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Multi-target Mechanism of Action of Curcumin in Rheumatoid Arthritis and Clinical Application

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Abstract:

Rheumatoid arthritis (RA) has become a common disease that poses a significant threat to human health, and its conventional therapeutic approaches exhibit certain limitations. In recent years, increasing attention has been directed toward the clinical application and underlying mechanisms of Curcumin in the treatment of RA. This article presents a literature review that systematically summarizes the pathogenesis of RA, the pharmacological properties of curcumin, its mechanisms of action in RA, as well as relevant clinical studies and their application within the framework of traditional Chinese medicine (TCM) syndrome differentiation. Existing evidence suggests that curcumin can effectively alleviate clinical symptoms in patients with RA and improve overall therapeutic outcomes. Its core mechanisms are primarily associated with the modulation of anti-inflammatory pathways. Meanwhile, the majority of studies have validated its role as a foundational therapeutic agent. In conclusion, curcumin demonstrates a certain degree of feasibility in the treatment of RA; however, further high-quality clinical trials are required to verify its safety and to strengthen the evidence base for its clinical feasibility.

Keywords: Rheumatoid arthritis, Curcumin, Multi-target mechanism, Inflammatory pathways, Osteoclast inhibition.

1. Introduction

Rheumatoid Arthritis (RA) is a chornic autoimmune disease characterized by the destruction of synovial membranes, joint cartilage, and bones. The disease course is recurrent. In the late stage, it's prone to cause joint deformity and loss of function, seriously affecting the quality of life of patients. It has become a common chronic disease that endangers human bone health worldwide.

At present, the clinical treatment for RA mainly involves non-steroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs, which can alleviate clinical symptoms to a certain extent. However,

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there are significant individual differences in therapeutic effects, and long-term use can lead to notable adverse reactions. Moreover, it's difficult to effectively prevent joint and bone destruction. Therefore, at this stage, the search for safe and effective treatment drugs and strategies that can simultaneously target multiple points has become an important direction in RA research.

Turmeric, as a traditional and commonly used Chinese medicinal herb, is pungent, bitter, warm, and enters the liver and spleen meridians. It has the effects of promoting qi circulation, breaking blood stasis, regulating menstruation, relieving pain, removing blood stasis, and reducing swelling. In clinical practise, it's often used in the treatment of arthralgia and blood stasis syndromes. Curcumin, as the core active component of turmeric, has multiple pharmacological activities such as significant anti-inflammatory, immune regulation, and anti-bone resorption effects, with low toxicity and high safety, providing a new candidate drug for the treatment of autoimmune diseases. In recent years, the application value of curcumin in the treatment of RA has gradually attracted attention. Relevant studies have found that it can alleviate the symptons of arthritis and prevent the destruction of bone and cartilage by regulating multiple inflammatory pathways, balancing immune cells, and inhibiting the differentiation of osteoclasts, demonstration of osteoclasts, demonstrating good clinical application potential. This article expounds the mechanism of action and clinical efficacy of curcumin in the treatment of RA and provides a reference basis for further basic research and clinical transformation and application of curcumin in the treatment of RA in the future.

2. Modern Medical Pathogenesis of RA

RA is a chronic autoimmune disease characterized mainly by chronic, symmetrical, polyarticular inflammation. Its pathogenesis can be divided into four main stages: initiation stage, immune cell activation stage, synovial inflammation and hyperplasia stage, and chronic injury and joint destruction stage.

2.1 Initiation Stage

The general etiology is attributed to two major factors: genetic and environmental factors. In individuals carrying RA-susceptible genes such as HLA-DR4 and HLA-DR1, the antigen-binding groove structure of their antigen-presenting cells (APCs) is abnormal, making them more prone to presenting citrullinated autoantigens rather than non-self antigens, laying the foundation for the activation of the autoimmune system. The heritability of these genes is approximately 50%–60%, but a single gene is insufficient to cause disease. Therefore, environmental factors also play a crucial role in initiating the pathogenic process. For instance, infections, smoking, and stress can activate the immune system, break immune tolerance, and trigger the production of autoantibodies.

