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Resveratrol as an Antiaging Drug: A Review of Articles

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Abstract

In recent decades, progressions in care of health have increased the average lifespan, increasing the old age population. This has led to an increase in periods of health problems or disabilities, and multiple diseases associated with aging are responsible for the largest health problems in the majority of developing nations. Many anti-aging approaches such as healthy lifestyles and medical therapies aimed at reducing the prevalence of bad health conditions and age-associated disease as Alzheimer disease, cardiovascular disease, renal impairment, and cancer. Grapes, peanuts, and blueberries are just a few examples of the many foods that contain resveratrol, numerous reports have shown its importance in antiaging therapy that decreases oxidative stress, lowers inflammation, enhances mitochondrial activity, and controls apoptosis. Throughout this review, we will describe the possible antiaging mechanisms of resveratrol and its effect on the extension of life span and many aging-related diseases.

Keywords: Aging related diseases, Antiaging mechanisms of resveratrol, Mitochondria, Oxidative stress, Resveratrol

ريسفيراترول كدواء مضاد للشيخوخة: مراجعة للمقالات

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الخلاصة

في العقود الأخيرة ، أدى التقدم في الرعاية الصحية إلى زيادة متوسط العمر ، مما أدى إلى زيادة عدد المسنين. لسوء الحظ ، أدى ذلك إلى زيادة فترات المشكلات الصحية أو الإعاقات ، كما أن الأمراض المتعددة المرتبطة بالشيخوخة هي المسؤولة عن أكبر المشاكل الصحية في غالبية الدول النامية. العديد من طرق مكافحة الشيخوخة مثل أنماط الحياة الصحية والعلاجات الطبية التي تهدف إلى الحد من انتشار الظروف الصحية السيئة والأمراض المرتبطة بالعمر مثل مرض الزهايمر وأمراض القلب والأوعية الدموية والفشل الكلوي والسرطان. العنب والفول السوداني والتوت هي مجرد أمثلة قليلة على العديد من الأطعمة التي تحتوي على ريسفيراترول ، أظهرت العديد من التقارير أهميته في العلاج المضاد للشيخوخة الذي يقلل من الإجهاد التأكسدي ، ويقلل من الالتهاب ، ويعزز نشاط الميتوكوندريا ويتحكم في موت الخلايا المبرمج. خلال هذه المراجعة، سوف نصف الآليات المحتملة المضادة للشيخوخة لدواء الريسفيراترول وتأثيره على إطالة العمر الافتراضي وعلى العديد من الأمراض المرتبطة بالشيخوخة.

الكلمات المفتاحية: الأمراض المرتبطة بالشيخوخة ، آليات مكافحة الشيخوخة للريسفيراترول، مايتوكوندريا ، الجهد التأكسدي،ريسفيراترول .

Introduction

As humans age and become more susceptible to both internal and external stimuli, increasing poor health problems and developing age-related diseases, they undergo a series of degenerative changes that cause oxidative stress to increase, inflammation to build up, cell apoptosis, and disruption to the architecture and functionality of cells and organs. As a result, the chance of having several diseases (such as sarcopenia, diabetes mellitus, malignancies, and neurological problems) and becoming more susceptible to morbidity with increasing age. To reduce the adverse health impacts of aging and avoid the start and progression of age-related illnesses, using the bioactive compounds contained in natural materials or traditional Chinese medicine might be an effective and secure approach to avoid aging and age-related illnesses [(1,2)].

The bioactive compounds known as polyphenols are abundant in plant-based diets and have a range of health-promoting effects via many pathways. Several foods, including grapes, peanuts, and blueberries, contain natural phenolic substances such as resveratrol. Resveratrol has shown several biological benefits, including antioxidant properties against cancer, inflammation, immunomodulation, hypertension, and high cholesterol level. Resveratrol has also shown efficacy in treating and preventing diseases of the cardiovascular system, cancer, neurological illnesses, and obesity [(3, 4)]. Moreover, multiple studies have shown resveratrol importance in aging treatment by lowering oxidative stress, decreasing inflammation, increasing the function of mitochondria, and regulating apoptosis [(5, 6)].

Therefore, particular attention is paid to the antiaging effects of resveratrol, longevity, and several ageing-related diseases. [2]

Resveratrol: The chemistry behind its health benefits

The chemical structure of Resveratrol is 3,5,4'-trihydroxystilbene (styrene double bond joined by two phenol rings), which is one of the polyphenol groups that act as an antioxidant found in nature and generated in a number of plants as a response to exposure to damage, UV exposure, ozone exposure, and fungal infection. There are two isomers of resveratrol in nature trans isomers and cis-isomers, and the most common physiological active form is the trans-resveratrol. In solution about 80% of trans-isomer is converted to cis-isomer of resveratrol after one hour of exposure to light, making resveratrol highly sensitive to sunlight and more vulnerable to Ultra Violet-induced isomerization. [7]

History of resveratrol

Initially, it was thought that resveratrol would only help to avoid heart disease. Resveratrol's cancer-fighting properties weren't discovered till (1997) once the author Jang and their coworkers showed this chemical had efficacy against the main carcinogenic phases, initiation, promotion, and progression [8].

