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REVIEW ARTICLE

Resveratrol for Atherosclerosis: Potential Mechanisms

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Abstract: Cardiovascular disease is a big problem around the world. At the heart of most serious cardiovascular diseases is such a pathology as atherosclerosis. Atherosclerosis is a complex set of interactions between inflammation, oxidative stress, lipid disorders, and other molecular, genetic, and lifestyle factors. It is this complexity and multicomponent nature of atherogenesis that make the treatment of atherosclerosis a non-trivial task. Currently, there are no entirely effective strategies for preventing or treating atherosclerosis. Nevertheless, various medications demonstrate varying degrees of effectiveness in relation to processes linked to atherogenesis. In this review, we reviewed a list of possible mechanisms that may contribute to the effectiveness of resveratrol against atherosclerosis.

Keywords: Resveratrol, Inflammation, Atherosclerosis, Cardiovascular Disease

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Introduction

Cardiovascular disease poses a major threat to human health, ranking as the top cause of death worldwide, responsible for about 7.8% of fatalities. Atherosclerosis, a form of cardiovascular disease, leads to the narrowing of blood vessels caused by the accumulation of fatty streaks and plaques, influenced by carbohydrates, lipids, and genetic factors [1]. In the studies conducted by Usai MV and co-authors, it has been noted that disruptions in blood lipid metabolism are strongly associated with atherosclerosis. Nonetheless, the exact mechanisms involved in the progression of this disease remain unclear [2]. Thus, it is crucial to examine how a high-fat diet contributes to the onset of atherosclerosis in order to discover possible therapeutic strategies to mitigate this condition.

Res Veratrol (RV) is a type of biological polyphenol. It can be used for therapeutic purposes in some cardiovascular diseases. A prior study demonstrated that RV has neuroprotective benefits in rats with ischemic injury, as it enhances brain energy metabolism and diminishes oxidative stress. Likewise, another investigation revealed that RV possesses anti-inflammatory and antioxidant characteristics. These properties can help suppress or prevent age-related cardiovascular diseases. Notably, RV has been shown to enhance cardiac contractions, making it a promising candidate for new clinical treatments. Additionally, RV exhibits cardioprotective effects in both primary and secondary prevention of cardiovascular

diseases, as evidenced by dietary and clinical studies. While the precise mechanisms by which RV exerts its effects on cardiovascular health are not yet fully understood, it is considered a potential therapeutic option for prevention and management.

Resveratrol Discovery and Structure

RV is a biological polyphenol characterized by a chemical structure that includes two aromatic rings linked by a methylene bridge. It naturally occurs in both trans and cis forms, but the therapeutic benefits are primarily associated with the trans-RV variant. With a molecular weight of 228.25, RV is found as a white powder, exhibiting a melting point of 253-255°C when extracted using methanol. Common sources of RV are mulberries, red grapes, Polygonum cuspidatum, cranberries, dark chocolate, pistachios, lingonberries, soybeans, blueberries, pomegranates, and soy. These products are often used as a source of RV due to their high concentration of the compound [3]. These sources are often used in RV supplements due to their high concentrations of RV. Non-edible plants like grass, lilies, and pine bark also produce RV. The levels of RV in grapes can range from 0.16-3.54 mg/g, while dried grape skins have an RV concentration of approximately 24 mg/g. Additionally, RV is found in various nuts and berries; for instance, cranberry juice contains around 0.2 mg/L of RV. When it comes to red wine, boasts a significantly higher variety of polyphenolic compounds compared to white wine, with RV concentrations varying from 0.1-14.3 mg/L across different red wine types. In contrast, white wine typically has RV levels between 0.1 and 2.1 mg/L. Unfortunately, due to these concentrations, it is not feasible to effectively supplement RV through the consumption of these foods or combinations.

The current recommendations for daily RV intake are primarily derived from animal studies and converted into human equivalents. However, precise recommendations for the therapeutic use of RV in humans are needed. Research has demonstrated that RV intake of 700-1000 mg/kg body weight per day is safe and does not produce toxic effects [4]. Short-term intake of up to 2 g per day is deemed safe. Clinical studies involving humans indicate that RV exhibits low toxicity and is generally well-tolerated. Several clinical trials have demonstrated that RV is pharmacologically safe, even at higher doses of up to 5 g per day. Furthermore, a year-long study revealed that a low dose of RV (8 mg per day) significantly reduced various cardiac risk factors [5].

Many research studies have shown that RV has considerable potential in enhancing overall health due to its antioxidant, anti-inflammatory, antiplatelet, cardioprotective, blood sugar-lowering, and anticancer effects. Recent findings suggest that RV may offer protection against specific neurodegenerative conditions, including Alzheimer's disease and obesity. Additionally, it has proven effective in managing osteoporosis in postmenopausal women with a low risk of breast cancer [6]. We provided the schematical illustration of resveratrol in Figure 1.

