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Research progress of Sinomenium in the treatment of rheumatoid arthritis and suggestions for future research

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Abstract
Rheumatoid arthritis (RA) is a chronic autoimmune joint disease. Its main pathological manifestations are joint cartilage, bone tissue injury, synovial hyperplasia, and chronic inflammation. At present, the pathogenesis of the disease has not been fully defined, and delaying the disease to improve joint function is the existing treatment. Sinomenium (SIN) is an effective ingredient in *Sinomenium acutum* (Thunb.) Rehd. et Wils., with anti-inflammatory, analgesic, immunosuppressive, anti-tumor, and other pharmacological activities, which is quite effective in the treatment of RA. There are many SIN compound preparations in the market, such as Zhengqing Fengtongning capsule, Zhubi Huoluo prescription, and Qinxitong tablet. They all exhibit good anti-RA effect with less adverse reactions. This study summarized the mechanism of action of SIN in the treatment of RA and further explored the possibility of SIN in the treatment of RA combined with other diseases for future research.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune joint disease with pathological manifestations such as joint cartilage and bone tissue injury, synovial hyperplasia, chronic inflammation, and pannus formation.[1] Patients often suffer from joint pain, deformity, and even loss of function, resulting in severe disability. RA affects about 1% of the global population, and its incidence in women is about three times that of men.[2] Its pathogenesis is complex and has not yet been clarified, which is mainly related to genetic factors, environmental factors, immune cells, cytokines, and autoantibodies.[3] Modern pharmacological researches have shown that Sinomenium (SIN) has pharmacological effects of anti-inflammatory, analgesic, immunosuppressive, anti-tumor, and is often used in the clinical treatment of RA, autoimmune diseases, tumors, and other diseases. SIN is mainly hydrochloride extracted from dried roots of *Sinomenium acutum* (Thunb.) Rehd. et Wils., including sinomenine hydrochloride, disinomenine, and sinoacutine. Relevant studies have shown that the mechanism of action of SIN has a certain relationship with the thalamic–pituitary–adrenal system. SIN has an ideal nonspecific anti-inflammatory effect, which can accelerate the secretion of adrenocortical hormones. It has a certain impact on immune regulation, immunosuppression, and reducing inflammation.[4,5] It has been prepared into Chinese patent medicine or sustained-release tablets, which is familiar as Zhengqing Fengtongning capsule. It has obtained a certain effect for treating RA.

Methods and Materials

The researchers searched the following seven databases: China National Knowledge Network (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, The Cochrane Library, and Embase, with the period of establishment until June 2024. The search terms included "Zhengqing Fengtongning capsule," "Zhengqing Fengtongning," "Sinomenium," "rheumatoid arthritis," and "RA."

Mechanism of SIN in the treatment of RA

Regulation of immune disorders

Immune disorders are the main mechanisms of RA pathogenesis, and many immune cells are involved, including T (T cell) and B lymphocytes (B cell), mononuclear/macrophages, and dendritic cells (DCs).[6] Activated CD4+T cells and MHC-II-positive antigen-presenting cells infiltrate the synovial membrane of the joint, initiating specific immune responses and leading to corresponding inflammatory manifestations of the joint.[7] A large number of studies have shown that SIN, the main component of Zhengqingfengtong capsule, has an immunomodulatory effect on many immune cells, such as T cells, mononuclear cells/macrophages, DCs, mast cells, and other factors related to immune response, such as cytokines, reactive oxygen species, nuclear factor-τ B, and cell adhesion molecules.[8] T-box transcription factor (T-Bet) is a helper T cell 1 (Th1) transcription factor and GATA-3 is a helper T cell 2 (Th2) transcription factor. Studies have shown[9] that SIN can reduce the levels of T-Bet, interferon γ (IFN-γ), IFN-γ/interleukin-4 (IL-4), and T-Bet/Gata binding protein-3 (GATA-3) in decidua and serum of recurrent spontaneous abortion mice. However, the expression levels of GATA-3 and IL-4 were not affected, suggesting that SIN could significantly inhibit the expression of Th1 and regulate the balance of Th1/Th2. Macrophages originate from monocytes and participate in multiple immune responses, including phagocytosis, processing and antigen presentation, regulation of body immunity, and tissue repair.[10] Studies have shown[11] that SIN can significantly increase the expression level of paired immunoglobulin-like receptor B, reduce the proportion of M1 macrophages, and play an immunomodulatory role by inhibiting M1 polarization of macrophages. DCs are the most functional professional antigen-presenting cells (APC) in the body, which can efficiently take up, process, and present antigens. Studies have shown that SIN can effectively inhibit the activation and proliferation of T cells and B cells, reduce the imbalance of Th1/Th2, and interfere with the differentiation of DC and other cell types.[12] Xie et al.[13] found that SIN can promote the apoptosis of mature DC 2.4 through the FAS pathway of apoptosis receptor, activating CASPASE 8, CASPASE 3, and PARP channel. By inhibiting the maturation of DC 2.4, the function of T cell activation is inhibited, and the immune regulation is played. In addition, SIN can reduce the expression of CD 80 and CD 86 on the surface of DC and inhibit its maturation, inhibit the production of interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), induce the secretion of interleukin-10 (IL-10) by DCs, inhibit the secretion of related inflammatory factors by DCs, affect the activation of T cells, and inhibit its mediated immune response and its antigen-presenting effect.[14] Mei et al.[15] found that SIN suppressed abnormal immune response by downregulating the expression of mannose receptors and reducing the content of related antibodies to effectively control the condition of RA.

