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Review

The therapeutic effect of resveratrol: Focusing on the Nrf2 signaling pathway

Tahereh Farkhondeh[a], Silvia Llorens Folgado[b], Ali Mohammad Pourbagher-Shahri[c], Milad Ashrafizadeh[d], Saeed Samarghandian[e,*]

[a] Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran
[b] Department of Medical Sciences, Faculty of Medicine of Albacete, Centro Regional de Investigaciones Biomédicas (CRIB), University of Castilla-La Mancha, 02008, Albacete, Spain
[c] Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[d] Department of Basic Science, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran
[e] Healthy Ageing Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran

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ABSTRACT

Resveratrol is a natural polyphenol derived from grapes, berries, red wine, peanuts amongst other fruits and nuts. Beneficial effects such as anti-inflammatory, antioxidant, hepatoprotective, neuroprotective, cardioprotective, renoprotective, anti-obesity, anti-diabetic, and anti-cancer of resveratrol have been demonstrated by preclinical and clinical research. A possibility is that these therapeutical effects are associated with modulation of the Nrf2 signaling pathway in the following way: resveratrol may potentiate Nrf2 signaling through blockage of Keap1, by means of changing the Nrf2 mediators, its expression and its nuclear translocation. This article reviews the evidence of the Nrf2 modulating hypothesis as a possible molecular mechanism underlying the medicinal properties of resveratrol.

1. Introduction

A critical transcription factor stimulating the synthesis of enzymes is the nuclear erythroid 2-related factor 2 (Nrf2). This molecule is involved in a number of biological functions including regulation of inflammation protein degradation, antioxidant metabolism, bio transformative reactions, as well as an indirect transformation of lipids and carbohydrates [1]. Translocation of Nrf2 into the nucleus stimulates the small musculoaponeurotic fibrosarcoma oncogene homologue (sMAF) dimerization [2]. It leads to the activation of the genes containing the antioxidant response element (ARE), which activates the transcription of antioxidant enzymes [3]. Thus, Nrf2 has a critical function in maintaining homeostasis following cellular stress by regulating involved genes. Nrf2 is modulated via three pathways: 1) PI3K (phosphatidylinositol 3-kinase)/Akt (Protein Kinase B), 2) epigenetics and 3) the Kelch-like ECH-associated protein 1 (Keap1)-Nrf2 [2]. Keap1 was found to suppress the Nrf2 pathway [4]. Under physiological conditions, Keap1 blocks Nrf2 and reduces its half-life by preserving Nrf2 in the cytoplasm and therefore, targeting it for proteasomal depreciation. However, Keap1 is subject to modification in its structure during oxidative stress, hence, it is not capable of inhibiting Nrf2 [4]. Therefore, Keap1, under conditions of oxidative stress, preserves Nrf2 in the cytoplasm. Nrf2 is activated through the PI3K/Akt signaling pathway [5].

Flavonoids have the power to modulate Nrf2 activation. Resveratrol (Res) (3, 5, 4/-trihydroxytrans-stilbene) (Fig. 1), is a flavonoid isolated from several fruits and including berries, grapes, red wine and peanuts [6–9]. In recent years, the use of Res as a nutraceutical compound has gained attention because of its therapeutic effects. This natural polyphenol has numerous pharmacological impacts, including hepatoprotective [10], anti-diabetic [11], anti-cancer [12], antioxidant [13], anti-inflammatory [14], cardioprotective [15] and ability to ameliorate dyslipidemia [16]. These extraordinary therapeutical effects may come mostly from its antioxidant activity. Several experimental studies have indicated that Res could modulate cell signaling involved in inflammation and oxidative stress. The current study focus on the health-protective effect of Res mediated by Nrf2 impact of Res on the Nrf2 in various pathological conditions.

* Corresponding author.
E-mail address: samarghandians1@nums.ac.ir (S. Samarghandian).

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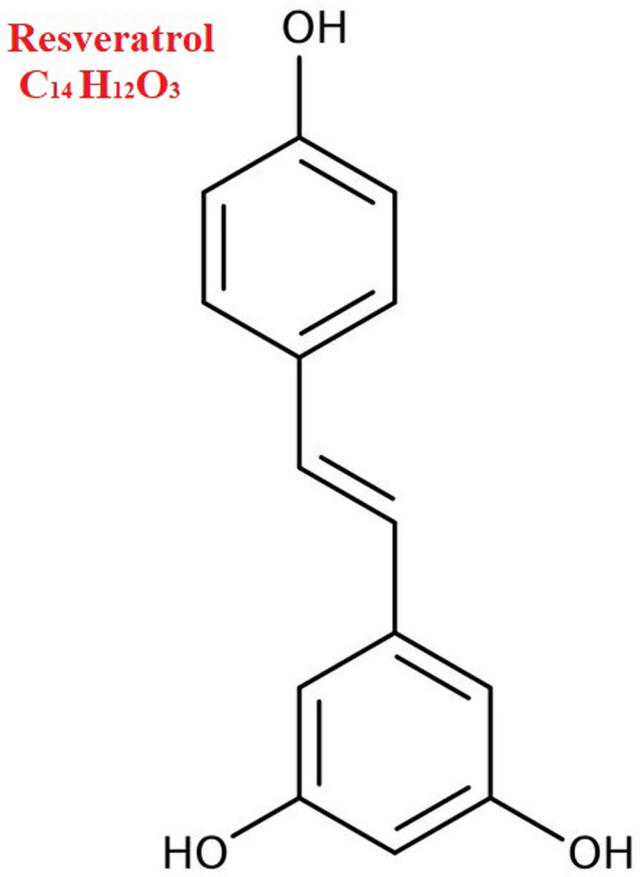

Fig. 1. Chemical structure of Res.

2. Neuroprotective effects

2.1. Neurodegenerative diseases

Alzheimer's disease (AD), is defined by the deposition of the protein beta-amyloid (Aβ) in the brain and memory impairment. Numerous studies indicated that antioxidants might be effective in delaying AD progression. In this context, Kong and co-workers [17] studied the impact of Res on an AD mice model and showed that both the content of nuclear Nrf2 and Nrf2 translocation into nuclear were elevated in Res-treated mice, while proceeding to increase the expression of HO-1. Therefore, Res could ameliorate the spatial memory in the experimental animals via increasing the SOD, glutathione peroxidase (GPx) and CAT expression and activity. Additionally, Res decreased malondialdehyde (MDA) brain levels in these mice activating the Nrf2/HO-1, indicating its potential to decrease the cell oxidative damage. Furthermore, they showed that Res improved AD by reducing Aβ protein expression in the brain of treated mice correlating this effect with a reduction of the estrogen receptor β (ERβ) expression and an increase the ERα expression at mRNA and protein levels and choline acetyltransferase (ChAT) protein and estradiol levels. These findings indicate that Res has a protective impact against AD similar to the estrogen. Chiang et al. [18] demonstrated that Res inhibited the effects of Aβ on neural stem cells via activating the AMPK pathway. Res prevented the Aβ-mediated increased nuclear factor-kappaB (NF-κB) levels in the neural stem cells. Res ameliorated Aβ-induced increase of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2)(pro-inflammatory enzymes), reversed and decreased the mRNA expression levels of antioxidative genes (GPx1, SOD-1, Nrf2, CAT, glutathione, and HO-1). Hui et al. [19] observed the neuroprotective effect of Res on PC12 toxicity which induced by Aβ1-42 through the PI3K/Akt Activation. They have shown neuroprotective Res-associated effect resulting in the activation of Nrf2 signaling pathway.

Vascular dementia (VaD) is a type of dementia caused by a decline in blood flow to the brain. Yadav and co-workers [20] assessed the efficacy of Res in a rat model of VaD. Due to the low bioavailability of Res, it was administered to rats loaded into solid lipid nanoparticles (Res-SLNs). They showed that Res-SLNs ameliorated cognitive impairment through a decline in protein carbonyls, lipid peroxidation, and ROS production as well as a raise in the Mn-SOD activity. These protective effects of Res-SLNs were related to the Nrf2/HO-1 signaling pathway. Parkinson's disease (PD) is a neurodegenerative disorder link to the loss of dopaminergic neurons in the substantia nigra. Factors such as mitochondrial dysfunction, endoplasmic reticulum (ER) stress oxidative damage, as well as neuroinflammation, have been involved in the PD pathogenesis. Gaballah et al. [21] assessed the potential impact of Res in rats that were injected with rotenone. They observed that Res ameliorated ER stress that was followed by a decline in the ER stress parameters in the brain as C/EBP homologous protein (CHOP) and glucose-regulated protein 78 (GRP78), leading to suppression of caspase-3 activation. In this rat model of PD, Res also modulated the balance between the oxidant-antioxidant systems by stimulating the Nrf2 signaling pathway.

