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REVIEW

Pharmacological Mechanisms and Therapeutic Potential of Resveratrol in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by chronic synovitis of the joints, accompanied by systemic involvement of multiple systems. Resveratrol (Res) is a natural polyphenolic compound found in various plants, particularly abundant in grape skins, red wine, and peanuts. This article summarizes the pharmacological effects of Res in RA. Res can alleviate RA symptoms through various mechanisms, including inhibiting the production of inflammatory cytokines, suppressing synovial cell proliferation and angiogenesis, and protecting joint cartilage. For extra articular manifestations, Res mainly exhibits the effects of reducing inflammation of RA pulmonary interstitial disease (RA-ILD), improving the degree of pulmonary fibrosis, and reducing periodontal damage. Animal model studies support the anti-arthritis effect of Res, while clinical trials provide preliminary evidence of its potential benefits in reducing pain and improving quality of life in RA patients. Although early studies have shown that Res has anti RA potential, more large-scale, multicenter clinical trials are still needed to validate its safety and efficacy.

Keywords: rheumatoid arthritis, resveratrol, pharmacological

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease. Due to the lack of comprehensive epidemiological research in certain areas, the global incidence of RA remains inadequately defined; however, it is suggested that the incidence rate among women is approximately three times that of men.[1–3] The main manifestations of RA are joint synovitis, synovial hyperplasia, and the formation of vascular opacities. Inflammation progressively damages bone and cartilage, leading to joint deformities.[4] In addition to joint involvement, extra-articular manifestations (EAMs) and comorbidities are common in RA,[5] primarily as a result of the disease's complex chronic inflammatory and autoimmune characteristics. These manifestations are diverse and frequently affect multiple organ systems, including the skin, cardiovascular system, lungs, eyes, and hematologic system.[6,7] If not treated in a timely manner or improperly, RA can cause progressive disability, systemic complications, greatly reduce the patient's quality of life, and even premature death.[8] Despite significant successes in preventing and alleviating disease activity in RA patients with the ongoing development of disease-modifying antirheumatic drugs (DMARDs), some patients still exhibit limited responses to DMARD therapy.[9] Therefore, it is imperative to develop new anti-arthritis therapies. Natural medicines, as a significant source of new drug molecules, possess the advantages of a broad spectrum of biological effects and minimal toxic side effects, making them a focal point for researchers in the study of various diseases and the development of therapeutic drugs.

Resveratrol (3,4′,5-trihydroxystilbene, Res) is a naturally occurring polyphenol that is widely found in grapes, peanuts, berries, and red wine.[10] An increasing body of evidence suggests that Res holds great potential in the prevention and treatment of a variety of diseases, including cardiovascular diseases, diabetes, obesity, cancer, and neurological disorders.[11–14] Notably, its anti-inflammatory, antioxidant, and immunomodulatory mechanisms demonstrated in these conditions provide a theoretical foundation for its application in chronic inflammatory diseases such as RA.[15,16] A schematic overview of these mechanisms is presented in Figure 1. In recent years, an increasing number of preclinical and clinical studies have also shown that Res exerts beneficial effects in the management of RA. Meanwhile, existing

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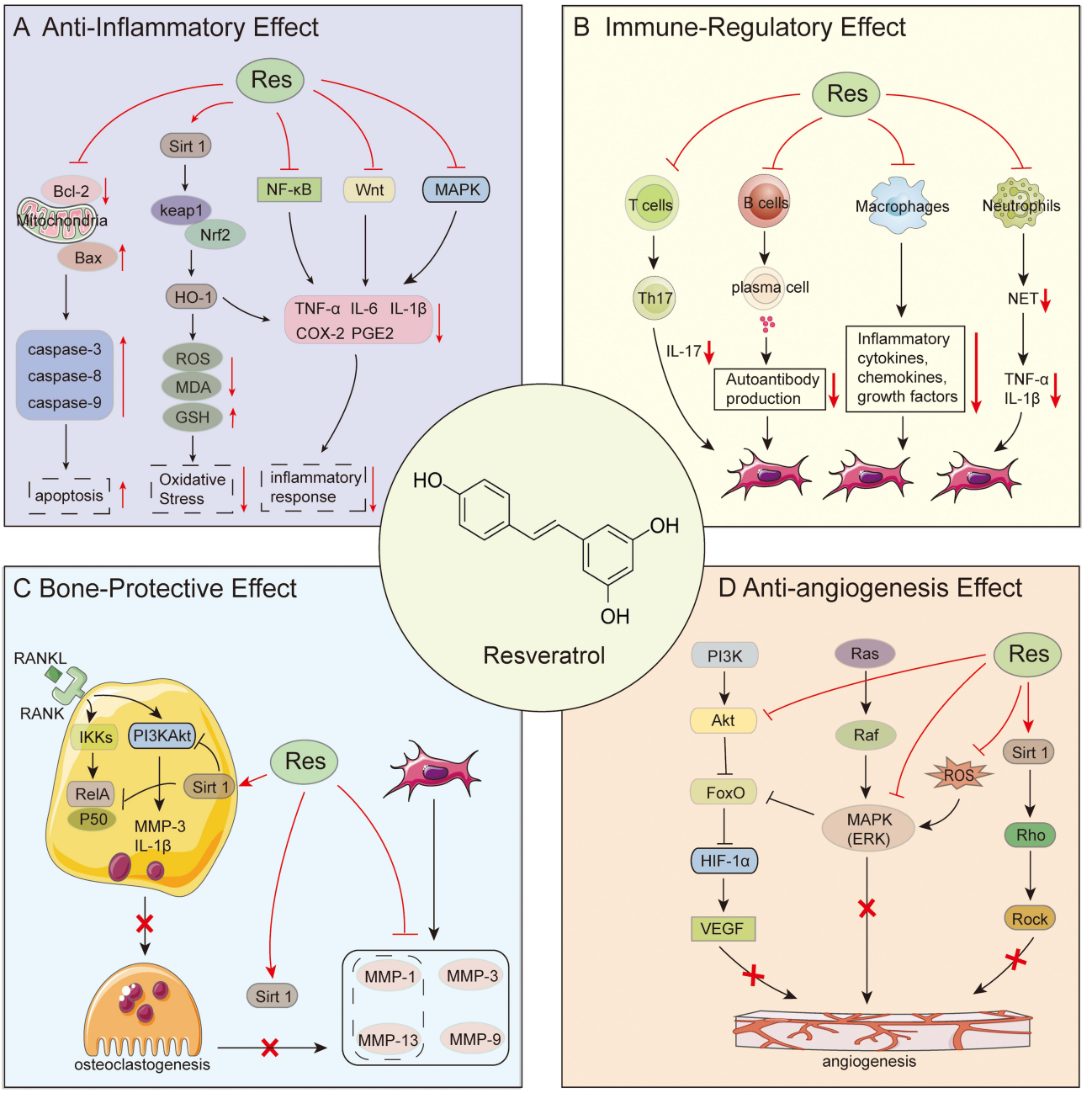