As phytoalexins (antimicrobial compounds that are produced by plants as a response to stresses), resveratrol gains more and more attention in the scientific community over the past few years and the evidence for its extensive wide range of biological and active pharmacological roles at the tissue cellular level, so it designated as an antioxidant [9], anti - inflammatory [10], anticarcinogenic [8], anti-aging [4,10,11], neuroprotection [12,7] and cardioprotector. [13-15]

Sources of resveratrol

In 1940, Resveratrol was discovered for the first time in the white hellebore roots (Veratrum grandiflorum O. Loes.) After that, in (1963) resveratrol was established as the major component of the dried roots of Japanese knotweed (Polygonum cuspidatum), and it has been known as Koj-Okon in Japan. This plant was previously utilized in traditional medicine in China and Japan for thousands of years for the treatment of heart disease, hyperlipidemia, gonorrhoea, favus, athlete's foot, and vessel inflammation [5]. After that, a large range of resveratrol has been recognized in over 70 species of many plants and fruits, including grapes, mulberries, blueberries, cranberries, peanuts, groundnuts, and pines Coconut and cocoa are now recognized as additional sources of resveratrol. Resveratrol is nearly entirely produced in the skin of grapes, especially those that have been infected by Botrytis cinerea, and its concentration peaks shortly before the grapes are ready to harvest. So the skin and seeds of grapes have the highest concentration of resveratrol. [7]

Mechanisms of resveratrol as an anti-Aging drug:

1. ***Antioxidant role of resveratrol***: Resveratrol's main protective effect against the state of oxidative stress is due to:

a. Lowering the reactive oxygen species (ROS) production.

b. Scavenging free radicals directly.

c. Enhancing the action of endogenous antioxidant enzymes (e.g., superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH).

d. Increasing antioxidant compounds and the upregulation of associated mitochondrial energy biogenesis genes.

Resveratrol reduces ROS production by decreasing the catalytic subunits (NOX proteins) and inhibits Rac1 membrane translocation, preventing p47phox (phox: phagocyte oxidase; it is one of the cytosolic proteins that form the phagocyte NADPH oxidase) from being phosphorylated to limit the ROS generation by NADPH oxidase. And through promoting mitochondrial biogenesis by proliferator-activated receptor-coactivator-1 (PGC-1) deacetylation, which is activated by SIRT1 (Silent Information Regulator 1), which reduces the generation of mitochondrial ROS, or by activates SIRT1 directly or indirectly by enhancing the activation of Lamin A or by using a PDE (phosphodiesterases) inhibition mechanism that also directly scavenging the ROS. [16, 11, 17, 18].

Resveratrol (RES) and Antioxidant enzymes, RES greatly rises the antioxidant enzyme activity and mitigates the harm brought on by oxidative stress [19,20]. Furthermore, it promotes the anti-oxidant enzymes genes expression like CAT, SOD, and anti-aging components like SIRT1 [21]. The most common SIRT1 target molecules include the FOXO (fork-head box O) transcription factors that help resveratrol's antioxidative effect by enhancing the antioxidant potential, like SOD and catalase, as well as endothelial nitric oxide (eNOS) [16].

Inglés and their colleague found that even at low nutritional doses of RES used as a treatment alone without any anticancer drugs (at concentrations ranging from 1 nM to 1.5 μM) of mammary gland tumor cells (MCF-7) for 48 hours, duration decreased peroxide levels. This result was caused by the induction of the PTEN (the phosphatase and tensin homolog) /Akt (protein kinase B) pathway through enhancing (PTEN), which is a common inhibitor of tumors that suppresses the action of phosphatidylinositol 3-kinase type I (PI3K), thereby resulting in a reduced level of phosphorylated-Akt (P-Akt) and the increased expression of antioxidant defense systems (CAT and SOD) [22], as in Figure (1).

