) for *qi*-tonification; *Si-wu* decoction (四物汤) for *blood*-tonification; *Zeng-ye* decoction (增液汤) for *yin*-tonification; *Si-shen* pill (四神丸) for *yang*-tonification.

Organ-tonifying herbs are: *Glycyrrhizae Uralensis Radix Preparata* (*Zhi-gan-cao*炙甘草) and *Rehmannia Glutinosa Radix* (*Di-huang*地黄) for heart-tonification; *Lycium Barbarum Fructus* (*Gou-qi-zi*枸杞子) and *Angelicae Sinensis Radix* (*Dang-gui*当归) for liver-tonification; *Panax Ginseng Radix* (*Ren-shen*人参) and *Atractylodis Macrocephala Rhizoma* (*Bai-zhu*白术) for spleen/stomach-tonification; *Panax Ginseng Radix* (*Ren-shen*人参) and *Astragalus Membranaceus Radix* (*Huang-qi*黄芪) for lung-tonification; *Cornus Officinalis Fructus* (*Shan-zhu-yu*山茱萸) and *Dioscorea Opposite Rhizoma* (*Shan-yao*山药) for kidney-tonification. The corresponding CM formulas are: *Zhi-gan-cao* decoction (炙甘草汤) for heart-tonification; *Yi-guan* decoction (一贯煎) for liver-tonification; *Shen-ling-bai-zhu* powder (参苓白术散) for spleen/stomach-tonification; *Bu-fei* decoction (补肺汤) for lung-tonification; *Liu-wei-di-huang* pill (六味地黄丸) for kidney tonification.

These herbs and formulas were described regarding their efficacy, reasonable use and unreasonable abuse specific to different patients with different symptoms. The scientific investigation on efficacy and safety of Chinese formulas will propel the acceptance and spread of TCM in the western world for the sake of patients worldwide.

Key words: Chinese herbal medicine, Chinese formula, Medicinal herbs, Theory of Chinese medicine
Received 16 November 2015; Accept 7 March 2016

Introduction

Chinese medicine (CM) represents an individualized and holism-based medicine with thousands of years experience for disease prevention and treatment. In recent years, it became part of complementary and alternative medicine for modern medicine. Remarkably, there is a considerable popularity for CM in industrialized Western countries. Especially since the economic development of China rapidly rose during the past few years, the interest of the general public on Chinese culture in general and on CM in particular seemed to increase even more. CM hospitals and practices of settled CM practitioners are booming and the export figures for CM products from China are constantly increasing since many years. The export volume of Chinese medicines reached $160 million in 2009, which is 30% more than in 1996[1]. However, analyses have shown that the readiness to use CM is not equally distributed among the general population in Western countries. Since CM is a Chinese classic philosophy-guided and clinical experience-based medicine in absence of quantitative standard, it has frequently been misunderstood and misapplied in the Western world due to language and culture barriers, resulting in inefficacy or toxicity of CM outside China. An orthodox and complete CM necessarily consists of the CM theory and clinic practice (diagnosis and therapy approaches). The CM theory is the basis for guiding the therapeutical practice, which determines the accuracy of diagnosis and the efficacy of therapy.

The CM theory was systematically described by the ancient medical book '*Yellow Emperor's Internal Classic*' (*Huang Di Nei Jing* 黄帝内经) in Han Dynasty China (206 BC-220 AD). It starts from the perspective of individualization and holism. For example, an important theory related to CM diagnosis, named pattern differentiation and treatment determination (*Bian-zheng-lun-zhi*辨证论治), emphasizes that patients with same disease should further be differently treated, while they have different pattern/syndrome (*Zheng*证) according to CM diagnosis[2]. Correct diagnoses are therefore of utmost importance for CM practice. CM diagnosis has four steps, including inspection (*Wang*望), listening and smelling (*Wen*闻), inquiry (*Wen*问), and pulse taking and palpation

as well as percussion (*Qie*切), for information collection of disease condition[3]. Inspection comprises the observation of vitality, behavior, complexion, physical build, posture, tongue, head and face, five sense organs, limbs, two lower orifices, skin, and excreta of patients. Listening and smelling means to listen to the voice of patients, such as speaking, breathing, coughing, vomiting, belching, and borborygmus, and smell the unusual odor and excreta of patients. Inquiry concerns to ask about disease conditions, subjective symptoms, history of illness, and living habits, etc. Pulse taking and palpation as well as percussion is the process to palpate patients′ pulse, skin, limbs, chest, abdomen, acupoints, etc[3–4]. With this information, doctors can determine as to which CM pattern/syndrome the patient has and decide on the optimal treatment. Every or every other week, patients need to see the doctor for re-evaluation of their disease conditions and follow-up of therapeutic treatment. The CM pattern/syndrome (*Zheng*证) is the basic unit of disease condition specifically used for guiding the corresponding therapy. Accurate diagnosis results in effective treatment and *vice versa*. Deficiency (*Xu-zheng*虚证) is the most common outcome of unhealthy conditions (unbalanced body states), composed by body deficiency (*qi*, *blood*-, *yin*-, *yang*-deficiency) and organ-deficiency (heart-, liver, spleen, lung, and kidney deficiency). Correspondingly, tonic herbs are used for treating diverse deficiencies as a main principle of CM. In this context, the question arises, as to which tonic herbs are commonly applied and how to ensure their clinical efficacy.

Traditionally, multi-herb formulas rather than single herbs are common CM medication in clinics, not only for tonic medication but in general. All herbs in a formula can be divided into four roles, consisting of sovereign (君), minister (臣), assistant (佐) and courier (使). The sovereign and minister herbs treat the main symptoms and rule a major function in the formula, the latter of which assist the former. The assistant herbs assist the sovereign and minister herbs to treat accompanying symptoms or hamper toxicity of the major herbs. The courier herbs have the function of leading all medicinal components directly into the pathological region or positively modulating the medicinal effects[3]. The compatibility of these roles in the formula is the principal foundation for its reasonable use. The interactions among each herb, such as mutual reinforcement, antagonism, or detoxification, etc., determine the formula's therapeutic efficacy[5]. The nature of herbs, including the four properties (cold, hot, warm and cool), the five tastes (sour, sweet, bitter, acrid and salty), as well as characteristics and meridian-tropism, should be considered by CM doctors to compose a formula or analyze the formula's efficacy. Except these “natural elements”, modern scientific studies also evaluate the efficacy of CM by clarifying the medicinal phytochemical basis and pharmacological modes of action of herbs and formulas.

This review intends to give a comprising overview on typical tonic herbs and formulas for understanding their efficacy, use principle, and application, on the basis of an extensive literature search in the PubMed database. The journals listed there meet high international quality standards. The non-consideration of publications, which are not listed in PubMed, was considered as quality criterion. The PubMed database has been mined for two major topics: (1) CM herbs for body tonifying, which are traditionally used to provide energy and to mediate physical strengthening of the body against *qi*, *blood*, *yin* or *yang* deficiency; (2) CM herbs for organ tonifying, which are traditionally used to nourish the internal organs and act against organ deficiencies and abnormalities. Their medicinal effects studied by modern scientific experiments are also considered and reviewed.

Our analysis is strictly based on scientific evidence from clinical trials performed after principles of Western medicine for the activity of herbal ingredients, in order to ensure objectivity and tracability of the argumentation in Western countries. Further reading is recommended on Chinese diagnosis and Chinese medicine[6]. Another issue that has to be taken into account is the possible toxicity of herbs. Especially in the broad public, medicinal herbs are considered as natural and, therefore, gentle and safe medicine in contrast to chemically synthesized drugs with their partwise severe side effects. Altough phytotherapy is effective and safe on its vast majority, cases of herbal poisoning have been described[7]. We have considered this aspect and specifically emphasized in the present report.

Body tonifying use

1. Overview

In CM, health is conceived as a blanced state among *qi*, *blood*, *yin* (dark), and *yang* (light), and disease appears, if these four elements fall out of balance[2]. The concept of deficiencies, somewhat like that of hypofunction in Western medicine, originated from the ‘*Yellow Emperors Internal Classic*’, signifying the abnormalities of essential natures of human health conditions. There are a large number of tonic prescriptions far distributed in China, which may lead to a first impression that the entire field is rather confusing. The reason for that is the large degree of individualization of CM practice, *e.g.* individual doctor makes individual diagnosis and treatment on individual patient according to their personal knowledge and experience. The treatment follows a holistic principle, in which the patient's whole body and even his life conditions are taken into consideration. By contrast, Western medicine with its reductionistic approach provides specific drugs for a specific disease-causing principle, *e.g.* a ligand molecule for a receptor. As there are considerable differences from patient to patient, a single herb is regarded as less helpful for all patients. Based on the main CM principles, each patient rather needs its individual herbal mixture (formula). These prescriptions may differ during the time period of treatment according to the disease course of the patient.

