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Review Article

Resveratrol in degenerative musculoskeletal diseases: a homology of medicine and food perspective

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Abstract: This review examines the therapeutic potential of resveratrol (RES) in managing degenerative musculoskeletal diseases (DMDs), including osteoarthritis (OA), osteoporosis, and sarcopenia. With the rising incidence of these diseases in aging populations, effective interventions are increasingly urgent. RES, a polyphenolic compound found in foods such as grapes and peanuts, has shown promise due to its antioxidant and anti-inflammatory properties. Acting within the framework of medicine and food homology, RES holds dual roles as both a dietary supplement and therapeutic agent. RES exerts its effects by modulating various signaling pathways, which collectively reduce inflammation, oxidative stress, and cellular apoptosis, thereby slowing the progression of DMDs. Clinical trials suggest that RES improves bone mineral density, alleviates OA symptoms, and helps preserve muscle mass. However, challenges like limited bioavailability and targeted delivery remain. Future research should focus on optimizing RES's bioavailability and exploring its synergistic effects with other natural compounds to enhance its therapeutic impact. Overall, RES exemplifies a holistic approach to DMDs management by integrating dietary and pharmacological benefits, offering a sustainable strategy for disease management and prevention.

Keywords: resveratrol; osteoarthritis; osteoporosis; sarcopenia; medicine and food homology

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1 Introduction

Degenerative musculoskeletal diseases (DMDs) encompass age-associated structural and functional impairments that affect muscles, bones, cartilage, joints, and surrounding connective tissues. This review centers on three highly prevalent DMDs: osteoarthritis (OA), osteoporosis (OP), and sarcopenia, each posing substantial public health challenges globally[1, 2]. According to the Global Burden of Diseases Study, in 2020, there were 595 million individuals worldwide suffering from OA, rendering it the seventh leading cause of years lived with disability[3]. In the USA, 10.3% of the non-institutionalized population aged 50 or older suffers from OP, a condition that weakens bone integrity and significantly elevates fracture risk[4]. Sarcopenia impacts 8%–36% of individuals under 60 and 10%–27% of those aged 60 and older globally, resulting in adverse outcomes such as mortality, falls, fractures, and cognitive impairment[5]. With global aging trends, the incidence of these DMDs is projected to rise, underscoring the urgency of effective intervention strategies[6, 7].

Despite the prevalence of these three major DMDs, current treatment modalities primarily focus on lifestyle modifications (such as weight loss, exercise, and dietary changes), pain management via medications, surgery, and/or alternative therapies. Nevertheless, effective strategies to halt the progression of DMDs remain elusive, necessitating further exploration of more efficacious treatments[8-11].

Resveratrol (RES, 3, 4', 5-trihydroxy-*trans*-stilbene), a non-flavonoid polyphenolic compound, was first isolated in 1963 from the roots of Japanese knotweed (*Polygonum cuspidatum*)[12]. It is a white powder with a melting point of 253–255 °C and a molecular

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weight of 228.25[13]. Figure 1 illustrates the sources, structure, and therapeutic effects of RES. As a natural phytoalexin produced by various plants, RES can be extracted from numerous natural sources, with notable concentrations found in common foods such as peanuts, grapes, blueberries, and apples[14, 15]. For example, the concentration of RES in fresh grape skins is approximately 5×10^{-2}–10×10^{-2} g/kg, while in red wine it can reach 1.5–3 mg/L[16]. Structurally, the presence of three hydroxyl groups in RES contributes to its potent antioxidant activity[16]. Furthermore, RES exhibits anti-inflammatory effects, likely through the inhibition of pro-inflammatory enzyme cyclooxygenase (COX)-1 and via Sirtuin (SIRT) 1-mediated pathways[17, 18]. Beyond alleviating oxidative stress and inflammation, RES's therapeutic benefits extend to cardiovascular protection, anti-aging, anti-metabolic syndrome, anti-cancer, and neuroprotection[18-22]. Numerous studies have demonstrated its efficacy in DMDs, such as suppressing the progression of OA[23, 24], exerting anti-osteoclastogenic effects in OP treatment[25], and improving mitochondrial function and oxidative stress to inhibit sarcopenia progression[26].

RES has also shown promise as a therapeutic agent for DMDs, either as a standalone treatment or in combination with other therapies. Randomized controlled trials (RCTs) indicate that RES, administered orally or as a dietary supplement, can alleviate OA symptoms[27-29], enhance bone mineral density (BMD)[30], and, when combined with exercise, more effectively reverse sarcopenia than exercise alone[31].

Dietarily, RES is notably present in the Mediterranean diet (MED), known for its high polyphenol content from foods like olive oil, nuts, red wine, legumes, fruits, and vegetables. The MED diet's anti-inflammatory and antioxidant effects are associated with reduced rates of cardiovascular and degenerative diseases[32, 33]. Specifically, RES, abundant in red wine, nuts, and vegetables within this diet, has been linked to reduced cartilage degradation in OA, preservation of muscle mass, and improved BMD, highlighting its therapeutic potential in DMDs prevention and treatment[34-36].

The concept of medicine and food homology (MFH) traces back to ancient China, referring to the integration of food (particularly traditional Chinese medicine) and medicinal materials that can serve dual roles. This approach aims to achieve enhanced health outcomes. Modern interpretations suggest that these materials possess nutritional and health-promoting functions[37, 38]. Given RES's dual efficacy as both a dietary and pharmacological agent in DMDs prevention and treatment, it represents a promising candidate within the MFH paradigm. This review explores the pathogenesis of DMDs, the mechanisms by which RES exerts therapeutic effects, and its potential treatment targets, aiming to provide a comprehensive perspective on RES's applicability in DMDs management from a MFH standpoint.

2 Pathophysiology, risk factors, and current therapies for DMDs

2.1 OA

OA is the most prevalent degenerative joint disorder, affecting millions worldwide. It is marked by progressive degeneration of joint cartilage and subchondral bone, subchondral sclerosis, cyst formation, synovial inflammation, osteophyte formation, and alterations in joint mechanics[39, 40]. Key risk factors identified by meta-analyses include obesity, female gender, previous joint injuries, and advanced age, which collectively exacerbate OA's progression and symptoms[41]. Obesity, for instance, promotes adipokine secretion (e.g., leptin) from adipose tissue, resulting in elevated levels of inflammatory cytokines such as interleuk (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which further intensify systemic inflammation and metabolic disruptions[42].

OA is a multifaceted process involving both inflammatory and metabolic factors. Inflammation encompasses active synovitis and systemic inflammation[43]. Previous research has frequently discussed the roles of growth factors and adipokines in OA. Growth factors such as transforming growth factor (TGF)-β, fibroblast growth factor (FGF), and growth differentiation factor 5 are crucial for the differentiation and maintenance of

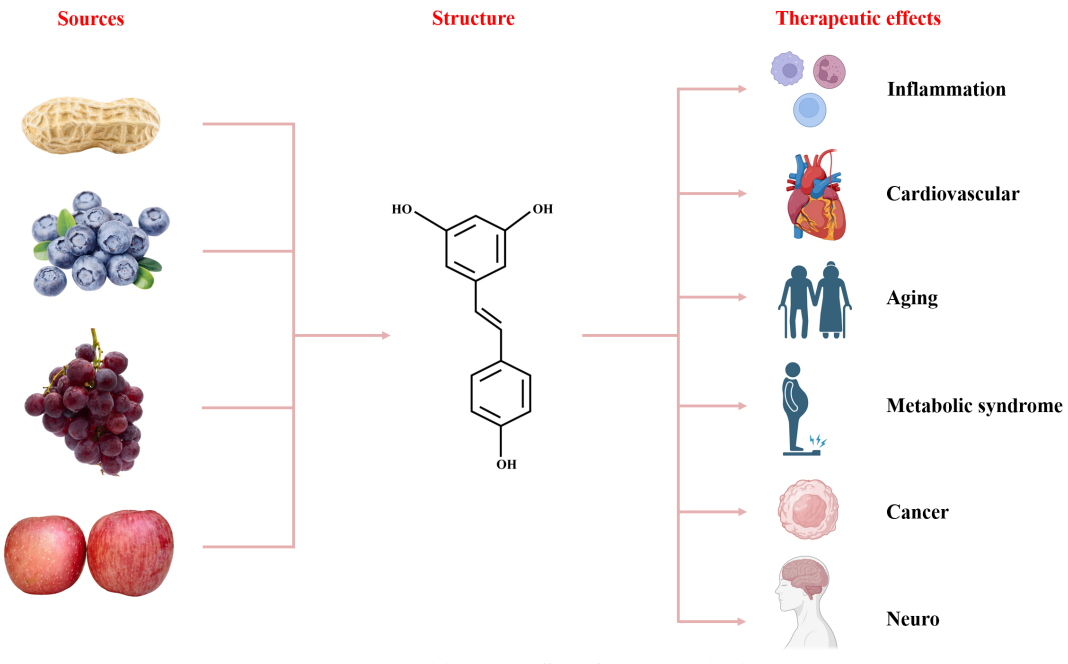

Figure 1 Sources, structure, and therapeutic effects of RES. (Created with BioRender.com)