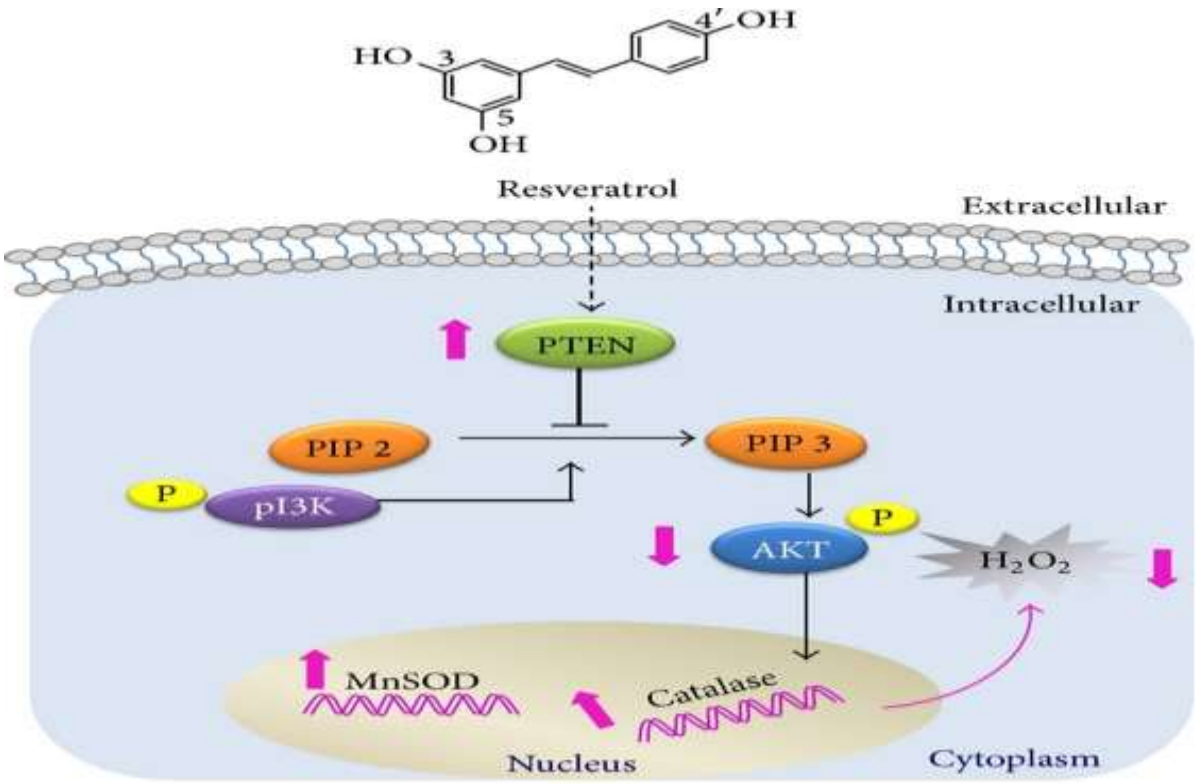

Figure 1. Resveratrol suppresses the activity of the PTEN/AKT pathway to increase the expression of antioxidant enzymes[22].

Other research demonstrated that ischemic reperfusion injury stimulates the p38/MAPK/iNOS pathway (MAPK: Mitogen activated protein kinase; iNOS: inducible nitric oxide synthase), which leads to severe oxidative stress; resveratrol inhibits the p38/MAPK/iNOS pathway, oxidative stress by reducing iNOS expression and the phosphorylation of p38/MAPK expression [23].

The antioxidant effect of RES responsible for its role in extending lifespan and its capability to combat aging-associated disorders result from a unique mechanism in which RES activates AMPK (Adenosine Monophosphate activated protein kinase), which immediately phosphorylates the transcription factor FoxO1 (fork-head box O1), causing its translocation and stabilization in the cellular nucleus, in the nucleus, this factor FoxO1 increases the gene transcription of antioxidant enzymes like superoxide dismutase and catalase enzymes.[24] As in Figure (2).

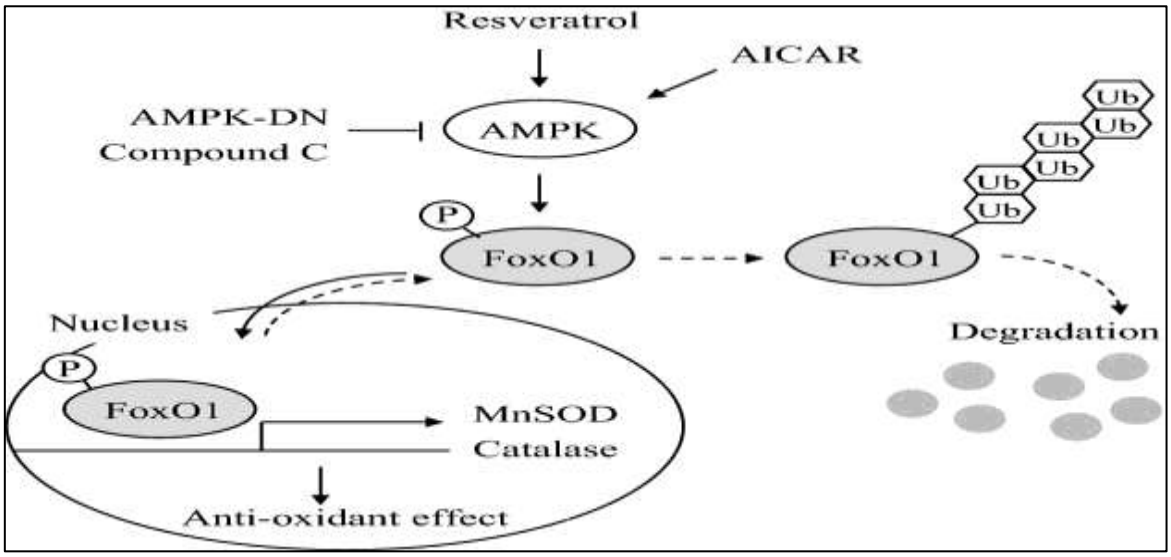

Figure 2. Resveratrol increases the activity of AMPK and Foxo1 to enhance the cellular expression of antioxidant enzymes [24].