Figure 1 Pharmacological Mechanism of Res in Pre-Clinical Studies. The anti-articular effect of Res on RA in pre-clinical studies. (**A**) The anti-inflammatory effect of Res on RA: Res reduces pro-inflammatory cytokines (TNF - α, IL-1 β, IL-6, PGE2, COX-2) by regulating signaling pathways such as MAPK, Wnt, MEK/Erk, NF - κ B, STAT3, etc; By activating or inhibiting signaling pathways such as SIRT1-Nrf2, Nrf2 Keap1, NF - κ B, etc., ROS generation is reduced and oxidative stress is suppressed, effectively reducing the inflammatory response of RA synovium; Regulating FLS behavior through mitochondrial pathways, autophagy, endoplasmic reticulum stress, and promoting cell apoptosis. (**B**) The immune-regulatory effect of Res on RA: Res exhibits immunomodulatory effects by reducing NET production, inhibiting Th17 cell numbers, lowering IL-17 production, regulating B cell function, inhibiting activated macrophages, restoring cytokine network balance, and metabolic homeostasis. (**C**) The bone-protective effect of Res on RA: Res exerts bone-protective effects by regulating Sirt-1, PI3K/Akt signaling pathways, or inhibiting inflammatory factors to reduce the production of MMPs and RANKL, thereby decreasing osteoclast formation. (**D**) Anti-angiogenesis Effect of Res on RA: Res can synergistically activate the FOXO transcription factors by modulating the PI3K/AKT and Ras/MEK/ERK pathways, thereby inhibiting angiogenesis. It also suppresses the MAPK signaling pathway by reducing the accumulation of reactive oxygen species (ROS), alleviating HIF-1α-mediated angiogenesis. Additionally, the activation of SIRT1 induced by Res restores metabolic homeostasis and impedes Rho/ROCK-mediated angiogenesis.

clinical studies have shown that Res exhibits good safety and tolerability at conventional doses and with short-term use. Healthy volunteers taking high oral doses of resveratrol (0.5–5.0 g) were generally well tolerated, with no serious adverse events reported; only a small number of participants experienced mild and reversible gastrointestinal discomfort or

changes in blood biochemical parameters.[17] Preliminary studies in patients with chronic diseases have also not reported any serious toxicity.[18] Given the remarkable advantages of Res in terms of efficacy and safety, a systematic discussion of its mechanisms of action is crucial for deepening our understanding of its potential therapeutic value in both articular and EAMs of RA. This review will focus on the effects and underlying mechanisms of Res on joint and extra-articular involvement in RA.

Anti-Inflammatory Effect

Effect of RES on Clinical Parameters and Inflammatory Parameters

RA is a typical inflammatory disease, and its pathological mechanism is mainly dominated by chronic inflammation caused by immune system abnormalities. RA is distinguished by its cardinal pathological feature, synovitis, which is manifested by the dysregulated proliferation of synovial tissue and the localized infiltration of a spectrum of immune and inflammatory cell populations; Numerous studies have shown that Res can reduce paw edema and alleviate inflammation in arthritis models.[19]

