Tripterygium wilfordii Inhibiting Angiogenesis for Rheumatoid Arthritis Treatment

Weisan Zhang, M.D., Fengtan Li, M.D., Wenyuan Gao, Ph.D.

Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease with a serious pre-vascular inflammatory phase, followed by significant increase in vessel growth. Inhibition of angiogenesis is a novel therapeutic strategy against RA. The Chinese herbal remedy *Tripterygium wilfordii*, Hook. f. (TwHf) has been reported to be therapeutically efficacious in the treatment of RA. Recent studies have revealed that treatment with TwHf extracts inhibit angiogenesis of RA, thereby elaborately attenuation RA symptom. This review mainly addresses the anti-angiogenesis effect of TwHf in treatment of RA.

Keywords: *Tripterygium wilfordii*, Hook f. (TwHf)■Rheumatoid arthritis (RA)■Angiogenesis■Vascular endothelial growth factor (VEGF)

Author affiliations: Weisan Zhang, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China; Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin 300020, China; Fengtan Li, Department of Radiology, Tianjin Medical University General Hospital, Tianjin 300020, China; Wenyuan Gao, Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin 300020, China

Correspondence: Fengtan Li, M.D., Department of Radiology, Tianjin Medical University General Hospital, Tianjin 300020, China., email: hejx@thepbpc.org

Correspondence: Wenyuan Gao, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China. Fax: +86 22 87401895., email: pharmgao@tju.edu.cn

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INTRODUCTION

Rheumatoid arthritis (RA), a major contributor to ruining global health, is characterized by joint-related chronic inflammation and concomitant destruction of cartilage and bone. Inflammatory mediators, such as pro-inflammatory cytokines and prostaglandins (PGs), play important roles in the pathogenesis of RA.[1] Understanding of the pathogenesis of RA demonstrates that angiogenesis is significant in the development of RA.[2]

Tripterygium wilfordii, Hook f. (TwHf) is a Chinese herb that has been traditionally used in clinics for RA treatment. Clinical and experimental studies have demonstrated its immunosuppressive, anti-inflammatory, and anti-angiogenesis mechanisms.[3–5]

Accumulated preclinical studies have reported that extracts from the root of TwHf present inhibitory effects on expressions of RA-related inflammatory factors, including pro-inflammatory cytokines, pro-inflammatory mediators, adhesion molecules, and matrix metalloproteinases by macrophages, lymphocytes, synovial fibroblasts, and chondrocytes.[6,7] Moreover, TwHf also suppresses proliferation of lymphocytes and synovial fibroblasts by inducing apoptosis. The anti-angiogenesis property of TwHf has been revealed in many recent research.[8,9] In this study, we briefly review the anti-angiogenesis effects and efficacy of TwHf extracts in the battle against RA.

ANGIOGENESIS IN RA

RA is kind of chronic systemic autoimmune inflammation, with the following invasive characteristics: arthrosynovitis, which is a progressive destruction of cartilage and bone; angiogenesis; and infiltration of inflammatory cells. The main clinical manifestations of RA include chronic, symmetry, multi-joint synovitis, and articular.[10,11] The cause of RA has not yet been fully elucidated by modern medicine[12]; however, RA may be related to immune regulation, infection, genetic makeup, environment, neuropsychological status, and other factors.[13,14]

Up to now, various pathogenesis of RA have been proposed, such as joint inflammation, autoimmune reaction, and angiogenesis. Numerous pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α, also promote the progression of joint destruction.[12] Among these factors, TNF-α launches the most critical inflammatory response to pathological changes of RA,[15] while IL-18 accentuates the production of vascular endothelial growth factor (VEGF), which plays an important role in angiogenesis in rheumatoid synoviocytes, via AP-1-dependent pathways as dose increases.[16,17]

In 1980, a low molecular weight angiogenic factor was detected in synovial fluids from RA patients; thus, angiogenesis was initially identified as a feature of RA.[18] Angiogenesis plays an essential part in new tissue development and tissue self-repair by generating new blood vessels from existing ones. So angiogenesis is involved in various diseases including diabetes, cancers, and chronic inflammatory conditions.[8] In recent years, a great number of studies has confirmed that angiogenesis was indispensable in perpetuating inflammatory and immune responses, as well as in ensuring growth of pannus and development of RA.[8] Angiogenesis also initiates and maintains of the synovial membrane infiltration in RA.[19] Many studies suggested that inhibit the formation of new blood vessel could prevent delivery of nutrients to inflammatory site and accelerate vessel regression and disease reversal. Further understanding of the molecular mechanisms supporting the pathogenesis of RA has been

discovered, and more and more novel targets playing roles in RA-associated angiogenesis have been identified valuable under the respect of therapeutic treatment to RA. Therefore, inhibiting angiogenesis was considered as a novel therapeutic strategy for RA.

