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REVIEW ARTICLE

MOLECULAR MECHANISMS AND THERAPEUTIC POTENTIAL OF RESVERATROL

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Abstract: Trans-resveratrol is a polyphenol that belongs to the stilbene family. In nature, resveratrol works primarily as a phytoalexin., it is synthesized by more than 70 plant species as a primary defense mechanism against environmental stressors, such as prolonged exposure to ultraviolet radiation or fungal and bacterial infections. Among the richest botanical sources is the *Vitis vinifera* plant whose fruits store this compound mainly in the skin of the grapes. Berries, blueberries and cranberries are a known source of resveratrol. *Polygonum cuspidatum* is a plant used as a source of resveratrol extraction for use in dietary supplements. Other sources of resveratrol include various trees like eucalyptus and floral species such as lilies. Several studies have documented different medicinal effects of resveratrol on human health, including its antioxidant, anti-inflammatory, cardioprotective, and neuroprotective properties. For human consumption, this antioxidant is available in a variety of everyday foods, especially red and purple fruits, peanuts, grapes and red wine. The maceration process of red wine, which includes the skin, seeds, and woody parts of the plant, facilitates a very high concentration of this compound, giving it great nutritional value. On a structural level, resveratrol is composed of two aromatic rings linked by a carbon-carbon double bond, allowing it to exist in cis and trans configurations. The trans form is the most stable and, therefore, the most used in health research. Its synthesis occurs through three condensation reactions mediated by the enzyme stilbene synthase. **Conclusions:** Trans-resveratrol is a naturally occurring polyphenolic stilbene synthesized by numerous plant species as part of their defense mechanisms against environmental stress conditions. It is found in human foods such as grapes, berries, peanuts, and red wine. Several studies have documented its potential benefits for human health.

Keywords: Medicinal properties, Resveratrol, Stilbene, Phenolics, Trans-resveratrol

INTRODUCTION

Resveratrol possesses multiple medicinal properties on human health. The five major biological activities are antioxidant, enhancer of enzyme activity, anti-inflammatory, cardioprotective and neuroprotective. First, it acts as a powerful antioxidant capable of neutralizing free radicals, inhibiting lipid peroxidation in cell membranes, and modulating oxidative stress at the mitochondrial level (Frémont *et al.*, 2000). Resveratrol enhances the activity of endogenous antioxidant enzymes and protects LDL and VLDL lipoproteins from oxidation (Draczynska-Lusiak *et al.*, 1998). It also has anti-inflammatory effects, as it inhibits the enzyme cyclooxygenase-2 (COX-2) and reduces the production of pro-inflammatory mediators such as nitric oxide and various cytokines such as TNF-α and interleukin-1β (Meng *et al.*, 2021., Martínez-Canabal *et al.*, 2005). The cardioprotective properties of resveratrol have been documented through several studies that report its ability of inducing vasodilation by increasing nitric oxide, preventing cardiac fibrosis, improving the lipid profile by reducing LDL cholesterol and triglycerides, and lowering blood pressure (Bonnefont-Rousselot *et al.*, 2016). Also, the neuroprotective properties are attributed to resveratrol since it directly combats brain oxidative stress and prevents the accumulation of pathological proteins associated with degenerative diseases, facilitating the cleaning of beta-amyloid peptides in Alzheimer disease and alpha-synuclein in Parkinson disease, in addition to activating Sirtuin 1 to improve synaptic plasticity (Rahman *et al.*, 2020).

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SOURCES OF RESVERATROL

Trans-resveratrol (3,4,5-trihydroxystilbene) is a polyphenol that belongs to the stilbene family (Soleas *et al.*, 1997). Resveratrol is an antioxidant produced by more than 70 plant species in response to situations of stress due to ultraviolet radiation or fungal infections (Maier-Salamon et. al., 2011). One of the richest sources is the *Polygonum cuspidatum* plant, whose root extracts are used in traditional Chinese and Japanese medicine., it has also been documented in trees such as eucalyptus, spruce, and the tropical deciduous tree *Bauhinia racemosa* (Soleas *et al.*, 1997).