Res has also shown neuroprotective effects in spinocerebellar ataxia type 3 (SCA3). This ataxia is the result of an abnormal expansion of polyQ in the ataxin-3 protein. A mutant form of this protein induces neurotoxicity and neurodegeneration in specific brain regions. Treatment with Res has been effective in contrast to ataxin-3 mutant caused neuronal damage in neuroblastoma cells and Drosophila models of SCA3. Res increased the antioxidant protein content (HO-1, CAT, SOD, GPx) and autophagy protein p62 expression, decreased reactive oxygen species (ROS) levels, corrected mitochondrial function, declined the expression of the mutant ataxin-3 protein. All actions incriminated the activation of Nrf2 by the Res, potentiating antioxidant genes expression and the autophagy of gene p62. The gene p62 protein binds Keap1 and facilitates translocation of Nrf2 in to nuclear. Furthermore, supplementation with Res ameliorated the motor function in SCA3 Drosophila through induction of Nrf2 activation [22]].

2.2. Neuroinflammation

Several in-vitro studies found that Res may prevent the occurrence of neurological disorders. For example, Rosa and co-workers [23] indicated that Res protected oligodendroglial cell function against lipopolysaccharide (LPS) exposition, by modulating oxidant-antioxidant system mediated by Nrf2/HO-1 signaling pathways. Res modulated intracellular content of GSH, ROS, and also the activity of glutamate-cysteine ligase (GCL), leading to regulation of the release of trophic factors by oligodendroglial progenitor cell. Bobermin and co-workers [24] investigated the anti-inflammatory mechanism of Res mediated by adenosine receptors, on primary astrocyte cultures exposed to LPS. However, the study indicated that Res could prevent the reduction in adenosine receptors mRNA levels LPS-induced. Indeed, Res could activate PI3K/Akt-Nrf2 in astrocytes exposed to LPS and also inhibit NFκB and p38 mitogen-activated protein kinase (p38 MAPK). Res up-regulated the heme oxygenase-1 (HO-1) expression in PC12 cells through ARE/Nrf2 signaling. Res ameliorated signal-regulated protein kinase 1/2 (ERK1/2) and Akt/protein kinase B activation in the PC12 [25]. Curcumin and Res protected astrocytes against H_2O_2 induced oxidative damage via Nrf2 activation [26]. Alcohol consumption in pregnancy hinders behaviour and function in infants. In rats, administration of highly concentrated ethanol (80 mM) induced the cerebellum neuronal death, but Res protected against apoptosis via ROS scavenging cerebellar neurons, leading to an increase in cell survival through the Nrf2 pathway [27].

2.3. Cerebral ischemic and hemorrhagic injuries

The progression of stroke as the second leading cause of death mortality is related to oxidative stress, inflammation, and apoptosis [28]. It is suggested that anti-oxidant and anti-inflammatory agents might decrease the extent of stroke-induced injury results from ischemic stroke [28]. In this context, Yang and co-workers [29] indicated that Res decreased neuronal damage induced via oxygen/glucose deprivation/reoxygenation (OGD/R) in the rat cerebral cortex via increased activation of Nrf2 signaling. The potentiation of Res on the Nrf2 pathway raised the activity of SOD, HO-1, quinone oxidoreductase 1 (NQO-1), NAD(P)H, and apoptotic proteins including declined the caspase-3 expression, Bcl-2, and thus, leading to neuronal apoptosis suppression. Shen et al. [10] found that pretreated neural stem cells (NSCs) with Res, significantly reduced NSCs death and the MDA levels, raising proliferation, SOD activity, and GSH content after OGD/R damage. They concluded that Res ameliorated NSCs injury and increased proliferation through enhancing the NQO1, Nrf2, and HO-1 expressions after OGD/R damage.

Abdel-Aleem and co-workers [30] showed the ability of Res to modulate the neuroprotective protein DJ-1 (Parkinson protein 7). This protein is an important antioxidant and cell survival regulator; however, during ischemia/reperfusion (I/R) events, both its expression pattern and the changes of its oxidized/reduced forms towards oxidized could alter its neuroprotective effect. In their work, Abdel-Aleem and co-workers found that Res reduced oxidized forms of DJ-1 levels and iNOS expression and increased GSH levels and SOD activity, resulting in increased survival of injured animals' model through the Nrf2 /PI3K/Akt survival pathway. Pre-treatment with Res (20 or 40 mg/kg, for seven days before hypoxia-ischemia induction) considerably improved the cerebral edema, infarct area, oxidative stress indices (GPx, CAT, SOD), inflammatory indices (TNF-a IL-6, IL-1b, and NF-κB) through marked the Nrf2/HO-1 upregulation in hypoxia-ischemia pups [31]. A stroke model in rodent astrocyte cultures showed Res protective effects via preserving mitochondrial coupling and antioxidant expression mediated by Nrf2 [32]. Ren et al. [33], found that Res pretreatment (15 and 30 mg/kg) inhibited neuronal damage in brain I/R injury in rat and mice models by ameliorating oxidative markers (decreased MDA levels and increased SOD activity) and decreasing caspase-3 protein expression, mediated by Nrf2/HO-1 signaling pathways. Kesherwani et al. [34] indicated the neuroprotective properties of Res (50 μM) mediated by Nrf2 in the spinal cord (T2–T10 and the dorsal column of rat) hypoxic injury in an *in vitro* model. Activation of Nrf2 by Res attenuated the oxidative damage (decreasing lipid peroxidase (LPO), increasing both GSH and SOD) and maintaining mitochondrial function. The spinal cord action potential of dorsal column assay and histological staining (with eosin and hematoxyline) confirmed the neuroprotective effects of Res.

During severe hemorrhage, mitochondrial dysfunction occurs. Reduction in blood flow to tissues leads to decreased availability of oxygen and nutrient. Jian and co-worker [35] found that the SIRT1 activity and the balance of glycolytic activity of mitochondria after trauma hemorrhage was decreased Res untreated rats in contrast with Res treated rats who showed restored activity and expression of SIRT1 mediated by Nrf2.

2.4. Traumatic brain injuries

Traumatic brain injury (TBI) is featured by cognitive impairment, in which oxidative stress, inflammation, and apoptosis are involved as molecular mechanisms. TBI is associated with primary and secondary injury severity in patients. Primary injury is called to the first collision that pushes the brain to be hit inside the skull. The primary injury results in immediate impacts including :direct trauma to the brain and Subarachnoid hemorrhage. The secondary stage of TBI consists of pathological events that cause hematomas, edema, and ischemia leading to a deterioration of the clinical symptoms [36]. The progression of the secondary lesion of TBI comprises several mechanisms, including oxidative stress, inflammation, and glutamate excitotoxicity [37–39]. Recent research indicates that Nrf2 has a substantial impact on the stimulation of the antioxidant enzyme expression and the decline of oxidative injury after TBI [40]. Many numbers of natural antioxidants have been indicated for protective effects against TBI through the Nrf2 activation [41,42]. Shi et al. [43] indicated that Res improved cognitive deficits in traumatic brain injury rats through a decrease in apoptosis and ROS generation following p38/Nrf2/HO1 signaling stimulation in the brain. Res ameliorated the phosphorylated p38 level, raising Nrf2 translocation into nuclear and the expression of HO1. The oxidative stress and apoptosis were considerably reduced following Nrf2 activation, leading to cognitive and spatial memory improvement [43].

2.5. Cardiovascular protective effects

The cardiovascular system is mostly affected by ROS. It has been found that natural flavonoids may potentially attenuate oxidative stress-induced cardiovascular disease. In this regard, Bai et al. [44] showed the therapeutic effects of Res on cardiac function in an endotoxemia experimental model and mouse cardiomyocytes. It is well known that LPS disturbs the redox homeostasis, enhancing oxidative stress and reducing antioxidant enzymes in hearts. These disturbances translate into poor cardiac contractility and Ca^{2+} transient by reduced sarco-endoplasmic reticulum Ca^{2+} (SERCA2a) activity. Res improved cardiac dysfunction induced by LPS via enhancing the activity of SERCA2a. In cardiomyocytes, Res ameliorated amplitude of contraction, the elongation of lengthening time, decreased Ca^{2+} transient and the activity of SERCA2a, and elevated superoxide production. It was found that Res protected against LPS-induced heart injuries by enhancing the Nrf2 activation. It seems that Res manages the expression of the antioxidant enzymes involved in the regulation of ER calcium by SERCA. During the ischemia/reperfusion process, an inflammatory reaction is induced, which causes damage related to myocardial ischemia-reperfusion dysfunction. Res presented therapeutic properties in a myocardial ischemia-reperfusion (MI/R) animal model, attenuating oxidative stress and inflammation by enhancing the Nrf2/ARE/HO-1 signaling [45]. Hao et al. [46], also reported that Res attenuated myocardial injury LPS-induced in both an animal model of sepsis and in primary human cardiomyocytes, by decreasing pro-inflammatory cytokines and increasing Nrf2 stimulation.

The cardio protector effect of Res has been investigated in co-administration with several drugs, which possess therapeutic properties but induce cardiotoxicity. The arsenic (As_2O_3) is considered a carcinogenetic substance; however, it shows a protective impact in acute promyelocytic leukemia. The use of As_2O_3 in this type of cancer is limited because it produces an increase of ROS in cardiomyocytes, oxidative DNA damage, and arsenic accumulation. Zhang et al. [47] reported the beneficial impact of Res in co-administration with As_2O_3 in rats. They found that the pretreatment with Res in As_2O_3-exposed rats, reduced As_2O_3-induced ROS production, DNA damage, and improved cardiac function reverting intracellular calcium and As2O3 accumulation, glutathione redox ratio and cAMP deficiency. They showed that these effects Res-associated were produced by activating the Nrf2/HO-1 pathway.