Three classes of therapeutic agents commonly used in current RA treatments: disease modifying anti-rheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs, and steroid and biological response modifiers.[8] These therapeutic agents clinically relieve the severity of RA, slow progression, and inhibit subsequent joint damage. Regarding their anti-angiogenic effects, DMARDs, such as methotrexate, penicillamine, and sulphasalazine, demonstrate suppressing action on angiogenesis in preclinical trials; Bucillamine and gold sodium thiomalate were reported to inhibit generation of VEGF[20]; Infliximab, endostatin, and cyclosporine may also attributed to downregulating VEGF and RA-associated angiogenesis.[21] However, clinical adverse effects with high frequency and high treatment cost limit the use of these therapies. Therefore, other strategies are also employed to obtain comparable outcome, such as treatment based on Chinese herb *Tripterygium Wilfordii*, Hook f. (TwHf). Meanwhile, collagen-induced arthritis (CIA) mice model exhibits joint swelling, synovitis, periosteal new bone formation, articular cartilage damaging, bone erosion, osteopenia, and infiltrated inflammatory cells in articular cavity, providing a good experimental arthritis animal model of RA to implement new investigations.[12]

TWHF IN TREATMENT OF RA

TwHf, one of the effective Traditional Chinese Medicines, frequently applied to cure RA. Long-term clinical practice proved that application of TwHf to RA could reduce or replace corticosteroids and (or) steroidal anti-inflammatory drugs, such modulation possesses obvious advantages of high efficiency and low toxicity.[22]

The Chinese herb TwHf, also known as "Lei Gong Teng", yellow vine wood, *Gelsemium elegans*, vegetable insecticide, and red medicine, belongs to the Celastraceae Tripterygium.[6] Its officinal part is the root, which is widely used in Chinese traditional treatment of diseases. Modern medicine and clinical pharmacology studies have confirmed that the extracts of TwHf presents several medicinal functions, such as anti-inflammatory, anti-tumor, immunomodulatory, and anti-fertility,[23] and are clinically used as one of the most common standard treatments for (auto) immune disorders including RA, immune complex nephritis, and systemic lupus erythematosus.[24–26]

TwHf has been identified to contain more than 70 components, including diterpenes, triterpenes, alkaloids, and glycosides, with 95% being terpenoids.[27] Chemical and pharmacological results document that three diterpenoids, namely, triptolide, tripdiolide, and triptonide, are the most abundant components, presenting immunosuppressive and anti-inflammatory effects in both in vitro and in vivo studies.[28,29] Among these diterpenoids, triptolide has been widely used in the treatment of RA. Clinical trials in China have revealed that alkaloids possess obvious and quick effects in alleviating joint swelling and pain, as well as lowering erythrocyte sedimentation rate.[12,30] Wilforidine had better effect on humoral immunosuppression of lymphocytes and lower cell toxicity.[31] In 2009, Goldbach-Mansky et al.[32] performed clinical trials to validate the disease-modifying effects of TwHf extracts on patients with RA. Recently, numerous human clinical trials of TwHf extracts have been reported for treatment of RA in randomized, double-blind, and placebo-controlled trials.[6,33,34] Understanding the modes of action and potential drug targets is important to effectively use TwHf for clinical therapy of RA. Although several mechanisms have already been identified, such as triggering apoptosis in lymphocytes and synovial fibroblasts, preventing their proliferation,[6] inhibiting the differentiation of Th17 cells, and suppressing CIA,[35] others still need to be investigated.

MOLECULAR MECHANISM OF ANTI-ANGIOGENIC TWHF

As mentioned previously, RA was correlated with excessive angiogenesis induced by abnormally large amounts of angiogenesis factors (e.g., VEGF, FGF-2, and hepatocyte growth factor) produced by aberrant cells, but not neutralized by enough natural angiogenesis inhibitors (e.g., angiostatin, endostatin, and thrombospondin).[36]

Aside from its anti-inflammatory properties, TwHf is usually adopted in anti-angiogenic therapies, which aim to suppress growth of new blood vessel (Fig. 1).[37] TwHf inhibits the generation of VEGF by downregulating the mRNA expression of VEGF.[38,39] Inflammation is closely related to VEGF, the expression of chondrocyte VEGF is low in the non-inflammatory, whereas high in inflammatory cases.[40] TwHf decreases the permeability of blood vessels, resulting in limited invasion of inflammatory cell,[41] such as inhibiting the activities of macrophages which invade blood vessel by secreting VEGF.[42,43] Moreover, TwHf may work like curcumin, which inhibits AP-1 binding protein complex, thereby inhibiting the synthesis of VEGF.[44] In addition, a number of studies have indicated that TwHf may indirectly suppress VEGF by restraining TNF-α.[45] TNF-α stimulates chondrocytes to secrete VEGF under any circumstances[46] by stimulating