According to the earliest pharmacopeia of China, ‘*Shennong Materia Medica*’ (*Sheng Nong Ben Cao Jing*神农本草经), all herbs can be divided into three grades (superior, middle, and inferior). Most tonic herbs are classified into the superior grade, which can be long-term used for strongly nourishing human life and treating diseases without toxicity.

Table 1. Representative CM herbs and formulas for body-tonifying. The presence of an herb in a formula is indicated by a dark dot (●).

Plants	*Bu-zhong-yi-qi* decoction	*Si-wu* decoction	*Zeng-ye* decoction	*Si-shen* pill
Astragalus membranaceus	●			
Panax ginseng	●			
Angelicae sinensis	●	●		
Rehmannia glutinosa		●	●	
Ophiopogon japonicus			●	
Scrophulariae ningpoensis			●	
Myristica fragrans				●
Psoralea corylifolia				●
Glycyrrhiza uralensis	●			
Citrus reticulata	●			
Cimicifuga foetida	●			
Bupleurum chinense	●			
Atractylodes macrocephala	●			
Ligusticum chuanxiong		●		
Paeonia lactiflora		●		
Schisandra chinensis				●
Evodia rutaecarpa				●
Ziziphus jujuba	●			●
Zingiber officinale	●			

The common character of tonic herbs is their efficacy of tonifying and strengthening against deficiencies, while the diversity among them is due to the various deficiencies (*qi*, *blood*, *yin*, and *yang*) they can treat. Consequently, the herbs of *qi*-tonifying, *blood*-tonifying, *yin*-tonifying, and *yang*-tonifying are specifically defined and classified. In general, herbs acting as sovereign and minister may decide the medicinal nature of the formula they composed. For example, *qi*-tonifying herbs (*Astragalus Membranaceus Radix* (*huangqi*) and *Panax Ginseng Radix* (*renshen*) add *qi*-tonifying activity to their corresponding formulas (*Bu-zhong-yi-qi* decoction).

To extract the most relevant information from the plethora of published CM literature, we screened the relevant publication and analyzed the bioactivities of the herbal components of CM formulas whose main herbs used for body tonifying are depicted in Table 1.

2. Representative formulas for body tonifying use

Bu-zhong-yi-qi decoction (补中益气汤)

Composition: 15 g *Astragalus Membranaceus Radix* (*Huang-qi*黄芪) as sovereign; 15 g *Panax Ginseng Radix* (*Ren-shen*人参), 15 g *Atractylodes Macrocephala Rhizoma* (*Bai-zhu*白术) and 15 g fried *Glycyrrhiza Uralensis Radix* (*Zhi-gan-cao*炙甘草) as ministers; 10 g *Angelica Sinensis Radix* (*Dang-gui*当归) and 6 g *Citrus Reticulata Pericarpium* (*Chen-pi*陈皮) as assistants; and 6 g *Cimicifuga Foetida Rhizoma* (*Sheng-ma*升麻), 12 g *Bupleurum Chinense Radix* (*Chai-hu*柴胡), 27 g *Zingiber Officinale Rhizoma* (*Sheng-jiang*生姜) and 6 granules *Zingiber Jujuba* (*Da-zao*大枣) as couriers.

Properties: *Bu-zhong-yi-qi* decoction, firstly recorded in '*Treatise on the spleen and stomach*' (*Pi Wei Lun* 脾胃论) by Li Dong-yuan in the year 1249, was commonly used as an efficient formula for spleen-*qi* descending and *qi* deficiency related disorders, such as chronic diarrhea, fatigue and myasthenia[8–9]. It was also effective to treat various symptoms (weakness caused by fatigue or illness), regulating functions of the digestive system (*e.g.* improving the appetite and protecting against gastrectasia or chemical injury), and strengthening the body's defenses against various infections[10–11]. Modern pharmacological studies further demonstrated a variety of biological activities of this formula, including anti-cancer, anti-aging, immunomodulation, radioprotection, and anti-inflammation effects)[12–16]. By using solid phase extraction column-high performance liquid chromatography-diode array detection-evaporative light scattering detection (SPEC-HPLC-DAD-ELSD), 10 major components were determined in *Bu-zhong-yi-qi* decoction, including astragaloside I, astragaloside IV, butylene phthalide, calycosin, formononetin, hesperidin, ligustilide, ononin, senkyunolide I, senkyunolide H[17]. Therein, astragaloside IV was found closely related to the *qi*-nourishing effect of *Bu-zhong-yi-qi* decoction, which is the primary compound in Radix *Astragalus Membranaceus*, demonstrating the major role of sovereign in the formula[18]. Furthermore, LC-MS/MS analysis qualitatively and quantitatively determined 20 constituents of *Bu-zhong-yi-qi* decoction blood plasma of rats using a dynamic triggered multiple reaction monitoring (DtMRM) algorithm[19]. A ^{1}H-NMR-based metabonomic study attempted to explain, how these constituents might exert their effects in rats with spleen-*qi* deficiency. Four metabolites (valine, leucine, O-acetyl-glycoproten, and lactate) present at abnormal levels were restored to normal contents by *Bu-zhong-yi-qi* decoction, indicating that the formula of modulated certain metabolic pathways (*e.g.* energy, protein, and glycolytic metabolism)[20]. Another potential mechanism of *Bu-zhong-yi-qi* decoction relates to the regulation of intestinal microflora in rats with spleen-*qi* deficiency, as revealed by ERIC-PCR (enterobacterial repetitive intergenic consensus-PCR) fingerprint analysis[21].

Si-wu decoction (四物汤):

Composition (per person per day): 12 g *Rehmannia Glutinosa Radix Preparata* (*Shu-di*熟地) as sovereign; 10 g *Angelicae Sinensis Radix* (*Dang-gui*当归) as minister; 12 g *Paeonia*

Lactiflora Radix (*Bai-shao*白芍) as assistant; 8 g *Ligusticum Chuanxiong Rhizoma* (*Chuan-xiong*川芎) as courier.

Properties: *Si-wu* decoction was originally recorded by '*Tai Ping Hui Min He Ji Ju Fang*太平惠民和剂局方' in Song Dynasty (960-1279AD) with *blood*- and *qi*-tonifying effects for the treatment of hematopoietic deficiency, gynecologic diseases (abortion, climacteric syndrome, dysmenorrhea, menoxenia, metrorrhagia, peri- or postmenopausal syndrome, etc.), cutaneous diseases (eczema, dermatitis, pruritus, urticaria, etc.), and chronic inflammation (chronic nephritis, pelvic inflammation, etc.)[22–25]. It has been reported to possess sedative, anti-pruritic, anti-inflammatory, anti-bacterial, anti-oxidative, and anti-coagulant activities as well as effects of promoting vasodilatation, hematopoiesis, cellular immunity, bone formation, and of protecting against radiation-induced bone marrow damage[26–28]. Numerous bioactive constituents have been found in *Si-wu* decoction, including phthalides (*E*-ligustilide, *Z*-ligustilide, *Z*-butylenephthalide, butylphthalide, senkyunolide A, etc.), phenols (ferulic acid, coniferyl ferulate, gallic acid, etc.), iridoid glycosides (paeoniflorin, catalpol, etc.), saccharides (sucrose, glucose and fructose, etc.), spathulenol, terpineol, benzeneethanamine, and cyclopropane[29–30]. Of these, ferulic acid and paeoniflorin have been recommended as the chemical markers for quality control of *Si-wu* decoction[31–33]. *Z*-ligustilide was most commonly reported as bioactive phthalide with activities of anti-bacteria, anti-inflammation, and anti-oxidant, which might be responsible for the similar activities of *Si-wu* decoction[29]. Recently, it was found that *Si-wu* decoction promotes hematopoiesis and immunity by increasing the number of peripheral leukocytes and four types of progenitor cells in bone marrow, *i.e.* colony-forming unit-granulocyte-macrophage (CFU-GM), colony-forming unit-mature erythroid (CFU-E), colony-forming unit-immature erythroid (BFU-E) and colony-forming unit-multipotential (CFU-mix) cells, which was contributed by free fructose in the *Si-wu* decoction[27]. Oral administration of pure fructose at a dose equal to that of free fructose in *Si-wu* decoction also showed positive effects on peripheral leukocytes, bone marrow progenitor cells and thymus index[27], indicating the importance of free fructose for the *blood*-tonifying effect against hematopoiesis deficiency. As expected, the sovereign *Shu-di* provides most of the free fructose in the *Si-wu* decoction[34], which plays a major role in the formula. Microarray-based mechanism studies showed that the *Si-wu* decoction might modulate seven different molecular pathways (pathways in cancer, ribosome biogenesis in eukaryotes, p53 signaling pathway, endocytosis, neuroactive ligand-receptor interaction, TGF-beta signaling pathway, and oxidative stress induced gene expression via Nrf2) and their relevant targets[35].