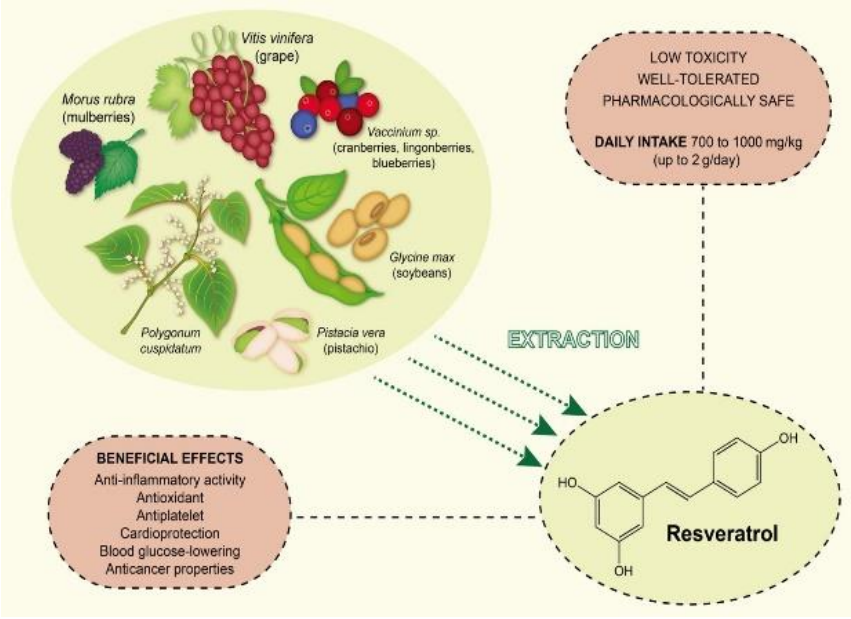

Fig. 1: Resveratrol: Structure, sources and benefits

Beneficial Effects of Resveratrol

We summarized the beneficial effects of resveratrol in Figure 2.

Anti-Inflammatory Activity

Research by Hsu et al. [7] demonstrated that resveratrol can effectively inhibit the transcription and translation of IL-6, leading to a decrease in the secretion of this pro-inflammatory cytokine by macrophages [7]. Additionally, when resveratrol was added to cultures of monocytes, a significant reduction in the levels of TNF-α and IL-8 both key inflammatory mediators was observed, with no signs of cytotoxicity. Resveratrol also markedly reduced the production of extracellular matrix proteins by pancreatic stellate cells, which are instrumental in the progression of pancreatic fibrosis [8, 9].

Furthermore, the study by Chen et al. [10] highlighted resveratrol's important role in inhibiting toll-like receptors that induce the expression of pro-inflammatory cytokines and chemokines, thereby stimulating both innate and adaptive immune responses [10]. In chondrocytes affected by osteoarthritis, resveratrol was shown to dose-dependently suppress the production of IL-6, IL-1, and TNF-α, as well as lower the activity of matrix metalloproteinase. However, it is crucial to understand that the effectiveness of these effects may vary with dosage and additional research is needed to clarify this.

In patients undergoing oral implant procedures, resveratrol treatment was associated with reduced serum levels of IL-1β, IL-17A, and TNF-α, while levels of IL-2, IL-6, and IL-10 increased [11]. Ma et al. [12] also found that resveratrol effectively inhibits NF-κB signaling by blocking the activities of NF-κB and IκB kinase and attenuating the phosphorylation of JAK/STAT pathways [12]. Additionally, resveratrol has demonstrated protective effects against intestinal ischemia-reperfusion injury by reducing mast cell degranulation and apoptosis in intestinal epithelial cells, thereby helping to prevent overall organ dysfunction.