2.2 Immune Cell Activation Stage

This stage is the central link in the pathogenesis of RA, in which T and B cells become activated, establishing immune inflammation and continuously amplifying inflammatory signals.

T-cell activation: Presented by HLA-shared epitope (HLA-SE) molecules, citrullinated antigens activate $CD4^+$ T cells and drive their differentiation into pro-inflammatory subsets. Th1 cells secrete large amounts of IFN-γ, while Th17 cells mainly produce IL-17A and IL-21 as effector cytokines. Meanwhile, the function of regulatory T cells is suppressed, so even an increase in their number fails to effectively inhibit inflammation. Special subsets such as cytotoxic $CD4^+$ CTLs highly express NKG7 and granzyme K, which can directly kill synovial cells; clonal expansion of memory T cells prolongs the inflammatory response, enabling sustained activation even after the initial trigger disappears.

B-cell activation: Activated $CD4^+$ T cells transmit signals and assist B cells in differentiating into plasma cells, which secrete large quantities of rheumatoid factor (RF) and anti-CCP antibodies. Autoantibodies bind to autoantigens to form immune complexes, which then deposit in the joint synovium, activate the complement system, and recruit neutrophils and macrophages, further amplifying the local inflammatory response and promoting disease progression to the next stage.

2.3 Synovial Inflammation and Hyperplasia Stage

The normal synovium consists of only 1–3 cell layers. However, under long-term stimulation by cytokines such as IL-1, TNF-α, and IL-17, fibroblast-like synoviocytes (FLS) proliferate excessively, and vascular endothelial cells also undergo massive hyperplasia, forming a granulation tissue-like lesion rich in neovascularization known as pannus. Cells at the pannus margin adhere tightly to articular cartilage and continuously erode the cartilage and bone tissue.

During pannus formation, pro-inflammatory factors, including TNF-α, IL-6, and IL-17, remain persistently high in concentration, activating FLS, macrophages, neutrophils, and other cells to release large amounts of proteases and oxygen-free radicals, which destroy cartilage collagen and proteoglycans. At the same time, osteoclasts are activated under the induction of RANKL and IL-17, leading

to increased subchondral bone resorption. The high permeability of newly formed synovial blood vessels causes local edema and circulatory disturbances, further exacerbating inflammation and forming a sustained pathological vicious cycle.

2.4 Chronic Injury and Joint Destruction Stage

Persistent long-term inflammation leads to a gradual loss of cartilage matrix, thinning of cartilage thickness, and eventual complete exposure of subchondral bone. Excessive activation of osteoclasts increases bone resorption, resulting in cystic changes, osteoporosis, and progressive narrowing of the joint space. Pannus erodes ligaments, tendons, and joint capsules, causing typical deformities such as ulnar deviation of the fingers and swan-neck deformity, ultimately leading to loss of joint function.RA is not merely a joint disease but also causes systemic inflammatory disorders. Pro-inflammatory factors such as IL-6 and TNF-α enter the systemic circulation and may affect the respiratory system, inducing interstitial pulmonary fibrosis; impact the cardiovascular system, increasing the risk of atherosclerosis, pericarditis, and other diseases; or cause cutaneous and ocular manifestations, including subcutaneous rheumatoid nodules, Sjögren's syndrome, and scleritis. It can also lead to hematological abnormalities such as anemia of chronic disease and thrombocytosis.