Zeng-ye decoction (增液汤)

Composition (per person per day): 30 g *Scrophularia Ningpoensis Radix* (*Yuan-shen*元参) as sovereign; 24 g *Rehmanniae Glutinosa Radix* (*Sheng-di*生地) and 24 g *Ophiopogon Japonicus Radix* (*Mai-dong*麦冬) as ministers. There is no assistant and courier.

Properties: *Zeng-ye* decoction, originally recorded in '*Treatise on Differentiation and Treatment of Seasonal Diseases*' (*Wen Bing Tiao Bian*温病条辨) by Wu Tang in 1798, was a classic formula used for treating yin-deficiency associated disorders, such as functional constipation and Sjogren syndrome[36]. Many bioactive components, including 5-HMF, harpagoside, acteoside, angoroside C, cinnamic acid, methylophiopogonanone A, methylophiopogonanone B, and ophiopogonin D, have been identified from *Zeng-ye* decoction. This formula ameliorated slow transit constipation by upregulating expression of vasoactive intestinal peptide in the intestinal tissue of patients, and also protect the submandibular glands in nonobese diabetic model of Sjogren syndrome by correction of Th1/Th2 cytokine imbalance. Acute *yin*-impairment is a commonly occurred clinic syndrome represented by body fluids loss and inner environment disturbance, which may be caused by hyperthermia or drug poisons. *Zeng-ye* decoction could alleviate such syndrome by modulating the extra- and intracellular ion homeostasis (Na^+, K^+, Ca^{2+}), retaining the Na^+-K^+-ATP enzymatic activity in cytomembrane, and protecting liver cells and thymic cells. The action mechanism of *Zeng-ye* decoction is associated with the clearance of oxygen radical and the regulation of apoptotic gene balance (bcl-2/bax).

Si-shen pill (四神丸)

Composition (per person per day): 6 g *Myristica fragrans* (*Bu-gu-zhi*补骨脂) as sovereign; 3 g *Myristica fragrans* (*Rou-dou-kou*肉豆蔻) as minister; 3 g *Schisandra chinensis* (*Wu-wei-zi*五味子) and 1.5 g *Evodia rutaecarpa* (*Wu-zhu-yu*吴茱萸) as assistants; 3 g *Ziziphus jujuba* (*Da-zao*大枣) as courier.

Properties: *Si-shen* pill is a famous CM formula known from '*Chen Shi Xiao Er Dou Zhen Fang Lun*陈氏小儿痘疹方论' in Southern Song Dynasty. It was commonly used to treat *yang* deficiency associated diseases, such as diarrhea, ulcerative colitis, allergic colitis, chronic colitis, irritable bowel syndrome, etc[37–39]. Psoralen and isopsoralen were identified from the sovereign (*Bu-gu-zhi*) with anti-aging and antineoplastic activities. Ursolic acid was identified from the minister (*Rou-dou-kou*) with bacteriostasis and antineoplastic activities. Schisandrin, evodiamine and rutaecarpine were identified from the assistants (*Wu-wei-zi* and *Wu-zhu-yu*) with anti-free radical, boost immunity, analgesia, bacteriostasis and antiemetic activities. Furthermore, polysaccharides and gingerol were identified from the couriers (*Da-zao* and *Sheng-jiang*) with antioxidative, antiglycative, antiapoptotic and gestroprotective activities in percentage content of 40%[40–45]. *Si-shen* pills exert anti-colitis effects by protecting the colonic mucosa against injuries and inhibiting apoptosis of colonic epithelial cells by downregulation of apoptosis-related genes (p38 MAPK, p53, caspase-3, c-jun, c-fos, Bax, and TNF-α), p38 MAPK signaling pathway genes as well as modulation of antioxidative proteins and genes (degradation of MOP and MAD, elevation of GSH-Px and SOD, and up-regulation of IL-4 and IL-10 mRNA expression) in colonic tissues[46–47].

Table 2. Representative CM herbs and formulas for organ-tonifying. The presence of an herb in a formula is indicated by a dark dot (●).

Plants	*Zhi-gan-cao* decoction	*Yi-guan* decoction	*Shen-ling-bai-zhu* powder	*Bu-fei* decoction	*Liu-wei-di-huang* pill
*Astragalus membranaceus**				●	
Stalactitum				●	
White quartz				●	
Magnolia officinalis				●	
Morus alba				●	
Aster tataricus				●	
Polygala tenuifolia				●	
*Panax ginseng**	●		●	●	
Poria cocos			●	●	●
Dioscorea opposita			●		●
Nelumbo nucifera			●		
Dolichos lablab			●		
Coix lacryma-jobi			●		
Amomum villosum			●		
Platycodon grandiflorum			●		
Adinophora stricta		●			
Lycium barbarum		●			
*Angelicae sinensis**		●		●	
Melia toosendan		●			
*Ophiopogon japonicus**	●	●		●	
Cinnamomum cassia	●			●	
Cannabis sativa	●				
Equus asinus	●				
*Rehmanniae glutinosae**	●			●	●
Cornus officinalis					●
Alisma orientalis					●
Paeonia suffruticosa					●
*Glycyrrhiza uralensis**	●		●	●	
Citrus reticulate				●	
*Atractylodes macrocephala**			●		
*Schisandra chinensis**				●	
*Evodia rutaecarpa**				●	
*Ziziphus jujube**	●			●	
*Zingiber officinale**	●			●	

Organ tonifying use

1. Overview

The *zang-fu* organ system is also a core concept of CM theory, involving five organs with five elements: 'heart' with fire, 'liver' with wood, 'spleen/stomach' with earth, 'lung' with metal, and 'kidney' with water. The organ in CM are not similar to the anatomical one defined by Western medicine, which has more extensive concept and represents the function of different systems. For instance, the 'heart' has functions of dominating metal activities, intelligence, and blood circulation, being associated with cardio-cerebral vascular system; the 'liver' dominates the flow of *qi* and blood, and also correlates with emotional changes. The 'spleen/stomach' dominates the digestive absorption and is closely related to the stomach function. The 'lung' is in charge of respiration and dominates the functions of mouth, nose, and trachea. The 'kidney' stores the congenital essence and governs bone metabolism responsible for the body growth, development, reproduction, and *yang* supplement[5]. Organ deficiency is an important pathogenesis basis for various syndromes and diseases. The CM theory has defined a nature of meridian-tropism specific to different organs for every herb of CM, determining the organ targets for the effect of each herb. Thus, applying formulas/herbs with certain meridian-tropism nature for treating corresponding organ deficiency can confirm the accuracy and specificity of the treatment and increase the clinical efficacy. The representative formulas and their herbs used for organ tonifying ('heart'-tonifying, 'liver'-tonifying, 'spleen/stomach'-tonifying, 'lung'-tonifying, and 'kidney'-tonifying) are depicted in Table 2.

2. Representative formulas for organ tonifying use

Zhi-gan-cao decoction (炙甘草汤) for 'heart'-tonification

Composition (per person per day): 12 g fried *Glycyrrhiza Uralensis Radix* (*Zhi-gan-cao*炙甘草) as sovereign; 50 g *Rehmannia Glutinosa Radix* (*Sheng-di*生地), 10 g *Ophiopogon japonicas* (*Mai-dong*麦冬), 6 g *Equus asinus* (*E-jiao*阿胶), 10 g *Cannabis sativa* (*Huo-ma-ren*火麻仁), 6 g *Panax Ginseng Radix* (*Ren-shen*人参), and 10 granules *Ziziphus jujuba* (*Da-zao*大枣) as ministers; 9 g *Cinnamomum Cassia Ramulus* (*Gui-zhi*桂枝) and 9 g *Zingiber Officinale Rhizoma* (*Sheng-jiang*生姜) as assistants.