Cheng et al. [45] showed that Res modulated inflammation and oxidative damage by stimulating the Nrf2/ARE activation in an ischemia/reperfusion rat model. Res protected myocardial infarction by reducing myeloperoxidase (MPO) and MDA levels in the myocardium as well as serum lactate creatinine kinase (CK) and dehydrogenase (LDH) levels and raising superoxide dismutase (SOD) and GPx activity. Gurusamy et al. [48] indicated the impact of 14 days administration of Res (2.5 mg/kg) in the myocardium of rat, which subjected to occlusion of the coronary artery. Res was administrated into the adult EGFP (enhanced green fluorescent protein) -labeled-cardiac stem cells

increased EGFP into the border zone of the myocardial cell. They found that the cardiac function and environment were improved in Res-administrated animals by increasing the nuclear expression of the redox effector factor 1 (Ref-1) and Nrf2 pathway, 1 week the left anterior descending coronary artery (LAD) occlusion group. In this line, Gorbunov et al. [49] treated stem cells derived from the LAD rat model heart with Res. They found that the survival of these stem cells increased as indicated by the Ki67 and the myocardium regenerated as shown by the EGFP expression for following the occlusion of the coronal artery in the Res-administrated stem cell group, through enhancing Nrf2/Ref-1 pathway.

2.6. Vasoprotective effects

Kim et al. [50] reported the protective effect of Res in cultured vascular smooth muscle cells, wire-injured femoral artery animal model and vascular occlusive disease (VOD). The abnormality in the growth of the blood vessel intimal layer is called neointima and is critical to the development of VOD. In this work, Res inhibited neointimal formation by potentiating Nrf2/HO-1 activation. Ungvari et al. [51] found that Res significantly enhanced the Nrf2 expression that affects NAD(P)H: HO-1, γ-glutamylcysteine synthetase, and NQO-1 in the arterial coronary endothelial cells. Res also markedly ameliorated mitochondrial dysfunction and oxidative damage caused by high glucose through the upregulation of Nrf2 in these cells. Vasodilation is impaired by high-fat diet (HFD), Res restored acetylcholine-induced vasodilation in microvasculature dependent of Nrf2 in an endothelial dysfunction mice model ((HFD)-fed mice). Also, Res inhibited apoptosis and oxidative in the femoral artery branches in HFD-fed mice. The findings suggests that the endothelial protective effects of Res are mediated by activation of Nrf2. Seo et al. [52] assessed the anti-atherogenic effect of Res in mouse atherosclerosis model of partial ligation of the left carotid artery. The findings indicated Res inhibited ICAM-1 (intercellular adhesion molecule-1) expression via transcriptional regulation of the FERM-kinase and Nrf2/ARE interaction, thereby blocking monocyte adhesion. FERM-kinase is a fragment of FAK (focal adhesion kinase); in this work, Seo et al. showed that Res induced FAK cleavage using in vitro as well as in vivo experiments.

2.7. Respiratory protective effect

Kode et al. [53] studied the protective impact of Res against oxidant damage caused by cigarette smoke extract (CSE). They showed that Res prevented CSE-induced ROS increased production and increased levels of GSH via activation of Nrf2, in human alveolar epithelial (A549) cells and human primary small airway epithelial exposed to CSE. CSE decreases the new synthesis of GSH by transcription impaired of glutamate-cysteine ligase catalytic (GCLC) subunit, and they observed that this event was correlated to the Nrf2 localization in the cytoplasm. They also found a rise in the nuclear content of Nrf2 in the epithelial lung cancer cells administrated with Res plus CSE, accompanying of GCLC mRNA increased expression and GCL activity. Zhang et al. [54] indicated that Res enhanced antioxidant capacity and decreased apoptosis in human bronchial epithelial cells (HBE1) exposed to CSE via activating Nrf2/HO-1 signaling. Li et al. [55] researched the impact of Res on SIRT1 and Nrf2 in the lung of mice exposed to paraquat (PQ). PQ is an herbicide that produces respiratory failure in humans and is correlated to high death. In this work, they observed that long-term PQ exposure inhibited the expression of SIRT1 in mice, and it is known that PQ also inhibits Nrf2 expression. Treatment with Res in mice exposed to PQ, increased SIRT1 and GSH expression levels and HO-1, SOD and CAT activity via Nrf2/ARE, but decreased the expression of MDA. This work showed that the agonism of Res on SIRT1 protected against PQ-induced lung damage, increasing antioxidative defenses in mice. He et al. [56] found that Res reversed mitochondrial damage, oxidative stress, inflammatory and profibrogenic factors (transforming growth factor β1, IL6, TNFα, and TGFβ1) and cell death induced by PQ in normal human bronchial epithelial cells (BEAS-2B) by activating Nrf2 signaling. They have found that Res acts as a SIRT1 activator enhancing its expression and improving lung injury.

Dong et al. [57] indicated that Res protected against high mobility group box 1 (HMGB1)-caused hyperpermeability in endothelial both in primary cultured mouse lung vascular endothelial cells (MLVECs) and lung of mice anesthetized with ventilator-induced lung injury (VILI), through an Nrf2-dependent mechanism. Res ameliorated HMGB1-induced decrease in vascular endothelial (VE)-cadherin expression as well as attenuated endothelial permeability and improved mitochondrial function, in primary cultured MLVECs. Res also attenuated VILI, including lung vascular hyperpermeability and further enhanced Nrf2 expression. Xu et al. [58] reported the effect of Res in an hypoxic pulmonary hypertension (HPH) rat model. Res diminished pulmonary arterial restoration and systolic pressure caused by hypoxia. It was also observed that Res considerably declined the pulmonary arterial smooth muscle cells (PAMSCs) proliferation in an estrogen receptor (ER)-independent method. Other studies have shown that Res can act like estrogens, exerting its protective effect by stimulating ERs signaling in vascular endothelial cells. Res declined the expression of HIF-1 α, infiltration of inflammatory cells around the pulmonary arteries, and declined ROS generation in hypoxic PAMSCs. In this work, Res attenuated HPH injury by inhibiting the MAPK/ERK1 and PI3K/AKT and enhancing Nrf2/Thioredoxin 1 (Nrf2/Trx-1) pathway.

2.8. Hepatoprotective effect

Rubiolo et al. [59] indicated that Res protected primary damage in hepatocytes induced by oxidative stress through the Nrf2 activation that modulates the phase II detoxifying enzymes and antioxidant expression. Sahin and co-workers [60] reported the beneficial impact of Res on the heat shock proteins, NF-κB and antioxidative enzymes (SOD, GPx and CAT) activities in liver of quails exposed to heat stress through enhancing Nrf2 pathway. Res also inhibited hepatotoxicity tilapia fish exposed to H2O2, indicated by the reduction level in lipid peroxidation and elevation level in antioxidant enzymes (NQO-1, HO-1, GSH-Px). Res suppressed Toll-like receptor-2 (TLR2)-Myd88-NF-κB activation, leading a reduction in the inflammatory hepatic injury. Res ameliorated immunotoxicity in the liver of fish, as evidenced by the up-regulation of hepcidin (HEP), complement 3 (C3), and lysozyme (LZM) mRNA levels. The anti-oxidative, anti-inflammatory, and anti-immunotoxicity impact of Res in the liver of fish were caused following the induction of Nrf2 signaling pathways [61]. Res ameliorated acute injury in the liver caused by LPS through suppressing NF-κB pathways and activating Nrf2/HO-1 in rats [62]. Res induced the HO-1 and paraoxonase-1 expressions in hepatocytes (HUH7) as well as increased Nrf2 transactivation [63]. In HepG2 cells, Res prevented acrylamide-induced impairment in mitochondrial function, cell death, and inflammatory cytokines production through stimulating the Nrf2/NQO-1 pathway [64].

2.9. Reno-protective effects

Administration of Res inhibited the progression of kidney injury by stimulating the Nrf2 signaling pathway. Wang and co-workers. [65] showed that Res ameliorated acute kidney injury (AKI) in a CLP model of rat pups by decreasing kidney injury molecule (KIM)-1expression, TNFα, and IL-1β that mediated by Nrf2 signaling pathway. Res also decreased inflammatory injury in kidney cells induced LPS, by activating Nrf2/HO-1 pathway. Res modulated the expression of SIRT1, AQP2, and Nrf2, NOX4, p47phox, Keap1, and COX and activation of c-Jun N-terminal kinase (JNK), MAPK/ERK, p38 and NF-κB, in mouse cortical cells treated with 4-hydroxy-2-hexenal (HHE) [66]. Res reversed human embryonic kidney (HEK293) cells damage induced by Ochratoxin A by increasing GSH levels and decreasing DNA damage,

which is regulated by the Nrf2 signaling pathway [67]. Res declined injury in renal cells exposed nicotine suppressing pro-oxidant p66shc transcription, via activation Nrf2/HO-1 pathway [68]. Res reduced the fibroblast growth factor-23 mRNA and elevated klotho and the Nrf2 mRNA levels in rat vascular smooth muscle cells (RASMCs) exposed to b-glycerophosphate [69]. Res attenuate injury produced by hypertension in spontaneously hypertensive rats (SHR), by activating Nrf2, thus Res activated phase II antioxidant enzymes, decreased oxidative damage, normalized of Na/K-ATPase regulation and angiotensin 1 receptor (AT1R)–G-protein signaling [70].