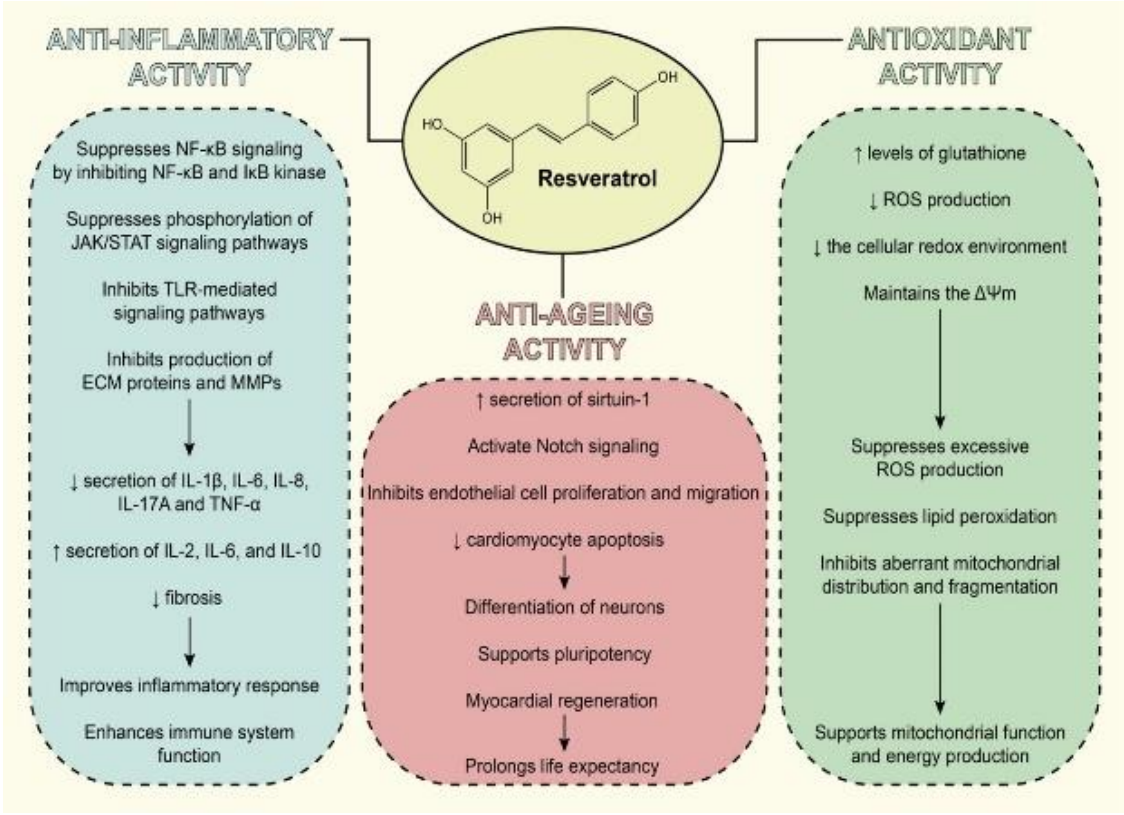

Fig. 2: Health-beneficial effects of resveratrol

Resveratrol's anti-inflammatory properties have been noted in both immune-mediated diseases and hyper-acute small intestinal inflammation. It has also been shown to prevent disruptions to macrophage lipid homeostasis and acceleration of cholesterol accumulation induced by glycation products [13].

Materials and Methods

Antioxidant Activity

Oxidative stress arises when there's an imbalance between the generation of Reactive Oxygen Species (ROS) and the body's antioxidant defenses, leading to a predominance of oxidants. This condition has been associated with various age-related ailments, including cancer, diabetes, chronic kidney disease, cardiovascular issues, and neurodegenerative disorders, as it can damage macromolecules and hinder their functions [14]. Furthermore, an overproduction of ROS can trigger inflammation, disrupt mitochondrial function, and result in cell death. Studies indicate that the auto-oxidation of glucose may also enhance the levels of ROS, exacerbating oxidative stress [15].

Resveratrol, a polyphenolic compound found in grapes, is recognized for its potent antioxidant capabilities, attributed to the three hydroxyl groups in its chemical structure. It effectively inhibits the excessive generation of ROS, abnormal distribution of mitochondria, and lipid peroxidation [16]. Research shows that resveratrol can elevate the levels of naturally produced glutathione and decrease the production of endogenous ROS in primary epidermal keratinocytes, contributing to a more favorable cellular redox environment [17]. Additionally, resveratrol helps prevent the rise of ROS and mitigates the decline in mitochondrial membrane potential in astroglial cells exposed to ammonia, which suggests its role in preserving cellular redox balance. Moreover, in fibroblasts treated with rotenone, resveratrol mitigates mitochondrial fragmentation, sustains mitochondrial membrane potential, and protects against the decline of oxidative phosphorylation, thereby offering a defense against the detrimental effects of ROS [18].

A recent investigation by Cheng et al. [19] demonstrated that resveratrol can inhibit hepatic steatosis in obese mice on a high-fat diet by mitigating oxidative stress and inflammation. This protective mechanism is evidenced by its ability to decrease lipid droplet accumulation in liver cells [19].

In another study, Wang et al. [20] found that treating epithelial cells with resveratrol protects against oxidative damage induced by hydrogen peroxide. Resveratrol was shown to enhance the expression and phosphorylation of zonula occludens proteins, such as occludin [20]. These protective effects are linked to reduced levels of Malon Di Aldehyde (MDA) and intracellular Reactive Oxygen Species (ROS), as well as elevated expression of antioxidant enzymes. Additionally, long-term administration of resveratrol has demonstrated a protective role against apoptosis and age-related oxidative stress, while also improving glucose tolerance in pancreatic cells of mice with type 2 diabetes.

Administering resveratrol at a daily dose of 5 mg/kg to diabetic rats has resulted in reduced oxidative stress and normalization of antioxidant status impacted by hyperglycemia. Rats with strep tozotocin-induced diabetes treated with resveratrol at doses of 10-20 mg/kg for four weeks exhibited decreases in advanced oxidation protein products (AOPP) and MDA, alongside increased activity of superoxide dismutase and catalase in the lens [21]. Furthermore, resveratrol treatment enhanced mitochondrial membrane potential while decreasing ROS production and preventing the release of cytochrome c from the inner mitochondrial membrane. In Wang et al. [20] study, resveratrol was found to mitigate the accumulation of 3-nitrotyrosine and the formation of 4-hydroxynonenal during the progression of diabetes-related cardiomyopathy. Diabetic rats receiving resveratrol showed lowered levels of MDA and total oxidants, combined with an overall increase in antioxidant capacity compared to untreated controls [22].

