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Review Article

Antioxidative Stress Mechanisms behind Resveratrol: A Multidimensional Analysis

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Over the past decade, oxidative stress was shown to be a key factor for various diseases. The term "antioxidant" also rapidly gained attention worldwide, viewed as beneficial in disease prevention. Resveratrol (RSV), a natural polyphenol, is a plant antitoxin formed in response to harmful environmental factors such as infection and injury. This antitoxin is found in grapes, strawberries, peanuts, or herbal medicines and exhibits many pharmacological effects involved in antitumor, anti-inflammatory, antiaging, and antioxidation stress mechanisms. Recently, numerous *in vitro* and *in vivo* experiments have shown that RSV harbors antioxidative stress properties and can be used as an antioxidant. Here, we review the free radical scavenging ability, antioxidant properties, signaling pathways, expression and regulation of antioxidant enzymes, and oxidative stress-related diseases associated with RSV.

1. Introduction

Oxidative stress refers to an imbalance between the antioxidant defense system and the production of free radicals, leading to increased reactive oxygen species (ROS) and tissue damage. Possible consequences of oxidative damage result in diabetes mellitus [1], coronary heart disease [2], rheumatoid arthritis [3], and aging. Recently, a new article published in *Cell* uncovered that ROS accumulation in *Drosophila melanogaster* and mice with severe sleep deprivation caused oxidative stress, ultimately leading to death. However, this phenomenon is reversed by the administration of antioxidant compounds or by the targeted expression of antioxidant enzymes [4]. Even though it is unclear how the oxidative stress response triggers the disease, searching for a substance with antioxidant properties should be of focus to prevent the occurrence of diseases.

More recently, plant polyphenols have attracted the attention of many scholars. Plant polyphenols have been shown as beneficial to health by possessing antioxidant stress properties [5, 6]. In particular, resveratrol (RSV) has attracted a great deal of attention since it is a potential antioxidant that can be used in various applications. Numerous *in vivo* and *in vitro* experiments have shown that RSV exerts antitumor, anti-inflammatory, anticancer, antioxidant stress, and antiaging effects [7, 8]. The antioxidant effects of RSV were first discovered when treating cardiovascular diseases [9].

Presently, RSV has been shown to relieve cardiovascular, aging, and neurological diseases. However, RSV and its influence on diseases have not yet been systematically reviewed. Therefore, in this review article, we summarize the properties of RSV, signal pathways, and diseases related to oxidative stress to provide ideas for disease prevention.

2. Background

RSV is a secondary metabolite extracted from plant roots that contain multiple natural biological activities [10, 11]. Most RSV derives from the diet, such as grape products (red wine) [12], peanuts, and mulberries. The content of RSV is the greatest in grape wines, then chocolates, followed by peanuts, strawberries, and herbal medicines [13]. Even though RSV is abundant in fresh grape juice, it is susceptible

to degradation from heat exposure and processing. RSV exists in two forms including cis-resveratrol and trans-resveratrol (Figure 1). Under certain conditions, such as UV irradiation or low pH, the two isomers may convert into one another [14]. Generally, trans-resveratrol is more stable than cis-resveratrol.