In the pathogenesis of RA, tumor necrosis factor (TNF) plays an important role, expressed in monocytes, fibroblast-like synovial cells (FLS), T cells, and B cells, mediating leukocyte activation, adhesion and migration as well as osteoclast (OC) activation.[16] Li et al.[17] separated mouse lymph node cells and added SIN at different concentrations, and found that the molecular expressions of cytokines TNF-γ and TNF-α in T cells were significantly reduced in a dose-dependent manner, thus improving arthritis symptoms. In addition, Wang et al.[18] conducted an in-depth study on the mechanism of SIN in the treatment of RA that has accepted by clinical practitioner. They found that the levels of follicular helper T cells and interleukin-21 (IL-21) were significantly reduced, thus improving the symptoms of patients with RA. Among all mentioned cells, helper T cells (Th) 17 and regulatory T cells (Tregs) are both T cells, but their functions in the human body are antagonistic to each other. From the cellular level, after SIN treatment, the proportion of Th17 cells with pathogenic effect was significantly reduced, while the proportion of Tregs with immunosuppressive effect was significantly increased, thus producing the therapeutic effect of RA.[19] Therefore, the

imbalance between the two is also one of the important reasons for the onset of RA, which also indicates that SIN can alleviate RA by regulating the balance of Th17/Tregs.[20]

Effect of SIN on bone and joint

Inhibition of joint inflammation

Rheumatoid arthritis is a chronic inflammatory disease with repeated attacks of joint inflammation, which can eventually cause joint deformity and dysfunction, seriously endangering the health of patients. How to control chronic joint inflammation more safely and effectively is the key to the treatment of RA. Studies have confirmed that proinflammatory (PIC) and anti-inflammatory factors (AIC) play an important role in the occurrence and progression of RA.[21] Qin et al.[22] induced rat synovial cell lines RSC-364 by IL-1β and found that SIN at different concentrations could inhibit the proliferation of RSC-364 induced by IL-1β, and inhibited joint inflammation by inhibiting the secretion of inflammatory factors interleukin-6 (IL-6) and matrix metallopeptidase 3 (MMP-3). Another rat experiment showed that after treatment with SIN, the expression levels of CC chemokine ligand 2 (CCL 2), collagen type II (COL II), and cartilage oligomeric matrix protein (COMP) and their mRNA and the ratio of phosphatidylinositol 3-kinase (PI3K), p-PI3K, protein kinase B (pkB, p-Akt) and p-Akt were significantly decreased in the articular cartilage layer of rats. At the same time, the expression levels of IL-1β, matrix metalloproteinase 13 (MMP-13), and TNF-α in the articular irrigation solution were significantly decreased.[23] SIN, on the other hand, inhibits inflammation by preventing the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. IL-1β can significantly promote the expression of NF-κB and IκK, inhibit the expression of IκB, and induce inflammation. SIN can significantly inhibit the expression of NF-κB and IκK, promote the expression of IκB, and significantly reduce the expression levels of IL-6, TNF-α, MMP-13, and ADAMTS5.[24]

Rheumatoid arthritis is a systemic disease that can influence tissues besides bones and joints. RA patients will also have extra-joint manifestations, causing damage to the heart, lungs, digestive tract, blood vessels and other tissues and organs of patients. SIN not only has a certain therapeutic effect on joint inflammation, but also has a certain therapeutic effect on inflammation of other non-joint tissues. Zhao et al.[16] found that SIN can inhibit the expression of inducible nitric oxide sythase (iNOS) and cyclooxygenase-2 (COX-2), as well as the NF-κB and JNK signaling pathways in vitro experiments. In vivo experiments, SIN can inhibit LPS-induced lung disease and inflammation, and reduce the expression levels of nitric oxide (NO), myeloperoxidase (MPO), TNF-α, and IL-6. Both in vivo and in vitro experiments have confirmed that SIN can alleviate inflammatory response by inhibiting the expression of inflammatory factors. Kim et al.[25] further used LPS-induced uveal inflammation to find that SIN inhibited protein leakage in a dose-dependent manner, downregulated the production of TNF-α and prostaglandin-E2 (PGE2), and inhibited the translocation of NF-κBP65 subunits into the nucleus. Systemic injection of SIN can inhibit the inflammation of the eye tissue, which also suggests that SIN may be a new therapeutic agent to control endogenous eye inflammation. In addition, SIN can significantly reduce TNBS-induced colitis in mice using 2,4,6-tri-nitrobenzene sulfonic acid (TNBS) induced colitis, and its therapeutic mechanism is related to the upregulation of TNF-α and interferon IFN-γ in colon induced by TNBS.[26] Firstly, SIN can alleviate skin photoaging. Tao et al.,[27] using HepG2 cells as a model, showed that SIN can significantly inhibit protein carbonylation and inhibit matrix metalloproteinases and IL-6 secreted by skin cells under TNF-α induction at a concentration of 333–300 μg/mL. It is suggested that SIN has the potential to relieve skin inflammation. Secondly, in the inflammatory response, sepsis is a systemic inflammatory reaction caused by infection, with a very high mortality rate. SIN hydrochloride can improve the autophagy activity of septicemia cells caused by cecal ligation puncture (CLP) in mice, reduce the release of inflammatory cytokines, reduce organ damage, and reduce the mortality of sepsis.[28]

Inhibit bone destruction

Bone injury and destruction is an important link in the occurrence and development of RA and is one of the main culprits causing joint deformity, rigidity, and dysfunction in patients. OCs are the main cause of bone destruction.[29] Mature OCs is an osteoclast precursor (OCP) formed by the binding of NF-κB receptor activating factor (RANK) and NF-κB receptor activating factor ligand (RANKL). Macrophage colony-stimulating factor (M-CSF) can promote the RANK expression of OCP. RANKL is mainly formed by osteoblasts (OBs). Osteopagin (OPG), also known as OC inhibitory factor, is a member of the tumor necrosis factor receptor superfamily and the only factor found so far that can directly downregulate the function of OCs. Meanwhile, as a bait receptor of RANKL, OPG has an inhibitory effect on its binding with RANK. These signaling factors play a key role in the process of RA bone injury and destruction.[30] SIN can increase the expression of OPG, decrease the expression of RANKL, and promote the differentiation and maturation of OB. Wang K et al.[31] activated mouse CD4+ T cells to detect the effects of SIN and aconitine on the expression of mouse helper T cell receptor activating factor ligand (RANKL). The results showed that SIN can reduce the expression of RANKL in activated T cells and indirectly inhibit RANKL-induced OC formation and bone resorption. To improve the bone damage caused by RA, some researchers applied SIN at different concentrations to pre-osteoblasts and found that SIN had no significant effect on the cell proliferation rate. To a certain extent, SIN could promote the differentiation and calcification of osteoblasts, and upregulate the expression of OPG while downregulate the expression of RANKL, thus promoting the differentiation and maturation of osteoblasts through the OPG/RANK/RANKL signaling pathway. It can be seen that SIN is expected to become an anti-osteoporosis drug in the future.[32,33] By establishing a collagen-induced RA (CIA) mouse model, SIN can increase the OPG/RANKL ratio in peripheral blood, inhibits CaN/NFAT signaling pathway and OC differentiation, indicating that SIN has osteoprotective effects on RA.[34]