3. Pharmacological Foundations of Curcumin in Traditional Chinese Medicine (TCM)

From the perspective of TCM theory, curcumin has the functions of promoting blood circulation, removing blood stasis, and supporting the body's vital energy. The pathogenesis of RA (RA) is that the stagnation of qi leads to poor blood circulation, resulting in blood stasis and blocking the meridians of the joints, thus causing joint swelling and tingling. The main active ingredient of turmeric, curcumin, has the effects of promoting blood circulation, removing blood stasis, regulating qi, and unblocking meridians, which corresponds to the pathogenesis of qi stagnation and blood stasis. Curcumin has a pungent taste and can promote the circulation of qi and blood. It has a bitter taste and can unblock the stagnant qi. This improves the poor blood circulation caused by qi stagnation and plays a role in promoting blood circulation. At the same time, turmeric is warm in nature and can warm and disperse the cold, qi stagnation, and stagnant blood in the body, restoring the normal flow rate of blood. Thus, it can relieve the stinging and swelling caused by joint blood stasis. In addition, RA is a chronic autoimmune disease. The core issue lies in immune disorder, weakened repair capacity, and persistent chronic inflammation. This is also a manifestation of the overall insufficiency of vital energy and a weak constitution. Curcumin is warm in nature. It can nourish qi and blood, unblock meridians, restore the functions of internal organs, continuously generate new qi and blood, thereby supporting the body's vital energy and enhancing the body's own ability to resist diseases and expel pathogenic factors. This can suppress the persistent inflammation caused by immune disorders, promote the repair of damaged joint meridians, and fundamentally improve the state of deficiency of vital energy.

4. Mechanism of Curcumin in the Treatment of RA

Modern pharmacology suggests that curcumin treats RA through multi-targeting.

4.1 RANKL Signal Pathway

Nuclear factor κB receptor activating factor ligand (RANKL) is one of the inflammatory stimulators of osteoclastogenesis, and there are many downstream pathways involved in its induction of osteoclastogenesis, including the NF-kB pathway and the MAPK cascade. In addition, the RANK-TRAF6 signalling axis links RANKL to a variety of downstream signals. RANK binds to TRAF6 in response to RANKL stimulation. Mutations in TRAF6 cause it to lose its osteoclastogenic activity, leading to osteosclerosis. Mutations in RANK lead to deletion of the TRAF6 binding site, which fails to restore the osteoclastogenic potential of RANK- /- haematopoietic precursor cells [1]. TRAF6, as a key bridging protein, is responsible for assembling signalling proteins, which trigger downstream signalling transduction [2-4]. Overall, RANK-TRAF6 signalling determines the signalling cascade downstream of RANKL. Dianshan Ke et al. used a combination of ex vivo and in vivo experiments to isolate mouse bone marrow-derived osteoclast precursors and induced their differentiation with RANKL, and then sorted out the $RANK^+$ from $RANK^+$ cells and $RANK^+$- cells using flow cytometry and transduced with lentivirus. The levels of autophagy and related pathways were assessed using Western blotting, co-immunoprecipitation, immunofluorescence, and transmission electron microscopy. In addition, a Tg-hRANKL mouse model was established to evaluate bone loss and osteoclast formation in vivo using Micro-CT, H&E staining, and TRAP staining. This study verified the effect of curcumin on autophagic activity of osteoclast precursors (OCPs) under RANKL intervention. Both curcumin and RANKL promote LC3 conversion

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rate as well as autophagosome and autophagolysosome formation in OCPs. However, the LC3II/ LC3I ratio as well as the number of autophagosomes and autophagic lysosomes in RANKL-promoted OCPs were inhibited by curcumin. In addition, this experiment investigated the effect of curcumin on the RANKL pathway by detecting the expression of several osteoclast-associated proteins, and confirmed that in the presence of RANKL, curcumin inhibited the expression of TRAF6 protein in osteoclast precursors in a concentration-dependent manner [5].

4.2 IKK Signal Pathway

Curcumin also blocks the phosphorylation and ubiquitination degradation of IκBα by inhibiting the activation of the IκB kinase (IKK) complex in the downstream pathway branches. Under normal conditions, IκBα degradation releases NF-κB heterodimers, mainly p65/p50, which cause nuclear translocation of the p65 subunit and enter the nucleus to initiate the transcription of target genes. NF-κB usually exists in the form of p65/p50 heterodimers and binds to IκBα to form a complex. In the experiment, peripheral blood mononuclear cells from RA patients were isolated and cultured into osteoblasts, and intervened with different concentrations of Cur (0, 2.5, 5, and 10 μmol/L), and then the expression of IκBα and phosphorylated IκBα were detected by Western blot in the cells of each group [6]. Studies have shown that IκBα degradation is inhibited by curcumin, and IκBα binding to p65 obscures the nuclear localisation signal on p65 and prevents it from being recognised by the importin α/β nuclear transport system. As a result, the NF-κB complex is unable to enter the nucleus through the nuclear pore complex (NPC) and remains in the cytoplasm, and NF-κB transcriptional activity is inhibited, blocking its transcriptional activation at the promoter of the nuclear factor of activated T cells 1 (NFATc1), a key transcription factor (TF) in osteoblast differentiation. Since NFATc1 is the main regulator of RANKL-induced osteoclast differentiation, its decreased expression will further inhibit the transcription of downstream osteoclast-specific genes (e.g., TRAP, Cathepsin K, DC-STAMP, etc.), thus inhibiting osteoclast differentiation and bone resorption, as show in the figure1.

