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 (O₂⁻), hydroxyl radical (OH⁻), hydrogen peroxide (H₂O₂), nitric oxide (NO), and nitrogen dioxide (NO₂) [15–18]. Based on its chemical structure, such as hydroxyl group on the ring and conjugated double bond structure. After tautomerism rearrangement and intracellular nucleophilic attack on intermediate quinone, a dihydropyridine 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/O²⁻ and DMPO/O₂⁻ in a concentration-dependent manner, proving that it has the ability to scavenge OH⁻/O₂⁻ [26]. Compared with butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tocopherol, and trolox, RSV has the activity of scavenging H₂O₂ 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 formation 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 (O²⁻), xanthine oxidase (O₂⁻ and H₂O₂), mitochondrial respiratory chain enzyme (O²⁻), 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 (O²⁻ and OH⁻) and non-free radicals (H₂O₂) [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 H₂O₂ and O²⁻ free radical activity scavenging experiments, the scavenging efficiency of 30 μg/mL of RSV reaches 19.5% and 71.8% for H₂O₂ and O²⁻, 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 O²⁻ 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 H₂O₂. However, when different concentrations of MPTP and RSV were administered together, H₂O₂ 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. pre-treated 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
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 1 (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
| Model | Types | Treatment time/ Dosage/Feeding regime | Disease | Beneficial effects | Mechanisms | Reference |
|-------|-------|--------------------------------------|---------|--------------------|------------|-----------|
| Nonobese GK rats | 10 weeks 20 mg/kg/day Intragastrical injection 48 hours | Type 2 diabetes | MDA content ↓, Serum GPx activity ↓, Liver CAT activity ↓ | Activated NF-κB signaling pathway | [50] |
| Male SD rats | 10 mg/kg/day Intraperitoneal injection 20 days | Ischemic reperfusion injury | NOx, MDA content ↓, SOD, GSH, CAT activity ↑ | Activated p38/MAPK | [51] |
| Male Wistar rats | 10 mg/kg/day Oral gavage 3 weeks | Periodontitis | iNOS expression ↓, OHdG expression ↑, NOx and nitrotyrosine formation ↓ | Activated the SIRT1/AMPK pathway | [52] |
| Male Wistar albino rats | 200 mg/kg/day Oral gavage 15 days | 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 | 20 mg/kg/day Intragastric gavage 24 hours | OHDA-induced Parkinson | TBARS, protein carbonyl levels ↓, Phospholipase A2 activity ↓, GPx, GR, CAT, and SOD activity ↓, COX-2 expression ↓ | Activated Nrf2 signaling pathway | [54] |
| Animal C57BL/6 mice | 40 mg/kg/day Oral gavage 7 days | Aging | Nox2 and Nox4 expression ↓, SOD1 and SOD2 expression ↑ | Activated AMPK and SIRT1 | [55] |
| Male ApoE-KO mice | 30/100 mg/kg/day Oral gavage 5 days | 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 | 25/50/100 mg/kg/day Intragastric gavage 10 weeks | Aging | SOD activity ↑, SOD mRNA expression ↑, Gpx activity ↑MDA level ↓, mtDNA deletion ↓ | | [57] |
| Adult male Wistar rats | 5/10/20 mg/kg/day Oral gavage 16 weeks | 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 | 250 mg/kg/day Oral gavage 6 weeks | 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 | 15/45 mg/kg/day Oral gavage | Nonalcoholic fatty liver disease | MDA level ↓, GSH/GSSH ↑, SOD activity ↑, ACO, CPT-1a activity ↑ | | [60] |
Table 1: Continued.