Relevant studies have shown[35] that SIN can inhibit the occurrence of bone destruction by reducing the levels of TNF-α, interleukin-1 (IL-1), IL-6, interleukin-17 (IL-17), and

other cytokines and inhibiting the activity of OC differentiation-related signaling pathways, such as NF-κB, nuclear factor of activated T cells 1 Gene (NFATc1), mitogen-activated-protein-kinases (MAPK), Ca^{2+}, Janus kinase (JAK)/signal transducers and activators of transcription (STAT) and other signaling pathways. In the established CIA mouse model, SIN inhibits the NF-κB signaling pathway by reducing the expression of NF-κB and phosphorylated κB inhibitory protein (p-IκB), and exerts a bone protective effect.[36] Wang et al.[37] constructed a rabbit knee osteoarthritis (KOA) model by papain-induced modeling, and the treatment group was treated with Zhengqing Fengtongning injection into the knee cavity. The results showed that Zhengqing Fengtongning injection could inhibit the apoptosis of chondrocytes and the degradation of extracellular matrix, protect chondrocytes, repair the damage of articular cartilage, and inhibit the destruction of bone.

Inhibit synovial hyperplasia of joints

Synovitis is a basic pathological change of RA, and synovial hyperplasia is the pathological basis of joint injury, deformity, and dysfunction.[38] RA FLS are the main components of synovial cells and play an important role in the occurrence and development of RA. With the continuous deepening of research, FLS-targeting therapy is promising to improve the condition without causing immunosuppression.[39] Sheng et al.[40] found that Zhengqing Fengtongning could induce apoptosis of FLS and reduce inflammatory response by inhibiting HOTAIRM1 expression and then upregulating miR-137 expression, thus playing a role in the treatment of RA. Studies have shown[41] that the low expression of miR-23b-3p in RA synovial fibroblasts has a targeting relationship with X-linked apoptosis suppressant protein (XIAP), which can inhibit the proliferation of FLS and promote their apoptosis. Li et al.[42] found that SIN can induce apoptosis of FLS and inhibit the proliferation of synovial cells by increasing the expression of miR23b-3p and decreasing the expression of fibroblast growth factor 9 (FGF9). Xu[43] found the mechanism of action of 95% alcohol extract SIN in the treatment of RA, and the results showed that they could alleviate inflammation, inhibit bone destruction, inhibit proliferation of macrophage cells and FLS, and reduce the expression of RANK and RANKL. The effect of 95% alcohol extract of the high dose group was more significant. Secondly, SIN can also inhibit the proliferation of FLS and the expression of Stimulation of alpha 7 nicotinic acetylcholine receptor (α-7nAChR) by inhibiting the extracellular-regulated kinase (ERK)/early Growth Response 1 (EGr-1) signaling pathway, and reducing the expression levels of IL-6, interleukin-8 (IL-8), and rheumatoid factor (RF) in joint synovium, to improve the uncomfortable symptoms during the onset of RA, thereby delaying the progression of RA.[44,45] Some research teams have found that SIN and paeoniflorin synergistic treatment of CIA are similar to RA disease, indicating that it may play a role in alleviating arthritis by downregulating the contents of TNF-α and IL-1β in serum and the protein expression levels of Matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) in bone tissue, and upregulating the protein expression levels of tissue inhibitor of metal protease 1 (TIMP-1). The combination of SIN and Heishun tablets can also reduce joint synovial cell proliferation, bone destruction, and pannus in CIA rats, and the therapeutic effect is better than that of the single drug group. The therapeutic mechanism may be related to the reduction of the release of inflammatory factors IL-17 and IL-23.[46]

The possibility of SIN in the treatment of RA and other diseases

Traditional Chinese medicine (TCM) doctors believe that some different diseases have the same cause or pathogenesis, and the same treatment method can be used, which is the concept of "treating different diseases with the same treatment" in TCM. The modern pharmacological research further suggests SIN may be a multipathway, multi-target drug, which has a prominent effect on the treatment of a variety of diseases, especially those involving inflammatory response and immune response.

Possibility of SIN in the treatment of RA combined with KOA

KOA is a degenerative disease in middle-aged and elderly people, and its causes are manifested in many aspects, such as joint abnormalities, joint damage, obesity, etc. Some patients have excessive weight bearing and fatigue, which makes them more susceptible to the disease. Long-term manifestations include knee joint swelling, stiffness, tenderness, deformity, and limited activity.[47] Previous studies have proved that SIN has good clinical efficacy and safety in the treatment of KOA.[47,48] In addition, Zhengqing Fengtongning can also play a role in combination with traditional Chinese medicine techniques. Liu et al.[49] gave meloxicam treatment to the conventional group, while the experimental group adopted minimally invasive techniques of TCM and intra-articular injection of Zhengqing Fengtongning. The results showed that after treatment, the total effective rate of the study group was higher than that of the conventional group ($P < 0.05$), suggesting that the ideal curative effect could be obtained by using the minimally invasive technique of traditional Chinese medicine and the intra-articular injection of Zhengqing Fengtongning. In addition, the levels of IL-1β, IL-6, and TNF-α in the study group were lower than those in the conventional group ($P < 0.05$), indicating that the combination of the minimally invasive technique of traditional Chinese medicine and the intra-articular injection of Zhengqing Fengtongning could effectively control inflammation. By combining the links among the compounds, intersection targets, signaling pathways, and biological processes, the relevant network pharmacology suggests that the treatment of KOA by SIN is the result of multi-pathway and multi-target interaction, and its mechanism of action is most closely related to apoptosis and inflammation. The mechanism of inflammation has been partially revealed in existing studies, but it is still necessary to conduct experimental studies on how to interfere with apoptosis to treat KOA and further reveal the mechanism of inflammation.[50]