In the antigen induced arthritis (AIA) rat model, Res significantly reduced joint swelling, downregulated histological scores of synovial tissues, and reduced the main pathological features of RA disease in the acute AIA model.[20] Res can significantly reduce serum levels of Interleukin-1β (IL-1β), C-reactive protein (CRP), and Prostaglandin E2 (PGE2), inhibit inflammatory responses, and alleviate the severity of acute AIA models. This is mainly achieved by inducing atypical autophagy pathways and limiting crosstalk with inflammation, regulating synovial proliferation, and thus exerting a protective effect.[21] In another antigen induced arthritis mouse model, Res significantly reduced joint edema, decreased inflammatory cytokines, alleviated joint damage, and reduced Neutrophil Extracellular Trap (NET) production and hyperalgesia by reducing inflammation mediated by Peptidyl arginine deiminase 4 (PADI4) and Cyclooxygenase-2 (COX-2).[22]

Similarly, in the adjuvant arthritis (AA) rat model, Res can significantly reduce joint edema, synovial hyperplasia, inhibit inflammatory cell infiltration and joint cartilage degeneration, reduce the expression of COX-2, PGE2, Malondialdehyde (MDA), promote the production of Superoxide Dismutase (SOD) and Interleukin-10 (IL-10), and significantly improve the histopathology of arthritis in AA rats.[19,23,24] Further mechanistic studies have shown that Res can inhibit oxidative stress and increase Mitochondria-derived reactive oxygen species (mtROS) production in AA rats by reducing autophagy proteins Beclin1, LC3A/B, and oxidative stress protein Manganese superoxide dismutase (MnSOD), thereby promoting Synovial fibroblasts (FLS) apoptosis.[23] Another study showed that Res can alleviate the severity of AIA in rats by inhibiting M1 polarization, restoring cytokine network balance and metabolic homeostasis.[24] Through microinjection of Calcium release-activated calcium modulator 1(ORAI1) and injection of ORAI1 SiRNA, it was found that ORAI1 may be a key target regulated by Res for fibroblast apoptosis. This study also found that Res exhibited partial dose-dependent inhibition of calcium pool manipulation calcium influx (SOCE), indicating that Res reduces calcium pool manipulation Ca2+influx by targeting the ORAI1-STIM1 complex and promotes apoptosis of fibroblast like synovial cells in adjuvant arthritis rats.[25] In addition, new drug delivery methods can improve the bioavailability of Res and even achieve better therapeutic effects. A study has designed a soluble microneedle (MNs) drug delivery system loaded with res nanocrystals (NC) for the treatment of RA. This delivery system prolongs the duration of Res in vivo and reduces inflammation by inhibiting excessive ROS during the development of RA, thereby suppressing the progression of RA.[26] Similarly, some researchers have developed a NE2 gel containing Res for local use. Through in vivo research, it was found that local treatment with Res can effectively reduce the activity of local macrophages and down regulate the levels of proinflammatory mediators (TNF - α, IL6, IL-1 β and COX-2).[27]

Similarly, in a collagen induced arthritis (CIA) rat model, Res improved the clinical and histopathological manifestations of inflammatory arthritis (synovium inflammation and cartilage bone destruction). Res mitigates the severity of RA by reducing the accumulation of ROS, inflammation, and angiogenesis in the synovial tissue. This may be related to Res inhibiting the MAPK signaling pathway by reducing ROS accumulation, thereby suppressing inflammatory response and cell proliferation, inducing cell apoptosis in synovial tissue, and alleviating HIF-1 α - mediated angiogenesis.[28] Research

has found that the Src kinase, STAT3, and Wnt signaling pathways are active in the CIA model, and Res can inhibit these signaling pathways and improve inflammatory arthritis.[29]

In vitro, early studies have found that curcumin and Res inhibit IL-1 β - or U0126-induced apoptosis of human articular chondrocytes, as well as downregulation of β 1-integrins and extracellular regulated protein kinases (Erk1/2), indicating that the anti-inflammatory and anti-apoptotic effects of Res and/or curcumin are at least partially mediated through the MEK/Erk signaling pathway.[30] In human synovial monocytes, Res exhibits anti-inflammatory properties in an ex vivo model of immune-mediated inflammatory arthritis, and produces additional effects when Res binds to methotrexate in lymphocyte dominated samples and samples from low disease activity patients.[31] In human rheumatoid arthritis synovial fibroblasts (RASF), upregulation of Sirt1 by Res can weaken the acetylation of c-Jun and c-Fos (AP-1 subunit) as well as NF - κ B, thereby inhibiting the COX-2 expression and PGE2 synthesis induced by bradykinin(BK) in human RASF, reducing BK mediated responses, and reflecting its anti-inflammatory effect.[32] A recent study found that in the establishment of a TNF - α - induced inflammatory cell model in rat primary fibroblast like synovial cells, pre-treatment with Res can time - and dose-dependent inhibit TNF - α - induced IL-1 β and IL-6 secretion, and upregulate Sirtuin 1 and corticotropin mRNA and protein expression. Res can effectively inhibit inflammatory responses, mainly by upregulating Sirt1 expression to regulate the active components of endogenous CST, thereby inhibiting synovial inflammatory responses.[33]

In summary, numerous in vivo and in vitro studies have shown that Res can effectively reduce the inflammatory response in RA through multiple mechanisms, including alleviating joint damage, inhibiting inflammatory cytokines and related signaling pathway activation, and promoting apoptosis of FLS. Both animal models and cell experiments have confirmed its anti-inflammatory and joint-protective effects. Despite these advances, current research remains focused primarily on mechanistic studies, and more systematic evaluation is needed regarding dose-response relationships, long-term safety, and clinical application prospects.