| Model                  | Types                  | Treatment time/Dosage/Feeding regime | Disease                                      | Beneficial effects                                    | Mechanisms                                      | Reference |
|------------------------|------------------------|-------------------------------------|----------------------------------------------|-------------------------------------------------------|--------------------------------------------------|-----------|
| HT22 cell              |                        | 12 hours                            | Glutamate-induced (2 mM) Alzheimer and Parkinson | HO-1 expression ↑. The cytoprotective of HT22 cells ↓ | Activated SIRT1 signaling pathway               | [61]      |
|                        |                        | 2.5-10 μM                           |                                              |                                                       |                                                  |           |
|                        |                        | Not given                           |                                              |                                                       |                                                  |           |
|                        |                        | 12 hours                            |                                              |                                                       |                                                  |           |
|                        |                        | 0.5/1/5 μM                          |                                              |                                                       |                                                  |           |
|                        |                        | Not given                           |                                              |                                                       |                                                  |           |
|                        |                        | 7 days                              |                                              |                                                       |                                                  |           |
| Oocytes                |                        |                                    |                                              |                                                       |                                                  |           |
| Bronchial epithelial   |                        | 100 mg/kg/days                      | HDM-induced asthma                          | Cell apoptosis ↓. ROS level ↓                         | Elevated the expression of SIRT1                | [63]      |
| cell                   |                        | Intraperitoneal injection           |                                              |                                                       |                                                  |           |
|                        |                        | 15 days                             |                                              |                                                       |                                                  |           |
| Vascular smooth muscle |                        |                                    |                                              |                                                       |                                                  |           |
| cells                  |                        | 50 mg/kg/day                        | Postovulatory oocyte aging                   | ROS level ↓. mtDNA copy number ↓. Mitochondrial function ↑ | Coordinated SIRT1 and AMPK signaling pathways   | [64]      |
|                        |                        | Intraperitoneal injection           |                                              |                                                       |                                                  |           |
|                        |                        | 24 hours                            |                                              |                                                       |                                                  |           |
|                        |                        | 0-100 μM                            |                                              |                                                       |                                                  |           |
|                        |                        | Not given                           |                                              |                                                       |                                                  |           |
|                        |                        | 48 hours                            |                                              |                                                       |                                                  |           |
|                        |                        | 5 μM                                |                                              |                                                       |                                                  |           |
|                        |                        | Not given                           |                                              |                                                       |                                                  |           |
|                        |                        | 24 hours                            |                                              |                                                       |                                                  |           |
|                        |                        | 10 μM                               |                                              |                                                       |                                                  |           |
| Neuronal cells         |                        |                                    |                                              |                                                       |                                                  |           |
| (N2A) cells            |                        |                                    |                                              |                                                       |                                                  |           |
| Human bronchial epithelial cells |        |                                    |                                              |                                                       |                                                  |           |
|                        |                        |                                    |                                              |                                                       |                                                  |           |

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; H2O2: 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$_2$O$_2$. 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$_2$O$_2$, 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$_2$O$_2$-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
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 H2O2-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.
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$_2$O$_2$: 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-like ECH-associated protein 1  
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.

**Acknowledgments**

This research was financially supported by the National Natural Science Foundation of China (Grant no. 31802140) and the Scientific Research Promotion Fund for the Talents of Jiangsu University (Grant no. 14JDG157).

**References**

[1] R. G. Larkins and M. E. Dunlop, “The link between hyperglycaemia and diabetic nephropathy,” Diabetologia, vol. 35, no. 6, pp. 499–504, 1992.

[2] V. Shukla, S. K. Mishra, and H. C. Pant, “Oxidative stress in neurodegeneration,” Advances in Pharmacological Sciences, vol. 2011, no. 1, 634 pages, Article ID 572634, 2011.

[3] G. Li, J. Fu, Y. Zhao, K. Ji, T. Luan, and B. Zang, “Alpha-lipoic acid exerts anti-inflammatory effects on lipopolysaccharide-stimulated rat mesangial cells via inhibition of nuclear factor kappa B (NF-κB) signaling pathway,” Inflammation, vol. 38, no. 2, pp. 510–519, 2015.

[4] A. Vaccaro, Y. K. Dor, K. Nambara et al., “Sleep loss can cause death through accumulation of reactive oxygen species in the gut,” Cell, vol. 181, no. 6, pp. 1307–1328, 2020.

