Chapter 16
Advances in Chinese Herbal Medicine for Rheumatoid Arthritis: Clinical Utilization and Efficacy, Mechanism of Action, and Safety

Xia Mao, Qiuyan Guo, Aiping Lu, Yanqiong Zhang, and Na Lin

Abstract Rheumatoid arthritis (RA) is a debilitating, systemic autoimmune disease that affects people around the world. The disease is characterized by chronic inflammation of the joints, which eventually results in cartilage and bone damage. An increasing number of patients with RA worldwide are seeking help from complementary and alternative medicine (CAM) to alleviate the severity of the disease and to improve physical conditions. Among these treatments, traditional Chinese medicine (TCM) is regarded as a powerful treatment option, and it has been used for RA therapy for thousands of years in China. TCM is characterized by a holistic theory that emphasizes maintaining the balance of the patient's whole body using Chinese herbal medicines (CHMs) with multiple bioactive ingredients. Some studies have revealed that many antiarthritic CHMs may exert anti-inflammatory and immunomodulatory effects by regulating the production of pro-inflammatory cytokines and immuno-related pathways. However, the precise molecular mechanisms underlying the anti-RA activities of CHMs have not been fully elucidated. Moreover, safety issues have also blocked the development of CHMs; therefore, it is of great significance for clinicians, researchers, and pharmaceutical companies to share responsibility by regulating the clinical use of CHMs, strengthening the basic toxicology research, and establishing a strict quality control system to ensure the safe use of CHMs and decrease the number of toxic cases. The present chapter illustrates the clinical utilization of CHMs acting on RA, elucidates their mechanisms of action, analyzes their limitations and problems, and discusses their development and application prospects.

Keywords Chinese herbal medicine • Clinical utilization • Molecular mechanism rheumatoid arthritis • Traditional Chinese medicine

X. Mao • Q. Guo • Y. Zhang (✉) • N. Lin (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: yqzhang@icmm.ac.cn; linna888@163.com

A. Lu
School of Chinese Medicine, Hong Kong Baptist University, Kowloon, Hong Kong

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Abbreviations

BGD	Baihu Guizhi decoction
CAM	Complementary and alternative medicine
CHMs	Chinese herbal medicines
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
DJD	Duhuo Jisheng decoction
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
FHD	Fangji Huangqi decoction
FLS	Fibroblast-like synoviocytes
GSZD	Guizhi Shaoyao Zhimu decoction
HLXL	Huo-Luo-Xiao-Ling Dan
IL	Interleukin
iNOS	Inducible nitric oxide synthase
JNK	Jun N-terminal kinases
MAPKs	Mitogen-activated protein kinases
MMPs	Matrix metalloproteinases
MTX	Methotrexate
NF-kB	Nuclear transcription-kB
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
OPG	Osteoprotegerin
PGE2	Prostaglandin E2
RA	Rheumatoid arthritis
RANK	Receptor activator of NF-kB
RANKL	Receptor activator of NF-kB ligand
SIN	Sinomenine
TCM	Traditional Chinese medicine
TGP	Total glucosides of paeony
TIMPs	Tissue inhibitor of metalloproteinases
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRAF	TNF receptor-associated factor
TRP	Transient receptor potential
TRPA	TRP ankyrin type 1
TRPM8	TRP melastatin type 8
TRPV1	TRP vanilloid type 1
TS	Total saponin
TSW3	Triterpenoid saponin W3
TWHF	*Tripterygium wilfordii* Hook F
VEGF	Vascular endothelial growth factor
WLY	Wen Luo Yin

WTD Wutou decoction
YLB Yi Shen Juan Bi pill

16.1 Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology. The overall prevalence of RA is approximately 0.5–1 % worldwide (Gibofsky 2014). Substantial variation existed regarding the incidence and prevalence of RA, implying its dynamic characteristic of the epidemiology (Gabriel and Michaud 2009), which is also a reflection of a well-accepted hypothesis that RA is caused by an environmental exposure or "trigger" in individuals who are genetically susceptible (Gibofsky 2012a). RA is manifested by synovial inflammation, insidious pain, morning stiffness, and joint swelling. It could result in erosion of the cartilage and bone and eventually cause joint deformity (Doan and Massarotti 2005). Moreover, patients with RA are more likely to suffer from myocardial infarction, atherosclerosis, stroke, and other complications (Avina-Zubieta et al. 2008), and they also tend to suffer from disability without appropriate and regular treatment. The management of RA should be commensurate with the characteristics and degree of the disease, which demands an integrated approach including both rheumatologists and orthopedic surgeons (Longo et al. 2015). Currently, the therapeutic strategies for the treatment of RA can be mainly divided into two categories. One category contains disease-modifying antirheumatic drugs (DMARDs), which consist of conventional DMARDs, including leflunomide, methotrexate (MTX), and sulfasalazine (Gibofsky 2012a). Extensive clinical experience has indicated that compared to leflunomide, the application of MTX, the "anchor" DMARD, may improve a patients' ability to remain on long-term therapy (Donahue et al. 2012). The second category contains biological agents, including tumor necrosis factor (TNF) inhibitors and non-TNF biologics (abatacept, rituximab, tocilizumab), which target the underlying pathophysiology of the disease and may alter disease progression (Gibofsky 2012b). Although these remedies have benefited many RA patients, their poor efficacies, high prices, and adverse effects are of common concern (Li et al. 2015a). Currently, an increasing number of RA patients have been seeking help from complementary and alternative medicine (CAM) for the alleviation of severe diseases and improvement of physical conditions.