Another study conducted by Javkhedkar et al. [71] also confirmed that water-administration of Res in the young SHR exerted protective effects by reducing oxidative damage and restoring total antioxidant content in tubular epithelial cells via Nrf2 activity. Oxidative markers, as 8-isoprostane and protein carbonyl levels, were reduced in Res treated-young SHR rats. These effects resulted in the reduction of interstitial inflammatory cells in the kidney and the lowering of blood pressure in SHR. Li et al. [72] showed the renoprotective effect of Res, as evidenced by decreasing inflammatory responses, apoptosis, and oxidative stress through stimulating Nrf2 expression, suppressing the TLR4/NF-κB signaling in NRK-52E cells.

2.10. Skin protective effect

Res activates Nrf2 signaling in the human keratinocytes and mouse epidermis, as evidenced by increasing the activity of the GST enzyme [73]. Res raised the survival of neonatal normal human epidermal keratinocyte cells (NHEKs) by modulating the ROS production dependent Nrf2 signaling pathway [74]. Kim and co-workers [75] showed the therapeutic effect of Res on ultraviolet (UV)-induced skin wrinkles. Res stimulated the Nrf2/HO-1 pathway in the skin, and also prevented metalloproteinases (MMP), leading to prevention UVB-induced photoaging. Liu and co-workers [76] also indicated that Res declined oxidative damage in human keratinocytes (HaCaT) exposed to UVA. Res elevated the HaCaT cells viability following exposure to UVA and protected them from damage induced by oxidative stress. Res degraded Keap1 and increased the Nrf2 content in the nucleus, leading a decrease in damage in HaCaT cells.

Res activated the Nrf2 pathway glutamylcysteinyl ligase and glutathione peroxidase-2 (GPx2) in the normal human keratinocytes (NHKs) [77]. Pastore and co-workers [78] indicated that Res modulated metabolically, inflammation, and proliferation in human epidermal keratinocytes (HEK) cell exposed to 6-formylindo[3,2-*b*]carbazole (FICZ) or UVA + UVB through Nrf2 signaling pathway.

2.11. Chemopreventive or chemoprotective effect

2.11.1. Reproductive protective effect

Some young women are recognized with reproductive cancer under chemotherapy [79]. The treatments induce ovarian aging and infertility by causing apoptotic death and damage in the genome of ovarian cells [80]. The maintenance of fertility and oocytes function is considered as the main issue for cancer patients under medication. Unfortunately, chemotherapy can stimulate aging processes in ovarian cells, leading to infertility in young patient's cancer. Germinal stem cells produce new ovarian cells and provide opportunities to cure infertility. Wu et al. [81] investigated chemoprotective functions of Res in mice exposed to busulfan plus cyclophosphamide as chemotherapy agents. They showed that Res-treatment at low (30 mg/kg/day) but not at high doses (100 mg/kg/day), improved ovarian aging, and declined oxidative damage in ovaries. Besides, low-dose Res-treatment presented the restoration ability of oogonial stem cells (OSCs) in mice exposed to chemotherapy agents. Wu et al. observed that Res administered after treatment with chemotherapy, recovered weight and morphology of the ovaries, raised the follicles number, 17β-estradiol, and decreased in follicle-stimulating hormone levels. Res decreased oxidative stress level in the ovaries caused by chemotherapy increasing SOD2 levels also decreased oxidative markers upregulating Nrf2 and SOD2 and activating the SIRT1/FOXO1 pathway. Kutuk et al. [82] investigated the impact of Res in signal transduction mediated apoptosis in 3T3 fibroblasts during exposure to 4-hydroxynonenal (HNE). Results showed that Res effectively prevented the stimulation HNE-induced caspase and c-Jun N-terminal kinase (JNK), and eventually apoptosis. Elevated phospho-c-Jun and c-Jun levels and activated AP-1 could be declined due to pretreatment of cells with Res. Moreover, decreased ARE binding activity of Nrf2 by HNE, was blocked by Res. This upregulation of Nrf2 ARE binding activity was considered, at least partly, to be responsible for anti-apoptotic effects of Res in exposure to HNE.

2.11.2. Anti-tumor effect

Cancer continues globally despite the progress of cancer treatment methods, such as anticancer drugs in recent decades [83]. Herbal drugs have been focused on as an alternative medicine to affect cellular signaling in an experimental model of cancer [84]. In this contest, Res might be an alternative treatment for cancerous patients. Kabel and coworker [85] investigated the impact of Res alone or in the combination of sitagliptin on an experimental model of renal carcinoma in rats. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor which applied to treat diabetes mellitus type 2. This drug may represent a new chemotherapeutic agent because it possesses cytotoxic effects on tumor cells by inhibition of autophagy. This work shows Res and sitagliptin-synergy established in the anti-inflammatory and antioxidant activities due to their modulatory effects on Nrf2/HO-1 and STAT3/NF-κB signaling. These compounds improved renal function and clear cell renal cell carcinoma. Sinagliptin alleviated oxidative damage, and Res produced a considerable rise in the activity of the antioxidant enzymes in treated clear renal cell carcinoma. Untreated clear cell renal cell carcinoma indicated a decline in the content of Nrf2/HO-1; the treatment with sitagliptin and resveratrol restored Nrf2/HO-1 content, which in turn ameliorated clear cell renal cell carcinoma. Kabel and co-workers observed that the metastatic effect was avoided with concomitant administration of Res. Both Res and sitagliptin, decreased xanthine oxidase, IL-6, TNF-α, TGF-β1, and LDH expressions in renal tissue. Zhou and co-workers [86] showed the preventive role of Res and its antitumor activity against breast cancer in animal models exposed to estrogen, was mediated via stimulation of the Nrf2 signaling and Nrf2-UDP-glucuronosyltransferase 1A8 (UGT1A8) axis, that it is responsible for controlling of breast cancer deterioration. In preclinical studies, the ability of Res to modulate detoxificant enzymes (phases I and II) has been demonstrated. The above-mentioned work suggested that the antitumor activity of Res was due to its hormonal modulator like effects on NRf2 signaling. They observed that Res decreased breast cancer the progression through up-regulation of Nrf2/UGT1A8 signaling in the experimental model of breast cancer. In the same line, Singh et al. [87] indicated that Res inhibited proliferative alterations in breast cells mediated by estrogen, and markedly decreased breast cancer progression and elevated tumor latency via induction the expression of Nrf2-mediated regulation antioxidant genes.

Res decreased growth and clonogenic potential of breast cancer cells (MCF-7) exposed to doxorubicin (DOX) through stimulation of Nrf2, leading to inhibition the apoptosis (Caspase-9 and Bax: Bcl-2 ratio), autophagy (Beclin-1, LC3) and inflammation (COX-2, NF-kB). Besides, Res prevented tumor progression and raised survival of Ehrlich ascitic carcinoma (EAC) cells in bearing mice exposed to DOX [88]. Administration of Res prevented estrogen-induced breast cancer in the human breast epithelial cell line (MCF-10A), via modulation of cap "n" collar (CNC) b-zip transcription factors-mediated Nrf2-dependent pathways [89]. Res exerted protective effects in K562 cells (erythroleukemia type cancer cell) through modulating Nrf2/ARE signaling [90].

Strong evidence indicated that Res declined hepatic carcinoma cell progression and oxidative damage and inflammatory cytokines that regulated by Nrf2 in rats [91]. Kim and co-workers [92] indicated that

Res caused mitochondrial biogenesis in Nrf2/ HO-1 activation in the HepG2 cells.

Besides chemopreventive, antitumoral effects, Res enhanced the tumor cell's sensitivity to chemotherapeutic drugs. Li and co-workers [93] found that Res ameliorated the resistance to adriamycin (a chemotherapy drug) through regulation of the PI3K/Akt/Nrf2 activation in promyelocytic leukemia cells (HL-60). Cheng and co-workers [94] showed that Res ameliorated the response of pancreatic cancer cells to gemcitabine, enhancing the efficacy of gemcitabine in pancreatic cancer therapy. In the work, they indicated that this impact of Res was due to its ability to inhibit the nutrient-deprivation autophagy factor-1 (NAF-1) expression in pancreatic cancer cells through stimulating Nrf2 signaling.

Res inhibited spleen dysplasia in broilers induced by high ambient temperature (HT) via stimulating the Nrf2 activating, thereby modulating oxidative stress indices (MDA, 8-OHdG, GSH, GPx, SOD and CAT activities) and apoptotic indices (caspase-9, caspase-3, Bax, and Bcl-2) [95]. Res prevented mouse colon cancer induced by the azoxymethane (AOM) through Nrf2/HO-1 signaling leading to a decline in the iNOS, COX-2, and aldose reductase (AR) expressions and increase in the activity of glutathione reductase (GSR) in [96].