Inhibition of Oxidative Stress

Oxidative stress plays a crucial role in the pathogenesis of RA, mainly by regulating the activity of pro-inflammatory cytokines, abnormal proliferation of synovial fibroblasts and fibroblast like synovial cells, activation of nitric oxide and prostaglandin E2, overgrowth of synovial blood vessels, generation of vascular opacities, lipid peroxidation and other pathological reactions that affect the expression of inflammatory responses, leading to oxidative damage in the body.[34]

Research has found that mitochondrial dysfunction may induce inflammatory responses in normal human synovial cells and make these cells sensitive, leading to an increase in IL-1 β - induced inflammatory responses, while Res can reduce inflammatory responses by reducing ROS production and NF-κB activation.[35] Meanwhile, Res can inhibit oxidative stress and increase mtROS production in AA rats by reducing autophagy proteins Beclin1, LC3A/B, and oxidative stress protein MnSOD, thereby promoting FLS apoptosis.[24] Further research has shown that Res can increase mitochondrial reactive oxygen species production, demonstrating the important role of reactive oxygen species in Res mediated RA-FLS apoptosis.[36] Res can exert a protective effect against arthritis by reducing PCNA, CD68, CD3, and monocyte chemoattractant protein-1 staining, as well as cytokine induced neutrophil chemoattractant protein-1 concentration in serum. It can also lower the levels of DNA damage marker 8-oxo-7,8-dihydro-20-deoxyguanine and upregulate peroxidase activity in synovial tissue.[20] Res can also promote the expression of Nrf2 and HO-1, reduce Keap1, inhibit the production of ROS and MDA, suppress the activation of NF - κ B and the proliferation and migration of RA-FLS, and activate Bcl-2/Bax to induce cell apoptosis.[37] Furthermore, Res can also suppress the generation of ROS and the proliferation of FLS by activating the silent information regulator 1 (SIRT1)/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway.[38]

In conclusion, oxidative stress plays a central role in the pathogenesis of RA. Numerous in vivo and in vitro studies have shown that Res can reduce inflammation-related ROS levels through various mechanisms, regulate autophagy and mitochondrial function, promote apoptosis of FLS, and activate antioxidant signaling pathways such as Nrf2/HO-1 and SIRT1. Evidence from different models supports its protective effects in reducing oxidative damage and inhibiting synovial inflammation. However, current research is mainly limited to basic experiments, and the clinical significance and long-term safety of Res's antioxidant effects require further investigation.

Regulation of Behavior of FLS

FLS play a crucial role in joint diseases such as RA. The behavioral characteristics of FLS, such as proliferation, migration, invasion, resistance to apoptosis, and secretion of cytokines, are its core functions in disease development.

Research has found that activation of caspase-8 is crucial for triggering Res induced apoptosis signaling through the mitochondrial pathway in RA FLS. Activated caspase-8 induces mitochondrial apoptosis events by inducing Bid cleavage, but does not alter the levels of Bax, Bcl xL, or Bcl2.[39] Interestingly, in another study, Res activated caspase-3 and caspase-9 in MH7A cells, but did not activate caspase-8, and upregulated the expression of nicotinamide adenine dinucleotide (NAD) dependent deacetylase sirtuin 1 mRNA and downregulated the expression of Bcl XL mRNA.[40] There is a certain difference between the two results, which may be related to differences in experimental cell models. In RA, autophagy is known to promote survival, inhibit FLS cell apoptosis, and participate in synovial hyperplasia. However, studies have found that Res can induce a decrease in autophagy, leading to mitochondrial dysfunction and abnormal mitochondrial morphology in FLS, resulting in cell apoptosis in FLS.[41] At the same time, studies have also found that Res can promote fibroblast like synovial cell apoptosis through mitochondrial dysfunction and endoplasmic reticulum stress.[42] In TNF - α - mediated RA-FLS cells, Res reversed autophagy, inhibited cell survival, and promoted apoptosis, which may be related to Res inhibiting the PI3K/AKT pathway, increasing p53 expression, reducing cyclin B1 expression, and further blocking the G2/M phase of cells.[43]

In conclusion, Res has been shown to promote FLS apoptosis through multiple mechanisms, including caspase activation, mitochondrial dysfunction, autophagy inhibition, and endoplasmic reticulum stress. Although some studies have reported differences in the specific apoptotic pathways involved, these discrepancies may be due to variations in experimental models. Overall, evidence from different studies supports the potential of Res to inhibit FLS proliferation and survival, thereby limiting synovial hyperplasia and joint destruction in RA.