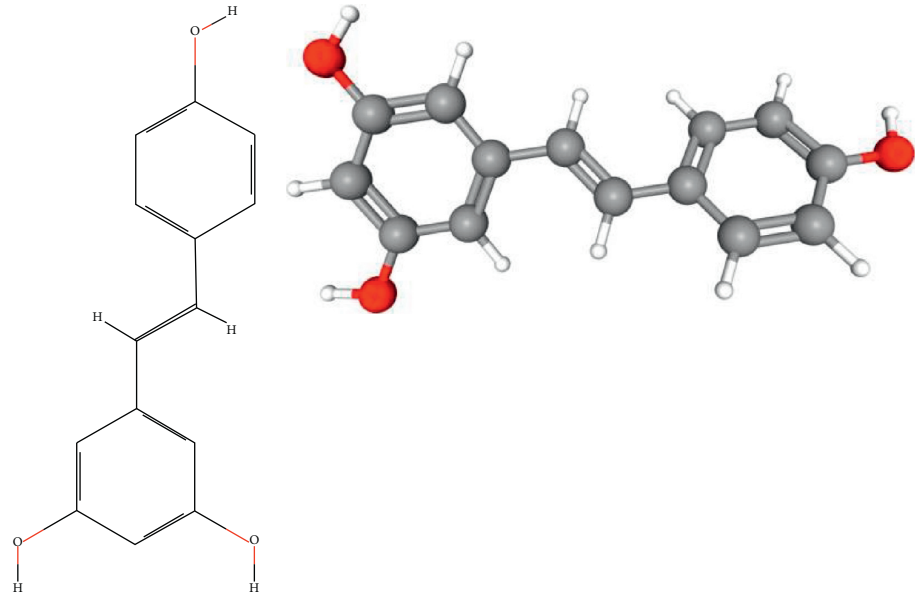
Many studies have shown that RSV has both direct and indirect effects. RSV has been proved to be an effective antioxidant for scavenging free radicals, including superoxide radical (O^{2-}), hydroxyl radical (OH^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and nitrogen dioxide (NO_2) [15–18]. Based on its chemical structure, such as hydroxyl group on the ring and conjugated double bond system, RSV was proved to be an antioxidant. Wang et al. reported that replacing the hydrogen in three hydroxyl groups with CH_3 or removing the hydroxyl group leads to reduced antioxidant activity, indicating that $4'$ hydroxyl activity is essential [19, 20]. Another study analyzing the structure of RSV confirmed this observation [21]. The existence of a conjugated double bond can make the electron more delocalized [22]. Hydrogen atom transfer (HAT) and sequential proton loss electron transfer (SPLET) are the main mechanisms of RSV scavenging free radicals [23]. Based on crystal structure and ab initio calculation experiment, it was found that dynamic flip-flop motion could lead to the alternate formation of hydroxyl groups and break hydrogen bonds on adjacent phenolic oxygen, which can transfer up to three hydrogen atoms. The results indicated that the free radical scavenging activity of RSV was based on HAT [24]. The electrons are transferred to the free radicals by the HAT process to form phenoxy radicals, which can delocalize unpaired electrons on the whole molecule. The unpaired electrons of resveratrol radical are located at the position of 3, and 5 hydroxyl groups near position 4 were more stable, resulting in the formation of RSV quinone structure. After tautomerism rearrangement and intracellular nucleophilic attack on intermediate quinone, a dihydrofuran dimer was produced [25]. Leonard et al. used the ESR spin trap technique to measure hydroxyl radicals generated by the Fenton reaction as well as superoxide radicals produced by the xanthine/xanthine oxidase system to find that RSV reduced DMPO/OH^- and DMPO/O^{2-} in a concentration-dependent manner, proving that it has the ability to scavenge OH^-/O^{2-} [26]. Compared with butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tocopherol, and trolox, RSV has the activity of scavenging H_2O_2 *in vitro*, but its effect is lower than that of the standard [27]. Scavenging NO free radical is through a non-free radical mechanism and has a higher scavenging efficiency compared with catechin [17]. Combining with metal ions can exert its chelating activity and prevent an excessive generation of hydroxyl radicals and further oxidation [22]. Other studies showed that RSV scavenges free radicals using endogenous antioxidant enzymes [19, 28]. Among them, NADPH oxidase (O^{2-}), xanthine oxidase (O^{2-} and H_2O_2), mitochondrial respiratory chain enzyme (O^{2-}), and endothelial functional nitric oxide synthase (eNOS) (NO) can cause ROS production [29]. Endogenous antioxidant enzymes, as an antioxidant defense system, can effectively remove ROS and reduce the production of mitochondrial superoxide [30].

Currently, the fast absorption and low bioavailability of RSV are some disadvantages of using it in the clinic. In clinical trials, 25 mg of RSV showed a 70% absorption rate in 1 hour, with peak plasma metabolite levels reaching 2 μM. However, the bioavailability of RSV was only 1% [31]. This occurs since absorbed RSV easily combines with glucuronic acid or sulfate in the intestines or liver [32]. Therefore, the bioavailability of RSV needs to be improved in the future.