[5] K. B. Pandey and S. I. Rizvi, “Plant polyphenols as dietary antioxidants in human health and disease,” Oxidative Medicine and Cellular Longevity, vol. 2, no. 5, pp. 270–278, 2009.

[6] Y. Peng, R. Y. Gan, H. B. Li et al., “Absorption, metabolism, and bioactivity of vetixin: recent advances in understanding the efficacy of an important nutraceutical,” Critical Reviews in Food Science and Nutrition, vol. 27, pp. 1–16, 2020.

[7] L. Frémont, “Biological effects of resveratrol,” Life Sciences, vol. 66, no. 8, pp. 663–673, 2000.

[8] H. Wu, L. Chen, F. Zhu, X. Han, L. Sun, and K. Chen, “The cytoxicity effect of resveratrol: cell cycle arrest and induced apoptosis of breast cancer 4T1 cells,” Toxins, vol. 11, no. 12, pp. 731–751, 2019.

[9] A. A. Bertelli, L. Giovannini, D. Giannessi et al., “Antiplalet activity of synthetic and natural resveratrol in red wine,” International Journal of Tissue Reactions, vol. 17, no. 1, pp. 1–3, 1995.

[10] M. Takaoka, “The phenolic substances of white hellebore (veratrum grandiflorum loes fil.) II,” Nippon Kagaku Kaishi, vol. 60, no. 12, pp. 1261–1264, 1939.

[11] R. Nakata, S. Takahashi, and H. Inoue, “Recent advances in the study on resveratrol,” Biological and Pharmaceutical Bulletin, vol. 35, no. 3, pp. 273–279, 2012.

[12] J. Burns, T. Yokota, H. Ashihara, M. E. J. Lean, and A. Crozier, “Plant foods and herbal sources of resveratrol,” Journal of Agricultural and Food Chemistry, vol. 50, no. 11, pp. 3337–3340, 2002.

[13] K. Pallauf, G. Rimbach, P. M. Rupp, D. Chin, and I. M.A. Wolf, “Resveratrol and lifespan in model organisms,” Current Medicinal Chemistry, vol. 23, no. 41, pp. 4639–4680, 2016.

[14] C. Brent, L. A. Trela, and Waterhouse, “Resveratrol: Isomeric molar absorptivities and stability,” Journal of Agricultural and Food Chemistry, vol. 44, no. 5, pp. 1253–1257, 1996.

[15] M. Valko, D. Leibfritz, J. Moncol, M. T. D. Cronin, M. Mazur, and J. Telser, “Free radicals and antioxidants in human health and disease,” The International Journal of Biochemistry & Cell Biology, vol. 39, no. 1, pp. 44–84, 2007.

[16] J. H. Holtzoff, K. A. Woodling, D. R. Doerge, S. T. Burns, J. A. Hinson, and P. R. Mayeux, “Resveratrol, a dietary polyphenolic phytoalexin, is a functional scavenger of peroxynitrite,” Biochemical Pharmacology, vol. 80, no. 8, pp. 1260–1265, 2010.

[17] Y. Sueishi and M. Hori, “Nitric oxide scavenging rates of solubilized resveratrol and flavonoids,” Nitric Oxide, vol. 29, pp. 25–29, 2013.
[18] S. Di Meo, T. T. Reed, P. Venditti, and V. M. Victor, “Role of ROS and RNS sources in physiological and pathological conditions,” Oxidative Medicine and Cellular Longevity, vol. 2016, Article ID 1245049, 44 pages, 2016.

[19] M. Wang, J. Li, M. Rangarajan et al., “Antioxidative phenolic compounds from sage (salvia officinalis),” Journal of Agricultural and Food Chemistry, vol. 46, no. 12, pp. 4869–4873, 1998.

[20] L. A. Stivala, M. Savio, F. Carafoli et al., “Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol,” Journal of Biological Chemistry, vol. 276, no. 25, pp. 22586–22594, 2001.

