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Review Article

Resveratrol in Rheumatological Diseases: A Systematic Review

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Abstract

Resveratrol is an antioxidant with anti-inflammatory and cell-protective properties. The aim of our article is to review the use of resveratrol in rheumatic diseases. PubMed/Medline, Embase, and Scielo were screened for articles on resveratrol and rheumatic diseases in the period between of January 1966 and March 2023. Five articles were depicted, including 481 patients. The included diseases were osteoarthritis (n = 3), rheumatoid arthritis (n = 1), and Takayasu arteritis (n = 1). The age varied from 32 to 58.2 years, and the female gender ranged from 62% to 74% in the studies. Disease duration ranged from 3.5 ± 3.2 to 9.4 ± 5.8 years. The resveratrol dosage went from 250 mg to 1000 mg/day. All those articles demonstrated improvements in the diverse rheumatic diseases, including pain intensity, function, disease activity (DAS 28), swelling joints, and reduced inflammation markers (erythrocyte sedimentation rate, C-reactive protein, interleukinIL-1, IL-6, and tumor necrosis factor). No side effects were detected in all studies. In conclusion, resveratrol seems to be a safe therapy for various rheumatic diseases, although the evidence is very limited. The improved subjective and objective complaints and laboratory parameters are promising. However, there is a need to reconfirm, reproduce, and investigate the topic in more extensive, well-controlled, double-blind, cross-over studies.

Keywords: Resveratrol, antioxidants, anti-inflammatory, rheumatological diseases, fibromyalgia

Introduction

Resveratrol or trans-resveratrol (t-Res) is a substance that has anti-inflammatory and chondroprotective effects.[1] It is easily found over the counter in most countries without any reported detrimental, severe, or toxic effects. There is evidence that supports the anti-inflammatory and antioxidative roles of t-Res in several joint cell types and also in T and B lymphocyte modulation.[2] In the same way, t-Res, when administered via oral or intra-articular, presents chondroprotective properties in models of osteoarthritis (OA) and rheumatoid arthritis (RA) by reducing proinflammatory and prodegradative soluble factors and also by immune cell modulation.[3] In addition, t-Res was evaluated in aging, cancer, neurological, cardiovascular, and liver disorders and also menopause.[3] The beneficial in vitro effects were demonstrated on various cell lines, including chondrocytes, synoviocytes, and T and B lymphocytes.[1,2]

New formulations with better availability should allow a better and accurate assessment of the supplement's efficacy in joint diseases,[4] including OA and RA patients, as an additional therapy to conventional pharmaceutical treatment. The objective of this article was to perform a systematic review to evaluate the effects of resveratrol supplementation on rheumatic diseases.

Methods

Literature Review

A systematic literature screening of articles published in PubMed, EMBASE, and Scielo in the period between January 1966 and March 2023 was conducted. We used the following MeSH entry terms: "resveratrol" OR "trans-resveratrol" AND "rheumatic" OR "rheumatologic" OR "systemic lupus erythematosus" OR "lupus" OR "rheumatoid arthritis" OR "spondyloarthritis" OR "Sjögren's syndrome" OR "myositis" OR "systemic sclerosis" OR "vasculitis" OR "Takayasu disease" OR "Wegener's disease" OR "granulomatosis with polyangiitis" OR "Kawasaki's disease" OR "polyarteritis nodosa" OR "livedoid vasculitis" OR "Churg-Strauss" OR "eosinophilic granulomatosis with polyangiitis" OR "osteoarthritis"" OR "gout"" OR "fibromyalgia." The literature search did not use language restrictions. We also screened all references of the selected articles in order to identify additional publications.

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Two authors (J.F.C. and A.L.) initially performed the literature screening and independently selected the abstracts of the articles. Then, in a second part, the same authors independently read all full-text articles that were selected. The authors followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[5] Finally, a form was constructed in order to extract the relevant information from the manuscripts, such as authors, year of publication, number of patients studied, age, gender, disease duration, study follow-up, resveratrol posology, outcomes, and side effects.

Results

Figure 1 shows the flowchart of the included articles.

Table 1 summarizes the studies of resveratrol treatment in rheumatic disease subjects.[6-10] Five articles were found, including 481 patients. The countries that reported those selected articles were Iraq (n=3), Egypt (n=1), and China (n=1). Four studies were randomized and controlled; 1 was an open trial. The investigated diseases were OA (n=3), RA (n=1), and Takayasu arteritis (n=1). Concerning OA trials, all patients were from the same rheumatology department; hence, they were counted as 1 study involving 110 subjects. Age varied from 32 ± 16 to 58.2 ± 9.1 years old, and female gender ranged from 62% to 74% in the included articles. Disease duration ranged from 3.5 ± 3.2 to 9.4 ± 5.8 years. The resveratrol dosage ranged from 250 mg to 1000 mg/day. The follow-up of all studies was 12 weeks.