3. Antioxidative Stress Effects Associated with RSV

3.1. RSV and Free Radicals. Under normal conditions, antioxidant enzymes, such as catalase, superoxide dismutase, and glutathione-S-transferase, remove ROS produced during mitochondrial oxidative respiration. ROS are divided into free radicals (O^{2-} and OH^-) and non-free radicals (H_2O_2) [33]. However, when there is stimulation by harmful factors, such as ultraviolet radiation and chemical reagents, defense systems are damaged and contribute to excessive ROS accumulation, leading to an imbalance in oxidative stress [34]. In H_2O_2 and O^{2-} free radical activity scavenging experiments, the scavenging efficiency of 30 μg/mL of RSV reaches 19.5% and 71.8% for H_2O_2 and O^{2-}, respectively, indicating that RSV had a strong efficiency for free radical scavenging [27]. Palsamy et al. reported streptozotocin-(STZ-) induced oxidative stress in diabetic rats where O^{2-} and OH^- levels in the kidney were relatively high and significantly reduced after RSV administration, indicating that RSV effectively scavenged free radicals [35]. As reported in another paper, neurotoxin 1-methyl-4-phenyl-1.2.3.6-tetrahydropyridine (MPTP) induces oxidative stress in *Drosophila melanogaster*, leading to an accumulation of H_2O_2. However, when different concentrations of MPTP and RSV were administered together, H_2O_2 content significantly decreased, implying that it contains free radical scavenging properties [36]. Hence, it is important to eliminate excessive free radicals to balance oxidative stress levels and to reduce oxidative damage.

3.2. RSV and Lipid Peroxidation. When oxidative stress occurs, excessive ROS levels attack polyunsaturated fatty acids on cell membranes, resulting in liposome peroxidation and lipid peroxides [37]. Malondialdehyde (MDA), a major product of lipid peroxidation, is also an important indicator of measuring the degree of cell damage. Manna et al. pretreated U-937 cells with 5 μM of RSV for 4 h and then incubated cells with different concentrations of tumor necrosis factor (TNF) for 1 h. Results showed that TNF-induced lipid peroxidation in U-937 cells but RSV and TNF cotreatment completely inhibited lipid peroxidation [38]. Another study found that RSV inhibited lipid peroxidation more effectively than the antioxidant vitamins C and *E*, which was attributed to its high lipophilicity and hydrophilicity [39–41]. Palsamy et al. investigated levels of lipid peroxidation in healthy rats treated with RSV, rats with STZ-induced diabetes, and



(a) (b)

Figure 1: The structure of resveratrol. (a) Chemical formula. (b) 3D structure diagram.

diabetic rats treated with RSV. Data revealed no significant differences in the RSV group and that MDA content in the diabetic group increased but then significantly decreased after the administration of RSV and eventually reached normal levels. This indicated that RSV inhibited lipid peroxidation induced by STZ [35]. These findings indicate that RSV has inhibitory properties on lipid peroxide formation.

3.3. RSV and Antioxidant Enzymes. The antioxidant system is mainly composed of antioxidant enzymes and nonenzymatic compounds [42]. Antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). SOD and CAT are key scavengers for O^{2-} and H_2O_2 and are the first defense system in cells [43]. Superoxide dismutase (SOD) converts O^{2-} to hydrogen peroxide and then CAT or GPx degrades it into oxygen and water. When 35% ethanol was administered to mice for 6 weeks, MDA production was increased in the liver, and SOD, CAT, GPx, and other enzymatic activities were reduced. However, when 5 g/kg of RSV was added daily during ethanol treatment, MDA synthesis was inhibited and antioxidant enzymatic activity improved [44]. Chen et al. used C57BL/6J mice to confirm that RSV alleviated ethanol-induced oxidative stress and found that it enhanced SOD activity in HepG2 cells but did not affect CAT and GPx activities [45]. Nonenzymatic compounds mainly include glutathione (GSH), which directly scavenges free radicals or acts as a cofactor for glutathione-S-transferase. The ability to resist oxidative stress weakens if GSH content decreases [46, 47]. Liu et al. explored apoptosis of human umbilical vein endothelial cells (HUVECs) induced by hydrogen peroxide. RSV administration increased HUVEC activity and SOD significantly increased GSH content [48]. RSV significantly improves the activity of certain antioxidant enzymes and reduces damage caused by oxidative stress. Thus, RSV should be used in research revolving around the treatment of various diseases.