chondrocytes, mediating gene expression through specific pathways, such as the Smad pathway activated by TGF-β and the MAPK pathway activated by FGF[44]. Synovial inflammation in OA includes synovial lining hyperplasia, fibrosis, and angiogenesis, with macrophages and T cells predominating, even in advanced disease stages[45,46]. Additionally, adipokines like IL-6, TNF-α, and leptin exhibit strong pro-inflammatory effects, aggravating synovial inflammation, cartilage breakdown, and joint pain. Conversely, adiponectin plays a protective role by upregulating tissue inhibitors of metalloproteinases and downregulating matrix metalloproteinase (MMP), which are involved in cartilage degradation. However, TNF-α fosters osteoclastogenesis, increasing bone resorption[47].

Mitochondrial dysfunction is also implicated early in OA pathogenesis. Chondrocytes in OA display reduced mitochondrial mass and DNA content, leading to disrupted mitochondrial homeostasis, an imbalance between reactive oxygen species (ROS) production, and antioxidant capacity. This results in metabolic dysregulation, matrix degradation, and eventual chondrocyte death, driving OA progression[48-50].

Current OA treatments primarily encompass basic therapy, pharmacological interventions, and surgical options. Basic therapy (health education, exercise therapy, physical therapy, and mobility aids) is the first-line treatment for all OA patients, regardless of medication use or joint replacement surgery[51-53]. However, in clinical practice, prescribing personalized and accurate exercise regimens is challenging, and patient compliance limits the efficacy of these treatments[54]. Pharmacological treatments primarily aim to relieve pain and enhance joint function, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and intra-articular injections of hyaluronic acid (for lubrication) and corticosteroids, although long-term use may exacerbate joint damage[55]. For patients with end-stage, severe OA unresponsive to conservative treatments, total joint replacement remains the preferred and most effective option[56]. However, the associated risks and complications of surgery may outweigh the benefits for elderly patients with poor overall health or severe comorbidities, often leaving them without effective treatment alternatives.

While no treatments currently halt OA progression, promising preclinical findings suggest that dual amylin-calcitonin receptor agonists and angiogenesis inhibitors, such as Lenvatinib, may alleviate OA symptoms; however, further in vivo studies are warranted[57,58]. Emerging therapies, including mesenchymal stem cells (MSCs), show potential for cartilage repair in animal models, but additional clinical studies are necessary to validate long-term efficacy and safety[59,60].

2.2 OP

OP, a metabolic bone disease, is characterized by low BMD, bone tissue degradation, microarchitectural destruction, compromised bone strength, and an increased risk of fractures due to disrupted bone homeostasis[61,62]. Age-related bone loss, particularly common in postmenopausal women, is largely due to an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts[63]. Estrogen deficiency is a significant risk factor, with a prevalence of 23% in women over 50, compared to 7% in men[64].

Bone, a specialized connective tissue, serves as the structural foundation for support and protection. Its cellular components derive from MSCs, which differentiate into osteoblasts and osteocytes, and from the hematopoietic system, yielding osteoclasts[65,66]. Bone tissue development and maintenance occur through a balance of bone formation by osteoblasts and resorption by osteoclasts. Osteoclasts, originating from myeloid cells, can resorb mineralized bone in three stages: attachment, polarization, and initiation/cessation of resorption. Excessive osteoclast-mediated resorption results in net bone mass loss[67]. Osteoblasts arise from bone progenitor cells induced by factors such as bone morphogenetic proteins (BMPs), TGF-β, insulin-like growth factors, and interleukins, which differentiate into tissues like cartilage and fibrous tissue[68]. In healthy bone tissue, the continuous cycle of osteoclast resorption and osteoblast formation is regulated by multiple systems, including the endocrine, nervous, and immune systems[69]. Although the causes of OP differ at various stages of life, the final outcome is often a reduction in peak bone mass[70]. The receptor activator of NF-κB ligand (RANKL) plays a crucial role in OP pathogenesis. RANKL, expressed by osteoblasts and stromal cells, binds to RANK on osteoclast precursors, initiating signaling that promotes osteoclastogenesis and enhances bone resorption[71,72].

Basic treatment for OP typically includes exercise, increased sunlight exposure, and supplementation with calcium and vitamin D. For patients with fragility fractures or those at high risk of fractures, antiresorptive therapies are commonly employed, primarily bisphosphonates (the most widely used), selective estrogen receptor modulators (SERMs, such as raloxifene and bazedoxifene), and RANKL antibodies (denosumab). These therapies inhibit bone resorption, thereby increasing bone density, improving quality, and reducing fracture risk, although they do not repair or enhance damage to trabecular architecture[73,74]. Estrogen and SERMs, including raloxifene and bazedoxifene, are primarily used in postmenopausal women; however, potential side effects limit their use[74,75]. Recent studies on monoclonal antibody therapy, such as romosozumab targeting sclerostin, have shown effectiveness in increasing BMD and reducing fracture risk in postmenopausal women with OP[76,77].

Innovative therapies are being explored for OP treatment. Zheng *et al.*[78] constructed bone homeostasis repair microcarriers to target the osteoporotic microenvironment, promoting spinal fusion in osteoporotic rats. Rajput *et al.*[79] reported the discovery of a novel adiponectin-derived short peptide that stimulates bone formation and inhibits resorption, potentially representing a new treatment for OP. Other recent drugs, such as vildagliptin, have been shown to enhance osteogenic differentiation of precursor osteoblasts and bone marrow-derived MSCs, thereby promoting bone anabolism and inhibiting resorption[80].

2.3 Sarcopenia

Sarcopenia is a progressive skeletal muscle disorder characterized by an accelerated decline in muscle mass, strength, and function, which significantly elevates the risk of adverse outcomes, including frailty, falls, and fractures[81,82]. The primary pathological manifestations of sarcopenia involve a reduction in both the size and number of type II muscle fibers, a decreased satellite cell count—cells crucial for muscle repair—and increased intramuscular and intermuscular fat infiltration[83].

In addition to aging, the most significant cause, other risk factors for sarcopenia include obesity, malnutrition, diabetes, physical inactivity, a sedentary lifestyle, or prolonged bed rest[5,84-86]. Interestingly, despite their apparent opposition, both obesity and malnutrition can lead to a decline in lean tissue, predominantly affecting skeletal muscle and the liver, which are essential in determining energy demands[87]. A particularly concerning variant is sarcopenic obesity, characterized by

simultaneous muscle loss and fat accumulation, which is common among older adults and exacerbates the detrimental impact of obesity on physical function[88]. In individuals with diabetes, the coexistence of sarcopenia and obesity reaches approximately 30%, underscoring an additive risk profile[89]. Furthermore, sarcopenia often coexists with OP, amplifying fracture susceptibility in older adults[90].

As with other DMDs, inflammation is pivotal in the pathogenesis of sarcopenia, particularly given its association with the primary risk factors of aging and obesity. Meta-analyses reveal notably elevated levels of inflammatory markers in sarcopenic individuals[91]. Increased adiposity and muscle catabolism contribute to oxidative stress, insulin resistance, and an upregulation of inflammatory cytokines, such as TNF-α, IL-6, IL-1, and various chemokines. This inflammatory cascade promotes cellular infiltration through nuclear factor κB (NF-κB), further compounding fat accumulation and muscle atrophy[88, 92]. Additionally, inflammation activates the NLRP3 inflammasome, leading to pyroptosis, a form of inflammatory cell death that exacerbates muscle degradation[92].