Immune-Regulatory Effect

In the pathogenesis of RA, immune cells play a crucial role. Immune cells trigger immune responses in synovium, leading to extensive infiltration of inflammatory cells and formation of vascular opacities. Interactions between different immune cells often amplify or exacerbate inflammatory responses.[44]

Neutrophils can also be recruited into joints by cytokines, which are powerful pain mediators and often cause inflammation.[22] In the AIA arthritis model, the level of NET is high, and the NET released from the joints induces the release of TNF - α and IL-1 β through Toll like receptors. These cytokines lead to increased expression of COX-2, resulting in hyperalgesia, while Res reduces the production of NET and hyperalgesia by reducing inflammation mediated by PADI4 and COX-2.[22] T cells and B lymphocytes, especially type 17 T helper cell (Th) - dependent pathways, are believed to play a critical role in the occurrence and persistence of diseases.[45–47] B cells may function by producing autoantibodies and acting as antigen-presenting cells.[48,49] In the CIA mouse arthritis model, Res can inhibit the production of Interleukin-4 (IL-4), Interleukin-13 (IL-13), and IFN γ in CIA mice, and downregulate IgG serum levels, which may be related to the decrease in Th17 cell numbers and IL-17 production. This suggests that Res may regulate mouse collagen induced arthritis by inhibiting Th17 and B cell function.[50] Monocytes and macrophages play a pathogenic role in RA primarily due to the production of pro-inflammatory cytokines, chemokines, growth factors, and free radicals.[51] To enhance bioavailability, some studies have encapsulated Res and modified the surface of micelles with bovine serum albumin (BSA) to construct pH-sensitive micelles. In vitro and in vivo validation has shown that Res reduces the levels of pro-inflammatory cytokines, clears excess ROS produced by activated RAW264.7 cells, and inhibits the formation of osteoclasts. Additionally, it can target inflamed joint areas, significantly alleviating joint inflammation symptoms, suppressing activated macrophages, improving synovial hyperplasia and inflammatory cell infiltration, and protecting cartilage.[52] Research has found that SIRT1 has anti-inflammatory properties, and SIRT1 deficiency is associated with immune abnormalities and metabolic changes related to AIA, which has been identified as a potential target for RA treatment. However, in the AIA rat model, insufficient expression of SIRT1 in white blood cells leads to polarization imbalance of monocytes. Res, as an agonist of SIRT1, can alleviate the severity of AIA in rats by inhibiting

M1 polarization, promoting IL-10 production, suppressing IL-1 β and IL-6 secretion, restoring cytokine network balance and metabolic homeostasis.[23]

In short, Res exerts its immunomodulatory effects in RA mainly by reducing NET formation, suppressing Th17 cell responses, regulating B cell function, and restoring monocyte homeostasis. In addition, Res inhibits activated macrophages, which helps to re-establish the balance of cytokine networks and metabolic homeostasis. These multifaceted actions contribute to its potential as an effective immunoregulatory agent in the treatment of RA.

Bone-Protective Effect

The development of RA leads to abnormal proliferation of synovial cells, releasing various cytokines. Continuous stimulation of inflammatory cytokines can lead to the formation of inflammatory synovial granulation tissue, forming synovial vascular opacities with inflammatory cells and small blood vessels.[53] Synovial vascular opacities secrete matrix metalloproteinases (MMPs) into the synovial fluid, which then transfer to the extracellular matrix, cutting the main components of cartilage, such as type II collagen, and diffusely degrading and reabsorbing cartilage from the side of the joint cavity.[54] Furthermore, cytokines directly stimulate the maturation of osteoclasts and induce the expression of Receptor Activator of Nuclear Factor-κB Ligand(RANKL) in synovial cells and T cells, thereby promoting osteoclast maturation.[54]

Due to the known impact of phytoestrogens on the biology of osteoblasts and osteoclasts, and the regulation of osteoclast activity by osteoblasts through RANKL expression, studies have found that Res inhibits RANKL induced NF - κ B acetylation and nuclear translocation in a time-dependent and concentration dependent manner. In addition, Res activation of Sirt-1 can induce Sirt-1-p300 binding in bone derived cells and pre osteoblasts, leading to RANKL induced NF - κ B deacetylation, NF - κ B transcriptional activation inhibition, and osteoclastogenesis.[55] Similarly, studies have confirmed through in vitro and in vivo studies that in RA, Res can regulate synovial cell invasion and reduce joint damage by upregulating Sirt1 and inhibiting the expression of MMP-1 and MMP-13.[53] Further research has found that Res can also reduce the expression of MMP-1, MMP-3, and MMP-9, and inhibit IL-1 β - induced RANKL expression and osteoprotegerin (OPG) expression. This suggests that Res may reduce joint damage by inhibiting the excessive production of MMPs and RANKL that cause chondrocyte degeneration and pathological bone resorption in RA.[56] In addition, Res also reduces TNF - α - induced production of IL-1 β and MMP-3 in RA FLS by inhibiting the PI3K/Akt signaling pathway, indicating that these molecular effects of Res on RA may be mediated by the aforementioned signaling pathways.[57]

Overall, these findings indicate that Res protects bone and cartilage in RA not only by downregulating catabolic enzymes and bone-resorbing factors such as MMPs and RANKL, but also by modulating key regulatory pathways including Sirt-1/NF-κB and PI3K/Akt. Through these coordinated mechanisms, Res helps to reduce joint destruction and thereby exerts a bone-protective effect.