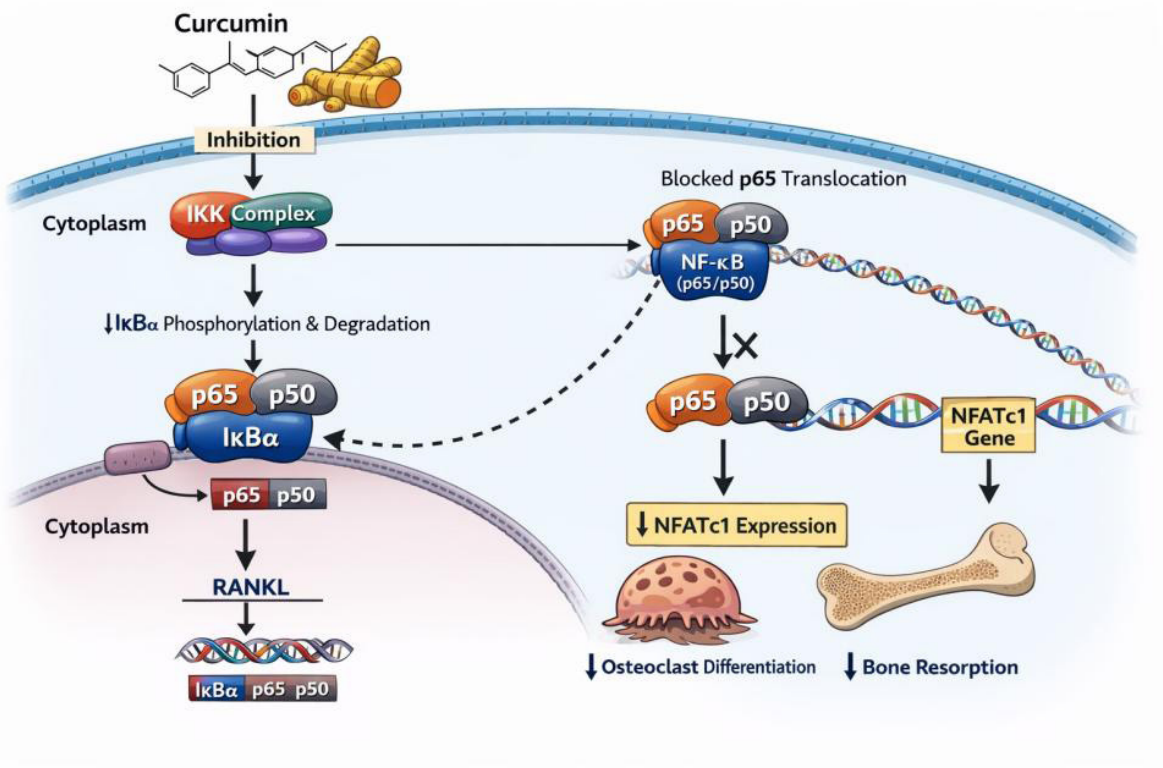

Fig. 1 IKK signal pathway (picture: original)

4.3 MAPK Signal Pathway

The MAPK/RANK/c-Fos/NFATc1 pathway is a key pathway involved in bone remodeling [7]. Curcumin inhibits osteoclast formation from peripheral blood mononuclear cells (PBMCs) of patients with RA (RA) by targeting multiple components of the three MAPK branches, namely ERK1/2, JNK, and p38. This effect is essential for preventing bone degeneration in RA [7].