4. Antioxidant Stress Mechanisms of RSV

All organisms contain a complex antioxidant system, making it difficult to identify the exact molecular mechanisms behind RSV and its antioxidant mechanisms [49]. Findings indicate that RSV exerts its antioxidant stress characteristics mainly through several signal pathways and also activates antioxidant enzymes in these pathways. Table 1 summarizes the application of RSV antioxidant properties in the treatment of diseases. We will now highlight the important signal pathways associated with RSV.

4.1. Nrf2 Signaling Pathway. Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates the expression levels of antioxidant genes and protects cells from oxidative stress damage. The antioxidant effects linked to this pathway are linked to the activation of genes containing antioxidant response elements (ARE) [68]. Kelch-like ECH-associated protein *l* (KEAP1) is a regulatory protein that controls the activity of Nrf2. In the absence of external stimulation, Nrf2 is in the cytoplasm and binds to inactivated KEAP1. When ROS accumulates, there are conformational changes in KEAP1, making it disassociate from Nrf2 and translocate into the nucleus [69]. Musculoaponeurotic fibrosarcoma (Maf) protein forms a heterodimer with Nrf2 and then combines with ARE to enhance the expression of downstream phase II antioxidant genes, producing antioxidant enzymes [70]. The function of proteins produced by the activation of the Nrf2/ARE pathway is mainly to remove ROS as well as exogenous/endogenous

Table 1: Summary of the application of RSV antioxidant properties in the treatment of diseases.

Model	Types	Treatment time/ Dosage/Feeding regime	Disease	Beneficial effects	Mechanisms	Reference
Animal	Nonobese GK rats	10 weeks 20 mg/kg/day Intragastrical injection	Type 2 diabetes	MDA content ↓. Serum GPx activity ↓. Liver CAT activity ↓	Activated NF-κB signaling pathway	[50]
	Male SD rats	48 hours 10 mg/kg/day Intraperitoneal injection	Ischemic reperfusion injury	NOx, MDA content ↓. SOD, GSH, CAT activity ↑	Activated p38/MAPK	[51]
	Male Wistar rats	20 days 10 mg/kg/day Oral gavage	Periodontitis	iNOS expression ↓. OHdG expression ↑. NOx and nitrotyrosine formation ↓	Activated the SIRT1/ AMPK pathway	[52]
	Male Wistar albino rats	3 weeks 200 mg/kg/day Oral gavage	Rotenone-induced Parkinson	Striatal DA level ↑. CHOP, GRP78 mRNA expression ↓. Striatal caspase-3, xanthine oxidase activity ↓. Striatal IL-1β, PC levels ↓. Glutathione peroxidase activity ↑	Activated Nrf2/ antioxidant defense pathway	[53]
	Male Wistar rats	15 days 20 mg/kg/day Introgastric gavage	OHDA-induced Parkinson	TBARS, protein carbonyl levels ↓. Phospholipase A2 activity ↓. GPx, GR, CAT, and SOD activity ↑. COX-2 expression ↓	Activated Nrf2 signaling pathway	[54]
	C57BL/6 mice	24 hours 40 mg/kg/day Oral gavage	Aging	Nox2 and Nox4 expression ↓. SOD1 and SOD2 expression ↑	Activated AMPK and SIRT1	[55]
	Male ApoE-KO mice	7 days 30/100 mg/kg/day Oral gavage	Cardiovascular diseases	SOD1, SOD2, SOD3, CAT, GPx1 mRNA expression ↑. Nox2 and Nox4 expression↓. 2-HE and ethidium ↓. MDA and 3-nitrotyrosine ↓. GCH1 mRNA expression ↑	Activated SIRT1	[56]
	Male SAM	5 days 25/50/100 mg/kg/day Introgastric gavage	Aging	SOD activity ↑. SOD mRNA expression ↑. Gpx activity ↑MDA level ↓ mtDNA deletion ↓		[57]
	Adult male Wistar rats	10weeks 5/10/20 mg/kg/day Oral gavage	Alcohol-induced cognitive deficits	Acetylcholinesterase activity ↓. Nitrite level ↓. Lipid peroxide ↓. GSH, SOD, CAT activity ↑. TNF-a, IL-1β, NF-kβ, caspase-3 levels ↓		[58]
	Female Wistar rats	16 weeks 250 mg/kg/day Oral gavage	Alcoholic liver disease	Liver AST, ALT levels ↓ CAT, GPx enzyme activity ↑. MDA level ↓. CYP2E1 protein expression ↓. Caspase 3 activity ↓SOD1, SOD2, SOD3, CAT, GPx mRNA expression ↑		[59]
	Male Zucker rats	6 weeks 15/45 mg/kg/day Oral gavage	Nonalcoholic fatty liver disease	MDA level ↓. GSH/GSSH ↑. SOD activity ↑. ACO, CPT-Ia activity ↑		[60]

Table 1: Continued.