[21] H. Cao, X. Pan, C. Li, C. Zhou, F. Deng, and T. Li, “Density functional theory calculations for resveratrol,” Bioorganic & Medicinal Chemistry Letters, vol. 13, no. 11, pp. 1869–1871, 2003.

[22] M. A. Hussein, “A convenient mechanism for the free radical scavenging activity of resveratrol,” International Journal of Phytomedicine, vol. 3, no. 4, pp. 459–469, 2011.

[23] A. Benayahoum, H. Amira-Guebailia, and O. Houache, “Homolytic and heterolytic O-H bond cleavage in trans-resveratrol and some phenanthrene analogs: a theoretical study,” Computational and Theoretical Chemistry, vol. 1037, pp. 1–9, 2014.

[24] F. Caruso, J. Tanski, A. Villegas-Estrada, and M. Rossi, “Structural basis for antioxidant activity of trans-resveratrol: ab initio calculations and crystal and molecular structure,” Journal of Agricultural and Food Chemistry, vol. 52, no. 24, pp. 7279–7285, 2004.

[25] S. Fabris, F. Momo, G. Ravagnan, and R. Stevanato, “Antioxidant properties of resveratrol and piceid on lipid peroxidation in micelles and monomamellar liposomes,” Biophysical Chemistry, vol. 135, no. 1–3, pp. 76–83, 2008.

[26] S. S. Leonard, C. Xia, B.-H. Jiang et al., “Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses,” Biochemical and Biophysical Research Communications, vol. 309, no. 4, pp. 1017–1026, 2003.

[27] I. Gülcin, “Antioxidant properties of resveratrol: a structure-activity insight,” Innovative Food Science & Emerging Technologies, vol. 11, no. 1, pp. 210–218, 2010.

[28] V.-L. Truong, M. Jun, and W.-S. Jeong, “Role of resveratrol in regulation of cellular defense systems against oxidative stress,” Biofactors, vol. 44, no. 1, pp. 36–49, 2018.

[29] N. Xia, A. Daiber, U. Förstermann, and H. G. Li, “Antioxidant effects of resveratrol in the cardiovascular system,” British Journal of Pharmacology, vol. 174, no. 12, pp. 1633–1646, 2017.

[30] C. Beauloye, L. Bertrand, S. Horman, and L. Hue, “AMPK activation, a preventive therapeutic target in the transition from cardiac injury to heart failure,” Cardiovascular Research, vol. 90, no. 2, pp. 224–233, 2011.

[31] T. Walle, F. Hsieh, M. H. DeLegge, J. E. Oatis, and U. K. Walle, “High absorption but very low bioavailability of oral resveratrol in humans,” Drug Metabolism and Disposition, vol. 32, no. 12, pp. 1377–1382, 2004.

[32] T. Walle, “Bioavailability of resveratrol,” Annals of the New York Academy of Sciences, vol. 1215, no. 1, pp. 9–15, 2011.

[33] F. Q. Schafer and G. R. Buettner, “Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple,” Free Radical Biology and Medicine, vol. 30, no. 11, pp. 1191–1212, 2001.

[34] S. Langård, “One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports,” American Journal of Industrial Medicine, vol. 17, no. 2, pp. 189–215, 1990.

[35] P. Palsamy and S. Subramanian, “Resveratrol protects diabetic kidney by attenuating hyperglycemia-mediated oxidative stress and renal inflammatory cytokines via Nrf2-Keap1 signaling,” Biochimica Et Biophysica Acta-Molecular Basis of Disease, vol. 1812, no. 7, 731 pages, 2011.

[36] A. O. Abolaji, A. O. Adedara, M. A. Adie, M. Vicente-Crespo, and E. O. Farombi, “Resveratrol prolongs lifespan and improves 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced oxidative damage and behavioural deficits in Drosophila melanogaster,” Biochemical and Biophysical Research Communications, vol. 503, no. 2, pp. 1042–1048, 2018.

[37] R. Nordmann, C. Ribière, and H. Rouach, “Implication of free radical mechanisms in ethanol-induced cellular injury,” Free Radical Biology and Medicine, vol. 12, no. 3, pp. 219–240, 1992.