Resveratrol also offers protection against ischemic spinal cord injury in rats by reducing plasma levels of AOPP, nitrites and MDA, while enhancing the enzymatic activity of catalase and superoxide dismutase. Additionally, resveratrol has been shown to alleviate oxidative stress in rats suffering from experimental periodontitis, chronic obstructive pulmonary disease and early-stage Alzheimer's disease [23].

In summary, the evidence suggests that resveratrol exerts therapeutic effects in cellular and animal studies involving elevated oxidative stress levels. Its action appears to involve reducing ROS formation and promoting compounds that function as antioxidants.

Anti-Aging Activity

Resveratrol has been shown to enhance lifespan across multiple species, including mice, honey bees, and fish. Administering resveratrol (500 mg/day) to slightly overweight healthy individuals resulted in increased gene expression and elevated levels of sirtuin-1 in the blood serum. Sirtuin-1 is a protein known for its numerous beneficial properties, including anti-inflammatory and anti-aging effects. It also plays a role in inhibiting degenerative diseases such as liver steatosis,

enhancing endothelial function, and preventing cancer [24]. Furthermore, a recent study demonstrated that resveratrol injections can slow the aging process of oocytes in middle-aged mice by promoting sirtuin-1 expression, enhancing mitochondrial function, and decreasing ROS production. In general, the mechanisms by which resveratrol prolongs life expectancy are similar to caloric restriction mechanisms [25].

While many studies have shown that resveratrol can extend lifespan, there is ongoing debate regarding its anti-aging properties. Recent research by Ramos-Gomez and others has indicated that resveratrol can cause mitochondrial dysfunction and shorten the lifespan of Saccharomyces cerevisiae [26]. Additionally, research indicates that dietary resveratrol does not lengthen the lifespan of certain mosquito species, including Anopheles stephensi and Drosophila melanogaster, nor does it influence the expression of genes associated with longevity or antioxidant enzymes. According to a study by Wang et al. [27], the lifespan-extending effects of resveratrol are influenced by several factors, including sex, dietary composition, and dosage [28]. For instance, a dosage of 400 micromoles of resveratrol was found to extend the lifespan of female Drosophila melanogaster on a high-fat diet, while lower doses showed no impact on the lifespan of females on a calorie-restricted or high-sugar and protein diet. Furthermore, it has been observed that the lifespan-extending effects of resveratrol can vary based on the genetic makeup of the organism and the specific model used in the investigations.

It is also worth mentioning that resveratrol has other positive effects on various tissue and cellular targets. According to the report of Hara et al. [29], resveratrol can cause a decrease in the degradation of damaged mitochondria, which was caused by vitrification in cattle embryos consisting of 8-12 cells, without affecting the ATP content or embryonic development [29]. Gorga and others found that resveratrol can reduce the expression of cyclones [30]. Resveratrol may also be the cause of the activation of sirtuin 1, which regulates the proliferation of immature Sertoli cells. Resveratrol also acts as an inhibitor of endothelial cell proliferation and migration and as an activator of Notch signaling.

Resveratrol has various positive effects on various tissues and cells. For example, in mouse neuroblastoma, resveratrol can cause differentiation of neurons. At the same time, in the case of monocytes, it promotes their transformation into macrophages. Recent studies also demonstrate that resveratrol supports pluripotency, as well as increases the self-renewal of mouse and human embryonic stem cells. Intragastric administration of resveratrol can increase capillary density, activate heart stem cells, and reduce cardiomyocyte apoptosis [31]. As a result, myocardial regeneration takes place following an acute myocardial infarction. Furthermore, resveratrol enhances lipid breakdown in brown adipose tissue by decreasing the expression of perilipin 5, which could potentially be the cause of weight loss and reduction of myocardial steatosis. Resveratrol has also been found to have antimicrobial activity against Staphylococcus aureus, Escherichia coli, Haemophilus in fluenzae, and Propionibacterium acnes [27, 32] reported that a six-month intake of 0.04% resveratrol improved fatigue resistance and functional and mechanical properties of skeletal muscles in elderly mice [32]. It is also worth mentioning that, with a daily dose of 500 mg, resveratrol can improve functional activity, as well as reduce joint pain in patients with osteoarthritis of the knee joint. Farrokhi and colleagues showed that a concentration of 120 μM resveratrol may serve as a potential treatment for atherosclerosis by lowering the levels of matrix metalloproteinase 9 [33]. Additionally, resveratrol has been found to alleviate allergic asthma, as well as symptoms related to depression and anxiety. Lastly, it can enhance testosterone levels and improve sperm quality by decreasing apoptosis in the testes.

Serious limitations of resveratrol are its bioavailability (less than 0.05 mg/mL) and poor solubility in water. For example, taking resveratrol at a dose of 25 mg leads to a plasma concentration below 10 ng/ mL. The plasma concentration reaches 500 ng/mL only after administering a substantial dose of 5000 mg. Research indicates that ingesting 500 mg of resveratrol in tablet form is usually well tolerated, resulting in a plasma concentration of approximately 70 ng/mL [34]. Overall, resveratrol is considered safe for consumption. However, it's worth mentioning that some side effects have been observed when taken in higher doses. Such side effects include: Flatulence, nausea, abdominal discomfort, diarrhea, anemia, acute damage to the tubules, vomiting, and renal failure in the form of gypsum and crystalline nephropathy. Nonetheless, the nephrotoxic effects of resveratrol were noted exclusively in patients diagnosed with multiple myeloma. Recent studies have found that exposure to resveratrol in doses up to 100 μM can disrupt the absorption of fatty acids and the oxidation of placental tissue. This effect, in turn, can have a negative impact on the development of the fetus [35]. Moreover, Kumaran et al. [36] found that a daily oral dose of resveratrol can cause thrombocytopenia in women with melasma [36].