Currently, there are no approved pharmacological therapies for sarcopenia, and treatment strategies primarily aim to reduce or delay the progression of muscle mass loss[93]. Existing guidelines do not endorse pharmacological interventions, and evidence supporting the efficacy of vitamin D supplementation and anabolic hormones for sarcopenia remains inconclusive[94]. Early preventative strategies, particularly resistance training combined with optimized nutritional intake, are widely regarded as beneficial for improving sarcopenia outcomes[93, 95]. A systematic review by Liu *et al.*[96] underscored the potential role of gut microbiota in sarcopenia, proposing that modulation of gut microbiota may offer a promising therapeutic avenue for enhancing muscle mass, thus providing a novel approach for sarcopenia prevention and treatment.

Recent *in vitro* studies have shown that forkhead box protein O1 (FOXO1) inhibitors can alleviate sarcopenia induced by primary sclerosing cholangitis, while strontium zinc silicate bioceramics have demonstrated efficacy in reducing bone loss and muscle atrophy in rats with concurrent OP and sarcopenia[97, 98]. Unacylated ghrelin has been shown to reverse age-related neuromuscular junction damage in elderly mice[99]. A recent RCT revealed the benefits of high-level plant protein/peptide supplements in increasing muscle mass, which can alleviate symptoms of OA in elderly patients with both sarcopenia and OA, demonstrating significant potential in DMDs treatment[100].

3 Therapeutic mechanisms of RES in DMDs

Table 1 provides a comprehensive overview of the effects of RES on DMDs in animal studies. The therapeutic effects of RES in DMDs are believed to stem from its multifaceted and interconnected mechanisms, including modulation of inflammation, regulation of apoptosis and cellular structure, and alleviation of oxidative stress and metabolic disorders, thereby engaging multiple signaling pathways. This section introduces key pathways and mechanisms, followed by a detailed examination of their roles in individual DMDs, to elucidate RES's therapeutic potential and molecular actions.

3.1 Key signaling pathways involved in RES action

The therapeutic efficacy of RES in DMDs is predominantly mediated through its regulation of critical signaling pathways,

Table 1 Main effect of resveratrol on DMDs in animal experiments

Type of DMDs	Experimental design and treatments	Results	Reference
OA			
	Albino male rats Groups including control group (laboratory chow), type 2 diabetes mellitus group (high carbohydrate and fat diet), protective group (high carbohydrate and fat diet + RES 30 mg/kg) For 12 weeks	Protection against articular cartilage changes caused by type 2 diabetes mellitus ↓Weight loss, blood glucose, glycosylated hemoglobin, MDA, SOD ↓Triglyceride, total cholesterol, low density lipoprotein-cholesterol, CRP, TNF-α	[24]
	New Zealand rabbits (6-week-old) Groups including normal control group, OA group (sodium nitroprusside-induced), OA + RES group	Prevents chondrocyte apoptosis (↑cell viability) Prevents changes in cartilage morphology (↑average length and width, elasticity/stiffness, adhesion force)	[145]
	Male SD rats (6-week-old) Groups including control group, sham group, lipopolysaccharide-induced group, experimental (RES + lipopolysaccharide) group For 8 weeks	↑ERK1/2, Smad2/3 ↓Degree of joint damage, IL-1β, IL-6, MMP13, TGF-β 1, SOX-9, COX-2, MMP3, OARSI, alanine aminotransferase	[129]
	Male Wistar rats Groups including control group, OA group, low-dose intra-articular RES (100 μg/80 μL, 3 times per week) group, low-dose intra-articular RES (1 mg/80 μL, 3 times per week) group	↑Cartilage thickness ↓Inflammation of the sub synovial zone, disc thickness, chondrocyte apoptosis, matrix metalloproteinase 13	[146]
	AGE-treated bovine knee joints (2–3 weeks old) Groups including resveratrol (50 μmol/L) group, curcumin (12 μmol/L) group, and eugenol (200 μmol/L) group For 8 days	Stronger binding to collagen II glycosylation sites Inhibits ribose-induced AGE cross-linking and its associated downstream biological reactions ↓Non-enzymatic glycation and enzymatic glycation degradation at matrix and cellular levels	[131]
	Male Wistar rats (6-week-old) Groups including control group, OA group, and RES (50 mg/kg per 3 days) group	↑TNF-α, IL-1β, IL-6, IL-18, HO-1, Nrf-2 ↓iNOS, NF-κB, AMPK, SIRT1, MDA, SOD, caspase-3/9	[173]
	New Zealand white rabbits Groups including normal control group, model control group, high-dose resveratrol (50 μmol/(kg·day)) group, middle-dose resveratrol (20 μmol/(kg·day)) group, low-dose resveratrol (10 μmol/(kg·day)) group For 2 weeks	↓The extent of cartilage destruction, loss of matrix proteoglycan cotent, chondrocyte apoptosis, NO	[144]

(Continued)

Type of DMDs	Experimental design and treatments	Results	Reference
OP			
	Female SD rats (3-month-old) Groups including control group, sham + sesame oil group, OVX + RES (40 mg/(kg·day)) group For 10 weeks	↑Number of trabeculae, OPG, OPG/RANKL, SOD, GSH-PX, FOXO1 ↓Trabecular space, RANKL, MDA, ROS, MMP-9, TRAP, cathepsin K, p-AKT	[174]
	Female mice (8-week-old) Groups including control group (sham), OVX group, OVX + RES 40mg/(kg·day)) group For 8 weeks	↑BV/TV, Tb.N, osteoblasts, ALP, Runx2, osterix, SIRT1, SOD, P1NP, nuclear FOXO1 ↓Tb.Sp, osteoclasts, c-telopeptide of type 1 collagen, caspase-3, acetylated FOXO1	[149]
	Female SD rats (5-week-old) Groups including control group (sham), OVX group, oxyresveratrol group (1, 10, 20 mg/(kg·day))	↑Bone volume per total volume ↓TRAP, round osteoclast, formation of actin rings, MAPK, phosphorylation of ERK, p38, and JNK, NFATc1	[175]
	Male Wistar rats (3-month-old) Groups including control group (sham), OP group, OP + low-dose RES (5 mg/kg) group, OP + middle-dose RES (25 mg/kg) group, OP + high-dose RES (45 mg/kg) group For 8 weeks	↑BMD, peak load and ultimate stiffness (%), SIRT1, IkBα ↓ALP, osteocalcin, femoral porosity, NF-κB/p65	[127]
	MC3T3-E1 cells (a mouse preosteoblast cell line) Groups including control group, HG-induced group, RES group, HG-induced + RES group For 2 weeks	↑Osteoblast-related genes (Osx, Col1, Opn and Runx2), antioxidant genes (HO-1 and NADPH quinone dehydrogenase 1), Nrf2, p-AKT, p-GSK3β, FYN ↓HG-induced TUNEL-positive cells, Bax/Bcl-2, C-CASPASE3, ROS	[176]
	Male SD rats (3-month-old) Groups including control group (normal saline), OP group (dexamethasone 5 mg/kg), OP + resveratrol group (5 mg/(kg·day) for low-dose, 45 mg/(kg·day) for high-dose) For 15 weeks	↑BMD, SIRT 1, LC3, Beclin-1, Atg7 ↓Alkaline phosphatase, osteocalcin, Akt phosphorylation, mTOR phosphorylation, TOM20, Hsp60	[151]
	Female SD rats (2 and 6 months old) Groups including control group (sham), OVX group, OVX + estradiol (0.8 mg/(kg·day)) group, OVX + low-dose RES (50 mg/(kg·day)) group, OVX + medium-dose RES (100 mg/(kg·day)) group, OVX + high-dose RES (200 mg/(kg·day)) group For 12 weeks	↑BMSC, Smad7, BMP2, Runx-2, miR-92b-3p, BMD, Conn.D, BV/TV, Tb.Th, Tb.N ↓TRAP-positive cell, Nox4, p-IκB-α, NF-κB, p65	[128]
Sarcopenia			
	Male SD rats (3–18 months old) Groups including young rats' control (chow diet) group, old rats control (chow diet) group, old rats HFD (20-week) group, old rats HFD + RES (10 + 10 weeks) group, old rats HFD + RES (20-week), old rats CD + RES (20-week) For 20 weeks	Alleviation of palmitate acid-induced cell death and muscle atrophy ↑HDL-C, PGC-1α, TFAM, mfn2, drp1, SOD, p-PKA, p-LKB1, p-AMPK ↓HFD-induced weight gain, decreased grip strength, decreased muscle mass, fat mass, lipid levels, abnormal mitochondrial count, MDA, ROS, mitochondrial ROS	[26]
	Male C57/BL6 mice (6-week-old) Groups including normal chow diet (10 kcal% fat) group, HFD (55.9 kcal% fat) group, HFD (55.9 kcal% fat) + RES (4 g/kg) group For 16 weeks	Reduction of HFD-induced obesity and skeletal muscle lipid content ↑CD4 cells ↓CD11b cells, F4/80, M1/M2, CD8 T cells, IL-6, TNF-α, IL-1β, p38, JNK, NF-κB, p65	[177]
	Male C57BL/6J mice (6-week-old) Groups including normal chow diet (10 kcal% fat) group, HFD (60 kcal% fat) group, HFD (60 kcal% fat) + RES (4 g/kg) group For 26 weeks	↑TAC, SOD, CAT, HO, NQO1, Nrf2 ↓HDF-induced weight gain	[178]
	Male ddY mice (8-week-old) Groups including control diet group and RES diet group For 32 weeks	Inhibition of age-related muscle atrophy in tibialis anterior ↑SIRT1 ↓Aging-associated cardiomyocyte hypertrophy, cardiomyocyte autophagy	[179]