Model	Types	Treatment time/ Dosage/Feeding regime	Disease	Beneficial effects	Mechanisms	Reference
Cell	HT22 cell	12 hours 2.5-10 μM Not given	Glutamate-induced (2mM) Alzheimer and Parkinson	HO-1 expression ↑. The cytoprotective of HT22 cells ↓	Activated SIRT1 signaling pathway	[61]
	Oocytes	12 hours 0.5/1/5 μM Not given	Doxorubicin-induced compromised fertility	ROS level ↓. CAT, Sod1, Gpx3 mRNA levels ↑. DNA damage ↓		[62]
	Bronchial epithelial cell	7 days 100 mg/kg/days Intraperitoneal injection	HDM-induced asthma	Cell apoptosis ↓. ROS level ↓	Elevated the expression of SIRT1	[63]
	Metaphase II oocytes	15 days 50 mg/kg/day Intraperitoneal injection	Postovulatory oocyte aging	ROS level ↓. MtDNA copy number ↓. Mitochondrial function ↑	Coordinated SIRT1 and AMPK signaling pathways	[64]
	Vascular smooth muscle cells	24 hours 0-100 μM Not given	Age-related vascular disease	SM2-MHC protein expression ↑. Contractile capacity ↑		[65]
	Neuroblastoma (N2a) cells	48 hours 5 μM Not given	Alzheimer	Peroxiredoxins mRNA expression ↑. H_2O_2 level ↓. ATP level ↑. Lipid peroxidation production ↓	Activated Nrf2	[66]
	Human bronchial epithelial cells	24 hours 10 μM Not given	PQ-induced pulmonary fibrosis	Cell death, ROS production, mitochondrial damage ↓ TNFα, IL-6, TGFβ1 ↓		[67]

Abbreviation: MDA: malondialdehyde; GPx: glutathione peroxidase; CAT: catalase; NOx: nitrogen oxides; SOD: superoxide dismutase; GSH: glutathione; iNOS: nitric oxide synthase; OHdG: 8-hydroxy-2 deoxyguanosine; DA: dopamine; CHOP: C/EBP homologous protein; GRP78: glucose-regulated protein 78; PC: protein carbonyl Nox2: NADPH oxidase 2; Nox4: NADPH oxidase 4; SOD1: superoxide dismutase 1; SOD2: superoxide dismutase 2; 6-OHDA: 6-hydroxydopamine; TBARS: thiobarbituric acid reactive substances; GR: glutathione reductase; COX-2: cyclooxygenase-2; SM2-MHC: smooth muscle myosin heavy chain; ROS: reactive oxygen species; mtDNA: mitochondrial DNA; IL-1β: interleukin-1β; ApoE-KO: apolipoprotein *E* knockout; GCH1 : GTP cyclohydrolase 1 2-HE: 2-hydroxyethidium; HO-1: heme oxygenase; SAM: senescence-accelerated mice; H_2O_2: hydrogen peroxide; CYP2E1: cytochrome; P450 2E1 AST: aspartate aminotransferase; ALT: alanine aminotransferase; TNF: tumor necrosis factor; ACO: acyl-coenzyme A oxidase; CPT-Ia: carnitine palmitoyltransferase-Ia; PQ: paraquat; TGF: transforming growth factor; ↑: upregulation; ↓: downregulation.