Anti-Angiogenesis Effect

Angiogenesis is crucial to the pathogenesis of inflammatory diseases, including RA. In the progression of RA, angiogenesis within the synovial tissue is a necessary condition for maintaining a chronic inflammatory state and synovial hyperplasia. The angiogenic process is sustained by various mediators, such as growth factors, primarily vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF), as well as pro-inflammatory cytokines, various chemokines, matrix components, cell adhesion molecules, proteases, and others.[58]

Research has shown that Res can inhibit angiogenesis and metastasis. Further studies have shown that inhibiting the PI3K/AKT and Ras/MEK/ERK pathways can synergistically activate Forkhead box O (FOXO) transcription factors, thereby inhibiting angiogenesis. The regulation of FOXO transcription factors by Res may play an important role in angiogenesis, which has physiological significance for the treatment of RA.[59] In the BIIC induced rat model, Res eliminated ROS and inflammation. Further research found that Res downregulated the increase in HIF-1 α levels and activation phosphorylation of MAPK and c-Jun N-terminal kinase in IL-1 β - stimulated cells, leading to G0/G1 cell cycle arrest and increased apoptosis levels. This suggests that Res may inhibit the MAPK signaling pathway by reducing ROS accumulation, thereby suppressing inflammation and cell proliferation, and inducing cell apoptosis in synovial

tissue, while alleviating HIF-1 α - mediated angiogenesis.[28] Some studies suggest that the RA environment is conducive to the glycolysis of VEC, providing sufficient energy to maintain Rho/ROCK activation, thereby promoting abnormal angiogenesis in a HIF-1 independent manner. Insufficient activation of SIRT1 is considered a key factor in related metabolic reprogramming, while RSV induced SIRT1 activation will restore metabolic homeostasis and hinder Rho/ROCK mediated angiogenesis.[60]

In conclusion, current studies indicate that resveratrol can regulate relevant molecules through multiple signaling pathways (such as PI3K/Akt, Ras/MEK/ERK, MAPK, and Rho/ROCK), inhibit neovascularization in synovial tissue, and reduce inflammation and tissue hyperplasia, thereby providing new potential strategies for the treatment of RA.

Anti-Extra-Arthritic Effect

RA is not limited to joints and may present with many extra articular manifestations and complications.[5] The lungs are often affected organs due to their abundant connective tissue and blood supply, and rheumatoid arthritis interstitial lung disease (RA-ILD) is a group of diseases characterized by interstitial fibrosis and inflammation. Research has found that Res can alleviate pulmonary fibrosis, increase autophagy flux, regulate the autophagy lysosome pathway, especially by improving the formation of autophagosomes. However, the therapeutic effect of Res is not uniform, and the degree of fibrosis improvement varies, which may be related to individual treatment differences of Res.[61] Similarly, studies have also confirmed that Res can alleviate fibrosis in RA related interstitial lung disease, reduce oxidative stress and inflammation in RA-ILD, and restore cellular autophagy. Combined with in vitro models, it has been further demonstrated that Res can inhibit TGF - β 1 expression, reduce AKT degeneration and activation, restore autophagy flux through the AKT/MEM175 pathway, and thereby alleviate inflammation and fibrosis in RA-ILD.[62] In addition, Res therapy can significantly improve lung diseases and prevent the production of pro-inflammatory cytokines. Meanwhile, Res inhibited the JAK/STAT/RANKL signaling pathway in RA-ILD rats, indicating that Res may improve lung disease in RA-ILD rats by regulating the JAK/STAT/RANKL signaling pathway.[63] Periodontal disease is a bacterial and chronic inflammatory disease that can cause damage to periodontal support structures.[64] Different studies have linked oral bacterial infections (measured by bacterial load or serum titers) to the triggering and progression of RA.[65] A study on the effects of continuous administration of Res on the progression of experimental periodontitis and arthritis in rats has found that it can regulate serum RF levels, reduce periodontal damage and local Anti-Cyclic Citrullinated Peptide Antibodies (ACCP) levels in RA patients, thereby reducing RA activity and severity, reducing inflammatory symptoms and joint damage of arthritis. Lower ACCPA gingival levels can also reduce periodontal damage.[66]

Regulation of autophagy, antioxidant, and anti-inflammatory activities by Res may help improve pulmonary disease, alleviate lung fibrosis, and reduce periodontal destruction associated with RA. Although these findings support the therapeutic potential of Res in treating extra-articular complications of RA, further clinical studies are needed to validate its efficacy and explore individual variability in treatment response.

Potential Effect of RES in Clinical Studies

There have been many preclinical studies showing the effectiveness of Res in various diseases, such as Alzheimer's disease,[67] diabetes,[68] knee osteoarthritis,[69,70] ulcerative colitis,[71,72] etc. Although there are few clinical related studies of Res on RA, there are also clinical studies to clarify the protective effect of Res on RA.

In a randomized controlled trial, two groups (10 participants in each group) of healthy participants with normal body weight were randomly assigned to either a placebo group or PCE extracted from Polygonum cuspidatum containing 40 milligrams of Res per day for 6 weeks. The results showed that PCE containing Res inhibited ROS generation in monocytes, the expression of TNF - α, IL-6, SOCS-3, as well as plasma concentrations of TNF - α and CRP, demonstrating that Res has good anti-inflammatory and reactive oxygen species inhibitory effects.[73] In another randomized clinical trial, 100 RA patients were randomly enrolled and divided into two groups of 50 patients each: the Res treatment group took 1 gram of Res capsules per day and received routine treatment for 3 months; The control group only received conventional treatment. The Res treatment group can significantly reduce swelling and tenderness, as well as disease activity scores of 28 joints. In addition, Res can also reduce the levels of CRP, ESR, MMP-3, TNF - α, and IL-6 in serum.[74]

The above two studies demonstrate that Res has good anti-inflammatory and antioxidant effects, reduces disease activity, and improves disease management. This indicates that Res has a therapeutic effect on RA and can be considered as an adjuvant therapy for traditional anti rheumatic drugs.