Notes: ALP, alkaline phosphatase; BV/TV, bone volume/tissue volume; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HFD, high fat diet; iNOS, inducible nitric oxide synthase; MDA, malonaldehyde; mTOR, mechanistic target of rapamycin; OARSI, Osteoarthritis Research Society International; OPG, osteoproprotegrin; OVX, ovariectomy.

including the NF-κB, arachidonic acid (AA), mitogen-activated protein kinase (MAPK), and NF-E2-related factor-2 (Nrf2) pathways. These pathways play crucial roles in regulating inflammation, oxidative stress, apoptosis, and cellular homeostasis[101, 102].

The NF-κB pathway, comprising heterodimers of p50/p52 and p65 proteins with transcription activation domains on the p65 subunit, serves as a major regulator of inflammatory responses[103, 104]. SIRT1, a NAD^+-dependent deacetylase with dual enzymatic activities of deacetylation and ADP-ribosylation, plays a pivotal role in antioxidative and anti-inflammatory processes and is regarded as a potential therapeutic target for anti-aging and metabolic regulation[105, 106]. In chondrocytes, RES has been shown to activate SIRT1 in a dose-dependent manner, which subsequently binds to and deacetylates NF-κB, effectively suppressing the inflammatory pathway[107, 108]. Notably, RES

upregulates *SIRT1* mRNA expression, leading to SIRT1 overexpression[104]. Through deacetylation of the NF-κB p65 subunit, SIRT1 inhibits NF-κB transcriptional activity, reducing the expression of inflammation-associated genes, such as *TNF-α*, *IL-6*, and *IL-1β*—mechanisms well-documented across various chronic inflammatory diseases. Additionally, SIRT1 deacetylates p53, thereby inhibiting the expression of p53-mediated apoptotic genes, such as Bcl (B-cell lymphoma)-2-associated X protein (*Bax*), to prevent excessive apoptosis in damaged cells[109]. This was further corroborated by Hori *et al.*[110], who demonstrated that SIRT1 modulation of p53 partially inhibits oxidative stress-induced apoptosis.

AA, a principal component of cell membrane phospholipids, is released in response to cellular damage or inflammatory stimuli, catalyzed by phospholipase A2. Its primary metabolic pathways, the COX and lipoxygenase (LOX) pathways, are established targets of anti-inflammatory drugs like NSAIDs, which alleviate inflammation and pain in OA by inhibiting COX activity[111]. RES inhibits the AA pathway by blocking the MAPK/NF-κB/AP-1 pathway, thereby downregulating COX-2 expression[112]. *In vitro* studies further demonstrate that RES can dose-dependently suppress COX-2 expression and inhibit NF-κB p65 translocation in human intestinal cells[113]. Moreover, Xin *et al.*[114] synthesized RES amide derivatives that showed potential as selective COX-2 inhibitors.

The MAPK pathway plays a critical role in cellular responses to stress by transmitting extracellular signals to intracellular targets. Key MAPK subtypes—extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK—regulate processes such as inflammation, cell differentiation, and apoptosis[115,116]. Activation of these pathways involves phosphorylation in a three-tiered kinase cascade: MAPK kinase kinase (MAPKKK) activates MAPK kinase (MAPKK), which then activates MAPKs like ERK, JNK, and p38 MAPK. Polyphenols such as RES can inhibit MAPK activation, thereby mitigating inflammatory responses[117].

Nrf2, regulated by Kelch-like ECH-associated protein 1 (Keap1) through the ubiquitin-proteasome pathway, is essential in responding to oxidative stress. Nrf2 activation is induced by reactive molecules that interact with Keap1[118], leading to the upregulation of antioxidant enzymes (e.g., superoxide dismutase (SOD) and glutathione peroxidase (GPx)) and the downregulation of pro-inflammatory cytokines, thus reducing inflammation and oxidative stress[119-121]. The interplay between Nrf2 and NF-κB underscores their complementary roles in cellular antioxidant and pro-inflammatory responses. Activation of Nrf2 has been shown to inhibit NF-κB, resulting in decreased inflammatory factor expression and attenuation of inflammation.

3.2 Mechanistic insights into RES's therapeutic effects

Inflammation, often considered an adaptive response, can also represent a chronic state characterized by persistent pro-inflammatory cytokine and lipid production, particularly in aging and DMDs[122,123]. Meta-analyses have demonstrated that RES has considerable potential in enhancing skeletal muscle structure, function, and performance, largely due to its potent anti-inflammatory properties[124]. By activating SIRT1, RES facilitates NF-κB deacetylation, thereby suppressing pro-inflammatory cytokines, and downregulates NF-κB activity in models of OA and OP[125-128]. In combination with bletilla striata polysaccharide, RES has been shown to inhibit COX-2 expression in early-stage OA models, further demonstrating its anti-inflammatory effects[129]. Additionally, RES inhibits the accumulation of advanced glycation end products (AGEs), which can induce COX-2 expression via NF-κB activation, thereby reducing inflammation[130]. Due to its strong affinity for arginine and lysine residues, RES competitively inhibits AGEs in chondrocytes, which would otherwise activate NF-κB and promote COX-2 expression[131,132]. This dual action of reducing pro-inflammatory mediator synthesis and alleviating pain and tissue damage underscores RES's therapeutic promise.

Apoptosis, or programmed cell death, is an evolutionarily conserved process essential for development and tissue homeostasis[133]. Triggered by intrinsic or extrinsic death signals, apoptosis is induced by stressors such as DNA damage, hypoxia, oxidative stress, and infection[134]. Hallmarks of apoptosis include cell shrinkage, chromatin condensation, nuclear fragmentation, and apoptotic body formation[135]. In DMDs, dysregulated apoptosis is a major pathological contributor to tissue degeneration and functional decline.

Oxidation, a chemical reaction involving electron loss, primarily refers to nutrient breakdown in cells to release energy, which is then converted to adenosine triphosphate (ATP) in mitochondria. However, oxidation also generates ROS as byproducts[136]. When ROS production surpasses the body's antioxidant defenses, oxidative stress ensues, causing cellular damage and contributing to DMDs and other conditions[137,138].

Metabolism encompasses the chemical reactions within organisms that sustain life, involving catabolic processes (energy release) and anabolic processes (biosynthesis), which are highly regulated through enzymatic reactions. RES exerts protective effects against oxidative stress primarily by activating the Nrf2 pathway, as detailed earlier. Nrf2 can upregulate the expression of various antioxidant enzymes, such as SOD and GPx, by binding to the antioxidant response element (ARE) in promoter regions[139]. Through Nrf2 activation, RES enhances cellular antioxidant capacity, helping to neutralize excess ROS and prevent oxidative damage[102]. This is particularly relevant to DMDs, as chronic oxidative stress contributes to ongoing muscle damage and the progression of degenerative diseases. Moreover, RES's activation of SIRT1 improves insulin secretion and sensitivity, promoting glucose uptake and utilization[140]. This is beneficial in DMDs, where metabolic dysregulation, such as insulin resistance, is common and a contributor to functional impairment and muscle degeneration[141,142]. Additionally, RES activates the AMPK pathway, which stimulates glucose uptake and fatty acid oxidation, promoting a shift from anabolic to catabolic processes to generate ATP during periods of energy demand[26,143]. This helps restore energy balance and reduces metabolic stress in muscle tissue, mitigating the metabolic disruptions seen in DMDs.