harmful substances. Studies have demonstrated that RSV activates Nrf2 through cell signal pathways such as PI3K/AKT and AMPK. Iwasaki et al. found that RSV mitigates T-cell apoptosis induced by H_2O_2. RSV results in phosphorylation of Ser9 glycogen synthase kinase 3β (GSK3β) by activating AMP-activated protein kinase (AMPK) and induces the expression of Nrf2/ARE-dependent antioxidant genes, such as heme oxygenase-1 (HO-1) [71]. RSV also protects against PC12 cell death induced by H_2O_2, mainly through the activation of ERK and Akt, causing Nrf2 nuclear translocation and upregulation of HO-1 expression [72]. Another study revealed that cigarette smoke induces oxidative stress in alveolar epithelial cells, where RSV protects cells from damage through the activation of Nrf2, upregulation of glutamate-cysteine ligase (GCL) expression, and induction of GSH [73]. At the same time, studies have shown that Nrf2 plays a crucial role in the oxidative stress response to atherosclerosis [74], ischemia-reperfusion injury [75], and hypertension [76]. Even though there is work revealing that RSV activates Nrf2 and induces the expression of downstream antioxidant enzyme genes, these interactions are complex and warrant further investigation.

4.2. NF-κB Signaling Pathway. NF-κB is a nuclear transcription factor that binds to the κB site of the kappa light chain gene of B cells [77]. It is mainly involved in regulating the expression of genes during inflammation and apoptosis. Currently, various diseases, such as diabetes and cancer, are associated with dysregulation of NF-κB expression [78, 79]. Activation of the NF-κB pathway is mainly regulated by ROS [78], which has been verified in mice with type 2 diabetes. Activated NF-κB promotes the expression of proinflammatory cytokines, such as cyclooxygenase-2 (COX-2) and tumor necrosis factor-α (TNF-α) [80, 81]. RSV inhibits TNF and H_2O_2-induced NF-κB activation in a dose- and time-dependent manner, all of which were confirmed in different cell lines, including U937, Jurkat, and L4 cells [38]. Soufi et al. investigated STZ-induced diabetic male Wistar rats and administered 5 mg/kg of RSV daily for 4 weeks to determine antioxidative stress properties. Results revealed that RSV increased SOD activity, decreased the GSSH/GSH ratio, and significantly reduced retinal NF-κB activity and the apoptosis rate compared to diabetic control rats [82]. Therefore, effective regulation of NF-κB activity is essential and studies behind the effects of RSV on this pathway are worthy of future work.

4.3. SIRT1 Signaling Pathway. Identification and analysis from *in vivo* and *in vitro* studies have confirmed that sirtuins play a significant role in many cellular functions. A total of seven sirtuins have been identified in mammals. SIRT1 is involved in cell function regulation and depends on NAD^+ to regulate the deacetylation of different proteins, such as histones, p53, and FOXO [83–85]. Studies have shown that these seven sirtuins are involved in antioxidant stress and metabolic processes [86, 87], where DNA damage repair and protective effects of cell stress damage are mediated by SIRT1, SIRT2, and SIRT6 [87]. Some studies illustrated that RSV does not directly activate SIRT1 but inhibits cAMP to make phosphodiesterase nondegradable, leading to AMPK activation, an increase in NAD^+ levels, and SIRT1 activation [88]. Ungvari et al. reported the effects of RSV on hyperglycemia-induced mitochondrial oxidative stress in human coronary artery endothelial cells (CAECs). This work revealed that mtROS production and hydrogen peroxide levels were significantly reduced and MnSOD expression levels, GSH content, and SIRT1 activity were increased. Furthermore, the overexpression of SIRT1 diminished mtROS production and increased MnSOD expression. This effect was weakened after SIRT1 knockout [89]. Another work investigated the protective effects of RSV on Tilapia under low temperature stress. Findings revealed that mRNA expression levels of sirtuin homologs (sirt1, sirt2, sirt3, sirt5a, and sirt6) increased and catalase (cat), uncoupling protein 2 (ucp2) and superoxide dismutase (sod1, sod2, and sod3) levels were also increased [90]. SIRT1 primarily responds to oxidative stress by regulating FOXO transcription factors (such as FOXO1, FOXO3a, and FOXO4) and PGC-1a regulators, which form transcription complexes to enhance the expression of antioxidant enzymes and to scavenge ROS [91]. Furthermore, there may be an overlap or interaction between the activities of SIRT1 and NF-κB [92]. Regulation of SIRT1 signaling involves FOXO and PGC-1a, but the interaction between SIRT1, NF-κB, and Nrf2 signaling pathways has not been clearly identified (Figure 2). Thus, this aspect still needs further work in order to provide optimal solutions for disease treatment.