Resveratrol is found in flowering plants such as lilies (*Veratrum grandiflorum* and *Veratrum formosanum*) and in the legume *Pterolobium hexapetalum* (Kumar *et al.*, 1988). A high content is present in the leaves when the plant is damaged by chemical treatments or subjected to stress situations (Soleas *et al.*, 1997., Maier-Salamon *et. al.*, 2011).

Resveratrol is present in several fruits that are part of the human diet, mainly in red and purple fruits such as blueberries (*Vaccinium spp.*), currant (*Vaccinum spp.*), and blackberries (*Morus spp.*). It can also be found in citrus fruits, apples, and peanuts (*Arachis hypogaea*). Another food rich in resveratrol is red wine (Maier-Salamon et. al., 2011), which provides the highest resveratrol content to human diet (Gambini *et al.*, 2013).

The resveratrol content in wine comes from the vines (*Vitaceae*), specifically from the skin, seeds, petioles, and woody parts (stems and peduncle), which are the richest in this compound (Gambini *et al.*, 2013). Because of this, red wine is richer in resveratrol than white wine, since the parts of the grape containing resveratrol are macerated during the red winemaking process (Gambini *et al.*, 2013).

CHEMICAL STRUCTURE OF RESVERATROL AND MECHANISMS OF ACTION

Resveratrol is a natural polyphenol. Figure 1 shows its structure which consists of two aromatic rings joined by a C-C double bond, generating 3,5,4′-trihydroxystilbene (Tian *et al.*, 2020). Because of the double bond, resveratrol has cis and trans configurations, the last one is the most used in health research, since this form is more stable (Zhang *et al.*, 2021).

In plants, resveratrol is synthesized as a defense mechanism mainly against fungal or bacterial infection or stress events (Koushki *et al.*, 2018). Furthermore, in plants it can be found in glycosylated form, which gives it bioavailability by having a better solubility and better partition coefficient, which facilitates the entry of polyphenols into enterocytes (Zhang *et al.*, 2021).

Resveratrol is a white powder that is synthesized through stilbene synthase via three consecutive condensation reactions between three molecules of malonyl-coenzyme A and one molecule of coumaroyl-coenzyme A (Perrone *et al.*, 2017).

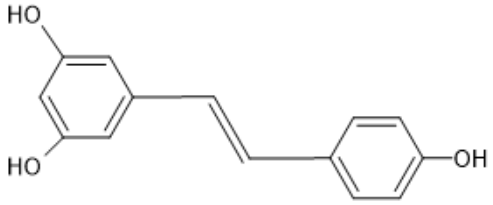

Figure 1. Chemical structure of resveratrol.

Some authors consider that the effects attributed to resveratrol on various pathological conditions, including skin aging, wound healing, fibrosis (Hecker *et al.*, 2022), endometriosis (Sienko *et al.*, 2023), and several types of cancer, are mainly associated with the antioxidant and anti-inflammatory properties of this compound. Delayed tissue repair, insufficient vascularization, infections, and prolonged inflammatory responses are among the major factors involved in these pathological conditions, all of which contribute to impaired wound healing. In this context, resveratrol has attracted considerable attention due to its potential to promote anti-inflammatory, antioxidant, and angiogenic effects (Hecker *et al.*, 2022).

Several studies suggest that resveratrol promotes the expression of vascular endothelial growth factor (VEGF) (Khanna *et al.*, 2002) and the activation of silent mating type information regulation 2 homolog 1 (SIRT1), both of which are regulatory molecules involved in angiogenesis (Huang *et al.*, 2019). In particular, in vitro and in vivo models (HUVECs and db/db mice) have demonstrated an overexpression of forkhead box O1 (FOXO1), a transcription factor regulated by SIRT1 (Huang *et al.*, 2019., Christovam *et al.*, 2019).

Regarding the mechanisms underlying the resveratrol antioxidant activity, the hydroxyl (OH) groups present in the aromatic rings of resveratrol play a fundamental role. These groups are capable of donating electrons or hydrogen atoms to stabilize free radicals before they induce oxidative damage to biomolecules such as lipids, proteins, or DNA. A simplified representation of this type of chemical reaction is shown below.

$$ROO\bullet + ArOH \rightarrow ROOH + ArO\bullet$$

where:

ROO• = peroxyl radical, one of the major reactive species involved in lipid peroxidation.