Resveratrol activates Nrf2 (nuclear factor erythriod2-related factor 2) which is an emergent manager of cellular function and conflict to oxidants, which in sequence cause up-regulation of a variety of antioxidant enzymes, RES frees Nrf2 from its cytoplasmic tether, allowing it to go into the nucleus where it starts the transcriptional activity of numerous antioxidative enzyme genes like SOD and CAT to lessen the oxidative stress state; so, it facilitates the transcription of numerous antioxidative genes and reduce oxidative stress [25,26], as in Figure (5).Moreover, it was discovered that resveratrol can reduce oxidative damage by inducing autophagy (which is considered a normal degradation process of the cell that removes the damaged abnormal protein and other cellular components to maintain homeostasis inside the cell), either by inducing autophagy-lysosome pathway master regulator which is transcription factor EB (TFEB), that stimulates the production of auto-phagosomes, lysosomes, and the fusion of these organelles to generate autolysosomes [27,28]. As in Figure (3), or by inhibiting mTOR signaling (mammalian Target Of Rapamycin: it is a main regulatory protein of different processes in the cell as cellular growth and metabolism and inhibits autophagy) through AMPK, which is a crucial energy sensor, modulates cell metabolism in order to maintain energy homeostasis. Senses the energy condition of the cell and activates the Ulk1 kinase (an autophagy-initiating kinase). RES may activate AMPK and inhibit mTOR, which leads to a connection between Ulk1 and AMPK and prevents mTOR from binding to UIK1, therefore AMPK phosphorylates Ulk1, activates Ulk1 kinase, and ultimately induces autophagy [29, 30], as in Figure (4).

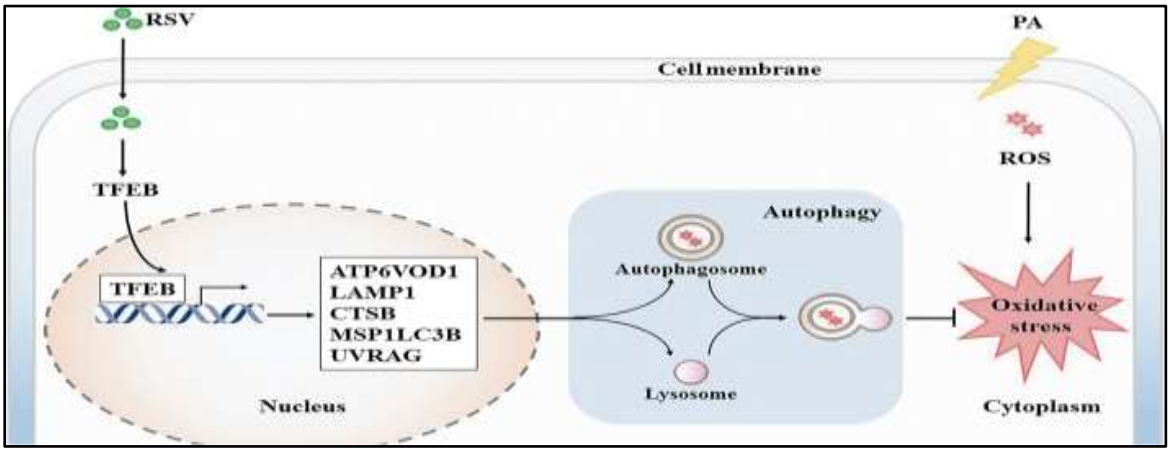

Figure 3. Resveratrol induces autophagy by activating TEFEB. [27]

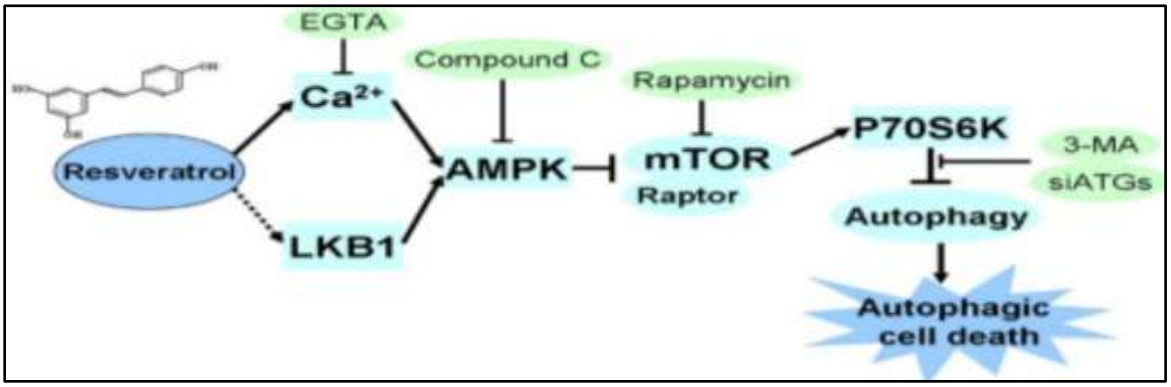

Figure 4. Resveratrol induces autophagy by inhibiting MTOR. [30]

2-Enhancement of mitochondrial function

In addition to ATP production, the mitochondrion has a vital role in the cellular processes such as the metabolism of amino acids, production of pyridine, modification of phospholipid, and regulation of calcium [29], so diminished and dysfunctional mitochondria are signs of aging and play an important role in accelerating body aging [31, 32]. Resveratrol decreases mitochondrial ROS production by encouraging mitochondrial biogenesis, as the proliferation of the mitochondria decreases the movement of electrons per unit of mitochondria, so reducing ROS production from mitochondria. In humans, Resveratrol raises the mass of mitochondria and their DNA content, as well as the component of the electron transport chain and the components that lead to biogenesis of the mitochondria. [33, 34]

In addition to Resveratrol inhibiting the mitochondrial ROS generation, it can also enhance mitochondrial antioxidant enzymes' defense mechanisms and so speeding the detoxification of ROS. Resveratrol increases the superoxide dismutase expression (SOD) in a SIRT1-dependent way. A direct up-regulation of SOD enhances mitochondrial production of hydrogen peroxide (H2O2) by binding to superoxide radicals and converting it to hydrogen peroxide (H2O2) which has the ability to pass through the mitochondrial membranes and diffused into the cell cytoplasmic component. RES administration decreases cytoplasmic H2O2 levels, by converted it to water by glutathione peroxidase (GSH) and catalase (CAT) in the cytoplasm. Resveratrol up-regulates these two antioxidant enzymes [35].