5. RSV and Oxidative Stress-Related Diseases

5.1. Neurodegenerative Diseases. The most common neurodegenerative diseases include Alzheimer's disease (AD) and Parkinson's disease (PD). By 2016, a total of 43.8 million people were diagnosed with dementia where 60% were caused by AD and 6 million were suffering from PD [93, 94]. According to statistics from Ray Dorsey and Nichols, 6.4 million and 3.2 million people passed away from dementia (including AD) and PD, respectively, in 2016 [94, 95]. Both AD and PD not only cause significant damage to health but also impact the social economy. Presently, there are both pharmacological and nonpharmacological treatments available for these diseases, but there is currently no cure [96]. Additionally, AD and PD are associated with oxidative damage and inflammation, so much research is concentrated on the therapeutic potential of antioxidants, such as RSV [97].

Oxidative stress is the most critical factor in the pathogenesis of AD. ROS accumulation leads to a decrease of antioxidant defense capacity and mitochondrial dysfunction, which ultimately causes neuronal damage. The neuroprotective effects of RSV have been proven in several AD models and are associated with increased SIRT1 activity [98–100]. RSV increases mRNA expression levels of CAT, SOD1, GST zeta 1, and SIRT1 as shown in lymphoblastic cell lines (LCLs) isolated from AD patients [101]. Learning and memory in rats with vascular dementia were explored by

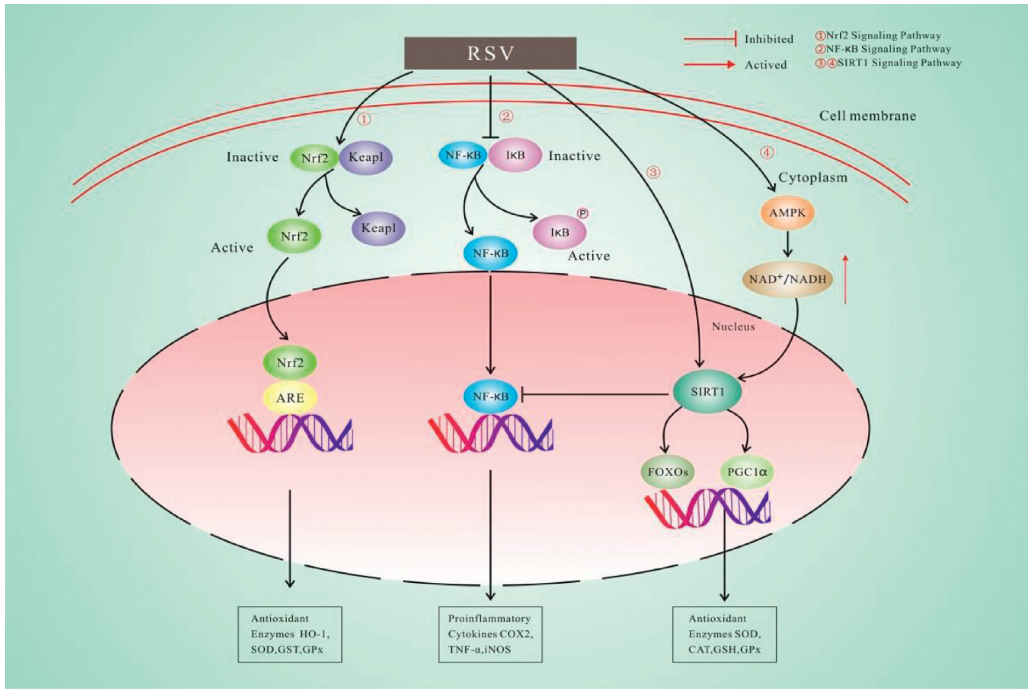


Figure 2: The signaling pathway of resveratrol to exert antioxidant properties.

Zhang et al., who found that SOD protein expression levels increased and MDA content decreased [102].

Mitochondrial dysfunction and oxidative stress are also causative factors in PD. The accumulation of oxidative stress caused by ROS can lead to neuronal death. Lindner et al. prepared RSV-loaded polysorbate80 (PS80) nanoparticles to observe the neuroprotective effects in PD mice. Results supported that the nanoparticle RVT reduced lipid peroxidation [103]. However, thus far, there are no clinical trials being performed investigating its safety. Therefore, efforts need to be made to fully understand the efficacy and safety of RSV for the treatment of AD and PD.