[38] S. K. Manna, A. Mukhopadhyay, and B. B. Aggarwal, “Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-κB, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation,” The Journal of Immunology, vol. 164, no. 12, pp. 6509–6519, 2000.

[39] S. Chanvitayapongs, B. Draczynska-Lusiak, and A. Y. Sun, “Amelioration of oxidative stress by antioxidants and resveratrol in PC12 cells,” Neuroreport, vol. 8, no. 6, pp. 1499–1502, 1997.

[40] S. Stojanovic, H. Sprinz, and O. Brede, “Efficiency and mechanism of the antioxidant action of trans-resveratrol and its analogues in the radical liposome oxidation,” Archives of Biochemistry and Biophysics, vol. 391, no. 1, pp. 79–89, 2001.

[41] M. A. Murcia and M. Martinez-tomé, “Antioxidant activity of resveratrol compared with common food additives,” Journal of Food Protection, vol. 64, no. 3, pp. 379–384, 2001.

[42] A. M. Pisoschi and A. Pop, “The role of antioxidants in the chemistry of oxidative stress: a review,” European Journal of Medicinal Chemistry, vol. 97, no. 31, pp. 55–74, 2015.

[43] M. Kopff, I. Zakrzewska, J. Czernicki, J. Klem, and M. Strzelczyk, “Red cell superoxide dismutase and catalase activity in multiple sclerosis,” Acta Biochimica Polonica, vol. 40, no. 1, pp. 154–157, 1993.

[44] A. Kasdallah-Grisa, B. Mornagui, E. Aouani et al., “Resveratrol, a red wine polyphenol, attenuates ethanol-induced oxidative stress in rat liver,” Life Sciences, vol. 80, no. 11, pp. 1033–1039, 2007.

[45] W.-M. Chen, L.-H. Shaw, P.-J. Chang et al., “Hepatoprotective effect of resveratrol against ethanol-induced oxidative stress through induction of superoxide dismutase in vivo and in vitro,” Experimental and Therapeutic Medicine, vol. 11, no. 4, pp. 1231–1238, 2016.

[46] M. Valko, “Free radicals and antioxidants in normal physiological functions and human disease,” The International Journal of Biochemistry, vol. 39, no. 1, pp. 44–84, 2007.

[47] C. Espinosa-Diez, V. Miguel, D. Mennerich et al., “Antioxidant responses and cellular adjustments to oxidative stress through induction of superoxide dismutase and improves 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced oxidative damage and behavioural deficits in Drosophila melanogaster,” Biochemical and Biophysical Research Communications, vol. 503, no. 2, pp. 1042–1048, 2018.
[50] K. Szkudelska, M. Okulicz, I. Hertig, and T. Szkudelski, “Resveratrol ameliorates inflammatory and oxidative stress in type 2 diabetic goto-kakizaki rats,” *Biomedicine & Pharmacotherapy*, vol. 125, Article ID 110026, 2020.

[51] S. Fu, R. Lv, L. Wang, H. Hou, H. Liu, and S. Shao, “Resveratrol, an antioxidant, protects spinal cord injury in rats by suppressing MAPK pathway,” *Saudi Journal of Biological Sciences*, vol. 25, no. 2, pp. 259–266, 2018.

[52] M. M. Khan, A. Ahmad, T. Ishrat et al., “Resveratrol attenuates oxidative stress and apoptosis in mouse oocytes,” *Journal of Alzheimer's Disease*, vol. 70, no. 1, Article ID e85495, 2014.

[53] H. H. Gaballah, S. S. Zakaria, M. M. Elbatsh, and N. M. Tahoon, “Modulatory effects of resveratrol on endoplasmic reticulum stress-associated apoptosis and oxidative-inflammatory markers in a rat model of rotenone-induced Parkinson’s disease,” *Chemico-Biological Interactions*, vol. 251, pp. 10–16, 2016.

