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Study on the Effect of Gentiana in the Treatment of Rheumatoid Arthritis based on IL-6

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Abstract: ***Rheumatoid arthritis (RA) is an autoimmune disease that affects multiple joints on both sides. Its characteristic is progressive symmetrical inflammation of the affected joints, leading to cartilage destruction and bone erosion. In recent years, the role of interleukin-6 (IL-6) in health and disease has received widespread attention, and the inflammatory pathways involved in IL-6 have also contributed to the occurrence and progression of rheumatoid arthritis (RA) to a certain extent. Gentiana has the effects of dispelling wind and dampness, clearing dampness and heat, relieving pain and dampness, and reducing deficiency heat. It is commonly used to treat diseases such as rheumatic pain, muscle and meridian constriction, bone steaming and tidal heat, and damp heat jaundice. Research has found that Gentiana can reduce bone destruction, anti-inflammatory and apoptotic effects by inhibiting the secretion of pro-inflammatory cytokine IL-6 and regulating the signaling pathways involved in IL-6, achieving the therapeutic goals of rheumatoid arthritis. This review first reviews the role of IL-6 cytokines in the occurrence and progression of RA, and summarizes the mechanism of IL-6 in the treatment of rheumatoid arthritis by Gentiana, in order to provide reference for clinical application.***

Keywords: Rheumatoid arthritis; IL-6; Inflammatory response; Gentiana; Mechanism of action.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease associated with progressive disability, systemic complications, and premature mortality. It is characterized by peripheral arthritis, chronic synovial inflammation and proliferation, damage to articular cartilage and joint capsules, ultimately leading to functional impairment [1]. RA patients in China account for approximately 1% of the global population. Studies indicate that about 80.46% of RA patients are female, approximately 84.70% test positive for rheumatoid factor (RF), and roughly 80% experience varying degrees of disease activity. Cartilage destruction and bone erosion are key pathogenic factors in RA [2]. Reported risk factors for RA include smoking, obesity, ultraviolet exposure, sex hormones, medications, alterations in gut, oral, and pulmonary microbiomes, periodontal disease (periodontitis), and infections. The pathogenesis of RA remains unclear, with potential contributions from immune cells, inflammatory cytokines, matrix metalloproteinases, genetics, and environmental factors. Interleukin-6 (IL-6) has been demonstrated as a pivotal cytokine in the disease pathogenesis, playing a crucial role in RA progression

by promoting T-cell and B-cell activation, autoantibody and acute-phase protein production, and stimulating synovial cells and osteoclasts [3]. Gentiana possesses efficacy in dispelling wind-dampness, clearing damp-heat, and alleviating arthralgia. Research indicates that Gentiana reduces tissue damage in rheumatoid arthritis, inhibits IL-6 inflammatory cytokine secretion, and alleviates inflammatory responses. This paper reviews the role of IL-6 in the onset and progression of RA and summarizes the therapeutic effects of Gentiana intervention on IL-6 in treating rheumatoid arthritis, providing reference for the clinical application of traditional Chinese medicine in RA treatment.

2. Overview of IL-6 Cytokine

IL-6 is a multifunctional cytokine with redundant biological activities. It is a small polypeptide with a molecular weight of 19–28 kDa, existing as a monomer composed of four α-helices. It consists of 184 amino acid residues, glycosylation sites, and two disulfide bonds. IL-6 is activated by interleukin-1β, tumor necrosis factor-α, prostaglandins, stress responses, and other cytokines [4]. Produced by macrophages, monocytes, T lymphocytes, fibroblasts, and endothelial cells, IL-6 binds to soluble IL-6R to induce vascular endothelial growth factor secretion. This promotes endothelial cell proliferation and migration, leading to neovascularization. It plays a crucial role in bone and cartilage destruction in rheumatoid arthritis (RA) and synovitis [5]. As an autoinflammatory mediator, IL-6 not only diminishes the body's ability to distinguish self from non-self but also promotes fibrosis and inflammatory responses. Its critical role in numerous autoimmune diseases has been demonstrated and targeted.

3. Mechanisms of IL-6 in RA

3.1 IL-6 Participation in Innate Immunity of RA

In innate immunity, IL-6 mediates the maturation of inflammatory infiltration by promoting neutrophil migration and monocyte infiltration, thereby driving local synovial inflammation. Macrophage infiltration in RA synovium correlates positively with the progression of joint destruction. IL-6 enhances the survival and proliferation of immune cells, contributing to the transition from acute to chronic inflammation. Under IL-6 stimulation, endothelial cells release chemokines that recruit other immune cells. It also synergizes with other pro-inflammatory cytokines to amplify osteoclast function, disrupting the normal equilibrium between osteoclast resorption and osteoblast formation. This leads to severe bone erosion at the cartilage-perichondrium interface [6]. Furthermore, it induces the expression of related tissue-degrading molecules such as receptor activator of nuclear factor kappa-B ligand (RANKL), prostaglandins, and matrix metalloproteinases. These mediate disease signs and symptoms including pain and swelling, as well as cartilage and bone degradation, thereby promoting the development of RA inflammation.