All those articles demonstrated improvements in the diverse rheumatic diseases parameters, including pain intensity, function, disease activity (DAS 28), swelling joints, and reduced inflammation biomarkers [erythrocyte sedimentation rate, C-reactive protein, interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)].

Main Points

- Resveratrol is an antioxidant with anti-inflammatory and cell protection properties.
- Five articles with 481 patients in osteoarthritis (n=3), rheumatoid arthritis (n=1), and Takayasu arteritis (n=1) were found.
- All those articles demonstrated improvements in the diverse rheumatic diseases, including pain intensity, function, disease activity (DAS 28), swelling joints, and reduced inflammatory biomarkers.

More specifically, Marouf et al[6] demonstrated a significant improvement in the pain and functional status of the OA patients, and they also observed an increase in aggrecan levels. Russain et al[7] and Marouf et al[8] showed improvements in pain and function after tRes supplementation in patients with AO. An Egyptian study revealed in subjects with RA a decrease in the DAS-28 index and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels as well as a reduction in biological marker levels (osteocalcin, metalloproteinase, TNF, and interleukin-6).[9] And the last study, evaluating Takayasu arteritis patients, observed a decrease in Birmingham Vascular Activity Score, CRP, ESR, and TNF.[10]

Importantly, no study has detected any adverse effects in all studied patients.

Table 2 summarizes a few studies of t-Res use in animal models of OA and RA. All of them showed benefits with this nutraceutical (see Table 2).

Discussion

This article is the first systematic review on the therapeutic effects of resveratrol in rheumatological disorders.

Trans-resveratrol is a stilbene molecule present in natural plants, including grapes, mulberries, and peanuts. It is observed to act beneficially on oxidation, aging, inflammation, and tumor scenarios.[11]

The silent information regulator 2 type 1 (SIRT-1 or sirtuin-1) is associated with obesity, diabetes, cardiovascular disorders, cancer, dementia, arthritis, osteoporosis, and OA.[12] Trans-resveratrol is a substrate-specific activator of human SIRT-1.[13] Trans-resveratrol is the most important compound that activates SIRT-1, mimicking the effects of restriction of calories.[14] Interestingly, SIRT-1 in OA cartilage reduces along the disease progression; it seems to play a regulatory role in OA.[15]

Resveratrol has several mechanisms of action that are related to its ability to scavenge reactive oxygen species, inhibit inflammation, reduce lipid peroxidation, prevent apoptosis, and promote cell survival.

In an animal model of RA, the authors verified that t-Res diminished blood and articular tissue levels of IL-1, IL-6, and TNF and also the soluble receptor of NF-κB.[16] In addition, NF-κB expression was reduced in mice fed with t-Res. It resulted in inflammatory alleviation and bone damage in collagen-induced arthritis.[16]

The present systematic review shows that all studies that evaluated resveratrol supplementation in different rheumatic diseases led to at least one benefit, with mild or absent adverse or toxic effects.

The present study's strengths are as follows: (i) only patients fulfilling the standardized criteria for rheumatological disorders were included and (ii) the inclusion of all kinds of study designs for using resveratrol in rheumatic diseases, except animal studies and in vitro studies. In this way, the authors believe all published reports of resveratrol in rheumatic patients were captured.

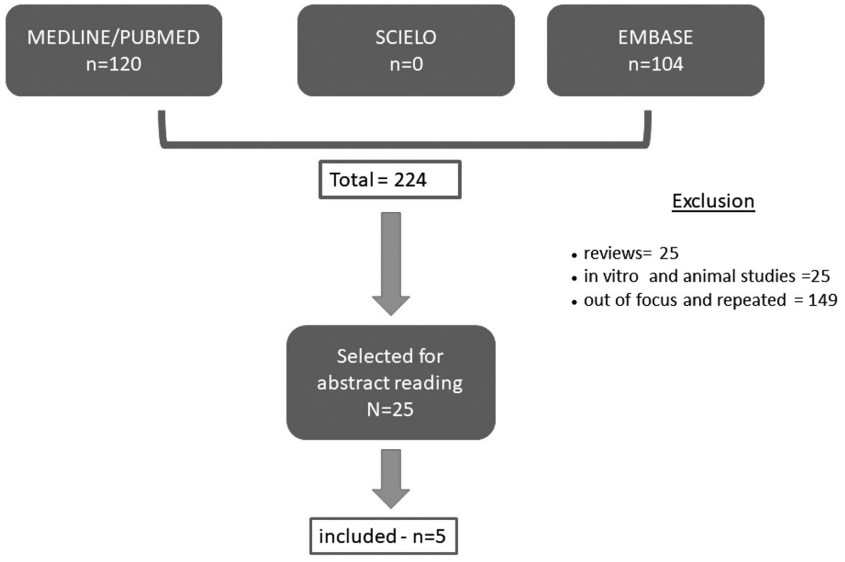

Figure 1. Flowchart of the included articles.