ArOH = aromatic phenolic group (Ar, i.e., aromatic ring., OH, i.e., hydroxyl group).

ROOH = stabilized hydroperoxide product.

ArO• = phenoxy radical stabilized by aromatic resonance.

In this antioxidant context, although the exact mechanism of action has not yet been fully elucidated, resveratrol has been associated with the regulation of superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT),

as well as with an increase in Nrf2 mRNA concentration and activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway (Roshani *et al.*, 2022., Chiou *et al.*, 2011) as shown in figure 2.

Additionally, resveratrol has been associated with the modulation of inflammatory signaling pathways, particularly through inhibition of nuclear factor kappa B (NF-κB) (Xu *et al.*, 2018) activation and reduction of pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α) (Wang *et al.*, 2020), interleukin-1β (IL-1β) (Malaguarnera, 2019), nitric oxide (NO) (Xia *et al.*, 2014), and cyclooxygenase-2 (COX-2) (Yi *et al.*, 2011), thereby contributing to attenuation of chronic inflammatory responses.

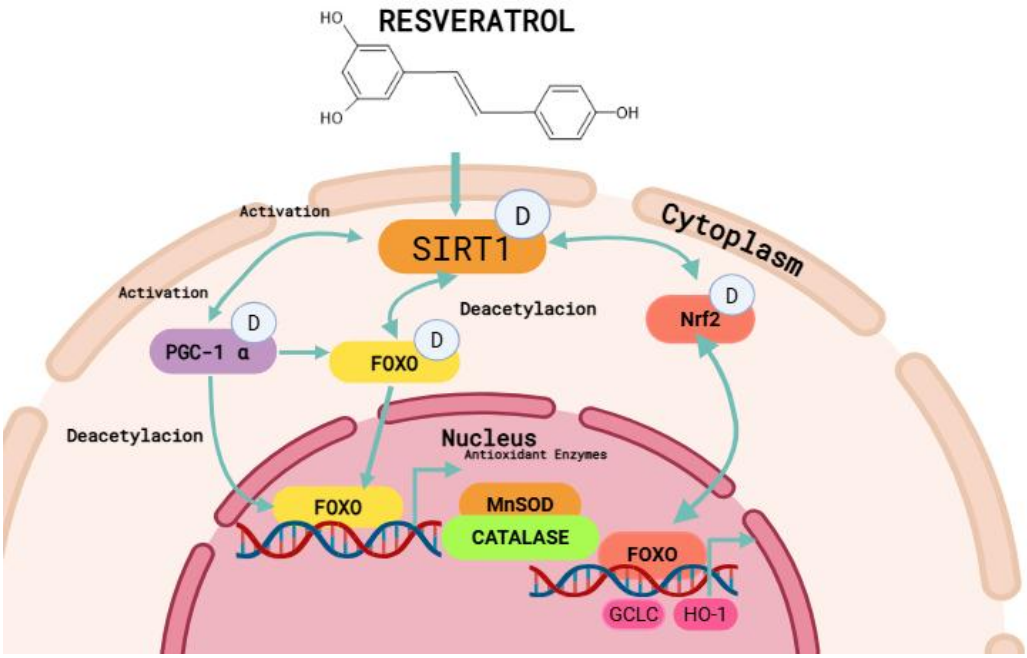

Figure 2. Resveratrol antioxidant pathway. Resveratrol exerts part of its antioxidant activity by activating SIRT1, an NAD+-dependent deacetylase that regulates multiple transcription factors related to cellular redox homeostasis. SIRT1 activation promotes the deacetylation of regulatory proteins such as FOXO, PGC-1α, and Nrf2, facilitating their transcriptional activity. Consequently, these factors migrate to the nucleus and induce the expression of various antioxidant genes, including manganese superoxide dismutase (MnSOD), catalase (CAT), heme oxygenase-1 (HO-1), and catalytic glutamate-cysteine ligase (GCLC). The result is an increase in cellular antioxidant capacity, a decrease in reactive oxygen species (ROS), and greater protection against oxidative stress.