2.11.3. Anti-infection effect

ROS is usually generated during infection diseases, leading to a reduction in the antioxidant content, and causes oxidative damage. Thus, antioxidants may be effective for protecting against infectious diseases. Resveratrol, a natural antioxidant agent, is being able to inhibit the progression of various infectious diseases. In this context, Bhattarai et al. indicated that Res could inhibit the decline in alveolar bone in a periodontitis animal model through potentiating the activity of Nrf2/HO-1, resulting in a decline in the ROS content and COX-2, MMP-9, and MMP-2, and expression TLR-4 [97]. It was also found that Res inhibited the periodontitis progression through activating the SIRT1/AMPK and rasing the antioxidant defenses by the Nrf2 pathway, resulting in a decline in the serum levels of 8-OHdG, NO, dityrosine, nitrotyrosine, and pro-inflammatory indices in inflamed gingival tissues of rats [98]. Zhang et al. [99] found that Res significantly ameliorated gastritis caused by Helicobacter pylori through stimulation of the Nrf2/HO-1 activation. Activated Nrf2/HO-1 signaling attenuated oxidative damage and inflammation in Helicobacter pylori-infected gastric mucosa. Zahlten and co-workers [100] indicated that Res inhibited the progression of cellular lung injury in lung epithelial cells exposed to Streptococcus pneumonia via the up-regulation of Nrf2 in lung epithelial cells and increasing the antioxidant content. Res also ameliorated acute lung infection in the septic animal model via modulating PI3K/Nrf2/HO-1 signaling, leading to a reduction in apoptosis, oxidative damage, and inflammation in the cell [101].

2.11.4. Anti-obesity effect

Obesity, the leading risk factor of cardio-metabolic diseases, is fast reaching epidemic proportions problem worldwide. Oxidative stress may cause and deteriorate obesity-related diseases [102]. The beneficial effects of flavonoids against obesity have been indicated in several studies.

Avila and co-workers [103] indicated the beneficial impact of Res on catecholamine-induced mortality in obese rats. It was found that Res ameliorated lipids and protein oxidation in the aorta and myocardium of the rat through induction of Nrf2/Keap1 antioxidant pathway. Res has a protective impact on an animal t model of obese/asthma [65]. It was indicated that Res reduced fasting blood sugar and serum lipid and ROS levels in obese, asthmatic, and obeseasthmatic rats via stimulating the Keap1/Nrf2 pathway. Rubio-Ruiz et al. [104] studied the Res plus quercetin (QRC) effects on fatty liver in a weanling rat model of metabolic syndrome. Res plus QRC decreased carbonylation and lipid peroxidation and also raised total antioxidant capacity through stimulating the expression of the Nrf2 signaling. Bagul and co-workers [105] indicated that Res improved blood glucose and also decreased insulin sensitivity, triglyceride, TBARS, NO levels, and increased SOD activity by activating the Nrf2 pathway in fructose-fed rats. Res protected against polychlorinated biphenyls (PCBs) induced impairment insulin signaling through activating Nrf2 signaling in adipose tissue [106]. Zagotta and co-workers [107] investigated the impact of Res on the plasminogen activator inhibitor (PAI-1) production in Simpson-Golabi-Behmel syndrome (SGBS) adipocytes and inflammatory human adipose tissue. Res decreased protein and mRNA expression of PAI-1 in SGBS adipocytes by activating Nrf2 signaling in the normal cellular condition through inhibition of the NFκB pathway in response to stressful circumstances. Res ameliorated the hemostasis of glucose and T-lymphocyte subdivision in the HFD model. Res decreased plasma leptin and lipids levels and oxidative markers, and also reduced the body weight in HFD mice by stimulating the PI3K/SIRT1 and Nrf2 signaling [108].

2.11.5. Anti-diabetic effect

Diabetes is a chronic metabolic disorder that is known by a disruption in the synthesis or function of insulin. Diabetes is caused by inflammation, apoptosis, and oxidative stress. Res modulated insulin signaling in adipose tissue, and also the inflammatory cascades in the rat received the high-fructose diet. Diabetes is related to protein glycation and advanced glycation end products (AGEs) [109]. AGE's progress diabetes by producing free radicals [102]. Res decreased the expression of eNOS, mTOR, PI3K, IRS-2, IRS-1, IR, and Akt peroxisome proliferator-activated receptor-gamma (PPARγ), iNOS, TNFα, IL-18, IL-1β, ALT, MDA and also increased Nrf2 and IL-10 in adipose tissue of rats [110].

Cheng and co-workers [111] found that Res regulated glucose uptake and insulin resistance in Hep G2 cells exposed to methylglyoxal. Res stimulated the extracellular signal-regulated kinase (ERK) signaling, leading to Nrf2/HO-1 activation and an increase in glyoxalase expression. Res ameliorated blood glucose level through modulating the Nrf2 pathway in the methylglyoxal exposed to mice pancreas [112]. Pretreatment with Res elevated insulin synthesis via the up-regulation of pancreatic-duodenal homeobox-1 (PDX-1) and PPARγ. Res also declined the negative regulator of insulin expression known as CCAAT/enhancer-binding protein beta (C/EBPbeta). Res stimulated the Nrf2 expression, which leads to a decline in oxidative damage [113]. Res modulated the expression of protein and gene including CAT and GPx in the liver of the STZ-diabetic rat model. Res elevated the activity of p-GPx levels accompanied through a raise in Sirtuin1 and Nrf2 and decreased NFκB gene expression [114]. Res alone or co-administration with rosuvastatin (RSU) ameliorated dysfunction of kidneys evidenced by a reduction in TGF-β1, urinary protein, and serum creatinine in diabetic rats. Res alone or co-administration with RSU ameliorated the oxidant-antioxidant content (raise in CAT, GPx, GSH, and SOD content with a reduction in MDA levels). The Res with RSU modulated Sirt1, FoxO1, the renal expression of TGF-β1, NF-kB/p65, fibronectin, and Nrf2 in the diabetic rats [115]. Res decreased creatinine and glucose plasmatic levels and urinary protein excretion, and ameliorated hypertrophy in kidneys. Res decreased the GSTM expression in diabetic rats. Res declined the proliferation in mesangial cells exposed to high glucose and declined expression of GSTM and Nrf2. The renoprotection of Res is mediated by Nrf2 expression in mesangial cells of rat [116]. Res modulated the levels of TNF-α, IL-1β, IL-6, NO, NF-κB p65 subunit, hydroxyl radical, C-peptide, plasma adiponectin, renal superoxide anion, and creatinine clearance as well as renal activities of AST, ALT, and ALP in STZ-nicotinamide-diabetic rats. Res treatment ameliorated the activities of glyoxalase-I, sorbitol dehydrogenase, and renal aldose reductase, as well as increased levels of serum AGE's in diabetic rats. Additionally, Res normalized the activities of GST, GPx, CAT, and SOD, GR and vitamins C and E, and protein carbonyls levels, hydroperoxides, lipid peroxides, and GSH levels in the kidney of diabetic rat. Res modulated the Nrf2/Keap1 renal expression in the diabetic rats. The findings indicated that the renoprotective effect of Res by ameliorating

oxidative damage in the kidney of diabetic rats [117]. Res ameliorated the renal function through downregulating pro-inflammatory signaling pathway components (TNF-α, IL-6, IL-1β, iNOS, and NF-κB) in STZ-diabetic rats [118].

You and co-workers [119] reported the protective impact of Aza Res–chalcone derivative 6b against cell fibrosis and hypertrophy in H9c2 myocardial cells exposed to high glucose through modulating apoptosis, inflammation and oxidant stress. Aza Res-chalcone derivative 6b ameliorated apoptosis, fibrosis, and hypertrophy in the heart of STZ-diabetic mice. Aza Res–chalcone derivative 6b ameliorated the expression of inflammatory and oxidative indices, without changing blood glucose and body weight through modulating NF-κB and Nrf2 pathway. The data indicated the modulatory effect of Aza Res-chalcone derivative 6b on NF- κB and Nrf2, leading to its protective in diabetic cardiomyopathy models.

In another study regarding the impact of Res on diabetic cardiomyopathy, Wang and co-workers [120] indicated the protective effects of Res against type 1 diabetes in FVB mice through modulating Nrf2 expression. Res had a protective effect vascular endothelium and retinal in diabetic rats by regulating the expression of Nrf2/HO-1 genes [121].

2.11.6. Immunomodulatory effect

Iwasaki et al. [122] indicated that Res has a vital impact on the Nrf2/ARE in human peripheral blood mononuclear cells. Zhang and co-workers [123] showed the protective impact of Res on rheumatoid arthritis fibroblast-like synoviocytes (RA-FLSs) exposed to H2O2 through the Nrf2/Keap1 signaling. Targeting the Nrf2/Keap1 pathway by Res was effective in the treatment of RA. Res exerted the beneficial impact in the osteoarthritis model in rats via ameliorating inflammation. Res suppressed IL-18, IL-1β, IL-6, and TNF-α expression levels, and declined the activity of caspase-3/9 in the osteoarthritis model in rat. Additionally, Res inhibited phosphorylated-(p)-AMP-activated protein kinase (AMPK), sirtuin 1 protein, NF-κB, and iNOS expression in an animal model of osteoarthritis. The findings suggested that Res improved osteoarthritis in experimental animals via suppressing NF-κB and enhancing Nrf-2/HO-1 activation [124]. Res improved idiopathic membranous nephropathy in mice via a decline in ROS generation and apoptosis, and also stimulation of Nrf2/HO1 signaling [125]. Achy-Brou et al. [126] indicated that the inhibitory impact of Res on NO release from stimulated primary peritoneal macrophages (PMs) cells related to the status of the transcription factor Nrf2.