3.2 IL-6 Participation in Adaptive Immunity in RA

Regarding adaptive immunity, both B lymphocytes and T lymphocytes are involved. IL-6 plays a crucial role in the specific differentiation of naive CD4+ T cells between innate and acquired immune responses. The interaction between IL-6 and transforming growth factor (TGF)-β promotes the differentiation of naive CD4+ T cells into Th17 cells, and elevated Th17 cell levels correlate positively with RA activity. Th17 lymphocytes produce cytokines including TNFα, IL-1β, IL-17, IL-21, and IL-22. These cytokines induce synovial fibroblast and macrophage activation, leading to synovial inflammation, vascular proliferation, and accelerated articular cartilage destruction, thereby contributing to RA progression.

IL-6 has been found to induce activated B cells to differentiate into antibody-producing plasma cells. Consequently, sustained excessive IL-6 synthesis leads to the production of autoantibodies—anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF)—which further drive inflammation by directly activating macrophages or triggering the complement cascade [7].

3.3 IL-6 Induces VEGF to Aggravate RA

Angiogenesis is a critical foundation in the pathological progression of RA. Certain hydrolases released by synovial vascular villi cause bone and articular cartilage destruction and functional loss. A key component in the generation and maintenance of synovial vascular villi is synovial angiogenesis. Vascular endothelial growth factor (VEGF) promotes the formation of synovial vascular plexuses in RA while also acting as a direct pro-inflammatory factor in the disease process, playing a crucial role in joint erosion and destruction [8]. IL-6 induces excessive VEGF production, leading to enhanced angiogenesis and increased vascular permeability—key factors in inflammatory pathology.

3.4 IL-6 Induction of JAK-STAT Pathway Participation in RA

The JAK (Janus Activated Kinase)-STAT (Signal Transducer and Activator of Transcription) pathway is one of the most critical signaling pathways in cytokine-mediated transcription, involved in cell differentiation, proliferation, apoptosis, and immune function—particularly crucial for regulating inflammation and immunity [9]. Extensive research has revealed abnormal activation of the JAK-STAT signaling pathway during RA. The JAK family comprises four members: JAK1, JAK2, JAK3, and TyK2 (tyrosine kinase 2). These members exhibit distinct molecular weights and are highly conserved evolutionarily. JAK3 is exclusively expressed in blood, vascular smooth muscle, and endothelial cells, whereas JAK1, JAK2, and TyK2 are widely distributed across multiple tissues and systems. JAKs play a crucial role in RA. IL-6 induces JAK1 to participate in signal transduction by binding and forming a receptor complex, activating the JAK1 kinase and contributing to the pathogenesis of RA. JAK2 induces downstream activation of STAT3 and STAT5, signaling through the IL-6 receptor to exert effects in inflammatory and autoimmune responses. JAK2 is known to be associated with multiple diseases, including rheumatoid arthritis, hematological disorders, diabetes, cancer, and other autoimmune diseases. Compared to healthy individuals, RA patients exhibit significantly increased JAK2 expression in synovial tissue [10].

STAT is a family of cytoplasmic proteins with transcription activation and signal transduction functions [11]. The STAT family comprises STAT1-4, STAT5A, STAT5B, and STAT6. STATs contain six highly conserved functional domains: the N-terminal conserved domain, helix domain, DNA-binding domain, linker domain, SH2 domain, and C-terminal transcription activation domain. They appear critical in RA FLS hyperplasia, synovial inflammation, and bone destruction. IL-6 has been demonstrated to activate STAT1 and exert both protective and pathogenic effects in RA synovitis via IFN-γ-mediated signaling pathways. Studies indicate STAT2 participates in RA-associated inflammation by forming an interferon-stimulated gene factor (ISGF3) heterodimeric transcription complex with STAT1 and interferon regulatory factor 9 (IRF-9). STAT3, the primary downstream regulator of the gp130 receptor, is activated by IL-6, IL-10, IFN-α/β, and other cytokines. It promotes chronic arthritis by modulating the abnormal growth and survival characteristics of RA synovial cells, further exacerbating clinical RA symptoms [12]. STAT4 modulates IL-12 and IL-23 and participates in RA inflammation by promoting the differentiation of CD4+ T cells into Th17 and Th1 cells.