Oxidative stress not only disrupts cellular metabolism but also exacerbates inflammation, creating a vicious cycle that drives the progression of DMDs. ROS act as signaling molecules that activate various pathways, including MAPK and NF-κB pathways, leading to the expression of pro-inflammatory genes. For example, ROS can inhibit MAPK phosphatases, preventing the inactivation of MAPK signaling[117]. This inhibition prolongs MAPK activation, resulting in the sustained expression of pro-inflammatory cytokines and enzymes, further aggravating chronic inflammation and tissue degeneration. RES's ability to both lower ROS levels and regulate these inflammatory pathways breaks this cycle, creating a more favorable environment for muscle repair and regeneration.

3.3 Mechanisms of RES in the treatment of OA

Figure 2 demonstrates the mechanism of RES in the treatment

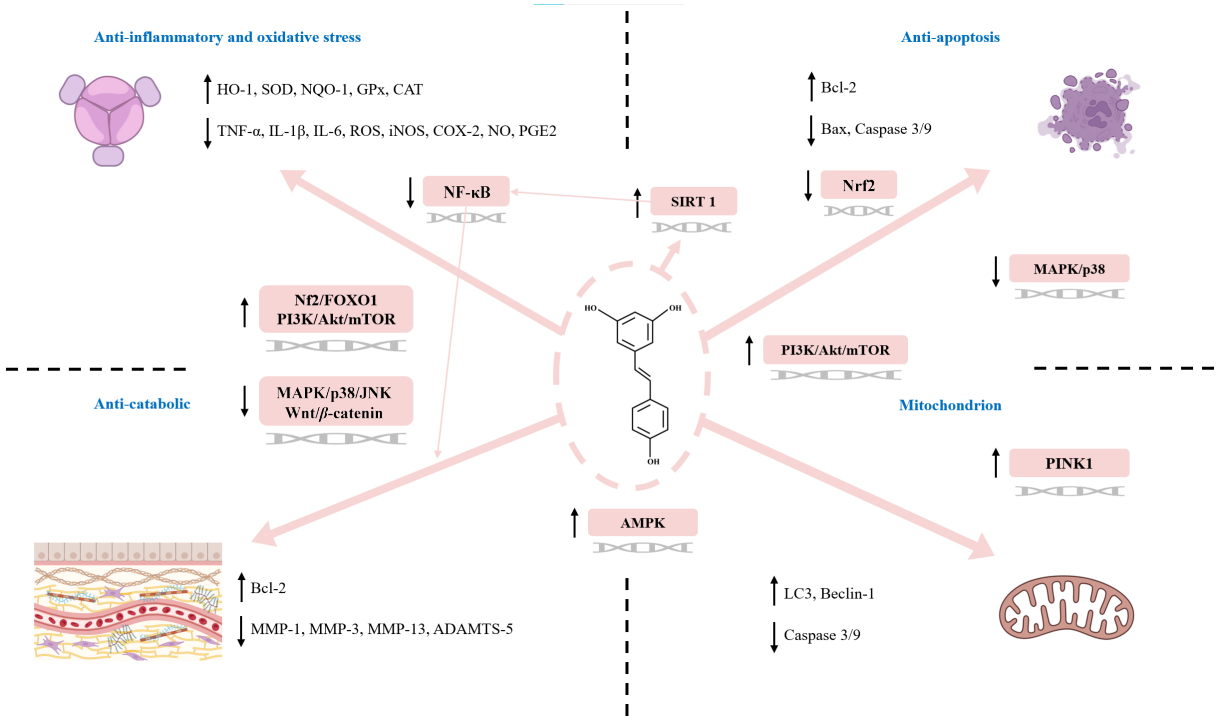

Figure 2 Mechanism of RES in the treatment of OA. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; NQO1, NAD(P)H quinone oxidoreductase 1; PGE2, prostaglandin E2; P1NP, procollagen I N-terminal propeptide. (Created with BioRender.com)

of OA. The therapeutic potential of RES in OA primarily stems from its regulatory effects on key inflammatory signaling pathways and its inhibition of oxidative stress. Inflammation is a crucial factor in the initiation and progression of OA, with the NF-κB signaling pathway playing a central role in modulating pro-inflammatory cytokine expression. During OA pathogenesis, NF-κB translocates from the cytoplasm to the nucleus, where it activates the transcription of pro-inflammatory genes, leading to the overproduction of cytokines such as IL-1β, TNF-α, and IL-6. These cytokines exacerbate cartilage degradation and promote synovial inflammation, accelerating disease progression[126]. Animal studies have shown that RES can significantly downregulate NF-κB expression in OA models, increasing levels of cartilage markers and reducing pro-inflammatory cytokine concentrations in the synovial fluid, ultimately alleviating OA-related inflammation[125,126]. Through its modulation of the NF-κB pathway, RES also suppresses COX-2 expression, thereby reducing the production of prostaglandins and other inflammatory mediators, which mitigates pain and tissue destruction associated with OA[129,130]. Due to its strong affinity for arginine and lysine residues, RES competitively inhibits the accumulation of AGEs in chondrocytes[131]. Since AGEs can induce COX-2 expression via NF-κB activation, RES not only reduces the synthesis of pro-inflammatory mediators but also alleviates pain and tissue damage driven by inflammation[132].

Cartilage degradation in OA is closely linked to chondrocyte apoptosis, which is triggered by pro-inflammatory cytokines and oxidative stress. Research by Wang[144] and Jin[145] has demonstrated that, although RES does not fully restore chondrocyte physiological functions, it effectively prevents chondrocyte apoptosis in OA by stabilizing the cytoskeleton and enhancing the expression of cytoskeletal proteins. This protective mechanism may involve the suppression of nitric oxide (NO) production and inhibition of NO-induced chondrocyte apoptosis. Similar to its anti-inflammatory effects, RES upregulates SIRT1 expression in chondrocytes, which inhibits the phosphorylation of p38, JNK, and ERK pathways, enhances the expression of the anti-apoptotic protein Bcl-2, and reduces levels of pro-apoptotic factors like Bax, as well as matrix-degrading enzymes such as matrix metalloproteinase MMP-1 and MMP-13. This combined effect results in a substantial reduction in chondrocyte apoptosis and extracellular matrix (ECM) degradation in OA[23]. Furthermore, RES's regulation of the SIRT1/NF-κB axis also leads to the suppression of IL-1β-induced catabolic enzymes, including ADAMTS-5, MMP-1, MMP-2, MMP-9, and MMP-13[23]. By inhibiting these enzymes, RES helps maintain cartilage integrity and slows down joint degeneration.

Excessive ROS disrupt chondrocyte metabolism, activating pro-inflammatory signaling pathways and further intensifying OA inflammation. The interaction between type 2 diabetes, oxidative stress, and inflammation is especially relevant to OA pathogenesis. RES's ability to inhibit oxidative stress and inflammation has shown protective benefits in rat models of type 2 diabetes-induced OA[24]. Combined with bletilla striata polysaccharides, another natural compound with antioxidant and anti-inflammatory properties derived from traditional Chinese medicine, RES also alleviates early OA inflammation[129]. Additionally, intra-articular injections of RES have been shown to suppress inflammation and chondrocyte apoptosis in experimentally induced OA models, further supporting its potential as a therapeutic agent for OA[146].