[54] M. M. Khan, A. Ahmad, T. Ishrat et al., “Resveratrol attenuates 6-hydroxydopamine-induced oxidative damage and dopamine depletion in rat model of Parkinson’s disease,” *Brain Research*, vol. 1328, pp. 139–151, 2010.

[55] E. N. Kim, M. Y. Kim, J. H. Lim et al., “The protective effect of resveratrol on vascular aging by modulation of the renin-angiotensin system,” *Atherosclerosis*, vol. 270, pp. 123–131, 2018.

[56] N. Xia, A. Daiber, A. Habermeyer et al., “Resveratrol reverses endothelial nitric-oxide synthase uncoupling in apolipoprotein E knockout mice,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 335, no. 1, pp. 149–154, 2010.

[57] G. S. Liu, Z. S. Zhang, B. Yang, and W. He, “Resveratrol attenuates oxidative damage and ameliorates cognitive impairment in the brain of senescence-accelerated mice,” *Life Sciences*, vol. 91, no. 17-18, pp. 872–877, 2012.

[58] V. Tiwari and K. Chopra, “Resveratrol abrogates alcohol-induced cognitive deficits by attenuating oxidative-nitrosative stress and inflammatory cascade in the adult rat brain,” *Neurochemistry International*, vol. 62, no. 6, pp. 861–869, 2013.

[59] P. Y. He, Z. P. Hou, C. J. Song et al., “Resveratrol ameliorates experimental alcoholic liver disease by modulating oxidative stress,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2017, Article ID 4287890, 10 pages, 2017.

[60] S. Gómez-Zorita, A. Fernández-Quintela, M. T. Macarulla et al., “Resveratrol attenuates steatosis in obese Zucker rats by decreasing fatty acid availability and reducing oxidative stress,” *British Journal of Nutrition*, vol. 107, no. 2, pp. 202–210, 2012.

[61] D.-W. Kim, Y.-M. Kim, S.-D. Kang, Y.-M. Han, and H.-O. Pae, “Effects of resveratrol and trans-3,5,4′-trimethoxy stilbene on glutamate-induced cyto toxicity, heme oxygenase-1, and sirtuin 1 in HT22 neuronal cells,” *Biomolecules and Therapeutics*, vol. 20, no. 3, pp. 306–312, 2012.

[62] J. Han, H. Wang, T. Zhang et al., “Resveratrol attenuates doxorubicin-induced meiotic failure through inhibiting oxidative stress and apoptosis in mouse oocytes,” *Aging*, vol. 12, no. 9, pp. 7717–7728, 2020.

[63] Y. Zhang, L. Guo, B. Y. Law et al., “Resveratrol decreases cell apoptosis through inhibiting DNA damage in bronchial epithelial cells,” *International Journal of Molecular Medicine*, vol. 45, no. 6, pp. 1673–1684, 2020.

[64] Q.-X. Liang, Y.-H. Lin, C.-H. Zhang et al., “Resveratrol increases resistance of mouse oocytes to postovulatory aging in vivo,” *Aging*, vol. 10, no. 7, pp. 1586–1596, 2018.

[65] A. M. Thompson, K. A. Martin, and E. M. Ruczidlo, “Resveratrol induces vascular smooth muscle cell differentiation through stimulation of SirT1 and AMPK,” *PLoS One*, vol. 9, no. 1, Article ID e85495, 2014.

[66] M. Manzczak, P. Mao, J. C. Calkins et al., “Mitochondria-targeted antioxidants protect against amyloid-β toxicity in Alzheimer’s disease neurons,” *Journal of Alzheimer’s Disease*, vol. 20, no. s2, pp. S609–S631, 2010.

[67] X. He, L. Wang, G. Szklarz, Y. Bi, and Q. Ma, “Resveratrol inhibits paraquat-induced oxidative stress and fibrogenic response by activating the nuclear factor erythroid 2-related factor 2 pathway,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 342, no. 1, pp. 81–90, 2012.