Properties: *Zhi-gan-cao* decoction is a classic formula originally noted in '*Treatise on Febrile Diseases*' (*Shang Han*

*Lun*伤寒论) by Zhang Zhong-jing in the year 219 (Eastern Han Dynasty of China) for treating symptoms with deficiency of both the heart-*yin* and heart-*yang*, such as arrhythmia, heart palpitations, shortness of breath, insomnia, premature ventricular contractions[48–49]. It nourishes heart *yin* and *yang*, tonifies heart *qi* and *blood*, strengthens the heart, and normalizes the pulse. Therefore, it is used for cardiovascular diseases for hundreds of years in China[50]. In this formula, *Glycyrrhiza uralensis* is applied for replenishing heart *qi*, *Panax ginseng* and *Ziziphus jujuba* are used for strengthening heart *qi* and promoting the produce of blood and restoration of normal pulse, *Rehmannia glutinosa*, *Ophiopogon japonicus*, *Equus asinus* and *Cannabis sativa* can give the effects of nourishing the heart-*yin*, and *Cinnamomum cassia* and *Zingiber officinale* warm and activate heart-*yang*[48]. Modern pharmacological studies have shown that *Zhi-gan-cao* decoction exerted anti-arrhythmia through amelioration of ventricular premature beat, ventricular tachycardia, and ventricular fibrillation. This mechanism may be associated with the modulation of ventricular cell action potentials, inhibition of platelet activation, and protection of myocardial endothelial cells[51–52]. Glycyrrhizic acid, ginseng saponins and *Ophiopogon* saponins have been reported to be the main effective ingredients responsible for the anti-arrhythmic activity of *Zhi-gan-cao* decoction[53].

Yi-guan decoction (一贯煎) for 'liver'-tonification

Composition (for each person per day): 30 g *Rehmannia Glutinosa Radix* (*Sheng-di*生地) as sovereign; 10 g *Angelicae Sinensis Radix* (*Dang-gui*当归), 15 g *Lycium Barbarum Fructus* (*Gou-qi-zi*枸杞子), 10 g *Adinophora stricta* (*Sha-shen*沙参) and 10 g *Ophiopogon japonicus* (*Mai-dong*麦冬) as ministers; 5 g *Melia Toosendan Fructus* (*Chuan-lian-zi*川楝子) as assistant.

Properties: *Yi-guan* decoction, a classic liver-tonifying CM formula, is originated from '*Supplement to the Classified Medical Records of Famous Physicians*' (*Xu Ming Yi Lei An* 续名医类案) by Wei Zhi-xiu in the year 1770 (Qing Dynasty of China) for treating liver diseases with liver-*yin* deficiency and liver-*qi* disorder by replenishing *yin* and soothing the liver[54]. It has apparent efficacy in preventing liver fibrosis and cirrhosis, protecting against liver injuries, improving liver function, and inhibiting hepatocarcinoma cells for the treatment of chronic liver diseases as well as liver cancer[55–57]. The major bioactive component of *Yi-guan* decoction, ferulic acid and catalpol, significantly inhibited the progression of liver fibrogenesis induced by carbon tetrachloride (CCL_4) in animal model[55]. The hepatoprotective and antifibrotic mechanism of this decoction is the suppression of serum glutamate oxaloacetate transaminase (GOT) and glutamic pyruvic transaminase (GPT), reduction of collagen α1-I, tissue inhibitor of metalloproteinase-1 (TIMP-1) and α -smooth muscle actin (α-SMA) in liver tissue, inhibition of hepatic stellate cells (HSCs) activation, up regulation of matrix metalloproteinase-9 (MMP-9), MMP-13, TIMP-2 and HGFα gene expression, and down regulation of MMP-2, TIMP-1, caspase-12, α-SMA, Bcl-2 and Afamin gene expression[55–57]. Furthermore, *Yi-guan* decoction induced HSCs apoptosis via ROS-mediated mitochondrial/caspase pathway (caspase-3 activation by ROS production and calcium release) and ER stress associated signaling pathway[58], and induced anoikis in hepatocarcinoma cells via inhibition of expression and phosphorylation of p38 MAPK and activation of intrinsic and extrinsic pathways of apoptosis[56]. The metabonomic analysis showed that *Yi-guan* decoction exerted antifibrotic effects by regulating the dysfunction of energy metabolism, amino acid metabolism, tryptophan metabolism, cytochrome P450 metabolism, and gut microflora metabolism[59].

Shen-ling-bai-zhu powder (参苓白术散) for 'spleen/stomach -tonification

Composition (per person per day): 4 g *Panax Ginseng Radix* (*Ren-shen*人参), 4 g fried *Atractylodis Macrocephala Rhizoma* (*Bai-zhu*白术) and 4 g *Poria cocos* (*Fu-ling*茯苓) as sovereigns; 4 g *Dioscorea Opposite Rhizoma* (*Shan-yao*山药), 2 g *Nelumbo Nucifera Semen* (*Lian-zi*莲子), 3 g fried *Dolichos lablab* (*Bian-dou*扁豆) and 2 g fried *Coix lacryma-jobi* (*Yi-yi-ren*薏苡仁) as ministers; 2 g *Amomum villosum* (*Sha-ren*砂仁) as assistant; 2 g *Platycodon grandiflorum* (*Jie-geng*桔梗) and 4 g fried *Glycyrrhiza Uralensis Radix* (*Zhi-gan-cao*炙甘草) as couriers.

Properties: *Shen-ling-bai-zhu* powder is a famous classical formula firstly recorded in '*Tai Ping Hui Min He Ji Ju Fang*太平惠民和剂局方' in Northern Song Dynasty (1087), which has the functions of tonifying spleen and stomach *qi* for treating deficiency of spleen and stomach[60]. In this formula, the *Panax Ginseng Radix*, *Rhizoma Atractylodis Macrocephala*, and *Poria cocos* are used as sovereigns to replenish *qi* for invigorating the spleen and excreting dampness; *Dioscorea Opposite Rhizoma* and *Nelumbo Nucifera Semen* are applied to assist the *Panax Ginseng Radix* to invigorate spleen and supplement *qi* and to exert anti-diarrhea, and the fried *Dolichos lablab* and fried *Coix lacryma-jobi* are applied to assist the *Atractylodis Macrocephala Rhizoma* and *Poria cocos* to tonify spleen and excrete dampness. The *Amomum villosum* as an assistant can be used for activating the spleen, harmonizing the stomach, promoting the circulation of *qi,* removing stagnation, and as couriers. The *Platycodon grandiflorum* promotes the lung function to facilitate *qi*, cleans the water channel of body, and carries herbal components to upstream; *Glycyrrhiza Uralensis Radix* tonifies the spleen and stomach, and coordinates all other herbs. Pharmacological studies showed that *Shen-ling-bai-zhu* powder inhibited oxidative stress, lipid peroxidation, inflammatory reaction, and hyperacidity during gastroenteropathy treatment[61–63]. The major bioactive compounds of this formula have been identified as saikosaponins, glucosides of peony, ginsenoside, atractylenolide, atractylodes macrocephalaon polysaccharide, and carboxymethylpachymaran, which protect organ tissues[64–68]. A known mechanism of this formula is the suppression of the p38 MAPK signaling pathway[63].

Bu-fei decoction (补肺汤) for 'lung'-tonification

Composition (for each person per day): 30 g *Astragalus Membranaceus Radix* (*Huang-qi*黄芪) as sovereign; 12 g *Panax Ginseng Radix* (*Ren-shen*人参), 12 g Stalactitum (*Zhong-ru*钟乳), 12 g *Glycyrrhiza Uralensis Radix* (*Gan-cao* 甘草) as ministers; 15 g *Cortex Cinnamomum cassia* (Rou-gui 肉桂), 15 g dried *Rehmannia Glutinosa Radix* (*Gan-di-huang* 干地黄), 15 g *Poria cocos* (*Fu-ling*茯苓), 15 g white quartz (*Bai-shi-ying*白石英), 15 g *Magnolia Officinalis Cortex* (*Hou-pu*厚朴), 15 g *Morus Alba Cortex* (*Sang-bai-pi*桑白皮), 15 g *Aster Tataricus Radix* (*Zi-yuan*紫苑), 15 g *Angelicae Sinensis Radix* (*Dang-gui*当归), 15 g *Schisandra chinensis* (*Wu-wei-zi*五味子), 15 g *Polygala Tenuifolia Radix* (*Yuan-zhi*远志), and 15 g *Ophiopogon Japonicus Radix* (*Mai-men-dong*麦门冬) as assistants; 15 g *Zingiber Officinale Rhizoma* (*Sheng-jiang*生姜), 15 g *Citrus Reticulatus Exocarpium* (*Ju-hong*橘红), 20 granules *Ziziphus jujuba* (*Da-zao*大枣) as couriers.