Studies have shown that Sinomenium acutum (Thunb.) Rehd. et Wils. extract can interfere with a variety of cell signaling pathways, including cell cycle, apoptosis,

proliferation, survival, invasion, angiogenesis, metastasis, anti-inflammatory, anticancer, hepatoprotective, antioxidant, cardioprotective, and antidiabetic effects, and has no significant toxicity during pharmacological screening. Studies have also shown that its non-specific anti-inflammatory effect is ideal, and it has a certain impact on immune regulation and immunosuppression, and can effectively reduce the levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and relieve local inflammation caused by knee arthritis. It can downregulate the expression of vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) in articular cartilage and synovial membrane of rabbits with knee osteoarthritis.[51] The key targets, the treatment of KOA by Sinomenium acutum (Thunb.) Rehd. et Wils. extract, are prostaglandin-endoperoxide synthase 1 (PTGS 1), PTGS 2, PPARG, Bcl-2, TGFB1 and CASP3. PTGS 1 and PTGS 2, also known as COX-1 or COX-2, are key enzymes that catalyze the biosynthesis of prostaglandin (PG) and play an important role in inflammation.[52] Other studies have shown that the transforming growth factor-β (TGFβ-1) gene can further promote nerve growth factor by encoding transforming growth factor, resulting in enhanced pain, which may be the reason why the treatment of KOA can directly relieve the pain of patients.[53]

Possibility of SIN in the treatment of RA combined with diabetic nephropathy

According to the diagram of SIN Active ingredient target-disease network, SIN mainly delays the progression of diabetic nephropathy (DN) through four active ingredients: β-sitosterol, 16-epi-isositsirikine, cepharanthine and SIN.[54] β-sitosterol is a kind of phytosterol, which has anti-inflammatory, antioxidant, antibacterial, lipid-lowering, antitumor, and other effects. Some studies have shown[55] that β-sitosterol can activate the antioxidant enzyme regulation activity of nuclear factor-erythroid 2 related factor 2 (NRF-2) and reduce renal toxicity in mice. Studies have shown that SIN can inhibit streptozotocin and regulate the JAK2/STAT3/SOCS1 pathway to improve DN. The study of Teng et al.[56] showed that SIN could effectively reduce the urinary protein of DN patients and reduce the inflammatory cytokines IL-6 and IL-8 in DN rats through its anti-inflammatory effect. At the same time, it can also prevent the fibrosis of DN rats and protect the kidney structure and function. 16-epi-isositsirikine and cepharanthine have not been fully studied in the field of DN. According to the enrichment analysis of GO function and KEEG pathway, which can be seen that the treatment of DN by SIN. SIN is related to the apoptosis pathway and AGE-RAGE signaling pathway. Studies have shown that apoptosis genes play an important role in the damage of DN cells. Some researchers found[57] that the AGE-RAGE pathway can activate NF-κB and lead to NF-κB activation through the activation of triphosphopyridine nucleotide (NADPH) oxidase, which ultimately leads to cell activation and tissue damage, and this process can be repeated to lead to a vicious cycle. In addition, it can stimulate vascular endothelial growth factor to cause increased vascular permeability, further leading to the production of proteinuria, can also increase the production of TGF-β1 and induce the enhancement of monocyte chemoattractant protein-1 (MCP-1) expression, so that glomerular sclerosis and renal tubulointerstitial, so that kidney fibrosis. By regulating apoptosis and the AGE-RAGE pathway, the plant can reduce the production of urinary protein, delay tissue damage, and delay the process of renal sclerosis.

In addition, SIN also has certain therapeutic effects on another nephropathy. Ni[58] found SIN may inhibit mesangial cell proliferation and reduce the local immune inflammatory response of the kidney through JAK2/STAT3 signaling pathway. Liu et al.[59] found that SIN may inhibit the activation of the PI3K/mTOR signaling pathway, reduce the expression of glomerular matrix synthetic proteins FN and COL4, improve mesangial matrix deposition and glomerular lesions, and thus achieve therapeutic effects on adriamycin nephropathy in rats. Bi et al.[60] used glucocorticoids combined with Zhengqing fengtongning tablets to treat IgA nephropathy patients with moderate albuminuria and found that the total effective rate of the combined treatment group was 83.3%, while of the hormone control group was only 66.7%. The results showed that glucocorticoid combined with SIN had a better curative effect on IgA nephropathy with moderate albuminuria than hormone therapy alone.

Possibility of SIN in the treatment of RA combined with gouty arthritis

SIN can effectively reduce the levels of proinflammatory cytokines such as TNF-α, IL-1β and IL-6 in the synovium of joint tissue, significantly improve the inflammatory microenvironment, inhibit cell apoptosis, prevent the destruction of tissues, relieve symptoms of joint swelling and pain, and improve the quality of life of patients, no matter it is used internally or externally. It plays a positive role in the clinical treatment of gouty arthritis. Zhengqing Fengtongning sustained release Tablet, a representative of SIN as the effective active ingredient, also has the effect of inhibiting acute and chronic inflammatory exudation, dispelling wind and dampness, and activating channels based on TCM theories. It can improve the local inflammatory microenvironment of joints, prevent further damage of joint tissues, and significantly and effectively alleviate clinical symptoms, with prominent advantages in anti-inflammatory, analgesic and bidirectional immunomodulatory effects. In addition, in the clinical treatment of gouty arthritis, the therapeutic effect of combined drug use will be more prominent, which can significantly and effectively reduce the inflammation and joint pain of patients, with ideal efficacy, safety, and reliability, and can be used as the guiding basis for clinical treatment.[61,62]

Possibility of SIN in the treatment of RA combined with Parkinson's disease

Relevant researchers[63] studied the effects of SIN on motor function, neuroinflammation, peripheral inflammation, oxidative stress, and inflammatory signaling pathways in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease mice. MPTP is a lipophilic

compound that can enter the brain through the blood-brain barrier and is rapidly converted to the toxic metabolite 1-methyl-4-phenylpyridine ion (MPP+) by monoamine oxidase-B (MAO-B). MPP+ is selectively absorbed by dopaminergic neurons through dopamine transporters, resulting in severe mitochondrial respiratory defects and promoting free radical formation in the mitochondria of dopaminergic neurons.[64] MPTP-induced animal models are similar to human Parkinson's disease in pathogenesis. Although they cannot completely reproduce the symptoms of Parkinson's disease, they are simple, practical, and affordable, so they are often used for Parkinson's disease-related research. The results[63] suggest that the TH protein expression level in the brain tissue of mice in the model group is significantly decreased, while the TH protein expression level of SIN can be significantly increased at medium and high doses, suggesting that SIN can improve the function of dopaminergic neurons in Parkinson's disease mice. In dopaminergic neurons, TH catalyzes tyrosine to produce L-DOPA, the precursor of dopamine, so TH expression is a marker of dopaminergic neurons, and the change of its expression level is closely related to the occurrence and development of Parkinson's disease.[65] et al.[66] found that SIN could inhibit MPP+-induced oxidative stress and apoptosis of SK-N-SH cells, possibly through the regulation of ANRIL/miR 626 pathway, which provided a new idea for the treatment of Parkinson's disease. The common mode of SIN influences the RA and other diseases are shown in Table 1 and Table 2.

