Mechanism of Gancao Fuzi Decoction in the treatment of Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that results in a series of inflammatory reactions in the joints, marked by pathologies such as articular bone destruction and erosive synovial inflammatory cartilage [1]. The bone destruction in RA arises from an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts [2]. The pathogenesis of RA remains unknown, and studies have indicated its close relationship with genetics, the environment, immune response, and other factors. Potential genes linked to RA susceptibility include major histocompatibility complex genes, like the single nucleotide polymorphism rs9277535 in the HLA-DP subunit HLA-DPB1, which is strongly associated with RA susceptibility in the Western Chinese population [3]. Furthermore, studies have also identified a correlation between major genes encoding the inflammatory CASPs (CASP1, CASP4, and CASP5) and RA [4]. Environmental factors, including smoking, diet, obesity, and infections, have the ability to trigger RA in susceptible individuals [5, 6]. Regarding the immune response, both immune dysregulation and overactivity can result in an inflammatory response, leading to excessive proliferation of synovial tissue, imbalanced distribution of osteoblasts and osteoclasts, and an irregular proportion of immune cells, culminating in the disease.

RA is classified within the arthralgia syndrome according to Traditional Chinese Medicine, and Gancao Fuzi Decoction (GCFZD), a remedy documented over 2,000 years ago in The Synopsis of the Golden Chamber for treating this ailment, has demonstrated its efficacy in clinical practice as confirmed by most traditional Chinese medicine practitioners [7]. Drawing from the accumulated experiences of these treatments, the author presents a summary of the available evidence for this therapeutic approach.

The Application of GCFZD for Treating RA

GCFZD contains key active ingredients like alkaloids, flavonoids, and saponins. It regulates various metabolic pathways, resulting in therapeutic effects on RA [8, 9]. In clinical randomized controlled trials, several studies have confirmed the effectiveness of GCFZD in significantly alleviating symptoms like joint pain and swelling, enhancing hand grip strength, and reducing parameters such as erythrocyte sedimentation rate, serum rheumatoid factor, interleukin-1 (IL-1), and tumor necrosis factor α (TNF-α) levels in RA patients [10, 11].

Suppression of Inflammatory Response

Huang Shun et al. found that compared with the control group, administering GCFZD to rats with RA reduced levels of acid-sensing ion channel 3 and hypoxia inducible factor-1α in their serum and synovial tissue. This leads to the inhibition of tissue acidification and a decreased inflammatory response, thus preventing and treating RA [12]. Research has found that GCFZD can significantly reduce TNF-α levels in synovial tissue, which inhibits the expression of Cyclin D1 and proliferating cell nuclear antigen proteins, enhances the expression of p53 and p21 proteins, and improves the development of RA by inhibiting the proliferation of synovial fibroblasts and the secretion of inflammatory factors [13].

Collagen-induced arthritis (CIA) rat experiments have demonstrated that GCFZD possesses an anti-inflammatory effect. It decreased IL-1β and TNF-α levels, while increasing IL-10 levels in the serum and joint fluids of rats [14]. Other scholars have found that GCFZD can inhibit the Gasdermin D protein-mediated programmed cell death process of lysogenic cells in CIA rats. Additionally, it reduces the secretion of IL-1β and IL-6, while promoting the secretion of IL-10, thereby alleviating RA symptoms in CIA rats [15].

Reducing bone destruction.

Nuclear factor kappa-B (NF-κB) is a crucial molecule involved in the normal development and pathological destruction of cartilage. Phosphorylation of NF-κB p65 promotes the transcription of related genes [16]. Blocking NF-κB signaling activation and regulating bone metabolism disturbance through the related genes could aid in controlling bone destruction occurring in RA. In experiments conducted on CIA mice, the high-dose group of GCFZD could substantially reduce the levels of NF-κB p65 and p-NF-κB p65 while inhibiting their expression in the ankle joints of CIA mice [17]. This could potentially lead to a significant attenuation of bone destruction.

Modulation of Immune Cells

The autoimmune system plays a crucial role in RA pathogenesis. Concerning adaptive immune cells, Yi Yankui et al. conducted a CIA experiment on mice and observed that, in each dose group, GCFZD significantly alleviated joint swelling, reduced the percentage of Th17 cells, and upregulated the percentage of Treg cells. Conversely, mice in the CIA group exhibited the opposite effect. This demonstrates that GCFZD modulates relevant serum cytokine levels, with modulation induced by restoring the imbalance of CD4+ T lymphocyte subsets, T helper type 17/ Regulatory T cells [18]. Scholars conducted experiments to measure the frequency of Th17 and Treg cells, related transcription factors, and the expression level of the microRNA-34a gene in mouse spleen. They found that the mechanism through which GCFZD regulates T helper type 17/ Regulatory T cells imbalance may involve microRNA-34a targeting forhead box protein 3-mediated regulation of immune cells [19].

According to the aforementioned studies, GCFZD exerts a therapeutic effect by regulating multiple genes and protein pathways. This has a beneficial impact on controlling synovial inflammation, arthritic bone destruction, and modulation of immune cells.

Discussion

In addition to RA, GCFZD has demonstrated effectiveness in various osteoarticular diseases, with no significant adverse effects reported. Based on the demonstrated efficacy and safety of this therapy, the utilization of GCFZD in RA treatment is becoming more prevalent in clinical practice. However, RA is a condition of extended duration, and certain studies have encountered the following issues: (1) many experimental studies involve only short-term observations of indicators and do not consider the long-term impacts of drug application; (2) the application of different drug doses and experimental models in fundamental studies investigating the mechanism of action introduces numerous confounding factors, thus augmenting the risk of results bias.
Furthermore, when considering the collective influence of effective components from traditional Chinese medicine and the varied nature of GCFZD, the elucidation of only a limited number of mechanisms of action and signaling pathways cannot comprehensively elucidate GCFZD’s therapeutic mechanism for RA. This suggests the application of network pharmacology methods to screen the drugs’ active ingredients and accurately determine traditional Chinese medicine’s active components through genomic, proteomic, and metabolomic experimental studies. This approach will facilitate the disclosure of pertinent mechanisms through validation experiments, thus assuming a pivotal guiding role for traditional Chinese medicine in addressing other osteoarthritic conditions.

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Author contributions
Rui Gong and You-Lie Yang conceived this study, carried out this study, and drafted the manuscript. Rui Gong and Jia-Xin Yuan designed the study, collected and analyzed the data. Xin-Ju Li was responsible for this manuscript and reviewed the article critically. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
RA, rheumatoid arthritis; HLA, Human leukocyte antigen; GCFZD, Gancao Fuzi Decoction; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; CIA, collagen-induced arthritis; NF-κB, nuclear factor kappa-B.

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