[68] T. M. Teixeira, D. C. Da Costa, A. C. Resende, C. O. Soulage, F. F. Bezerra, and J. B. Daleprane, “Activation of Nrf2-antioxidant signaling by 1,25-dihydroxycholecalciferol prevents leptin-induced oxidative stress and inflammation in human endothelial cells,” *The Journal of Nutrition*, vol. 147, no. 4, pp. 506–513, 2017.

[69] E. B. Menshchikova, N. K. Zenkov, V. O. Tkachev, A. E. Lemza, and N. V. Kandalinshtein, “Protective effect of ARE-Inducing phenol antioxidant TS-13 in chronic inflammation,” *Bulletin of Experimental Biology and Medicine*, vol. 155, no. 3, pp. 330–334, 2013.

[70] X. Kou, M. Kirberger, Y. Yang, and N. Chen, “Natural products for cancer prevention associated with Nrf2-ARE pathway,” *Food Science and Human Wellness*, vol. 2, no. 1, pp. 22–28, 2013.

[71] K. Iwasaki, P. D. Ray, B.-W. Huang, K. Sakamoto, T. Kobayashi, and Y. Tsuji, “Role of AMP-activated protein kinase in ferritin H gene expression by resveratrol in human T cells,” *Biochemistry*, vol. 52, no. 30, pp. 5075–5083, 2013.

[72] C.-Y. Chen, J.-H. Jang, M.-H. Li, and Y.-J. Surh, “Resveratrol upregulates heme oxygenase-1 expression via activation of NF-E2-related factor 2 in PC12 cells,” *Biochemical and Biophysical Research Communications*, vol. 331, no. 4, pp. 993–1000, 2005.

[73] A. Kode, S. Rajendrasozhan, S. Cai, S.-R. Yang, I. L. Megson, and I. Rahman, “Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells,” *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 294, no. 3, pp. L478–L488, 2008.

[74] J. J. Boyle, M. Johns, J. Lo et al., “Heme induces heme oxygenase 1 via Nrf2,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 31, no. 1, pp. 2685–2691, 2011.

[75] Z. Cao, H. Zhu, L. Zhang, X. Zhao, J. L. Zweier, and Y. Li, “Antioxidants and phase 2 enzymes in cardiomyocytes: chemical inducibility and chemoprotection against oxidant and simulated ischemia-reperfusion injury,” *Experimental Biology and Medicine*, vol. 231, no. 8, pp. 1353–1364, 2006.

[76] V. Malec, O. R. Gottschald, S. Li, F. Rose, W. Seeger, and J. Hänze, “HIF-1α signaling is augmented during intermittent hypoxia by induction of the Nrf2 pathway in NOX1-expressing adenocarcinoma A549 cells,” *Free Radical Biology and Medicine*, vol. 48, no. 12, pp. 1626–1635, 2010.
R. Sen and D. Baltimore, "Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanism," *Cell*, vol. 47, no. 6, pp. 921–928, 1986.

M. J. Morgan and Z.-G. Liu, "Crosstalk of reactive oxygen species and NF-κB signaling," *Cell Research*, vol. 21, no. 1, pp. 103–115, 2011.

S. Vallabhapurapu and M. Karin, "Regulation and function of NF-κB transcription factors in the immune system," *Annual Review of Immunology*, vol. 27, no. 1, pp. 693–733, 2009.

X. Y. Zheng, S. Y. Zhu, S. F. Chang et al., "Protective effects of chronic resveratrol treatment on vascular inflammatory injury in streptozotocin-induced type 2 diabetic rats: role of NF-κB signaling," *European Journal of Pharmacology*, vol. 720, no. 1-3, pp. 147–157, 2013.

R. Guo, B. Liu, K. Wang, S. Zhou, W. Li, and Y. Xu, "Resveratrol ameliorates diabetic vascular inflammation and macrophage infiltration in db/db mice by inhibiting the NF-κB pathway," *Diabetes and Vascular Disease Research*, vol. 11, no. 2, pp. 92–102, 2014.