Properties: *Bu-fei* decoction is a classical formula developed by Sun Si-miao and recorded in '*Essential Recipes for Emergent Use worth a Thousand Gold*' (*Bei Ji Qian Jin Yao Fang*备急千金要方) in the year 652 (Tang Dynasty of China). It enhances lung immune function and has therapeutic effectsagainst lung-deficiency associated disorders, such as lung-distention, dyspnea syndrome, phlegm retention, and internal injury cough. The treatment principle of strengthening vital *qi* combined with dispelling blood stasis and resolving phlegm is the basis of this formula[69]. From the perspective of CM theory, in *Bu-fei* decoction, the sovereign *Astragalus membranaceus* directly tonifies the spleen and supposts the lung. The ministers can together facilitate the sovereign's effect. The assistants can moisten the lung *yin* and regulate lung *qi*, and the couriers reconcile lung and spleen. Randomized, double blinded, placebo-controlled, and multicenter clinical studies revealed that *Bu-fei* decoction exerted therapeutic effects on patients with stable chronic obstructive pulmonary disease (COPD) by anti-inflammatory regulating the abnormal serum levels of TNF-α, IL-8, IL-6, and TGF-β1 to normal levels[36,69]. Rat experiments showed that *Bu-fei* decoction corrected plasma levels of endothelin, nitrix oxide, MDA, and SOD and improved immunological indices of thymus and spleen[70–71]. Furthermore, this formula also affected neurotransmitters in enteric nervous system of rats with lung-*qi* deficiency[72].

Liu-wei-di-huang pill (六味地黄丸)

Composition (per person per day): 6 g cooked *Rehmannia Glutinosa Radix* (*Shu-di*熟地) as sovereign; 3 g *Cornus Officinalis Fructus* (*Shan-zhu-yu*山茱萸) and 3 g *Dioscorea Opposite Rhizoma* (*Shan-yao*山药) as ministers; 2 g *Alisma Orientalis Rhizoma* (*Ze-xie*泽泻), 2 g *Paeonia Suffruticosa Cortex* (*Mu-dan-pi*牡丹皮) and 2 g *Poria cocos* (*Fu-ling*茯苓) as both assistants and couriers.

Properties: *Liu-wei-di-huang* pill, a well-known classical formula for kidney nourishment, was first recorded by '*Knack of Prescription in Pediatrics*' (*Xiao Er Yao Zheng Zhi Jue*小儿药证直诀) in the year 1119 (Northern Song Dynasty). It has long been clinically used in treatment of kidney-deficiency associated disorders covering immune, endocrine, digestive, respiratory, urinary and circulatory systems, such as alopecia, backache, dizziness, menoxenia, tinnitus, weakness and soreness of waist and knees, etc.[73]. Modern pharmacological studies further demonstrated its efficacy of anti-hypertension, anti-aging, anti-osteoporosis, anti-inflammatory, anti-oxidative stress, treating diabetes type II, reducing blood sugar levels, regulating blood lipid, modulating neuronal and synaptic function, improving cognition and memory, protecting organ (kidney, heart, liver, neurons) function, and so on[61,74–81]. This formula alleviates osteoporosis through up-regulating the expression of Lrp-5, β-catenin, Runx2 and Osx, which are involved in the Wnt/β-catenin signaling pathway[81]. Furthermore, it protects dopaminergic neurons against oxidative damage and neuronal apoptosis through enhancing antioxidant defense (SOD, GSH), decreasing ROS production, down-regulating NADPH oxidases (Nox2 and Nox4), improving mitochondrial membrane potential, increasing anti-apoptotic protein Bcl-2 expression, and down-regulating apoptotic signaling (Bax, cytochrome c, cleaved-caspase-3) in neurons[80]. *Liu-wei-di-huang* ameliorates cognitive impairments through protecting normal synaptic transmission, improving mitochondrial function, and modulating target gene expression (*DUSP12*, *NSF*, *STUB1*, *CaMKIIα*, *AMFR*, *UQCRFS1*, *etc.*)[82]. Chemical analyses revealed many bioactive constituents of *Liu-wei-di-huang* pill, namely 5-hydroxymethyl furfural, daidzein, alisol B-23 acetate, dihydromelittoside, gallic acid, genistein, hippurate, loganin, morroniside, paeoniflorin, benzoylpaeoniflorin, paeonal, and sweroside, which are responsible for the formula's therapeutic efficacy[83–86].

Representative single herbs

A large number of herbs are constituents of formulas for body or organ tonifying. A few representative examples, which have been investigated in more detail, are mentioned in the following:

Aconitum carmichaeli (tianxiong): As shown by Cao et al. (2001), a decoction of processed *tianxiong* strengthened the antifatigual ability and prolonged the survival time of low-temperature swimming for mice. It also and promotes immunization in rats[87]. Speaking in terms of CM, *tianxiong* is able to reinforce the kidney *Yang*, which reconfirms the conclusion of "replenishing the fire of vital gate and the *Qi* of kidney" recorded in Chinese historical literature and proved by overseas clinical practice. Since *Aconitum* species contain the highly toxic aconitin, tianxiong was always pre-processed for detoxication before use. Therefore, in clinic, most decocted samples of tianxiong are processed and detoxicated.

Tu Si Zi (Cuscuta Japonica Semen), Chuan Duan (Dipsacus Asperoides Radix), Nuzhenzi (Ligustrum Lucidum Fructus), Gouqizi (Lycium Barbarum Fructus): Stressed mice were used to analyze the effect of tonic herbs such as *tusizi*,

chuanduan, *nuzhenzi*, *gouqizi* on cytoplasmic calcium levels during immune cell reproduction as well as on membrane fluidity of splenetic lymphocytes and interleukin levels[88]. The tonic herbs improved the proliferative capability of spleen lymphocytes in stressed mice, reduced calcium concentrations, and recovered the fluidity of cell membranes. Furthermore, interleukin-2 and interleukin-2 receptor were significantly increased. The combination of the four tonic herbs proved to be more effective, facilitating cellular DNA synthesis and reducing the retention period in the G0/G1 cell cycle phase. Hence, these tonic herbs modulated the reproductive function of spleen lymphocyte and relieved the unfavorable response of stress on the organism.

Astragalus membranaceus: A platinum-based two-drug regimen is currently the standard of care for patients with advanced non-small-cell lung cancer (NSCLC). However, chemotherapy-induced side effects still remain a significant clinical problem. *Astragalus* polysaccharide (APS) is a polysaccharide isolated from the root of *Astragalus membranaceus*, which is commonly used in CM. Guo et al.[89] designed this randomized trial to determine whether *Astragalus membranaceus* injection combined with vinorelbine and cisplatin offered an improved quality of life complared to chemotherapy alone in 136 patients with advanced NSCLC[89]. Secondary objectives were tumor response, toxicity, and survival results. Objective response rates and mean survival times were not significantly different between borh regimens. After three treatment cycles, there were significant improvements in the *Astragalus membranaceus*-containing regimen regarding quality of life, physical function, fatigue, nausea and vomiting, pain, and loss of appetite. Hence, *Astragalus membranaceus* integrated into standard chemotherapy revealed significant beneficial effects in patients with advanced NSCLC.