Conclusion and Future Directions

RA is a chronic inflammatory and autoimmune disease, with main pathological processes including synovitis, autoimmune response, cartilage and bone damage. If left untreated or improperly treated, patients may even exhibit various extra articular manifestations, including involvement of the lungs, cardiovascular system, nervous system, and musculoskeletal system.

In this review, we summarized the protective effects of Res on RA in anti-inflammatory, immune regulation, bone protection, angiogenesis, and extra articular anti-inflammatory aspects (Table 1). Firstly, Res can reduce synovial inflammation by lowering joint clinical parameters and inflammatory cytokines, inhibiting oxidative stress, and regulating FLS behavior. Secondly, Res exhibits immunomodulatory effects by reducing NET production, inhibiting Th17 and regulating B cell function, restoring monocyte homeostasis, inhibiting activated macrophages, restoring cytokine network balance and metabolic homeostasis. Thirdly, Res inhibits the production of MMPs, regulates the secretion of OPG and RANKL, and the formation of osteoclasts by modulating the Sirt-1 and PI3K/Akt signaling pathways or suppressing inflammatory factors, thereby exerting a bone protective effect. Fourthly, Res exerts anti proliferative and anti-angiogenic effects by regulating FOXO transcription factors, MAPK signaling pathway, and Rho/ROCK. Fifth, for extra articular manifestations, Res mainly

Table 1 Potential Mechanism of Res in Pre-Clinical Studies

Therapeutic Effect		Experimental		Dosage	Molecular Mechanism	Signaling Pathway
		In vivo	In vitro			
Anti-Inflammatory Effect	Effect on clinical parameters and inflammatory cytokines	AIA model	-	12.5 mg/kg/d	Reduced knee swelling, synovial hyperplasia, inflammatory markers, and oxidative damage; PCNA, CD68, CD3, MCP-1, 8-oxo-dG↓;[20]	-
		AIA model	-	12.5 mg/kg/d	p62, caspase-3, PARP, Ang-1, VEGF, IL-1β, CRP, PGE2, NF-kB↓;	Non-canonical autophagy[21]
		AIA model	-	25 mg/kg	Inhibited joint hyperalgesia; decrease in articular edema, inflammatory cytokines; PADI4, COX-2, NF-κB, NET↓;[22]	-
		AA model	Monocytes	50 mg/kg/d; 25 μM	Triglyceride, lactate and pyruvate, IL-10, SIRT1↑; IL-1β, IL-6↓;	AMPK/SIRT1[23]
		AA model	-	5,15,45mg/kg	Decreasing the swelling degree of the paw; MDA↓; SOD, Beclin1, LC3A / B, MnSOD, SIRT3, mtROS↑;[24]	-
		AA model	FLS	45mg/kg; 200 μM	Promote FLS apoptosis; SOCE, IL-1, IL-6, IL-8, TNF-α↓; IL-10↑;[25]	-
		CIA model	RSC-364	200,400 mg/kg	Suppress the inflammatory response and cell proliferation; HIF-1α, ROS, MDA↓; SOD↑;	MAPK[28]
		CIA model	-	20 mg/kg/day	Ameliorated synovitis and cartilage bone destruction; Wnt5a, MAPK3, Src kinase, STAT3↑;	Src kinase, STAT3, Wnt[29]
		-	Chondrocyte	10 μM	Inhibited apoptosis; anti-inflammatory;	MAPK[30]
		-	SFMCs	25 μM	Anti-inflammatory;[31]	-
		-	RASF	-	Inhibited the phosphorylation and acetylation of p65, c-Jun, Fos COX-2/PGE2↓;	AP-1 and NF-κB[32]
		-	FLSs	100 μM	Inhibits the inflammatory; IL-1β, IL-6↓;	Sirt1/CST[33]

(*Continued*)

Table 1 (Continued).