Bigagli et al. [127] indicated the antioxidant and anti-inflammatory impact of Res in the human granulocytes and monocytes induced by phorbol myristate acetate (PMA) and in macrophages RAW264.7 stimulated with LPS. Res inhibited the oxidative damage, and CD11b expression in the human granulocytes and monocytes induced with PMA. Res also suppressed the expression of NO, iNOS, miR-146a, IL-1β, TNFα, COX-2, and prostaglandin E2 (PGE2). Res showed anti-inflammatory impact through activation of Nrf2.

2.11.7. Anti-aging effect

Advancing in age is accompanied by the various diseases in the brain, lung, cardiac, vessels, liver, and renal tissues [128]. Natural antioxidants may be effective against age-related diseases. In this context, Kim and co-workers [129] reported that Res has a protective impact against renal damage in aging C57BL/6 mice. Res ameliorated kidney function and histopathological alterations, and inflammation in old mice through activation Nrf2/HO-1 signaling. Fischer et al. [130] indicated that synthetic Res derivatives stilbenes increased the longevity of Caenorhabditis elegans via decreasing ROS production and accumulation in the presence of sirt-2.1 (sirtuin), skn-1 (Nrf2), and daf-16 (FoxO) in loss mutant strains. Treatment of aged vascular smooth muscle cells (VSMCs) with Res (1 μ M) reversed aging-induced NF-KB. Res also ameliorated mitochondrial ROS generation through activating Nrf2 in aged VSMCs. The inhibitory impact of Res on inflammatory mediators in the aged VSMC secretome indicated its vasoprotective effect in animal models of aging [131].

2.11.8. Reproductive protective effect

Res ameliorated the antioxidant content [CAT, GPX1, GPX4, SOD1, HO1, glutamate-cysteine ligase modifier (GCLM), UDP glucuronosyltransferase family 1 member A1 (UGT1A1) and microsomal glutathione S-transferase 1(MGST1) in the placenta of sows and piglets through Keap1/Nrf2 pathway and Sirt1 [132]. Gurusinghe and co-workers [133] also studied the effect of Res on antiangiogenic factors and placental oxidative stress in HUVECs. Res reduced oxidative stress, activin A, and soluble forms-like tyrosine kinase-1 (sFlt1) in the placenta. Res decreased TNF-α which induced endothelial expression of endothelin-1, E-selectin, ICAM1, and, VCAM1, leading to a decrease in the permeability of endothelial monolayer. Res ameliorated the placental and endothelial dysfunction through the modulation of Nrf2. Res exerted protective effects against oxidative damage caused by di-(2-Ethylhexyl) phthalate (DEHP) in the testes of rats. Res ameliorated total antioxidant capacity (TAC) and GSH reduced levels and elevated MDA levels in the testes of DEHP-treated rats through activating Nrf2/HO-1 signaling [134]. Res ameliorated the testicular tissue apoptosis in the diabetic mice model through Akt-induced activation of Nrf2 through decreasing of p62-dependent Keap1 expression [135]. Res ameliorated prostate damage in the rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) during GD10 to PND21 period through activation of Nrf2 pathway [136]. Table 1 indicates the preclinical studies on the protective impact of Res via activating the Nrf2 signaling.

3. Conclusion

The Nrf2 pathway possesses a critical function in the modulation of inflammatory responses and oxidative stress as well as protein, lipid and carbohydrates synthesis, metabolism, and degradation. Nrf2 regulation is essential to maintain homeostasis of cellular function and inhibit the progression of several pathological conditions. The present review has concentrated on the modulatory impact of Res on the Nrf2 signaling pathways. The Nrf2 pathway activation exerted neuroprotective, cardioprotective, renoprotective, hepatoprotective, anti-diabetic, anti-obesity, anti-tumor, and anti-aging activities. Res also has a protective effect on skin respiratory, infections, immune system diseases. which Res activates the transcriptional activity of Nrf2. Res potentiates the expression of Nrf2 through dissociation of Nrf2-Keap1 binding and increases the translocation of Nrf2 into the nucleus. Res dissociates the bindings between Nrf2-Keap1 through increase the interaction between p62-Nrf2. Res also activates Nrf2/ARE via stimulation p38 MAPK and SIRT1/FOXO1 signaling. Res elevates the Nrf2 expression through suppression of the inhibitory signaling (Fig. 2).

Res modulated MDA, GSH, GPx, GST and SOD levels, ROS production, IL-6, TNF-α, Bax/Bcl-2-caspase-3, and IL-1β, and other inflammatory cytokines and oxidative stress in several tissues (Figs. 3–4). Res modulates cell proliferation and detoxification through activation of Nrf2/ARE signaling (Fig. 5).

In conclusion, it was found that Res modulates the Nrf2 activation by inhibiting Keap1, Nrf2 gene expression, changing the upstream mediators of Nrf2, and potentiating the nuclear translocation of Nrf2. Due to very limited human studies in this field, the present review could not introduce Res as the suitable Nrf2 modulatory agent for improving human diseases. Therefore, more researches are required to indicate the molecular mechanisms of Res protective effects and its impact on the Nrf2 signaling pathway.

Funding

Not applicable

Table 1
Preclinical studies.

Agents	Effect(s), Pathology	In vitro	In vivo	Finding's remarks	Ref
Resveratrol	Neuroprotective, AD		AD mice model	Decreased oxidative stress via increasing Nrf2 content, its nuclear translocation rate, and HO-1 expression	(17)
Resveratrol	Neuroprotective, AD	Human neural stem cells	–	Ameliorated Aβ-induced increase of pro-inflammatory enzymes, reversed the decreased mRNA expression levels of antioxidative genes	(18)
Resveratrol	Neuroprotective, AD	PC12 cells	–	Activation of the PI3K/Akt signaling pathway via stimulation of the Nrf2 pathway	(19)
Resveratrol	Neuroprotective, Dementia	–	A rat model of vascular dementia	Reduced ROS production, lipid peroxidation, protein carbonyls and increased the activity of Mn-SOD via Nrf2/HO-1 signaling pathway	(20)
Resveratrol	Neuroprotective, rotenone-induced PD	–	Rats	Balanced redox system by stimulating the Nrf2 pathway	(21)
Resveratrol	Neuroprotective, Spinocerebellar ataxia type 3	SK-N-SH-MJD78 cells	Drosophila	Increased antioxidant protein content and autophagy protein p62 expression, decreased ROS levels, corrected mitochondrial membrane potential, decreased the expression of mutant ataxin-3 protein and its aggregations via activation of Nrf2 pathway	(22)
Resveratrol	Anti-neuroinflammation	Oligodendroglial cells	–	Modulated intracellular ROS, GSH levels, and GCL activity regulated trophic factors levels via Nrf2/HO-1 pathways	(23)
Resveratrol	Anti-neuroinflammation, Exposure to LPS	Primary astrocyte cultures	–	Inhibited NFκB and p38 MAPK and activated PI3K/Akt-Nrf2 pathway	(24)
Resveratrol	Anti-neuroinflammation	PC12 cells	–	Up-regulated heme oxygenase-1 (HO-1) gene expression via activation of Nrf2	(25)
Resveratrol, Curcumin	Neuroprotective	Astrocytes	–	Inhibited oxidative stress through activation of the Nrf2 pathway	(26)
Resveratrol	Neuroprotective, Fetal alcohol spectrum disorders	Cerebellar granule neurons	–	Scavenging ROS and increase in cell survival through the Nrf2 pathway	(27)
Resveratrol	Neuroprotective, Ischemic and hemorrhagic injury	Rat cortical neurons	–	Increased the activity of SOD, NQO-1, HO-1, and inhibition of neuronal apoptosis via increasing the activation of the Nrf-2 pathway	(29)
Resveratrol	Neuroprotective, Ischemic and hemorrhagic injury	Neural stem cells	–	Ameliorated injury and stimulated proliferation via upregulating the expression of Nrf2, HO-1, and NQO1	(10)
Resveratrol	Neuroprotective, Ischemic and hemorrhagic injury	–	Rats	Reduced oxidized DJ-1 levels and iNOS expression and increased GSH levels and SOD activity; Increased survival through the Nfr2 /PI3K/Akt pathway	(30)
Resveratrol	Neuroprotective, Ischemic injury	–	Rats	Attenuated cerebral edema, infarct area, oxidative stress indices, inflammatory indices through upregulation of Nrf2/HO-1	(31)
Resveratrol	Neuroprotective, Ischemic injury	Rodent astrocyte cultures	–	Maintaining mitochondrial coupling and antioxidant protein expression via Nrf2 pathway	(32)
Resveratrol	Neuroprotective, Ischemic injury	–	Mice	Ameliorating oxidative markers and decreasing caspase-3 protein expression via the Nrf2/HO-1 pathway	(33)
Resveratrol	Neuroprotective, Ischemic injury	–	Rats	Decreasing lipid peroxidase, increasing GSH and SOD and maintaining mitochondrial function via activation of the Nrf-2 pathway	(34)
Resveratrol	Neuroprotective, Hemorrhagic injury	–	Rats	Restored activity and expression of SIRT1 via Nrf2 pathway	(35)
Resveratrol	Neuroprotective, Traumatic brain injuries	–	Rats	Decrease apoptosis and ROS generation via activation of p38/ Nrf2/HO1 pathway	(36)
Resveratrol	Cardiovascular protection, LPS exposure	Adult mouse cardiomyocytes	Endotoxemia mouse model	Protected the heart through promoting the Nrf2 signaling and modulating the expression of antioxidant enzymes, involved in ER calcium regulation through SERCA	(37)
Resveratrol	Cardiovascular protection, LPS exposure	Primary human cardiomyocytes	Mouse model of sepsis	Decreasing pro-inflammatory cytokines and increasing Nrf2 activation	(39)
Resveratrol	Cardiovascular protection, arsenic exposure	–	Rats	Reversed intracellular calcium, glutathione redox ratio, and cAMP deficiency levels via Nrf2-HO-1 pathway	(40)
Resveratrol	Cardiovascular protection, Ischemic injury	–	Rats	Modulated inflammation and oxidative stress through inducing the activation of the Nrf2/ARE pathway	(38)