Table 1. Studies of Resveratrol in Rheumatic Diseases

Author (Year)	Study Design	Country	N	Age (years old)/ gender	Disease	Disease Duration	Resveratrol D0se (mg/day)	Follow-up	Outcome	Side Effects
Marouf et al (2021)[6]	Open-labeled noncontrolled clinical trial	Iraq	110	58.2 ± 9.1 74% females	Osteoarthritis	3.5 ± 3.2 years	500 mg plus meloxicam	12 weeks	Resveratrol leads to: • Non-significant reduction in the serum level of Coll 2-1 • Significant increase in aggrecan serum level • Improved pain • Improved patients' activity and functional status	None
Hussain et al (2018)[7]	Double blind, placebo controlled, randomized multicenter	Iraq	110	58.2 ± 9.1 74% females	Osteoarthritis	3.5 ± 3.2 years	500 mg	12 weeks	Resveratrol improved compared to placebo: • Pain • Functions • Associated symptoms	None
Marouf et al (2018)[8]	Randomized placebo controlled	Iraq	110	58.2 ± 9.1 74% females	Osteoarthritis	3.5 ± 3.2 years	500 mg plus meloxicam	12 weeks	Resveratrol reduced: • Pain severity • Interleukins 1 and tumor necrosis factor	None
Khojah et al (2018)[9]	Randomized, controlled trial	Egypt	100	46.5 ± 12.3 72% females	Rheumatoid arthritis	9.4 ± 5.8 years	1000 mg	12 weeks	Resveratrol reduced: • Disease activity-28 • The 28-joint count for swelling and tenderness • C-reactive protein, erythrocyte sedimentation rate • Undercarboxylated osteocalcin, matrix metalloproteinase-3, tumor necrosis factor alpha, and interleukin-6	None
Shi et al (2016)[10]	Randomized double-blind and placebo-controlled trial	China	271	32 ± 16 62% females	Takayasu arteritis	NA	250 mg	12 weeks	Resveratrol decreased: • Birmingham Vascular Activity Score (BVAS) • Erythrocyte sedimentation rate (ESR), plasma levels of C-reactive protein, and TNF	None

Table 2. Animal Studies on The Use of Resveratrol Supplementation in Osteoarthrtiis and Rheumatoid Arthritis Experimental Models

Auhor (Year)	Animal Model	Resveratrol Dosage	Variables Studied	Follow-up	Outcome	Side Effects
Ebrhaim et al (2022)	Diabetes induced by streptozotocin (osteoarthritis)	30 mg/kg for 14 days	Damage to the knee joints and loss of proteoglycans from the articular cartilage, w (osteoarthritis)	12 weeks	Osteoarthritis was effectively but not completely protected by resveratrol. Trans-resveratrol (t-Res) reduced hemoglobin A1c, hyperlipidemia, inflammation, and oxidative stress	None
Elmali et al (2005)	Rabbits underwent unilateral anterior cruciate ligament transection (osteoarthritis)	10 μmol/kg resveratrol in dimethylsulphoxide in the knees once daily for 2 weeks	Cartilage tissue and synovium were evaluated with a histological scoring system	10 weeks	Significantly reduced average cartilage tissue destruction score of 1.7 in the resveratrol group vs. 2.8 in the control group ($P = .016$). Loss of matrix proteoglycan content in cartilage was also much lower, as determined by safranin O staining. Scores of synovial inflammation did not show difference between groups (1.3 vs. 2.2; $P = .057$).	None
Ma et al (2020)	Monosodium iodoacetate-induced mice (osteoarthritis)	10 and 20 mg/kg intragastric	Cartilage degeneration and inflammation using macroscopic evaluation, hematoxylin and eosin (HE) staining, and micro-magnetic resonance imaging.	4 weeks	Inhibits intracellular and mitochondrial reactive oxygen species (ROS) generation and mitochondrial membrane depolarization using DCFH-DA, MitoSOX Red, and JC-1 assay as well. IL-1β stimulates TLR4 activation and Syk phosphorylation in chondrocytes, while amurensin H inhibits TLR4/Syk signals and downstream p65 phosphorylation and translocation in a time- and dose-dependent manner.	None
Li et al (2021)	Temporomandibular joint osteoarthritis model of mice injected with collagenase (osteoarthritis).	100 μg/10 μL injected 3 times 1 week for 4 weeks	COX-2, P65, MMP1, MMP13, COL2, and ACAN were measured by RT-PCR. Morphological changes of mandibular condylar cartilage (MCC) were studied with HE staining	5 weeks	Trans-resveratrol downregulated COX-2/NF-κB/MMP expression and increases cartilage markers. In HE, cartilage was a little bit smoother than the OA group, and cartilage thickness was increased. In addition, t-Res reversed the damage of MCC of OA mice to some extent	None
Yang et al (2018)	Bovine type-II collagen (BIIC)-induced Sprague–Dawley rat arthritis model and an in vitro RA model based on interleukin (IL)-1β-stimulated rat synovial cells (rheumatoid arthritis)	200 or 400 mg/kg	Synovitis and pathological hallmarks such as inflammatory cell infiltration and angiogenesis in the synovial tissue	8 weeks	Trans-resveratrol abolished BIIC-induced ROS and inflammation. downregulated the increase in the levels of hypoxia-inducible factor-1α and that of the activated phosphorylation of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase in IL-1β-stimulated RSC-364 cells	None