4. Gentiana

Gentiana is the dried root of Gentiana scabra, Gentiana triflora, Gentiana scabra var. plants belonging to the Gentianaceae family. It possesses the efficacy of dispelling wind-dampness, clearing damp-heat, and alleviating arthralgia. First documented in the Divine Farmer's Classic of Materia Medica as a medium-grade herb, it addresses cold-heat pathogens, cold-dampness, wind-arthralgia, joint pain, water retention, and promotes urination. Dubbed the "moisturizing agent among wind-dispelling herbs," it is clinically used to treat joint pain and swelling, tendon stiffness, and related discomforts. Modern pharmacological research indicates that Gentiana also possesses anti-inflammatory analgesic, immunomodulatory, hepatoprotective, and antiviral effects. Its active component, gentianin, can reduce joint tenderness and swelling indices in rheumatoid arthritis (RA) patients while alleviating inflammatory responses and improving immune function. Additionally, Gentiana contains multiple active components such as cycloartenols, lignans, flavonoids, and triterpenoids that inhibit inflammatory responses [13].

5. Mechanism of Action of Gentiana in Treating RA

5.1 Reduction of Inflammatory Cytokines

Gentiana suppresses inflammatory responses by regulating the expression levels of inflammatory cytokines in RA patients, thereby alleviating symptoms such as local hyperemia, edema, and pain. Li Shun et al. [14] found that Notopterygium and Gentiana Formula, used to treat wind-cold-dampness-type rheumatoid arthritis, reduced IL-1β, IL-6, and IL-17 levels in RA patients, thereby mitigating inflammatory reactions. Wu Chen et al. [15] demonstrated that single-ingredient Gentiana, single-ingredient Weilingxian, and the Gentiana-Weilingxian combination all inhibited the proliferative activity of RA FLSs, promoted FLS apoptosis, and suppressed IL-6 expression, providing experimental support for Gentiana's therapeutic efficacy in RA.

5.2 Regulation of Vascular Endothelial Growth Factor (VEGF)

As a cytokine regulating vascular endothelium, VEGF promotes synovial angiogenesis by binding to its receptor, increases vascular permeability alterations, and enhances inflammatory cytokine release, thereby inducing the onset and progression of inflammatory diseases. Studies confirm that serum VEGF levels are elevated in RA patients and correlate closely with synovitis severity and disease activity. Li Sa et al. [16] found that the combination of Gentiana and Weilingxian effectively reduced toe swelling in RA model rats. The mechanism may involve suppressing RF inflammatory responses in rat serum, inhibiting VEGF expression and secretion, and reducing joint angiogenesis and synovial vascularization to exert therapeutic effects on RA. Wang Rong et al. [17] observed that the combination of Gentiana and Stephania, which balances cold and heat properties, can regulate VEGF expression in rheumatic-type RA model rats, demonstrating remarkable efficacy in RA treatment.

5.3 Modulating the JAK-STAT Pathway

In treating RA, Gentiana offers novel therapeutic approaches by modulating the JAK-STAT pathway. Yang et al. [18] demonstrated that downregulating IL-6 to block JAK/STAT signaling improved hippocampal histopathology and synaptic interface structure in collagen-induced arthritis rats, thereby alleviating RA-associated depression. Yang Lin et al. [19] observed that the ethanol extract of Coptis

chinensis exhibited significant inhibitory effects on adjuvant-induced arthritis in rats. This effect may be attributed to its suppression of IL-6 and TNF-α expression in serum and its regulation of the JAK2/STAT3 pathway, thereby mitigating inflammatory responses in RA.

6. Summary

The pathogenesis of RA is complex, and the formation of vascular synovial membranes caused by target tissue damage to the joint synovium by inflammatory cytokines is a key pathogenic factor in the progression of rheumatoid arthritis. This paper reviews the mechanism of Coptis chinensis in treating rheumatoid arthritis based on IL-6, demonstrating that it alleviates inflammatory responses by suppressing the expression of inflammatory cytokines, thereby relieving clinical discomfort in RA patients. However, current research on the mechanisms underlying Gentiana's treatment of RA remains incomplete. Furthermore, the target mechanisms of Gentiana combined with other Chinese herbal medicines in treating RA require further investigation in animal studies. Future research should delve deeper into molecular biology, therapeutic targets, pharmacologic mechanisms, and clinical applications. Such efforts hold significant importance for realizing the value of traditional Chinese medicine in preventing and treating RA.

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