3.4 Mechanisms of RES in the treatment of OP

RES plays an important role in the treatment of OP. Two meta-analyses that analyzed 15 and 13 animal studies, respectively, indicated that RES significantly increased bone density, trabecular number, and trabecular bone volume density in osteoporotic rats[147,148]. These effects are mediated through multiple physiological and molecular pathways, as illustrated in Fig. 3. The

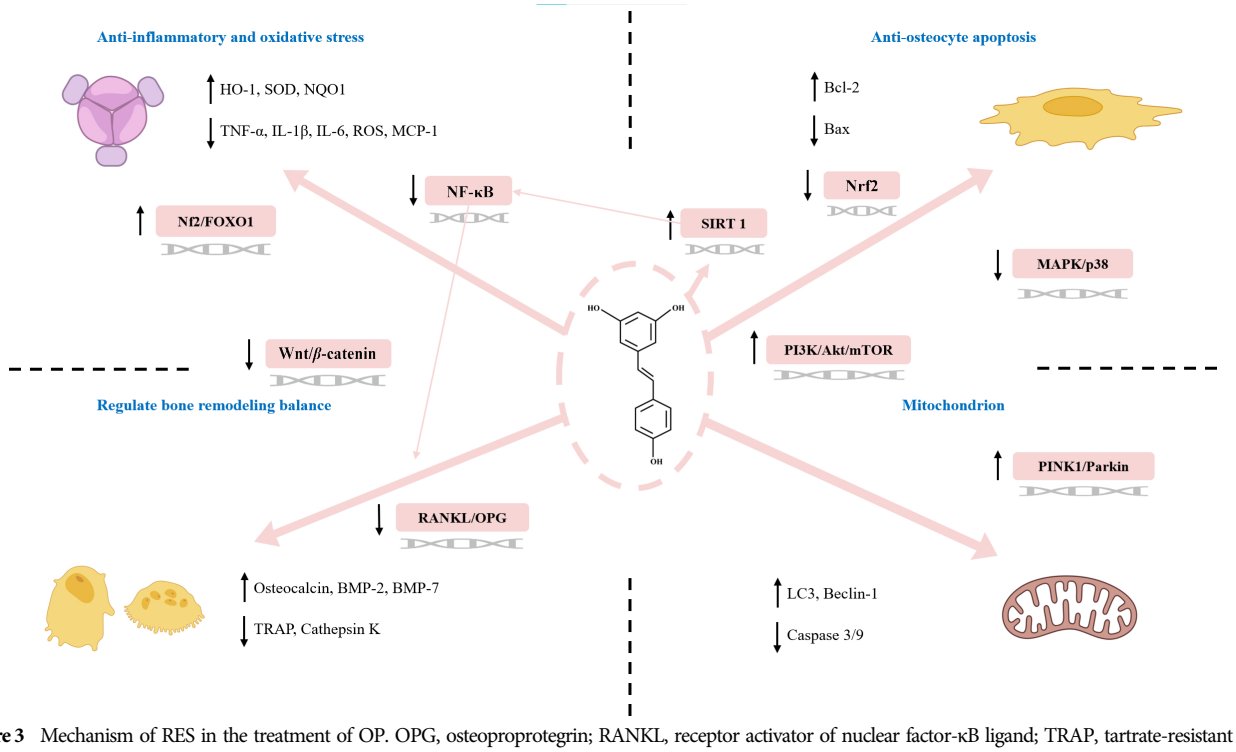

Figure 3 Mechanism of RES in the treatment of OP. OPG, osteoprotegrin; RANKL, receptor activator of nuclear factor-κB ligand; TRAP, tartrate-resistant acid phosphatase. (Created with BioRender.com)

primary mechanism centers on RES's ability to regulate the balance between bone resorption and bone formation during bone remodeling. Similar to its effects in OA, RES achieves this balance by inhibiting inflammatory responses, modulating oxidative stress, and improving bone cell apoptosis and metabolic function.

RES influences bone formation and resorption through various signaling pathways. For bone formation, RES promotes osteoblast proliferation and differentiation by activating SIRT1, which in turn upregulates bone formation markers such as osteocalcin and BMPs[127]. Concurrently, RES reduces bone resorption mediated by osteoclasts by inhibiting osteoclast activation. This suppression is thought to result from the downregulation of osteoclast-related genes via decreased NF-κB activity in osteoclasts[128].

Chronic inflammation is a significant pathological factor in OP, as sustained pro-inflammatory cytokine expression accelerates bone resorption and inhibits bone formation. Through modulation of the SIRT1/NF-κB pathway, RES reduces the production of pro-inflammatory cytokines, including TNF-α and IL-6, thereby mitigating inflammation-induced bone loss[127, 128]. Furthermore, SIRT1 activation inhibits the expression of the pro-apoptotic factor Bax, while enhancing glucose uptake in bone tissue. This results in increased expression of the anti-apoptotic protein Bcl-2, which reduces osteoblast apoptosis and mitigates bone loss associated with metabolic disorders.

Oxidative stress is another critical pathological factor in OP. Excessive ROS not only causes direct damage to bone cells but also accelerates bone resorption by promoting osteoclastogenesis. RES effectively mitigates ROS production and accumulation by activating the Nrf2 pathway[139]. Animal studies have demonstrated that RES significantly reduces oxidative stress by activating the SIRT1/FOXO1/Nrf2 signaling axis, enhancing osteogenesis and bone matrix formation in osteoporotic models[149, 150].

Recent research has also indicated that RES's therapeutic effects in OP may be mediated through enhanced mitochondrial autophagy. Animal studies have shown that RES increases SIRT1 expression in osteocytes of osteoporotic rats, facilitating mitochondrial autophagy via the PI3K/AKT/mTOR signaling pathway to protect osteoblasts from stress-induced damage[151]. This process helps maintain mitochondrial quality and function, which is essential for bone cell health and energy homeostasis.

3.5 Mechanisms of RES in the treatment of sarcopenia

Sarcopenia is primarily driven by aging-related chronic inflammation, oxidative stress, and disturbances in protein metabolism. RES addresses these pathogenic mechanisms through multiple key pathways, as illustrated in Fig. 4.

Oxidative stress is a major contributor to muscle atrophy. When the production of ROS surpasses the body's antioxidant defenses, muscle cells incur damage, initiating the onset of sarcopenia. RES can mitigate ROS accumulation and enhance mitochondrial function via the PKA/LKB1/AMPK signaling pathway, effectively reducing oxidative stress and slowing the progression of sarcopenia[26]. By improving mitochondrial function, RES helps preserve muscle cell integrity and function, which is crucial for combating age-related muscle degeneration.

Inflammation plays a significant role in exacerbating muscle degradation. Pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α, accelerate muscle atrophy by activating catabolic pathways and suppressing anabolic signaling. RES's activation of SIRT1 reduces the expression of pro-inflammatory cytokines by deacetylating and inhibiting the NF-κB pathway, thereby protecting muscle tissue from inflammation-induced damage[110]. Additionally, RES modulates macrophage polarization, promoting a shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, which reduces inflammation and supports tissue repair. This shift is particularly beneficial for individuals with sarcopenia, who often experience chronic low-grade inflammation[152].

Protein homeostasis is critical for maintaining muscle health, and disruptions in protein metabolism are a key factor in