Traditional Chinese medicine (TCM), which is based on empirical applications of experience from thousands of years, has become a crucial component of the modern medical system and has been extensively used as CAM in clinical practice. TCM is characterized by a holistic theory, which emphasizes maintaining the balance of the patients' whole body using Chinese herbal medicines (CHMs) that consist of multiple bioactive ingredients based on syndrome (ZHENG in Chinese) differentiation (Li et al. 2015b; Zhang et al. 2010). According to the theory of TCM, RA is an impediment disease ("Bi" syndrome), which is a group of diseases caused

by the invasion of wind, cold, dampness, or heat pathogen into the human body (He et al. 2014). Compared to western medicine, CHMs excel in their lower prices, higher security, and feasibility of long-term administration (Jiang et al. 2012). Regarding the administration, CHMs used in clinics are usually classified into drugs for external use, such as CHM bath, acupoint application therapy, and ion introduction, and for internal use, such as single herbs, herbal formulae, and Chinese patent medicines (Qi et al. 2010). These have been regarded as indispensable strategies to alleviate the conditions and to enhance the life quality of RA patients.

The present chapter illustrates the clinical utilization of CHMs for RA, elucidates their mechanisms of action, analyzes their limitations and problems, and discusses their development and application prospects.

16.2 Clinical Utilization and Efficacy of CHMs in the Treatment of RA

TCM has been applied in the treatment of RA since ancient times in China. Several pathological factors, including weakness, the insufficiency of vital qi, and the invasion of cold and dampness, are always related to RA (Liu and Liu 2011). TCM practitioners determine the appropriate therapeutic schedules based on the categorization of patients through syndrome differentiation, such as a hot pattern, cold pattern, and deficiency pattern (Yuan et al. 2015). Moreover, the anti-inflammatory and antiarthritic activities of multiple CHMs applied in the treatment of RA have been proven through animal experiments and clinical trials (Venkatesha et al. 2011). In this section, we would like to illustrate the clinical utilizations and efficacies of CHMs in the treatment of RA.

16.2.1 Application of CHMs for External Use in the Treatment of RA

16.2.1.1 CHM Bath

A CHM bath is an ancient therapeutic approach in RA therapy and has been regarded as a supplementary method to assist with conventional therapeutic strategies, such as medications, acupuncture, etc., to enhance their therapeutic effectiveness. A CHM bath is a combination of heat therapy and medication, that is, to immerse the whole body or limbs of RA patients in a CHM soup, which exerts antiarthritic effects by dilating the capillaries in the skin and subcutaneous tissues, accelerating blood circulation, and improving drug absorption and infiltration into the lesion site. Moreover, when patients are soaking in the CHM liquid, their active or passive exercises may contribute to the improvement of their physical functions (Li 2001). In TCM theory, CHM baths can expel evil wind, remove dampness, and disperse

cold by warming the meridians, which coincides well with the pathogenesis of RA (Zhu et al. 2011). Clinically, there are no fixed formulae for CHM baths. Clinicians make prescriptions according to the physical condition and disease severity of the RA patients. Herbs that have functions of dispelling wind and dampness, stimulating blood circulation, removing blood stasis, and causing muscle and joint relaxation are frequently used (Li 2001). Among them, *Carthami flos* (Honghua), *Angelicae pubescentis* Radix (Duhuo), *Lonicerae japonicae* Caulis (Rendongteng), and *Salviae miltiorrhizae* Radix et Rhizoma (Danshen) are representative herbs (Zhu et al. 2011). Interestingly, growing evidence shows that CHM baths can improve patients' joint function and quality of life and enhance the efficiency of conventional medical treatment in combined applications (Christie et al. 2007). However, although there are no obvious toxicities or side effects, patients suffering from dermatosis, acute inflammation, malignant tumors, severe cardiac insufficiency, and hypertension should avoid CHM baths (Li 2001).

16.2.1.2 Acupoint Application Therapy

Acupoint application therapy prevents and treats diseases under the guidance of a unique theory of TCM, the so-called preventive treatment of diseases. This therapy is performed by applying a mixed herbal cone cake into acupoints on the human body (Yang et al. 2015), and it has been well accepted by RA patients both alone and in combination with other therapies.

Clinically, Qubi analgesic gel paste acupoint application, midnight-noon ebb-flow acupoint application, and Leima adhesive plaster are the three most common therapeutic strategies in the treatment of RA, and they can improve the patients' balance ability and achieve good therapeutic effects (Wang et al. 2013; Gao et al. 2013). Moreover, Chinese herbs such as *Aconite radix* (Chuanwu), *Sinomenii caulis* (Qingfengteng), Moschus (Shexiang), and *Carthami flos* (Honghua) that can dispel wind and dampness can activate blood circulation and remove stasis and are frequently applied to produce herbal cone cakes and act on Dazhui, Tsusanli, Waiguan, Yangliquan, and other related acupoints (Du et al. 2013). It has been shown that acupuncture combined with the acupoint application of CHMs may improve immunologic function, enhance the physical conditions of RA patients, and achieve better therapeutic effects than the sole application of acupuncture (Chen et al. 2014).

16.2.1.3 Ion Introduction of CHM

Ion introduction of CHM electrically transports ionic particles into tissues through the skin by the application of certain devices (Kim et al. 2009). This technique can be used not only to deliver molecules into the body but also to monitor drugs and biomarkers in the clinical environment (Sieg and Wascotte 2009). Ion introduction serves as a complementary therapy in the treatment of many diseases, such as

topical anesthesia, endodontics, and temporomandibular joint disorders (Girenes and Ulusu 2014).