There is growing evidence that resveratrol regulates mitochondrial activity, hence slowing the ageing. Many studies proved that RES treatment improved the SIRT1 expression, thereby affecting mitochondrial biogenesis via the SIRT1 and AMPK up-regulation. Furthermore, resveratrol is considered a good activator of mitochondrial autophagy and removes the degenerated mitochondria in oocytes and granulosa cells that are taken from aged cows. Hence, maintain cellular equilibrium and replenish mitochondria. Resveratrol has the potential to raise the quantity of mitochondrial DNA (mtDNA) copies and increase the amount of ATP in the oocyte can improve the quality of oocytes and promote their development to the blastocyst stage. Researchers mentioned that the mitochondrial effect of RES is linked to its control of mitochondrial biogenesis and degradation [36].

Another investigation revealed that as zebra fish retinas aged, the integrity of mtDNA, mtDNA copy number, mitophagy of mitochondria, and the genes expression of antioxidant enzymes declined, furthermore there is an increase in the inflammation and the activity of Akt/mTOR (AKt: serine/threonine kinase previously known as protein kinase B)/mTOR (mammalian target of Rapamycin) which inhibit autophagy and decrease mitochondrial biogenesis. Resveratrol therapy may restore the integrity and function of mitochondria, in addition to the down regulation of the Akt/mTOR pathway in the retina of zebra fish, hence reversing age-related alterations [37], as in Figure (5).

In addition, other research revealed that injection of resveratrol greatly enhanced mitochondrial activity and reduced the damage caused by oxidative stress in postovulatory ageing oocytes in middle-ageing mice. RES administration also reduced the aging-related degradation of oocytes, increased SIRT1 antiaging protein expression, lowered the quantity of ROS, and inhibited the pathway of apoptosis which demonstrates the influence of multiple factors on ageing. [38] .

3-*The regulation of apoptosis*

Apoptosis is triggered as a reaction in response to intracellular or extracellular damage for the preservation of homeostasis. On the one side, apoptosis removes damaged and dysfunctional cells, such as tumor cells. In contrast, apoptotic dysregulation was crucial in the establishment of diseases associated with aging for Examples the promotion of neurodegenerative disorders by excessive neuronal apoptosis [39, 40]. Numerous studies demonstrated that resveratrol might control apoptosis to stave off aging and age-related disorders, In an *in vivo* study, impairment of learning and memory ability in aged rats was induced by sevoflurane and nitrous oxide, accompanied with neuronal apoptosis, but pretreatment with resveratrol modified the performance of learning and memory and suppressed neuronal apoptosis by up-regulating the expression of Sirt1 in aged rats [41], RES by its ability to decrease the ROS it can preserve the mitochondrial DNA and the oxidative phosphorylation chain so improve the ATP production, prevent cellular apoptosis, in addition to that RES protect the mitochondrial membrane transition pore so inhibit the releasing of cytochrome C and inhibiting the caspases that lead to inhibit apoptosis [42] .

Samy and their colleague mentioned the possible protective mechanism of RES in germ cells and testicular tissue in rats intoxicated with cadmium chloride might potentially be mediated by its apoptosis-promoting properties; moreover, RES boosted or enhanced the expression of antiapoptotic protein Bcl-2, and lowered the pro-apoptotic protein p53 and Bax genes in both healthy and cadmium-chloride- poisoned rats [43].

The Parkinsonian toxin (1-methyl-4-phenylpyridinium ion (MPP(+)) neurotoxin accountable for the abrupt onset of Parkinson's symptoms similar to Parkinson symptom's in humans, monkeys, and mice, and induced state of oxidative stress and apoptosis in dopaminergic neurons. Resveratrol therapy mitigated the oxidative stress generated by Parkinsonian toxin in dopaminergic neurons. Resveratrol reduced neuronal cell death via regulating the Bax pro-apoptotic protein and Bcl-2 anti-apoptotic [44].

Bournival et al., shown that resveratrol and quercetin inhibit apoptosis through a drop in the Bax mRNA expression, and a substantial elevation in the expression of Bcl-2 mRNA, the administration of resveratrol before the MPP(+) causes the Bax/Bcl-2 protein ratio falls. Thus, it can actually reduce the apoptotic cell death mediated by MPTP. In addition, the Apoptosis-Inducing Factor (AIF) is a factor that induces apoptosis generated by mitochondria early during apoptotic processes. The molecule is subsequently transformed in to the nucleus and causes DNA fragmentation. The authors

demonstrate that MPTP induces a significant Cytochrome C release and translocation of AIF from cellular organelle (mitochondria) to inside the nucleus, resveratrol inactivates these steps by inhibiting the AIF translocation to the nucleus and the release of cytosolic Cytochrome C, Therefore establishing a neuroprotection role for these two natural polyphenolic compound and a strong anti-apoptotic potential for these two polyphenols. Resveratrol because of its powerful antioxidant can suppress the fragmentation of DNA and the activation of caspase-3 factor and reduced the cleavage of the nuclear polymerase enzyme to inhibit DNA fragmentation [45].