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Table 1 (*continued*)

Agents	Effect(s), Pathology	In vitro	In vivo	Finding's remarks	Ref
Resveratrol	Cardiovascular protection, Ischemic injury	Adult cardiac stem cells	Rats	Improved cardiac function and environment through increasing the nuclear expression of the Nrf2 and redox effector factor 1 (Ref-1) pathway	(41)
Resveratrol	Cardiovascular protection, Ischemic injury	Stem cells isolated from the Ischemic/ Reperfusion rat model heart	–	Induced expression of cell proliferation marker Ki67 and differentiation of stem cells towards the regeneration of the myocardium through enhancing Nrf2/Ref-1 pathway	(42)
Resveratrol	Vasoprotective, vascular occlusive disease	Cultured vascular smooth muscle cells	Wire-injured femoral artery mouse model	Inhibitory impact on neointimal formation through enhanced activation of the Nrf2/ HO-1 pathway	(43)
Resveratrol	Vasoprotective, High fat diet	Cultured coronary arterial endothelial cells	Endothelial dysfunction mice model	Ameliorated mitochondrial dysfunction and cellular oxidative stress through the upregulation of Nrf2. Restored acetylcholine-induced vasodilation via Nrf2 pathway	(44)
Resveratrol	Vasoprotective, Atherosclerosis	–	Mice	Blocking monocyte adhesion through inhibiting the expression of intercellular adhesion molecule-1 via transcriptional regulation of the FERM-kinase and Nrf2/ARE pathway	(45)
Resveratrol	Respiratory protection, Exposure to cigarette smoke extract	Human primary small airway epithelial and human alveolar epithelial (A549) cells	–	Prevented ROS increased production and increased levels of GSH via activation of Nrf2	(46)
Resveratrol	Respiratory protection	Human bronchial epithelial cells	–	Enhanced antioxidant capacity and decreased apoptosis via activating Nrf2/HO-1 pathway	(47)
Agonism of Resveratrol	Respiratory protection, exposure to paraquat	–	Mice	Increased SIRT1 and GSH expression levels and HO-1, SOD and CAT activity via Nrf2/ARE	(48)
Resveratrol	Respiratory protection, exposure to paraquat	Human bronchial epithelial cells (BEAS-2B)	–	Reversed mitochondrial damage, oxidative stress, inflammatory and profibrogenic factors (TNFα, IL6 and transforming growth factor β1, TGFβ1) and cell death by activating Nrf2 pathway	(49)
Resveratrol	Respiratory protection, Sepsis-induced acute lung injury	–	Rats	Decreased lung injury score, levels of MDA and 8-Hydroxyguanosine (8-OHdG), and caspase-3, increased SOD activity via Nrf2/HO-1 pathway	(29)
Resveratrol	Respiratory protection, Hypoxic pulmonary hypertension	Pulmonary arterial smooth muscle cells	Rats	Alleviated right ventricular systolic pressure and pulmonary arterial remodeling via inhibiting the MAPK/ERK1 and PI3K/ AKT and enhancing Nrf2/Thioredoxin 1 (Nrf-2/Trx-1) pathway	(51)
Resveratrol	Hepatoprotection	Primary hepatocytes	–	Protected from oxidative stress damage through the activation of the Nrf2 pathway	(52)
Resveratrol	Hepatoprotection, exposure to heat stress	–	Quails	Protection through increasing NF-κB and antioxidative enzymes (SOD, CAT, and GPx) activities via enhancing the Nrf2 pathway	(53)
Resveratrol	Hepatoprotection, Exposure to heat stress	–	Tilapia fish	Anti-oxidative, anti-inflammatory and anti-immunotoxicity effects via induction of Nrf2 pathways	(54)
Resveratrol	Hepatoprotection, Exposure to LPS	–	Rats	Ameliorated acute liver injury through activating Nrf2/HO-1 and suppressing NF-κB pathways	(55)
Resveratrol	Hepatoprotection	–	Hepatocytes (HUH7)	Protection via induction of antioxidant enzymes HO-1 and paraoxonase-1 and increasing Nrf2 transactivation	(56)
Resveratrol	Hepatoprotection, Exposure to acrylamide	HepG2 cells	–	Prevented mitochondrial function, cell death, and inflammatory cytokines production, through stimulating the Nrf2/NQO-1 pathway	(57)
Resveratrol	Reno-protection, Acute kidney injury	kidney cells	Rats	Reducing TNFα, IL-1β, and kidney injury molecule (KIM)-1 expression via the Nrf2 signaling pathway; Decreased inflammatory response in kidney cells through activation of Nrf2/HO-1	(58)
Resveratrol	Reno-protection, Exposure to Ochratoxin A	Human embryonic kidney (HEK293) cells	–	Increasing GSH levels and decreasing DNA damage via the Nrf2 pathway	(60)
Resveratrol	Reno-protection, Exposure to nicotine	Renal cells	–	Suppressing pro-oxidant p66shc transcription via activation of Nrf2/HO-1 pathway	(61)
Resveratrol	Reno-protection, Exposure to b-glycerophosphate	Rat vascular smooth muscle cells	–	Protection through reduced mRNA level of fibroblast growth factor-23, elevating mRNA levels of klotho and Nrf2 activity	(62)
Resveratrol	Reno-protection	–	Spontaneously hypertensive rats	Activation of phase II antioxidant enzymes, normalization of angiotensin 1 receptor (AT1R)–G-protein signaling and Na/K-ATPase regulation via activating Nrf2 pathway	(63)

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Table 1 (*continued*)