Ion introduction of CHM is often applied in combination with other therapies, including conventional medical treatments and acupuncture, in RA therapy. According to TCM theory, the obstruction may cause pain. Chinese medicinal herbs that can promote blood circulation, remove blood stasis, dispel the wind, remove meridian obstructions, dispel cold, and remove dampness are often combined with certain devices to deliver the active ingredients of the herbs deeper into the joints and to achieve better efficacy (Zhang 2002). Growing clinical evidence has shown that ion introduction of CHM may accelerate the functional recovery of RA patients and enhance the therapeutic efficacy of CHM with little side effects (Zhang et al. 2011). However, this therapy is not suitable for patients suffering from severe heart disease, active tuberculosis, hyperpyrexia, and bleeding disorders (Fan and Xia 2007).

16.2.2 Application of CHMs for Internal Use in the Treatment of RA

16.2.2.1 Extracts of CHM Administration

In recent years, numerous studies have been conducted to investigate the prominent active components contained in Chinese medicinal herbs, following that extracts of CHMs have received more popularity due to its better efficacy and fewer adverse effects with the development of pharmaceutical technology. The detailed information about these herbs is provided below.

Tripterygium wilfordii Hook F (TWHF), also known as "Lei Gong Teng" in China, have been widely applied in the treatment of several autoimmune and inflammatory diseases such as ankylosing spondylitis, psoriasis, and especially RA. It has been reported that its ethanol/ethyl acetate extract and chloroform-methanol extract could maximize therapeutic benefit and minimize toxicity (Bao and Dai 2011). Clinical trials assessed by the attainment of ACR20 response criteria had proven that TWHF extract administration resulted in greater therapeutic efficacy than a conventionally used western drug, sulfasalazine, when the treatment for RA lasted for more than 24 weeks (Goldbach-Mansky et al. 2009). Moreover, during a 6-month study, the treatment with ethanol/ethyl alcohol extract (180 mg/day) of TWHF could significantly improve the clinical signs and syndromes of RA patients, such as joint pain, joint swelling, overall well-being as well as in several indicators of inflammation including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and pro-inflammatory cytokine interleukin (IL)-6, suggesting great enhancement in active RA achieved by TWHF extracts (Macfarlane et al. 2011). In recent years, several bioactive ingredients extracted from TWHF have been further prepared into capsules, pellets, and powders for the treatment of RA (Lv et al. 2015),

including *Tripterygium wilfordii* tablets, tripterygium glycoside tablets, and triptolide tablets, all of which have been extensively applied in clinics for RA therapy.

Sinomenii caulis (Qingfengteng), recorded by the Chinese Pharmacopoeia 2005 (Anonymous 2005), is an ancient Chinese medicinal herb and has been utilized to treat rheumatic diseases for more than a thousand years. It contains many active alkaloids, among which sinomenine (SIN) has been proved to be predominant in anti-inflammatory, antirheumatic, as well as immunosuppressive effects (Zhao et al. 2005). SIN preparation has been recorded in drug standard set by the Chinese Health Ministry and has been widely used in RA therapy in clinics (Chinese Pharmacopoeia 2005). Studies have been performed to compare the efficacy of SIN preparation with those of nonsteroidal anti-inflammatory drugs (NSAIDs). It has been indicated that SIN treatments could be more desirable regarding the total cases of RA patients whose clinical manifestations were significantly enhanced than NSAIDs. Moreover, SIN preparations possess better efficacy in improving the major syndromes of RA such as morning stiffness, joint pain, and swelling and clinical indicators of RA including ESR and CRP with dermato-mucosal adverse effects, which could be completely under the control by antihistamine reagents (Xu et al. 2008). SIN preparations are valuable remedies to treat RA in clinics.

Total glucosides of paeony (TGP) is composed of active components obtained from the roots of a conventional Chinese medicinal herb named *Paeoniae radix* Aiba (Baishao). It has been approved by the State Food and Drug Administration of China as a disease-modifying drug since 1998 and has been utilized in the treatment of RA for centuries (He and Dai 2011). In clinics, it is frequently applied in combination with MTX or leflunomide. It has been indicated that this combination remedy could greatly improve the registered indexes of RA patients such as the time of morning stiffness, the number of swelling joints, grip strength, ESR, CRP, and blood rheumatoid factor when the treatment lasted for 8 weeks (Zhang et al. 2007). Moreover, patients in combination therapy could achieve a better European League against rheumatism response than the sole application of western medicine, and the addition of TGP could significantly alleviate the severe hepatotoxicity resulting from MTX or leflunomide, observed in RA patients who have received therapy for 12 weeks (Chen et al. 2013).

16.2.2.2 Chinese Patent Medicine

Chinese patent medicine refers to CHMs made in the forms of pills, pulvis, emplastrum and unguentum, pellets and capsules, etc., which have the characteristics of being convenient to carry and store and have been regarded as the "essence" of TCM (Gao et al. 2014). In the clinical setting, Chinese patent medicines, such as the Xinfeng capsules, Simiao pills, Yi Shen Juan Bi pill (YLB), and Biqi capsule, are frequently used in the treatment of RA (Zhang et al. 2010).

The Xinfeng capsule is an extensively used commercial antiarthritic Chinese patent medicine and is composed of several herbs, including *Astragali radix* (Huangqi), *Coicis semen* (Yiyiren), TWHF, *Scolopendra* (Wugong), etc., which can invigorate

the function of the spleen and resolve dampness. Clinical trials have proved that it could significantly reduce the total score of pain and swelling in involved joints and the level of uric acid and high-sensitivity CRP and also improve RA disease activity index and serum iron reserve (Huang et al. 2013a, b). Also, it has been found to exert amelioration effects in the abarticular pathologic changes in patients with active RA (Liu et al. 2014), indicating that it is a reliable therapeutic remedy.