Therapeutic Effect		Experimental		Dosage	Molecular Mechanism	Signaling Pathway
		In vivo	In vitro			
Anti-Inflammatory Effect	Inhibition of Oxidative Stress	-	Synoviocytes	10 μM	Reduced the inflammatory response; COX-2, PGE2, IL-8, ROS↓;	NF-kB[35]
		-	FLS	50,100,200,400μM	Induced apoptosis; Beclin1, LC3A/B, SIRT3, MnSOD↓; mtROS↑;[24]	-
		-	RA-FLSs	25,50,100,200μM	Induced apoptosis; Bax, ROS, MnSOD↓; Bcl-2↑;[26]	-
		AIA model	-	12.5 mg/kg/d	Enhancing the activity of antioxidant enzymes;[20]	-
		-	RA-FLSs	1,10,20,40μM	Induce apoptosis; inhibiting cell proliferation and migration; Nrf2, HO-1, Keap1, ROS, MDA, NF-κB↓;	Nrf2–Keap1[37]
		AA model	FLSs	10 mg/kg 100μM	Decreased antioxidant enzymes; inhibited FLS proliferation; inhibited oxidative stress; ROS↓;	SIRT1-Nrf2[38]
	Regulation of behavior of FLS	-	RA-FLSs	100μM	Induce apoptosis; activation caspase-8	Mitochondrial pathway[39]
		-	MH7A	100μM	Induce apoptosis; suppress hyperplasia; Bcl-XL↓; caspase-3, caspase-9, sirtuin 1↑;[40]	-
		-	FLSs	40,80,160,320μM	Induce apoptosis; suppress hyperplasia; LC3A/B, ATG75↓;[41]	-
		-	FLSs	50,100,200,400μM	Induce apoptosis;	Mitochondrial pathway[42]
		-	RA-FLSs	50μM	Suppress hyperplasia; induce apoptosis; Beclin-1↓;	PI3K/AKT[43]
Immune-Regulatory Effect		AIA model	-	25 mg/kg	Reduces NET production and hyperalgesia; reduce inflammation;[22]	-
		CIA model	-	15 or 20 mg/kg	Inhibit Th17 and B cell function; IL-4, IL-13, IFNγ, IgG↓;[50]	-
		AA model	Monocytes	50 mg/kg/d 25μM	Impair the inflammatory polarization of monocytes; IL-10↑;	AMPK/SIRT1[23]
Bone-Protective Effect		CIA model	FLSs	2.5,10mg/kg/d 1,3,10 μg/mL	Inhibited the invasive; reduce the degree of joint damage; MMP1, MMP13↓; Sirt1↑;[53]	-
		-	RA-FLSs	-	MMP-1, MMP-3, MMP-9, RANKL, OPG↓;[56]	-
		-	RA-FLSs	6.25,12.5,25,50μM	Anti-inflammatory; IL-1β, MMP-3↓;	PI3K/AKT[57]
Anti-angiogenesis Effect		CIA model	RSC-364	200,400mg/kg 25,50μM	Suppress the inflammatory response and cell proliferation; suppressing angiogenesis; ROS, HIF-1α↓;	MAPK[28]
		-	HUVECs	25μM	Inhibited pro-angiogenesis cytokines production and glycolysis; anti-angiogenesis	Rho/ROCK[60]
Anti-Extra-Arthritic Effect		CIA model	MRC-5	10 mg/kg	Attenuates pulmonary fibrosis, increases autophagic flux;	Autophagy–lysosome[61]
		CIA model	MRC-5	1mg/mL 20,40,60,80μM	Attenuates pulmonary fibrosis; reduces oxidative stress and inflammation	AKT/TMEM175[62]
		AA model	-	10 mg/kg/d	Ameliorated the lung disease, prevented pro-inflammatory cytokines;	JAK/STAT/RANKL[63]
		CIA model	-	10 mg/kg	Reduce the inflammatory signs of arthritis and articular damage; reduce periodontal damage[66]	-

reduces inflammation of RA-ILD and improves the degree of pulmonary fibrosis in arthritis models; In addition, Res can regulate the local levels of serum RF and ACCP, reducing periodontal damage. Although in vitro and animal model studies have shown that Res has potential therapeutic effects, especially in anti-inflammatory aspects, its mechanism of action still needs further investigation. Therefore, there is an urgent need for more preclinical research in the future, especially in the areas of immune regulation, bone protection, anti-angiogenesis, and anti-extra articular effects.

Although the number of high-quality clinical studies on Res in the treatment of RA remains limited and the overall level of clinical evidence requires improvement, preliminary data already indicate a positive trend toward enhancing patient health outcomes. These clinical observations are consistent with Res's well-established anti-inflammatory and immunomodulatory activities demonstrated at the cellular and animal levels. However, current research has primarily focused on molecular mechanisms, while a deeper understanding of Res's clinical efficacy across different RA subgroups —such as those with varying disease activity, serological status, or comorbidities—and its long-term safety and tolerability profiles remains an urgent need. Furthermore, as a natural compound, Res faces inherent pharmacokinetic challenges, including low bioavailability and rapid metabolism, which significantly hinder its clinical effectiveness. Future studies should therefore incorporate advanced drug design strategies, such as structural modifications, and develop innovative delivery systems to systematically address these limitations and maximize Res's therapeutic potential. In summary, due to its unique multi-target mechanisms and the ability to intervene in key pathological processes of RA, Res shows promise distinct from conventional therapies and offers new directions for overcoming inadequate treatment responses in certain patient populations. Thus, continued efforts in comprehensive preclinical optimization and well-designed clinical trials are essential to facilitate the translation of Res into a clinically impactful anti-RA therapy.

In summary, Res, as a multifunctional natural compound, has demonstrated broad potential in the treatment of RA, particularly in its anti-inflammatory, antioxidant, and immunomodulatory functions, which may provide new therapeutic strategies for the comprehensive management of RA. However, to include Res in the standard treatment system for RA, more clinical data is needed to support it.

Ethics

There are no ethical issues involved in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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