4.3.1 ERK signal pathway

Specifically, in the ERK pathway, binding of extracellular growth factors such as EGF, FGF, etc. or cytokines to the receptor tyrosine kinase (RTK) on the cell membrane induces dimerization of the receptor and autophosphorylation of tyrosine residues, which in turn recruits the articulatory protein Grb2 and the guanosine exchange factor SOS. Subsequently, SOS facilitates the transition of the small GTPase Ras protein from GDP-bound to GTP-bound state to a GTP-bound activated state. Activated Ras-GTP further recruits and activates Raf kinase (MAPKKK), promoting the activation of Raf phosphorylation, whereas curcumin blocks this pathway by inhibiting the activation of Raf phosphorylation, resulting in a decrease in the downstream phosphorylation of MEK1/2 (MAPKK) and ERK1/2 (MAPK), and consequently a decrease in the number of TFs that translocate to the nucleus to phosphorylate ERK1/2.Subsequently, SOS promotes the small GTPase Ras protein by reducing the number of GDP-conjugated TFs, which regulates the expression of target genes leading to a decrease in the expression of inflammation-associated genes, which ultimately manifests itself as an inhibition of synoviocyte cellular proliferation and inflammation, as show in the figure2.

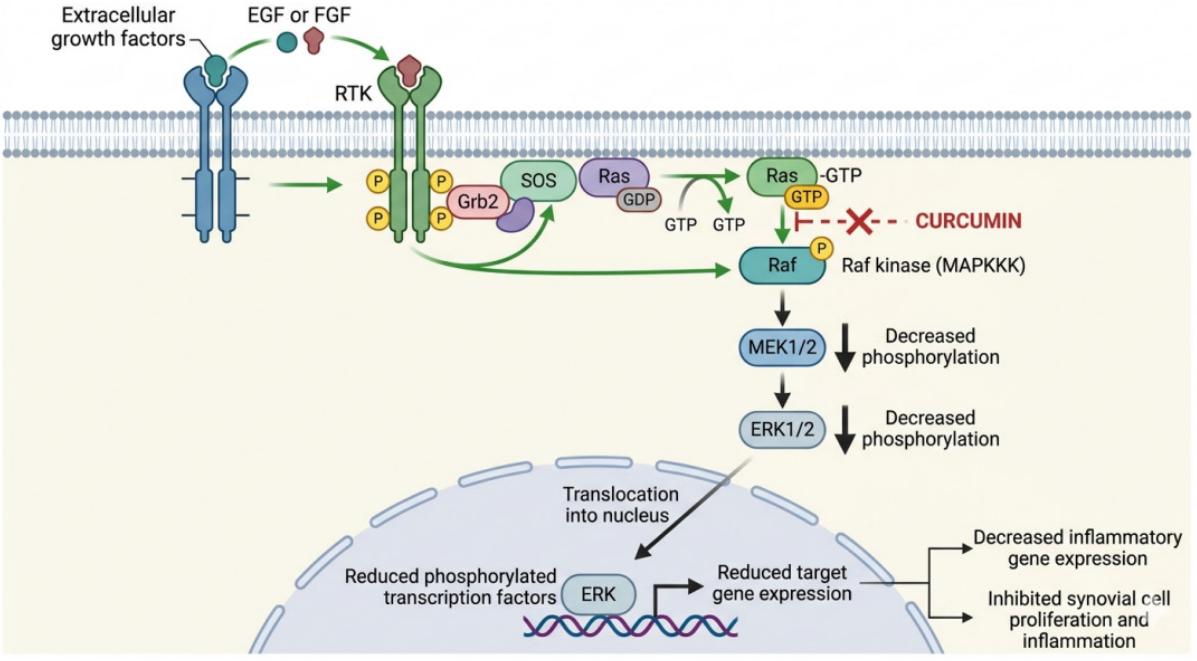

Fig. 2 MAPK(ERK) signal pathway (picture: original)