The Simiao pill, consisting of *Phellodendri chinensis* Cortex (Huangbo), *Atractylodis rhizoma* (Cangzhu), *Achyranthis bidentatae* Radix (Niuqi), and *Coicis semen* (Yiyiren), is a well-known Chinese patent medicine for the treatment of RA with a precise compatibility. In clinics, modified Simiao pills are widely used for accurate individual RA therapies according to the syndromes and signs of RA patients. It has been demonstrated that modified Simiao pill could greatly improve the index of blood uric acid, blood leukocyte count, score of clinical symptoms, etc., and also has been proved to exert a better therapeutic efficacy than western medicine such as MTX with the advantages of low prices and readily availability (Zhao et al. 2013), indicating that it is a promising formula in clinics.

YLB is the pill form of a formula that was first prepared by the National TCM master Zhu Liangchun, and it is composed of 20 herbs including *Zaocys* (Wushaoshe), *Scorpio* (Quanxie), *Scolopendra* (Wugong), and *Corydalis rhizoma* (Yanhusuo), which can expel evil wind and remove dampness. It has been proven to have superior efficacy in the treatment of RA patients with kidney deficiency patterns (Zhou et al. 2007). Clinical trials have demonstrated that YLB could achieve more improvement on life quality and syndromes of RA patients such as arthralgia, joint pain, and joint tenderness than MTX and sulfasalazine after 24-week treatment although with relatively lower ACR20 and ACR50 responses (He et al. 2008).

Biqi capsule is composed of several traditional Chinese medicinal herbs such as *Codonopsis radix* (Dangshen), *Astragali radix* (Huangqi), and *Salviae miltiorrhizae* Radix et Rhizoma (Danshen) and has become an important Chinese patent drug for RA therapy in clinics. Studies have shown that Biqi capsule possesses favorable therapeutic outcomes especially for RA patients with qi deficiency and blood stasis syndrome including alleviating the degree of joint pain, the tender joint number, and the swollen joint number and shortening the morning stiffness time with no obvious adverse reaction (Liu et al. 2006). Moreover, its combination use with western medicine such as MTX showed better clinical efficacy than the application of Biqi capsule and MTX alone, indicating that it could be regarded as an effective treatment program for RA (Jie et al. 2012).

16.2.2.3 TCM Herbal Formulae

The administration of TCM herbal formulae, which are complex mixtures of herbs with multiple bioactive ingredients, is a notable feature of treatment based on holistic principles. The increased efficacy and decreased toxicity of TCM herbal formulae may arise as a result of complex synergistic or antagonistic interactions among different formula components, which meet the requirements of complex disease

treatment in a systematic manner (Mao et al. 2015). Regarding the RA treatment, several classic TCM herbal formulae, such as Fangji Huangqi decoction (FHD), Wutou decoction (WTD), Guizhi Shaoyao Zhimu decoction (GSZD), Baihu Guizhi decoction (BGD), and Duhuo Jisheng decoction (DJD), have been extensively used for thousands of years (Liu and Liu 2011). Also, proved recipes prescribed by experienced clinicians have also obtained much recognition due to their satisfactory therapeutic effects. In clinics, the compositions and doses of these formulae are adjusted by clinicians by the syndromes and signs of RA patients.

FHD, composed of *Stephaniae tetrandrae* Radix (Fangji), *Astragali radix* (Huangqi), *Atractylodis macrocephalae* Rhizoma (Baizhu), *Glycyrrhizae radix* et Rhizoma (Gancao), *Zingiberis rhizoma* (Shengjiang), and *Jujubae fructus* (Dazao), is an ancient and effective remedy for the treatment of painful inflammatory disorders, such as RA, as well as the pain and edema caused by abdominal pain. In TCM theory, this remedy can relieve the symptoms of RA patients by replenishing qi to invigorate the spleen and eliminate dampness. Studies have indicated that FHD could significantly shorten the time of morning stiffness, alleviate joint pain, and exert a protective effect on the lung, liver, and kidney, of which mechanisms may be related to peripheral nociceptive pathway such as prostaglandins (Lin et al. 2015). Its components *Stephaniae tetrandrae* Radix (Fangji) and *Astragali radix* (Huangqi) play the most prominent role in this formula.

WTD, originating from the "Synopsis of Golden Chamber" (Chinese name: Jin Gui Yao Lue), is a famous TCM formula for the treatment of RA patients with cold pattern and joint pain with a history of more than a thousand years (Dai et al. 2014). It contains five herbs, including *Aconite radix* (Chuanwu), *Ephedrae herba* (Mahuang), *Astragali radix* (Huangqi), *Paeoniae radix* Aiba (Baishao), and *Glycyrrhizae radix* et Rhizoma (Gancao). In clinics, a prominent effectiveness can be observed when this formula is used for the treatment of RA characterized by an acute onset of severe pain. The formula exerts protective effects against joint destruction, inhibits the swelling of the limbs, and alleviates the severity of the disease. Numerous studies have shown that WTD in a combination of western medicine could enhance the therapeutic efficacy, shorten the treatment course of western medicine, as well as improve the life quality of RA patients in clinics (Hu 2011).