Another study found that as rats aged, their ability to do exercise and voluntary movement declined and their levels of p53, a pro-apoptotic protein, and DNA fragmentation increased. However, the treatment with resveratrol enhanced physiological activity and increased the expression level of the anti-apoptotic protein in old aged rats by activating Sirt1 deacetylase activity leading to the promotion of Foxo1 (forkhead box protein O1), and p53 inhibition, thereby this way it can regulate apoptotic protein levels Bax and anti-apoptotic protein Bcl-2, that responsible for the regulation of apoptosis. [1] As in Figure (5).

Ischemic reperfusion injury causes apoptosis raises, tissue damage, and function loss, in this study TUNEL experiments revealed that RES administration decreases the number of apoptotic cells induced by ischemic reperfusion injury (IRI), suggesting that RES has an anti-apoptotic impact. Increasing ROS inside the cell promotes the intrinsic pathway of mitochondria-mediated apoptosis as a result of oxidative stress responses in IRI. Causes Caspase-8 and caspase-9 activation these are essential markers of the intrinsic pathway of apoptosis (mitochondria pathway), RES down regulated both factors (caspase 8 and 9), and inhibited cell death by down regulating the caspase cascade [46].

4-*The inhibition of inflammation*

Persistent low-grade inflammation, or inflammageing, is a common consequence of getting older; since the progression of age and age-related metabolic diseases have both been linked to inflammation, making it a significant threat to mortality and morbidity in the geriatric [47,48].

Some studies propose that RES may have an antiaging effect via lowering inflammation. Interleukin-1 (IL-1), Interleukin-8 (IL-8), Tumor necrosis factor (TNF), and Monocyte chemoattractant protein-1 (MCP-1) were among the pro-inflammatory cytokines whose production was significantly reduced by resveratrol through activate Sirt1 protein that causes inhibition of nuclear-factor kappa B (NF-kB) activities thereby lower the levels of inflammatory biomarkers [49,50], as in Figure (5).

Another study produced cultured hippocampus astrocytes using neonatal, adult, and old age rats and discovered that in progressing age the amounts of pro-inflammatory cytokines rise in hippocampal astrocytes while antioxidant defenses declined. Resveratrol therapy dramatically decreased TNF-α and IL-1 levels and improved anti-oxidant defense mechanism [49].

In addition, aged senescence-accelerated animals exhibited a decrease in anti-apoptosis and antioxidant capabilities, Sirt1 expressions, and raises in an inflammatory response and in the expression of (NF-kB) protein. Resveratrol treatment might raise the expression of Sirt1 mRNA and reduce the expression of NF-kB, hence RES employing an anti-aging effect [51].

Nrf2 (Nuclear factor erythriod2-related factor 2) may be an important RES target in reducing oxidative damage. In mice liver models with ischemic reperfusion injured (IRI), the Nrf2 activation was demonstrated to TLR4 (Toll-like Receptor 4) pathway regulation, which is a significant cascade of inflammation in ischemic injury, and TLR4 is a kind of receptor demonstrated on cells surface membranes which stimulated by IRI, that activate TLR4 signaling pathway which in turn stimulate further signaling cascades that end with activation of NF-kB inflammatory protein, RES therapy in the rat IRI model dramatically decreased NF-kB expression, inhibited the TLR4/NF-kB signaling pathway, and reduced oxidative stress-induced inflammatory responses [46] .