F. G. Soufi, D. Mohammad-Nejad, and H. Ahmadieh, "Resveratrol improves diabetic retinopathy possibly through oxidative stress - nuclear factor κB - apoptosis pathway," *Pharmacological Reports*, vol. 64, no. 6, pp. 1505–1514, 2012.

R. A. Frye, "Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins," *Biochemical and Biophysical Research Communications*, vol. 273, no. 2, pp. 793–798, 2000.

S. Jarolim, J. Millen, G. Heeren, P. Laun, D. Goldfarb, and M. Breitenbach, "A novel assay for replicative lifespan in," *FEMS Yeast Research*, vol. 5, no. 2, pp. 169–177, 2004.

B. Chen, W. Zang, J. Wang et al., "The chemical biology of sirtuins," *Chemical Society Reviews*, vol. 44, no. 15, pp. 5246–5264, 2015.

M. F. Oellerich and M. Potente, "FOXOs and sirtuins in vascular growth, maintenance, and aging," *Circulation Research*, vol. 110, no. 9, pp. 1238–1251, 2012.

T. Nakagawa and L. Guarente, "Sirtuins at a glance," *Journal of Cell Science*, vol. 124, no. 6, pp. 833–838, 2011.

S.-J. Park, F. Ahmad, A. Philp et al., "Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting camp phosphodiesterases," *Cell*, vol. 148, no. 3, pp. 421–433, 2012.

Z. Ungvari, N. Labinskyy, P. Mukhopadhyay et al., "Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 297, no. 5, pp. H1876–H1881, 2009.

M.-C. Wang, Y.-C. Wang, H.-W. Peng et al., "Resveratrol induces expression of metabolic and antioxidant machinery and protects tilapia under cold stress," *International Journal of Molecular Sciences*, vol. 21, no. 9, p. 3338, 2020.

Y. Olmos, F. J. Sánchez-Gómez, B. Wild et al., "αSirt1 regulation of antioxidant genes is dependent on the formation of a FoxO3a/PGC-1α complex," *Antioxidants & Redox Signaling*, vol. 19, no. 13, pp. 1507–1521, 2013.

S.-R. Yang, J. Wright, M. Bauter, K. Seweryniak, A. Kode, and I. Rahman, "Sirtuin regulates cigarette smoke-induced proinflammatory mediator release via RelA/p65 NF-κB in macrophages in vitro and in rat lungs in vivo: implications for chronic inflammation and aging," *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 292, no. 2, pp. L567–L576, 2007.

M. G. Erkkinen, M.-O. Kim, and M. D. Geschwind, "Clinical neurology and epidemiology of the major neurodegenerative diseases," *Cold Spring Harbor Perspectives in Biology*, vol. 10, no. 4, Article ID a033118, 2018.
C. Zhang, L. Wang, X. H. Zhao, X. Y. Chen, L. Yang, and Z. Y. Geng, "Dietary resveratrol supplementation prevents transport-stress-impaired meat quality of broilers through maintaining muscle energy metabolism and antioxidant status," *Poultry Science*, vol. 96, no. 7, pp. 2219–2225, 2017.

C. Zhang, J. Luo, B. Yu et al., "Dietary resveratrol supplementation improves meat quality of finishing pigs through changing muscle fiber characteristics and antioxidative status," *Meat Science*, vol. 102, pp. 15–21, 2015.

S. Davinelli, G. Scapagnini, F. Marzatico, V. Nobile, N. Ferrara, and G. Corbi, "Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: a randomized, placebo-controlled study," *Maturitas*, vol. 96, pp. 77–83, 2017.

W. Li, X. Yang, Q. Song et al., "Pyridoxine-resveratrol hybrids as novel inhibitors of MAO-B with antioxidant and neuroprotective activities for the treatment of Parkinson’s disease," *Bioorganic Chemistry*, vol. 9710377 pages, 2020.

Y. Fan, X. Zeng, J. Yi, and Y. Zhang, "Fabrication of pea protein nanoparticles with calcium-induced cross-linking for the stabilization and delivery of antioxidative resveratrol," *International Journal of Biological Macromolecules*, vol. 152, pp. 189–198, 2020.