Discussion

RA is an aggressive and destructive autoimmune disease, accompanied by cartilage erosion, bone loss, and joint destruction, which can eventually cause joint deformity and dysfunction, seriously harming the health of patients. At present, nonsteroidal anti-inflammatory drugs (NSAIDS), glucocorticoids, antirheumatic biological agents, and other drugs are mainly used in clinical treatment, but there are differences in the efficacy of these drugs. For example, NSAIDs are easy to cause gastrointestinal bleeding, and glucocorticoids can induce necrosis of the femoral head,[63] so there is an urgent need for drugs that can effectively treat RA with fewer adverse reactions. SIN has a variety of pharmacological effects such as regulating immunity, inhibiting joint inflammatory response, inhibiting bone destruction and joint synovial hyperplasia, etc. By downregulating the expression of inflammatory factors, inhibiting the activity of immune cells, thereby inhibiting synovial hyperplasia and alleviating bone destruction, RA is treated. At present, the clinical application of SIN has been extensive, and the treatment of RA has achieved exact efficacy, and its safety has also been verified.[3] At the same time, SIN, as a multi-target drug, can treat RA combined with other diseases and has a broad application prospect in clinical treatment.

However, there are some limitations in the study of SIN. Firstly, the studies on SIN's antirheumatoid arthritis are not in-depth enough. Most researchers still focus on SIN's

Table 1 The mechanism and effect of SIN in treating rheumatoid arthritis.

Mechanism		Influence
Regulation of immune disorders	Decrease	Th1; DC 2.4; TNF-γ; TNF-α; Th17; Tfh; IL-21;
	Increase	Tregs
Inhibition of joint inflammation	Decrease	IL-6; MMP-3; CCL 2; COL II; COMP; MMP-13; IL-1β; TNF-α; NF-κB; IκK; ADAMTS5
	Increase	IκB
Inhibit bone destruction	Decrease	RANKL; IL-1; IL-6; IL-17; NF-κB; p-IκB
	Increase	OPG
Inhibit synovial hyperplasia of joints	Decrease	HOTAIRM1; ERK/EGr-1
	Increase	miR23b-3p

Table 2 The SIN influences the rheumatoid arthritis and other diseases.

	Name	Influence	
SIN	RA	Decrease	Th1; DC 2.4; TNF-γ; TNF-α; Th17; Tfh; IL-21; IL-6; MMP-3; CCL2; COL II; COMP; MMP-13; IL-1β; ADAMTS5; RANKL; IL-1; IL-17; NF-κB; IκK; p-IκB; HOTAIRM1; ERK/EGr-1
		Increase	Tregs; IκB; OPG; miR23b-3p
	KOA	Decrease	IL-1β; IL-6; TNF-α; VEGF; NGF; TGFβ-1
	DN	Decrease	IL-6; IL-8; urinary protein
		Regulation	AGE-RAGE
	Gout	Decrease	TNF-α; IL-1β; IL-6
	Parkinson	Decrease	TH protein (low SIN)
		Increase	TH protein (medium and high SIN)

inhibition of inflammatory factors, and there is insufficient understanding of SIN's regulation of immune response and its influence on chondrocytes. Secondly, the standard of clinical drug use needs to be unified, and its drug safety needs to be verified over a longer period and on a larger scale.[3] At the same time, there is no uniform standard for the recommended dose of SIN for treating different diseases. Each Zhengqing Fengtongning sustained-release tablet contains 60 mg SIN, but there is no clear recommended dose for RA, and the recommended dose for bone and joint diseases is one to two tablets each time, twice a day, and 2 months for a course of treatment. The recommended dosage for patients with chronic nephritis (common type) is two tablets each time, twice daily, and 3 months for a course of treatment. Thirdly, there are various applications in SIN compound preparations. At present, an innovative treatment to clear rheumatism-triple sequential therapy, which promotes the drug treatment into three parts: subcutaneous administration, injection administration, and oral administration, has received unanimous clinical approval. However, the indications and contraindications of various methods are still unclear, and follow-up studies should consider further clarifying the advantages of various drug administration and further improving the bioavailability and clinical efficacy of drugs. Fourth, the combined application of SIN and other drugs calls for further in-depth study. Additionally, the therapeutic efficacy resulting from the combination of SIN with other drugs also requires further exploration, which holds great significance for the selection of clinical treatment options. Fifth, the safety of SIN has been confirmed, but our research on adverse reactions is insufficient. Most researchers have found that patients have mild adverse reactions, such as allergic reactions gastrointestinal reactions, etc. Although most subjects can significantly relieve or even disappear symptoms after drug withdrawal or symptomatic treatment, the mechanism of their occurrence is not clear enough and attention is not paid to individual cases, which poses challenges to the safety of clinical treatment.[16]