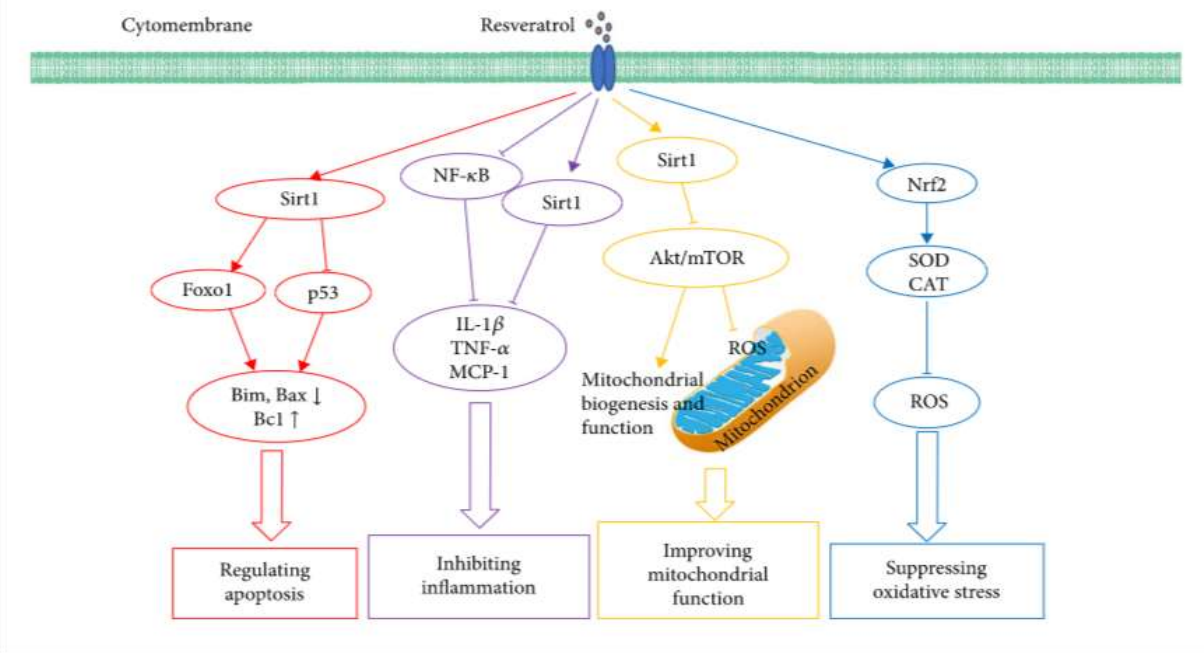

Figure 5. the antiaging effects of resveratrol [1].

Experimental trials

Resveratrol's contribution to extended lifespan

Longevity is a crucial objective of multiple anti-aging researches and a significant indicator of antiaging effectiveness, and several studies have demonstrated that resveratrol can enhance lifespan.

Autophagy may facilitate the elimination of defective proteins, and organelles like endoplasmic reticulum, and mitochondria from the cell which play important role in life extension and anti-aging properties [52]. Morselli and their colleague mentioned that resveratrol might induce autophagy *in vitro* in cells of human and *in vivo* in Caenorhabditis elegans; furthermore, it can extend the lifespan of C. elegans, however, this influence was inhibited in the presence of a SIRT1 knockdown or knockout; and results revealed that resveratrol increased lifespan by inducing autophagy in a Sirt1-dependent manner [53].

In another study, researchers looked at how the thymol and RES affected the lifespan of honey bees and showed that resveratrol-feeding bees lived 25 days longer than the thymol-feeding bees or control syrup-feeding bees [54]. By ROS scavenging activity and providing more neuroprotection, resveratrol administration increased the adult lifespan of both male and female flies, without compromising reproduction [55]. Fish given resveratrol performed better in cognition and locomotors activities than control fish, and the Senescence-related galactosidase activity and lipofuscin production were suppressed by RES, two histological markers of ageing [56]. superoxide dismutase (SOD) and glutathione peroxidase (GPx1), as described in a study by Zhang. When RES was given, it can mitigate the kidney morphological changes and reduce renal fibrosis brought on by As2O3. Increased renal function was also seen by lower levels of serum urea nitrogen and creatinine after RES therapy. [68]

Also, resveratrol has anti-fibrotic activity in a variety of tissues in recent investigations; the authors found that resveratrol reduces epithelial-mesenchymal transition (EMT) and extracellular matrix deposition (ECM). By inhibiting the epithelial to mesenchymal cells transition and also inhibiting the deposition of extracellular matrix (ECM), In rats with unilateral ureteral obstruction (UUO), resveratrol in a dose of 20mg/kg/day showed a significant decrease in serum creatinine, less cell growth, less EMT, and less ECM being produced. Patients with fibrotic kidney disorders may benefit from RES treatment. [69]

Neurodegenerative disorders and the role of resveratrol

Kodali and their colleague mentioned that the main neurodegenerative diseases risk factor is aging is which associated with autophagy dysregulation, neuronal apoptosis, and inflammation in the brain, and raised oxidative stress, resulting in advanced loss of memory and poor motor response. The authors used intraperitoneal (I.P.) injections of 40 mg/kg resveratrol or a placebo on elderly male F344 rats for a period of four weeks. Animals given resveratrol showed enhanced cognitive abilities, including better learning and memory as well as elevated mood responses. The hippocampus has shown an increase in resveratrol-induced microvasculature and net neurogenesis and a decrease in hypertrophy of astrocyte and microglial activation [57].

Other studies revealed that resveratrol promoted neurogenesis in the hippocampus, reduced

neuroinflammation and oxidative stress, and increased neurotransmitter release, all of which acted as protective mechanisms against neurodegenerative disorders. The results reported that chronic administration of 20 mg/kg for 14 weeks in aged rats so by increasing the release of brain neurotransmitters such as serotonin, norepinephrine, and dopamine, resveratrol prevented the deterioration of cognitive abilities that occurs with ageing. These alterations resulted mostly from elevated levels of the enzymes tyrosine hydroxylase TH and tryptophan hydroxylase (TPH). (58, 59)

Cardiovascular disorder and the role of resveratrol

Recent studies reported that Aging increases the risk of cardiovascular diseases because it with redox imbalance, endothelial dysfunction, and impaired vascular function and resveratrol treatment improves cardiovascular health by decreasing atherosclerotic changes in blood vessels (60, 61).

Furthermore, Rajapakse et al., mentioned that resveratrol at a dose of 40mg/kg can protect against arterial ageing in male C57BL/6 mice by reducing aorta medium thickness, inflammation, fibrosis, and oxidative stress in comparison to the control group. (62) .In summary, resveratrol performed its cardio-protective role through adjusting the renin angiotensinogen system activity, and diminishing oxidative stress.