***Turmeric*, PHY-906, *Huachansu* (dried *Bufo* toad skin), *Kanglaite* (*Coix lachryma-jobi*; Job Tears):** In addition to the above mentioned study, numerous studies have indicated that CM can be used to enhance the efficacy of and diminish the side effects and complications caused by chemo- and radiotherapy. Qi et al. (2010) reviewed the literature on this topic[90]. The authors discussed Chinese herbs that are commonly used by cancer patients for treating the cancer and/or reducing the toxicity induced by chemo- or radiotherapy, *e.g. Astragalus*, *Turmeric*, *Ginseng*, TJ-41, PHY906, *Huachansu* injection, and *Kanglaite* injection. Clinical studies have shown that these Chinese herbal medicines are advantageous in terms of suppressing tumor progression, increasing the sensitivity of chemo- and radio-therapeutics, improving an organism's immune system function, and lessening the damage caused by chemo- and radio-therapeutics. Furthermore, the authors gave an overview on clinical trials on Chinese herbal medicines as adjuvant cancer treatment. By reducing side effects and complications during chemo- and radio-therapy. These Chinese herbal medicines have a significant effect on reducing cancer-related fatigue and pain, improving respiratory tract infections and gastrointestinal side effects including diarrhea, nausea, and vomiting, protecting liver function, and even ameliorating the symptoms of cachexia.

Cistanche deserticola: A phenylethanoid-rich extract of *Cistanche deserticola* Y.C. Ma, evaluated by Cai et al. (2010) for antifatigue activity in mice[91]. The swimming time to exhaustion was significantly longer in the treatment groups than in the control group. The serum creatine kinase, lactate dehydrogenase and lactic acid levels were significantly decreased in the treatment groups, while the hemoglobin and glucose contents were significantly increased. The authors concluded that the *Cistanche deserticola* extract enhanced the swimming capacity of mice by decreasing muscle damage, delaying the accumulation of lactic acid and by improving the energy storage.

Ganoderma lucidum: The mushroom *Ganoderma lucidum* has been widely used in Asian medicine to treat various diseases, including cancer, diabetes, and neurasthenia. A randomized, double-blind, placebo-controlled study of Tang et al. (2005) investigated the efficacy and safety of a polysaccharide extract of *Ganoderma lucidum* (Ganopoly) in 132 patients with neurasthenia[92]. Ganopoly or placebo was orally applied at 1,800 mg three times a day for 8 weeks. Efficacy assessments comprised the Clinical Global Impression (CGI) improvement of severity scale and the Visual Analogues Scales for the sense of fatigue and well-being. In 123 assessable patients at the end of the study, Ganopoly treatment resulted in significantly lower scores in the CGI severity score and sense of fatigue. The score at day 56 in the sense of well-being increased from baseline to 38.7% in the Ganopoly-treated group compared with 29.7% in the placebo group. Ganopoly was well tolerated by the study patients. These findings indicated that Ganopoly was significantly superior to placebo with respect to the clinical improvement of symptoms in neurasthenia.

In a controlled study, Wicks et al. (2007) evaluated the safety and tolerance of oral administration of *Ganoderma lucidum* (2 g extract twice daily for 10 consecutivce days) in 16 human volunteers[93]. During the study, information from subjective questionnaires were obtained, electrocardiograms, complete blood counts, blood chemistry analysis and urinalysis were performed. No adverse effects were observed after extract intake. Although there were no obvious changes in CD4, CD8, and CD19 levels after the extract, CD56 cell count increased during the study and returned to baseline 10 days after the herbal intake. However, due to relatively high variability and small sample size, this CD56 increase did not achieve statistical significance, and remains to be re-evaluated in the future.

Lentinus edodes, Ganoderma lucidum,* and *Cordyceps sinensis: Not only *Ganoderma lucidum*, but many other mushrooms as well have been used in CM since ages, *e.g. Lentinus edodes*, and *Cordyceps sinensis*. A review of Chang and Wasser (2012) reported on mushroom polysaccharide

compounds investigated in Phase I-III clinical trials[94]. The authors stated that mushrooms were superior compared to different types of dietary supplemental tonics. The advantages of using mushroom-based dietary supplements are their higher safety as opposed to herbal preparations because: 1) The overwhelming majority of mushrooms used for the production of dietary supplements are commercially cultivated and not gathered in the wild. 2) Mushrooms are easily propagated vegetatively and thus derive from one clone. The mycelium can be stored for a long time, and the genetic and biochemical consistency can be monitored even after long times. 3) A major advantage may be that many mushrooms can be maintained as mycelial biomass in submerged cultures.

The beneficial effects of *Cordyceps sinensis* are also highlighted in the review by Zhu et al. (1998), which reports on *in vivo* studies and clinical trials of more than 2000 patients[95]. These studies show the main effects of the fungus in oxygen-free radical scavenging, antisenescence, endocrine, hypolipidemic, antiatherosclerotic, and sexual function-restorative activities. The safety of the fungus, its effects on the nervous system, glucose metabolism, the respiratory, hepatic, cardiovascular, and immune systems, immunologic disease, inflammatory conditions, cancer, and diseases of the kidney were also reviewed.

Schisandra chinensis: *Schisandra* berry or *Wu Wei Zi*, meaning the "the fruit of five tastes" in Chinese, is a commonly used herb in CM. Based on the "Five-Element" theory in CM, while the "five tastes" of *Schisandra* berry refer to its influence on the five visceral organs in the body, ancient Chinese herbalists specifically trumpeted the berry's beneficial effect on the *Qi* of the five visceral organs. "*Qi*" is a Chinese term used as a broad description of energy-dependent body functions[96]. Xia et al. (2011) investigated the influence of *Schisandra Chinensis Fructus* on the function of the pituitary-testis axis and carbohydrate metabolism in 34 male rats undergoing experimental navigation and strenuous exercise[97]. The quiescent control group showed significantly lower glutamate levels and higher testosterone levels than the stress control, but there was no significant difference in the corticosterone levels between the two groups. Compared with the stress control group, both the glutamate and corticosterone levels were remarkably decreased in the *Schisandra Chinensis Fructus* group, but the testosterone levels showed no significant change. There were no significant differences in the serum luteinizing hormone levels among the three groups. Ultrastructural pathology showed a significant reduction of secretory granules in the pituitary cells in the stress control group compared with the quiescent control group and a markedly increased number of granules in the cytoplasm in *Schisandra Chinensis Fructus*-treated group compared with the stress control group. Changes as mitochondrial swelling, increase of electron density and decrease or disappearance of mitochondrial cristae were also found in the Leydig cells of the stress control group and no significant differences were observed in the testicular cells between thes two groups. The authors concluded that intragastric administration of *Schisandra Chinensis Fructus* protected the pituitary-testis axis and reduced the blood glutamate levels in stressed rats.

Acanthopanacis senticosus: Wu et al. (1998) investigated the effect of *Acanthopanacus Senticosus Radix* (*ciwujia*) preparation on human exercise performance in 13 healthy volunteers in an age range of 50-57 years[98]. Under constant endurance load with 75 W, the respiratory quotient after taking *Ciwujia* preparation was reduced to 0.88 from 0.96, which implied that the utilization of lipid increased with 27.2% as energy fuel during exercise. The heart rate was reduced by 8.7%, and oxygen uptake per heart beat increased with 16.18%. These results indicated that the *Ciwujia* preparation increases oxygen uptake, spared glycogen in muscle and improved exercise endurance and work performance in human subjects.

Gymnostemma pentaphylla: Total saponins were extracted from *Gynostemma pentaphylla* for an animal study performed by Zhang et al. (1990) to investigate their effect on weight of immune organs, content of anti-SRBC hemolysin, rate of special Ea-RFC form immunity impairment due to cyclophosphamide treatment in mice[99]. *Gynostemma pentaphylla* saponins markedly acted against the immunity inhibition caused by cyclophosphamide treatment. The saponins restored the immune indices to normal values. Furthermore, the saponins prevented from fatigue.

Epimedium wushanense* and *E. pubescens: The effects of tonifying the kidney and strengthening *Yang* by extracts of *Epimedium wushanense* and *E. pubescens* were studied by Zheng et al. (1995)[100]. Both two herbs decreased the concentration of plasma middle molecular substances and increased the concentration of plasma sulfhydryl group of *Yang*-deficiency in mice. The authors suggest that the tonifying and strengthening effects of *Epimedium Herba* may result from its effects on middle molecular substances and sulfhydryl group strengthening the body's resistance and eliminating invading pathogenic factors.

Rhodiola crenulata* and *Ginkgo biloba: Zhang et al. (2009) investigated, whether a herbal supplement consisting of *Rhodiola crenulata* and *Gingko biloba* enhances the endurance performance of 67 healthy male volunteers (age ranges from 18 to 22 years old) and change relevant hormones in a favorable manner[101]. Treatment was performed for seven weeks and compared to a placebo group. The treatment group displayed a significantly greater baseline-to endpoint increase in maximal oxygen uptake than the placebo group. At the endpoint, the serum cortisol level was unchanged in the RGC group compared with the baseline, but it was significantly elevated in the placebo group. The endpoint ratio of testosterone to cortisol, a surrogate for overtraining and fatigue in endurance exercises, was also indifferent compared with the baseline in the treatment group, but significantly decreased in the placebo group. The authors conluded that the combined herbal supplement of *Rhodiola* and *Gingko* improved the endurance performance by increasing oxygen consumption and protecting against fatigue.