In the future, we should actively focus on relevant research on SIN to provide help for clinical treatment and the occurrence and development of the RA. Firstly, we should actively study the effect of SIN on the immune regulation of RA patients and further clarify the mechanism of its treatment of RA. In addition, attention should be paid to the possibility of SIN in treating RA combined with other diseases, especially orthopedic diseases caused by inflammation, such as KOA and gout. The current research advancements regarding SIN in the treatment of orthopedic ailments predominantly center on its application in treating RA, osteoarthritis (OA), and gouty arthritis. The scope of target diseases for SIN merits further exploration. For instance, relevant studies have demonstrated that SIN exerts a certain curative effect on diabetic nephropathy. Consequently, we can further investigate the potential of SIN in treating other types of nephropathy in the future. Moreover, the major pathological alterations in RA are closely associated with joint synovitis. In the future, the possibility of using SIN to treat acute synovitis can be explored, and the specific indications for treating various arthritis types with SIN can be further delved into, which will contribute to the formulation of future clinical treatment. Secondly, SIN is effective in the treatment of KOA. The occurrence and development of KOA are related to inflammation and apoptosis of chondrocytes to some extent. Therefore, further studies on the effect of SIN on chondrocytes should be considered to further clarify the mechanism of SIN and help us understand the pathogenesis of KOA. Thirdly, we should further test to determine the optimal dose of SIN for RA. The age distribution span of RA patients is large, and the influence of SIN on patients of different age groups and different weight should be paid attention to in future treatment. For patients with RA combined with other diseases, the optimal dose and administration mode of SIN should be further defined, so that patients can obtain the maximum clinical benefit and therapeutic effect. The diverse administration methods of SIN mainly consist of subcutaneous administration, injection administration, and oral administration. Nevertheless, there is a dearth of relevant research regarding the therapeutic effects of these three distinct administration modes on diseases. It will be necessary to conduct further investigations into the potential of different administration modes for various diseases. At the same time, drug dosage forms can be innovated, for example, targeting preparations can be considered to further accurately act on a target; Fourthly, the side effects of clinical use of SIN are low, and the safety has been effectively verified. However, we should pay attention to the study of individual cases. Immune response is a mechanism existing in the whole body, and some patients' adverse reactions may have a certain connection with the treatment mechanism of SIN. Paying attention to individual cases of adverse reactions can help us further understand the mechanism of SIN and the pathogenesis of RA. In addition, the adverse reactions of SIN to patients need to be further studied in order to better help future clinical treatment; Fifth, we should try to explore the other extracts of Chinese medicine. SIN is an effective extract of Caulis Sinomenii. *Collected Works of Materia Medica*, the classic works of TCM, said: "all the rattan Chinese medicine can pass through the meridian into the collaterals."[64] This suggests that rattan Chinese medicine may have a good effect on joint pain diseases, and we can consider further studying the effects of extracts of other rattan drugs, such Stem of Suberect Spatholobus, Kadsura Pepper Stem and common threewingnut root in the treatment of orthopedic diseases in future studies.

Conclusion

SIN mainly regulates immunity, inhibits joint inflammatory response, inhibits bone destruction, inhibits joint synovial hyperplasia and other pharmacological effects, which is also the main mechanism of action in the treatment of RA. In addition, SIN also has the potential to treat other diseases associated with RA, such as KOA, gout, Parkinson's disease and DN. However, the mechanism of SIN in the treatment of related diseases needs to be further studied, the adverse reactions of SIN on human body, the optimal dose of SIN and the way of administration need to be further studied to provide effective support for further clinical application. All in all, SIN is effective in the treatment of RA, and its safety has been effectively recognized.

It should be actively considered for the clinical treatment of RA, and further research is needed in the future to explore the clinical value of SIN.

Authors Contribution