The role of resveratrol on kidney diseases

Many authors discovered that the RES Administration increases the function of mitochondria in kidneys by increasing the expression of SIRT1 (Silent Information Regulator 1) and PGC-1α (peroxisome proliferator-activated receptor co-activator 1α) deacetylation, this is one of the resveratrol's most essential kidney protecting mechanisms. (63)

A new study revealed that RES decreases renal glomerulosclerosis in old mice, and by SIRT1-mediated klotho expression, it can decrease kidney oxidative stress. (64)

Additionally, Kim mentioned that the kidney damage and tubular apoptosis produced by cisplatin were attenuated by resveratrol administration because it activated SIRT1, resulting in p53 deacetylation. All of this evidence suggests that the administration of resveratrol, by activating SIRT1 and its target pathways, could serve as a treatment against kidney ageing (65).

Another study showed Male Wistar rats had decreased the damage that results from oxidative stress, DNA damage, hypertrophy of the kidney, mesangial matrix expansion, renal fibrosis, and caspase-3 protein, after being treated with 5 mg/kg/day resveratrol for 45 days (66).

When RES was given to diabetic rats chronically (5 mg/kg/day for 16 weeks), the serum SOD activity of the animals increased dramatically, whereas the levels of thiobarbituric acid reactive substances (TBARS) and the ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) dropped. After RSV treatment, the level of TNF- and IL-6 decreased significantly, indicating anti-inflammatory benefits. (67)

Furthermore, Treatment of Wistar rats with arsenic-trioxide (As2O3) induced renal fibrosis but After 8 days of therapy with RES (8 mg/kg every other day), oxidative stress was significantly reduced as measured by malondialdehyde (MDA) and ROS production, and elevated levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx1), as described in a study by Zhang. When RES was given, it can mitigate the kidney morphological changes and reduce renal fibrosis brought on by As2O3. Increased renal function was also seen by lower levels of serum urea nitrogen and creatinine after RES therapy (68).

Also, resveratrol has anti-fibrotic activity in a variety of tissues in recent investigations; the authors found that resveratrol reduces epithelial-mesenchymal transition (EMT) and extracellular matrix deposition (ECM). By inhibiting the epithelial to mesenchymal cells transition and also inhibiting the deposition of extracellular matrix (ECM), In rats with unilateral ureteral obstruction (UUO), resveratrol in a dose of 20mg/kg/day showed a significant decrease in serum creatinine, less cell growth, less EMT, and less ECM being produced. Patients with fibrotic kidney disorders may benefit from RES treatment. (69)

Effect of resveratrol on the testes

Resveratrol (RES) can be employed as a treatment agent for male infertility brought on by VCD testicular damage. The reactive chemical vinylcyclohexane diepoxide (VCD) is widely employed in the production of paints and adhesives. The increasing number of apoptotic cells caused by VCD was decreased by RES therapy at 20 mg/kg once daily and protects against lipid peroxidation and DNA damage that results from oxidative stress that has been produced by VCD. As oxidative stress in the seminiferous tubules has been shown to be reduced by RES, and sperm maturation is thought to be enhanced. (70)

Current research demonstrates that treatment with Resveratrol provides considerable protection against Benzo(a)pyrene [B(a)P], a hazardous environmental Polycyclic Aromatic Hydrocarbon, via scavenging ROS, and altering anti-oxidant enzyme transcriptional regulation. In addition, Resveratrol inhibited stress kinase activation like p38 MAPK and enhanced Steroidogenic acute regulatory protein (StAR) protein expression and steroidogenesis. Furthermore, Resveratrol therapy effectively restored testosterone production. (71)

Resveratrol improves spermatogenesis as seen in cryptorchidism-affected mice, where resveratrol

was able to preserve spermatogenesis after a daily dosage treatment [72].

Eman mentioned that treatment with 20 mg/kg of resveratrol for 4 weeks in male rat help in healing testicular damage induced by tramadol as Resveratrol provides protection from lipid peroxidation and DNA damage. Resveratrol has also been shown to increase sperm maturation and viability in seminiferous tubules. It also reduces the number of apoptotic cells caused by tramadol. [73]

In conclusion, Resveratrol improves testicular changes in different pathologies by reducing ROS and elevated antioxidant enzymes level, improving the steroidogenesis and spermatogenesis and increasing sperm viability and reducing apoptosis.

Conclusion

One of the most studied bioactive compounds in food is resveratrol. Many studies have shown the importance of RES in treatment and prevention of illnesses associated with aging, including cardiovascular disease, cancer, Alzheimer's disease, diabetes, liver diseases, and Parkinson's disease; and the resveratrol's anti-aging impact was achieved through a number of different mechanisms, including its ability to decrease oxidative stress, limit inflammation, regulate the mitochondrial activity, and control apoptosis. The anti-aging and disease-fighting effects of resveratrol have been well-documented, but further studies are required to prove these claims and determine the optimal dosage and length of treatment. Treatments and the most efficacious doses can be employed for them.

Conflict of Interest

The authors have no conflict of interest.

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Author Contribution

The authors confirm contribution to the paper as follow: study conception and design: Wasan waadallah al-hassawi; writing and draft manuscript preparation: Wasan waadallah al-hassawi, Maha Abdul-Jabbar al-sammak. All authors reviewed and approved the final version of the manuscript.

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