4.3.2 JNK signal pathway

In the JNK branch, the Tumor Necrosis Factor Receptor (TNF receptor) or Toll-like receptor (Toll-like receptor) is activated in response to inflammatory stimuli or cellular stress conditions, and recruits the articulatory proteins TNF receptor associated factor 6 (TRAF6) or TNF receptor associated factor 6 (TRAF6) or TNF receptor associated factor 2 (TRAF2), which in turn activates upstream ASK1 and TAK1 (MAPKKK), followed by MAPKKK activation of MKK4 and MKK7 (MAPKK) through phosphorylation, and activated MKK4/MKK7 further activation of JNK through dual phosphorylation of the Thr/Tyr sites. In this pathway, curcumin blocks the pathway mainly by inhibiting this site, which greatly reduces the dimerization of JNK and its translocation into the nucleus, thus decreasing the phosphorylation of multiple TFs and inhibiting the formation of the AP-1 TF complex, which disrupts the expression of inflammatory genes, as show in the figure3.

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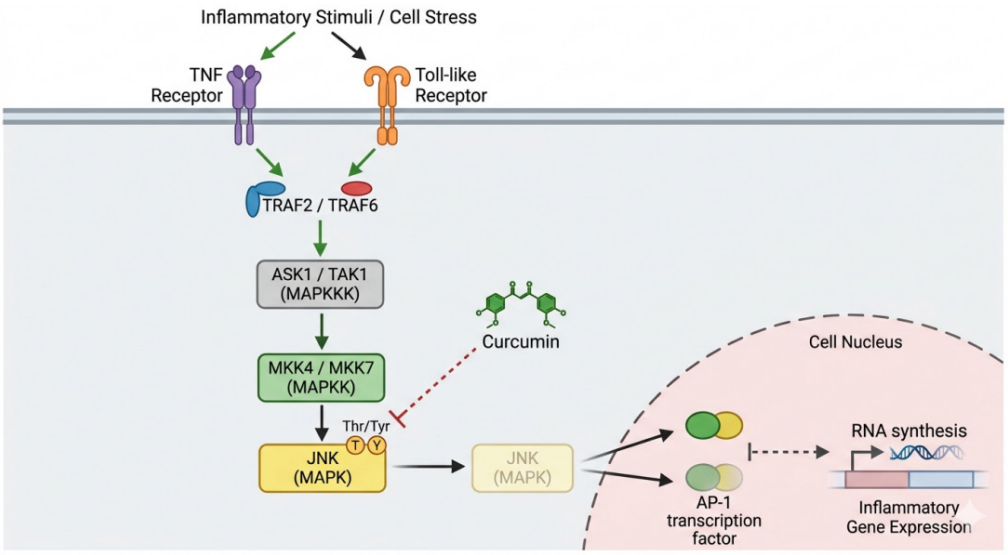

Fig. 3 MAPK(JNK) signal pathway (picture: original)

4.3.3 p38 signalling pathway

In the p38 pathway, inflammatory stimuli such as TNF-α, IL-1β, lipopolysaccharide (LPS) and reactive oxygen species (ROS) activate the Tumor Necrosis Factor Receptor or Toll-like receptor on the cell membrane, thereby initiating downstream signal transduction. Activation of the receptor further activates the upstream MAPK kinase kinase (MAPKKK), i.e., Transforming growth factor beta-activated kinase 1 (TAK1). TAK1 then activates MAPK kinases (MAPKK), including MKK3 and MKK6, through phosphorylation, and activated MKK3/MKK6 further activates p38 MAPK through dual phosphorylation at the Thr/Tyr site. curcumin inhibits the phosphorylation of p38 MAPK, thereby blocking MAPK-p38 signaling and reducing the activation of downstream TFs. Factor activation levels and inhibit the expression of inflammatory factors such as TNF-α, IL-6, and COX-2. By inhibiting this inflammatory pathway, curcumin is able to reduce synovial inflammatory response and inhibit cartilage destruction, thus exerting anti-inflammatory effects in the treatment of RA, as show in the figure4.