The half-life of resveratrol is approximately 1.5 h. This is due to the fact that it quickly decomposes in the liver and is absorbed in the intestine. When consumed, the active transport of resveratrol through intestinal epithelial cells leads to the absorption of 77-80% of resveratrol into the bloodstream. It associates with lipoproteins and albumin, allowing this polyphenol

to be readily released from these complexes and taken up by cells. Approximately 49-61% of resveratrol is eliminated through urine [37].

More complex formulations have been developed to increase the bioavailability of this compound. Such compositions include nanostructured lipid carriers and nanoparticles containing resveratrol. Researchers attempted to enhance the bioavailability of resveratrol in rats by using 3,5,4'-tri-O-acetylresveratrol (TARES), an acetylated prodrug that can be enzymatically converted into active trans-resveratrol within cells [38].

Resveratrol Enhances Atherosclerosis Management by Blocking the TGF/ERK Signaling Pathway

Resveratrol has demonstrated positive effects on cardiovascular diseases, primarily through its influence on the ERK and TGF signaling pathways. By inhibiting ERK/eNOS-Thr495 in Endothelial Cells (ECs), it helps reduce oxidative stress induced by Low Shear Stress (LSS). This protective effect can prevent the development of atherosclerotic lesions that are caused by LSS. In a rat model of cardiac hypertrophy, resveratrol has been shown to activate SIRT1. This activation helps modulate the TGF-β1/p-Smad3 signaling pathway, thereby reducing cardiac hypertrophy, fibrosis and enhancing cardiac function [39]. Additionally, by inhibiting the TGF-β/Smad2/3 pathway, SIRT1 plays a role in regulating End MT, which further helps decrease cardiac fibrosis. Furthermore, resveratrol can impede TGF-β1-induced proliferation and collagen secretion in cardiac fibroblasts by downregulating miRNA-17 and influencing Smad7 levels. With the involvement of Smad7, this process enhances the negative regulation of the TGF-β1/S mad signaling pathway. Resveratrol, among other things, can help reduce heart failure and hypertrophy caused by High Glucose (HG) [40]. This becomes possible due to the inhibition of the NF-kB and TGF-β/Smad3 pathways, which depend on the receptor of the end products of accelerated glycation. For a more detailed study of the effect of the drug, a study was conducted on a model of acute myocardial infarction in rats. In this case, resveratrol demonstrated a cardio-protective effect by enhancing cardiac function and reducing interstitial atrial fibrosis, which can be achieved by inhibiting the NLRP3 inflammsome some and blocking the TGF-β1/Smad2 signaling pathway. Additionally, resveratrol has been shown to impede tumor cell metastasis and invasion by modulating the TGF signaling pathway. For instance, it has been observed to suppress TGF-β1-induced Epithelial-Mesenchymal Transition (EMT) and to inhibit the invasion and metastasis of lung cancer [41]. In Figure 3, we illustrated the signaling pathways by which resveratrol alleviates atherosclerosis.

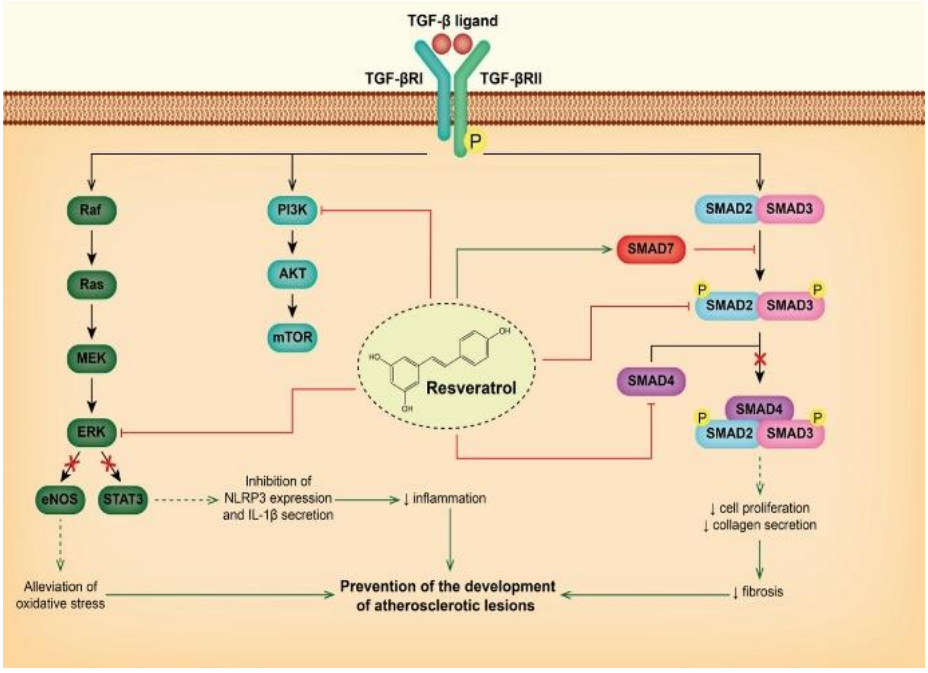

Fig. 3: Resveratrol alleviates atherosclerosis by inhibiting TGF-β/Smad, TGF-β/ERK and PI3K/AKT/mTOR signaling pathways