MEDICINAL PROPERTIES OF RESVERATROL

Antioxidant

Resveratrol is recognized for its potent antioxidant activity, as its protective effect is based on its ability to neutralize free radicals and prevent oxidative tissue damage (Tan *et al.*, 2019).

One of its mechanisms is the inhibition of lipid peroxidation in cell membranes, which helps preserve their structural and functional integrity. By protecting membranes, resveratrol reduces the harmful effects of oxidative stress on living cells (Frémont *et al.*, 2000).

Additionally, resveratrol exerts antioxidant effects at the mitochondrial level. It has been shown in isolated brain mitochondria that compounds with estrogenic activity can inhibit mitochondrial respiration and the activity of complex III of the electron transport chain by competing with coenzyme Q. This effect is relevant, since this complex is an important source of reactive oxygen species (ROS). Therefore, its antioxidant action depends not only on the uptake of unpaired electrons but also on the direct modulation of free radical-generating sites (Zini *et al.*, 1999).

On the other hand, resveratrol can increase the activity of endogenous antioxidant enzymes and decrease the production of ROS, strengthening the cellular defense systems against oxidative stress. In this context, it has been observed that the oxidation of lipoproteins such as LDL and VLDL contributes to tissue damage and cell death due to their internalization into cytotoxic forms (Draczynska-Lusiak *et al.*, 1998).

Antiinflammatory

The inflammatory response is an adaptive mechanism that begins with the detection of molecular signals of exogenous and endogenous origin, which can be triggered by signs of danger, such as infections or tissue injury (Herold *et al.*, 2019). These molecular signals are recognized by

pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), triggering intracellular signaling cascades, such as kinases and transcription factors. These signaling pathways can promote the production of a variety of inflammatory mediators such as cytokines (interleukin (IL-1β) and tumor necrosis factor-α (TNFα)), thus promoting the development of inflammation (Meng *et al.*, 2021).

Within these mechanisms, a key enzyme is cyclooxygenase-2 (COX-2), an inducible isoform that is expressed in response to different inflammatory stimuli (Martínez-Canabal *et al.*, 2005). COX-2 catalyzes the conversion of arachidonic acid into prostaglandins, signaling molecules that regulate inflammation by acting as autocrine and paracrine messengers (Martínez-Canabal *et al.*, 2005., García Meijide *et al.*, 2000).

In this regard, bioactive compounds such as resveratrol exert anti-inflammatory effects by modulating different points of these pathways. Resveratrol has been reported to be able to inhibit the production of pro-inflammatory mediators, such as nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α) in lipopolysaccharide-stimulated Kupffer cells, which contributes to attenuating the inflammatory response associated with oxidative damage (Kawada *et al.*, 1998).

Likewise, experimental studies have shown that resveratrol supplementation can regulate cytokine expression, promoting an anti-inflammatory profile. In *Fabius Maximus* fish, the administration of 500 mg/kg of feed increased the levels of transforming growth factor β (TGF-β) mRNA while inhibiting the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-8 (Meng *et al.*, 2021).

Finally, recent in silico evidence suggests that resveratrol can be biotransformed by the gut microbiota into metabolites such as stilbendiol and stilbenol, which not only retain their biological activity but could also have a greater affinity for the COX-2 enzyme, a relevant therapeutic target in chronic inflammatory diseases (Niño Sánchez *et al.* 2025).

Cardioprotective

Among cardioprotective effects attributed to resveratrol is its ability to attenuate pathological cardiac remodeling. This effect has been associated with the prevention of cardiac fibrosis and maladaptive hypertrophy by preserving regulatory proteins such as phosphatase and tensin homologue (PTEN) and the modulation of mitogen-activated protein kinase (MAPK) signaling pathways, including extracellular signal-regulated kinase (ERK1/2), thereby limiting abnormal growth and dysfunction (Bonnefont-Rousselot *et al.*, 2016).

Resveratrol can improve vascular health by regulating nitric oxide. Evidence shows a low incidence of cardiovascular diseases in the French population even though the French diet is high in saturated fats., this phenomenon is attributed to the continued moderate consumption of red wine rich in polyphenols such as resveratrol (Bonnefont-Rousselot *et al.*, 2016).