GSZD, originally recorded in the "Synopsis of Golden Chamber," is a classic formula in RA therapy. It comprises the following nine herbs: *Cinnamomi ramulus* (Guizhi), *Paeoniae radix* Aiba (Baishao), *Glycyrrhizae radix* et Rhizoma (Gancao), *Ephedrae herba* (Mahuang), *Zingiberis rhizoma* Recens (Shengjiang), *Atractylodis macrocephalae* Rhizoma (Baizhu), *Anemarrhenae rhizoma* (Zhimu), *Saposhnikoviae radix* (Fangfeng), and *Aconiti lateralis* Radix Preparata (Fuzi). The formula has been regarded as a vital formula in the treatment of chronic RA, which is manifested by joint deformation, body weight loss, dizziness, nausea, vomiting, fatigue, shortness of breath, and pain in multiple joints. Studies have shown that it could significantly alleviate the progression of the disease, improve related indexes such as CRP and ESR, and improve patients' quality of life (Xu et al. 2004).

BGD is another classic formula recorded in the "Synopsis of Golden Chamber" for RA treatment. In contrast to WTD, this remedy is superior to treat RA with the

hot pattern, which is characterized by severe pain with hot, red, and inflamed joints, and the joint pain could be alleviated by applying cold to the joints (Lu et al. 2012). It could significantly alleviate syndromes of RA patients with hot pattern and improve their quality of life.

16.3 Pharmacological Mechanisms of CHMs Acting on RA

TCM, as a comprehensive and unique medical system, has excited worldwide interest. As a major component of TCM, CHMs are characterized by their complex nature. Subsequently, the ingredient profiling and molecular mechanisms of CHMs have not been fully elucidated, despite the considerable efforts made by many research groups. These limitations have hindered the application of CHMs in mainstream medicine and the modernization of TCM (Cooper 2007). In this section, we focus on the recent progress in elucidating the underlying mechanisms of CHMs acting on RA.

TWHF has an established history of its application in the treatment of RA. It has been proven to contain more than 70 components. Among them, tripdiolide, triptonide, and triptolide have been reported to exert the immunomodulatory and anti-inflammatory effects validated in both in vitro and in vivo studies (Qiu and Kao 2003). For instance, triptolide functions as an anti-inflammatory agent by inhibiting the production of nitric oxide (NO) and the expression of inducible nitric oxide synthase (iNOS), which lead to the inhibition of nuclear transcription-kB (NF-kB) and Jun N-terminal kinase (JNK) activation, TNF-α-induced cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) production, as well as lymphocyte proliferation (Wang et al. 2004; Zhang et al. 2004; Shao et al. 2004). Then, triptolide may play a protective role on cartilage by interfering with collagen-induced arthritis augmented expression of key enzymes including matrix metalloproteinases (MMPs)-13 and MMPs-3 in the pathological changes of cartilage (Lin et al. 2007). Also, its inhibitory effects on proMMPs-1 and proMMPs-3 and the simultaneous upregulation of tissue inhibitor of metalloproteinases (TIMPs) in IL-1 – treated synovial fibroblasts – may also contribute to the protective role of triptolide on cartilage (Lin et al. 2001). As one of the vital manifestations during RA progression, focal bone destruction within affected joints often severely influences the quality of patients' life. A recent study of Liu et al. has indicated that triptolide may attenuate bone destruction in RA partially by regulating receptor activator of NF-kB ligand/receptor activator of NF-kB/osteoprotegerin (RANKL/RANK/OPG) signal pathway to inhibit osteoclast formation (Liu et al. 2013a, b, c). The authors also indicated that triptolide might exert therapeutic effects on angiogenesis, an essential event in the development of RA, by the downregulation of angiogenic activators and the inhibition of mitogen-activated protein kinase downstream signal pathway activation (Kong et al. 2013). Moreover, Lu et al. found that triptolide could effectively inhibit the bioactivity of IL-18 and its receptor in phorbol 12-myristate 13-acetate-stimulated

RA synovial fibroblasts, highlighting a potential mechanism in RA therapy (Lu et al. 2008).

In addition to triptolide, celastrol is another single compound derived from TWHF with anti-inflammatory and bone protection properties. A recent study has reported that celastrol may directly inhibit the formation and function of osteoclast and be used as a novel medication management of RA in preventing bone destruction (Gan et al. 2015). Li et al. also found that celastrol could suppress the migration and invasion of fibroblast-like synoviocytes (FLS) by inhibiting Toll-like receptor (TLR) 4/NF-kB-mediated MMP-9 expression (Li et al. 2013a, b).

SIN is an alkaloid isolated from the stem of Chinese medicinal plant named *Sinomenii caulis* (Qingfengteng) and has been extensively used to treat RA diseases in China and Japan (Xu et al. 2008). Growing evidence show the anti-inflammatory and arthritis amelioration effects of SIN (Liu et al. 2005). For example, the administration of SIN could suppress inflammation response and joint destruction by targeting myeloid differentiation primary response protein 88 signaling (Mu et al. 2013). SIN could attenuate the formation of osteoclast and *M. tuberculosis* H37Ra-induced bone loss by mediating RANKL signaling pathways (Li et al. 2013). SIN exerts the inhibitory effects on cell invasion and migration abilities in a concentration-dependent manner by suppressing the expression of CD147, MMP-2, and MMP-9 in activated human monocytic THP-1 cells (Ou et al. 2011).