Lycium barbarum: The red-colored fruits of *Lycium barbarum* (Wolfberry, *Gouqi*, or *Goji*) have been used for a long time as an ingredient in Chinese cuisine and brewing, and also in traditional Chinese herbal medicine for improving health. The fruits are a tonic medicine and are a long-term healthy food without side effect. *Goji* berries and juice are being sold as health food products in western countries and praised in advertisements and in the media for well-being. The popularity of *Goji* products has rapidly grown over the last years thanks to efficient marketing strategies. *Goji* is a relatively new name given to *Lycium barbarum* and *L. chinense*, two close species with a long tradition of use as medicinal and food plants in East Asia, in particular in China. While only *L. barbarum* is officinal, the fruit (*Lycium Barbatum Fructus*) and the root bark (*Lycium Barbatum Cortex Radicis*) of both species are used in the folk medicine[102]. An increase in the demand for natural healthy food, *Lycium Barbatum Fructus* has suggested as a source of healthy foods[103]. A purified component of *Lycium barbarum* polysaccharide (LBP-X) was isolated from *Lycium barbarum* L. by Luo et al. (2000), which was tested in mice[104]. LBP-X induced a remarkable adaptability to exercise load, enhanced resistance and accelerated elimination of fatigue. LBP-X enhanced the storage of muscle and liver glycogen, increased the activity of LDH before and after swimming, decreased the increase of blood urea nitrogen after strenuous exercise, and accelerated the clearance of blood urea nitrogen after exercise.

Feng et al. (2010) studied the prevention of a milk-based wolfberry preparation on cognitive dysfunction in a prenatal stress model with rats[105]. Prenatal stress caused significant decrease in cognitive function (Morris water maze test) in female offspring. Pretreatment of the mother rats with wolfberry significantly prevented the prenatal stress-induced cognitive dysfunction. *In vitro* studies showed that wolfberry dose-dependently scavenged hydroxyl and superoxide radicals (determined by an electron spin resonance spectrometric assay), and inhibited $FeCl_2$/ascorbic acid-induced dysfunction in brain tissue and tissue mitochondria, including increases in reactive oxygen species and lipid peroxidation and decreases in the activities of complex I, complex II, and glutamate cysteine ligase. These results suggest that dietary supplementation with wolfberry may be an effective strategy for preventing the brain oxidative mitochondrial damage and cognitive dysfunction associated with prenatal stress.

Amagase et al. (2009) investigated the effects of *Lycium barbarum* preparation standardized for polysaccharide content in a 30-day randomized, double-blind, placebo-controlled clinical study[106]. The study population included 50 Chinese healthy adults aged 55 to 72 years. *In vivo* antioxidant markers, consisting of serum levels of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and lipid peroxidation (indicated by decreased levels of malondialdehyde, MDA) were examined preintervention and postintervention with the extract or placebo (120 mL/d). In the treatment group, antioxidant markers significantly increased by 8.4% for SOD and 9.9% for GSH-Px between the preintervention and postintervention measurements, whereas MDA were significantly decreased by 8.7%. In addition, the SOD, GSH-Px, and MDA levels in the treatment group were significantly different from those in the placebo group at the postintervention time point, with increases of 8.1% and 9.0% and a decrease of 6.0%, respectively. No significant differences were detected between the preintervention and postintervention time points in the placebo group. These results indicate that *Goji* increased antioxidant efficacies in humans by stimulating endogenous factors and suggest that continued use beyond 30 days might help prevent or reduce free radical-related conditions.

Cuscuta chinensis* and *C. australis: Lin et al. (2003) analyzed the effects of immune enhancement, anti-fatigue and anoxia tolerance on mice of four kinds of dodder seeds[107]. All four kinds of dodder seeds enhanced the phagocytosis of macrophage of mice and increased the weights of thymus and spleen of immature mice. They prolonged the survival time of stressed mice in the swimming test and lacking oxygen. *Cuscuta chinensis* Lam. and *C. australis* R. Br. had better effects than the other two kinds, and the water extracts had better effects than alcohol extracts. The authors speculated that the polysaccharide in seeds could be responsible for these effects.

Ligustrum lucidum: *Nuzhenzi*, the fruit of *Ligustrum lucidum* Ait. (Oleaceae) is commonly used as tonic for kidney and liver. Lin et al. (2007) investigated the antioxidant activities of ethanol extract of *Ligustrum lucidum* fruits (ELL) and its effects on butylated hydroxytoluene (BHT)-induced oxidative stress in rats[108]. Results showed that ELL possesses weak antioxidant activities. Compared to the BHT (1000 mg/kg)-treated group, results showed that ELL at 250, 500 and 1000 mg/kg significantly reduced the levels of blood urea nitrogen (BUN), serum glutamic pyruvic transaminase (sGPT), glutamic oxaloacetic transaminase (sGOT), alkaline phosphatase (sALP), lactate dehydrogenase (LDH), triglyceride (TG) and creatinine (Cr), as well as LDH in bronchoalveolar lavage fluid (BALF). It also significantly decreased the level of lipid peroxides in liver and lung. In addition, ELL significantly enhanced the levels of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in these organs. Histopathological evaluation of the tissues revealed that ELL reduced the incidence of lung lesions, while the liver and kidney tissues were not affected by BHT administration. Taken together, the protective effect of ELL against acute BHT-induced oxidative stress in rats could be through the upregulation of antioxidant enzymes.

Panax ginseng: *Ginseng* is a herbal medicine in widespread use throughout the world. Its effect on the brain and nervous system has been investigated. It has been suggested, on the basis of both laboratory and clinical studies, that it may have beneficial effects on cognitive performance. An overview of the published clinicalstudies shows contradictory results. Therefore definitive conclusions may not be drawn at present.

Lee et al. (2009) assessed the clinical evidence for or against ginseng as a treatment for Alzheimer's disease (AD)[109]. Two

randomized clinical trials met all inclusion criteria. They assessed the effectiveness of ginseng as an adjunct to drug therapy on cognitive function compared with conventional drug therapy. Their results suggested significant effect in favor of *ginseng* on the Mini-Mental Status Examination (n = 174, weight mean difference (WMD), 1.85) and on the Alzheimer's Disease Assessment Scale (ADAS)-cognitive (n = 174, WMD, 3.09). Both of these studies are burdened with serious methodological limitations. Therefore, the evidence for *ginseng* as a treatment of AD is scarce and inconclusive.

Geng et al (2010) evaluate the efficacy and adverse effects of *ginseng* given to improve cognitive performance in healthy participants, participants with cognitive impairment or dementia. To highlight the quality and quantity of research evidence available. All double-blind and single-blind randomized, placebo controlled trials assessing the effects of *ginseng* on cognitive function were eligible for inclusion. Interventions were considered to be *ginseng*, if they were compounds containing ginseng or active agents of the *Panax* genus as the major component. Nine randomized, double-blind, placebo controlled trials meeting the inclusion criteria were identified. Eight trials enrolled healthy participants, and one was of subjects with age-associated memory impairment (AAMI). Only five of the identified trials had extractable information and were included in the analysis. Four studies investigated the effects of *ginseng* extract and one assessed the efficacy of *ginseng* compound HT008-1. All of these trials investigated the effects of *ginseng* on healthy participants. Pooling the data was impossible owing to heterogeneity in outcome measures, trial duration, and *ginseng* dosage. Results of the analysis suggested improvement of some aspects of cognitive function, behavior and quality of life. No serious adverse events associated with *ginseng* were found. The authors concluded that there is a lack of convincing evidence to show a cognitive enhancing effect of *Panax ginseng* in healthy participants and no high quality evidence about its efficacy in patients with dementia. Randomized, double-blind, placebo-controlled, parallel group trials with large sample sizes are needed to further investigate the effect of *ginseng* on cognition in different populations, including dementia patients.