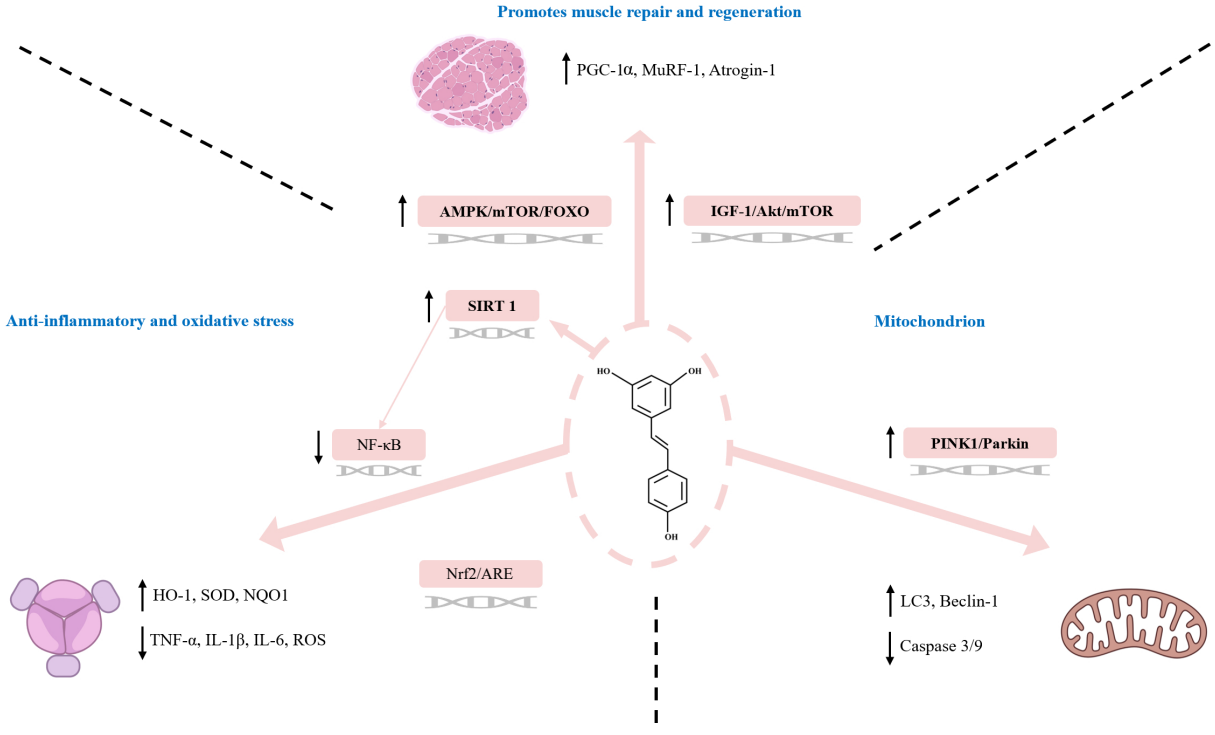

Figure 4 Mechanism of RES in the treatment of sarcopenia. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-1α. (Created with BioRender.com)

sarcopenia. RES promotes autophagy through the activation of the SIRT1/AMPK pathway, facilitating the clearance of damaged proteins in aging muscle cells and slowing muscle atrophy[153]. Moreover, RES enhances anabolic pathways such as the mechanistic target of rapamycin (mTOR) and insulin-like growth factor-1 (IGF-1), which promote the synthesis of new proteins and restore protein balance. This dual mechanism-supporting both the breakdown of damaged proteins and the synthesis of new ones—demonstrates RES's capacity to restore protein homeostasis in sarcopenia[151].

Muscle regeneration depends on the activity of satellite cells, which are essential for repairing and regenerating damaged muscle fibers. However, aging results in a decline in both the quantity and functionality of satellite cells, impairing muscle recovery. RES promotes muscle fiber regeneration by reducing oxidative stress and enhancing satellite cell function. Experimental studies have shown that RES can reverse mitochondrial dysfunction and oxidative stress by activating the PKA/LKB1/AMPK pathway, effectively preventing muscle atrophy in aging models[26]. This makes RES a promising candidate for treating sarcopenia by supporting the regeneration and repair of muscle tissue.

4 Clinical applications of RES in DMDs: a medicine and food homology approach

In treating DMDs, the concept of MFH highlights the unique advantages of combining dietary and medicinal approaches. As a natural polyphenol, RES shows significant promise in alleviating joint inflammation, reducing bone loss, and improving muscle function, owing to its anti-inflammatory, antioxidant, and bone-protective effects[27,30,154]. It has therefore become a prominent ingredient in DMDs treatments. Found in foods such as grapes, blueberries, and nuts, RES can act as both a pharmaceutical intervention and a dietary supplement, offering patients a low-risk, continuous health management strategy.

4.1 Dietary and medicinal sources: clinical trials and evidence-based applications

Polyphenols, one of the most common plant bioactive compounds, are widely present in various foods. A diet rich in polyphenols, like the MED, is characterized by high levels of plant-based foods and polyphenols, providing anti-inflammatory, antioxidant, lipid-lowering, and insulin-sensitivity benefits[155,156]. Previous research has revealed the beneficial effects of dietary polyphenols in preventing hypertension, cardiovascular disease, diabetes, and neurodegenerative diseases[157-160].

As a well-known polyphenol, RES is abundant in everyday foods such as peanuts, grapes, blueberries, and apples, and it functions dually as a dietary supplement and therapeutic agent, increasingly capturing clinical interest. Although clinical trials are not extensive, most show promising results, as detailed in Table 2. For example, a 12-week study by Valsamidou *et al.*[27] evaluated 60 OA patients divided into two groups: one receiving a RES polyphenol supplement and the other an active comparator (ascorbic acid). The polyphenol group showed significant reductions in OA-related pain. Another 12-week trial with 60 participants demonstrated that RES supplementation combined with exercise is both safe and effective in enhancing mitochondrial function and physical activity measures in older adults with impaired physical function[161].

Furthermore, a 24-month randomized, double-blind, placebo-controlled, two-phase crossover trial showed that 75 mg of RES twice daily significantly reduced bone loss in the lumbar spine and femoral neck, underscoring RES's bone-protective properties[30]. Another RCT by Ornstrup *et al.*[162] indicated that high-dose RES supplements could increase BMD and alkaline phosphatase levels by promoting bone formation or mineralization, further validating its potential in OP treatment. Additionally, an RCT involving

Table 2 Effect of resveratrol on DMDs in clinical trials

Type of DMDs	Participants and study design	Results	Reference
OA			
	28 mild-to-moderate OA participants Participants were treated with resveratrol 500 mg/day For 90 days	↑Aggrecan ↓VAS, KOOS	[163]
	142 OA participants Groups including control group (placebo) and treatment group (resveratrol 40 mg/day) For 6 months	Did not reduce OA pain compared to placebo group	[166]
	60 OA participants (aged ≥ 35 years old) Groups including polyphenol supplement group and ascorbic acid comparator capsule group	↑Emotional well-being, physical functioning, bodily pain ↓VAS, WOMAC pain, WOMAC physical function, WOMAC total score	[27]
	Older adults with functional limitations (aged ≥ 65 years old) Groups including control (exercise + placebo) group, exercise + 500 mg/day resveratrol group, and exercise + 1,000 mg/day resveratrol group For 12 weeks	↑Walking distance, walking endurance, gait speed, quadriceps strength, citrate synthase, COX activity, mitochondrial DNA, skeletal muscle mitochondrial relative protein abundance ↓VCAM-1, E-Selectin, and IL-6	[161]
OP			
	76 healthy postmenopausal women (aged 50–55 years old) Groups including control group (placebo) and treatment group (dietary supplement containing 10 mg equol and 25 mg resveratrol) For 12 weeks	↑Osteocalcin, bone-specific alkaline phosphatase, BMD ↓Deoxypyridinoline, tartrate-resistant acid phosphatase 5b	[165]
	123 central obesity males (aged 65–80 years old) Groups including control group (placebo) and RES low group, RES high group For 16 weeks	↑BMD, BAP, P1NP, Osteocalcin, AP	[162]
	146 healthy postmenopausal women (aged 45–85 years old) Groups including control group (placebo) and treatment group (Veri-te resveratrol capsules containing 75 mg of >98% of *trans*-resveratrol) For 24 months	↑BMD of lumbar spine, femoral neck and total hip ↓C-terminal telopeptide type-1 collagen	[30]
Sarcopenia			
	36 young, untrained males Groups including placebo (1,000 mg/day methylcellulose) group, RES-500 (500 mg/day RES + 500 mg/day methylcellulose) group, and RES-1000 (1,000 mg/day RES) group for 7 days Then induce plyometric-exercise-induced cuscle damage	Recovery relative peak power, relative mean power, fatigue index Reduces muscle pain, creatine kinase, lactate dehydrogenase	[154]
	38 healthy older participants (aged 65–80 years old) Groups including placebo group and RES multi-ingredient supplementation (contains 50 mg RES) group For 12 weeks	↑Sarcopenia index (appendicular lean mass), maximal voluntary contraction, peak power, vitamin D blood levels	[180]
	30 healthy older participants (aged 65–80 years old) Groups including control group (exercise + placebo) and RES (exercise + RES 500 mg/day) group For 12 weeks	↑Maximal oxygen consumed after exercise, mitochondrial volume density, knee extension strength (peak torque, mean peak torque and mean power) improvement with exercise, type I and II A fiber sizes, total muscle nuclei (satellite cells and myonuclei) cells and myonuclei)	[31]

Notes: AP, alkaline phosphatase; KOOS, knee injury and osteoarthritis outcome score; P1NP, procollagen I N-terminal propeptide; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.

500 and 1,000 mg doses of RES twice daily reported reduced exercise-induced muscle damage with no adverse effects, highlighting its potential in muscle preservation[154].