It is important to highlight that resveratrol has the ability to increase the availability of nitric oxide, which consequently promotes vasodilation, as well as having an antisclerotic effect since it modifies the lipid profile by decreasing triglycerides and LDL cholesterol, even by increasing HDL, it also inhibits the migration of vascular smooth muscle cells, thus reducing the formation of atheromatous plaque (Gal *et al.*, 2021). Several human studies have shown that at high doses (>150 mg/day), resveratrol reduces systolic blood pressure (Gal *et al.*, 2021).

Neuroprotective

Resveratrol has antioxidant and anti-inflammatory properties and therefore acts as a neuroprotectant by reducing the accumulation of toxic proteins and oxidative stress in the brain (Rahman *et al.*, 2020).

The antioxidant action, in which enzymatic modulation occurs, reduces the concentrations of inducible nitric oxide synthase and increases the production of hemooxygenase-1 (HO-1), strengthening the antioxidant defenses of the neurons (Rahman *et al.*, 2020).

The modulation of pathological proteins of various diseases such as Alzheimer disease facilitates the cleaning of beta-amyloid peptides, reduces the formation of senile plaques, and promotes the non-amyloidogenic cutting of the amyloid precursor protein. In Parkinson disease resveratrol prevents the accumulation of alpha-synuclein, a protein that affects neuronal movement and function. In multiple sclerosis, resveratrol helps to maintain healthy nerve cells and contributes to myelin repair (Sánchez-Nieto *et al.*, 2023).

Resveratrol has been associated to the activation of the enzyme Sirtuin 1, which contributes to reducing apoptosis in hippocampal cells, facilitating neurogenesis, and improving synaptic plasticity, as well as improving mitochondrial function, providing greater energy efficiency to neurons (Vivar-Altamirano *et al.*, 2024).

Anti-aging

Resveratrol has been reported to have protective effects against UVB-induced photoaging by reducing the expression of matrix metalloproteinases (MMPs) and inflammatory factors. This is achieved through the inhibition of MAPK and COX-2 signaling pathways, as well as the inhibition of caspase activation and by acting on VEGF-β to induce anti-apoptotic effects (Cui *et al.*, 2022).

Similarly, resveratrol restores the cell cycle by activating autophagy and reducing reactive oxygen species (ROS) through adenosine monophosphate-activated protein kinase (AMPK) phosphorylation to mitigate the effects of UVA-induced photoaging (Xia *et al.*, 2024).

One of the effects of aging is the loss of bone volume, which is reflected in a greater likelihood of

bone damage and fractures. It has been found that the administration of resveratrol in old rats increases bone volume, as well as a greater number of bone trabeculae and less space between them. Consequently, resveratrol has been reported to promote osteoblast proliferation (Fernández-Tresguerres *et al.*, 2014).

On the other hand, although resveratrol is widely recognized as an anti-aging agent, its bioavailability is low, which is why modifications to resveratrol have been explored. Resveratrol modified with a 4-hydroxy-3′-trifluoromethoxy group has been reported to have increased accumulation in inflammatory cells. In a group of mice aged by D-galactose, mice treated with resveratrol modified with a 4-hydroxy-3′-trifluoromethoxy group were shown to improve age-related changes in the hippocampus and cholinergic system dysfunction by inhibiting NO production, reducing ROS, and inhibiting oxidative cytotoxicity (Liang *et al.*, 2024).

CONCLUSION

Resveratrol is a pleiotropic molecule with immense therapeutic potential against chronic diseases.

Resveratrol has the ability of intervening in multiple cellular targets, from the direct modulation of inflammatory pathways to the protection of mitochondrial function and the activation of enzymatic pathways linked to cellular longevity, such as Sirtuin 1.

However, the documented medical literature also reveals a fundamental biomedical challenge for its large-scale clinical implementation due to low natural bioavailability in the body. Although its glycosylated form partially improves cellular absorption, its rapid metabolism limits its *in vivo* effects. Ultimately, resveratrol represents an invaluable bridge between natural nutrition and the biotechnological development of the future.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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