Guanghui Zhou contributed to original draft writing and literature search and screening; Zhuoxu Gu contributed to literature search and screening and manuscript editing; Xianquan Zhang contributed to literature screening; Lingfeng Zeng contributed to the acquisition of funding and the provision of conceptualization; Jun Liu contributed to conceptualization. Guanghui Zhou and Zhuoxu contributed equally to this work. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare no conflicts of interest.

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References

1. Jiang Q. International Clinical Practice Guidelines for Chinese medicine rheumatoid arthritis (2019-10-11). World Chinese Med. 2019;15(20):3160–8.
2. Xu HY, Kuang NZ, Zhang YJ, et al. Research progress in the treatment of rheumatoid arthritis. J Nanchang University. 2019;60(05):97–102.
3. Hu C, Tu RD, Leng WF, et al. Research progress of Zhengqing Fengtongning in treatment of rheumatoid arthritis. J Pract Trad Chinese Med. 2023;39(5):1048–50.
4. Wan YY, Liu CX, Zhang JH, et al. Analysis on the efficacy and safety of Zhengqing Fengtongning injection in the treatment of osteoarthritis. Guiding J Trad Chinese Med Pharm. 2019;25(14):105–9.
5. Wang XC, Yi TX, Leng WF, et al. Effect of Zhengqing Fengtongning combined with triamcinolone acetonide injection on knee joint osteoarthritis. J Pract Trad Chinese Med. 2019;35(09):1111–2.
6. Wang Y, Wang LW. Research progress on pathogenesis of immune cells and cytokines in rheumatoid arthritis. Chinese J Rehab Med. 2007;2007(04):370–373.
7. Jian L, Equilibria Z, Cao YH. Xinfeng capsule promotes apoptosis of CD4−+T cells in peripheral blood of patients with rheumatoid arthritis by regulating apoptosis-related proteins. Rheumatism Arthritis. 2019;8(01):15–20.
8. Zhou YY, Liu YL, Lin LF, et al. Research progress of Sinomenium and its new dosage forms in the treatment of rheumatoid arthritis. Chinese Trad Herbal Drugs. 2001;52(24):7709–17.
9. Luo J, Wang Y, Qi Q, et al. Sinomenium improves embryo survival by regulating Th1/Th2 balance in a mouse model of recurrent spontaneous abortion. Med Sci Monit. 2021;27:e927709. https://doi.org/10.12659/MSM.927709
10. He HP, Xu GH, Lin J, et al. The role of macrophages in rheumatoid arthritis. J Med Res. 2019;51(02):8–11.
11. Wei ZQ, Bao CH, Chen YX, et al. Sinomenium increases expression of paired immunoglobulin receptor B and inhibits classical activation of macrophages. Acta Pharm Sinica. 2018;56(06):1644–52.
12. Huang H, Hu MY, Xu L, et al. Research progress on immunosuppressive mechanism of Sinomenium. Chinese Trad Herbal Drugs. 2022;53(01):261–9.
13. Xie YM. Effect of Sinomenium on DC2.4 maturation and mechanism of inducing apoptosis in DC2.4. China: Chengdu University of Traditional Chinese Medicine; 2016.
14. Zhang XY. Effect of Sinomenium on CD80/CD86 on BMDC surface of mice model of rheumatoid arthritis. China: Chengdu University of Traditional Chinese Medicine; 2016.
15. Mei X. Effect of Sinomenium on mannose receptor expression and related antibody in rheumatoid arthritis model rats. China: Chengdu University of Traditional Chinese Medicine; 2014.
16. Hu JW, Ding C, Wu Y, et al. Research progress of Sinomenium and its preparations in the treatment of rheumatoid arthritis. J Shaanxi Univ Chinese Med. 2019;47(3):1–7.
17. Li XJ, Wang PX, Liu L, Chen GX, Zhao JX. Effects of Sinomenium on activation of T lymphocytes and expression of TH1 intracellular cytokines. Chinese J Immunol. 2004;2004(04):249–52.
18. Wang GF. Effect of Qingfengteng decoction on Tfh, IL-21 and anti-CCP antibody in patients with rheumatoid arthritis. Modern Pract Med. 2019;31(08):1005–7.
19. Ma LW, Yu D, Wu JK, et al. Mechanism of action of Chinese medicine and active ingredients in treatment of rheumatoid arthritis. Hebei Med J. 2019;42(18):2832–6.
20. Li N, Deng J, Zhou JR, et al. Effect of Sinomenium on the ratio of auxiliary T lymphocytes 17/regulatory T lymphocytes in peripheral blood of patients with rheumatoid arthritis. Shanghai Med J. 2013;36(03):254–8.
21. Mateen S, Zafar A, Moin S, et al. Understanding the role of cytokines in the pathogenesis of rheumatoid arthritis. Clin Chim Acta. 2016;455:161–71. https://doi.org/10.1016/j.cca.2016.02.010
22. Qin YX, Guo MZ. Effects of Sinomenium on proliferation and inflammatory factors of rat synovial cell line RSC-364 induced by IL-1β. Acta Chinese Med Pharmacol. 2019;50(05):34–9.
23. He L, Ge ZZ, Wu YQ, et al. Effect of Sinomenium on ankle arthritis in rats through PI3K/Akt signaling pathway. Northwest Pharm J. 2019;37(03):71–6.
24. Fu MY, Yang JY, Wen X, et al. Sinomenium inhibits IL-1β-induced inflammation and degeneration of intervertebral disc endplate chondrocytes by blocking the activation of NF-κB pathway. Chinese J Gerontol. 2019;42(16):4045–9.
25. Kim T W, Han J M, Han Y K, et al. Anti-inflammatory effects of *Sinomenium acutum* extract on endotoxin-induced uveitis in Lewis rats. Int J Med Sci. 2018;8:758–64. https://doi.org/10.7150/ijms.24834
26. Cheng H, Xia B, Guo Q, et al. Sinomenium attenuates 2, 4, 6-trinitrobenzene sulfonic acid-induced colitis in mice. Int Immunopharmacol. 2007;7(5):604–11. https://doi.org/10.1016/j.intimp.2007.01.003