TGP, derived from the root of a Chinese herb *Paeoniae radix* Aiba (Baishao), contains more than 90 % paeoniflorin and has received wide popularities in China, Korea, and Japan due to its prominent anti-inflammatory, hepatoprotective, and immunomodulatory effects in the treatment of RA (Chang et al. 2009). It has been proved that TPG exerts anti-inflammatory effects through inhibiting the production of inflammatory mediators and chemokines and leukocyte migration. Also, TGP ameliorates synovitis, a major pathological change occurred in RA patients, by regulating the balance of differentiation and function of Th1/Th2 cells and secretion of pro-inflammatory cytokines originated from lymphocytes, macrophages, and FLS (He and Dai 2011). Notably, TGP also exerts protective effects on joint destruction by reducing the secretion of cartilage degradation enzymes MMPs including MMP-1 and MMP-3, which mainly account for the degradation of cartilage (Zhang and Dai 2012).

Curcumin, derived from the rhizome of *Curcuma longa L.*, Zingiberaceae, has remarkable pharmacological and biological activities such as anti-inflammation and antioxidation against various chronic diseases, including RA (Recio et al. 2012). It has been indicated that curcumin may possess inhibitory effects on the growth and apoptosis of synovial fibroblasts, which was related to the proteolytic activation of caspase-3 and caspase-9 and modulation of poly(ADP-ribose) polymerase protein. Park et al. demonstrated that curcumin could reduce the expression of COX-2, a type of COX prominently involved in the process of inflammatory, partially by inhibiting PGE2 release (Park et al. 2007). Shakibaei et al. also revealed that curcumin might alleviate or reverse the breakdown of degenerative articular chondrocytes stimulated by IL-1β by antagonizing the activation of caspase-3 and matrix production (Shakibaei et al. 2005). Huang et al. also found the anti-inflammatory

effects of curcumin, which might be associated with its suppression on the NF-kB and inflammatory loop (Huang et al. 2013). Notably, curcumin is frequently used in combination with other medications in RA therapy including resveratrol and MTX to benefit therapeutic efficiencies in clinical practice. For example, the combination of curcumin with resveratrol could antagonize the destruction of human articular chondrocytes in RA patients by activating the extracellular-regulated protein kinase signaling pathway, which might be associated with the differentiation and survival of chondrocyte (Shakibaei et al. 2011). Curcumin could synergistically support the therapy of MTX through its influence on arachidonic acid, thromboxanes, neutrophils, and lymphocytes. Interestingly, curcumin could also circumvent the hematological toxicities induced by MTX via suppressing the delivery of IL and leukotrienes, sufficiently making up this vital deficiency induced by western medicine (Banji et al. 2011).

The dry root of *Anemone flaccida* Fr. Schmidt (Diwu) is extensively used in clinical prescriptions in RA therapy, mainly excelling in anti-inflammatory, healing fractures and benefiting bone destruction (Han et al. 2013). Triterpenoid saponin W3 (TSW3), the major active ingredient in this plant, exerts anti-inflammatory, immunomodulatory, and analgesia effects (Cheng et al. 2008). Osteoclast plays an important role in the pathogenesis of RA and might result in excessive bone resorption within inflamed joints (Tanaka et al. 2001). The studies have indicated that TSW3 could inhibit the RANKL-induced osteoclast differentiation through downregulating the expression of a signaling adaptor molecule TNF receptor-associated factor (TRAF) 6, leading to the activation of mitogen-activated protein kinases (MAPKs) and NF-kB pathways, as well as the downregulation of two osteoclastogenic transcription factors including c-Fos and nuclear factor of activated T cells (Kong et al. 2015a, b). Also, the total saponin (TS) derived from this plant possesses antiarthritic effects and is undergoing the clinical trial in phase III in the treatment of RA (Huang et al. 2014). It has been clarified that the inhibitory effects of TS on the RANKL-induced osteoclast differentiation and bone destruction were mediated by inhibiting TRAF6 expression and suppressing JNK and p38 MAPKs and NF-kB activation. Subsequently, it downregulated the expression of a c-Fos and nuclear factor of activated T cells, which functions similarly in the way of W3 (Kong et al. 2015). Moreover, Liu et al. indicated that TS could attenuate focal and system bone destruction partially by modulating RANKL/RANK/OPG signal pathway, which has been demonstrated to play a crucial role in the process of bone loss and to inhibit the release of pro-osteoclastogenic cytokines (Liu et al. 2015).

Nobiletin, a citrus polymethoxy flavonoid, possesses numerous pharmacological activities including anti-inflammatory against various arthritic diseases. MMPs, the synthesis and secretion of which are mainly mediated by pro-inflammatory cytokines including IL-1, TNF-α, and IL-6, play an essential role in the destruction of matrix components in the pathological process of RA (Woessner 1991). Recent studies have indicated that nobiletin may suppress the secretion of proMMP-1, proMMP-3, and proMMP-9 partially by inhibiting the production of pro-inflammatory cytokines (Lin et al. 2003). Also, nobiletin also exerts inhibitory effects on PGE2 production in human synovial fibroblasts, which is an important

inflammatory mediator due to its upregulation of vascular permeability (Ishiwa et al. 2000). Moreover, nobiletin could prevent cartilage destruction against RA through interfering with the expression of a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS)-4 and ADAMTS-5 (Imada et al. 2008). Murakami et al. proved that nobiletin could inhibit the osteoclastogenesis induced by RANKL possibly by suppressing MAPKs and blocking the differentiation of two key transcription factors including activator protein-1 and NF-kB (Murakami et al. 2007).