5.2. Aging. Aging is a programmed biological process caused by the interaction of genetic factors and adverse environmental factors. It is accompanied by changes such as increased inflammation, increased ROS, and mitochondrial function damage, as well as related chronic diseases. Among these, oxidative stress is one of the main causes of aging. RSV has been illustrated to extend lifespan in different animal models [104]. *In vitro* experiments showed that SIRT1 is associated with aging. In the H_2O_2-induced oxidative stress aging model, SIRT1 mRNA expression levels decreased and increased in a dose-dependent manner after RSV administration. In addition, the aging marker β-galactosidase also decreased [105]. Studies have also shown that RSV effects depend on the expression of antioxidant genes. Using RNAi technology to knock out SOD1 in *Drosophila melanogaster*, 200 μM of RSV increased the lifespan of female Sod1 RNAi flies to 9% under a standard diet [106]. Others believe that AMPK is the culprit of aging, since AMPK may activate FOXO and Nrf2 and inhibit NF-κB [107]. Afzal et al. found that various stress responses were induced in PREP cells, ROS levels decreased, and antioxidant capacity increased, indicating that RSV has potential in protecting cells from injury stress and also has potential in prolonging the lifespan. Furthermore, HP1γ, a marker of cell senescence, was significantly downregulated in treated cells [108]. Altogether, the antiaging properties of RSV are being thoroughly studied. Even though its clinical safety and efficacy have not yet been proven, RSV shows bright prospects in terms of antiaging strategies.

6. Conclusion

Over the past decade, the term "antioxidation" has become a hot topic on the Internet. Presently, the cosmetics and health care industries sell products using the term "antioxidant" in their ingredients. A polyphenol compound with natural activity, RSV shows the most potential and is a valuable commodity, as validated in various animal models. The antioxidant stress properties associated with RSV have been described in numerous animals and cell experiments [36, 80]. This article summarized the antioxidative stress properties of RSV, providing evidence that it can be used as a food additive that prevents disease and maintains health. Studies have shown that the basal diet supplemented with 400 mg/kg RSV can significantly improve feed utilization and growth performance of broilers [109]. The supplementation of 300 mg/kg and 600 mg/kg of RSV in the basic diet can significantly improve the activity of lactate

dehydrogenase, GPx activity, and its mRNA level, reduce MDA content, and improve the total antioxidant capacity of finishing pigs [110]. 25 mg of RSV from *Vitis vinifera*, taken as a standard dietary supplement for 12 weeks, was found to improve the quality of life associated with menopause in healthy women [111]. However, the low bioavailability of RSV is a property that needs to be further improved. Currently, many studies have confirmed that RSV nanoparticles have a greater ability to scavenge active free radicals (DPPH and ABTS+) and higher bioavailability and can further promote intestinal absorption. Li et al. synthesized a series of pyridoxine-resveratrol hybrids, where 12a, 12g, and 12l have better antioxidant activities and strong inhibitory effects on MAO-B, providing treatment direction of PD [112]. Fan et al. prepared RES-PPI nanoparticles to find that RSV enhanced thermal stability and did not degrade. In addition, its ability to remove DPPH and ABTS was enhanced [113]. This research broadens the application of RSV, but there are many problems that need to be solved before it can be used in the treatment of humans.

Abbreviation

RES: Resveratrol
ROS: Reactive oxygen species
ESR: Electron spin resonance
DMPO: 5,5-Dimethyl-1-pyrroline-N-oxide
H_2O_2: Hydrogen peroxide
SOD: Superoxide dismutase
CAT: Catalase
GPx: Glutathione peroxidase
MPTP: Methyl-4-phenyl-1.2.3.6-tetrahydropyridine
MDA: Malondialdehyde
TNF: Tumor necrosis factor
GSH: Glutathione
Nrf2: Nuclear factor-erythroid 2-related factor 2
ARE: Antioxidant response elements
KEAP1: Kelch-1ike ECH-associated protein l
AMPK: AMP-activated protein kinase
HO-1: Heme oxygenase-1
NF-κB: Nuclear factor-kappa B
SIRT1: Sirtuins
FOXO: Forkhead box
UCP2: Uncoupling protein 2
STZ: Streptozotocin nicotinamide.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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