By modulating the ERK signaling pathway, resveratrol also has a beneficial effect. So, based on the available data, we can talk about the potential therapeutic efficacy in allergic diseases, inflammatory diseases, cerebral hemorrhage, diabetic

cardiomyopathy, and cancer. Thus, in lung cancer, due to the signaling pathways of endoglin and ERK, resveratrol promotes the growth of tumor microvessels [42]. At the same time, in melanoma cells, due to suppression of the ERK/PKM2/Bcl-2 axis, resveratrol has been found to induce apoptosis and promote melanogenesis in HT-144 melanoma cells while simultaneously inhibiting cell proliferation, likely due to its effects on the MER/ERK signaling pathway. Additionally, it exhibits anti-inflammatory properties by blocking mitochondrial and nuclear phosphorylation of ERK1/2 and STAT3 in human intestinal mast cells [43].

Research indicates that resveratrol directly influences the TGF/ERK signaling pathway and there may be a feedback loop between ERK signaling and TGF-β, whereby ERK contributes to the expression of TGF-β triggered by High Glucose (HG). By inhibiting the ROS/ERK/TGF-β/periostin pathway, resveratrol can enhance the differentiation of myofibroblasts. In a study investigating the therapeutic effects of resveratrol on rats suffering from cerebral hemorrhage due to reperfusion injury, it was shown to reduce neuronal cell apoptosis and inflammation by targeting the TGF-β-ERK signaling pathway [44].

The TGF/ERK signaling pathway plays a vital role in mediating the therapeutic potential of resveratrol with numerous pathological mechanisms. In AS, resveratrol has a cardioprotective effect. It inhibits VSMC proliferation, MMP synthesis, EndMT, inflammatory response, biglycan synthesis, AF proliferation, and migration by inhibiting the TGF/ERK signaling pathway. It is also important to point out that resveratrol has significant therapeutic prospects for atherosclerosis and other pathological conditions by regulating the TGF/ERK signaling pathway [45].

Resveratrol Reduces Atherosclerosis Caused by a High-Fat Diet and LPS in ApoE−/− Mice While also Preventing the Activation of CD4+ T Cells

In their research, Zhou et al. [45] established that RV effectively reduced atherosclerosis induced by a High-Fat Diet (HFD) and LPS in ApoE−/− mice [46]. The study indicated that RV treatment significantly lowered lipid accumulation on the vessel walls and modulated cytokine secretion. Furthermore, evidence showed that this treatment inhibited the proliferation and activation of CD4+ T cells both in vivo and in vitro. Notably, RES treatment decreased the expression of Dnmt1 and Dnmt3b in CD4+ T cells, which was associated with their suppressed proliferation and activation.

The authors observed that by the 10th week of the experiment, RV significantly lowered elevated levels of Total Cholesterol (TC) and Tri Glycerides (TG). By week 20, it also curtailed TC, TG, and LDL-C and improved HDL-C function. RV has been the subject of extensive research for its capacity to promote lipolysis, inhibit adipocyte differentiation, reduce TC accumulation, facilitate the breakdown of oxidized LDL, and regulate serum lipid levels. The findings support the efficacy of RV in managing lipid levels in blood serum and suggest that its effects may be sustained over time [47].

In contrast to the regulation of serum lipid levels, RV reduced the development of atherosclerosis induced by Trimethyla Mine-N-Oxide (TMAO) in ApoE−/− mice. RV also alleviated atherosclerosis associated with systemic lupus erythematosus, improved atherosclerosis induced by a High-Fat Diet (HFD) in LDLR−/− mice, and facilitated atherosclerosis in high-fat mice (mice with a partially ligated left carotid artery). The results obtained are also consistent with previous studies that indicate a beneficial effect of RES on atherosclerosis [48].

Lipo Poly Saccharides (LPS) are risk factors for inflammation that can increase with gram-negative bacterial infections. Elevated LPS levels can easily cause low-grade inflammation. This represents an additional risk factor for the onset of atherosclerosis [49].

Resveratrol has been observed to alleviate the symptoms of atherosclerosis through multiple mechanisms. It modulates the production of vasoconstrictors and vasodilators, decreases inflammation, and mitigates oxidative stress and the generation of reactive oxygen species. Despite these findings, the exact mechanisms through which resveratrol improves atherosclerosis remain not entirely clarified [50]. Research by Zhou et al. [50] has revealed an additional way resveratrol contributes to the management of atherosclerosis by inhibiting the activation of CD4+ T cells. In their study, resveratrol was shown to down-regulate Dnmt1 and Dnmt3b in CD4+ T cells, leading to the suppression of their activation [51].