A systematic review of randomized controlled trials in patients with chronic fatigue syndrome (CFS), also termed myalgic encephalomyelitis (ME) was undertaken by Alraek et al. (2011) to summarize the existing evidence from randomized controlled trials (RCTs) of CAM treatments in this patient population[110]. All RCTs of any type of complementary and alternative medicine (CAM) used for treating CFS were included, with the exception of acupuncture and complex herbal medicines; studies were included regardless of blinding. Controlled clinical trials, uncontrolled observational studies, and case studies were excluded. A total of 26 RCTs, which included 3,273 participants, met our inclusion criteria. The CAM therapy from the RCTs included the following: mind-body medicine, distant healing, massage, *tuina* and *tai chi*, homeopathy, *ginseng*, and dietary supplementation. Studies of *qigong*, massage and *tuina* were demonstrated to have positive effects, whereas distant healing failed to do so. Compared with placebo, homeopathy also had insufficient evidence of symptom improvement in CFS. Seventeen studies tested supplements for CFS. Most of the supplements failed to show beneficial effects for CFS, with the exception of NADH and magnesium. The results of this systematic review provide limited evidence for the effectiveness of CAM therapy in relieving symptoms of CFS. However, the authors were not able to draw firm conclusions concerning CAM therapy for CFS due to the limited number of RCTs for each therapy, the small sample size of each study and the high risk of bias in these trials.

Ginkgo biloba: The semen of the maidenhair tree, *Ginkgo biloba*, have long been used in China as a traditional medicine for various disorders, including phlegmatic dyspnea, cough, leukorrhagia and enuresis. However, the current literature reported that the leaves are active against memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. We are aware that the use of leaves does not correlate with the traditional use, we discuss their phytotherapeutical utility in modern Chinese medicine nowadays. The benefit of *Ginkgo biloba* has been discussed controversially.

The *Ginkgo biloba* extract EGb 761 interferes with pathomechanisms relevant to dementia, such as Abeta aggregation, mitochondrial dysfunction, insulin resistance, and hypoperfusion. The efficacy of EGb 761 in the treatment of dementia (Alzheimer's disease and vascular dementia) has been reviewed by Kasper and Schubert (2009) in 10 randomized, controlled, double-blind clinical trials[111]. In three of the four large trials conducted in accordance with recent recommendations EGb 761 was significantly superior to placebo with respect to cognitive performance and one or more further (global, functional or behavioral) outcomes demonstrating the clinical relevance of the findings. The findings from the six smaller trials are in line with those of the large trials. One trial was inconclusive, but of questionable external validity due to uncommonly rigorous patient selection. Subgroup analyses of this study together with the findings from the most recent clinical trial suggest that EGb 761 may be most beneficial to patients with neuropsychiatric symptoms, who actually constitute the majority of dementia patients. Delay in symptom progression, rates of clinically significant treatment response and numbers needed to treat (NNT) found for EGb 761 are in the same range as those reported for cholinesterase inhibitors. In an exploratory trial comparing EGb 761 and donepezil, no statistically significant or clinically relevant differences were seen. Hence, EGb 761 has its place in the treatment of dementia.

To assess the efficacy and safety of *Ginkgo biloba* for dementia or cognitive decline, randomized, double-blind studies, in which extracts of *Ginkgo biloba* at any strength and over any period were compared with placebo for their effects on people with acquired cognitive impairment, including dementia, of any degree of severity were analyzed by Birks et al. (2009) in continuation of a former study published in 2007[112–114]. Thirty-six trials were included, but most were small and of duration less than three months. Nine trials were

of six months duration (2016 patients). These longer trials were the more recent trials and generally were of adequate size, and conducted to a reasonable standard. Most trials tested the same standardized preparation of *Ginkgo biloba*, EGb 761, at different doses, which are classified as high or low. The results from the more recent trials showed inconsistent results for cognition, activities of daily living, mood, depression and carer burden. Of the four most recent trials to report results three found no difference between *Ginkgo biloba* and placebo, and one found very large treatment effects in favor of *Ginkgo biloba*. There are no significant differences between *Ginkgo biloba* and placebo in the proportion of participants experiencing adverse events. A subgroup analysis including only patients diagnosed with Alzheimer's disease (925 patients from nine trials) also showed no consistent pattern of any benefit associated with *Ginkgo biloba*. The authors concluded that *Ginkgo biloba* appeared to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that *Ginkgo biloba* has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.

The meta-analyses of Birks et al. remained not without contradiction. Bornhöft et al. (2008) stated that the reason for such the moderate interpretation of Birks and colleagues may lie in the preference of internal validity such as randomization and blinding, sometimes at the expense of external validity (conditions of everyday practice)[115]. Therefore, Bornhöft et al. (2008) re-analyzed the clinical trials evaluated by an earlier meta-analysis of Birks et al. from the year 2002 in the light of the following questions: 1) To what extent are criteria of external validity considered? 2) Does the additional evaluation of external validity lead to differences in the estimation of efficacy? 3) What are the results of our analysis in regard to the efficacy of *Ginkgo biloba* extract? The criteria for evaluating external validity were developed by consulting physicians specialized in geriatrics, experts in herbal pharmaceutics and affected/ related individuals (patients and relatives). Thirty-four placebo-controlled clinical trials with a total of 37 comparisons were re-analyzed. Twenty-one trials showed significant results in favor of the *Ginkgo* application in more than 50% of investigated outcome parameters, eight were significant for less than 50% of the parameters, four showed a trend in favor of *Ginkgo*, and only two studies (with four comparisons) found no advantage for *Ginkgo*. None of the studies considered all criteria of external validity. Out of the seven studies with relatively high external validity and good overall quality, five showed a significant result in more than 50% of parameters, two in ≤50%. Severe adverse effects were not mentioned in the studies. The authors concluded that sufficient evidence of the efficacy of *Ginkgo biloba* extracts in the treatment of dementia of vascular origin and Alzheimer disease was provided in spite of methodological limitations.

Weinmann et al. (2010) performed a meta-analysis of the effects of *Ginkgo biloba* in Alzheimer's disease as well as vascular and mixed dementia covering a variety of outcome domains[116]. Nine trials using the standardized extract EGb761(R) met the inclusion criteria. Trials were of 12 to 52 weeks duration and included 2372 patients in total. In the meta-analysis, the standardized mean differences (SMDs) in change scores for cognition were in favor of *Ginkgo* compared to placebo, but did not show a statistically significant difference from placebo for activities in daily living (ADLs). Heterogeneity among studies was high. For the Alzheimer subgroup, the SMDs for ADLs and cognition outcomes were larger than for the whole group of dementias with statistical superiority for *Ginkgo* also for ADL outcomes. Drop-out rates and side effects did not differ between *Ginkgo* and placebo. No consistent results were available for quality of life and neuropsychiatric symptoms, possibly due to the heterogeneity of the study populations. In conclusion, *Ginkgo biloba* appeared more effective than placebo. Effect sizes were moderate, while clinical relevance is, similar to other dementia drugs, difficult to determine.

Discussion

Tonification is a central issue in CM, as it restores the balance of the human body and thereby prevents the development of diseases and treats existing diseases. The sophisticated CM theory and the rich Chinese flora led to a plethora of herbal formulas for body and organ tonifying. The large assortment of single herbs and complex recipes reflects the wide diversity of practical use of CM doctors, which mostly depends on their personal knowledge and experience. On the other hand, the use of herbs may also depend on the availability of plants, which may vary from province to province.

Based on the millennia-old tradition, enormous efforts have been undertaken during the past two decades to investigate the scientific basis of this experience-based knowledge of CM. Although some researchers may have the improvement of old formulas in mind, the main value of these investigations is that they provide compelling scientific evidence on the efficacy and safety of CM formulas. For CM doctors deeply rooted in the Chinese tradition this might be elusive, since modern herbs only confirm what is already known since ages and CM cannot be further improved. Although this opinion may be justified, the scientific confirmation of traditional Chinese herbal medicine has more far-reaching implications. China has opend its borders and Chinese culrure spreads all over the world. The acceptance of CM in the Western world will be much higher, if the efficacy can be demonstrated by methods of western medicine.

In a sense, the Chinese *yin* (traditional Chinese herbal medicine) and the western *yang* (scientific Chinese herbal medicine) may serve as a metapjer to illustrate that these two different cultures can complement each other for the sake of patients in East and West and everywhere on this globe.

Acknowledgments

This work has been funded by the Deutsche Forschungsgemeinschaft, grant 2015/1 (GRK“Life Science-Life Writing”).

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