These studies underscore RES's broad benefits in treating DMDs, either as a standalone therapy or in conjunction with other medications. For example, a 90-day study with 28 OA patients receiving 500 mg/day of RES reported improvements in mobility and functional status[163]. In another double-blind, placebo-controlled, randomized multicenter study, combining 500 mg/day of RES with meloxicam improved pain and physical function in OA patients, demonstrating greater safety and efficacy compared to meloxicam alone[164]. Moreover, the combination of RES with equol positively modulated bone turnover biomarkers and improved BMD, supporting its synergistic role in enhancing musculoskeletal health[165].

However, not all clinical results have been consistent. A recent randomized, placebo-controlled trial involving 142 participants across three tertiary care centers in France did not find RES supplements effective in reducing pain in OA patients[166]. This study cohort, however, included patients with more severe symptoms (e.g., long-term high pain levels, activity limitations, and structural damage). Additionally, the outcome assessment was limited to self-reported joint pain without supporting blood or synovial fluid analyses. This discrepancy highlights the need for larger, well-designed trials to refine the understanding of RES's clinical efficacy across various DMDs subtypes.

4.2 Integrating diet and therapeutic approaches: the concept of medicine-food homology

As mentioned earlier, the concept of MFH originated in ancient

China, emphasizing that many natural substances possess both nutritional and therapeutic properties[38]. This perspective represents a fusion of traditional and modern medical principles and aligns with contemporary ideas of functional foods and nutraceuticals. RES, a potent polyphenol naturally present in various foods, exemplifies this integration, making it an ideal candidate for DMDs treatment within the MFH framework. Its anti-inflammatory, antioxidant, and bone-protective properties support its use in a holistic approach to managing musculoskeletal health. Unlike conventional drug treatments that target specific symptoms or pathways, RES's presence in food offers a more comprehensive approach. Incorporating RES-rich foods into the diet, or using it as a supplement, allows for sustained, low-dose therapeutic effects, potentially preventing or slowing DMDs development.

From a clinical perspective, RES's dual role as a dietary component and therapeutic agent is increasingly acknowledged. When administered as a drug, RES reaches its maximum plasma concentration (<10 ng/mL), within 30–90 mins, but its bioavailability is relatively low[13]. However, found in accessible foods like grapes, berries, and nuts, RES is particularly relevant to diets such as the MED, which is naturally rich in polyphenols. This diet has been associated with reduced inflammation, improved cardiovascular health, and the prevention of numerous chronic diseases. Within this dietary framework, RES is a valuable component, particularly for its potential to prevent cartilage degradation in OA, maintain BMD, and support muscle health. The synergistic effects of RES with other polyphenols in polyphenol-rich diets could further enhance these health benefits by targeting multiple pathways involved in DMDs pathogenesis. Thus, integrating RES into dietary practices and supplementation aligns with the MFH approach, providing convenient, sustained support for musculoskeletal health.

Beyond its potential role in DMDs prevention, RES's relevance in MFH extends to long-term preventive healthcare. Unlike isolated pharmacological treatments, RES can be easily incorporated into daily life through dietary sources, offering sustained low-dose therapeutic benefits. Additionally, while some studies, such as the oral resveratrol in knee osteoarthritis study mentioned previously, have reported limited effects on severe DMDs, RES has shown no significant risk of serious side effects[166]. Studies suggest that RES intake in the range of 700–1,000 mg/kg body weight per day has no toxicological effects[13]. This safety profile is particularly advantageous for elderly individuals or those with comorbidities who require long-term therapeutic strategies. The MFH perspective positions RES as part of a comprehensive lifestyle approach to DMDs management, reinforcing the interconnectedness of nutrition and medicine in supporting overall health.

5 Conclusions and future perspectives

RES represents a unique bridge between dietary and pharmacological approaches, embodying the principles of MFH. Its potent anti-inflammatory, antioxidant, and musculoskeletal protective effects make it a promising candidate for the prevention and treatment of DMDs. By integrating RES into dietary habits and pharmacological strategies, a holistic health management paradigm can be developed, offering comprehensive solutions to address DMDs.

Future research should prioritize optimizing the bioavailability of RES, a key challenge that limits its clinical efficacy. While RES is readily absorbed when administered orally, its rapid metabolism and low solubility contribute to limited systemic availability, reducing its therapeutic potential[167]. Furthermore, RES is primarily distributed to organs with high blood flow, such as the liver, kidneys, and heart, with limited accumulation in bones and joints[168]. Therefore, enhancing RES's distribution to bones and joints and improving its bioavailability could be effective strategies to increase its efficacy in DMDs treatment. Promising advances in drug delivery systems, such as nanoparticle encapsulation, conjugation with bioenhancers, and the development of RES derivatives, have shown potential to increase bioavailability and extend its half-life, thereby enhancing clinical efficacy[114, 169-171]. Future applications in DMDs could focus on further refining these delivery technologies to improve RES's targeted accumulation in bones and joints.

Expanding on future directions, a promising area lies in exploring the synergistic effects of RES with other natural compounds. For example, combining RES with curcumin, another polyphenol with strong anti-inflammatory and antioxidant properties, has demonstrated synergistic effects in preclinical studies. A study by Mehta *et al.*[131] showed that a combination of RES and curcumin could significantly reduce glucose-induced glycation and degradation in cartilage models, suggesting a potential therapeutic avenue for OA management. Similarly, quercetin, known for its robust anti-inflammatory effects, may complement RES's mechanisms of action by further suppressing pro-inflammatory cytokines and oxidative stress. These combinations could enhance therapeutic outcomes, targeting multiple pathways involved in cartilage preservation, bone remodeling, and muscle health. Future clinical research could investigate personalized protocols that tailor RES dosages and combination therapies based on patients' metabolic profiles and specific DMDs subtypes, maximizing its therapeutic effectiveness. These strategies could advance the translational application of RES for DMDs treatment, offering patients more effective, safe, and sustainable management options.

In addition to natural compound synergy, the potential for combining RES with existing therapeutic approaches presents another advanced and integrative direction. For instance, RES could be paired with physical therapies such as resistance training or mobility exercises, which are foundational in sarcopenia management. RES enhances mitochondrial function and muscle regeneration, and its combined use with exercise may amplify these benefits. Similarly, RES could complement pharmacological agents like bisphosphonates for OP or hyaluronic acid injections for OA[172]. A dual approach might not only improve symptom relief but also address the underlying mechanisms of disease progression, such as inflammation, oxidative stress, and cellular apoptosis. Future research should further evaluate these combinations in large-scale, long-term clinical trials to establish efficacy and safety profiles.

However, there is a need for long-term clinical studies to evaluate the sustained impact of RES on DMDs, especially in elderly populations and those with other chronic conditions. Although RES's short-term benefits in reducing OA pain, increasing BMD, and improving muscle function have been documented, evidence of its long-term effects remains limited. Conducting extensive, long-term studies is essential to better understand its impact over time and to fully establish its safety profile for chronic use. Moreover, integrating RES into personalized treatment protocols could enhance outcomes for diverse patient populations. Personalized medicine approaches

that incorporate individualized metabolic and genetic profiling can help tailor RES dosages and combinations for maximum efficacy. For example, patients with metabolic disorders or those at higher risk of oxidative stress might benefit from higher doses of RES or its combination with metabolic regulators like metformin or insulin sensitizers.

Moreover, RES's potential extends beyond therapeutic applications to the development of functional foods and nutraceuticals that could offer preventive benefits for musculoskeletal health. Functional foods enriched with RES and complementary polyphenols could provide targeted support for bone and muscle health, offering convenient and cost-effective options to promote public health. Personalized nutrition approaches, tailored to individual metabolic characteristics and genetic predispositions, could further enhance the efficacy of RES, particularly when combined with other DMDs therapies[164]. By integrating these approaches, RES could play a central role in personalized and preventive healthcare, especially for aging populations at higher risk for DMDs.

In summary, RES exemplifies the potential of integrating dietary and pharmacological strategies for comprehensive health management. Its role in musculoskeletal health underscores the importance of multifaceted approaches that utilize dietary components to offer preventive and therapeutic benefits, potentially in combination with other treatment modalities. As ongoing research continues to clarify RES's mechanisms and optimize its applications, RES is positioned to become a cornerstone in the integrated management of musculoskeletal health, offering sustainable, personalized approaches to chronic disease prevention and treatment.

Conflicts of interest

The authors declare that there are no conflicts of interests in this work.

Acknowledgements

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