The most common type of T cell found in atherosclerotic plaques is the CD4+ T cell. These cells are involved in all stages of atherosclerosis. Naive CD4+ T cells express high levels of CD62L, a molecule critical for their migration into lymphoid tissue, but its expression decreases upon activation. Activated CD4+ T cells increase their expression of CD44 and CD25 and secrete inflammatory cytokines in response to antigen signals. These cells multiply and contribute to the progression of inflammation, exacerbating atherosclerosis [52].

Resveratrol has been demonstrated to inhibit the proliferation and activation of CD4+ T cells in both atherosclerotic mice and in vitro cultures of splenic CD4+ T cells. This indicates that resveratrol may enhance atherosclerosis outcomes by limiting the growth and activation of these immune cells [53].

CD4+ T cells play a crucial role in the adaptive immune response and inflammation driven by their activation significantly contributes to the onset and progression of atherosclerosis, primarily through the release of pro-inflammatory cytokines. Notably, resveratrol has been found to elevate levels of TGF-β1 and IL-10 while diminishing the secretion of IL-6. A deficiency in IL-10-producing CD4+ T cells correlates with a heightened risk of advancing coronary atherosclerosis, while persistent IL-6 production can result in chronic inflammatory issues. The anti-inflammatory effects provided by TGF-β1 become less effective as atherosclerosis advances [54].

Additionally, resveratrol is known to boost IL-2 production, a pro-inflammatory cytokine tied to cardiovascular disease progression, yet it also stimulates the generation of regulatory T cells (Tregs), which offer protective effects against atherosclerosis. The implications of increased IL-2 levels in the context of atherosclerosis remain under investigation. Resveratrol not only fosters lymphocyte proliferation and IL-2 production but also regulates cytokine release and inhibits both the activation and proliferation of CD4+ T cells. Together, these observations suggest that resveratrol may suppress the immune response mediated by CD4+ T cells in individuals with atherosclerosis [55].

Research on resveratrol has revealed its capacity to influence multiple targets and molecular functions, owing to its diverse biological activities, which encompass antioxidant, anti-cancer, and anti-inflammatory effects, along with its role in the prevention and treatment of cardiovascular diseases. Numerous animal studies and clinical trials have investigated resveratrol, illustrating its moderate efficacy in addressing various pathological conditions [56].

In animal models, resveratrol has been shown to ameliorate atherosclerosis by modulating the levels of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) and cholesterol 7α-hydroxylase (CYP7A1). This regulation leads to a reduction in total cholesterol, triglycerides, and Low-Density Lipoprotein (LDL) cholesterol while promoting an increase in High-Density Lipoprotein (HDL) cholesterol. Moreover, resveratrol's antioxidant properties help diminishes the oxidation of low-density lipoproteins, contributing to atherosclerosis prevention.

The anti-inflammatory effects of resveratrol are also significant, as it inhibits the release of inflammatory cytokines, including IL-1β, IL-6 and TNF-α, as well as obstructing inflammatory signaling pathways like NF-kB [43]. Furthermore, resveratrol may facilitate improvements in atherosclerosis by inhibiting platelet aggregation and promoting platelet apoptosis. Throughout preclinical investigations, resveratrol has demonstrated potential therapeutic effects across all stages of atherosclerosis progression.

While animal studies show that resveratrol can have an anti-atherosclerotic effect, clinical trials are still limited. Also, an important factor is the content of lipids in blood plasma. The impact of resveratrol on plasma lipid levels differs among healthy individuals and those with cardiovascular diseases. The limitations of clinical studies on the treatment of atherosclerosis with resveratrol are due to the limited size and heterogeneity of the study groups, along with the use of various research schemes, doses, and duration of taking resveratrol supplements. Therefore, further well-controlled clinical trials are needed to evaluate the anti-atherosclerotic effect of resveratrol at all stages of the atherosclerotic process, in addition to its effect on the level of lipids in blood plasma [57].

Dnmt1 is responsible for maintaining DNA methylation. Dnmt3b plays a key role in initiating de novo methylation. Irregular levels of dnmt expression are linked to several human diseases, such as atherosclerosis, positioning dnmt as a potential target for therapeutic interventions in epigenetic regulation. Targeted inhibitors of dnmt may help modulate their expression and could potentially correct dysfunctional cellular mechanisms. Additionally, resveratrol has been recognized as a modulator of Dnmt expression. Moreover, most studies indicate that resveratrol functions as a Dnmt inhibitor in various cell types [58].

Research has indicated that resveratrol lowers the expression of Dnmt1 and Dnmt3b in CD4+ T cells, which seems linked to a reduction in the activation of these cells. Nevertheless, it is still uncertain whether resveratrol’s inhibitory effect on CD4+ T cell activation directly stems from the downregulation of Dnmt1 and Dnmt3b. Additional studies are needed to clarify the connection between these elements [59].