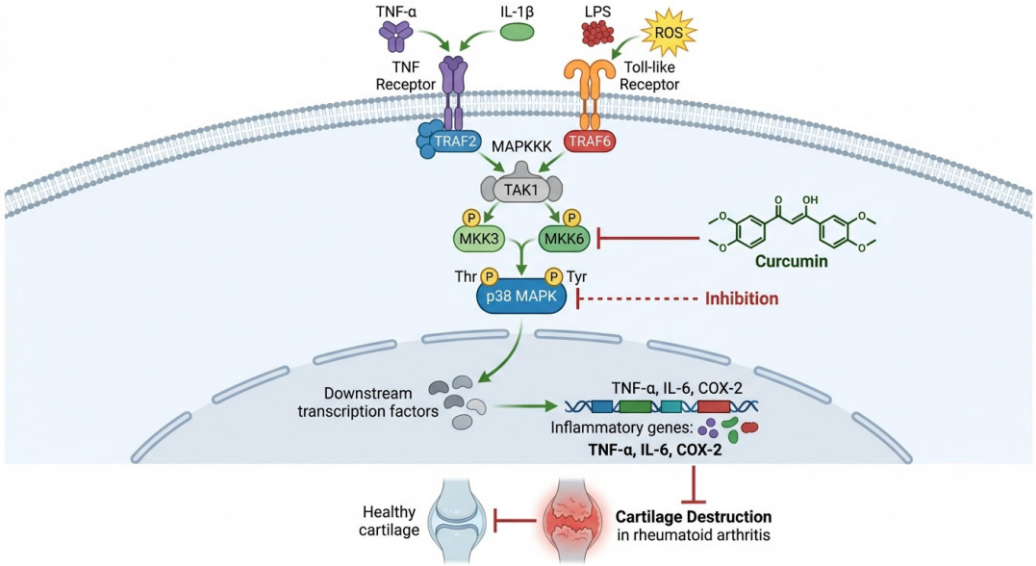

Fig. 4 MAPK(p38) signal pathway (picture: original)

4.4 Immune Pathway

In addition, curcumin regulates T-cell immune homeostasis in the immune pathway.

Th17 cells, a subpopulation of Th cells discovered in recent years, mainly secrete IL-17, which is involved in

different phases of RA, including inflammatory response, cartilage destruction, and bone erosion. Tregs are regulatory T cells with unique immunosuppressive functions, which can play a negative immunoregulatory role by secreting the inflammation-suppressing cytokine TGF-β1 [8], and play an important role in the maintenance of autoimmune tolerance. Therefore, regulating the balance of Th17/Treg cells may be clinically important in improving clinical symptoms and preventing joint damage in RA. 30 RA patients with a mean age of 52 years were included in this study.10 m L of fresh peripheral venous blood was collected from each subject and collected into heparin vacuum blood collection tubes.CD4+ T cells were isolated using RosetteSep stem cell technology and the purity of CD4+ T cells was detected by flow cytometry. Intervention of CD4+ T cells in RA patients with 1μg/m L curcumin resulted in a significant decrease in the percentage of Th17 cells and a significant increase in the percentage of Treg cells. Consistent with this, 1μg/m L curcumin significantly reduced IL-17 levels in cell culture supernatants from RA patients, but significantly increased TGF-β1 levels. These data suggest that curcumin specifically reduces the in vitro differentiation of Th17 cells from CD4+ T cells in RA patients, while promoting their differentiation to Treg cells. And curcumin could modulate the function of Th17 and Treg cells in RA patients by decreasing IL-17 and increasing TGF-β1 production, but had no effect on T cell immune homeostasis in healthy patients [9].