WTD is a classic formula for the treatment of RA, especially RA patients with the cold pattern, as previously described (Hu 2011). However, its pharmacological mechanisms have not been fully clarified. Recent studies have indicated that the anti-inflammatory effects of WTD were closely associated with its inhibition of pro-inflammatory cytokines including IL-β and TNF-α and its regulation on the TLR2/TRAF6/Faslg signal pathway (Xu et al. 2010). Accumulating studies have indicated that the pathological process of RA may frequently be accompanied by chronic inflammatory pain (Chiu et al. 2012). Members of the transient receptor potential (TRP) ion channel family especially TRP vanilloid type 1 (TRPV1), TRP ankyrin type 1 (TRPA1), and TRP melastatin type 8 (TRPM8) ion channels are closely involved in the induced inflammatory nociceptive responses (Sousa-Valente et al. 2014). Wang et al. found that WTD could possess antinociceptive property through decreasing mechanical and thermal hypersensitivities, partially resulting from its suppression of the expression of TRPV1, TRPA1, and TRPM8 (Wang et al. 2015). Interestingly, network pharmacology-based approaches have also been used to investigate the underlying mechanisms of WTD. Zhang et al. pointed out that WTD could alleviate RA possibly by reversing the imbalance of the nervous, endocrine, and immune systems, which markedly influence the pathological progression of RA (Zhang et al. 2015).

GSZD excels in the treatment of RA with hot pattern (Xu et al. 2004). An integrative method that combines both network analysis and experimental validation has also been applied to investigate the pharmacological mechanisms of GSZD acting on RA. The authors identified a candidate GSZD-targeted signal axis and found that GSZD plays a role in the treatment of RA partially by regulating inflammation-immune system imbalance (Guo et al. 2016).

Huo Luo Xiao Ling (HLXL) Dan, composed of *Angelicae sinensis* Radix (Danggui), Olibanum (Ruxiang), *Salviae miltiorrhizae* Radix et Rhizoma (Danshen), and *Myrrha* (Moyao), is a well-known herbal formula, and its modified versions have been applied to treat RA (Yu et al. 2013). Pharmacological studies have indicated that HLXL could alleviate the severity of ongoing inflammatory in RA, which might be associated with its alteration in T cells by regulating the antibody response against the RA-associated antigen (the mycobacterial heat-shock protein 65) and the serum level of NO (Yang et al. 2011). HLXL also exerts protective effects against arthritic bone destruction in adjuvant arthritis model, which was mediated by its regulatory effects on the mediators of bone remodeling (Nanjundaiah et al. 2013).

FHD extract possesses antinociceptive, anti-inflammatory, and immune-modulatory activities, some of which was validated in rodents with the acetic acid-induced writhing response, carrageenan-induced edema test, and formalin-induced licking test (Chen 2012). Regarding its antinociceptive effect, a recent study has demonstrated that the pretreatment with FHD extract could decrease acetic acid-induced writhing response and significantly prevent the late phase of formalin-induced licking response (Taber et al. 1969). Also, FHD produces marked antinociceptive activities in a dose-dependent way, which might be associated with the peripheral systems of pain pathway (Lin et al. 2015). Importantly, growing evidence show that almost all herbs in FHD may possess anti-inflammatory effects synergistically by regulating NF-kB, iNOS, and COX-2/prostaglandin pathway and by inhibiting the release of pro-inflammatory cytokines (Lin et al. 2015).

Wen Luo Yin (WLY), originated from the classic formula Guizhi Fuzi decoction and ZhuFu decoction, has been extensively applied in the treatment of RA with a cold pattern in clinics, especially excelling in the RA patients presented by obvious pain. WLY could alleviate pain, inflame joint swelling, and also inhibit the excessive secretion of synoviocytes. These possibly may be due to the decreased number of Golgi apparatus, rough surface endoplasmic reticulum, dense bodies, matrix filaments, and vacuoles, which are involved in the ultrastructures of synoviocytes (Li et al. 2002). Angiogenesis has been considered as an important event in affecting inflammatory and immune responses and further interfering with the pathological process of RA (Thairu et al. 2011). Liu and the group have reported that WLY exerts significant anti-angiogenic effects by suppressing the expression of numerous of angiogenic activators, including TNF-α, IL-1β, IL-17, vascular endothelial growth factor (VEGF), VEGF receptor, angiopoietins, and epidermal growth factor. All these participate in the progression of neovasculature by mutual interaction in the sera of collagen-induced rats in human FLS of RA and human umbilical vein endothelial cells induced by IL-1β, indicating that WLY is a promising therapeutic remedy in RA (Liu et al. 2013).

These previous studies have successfully identified the biological activities and targets of a herb or herbal formula and elucidated their molecular mechanisms for RA treatment. Many research techniques, such as flow cytometry analysis, cell differentiation assays, quantitative real-time PCR, Western blot analysis, cell migration assays, cell proliferation assays, and luciferase assays, have been commonly performed in the experimental studies. With the rapid progress in bioinformatics, system biology, and polypharmacology, network pharmacology has attracted much attention because it can reveal the underlying complex interactions between an herbal formula and cellular proteins, as well as can influence their interactions on the function and behavior of the system. It shifts the “one target, one drug” paradigm to the “network target, multicomponent” strategy (Li et al. 2007). Above all, the combination of the conventional experimental approaches and network pharmacology strategies can provide a powerful means of modern research on TCM in the future.

16.4 Safety and Adverse Effects of CHMs Acting on RA

CHMs perform well in clinical practice and have a bright future in the treatment of RA. However, the safety of CHMs has been a widespread concern due to their complex chemical nature and lack of proper evaluation methods, especially after recent consecutive reports of adverse drug reactions. Because CHMs are often used in humans for an extended period, continuous surveillance of patient safety during CHM treatments may be a convenient and powerful way to detect any potential harm caused by CHM therapy.