Resveratrol Provides Protection against Atherosclerosis by Inhibiting the PI3K/AKT/mTOR Signalling Pathway in Mouse Models of Atherosclerosis

Previous research has indicated that resveratrol can lower inflammatory cytokine levels in rabbit models of atherosclerosis. A recent study conducted by Ji et al. [60] assessed the therapeutic effects of resveratrol in atherosclerosis model mice and explored its influence on the PI3K/AKT/mTOR signaling pathway in Human Umbilical Vein Endothelial Cells (HUVECs) [59]. The results revealed that resveratrol treatment led to an increase in the expression of AKT, PI3K, and mTOR, as well as an enhanced ratio of phosphorylated to total proteins in UVECs. Moreover, resveratrol administration resulted in elevated levels of Total Cholesterol (TC), Trigly Cerides (TG), Low-Density Lipoprotein cholesterol (LDL-c), and High-Density Lipoprotein cholesterol (HDL-c) in the serum of atherosclerosis-afflicted mice. Additionally, the study found that resveratrol exhibited anti-inflammatory effects, which may contribute to its ability to combat atherosclerosis.

Further research has shown that resveratrol, a polyphenolic compound, protects HUVECs from TNF-α induced damage by activating sirtuin-1, which inhibits the expression of NF-kB and the p38 MAPK pathway. Treatment with resveratrol also reduced levels of the inflammatory marker C-reactive protein (CRP), leading to diminished atherosclerotic lesions and improved lipid metabolism in female transgenic mice. Other studies have revealed that HMG-CoA reductase inhibitors can mitigate chronic inflammation related to atherosclerosis resulting from dietary cholesterol [61]. Resveratrol has also been associated with weight loss in mice with atherosclerosis, leading to improved disease pathology.

Recent findings suggest a complex relationship between coronary atherosclerosis and liver function, as elevated triglyceride and LDL cholesterol levels have been noted in patients with atherosclerosis. Nevertheless, resveratrol has been shown to lower total cholesterol, LDL cholesterol, HDL cholesterol, and serum triglycerides in atherosclerosis model mice. Additionally, it reduced the activity of HMG-CoA reductase and other enzymatic markers, including alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, and aspartate aminotransferase in these mice. This suggests a potential connection between atherosclerosis and liver dysfunction [62].

Resveratrol has exhibited a variety of pharmacological effects, such as antioxidant, antitumor, and anti-inflammatory properties, as well as the regulation of glucose and lipid metabolism. In a study, it was found that resveratrol improved lipid metabolism in atherosclerosis model mice. Serum levels of MMP-9 are typically associated with carotid artery atherosclerosis and lesion vulnerability. In Ji et al. [59] research, treatment with resveratrol significantly decreased the levels of MMP-9 and CD40L in arterial lesion tissues, indicating a potential protective role against atherosclerotic lesions in mice. The same study found that statin treatment improved intima-media thickness of the carotid arteries, correlating with a regression of atherosclerosis. Additionally, serum LDL-C levels can indicate the severity of coronary atherosclerosis, and resveratrol treatment was associated with a significant reduction in the extent of atherosclerosis in mice. Furthermore, resveratrol was found to enhance lipid metabolism in high-fat diet-fed atherosclerosis model mice, potentially boosting its anti-atherosclerotic effects and reducing cardiovascular risks. However, it has been suggested that decreases in HDL cholesterol levels might negatively impact the effectiveness of resveratrol treatment for high-fat diet-induced atherosclerosis, warranting further investigation into its anti-atherosclerotic mechanisms in human endothelial cells exposed to oxidized low-density lipoprotein [59].

Everolimus, a drug that inhibits mTOR, has proven effective in preventing atherosclerosis in LDLR-/- mice, even under conditions of severe hypercholesterolemia. Prior studies have suggested that targeting the PI3K/AKT/mTOR signaling pathway in vascular endothelial cells could serve as a promising therapeutic strategy for atherosclerosis treatment [63].

These studies indicated that activating this pathway offers protective benefits against atherosclerosis, while its inhibition may promote apoptosis in human endothelial cells induced by oxidized LDL, thus preventing disease progression. Current research has demonstrated that resveratrol treatment can suppress the PI3K/AKT/mTOR signaling pathway in vascular endothelial cells from mice with atherosclerosis. Notably, overexpression of PI3K negated the effects of resveratrol on the expression of AKT and mTOR in these cells. However, more studies are required to assess the therapeutic effectiveness of resveratrol in atherosclerosis patients. Additionally, it is crucial to examine the dissociation/inhibition constants (KD/KI) associated with resveratrol molecules. Collectively, these findings imply that resveratrol may positively influence the progression of atherosclerosis by modulating the PI3K/AKT/mTOR signaling pathway [64].

Conclusion

Resveratrol is a natural substance. Numerous studies have looked at the anti-inflammatory, antioxidant, and anti-aging properties and effects of resveratrol. All these properties were considered both independently and concerning the pathology of interest to us. As for the anti-inflammatory action of resveratrol, this effect in terms of atherosclerosis suppression may be associated with inhibiting the TGF/ERK signaling pathway, downregulating the PI3K/AKT/mTOR signaling pathway, and inhibiting the activation of CD4+ T cells. These effects have been shown in model mice. Further research will assess the relevance of these effects to the clinical use of resveratrol.

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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