27. Tao CS. Preliminary study on the role of Sinomenium in melanin synthesis and skin inflammation and its external preparation. China: Naval Medical University; 2017.
28. Jiang Y, Gao M, Wang W, et al. Sinomenium hydrochloride protects against polymicrobial sepsis via autophagy. Int J Mol Sci. 2015;2015(2):2559-73. https://doi.org/10.3390/ijms16022559
29. Wu M Y, Li C J, Yiang G T, et al. Molecular regulation of bone metastasis pathogenesis. Cell Physiol Biochem. 2018;46(4):1423-38. https://doi.org/10.1159/000489184
30. Coury F, Peyruchaud O, Machuca-Gayet I. Osteoimmunology of bone loss in inflammatory rheumatic diseases. Front Immunol. 2019 ;10:679. https://doi.org/10.3389/fimmu.2019.00679
31. Wang K, Zeng XZ, Tao L, et al. Effects of Sinomenium combined with aconitine on RANKL expression and osteoclast formation in CD4~+ T cells. Pharmacol Clin Chinese Mater Med. 2016;32(03):61-5.
32. Zou Y, Li H, Shangjiang YZ, et al. Effects of *Sinomenium hydrochlorideaspirin* on proliferation, differentiation, mineralization of MC3T3E1 cells and its possible mechanism. Jiangxi Med J. 2018;53(02):119-21.
33. Ding CZ, Yao Y, Fang Y, et al. Effects of Sinomenium on serum OPG/RANKL and IL-17 levels in collagen-induced arthritis rats [J]. Journal of Nanjing University of Traditional Chinese Medicine,2012,28(04):330-333.
34. Zhang HR, Ji JY, Hou XQ, et al. Effect of Sinomenium on CaN/NFAT pathway on CIA bone destruction. Chinese J Immunol. 2019;36(12):1447-52.
35. Ji JY, Guo Z, Huang YG, et al. Research progress of Sinomenium in inhibiting bone destruction in rheumatoid arthritis. J Pract Med. 2019;35(14):2338-41.
36. Ji JY. Study on the mechanism of Sinomenium regulating NF-κB signaling pathway to inhibit the differentiation of MDSC into OC in CIA mice. China: China Three Gorges University; 2021.
37. Wang ZL. Effect of Zhengqing Fengtongning injection on expression of β-CATENIN, MMP-13 and TGF-β in rabbit KOA model. China: Heilongjiang Academy of Chinese Medicine; 2021.
38. Shen RM, Li GQ, Li L, et al. lncRNA RGMB-AS1 regulates proliferation, migration and invasion of synovial fibroblasts in rheumatoid arthritis by targeting miR-129-5p. Curr Immunol. 2002;42(05):387-94.
39. Cai H, Zhang BB. Research progress of fibroblast-like synovial cells in rheumatoid arthritis. Modern Med J. 2017;45(09):1362-6.
40. Sheng XH, Xie XF. Effect of Zhengqing Fengtongning sustained-release tablet on apoptosis of synovial fibroblast-like cells in human rheumatoid arthritis by regulating HOTAIRM1/miR-137 axis. Chinese J Immunol. 2019;37(20):2475-81.
41. Cai ST, Sun JT, Wei X. The mechanism of miR-23b-3p targeting XIAP to regulate the proliferation and apoptosis of synovial fibroblasts in rheumatoid arthritis. Chinese J Pathophysiol. 2019;35(07):1310-5.
42. Li J, Fu TT, Zhang GF, et al. Sinomenium induces apoptosis of human rheumatoid arthritis fibroblast-like synovial cells by miR-23b-3p/FGF9. Chinese J Pathophysiol. 2019;36(09):1653-60.
43. Xu J. Study on the therapeutic effect and mechanism of ethanol extract of Sinomenium in the treatment of rheumatoid arthritis. China: Nanjing University of Chinese Medicine; 2015.
44. Han J. Experimental study of Sinomenium against synovial-related cytokines in rheumatoid arthritis. China: Chengdu University of Traditional Chinese Medicine; 2013.
45. Yi L, Lyn Y J, Peng C, et al. Sinomenium inhibits fibroblast-like synoviocyte proliferation by regulating alpha7nAChR expression via ERK/Egr-1 pathway. Int Immunopharmacol. 2018;56:65-70. https://doi.org/10.1016/j.intimp.2018.01.015
46. Ouyang L. Study on efficacy of Qingfengteng combined with Heishun tablet in treatment of rheumatoid arthritis. China: Hunan University of Chinese Medicine; 2019.
47. Yang J. Clinical effect of Zhengqing Fengtongning on degenerative knee arthritis. Inner Mongolia J Trad Chinese Med. 2001;40(7):32-3 [in Chinese].
48. Guo JQ. Effect of Zhengqing Fengtongning Tablet combined with Febuxostat Tablets on gouty arthritis. Clin Res. 2019;27(3):118-9.
49. Liu JF, You ZX, Yang CG. Effect of minimally invasive technique of traditional Chinese medicine combined with Zhengqing Fengtongning intraarticular injection on knee osteoarthritis. Inner Mongolia J Trad Chinese Med. 2019;42(7):91-3.
50. Rong QJ, Yang S, Han JC, et al. Mechanism of action of *Sinomenium acutum* in intervention against knee osteoarthritis: A study based on network pharmacology and molecular docking. Hunan J Trad Chinese Med. 2019;39(10):170-6.
51. Zheng J, Wang RH, Kou JS, et al. Effects of Sinomenium on the expression of endothelial growth factor and nerve growth factor in cartilage and synovial blood vessels of rabbit model of knee osteoarthritis. Chinese J Inform Trad Chinese Med. 2016;23(03):38-41.
52. Liu Z, Sun J, Liang T, et al. Increased expression of cyclooxygenase-2 in synovium tissues and synovial fluid from patients with knee osteoarthritis is associated with downregulated microRNA-758-3p expression. Exp Ther Med. 2021;22(3):1001. https://doi.org/10.3892/etm.2021.10433
53. Ma AX, Kou JS, Lu XH. Study on the mechanism of Sinomenium intervention in knee osteoarthritis rats based on RNA-Seq technique. Chinese J Integr Trad Western Med. 2018;44(1):77-83.
54. Wu ZY, Chen ZQ, Song WG, et al. Study on the mechanism of the treatment of diabetic nephropathy based on network pharmacology. Hunan J Trad Chinese Med. 2022;38(4):156-61.
55. Sharmila R, Sindhu G, Arockianathan P M. Nephroprotective effect of beta-sitosterol on N-diethylnitrosamine initiated and ferric nitrilotriacetate promoted acute nephrotoxicity in Wistar rats. J Basic Clin Physiol Pharmacol. 2016;27(5):473-82. https://doi.org/10.1515/jbcpp-2015-0085
56. Teng J, Zhao LJ, Zhou SH, et al. Research progress of Sinomenium hydrochloride in the treatment of nephropathy. Guiding J Trad Chinese Med Pharm. 2019;25(16):120-4.
57. Yang CM, Yang ZX, Ma XL. Research progress of AGE-RAGE signaling pathway in diabetic nephropathy. Acta Chinese Med. 2019;34(09):1864-8.
58. Ni HM. Protective effect of Sinomenium hydrochloride on mesangial proliferative glomerulonephritis in rats. China: Guangdong Pharmaceutical University; 2021.
59. Liu Y, Li PY, Zhang QH, et al. Effect of Sinomenium on PI3K/mTOR signaling pathway and mesangial hyperplasia in adriamycin nephropathy rats. J Clin Nephrol. 2001;21(04):314-9.
60. Bi GY, Liu CH, Xu J, et al. Clinical observation of 24 cases of IgA nephropathy with moderate albuminuria treated by glucocorticoid combined with Zhengqing Fengtongning. J Trad Chinese Med. 2013;19(05):52-4.
61. Duan XY, Huo ZP, Feng XC, et al. Progress of pharmacological research on Sinomenium in the treatment of gouty arthritis. Tianjin Pharm. 2019;36(1):73-8.
62. Chen X, Mao B, Che DY, et al. Clinical observation of electro-porous transdermal administration of Zhengqing Fengtongning Injection in the treatment of gouty arthritis. J Emerg Trad Chinese Med. 2014;23(04):706-8.
63. Zhang LY, He CH, Zhao ZZ, et al. Neuroprotective effect of Sinomenium regulating GSK3β/Nrf2/HO-1 and NF-κB signaling pathway in mice with Parkinson's disease. Trad Chinese Drug Res Clin Pharmacol. 2019;35(05):607-14.

64. Langston J W. The MPTP story. J Parkinsons Dis. 2017;7(s1):S11–S19. https://doi.org/10.3233/JPD-179006
65. Nagatsu T, Nakashima A, Watanabe H, et al. Neuromelanin in Parkinson's disease: Tyrosine hydroxylase and tyrosinase. Int J Mol Sci. 2022;23(8):4176. https://doi.org/10.3390/ijms23084176
66. Huo YH, Wang J, Yin LX. Sinomenium alleviates MPP+ induced SK-N-SH cell damage by ANRIL/miR-626 axis. Chinese J Pathophysiol. 2019;36(08):1404–12.
67. Zhang YH, Wen WL, Zhang WY, et al. Treatment of rheumatoid arthritis by injection of Sinomenium solid lipid nanoparticles under fluorescence confocal microscope. China J Chinese Mater Med. 2019;48(14):3786–92.
68. Dong HY, Cong Y, Wu CS, et al. Clinical effect of acupuncture and moxibustion combined with Zhengqing Fengtongning injection on knee joint swelling pain of rheumatoid arthritis. Inner Mongolia J Trad Chinese Med. 2023;42(7):117–8.