HLXL is a TCM formula for the treatment of a variety of immune disorders, including RA. By feeding HLXL to Lewis rats for 6 weeks consecutively, its toxicity was assessed. During the experiments, abnormal behavioral changes and standard manifestations of toxicity were documented (Zhang et al. 2009). Moreover, the blood biochemistry and histopathological variations of the tissues were examined to assess its toxicity. No adverse reactions or toxicity from this formula was observed at normal doses when taking all of the parameters together. Therefore, HLXL is reliable in RA therapy (Yang et al. 2011).

Fuzi (the lateral root of *Aconitum carmichaeli*) is a well-known herb for its bilateral effects, including both effectiveness and toxicity. Aconitine, mesaconitine, and hypaconitine are mainly responsible for its high toxicity. In clinical practice, Fuzi is processed by hydrolyzing toxic components into nontoxic derivatives, resulting in a toxicity reduction (Huang et al. 2007). Studies have been conducted to investigate whether the therapeutic efficacy of Fuzi remains after processing. In adjuvant-induced arthritic rats, it has been proven that processed Fuzi with 120 min decoctions could achieve the same therapeutic efficacy as the products processed for less time (Tong et al. 2013), indicating a non-interdependent relationship between its therapeutic effectiveness and toxicity.

Regarding TWHF, recent studies have reported that the efficacy and toxicity of this CHM are dose dependent (Zhao et al. 2015). The adverse effects of TWHF may be involved in many aspects of human body, such as gastrointestinal tract disturbances, dermatosis, reproductive system malfunction in both males and females, acute hepatotoxicity, and nephrotoxicity (Bao and Dai 2011). It could also lead to the blood system adverse events including the white blood cell decreasing, hemoglobin decreasing, and platelet decreasing (Li et al. 2015c). Triptolide is regarded to be the main contributor to these toxicities. Terpene triptonide and alkaloids in TWHF have been proved to be of no toxicological concern at the dosage of 20-fold of the therapeutic dose. Detoxification of TWHF could be achieved by metabolic eliminations, leading to less reactive metabolites. Moreover, safety issues should be taken into more consideration when it is coadministered with other cyclophosphamide inhibitors or glutathione-depleting agents (Li et al. 2015). TWHF could be a promising drug with the further in-depth investigation of its efficacy and toxicity.

Insect medicine excels in expelling evil wind and removing dampness in RA therapy. *Scorpio*, *centipede*, and *Agkistrodon* are representative insects. However, modern pharmacological studies indicate that homologous proteins such as toxic

protein and histamine-like substance in these insects could exert toxic effects or allergic reactions if not properly used (Li and Liao 2011).

Asarum is a key herb in the treatment of arthrodynia. Volatile oils are its active constituent. The safrole containing in volatile oils could lead to several side effects, such as respiratory paralysis or arrhythmias (Li and Liao 2011).

Given all the issues mentioned above, it is clinically important to harness CHM advantages and bypass the disadvantages. The adverse effects of CHMs can be confined within a reasonable range by appropriate methods such as the standardization of CHM production, CHM processing, proper combination, and correct dose administration based on different pathological conditions. Moreover, the more information we obtain about the safety and adverse events of CHM therapies, the greater the likelihood that physicians trained in conventional medicine will be encouraged to use such medicines. Therefore, further studies are required to generate data and information on the adverse effects of existing CHM therapies for the treatment of RA.

16.5 Perspective

CHMs have been recognized extensively to benefit RA patients due to their efficacies, minimal adverse effects, affordable price, therapeutic effects, and possibility of long-term application. However, the following limitations and issues need our consideration.

First, TCM is characterized by individualized treatment. Clinicians make prescriptions according to the syndromes and signs of patients and classify them into different patterns such as hot pattern, cold pattern, deficiency pattern, etc. It is important to clarify the molecular mechanisms of pattern and CHMs. Gaps in knowledge regarding the characteristics and mechanisms of CHMs acting on different patterns of RA still exist due to the complexities of CHMs and limitations of investigative techniques.

Second, cognized consensus standard regarding the safety of CHMs has not been completed. The efficacy of CHMs against RA has long been based on empiricism. Although the appropriate compatibility of herbs could enhance the therapeutic efficacy and reduce toxicity such as the coadministration of *Bupleuri radix* (Chaihu) and *Pinelliae rhizoma* (Banxia) (Liu et al. 2013a, b, c), its safety cannot be fully guaranteed. The application of several modern research tools, such as gene expression microarrays, proteomics, and biological molecular networks, may shed light on a holistic understanding of CHMs. Thus, offer an interface where CHMs and conventional medicine can find common ground to investigate the mechanisms of action of therapeutic products and to enhance their practical use for the ultimate benefit of the patients (Venkatesha et al. 2011).

Finally, efforts are needed to standardize the safety assessment of CHMs, in-depth toxicity-related studies of CHMs, and safer advanced preparation technology, such as nano-drug delivery and other targeted drug delivery. Also, refinement in

trial-related issues, such as sample size, explicit inclusion/exclusion criteria, consistent standards for assessing the outcome of therapeutic intervention, and proper statistical analysis are other issues for consideration (Efthimiou and Kukar 2010).

Thus, the future studies that combine the routine application of CHMs and advanced technologies will be essential to explore fully the therapeutic effects, mechanisms, and safety of CHMs acting on RA. There is a promise that CHMs may receive increasing therapeutic approvals and may benefit RA patients in a more effective way.

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