(*Continued*)

Table 2. Animal Studies on The Use of Resveratrol Supplementation in Osteoarthrtiis and Rheumatoid Arthritis Experimental Models (*Continued*)

Auhor (Year)	Animal Model	Resveratrol Dosage	Variables Studied	Follow-up	Outcome	Side Effects
Fernández-Rodríguez et al (2021)	Adjuvant-induced arthritic Lewis rats (rheumatoid arthritis)	12.5 mg/kg/day by oral gavage from 2 months before arthritis induction	Histopathology of synovial proliferation, autophagy, and inflammatory response.	8 weeks	Resveratrol significantly reduced p62 expression Ang-1 and Vascular endothelial growth factor (VEGF) signals. Finally, resveratrol significantly reduced the serum levels of IL-1β, C-reactive protein (CRP), and PGE2, as well as nuclear factor kappa β synovial tissue expression, which showed a significant correlation with p62 expression	None
Wang et al (2020)	Adjuvant-induced arthritic Sprague–Dawley rats (rheumatoid arthritis)	10 mg/kg intragastric	Arthritis assessment, oxidative stress measurement, histological examination, and immunohistochemical staining	24 days	Decreased arthritis scores and serum levels of antioxidant enzymes, attenuated paw swelling, synovial hyperplasia, inflammatory cell infiltration, and cartilage degradation, as well as inhibited synoviocyte proliferation. Inhibited ROS production and fibroblast-like synoviocytes (FLS) proliferation through activating the silent information regulator 1/ nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. Nuclear factor kappa β was confirmed to negatively regulate miR-29a-3p and miR-23a-3p expression	None
Wahba et al (2016)	Adjuvant-induced arthritic albine rats (rheumatoid arthritis)	10 mg/kg/day or fenofibrate (100 mg/kg/ day) for 7 consecutive days.	Measured rheumatoid factor (RF), matrix metalloprotinease-3 (MMP-3) cartilage oligomeric matrix protein (COMP), immunoglobulin G (IgG), antinuclear antibody (ANA), tumor necrosis factor-alpha (TNF-α), IL-10, myeloperoxidase (MPO), CRP, malondialdehyde (MDA) and glutathione (GSH). No joint histopathological study was performed		RF, MMP-3, COMP, IgG, ANA, TNF-α, MPO, CRP, and MDA were decreased. Interleukin-10 and GSH were significantly increased. Resveratrol treatment restored smooth articular surface with some articular cartilage hypercellularity and aggregation of chondrocytes	None

There were some limitations in the studies herein evaluated. For example, no comparison was available between classical pharmaceutical treatments and t-Res in rheumatological diseases. In addition, the low number of participants and the short time of follow-up, except for OA, are important drawbacks. Finally, only a few rheumatic diseases were included (OA, Takayasu arteritis, and RA). It is desired to evaluate the effect of resveratrol on other rheumatological and autoimmune conditions. Future studies in this field should include a larger number of subjects with more long-term observation and better academically designed protocols to decipher the therapeutic mechanism and the role of t-Res in rheumatic conditions.

Conclusion

Trans-resveratrol was evaluated only in 3 rheumatic disorders: OA, Takayasu arteritis, and RA. Nevertheless, almost all analyzed studies demonstrated that this nutritional supplement seems to be effective in reducing signs and symptoms of rheumatic conditions (pain, functionality, activity, and inflammatory biomarkers) without side effects. Although this evidence is very limited since there are only 5 articles in this field, based on the above, it is concluded that t-Res surges as an alternative supplement to be explored in rheumatology.

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