5. Clinical Research

Dr Mohammad Bagherniya et al. have found curcumin to have significant efficacy in the clinical treatment of RA through a number of clinical trials. In a double-blind, placebo-controlled clinical study, two groups of RA patients were given 250 mg and 500 mg of a turmeric matrix preparation (containing bioavailable curcumin) twice daily for 90 d [10]. The clinical symptoms of the patients improved, and the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), visual analogue scale scores, rheumatoid factor (RF), 28 joint disease activity (DAS - 28), and the RF, were significantly higher in the RA patients when compared with those in the baseline and placebo groups. The improvement in, RF, DAS - 28 scores and American College of Rheumatology (ACR) scores, appeared to be more effective in high dose formulations [7]. A systematic evaluation of six studies (involving 259 patients with RA of 6-12 weeks duration) showed that the effect of curcumin in reducing DAS - 28 score, VAS score and increasing ACR - 20 score varied from one study to another and no serious side effects were reported with curcumin consumption, so curcumin can be used as a safe drug for the treatment of RA [11]. However, its inherent hydrophobic nature has led to many limitations in its pharmaco kinetics. For example, it has low absorption and poor bioavailability when administered orally, with only about 1% bioavailability in rats, as well as rapid metabolism and high body clearance. On the other hand, curcumin usually requires a high dose (generally greater than 3.6 g-d-^{1}) to produce significant pharmacological effects, and these factors have largely limited its further clinical application. In response to these issues, in recent years researchers have developed a variety of novel curcumin formulations with a view to improving its in vivo absorption and increasing its bioavailability. For example, drug delivery systems have been reported including liposomes, solid dispersions, polymeric micelles, cyclodextrin inclusion complexes, microspheres, and various nanoformulations, etc., and these novel formulations provide new ideas and directions to enhance the clinical value of curcumin to some extent.

6. Conclusion

This review systematically summarizes the pathogenesis of RA, the pharmacological mechanisms of curcumin, and its multi-target therapeutic effects on RA, including the regulation of inflammatory pathways (NF-κB, MAPK), inhibition of osteoclast differentiation via RANK-RANKL-TRAF6 signaling, and restoration of the Th17/Treg immune balance. Clinical studies further indicate that curcumin can alleviate clinical symptoms, reduce inflammatory markers (ESR, CRP), and improve DAS-28 with a favorable safety profile. Collectively, curcumin demonstrates significant potential as a natural adjunctive therapy for RA, acting through multiple mechanisms to address both inflammation and bone destruction. However, current evidence is limited by the low oral bioavailability and rapid metabolism of curcumin, as well as the lack of large-scale, high-quality clinical trials. Future research should focus on optimizing novel drug delivery systems (e.g., nanoparticles, liposomes) and conducting well-designed multicenter trials to validate its long-term safety and clinical efficacy, thereby facilitating the translation of curcumin into routine RA management.

With the continuous advancement of precision medicine and nanotechnology, the therapeutic potential of curcumin in rheumatoid arthritis is expected to expand considerably in the future. Emerging delivery strategies, including lipid-based carriers, polymeric nanoparticles, hydrogels, and targeted nanoformulations, may significantly improve the stability, absorption efficiency, and tissue-specific accumulation of curcumin, thereby overcoming its current pharmacokinetic limitations. In addition, future studies may

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further clarify the synergistic effects between curcumin and conventional disease-modifying antirheumatic drugs (DMARDs), which could contribute to reducing drug dosage and minimizing long-term adverse reactions in RA patients. Increasing attention is also being directed toward the regulation of immune metabolism, gut microbiota, and epigenetic modifications in autoimmune diseases. As a natural compound with multi-target biological activity, curcumin may provide broader therapeutic benefits beyond anti-inflammatory effects alone. Therefore, integrating curcumin into personalized and combination-based treatment strategies could represent a promising direction for the long-term management of RA.

Despite the encouraging findings reported in current studies, several limitations remain and should be acknowledged. First, many experimental studies were conducted using animal models or in vitro cell systems, which cannot fully replicate the complex pathological environment and individual variability observed in human RA. Second, the majority of available clinical trials involved relatively small sample sizes and short intervention periods, limiting the reliability of conclusions regarding long-term efficacy and safety. In addition, differences in curcumin formulations, dosage regimens, and assessment criteria among studies may introduce heterogeneity and reduce comparability between results. Some mechanistic pathways associated with curcumin have also not been completely clarified, particularly regarding its interactions with immune signaling networks and systemic metabolic regulation. Furthermore, the poor oral bioavailability of curcumin remains a major obstacle affecting its translational application in routine clinical practice. Consequently, more standardized experimental designs and large-scale multicenter investigations are still required to provide stronger evidence for its clinical utilization in RA treatment.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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