Agents	Effect(s), Pathology	In vitro	In vivo	Finding's remarks	Ref
Resveratrol	Reno-protection	proximal tubular epithelial cells	Spontaneously hypertensive rats	Reducing oxidative stress and restoring total antioxidant activity by the restoration of the Nrf2 activity	(64)
Resveratrol	Reno-protection	NRK-52E cells	–	Decreasing inflammatory responses, oxidative stress, and apoptosis through up-regulating Nrf2 expression	(65)
Resveratrol	Skin protection	Mouse epidermis, human keratinocytes	–	Increasing the activity of GST enzyme via activating Nrf2 signaling	(66)
Resveratrol	Skin protection	Neonatal normal human epidermal keratinocyte cells	–	Increased cell viability by modulating the ROS production dependent Nrf2 signaling pathway	(67)
Resveratrol	Skin protection	–	Mice model of ultraviolet (UV)-induced skin wrinkles	Prevention of photoaging via stimulating Nrf2-dependent antioxidant enzymes including HO-1 in liver and skin	(68)
Resveratrol	Skin protection, exposure to UVA	Human keratinocytes (HaCaT)	–	Protection against oxidative stress via degrading Keap1 protein and increasing Nrf2 accumulation in the nucleus	(69)
Resveratrol	Skin protection	Normal human keratinocytes	–	Activating the Nrf2 pathway glutamylcysteinyl ligase and glutathione peroxidase-2 (GPx2)	(70)
Resveratrol	Skin protection, exposure to UVA + UVB	Human epidermal keratinocytes	–	Protection via modulating metabolic, inflammation and proliferation through Nrf2 pathway	(71)
Resveratrol	Chemoprotective, busulfan/ cyclophosphamide-induced accelerated ovarian aging	–	Mice	Attenuated oxidative stress level by increasing SOD2 levels, decreased both 4-hydroxynonenal and nitrotyrosine markers via upregulating Nrf2 and SOD2 and activating the SIRT1/FOXO1 pathway	(74)
Resveratrol	Chemoprotective, Exposure to 4-hydroxynonenal	3T3 fibroblasts	–	Anti-apoptotic effects via upregulation of Nrf2 ARE binding activity	(75)
Resveratrol, sitagliptin	Anti-tumor, renal carcinoma	–	Rats	Anti-inflammatory and antioxidant properties via affecting STAT3/NF-κB signaling and Nrf2/HO-1 pathway	(78)
Resveratrol	Anti-tumor, estrogen-induced breast cancer	–	Rats	Indicated a possible role of Nrf2 in controlling estrogen glucuronidation metabolism and homeostasis via hormonal modulatory effects based on NRF2 pathway, decreased the progression of breast cancer through up-regulation of Nrf2/ UGT1A8 signaling	(79)
Resveratrol	Anti-tumor, estrogen-induced breast cancer	–	Female August Copenhagen Irish rats	Protection against oxidative DNA damage via increasing expression of NRF2-regulated antioxidant genes NQO1, SOD3 and OGG1	(80)
Resveratrol	Anti-tumor, exposure to doxorubicin	breast cancer cell (MCF-7)	–	Decreased growth and clonogenic potential through inhibition the inflammatory cytokines (NF-kB, COX-2), autophagic flux (LC3, Beclin-1), redox regulation (Nrf2) and apoptosis (BAX: BCL-2 ratio and Caspase-9).	(81)
Resveratrol	Anti-tumor, estrogen-induced breast cancer	Human breast epithelial cell line (MCF-10A)	–	Prevented cancer in MCF-10A cells through regulation of cap "n" collar (CNC) b-zip transcription factors-mediated Nrf2-dependent pathways	(82)
Resveratrol	Anti-tumor	K562 cells (erythroleukemia type cancer cell)	–	Modulating NQO1 involving the ARE, increase in the phosphorylation of Nrf2	(83)
Resveratrol	Anti-tumor, hepatic carcinoma	–	Rats	Modulation of oxidative stress and reduction of inflammatory cytokines mediated by Nrf2	(84)
Resveratrol	Anti-tumor	HepG2 cells	–	Induced mitochondrial biogenesis via nitric oxide (NO) biosynthesis, guanosine 3¢,5¢-monophosphate (cGMP) synthesis, Nrf2-dependent HO-1 activation, and endogenous carbon monoxide (CO) production	(85)
Resveratrol	Anti-tumor	Human promyelocytic leukemia cells (HL-60)	–	Ameliorated the resistance to adriamycin (a chemotherapy drug) through regulation of the PI3K/Akt/Nrf2 signaling pathway	(86)
Resveratrol	Anti-tumor	pancreatic cancer cells	–	Enhancing the efficacy of gemcitabine in cancer therapy via inhibiting the nutrient-deprivation autophagy factor-1 expression through activating Nrf2 signaling	(87)

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Table 1 (*continued*)

Agents	Effect(s), Pathology	In vitro	In vivo	Finding's remarks	Ref
Resveratrol	Anti-tumor, high ambient temperature (HT)-induced spleen dysplasia	–	Broilers	Inhibited dysplasia through modulating oxidative stress indices (MDA, 8-OHdG, GSH, GPx, SOD and CAT activities) and apoptotic indices (Bax, Bcl-2, caspase-3, and caspase-9) via activation of Nrf2 signaling pathway	(88)
Resveratrol	Anti-tumor, azoxymethane-induced colon tumorigenesis	–	Mice	Enhanced expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1) and glutathione reductase (GR), via activation of Nrf2 signaling	(89)
Resveratrol	Anti-infection, exposure to LPS	Human gingival fibroblasts	–	Reducing the expression of COX-2, MMP-2, MMP-9, and TLR-4, mediated by Nrf2/HO-1 signaling pathway	(90)
Resveratrol	Anti-infection	Helicobacter pylori-infected mucosa	–	Ameliorated oxidative stress and inflammation through activation of the Nrf2/HO-1 pathway	(92)
Resveratrol	Anti-infection	–	Inflamed gingival tissues of rats	Attenuated alveolar bone resorption and antioxidant defenses by Nrf2 pathway	(91)
Resveratrol	Anti-infection, exposure to Streptococcus pneumonia	Lung epithelial cells	–	Reduced oxidative stress via the up-regulation of Nrf2 pathway	(93)
Resveratrol	Anti-infection	–	Septic rat	Modulating PI3K/Nrf2/HO-1	(94)
Resveratrol	Anti-obesity, exposure to Catecholamine	–	Obese rats	Ameliorated oxidative damage in myocardium and aorta through induction of Nrf2/Keap1 pathway	(96)
Resveratrol	Anti-obesity	–	A rat model of obese/asthma	Antioxidative by inducing the activation of the Keap-1/Nrf2 pathway	(58)
Resveratrol, quercetin	Anti-obesity	–	A weanling rat model of metabolic syndrome	Decreased lipid peroxidation and carbonylation, increased total antioxidant capacity and GSH, CAT, SOD, GST, and GR through stimulating the expression of Nrf2 signaling pathway	(97)
Resveratrol	Anti-obesity	–	fructose-fed rats.	Improved insulin sensitivity, blood glucose, triglyceride, uric acid, decreased TBARS and NO levels and increased SOD activity as well as hepatic oxidative stress through activating Nrf2 pathway	(98)
Resveratrol	Anti-obesity, exposure to polychlorinated biphenyls	3T3-L1 adipocytes	C57BL/6 mice	Reversed glucose and insulin tolerance through activating Nrf2 signaling in adipose tissue	(99)
Resveratrol	Anti-obesity	Simpson-Golabi-Behmel syndrome adipocytes, inflammatory human adipose tissue	–	Modulated PAI-1 expression under inflammatory conditions through inhibition of the $NF_{\kappa}B$ pathway, Nrf2 was not involved in this modulation	(100)
Resveratrol	Anti-obesity, High fat diet	–	Obese mice	Activated the Nrf2 signaling pathway-mediated antioxidant and anti-inflammation mechanisms	(101)
Resveratrol	Anti-diabetic, methylglyoxal-induced insulin resistance	–	Hep G2 cells	Activated the extracellular signal-regulated kinase pathway resulted in Nrf2 nuclear translocation and increase of HO-1 and glyoxalase expression levels	(104)
Resveratrol	Anti-diabetic, exposure to methylglyoxal	–	Mice	Ameliorated blood glucose level through modulating the Nrf2 pathway	(105)
Resveratrol	Anti-diabetic, exposure to methylglyoxal	Insulin-secreting beta cells	–	Decreased oxidative stress via activating the expression of Nrf2	(106)
Resveratrol	Anti-diabetic, Exposure to STZ	–	Diabetic rats	Elevated the activity of p-GPx, Sirtuin1 and Nrf2 pathway, Decreased NFκB gene expression	(107)
Resveratrol, Rosuvastatin	Anti-diabetic	–	Diabetic rats	Ameliorated renal dysfunction via modulating expression of TGF-β1, fibronectin, NF-kB/p65, Nrf2, Sirt1 and FoxO1	(108)
Resveratrol	Anti-diabetic, Renal complications	–	Diabetic rats	Inhibited the proliferation of mesangial cells via up-regulation of GSTM and Nrf2 expressions	(109)
Resveratrol	Anti-diabetic, exposure to STZ-nicotinamide, renal complications	–	Diabetic rats	Ameliorating oxidative stress via modulating the renal expression of Nrf2/Keap1	(110)
Resveratrol	Anti-diabetic, Exposure to STZ	–	Diabetic rats	Ameliorated the renal function through normalizing renal expression of pro-inflammatory signaling pathway components (iNOS, NF-κB, Nrf2, IL-1β, IL-6, IL-8, and TNF-α)	(111)
Aza Resveratrol –chalcone derivative Resveratrol	Anti-diabetic, exposure to high glucose	H9c2 myocardial cells	–	Ameliorated the expression of inflammatory cytokines and oxidative through modulating NF-κB and Nrf2 pathway	(112)

(*continued on next page*)

Table 1 (*continued*)

Agents	Effect(s), Pathology	In vitro	In vivo	Finding's remarks	Ref
Resveratrol	Anti-diabetic, Cardiomyopathy	–	Mice	Protective effects against type 1 diabetes through modulating Nrf2 expression	(113)
Resveratrol	Anti-diabetic	–	Diabetic rats	Protecting vascular endothelium and retinal in diabetic rat through modulating the expression of Nrf2/HO-1 genes	(114)
Resveratrol	Immunomodulatory	Jurkat T cells and human peripheral blood mononuclear cells	–	Nrf2 nuclear accumulation and subsequent binding to the ferritin H ARE induced by resveratrol was dependent on activation of AMPKα, but not PI3K/Akt. Protected against oxidative stress-induced cytotoxicity	Iwasaki et al. (115)
Resveratrol	Immunomodulatory, rheumatoid arthritis via H_2O_2 treatment	Fibroblast-like synoviocytes	–	Protective effects through the Nrf2–Keap1 signaling pathway	(116)
Resveratrol	Immunomodulatory, Osteoarthritis	–	Rats	Improved inflammatory damage and protected against osteoarthritis via NF-κB and HO-1/Nrf-2 pathway	(117)
Resveratrol	Immunomodulatory, idiopathic membranous nephropathy	–	Mice	Improved nephropathy through inhibition of ROS production and apoptosis, and also up-regulation of Nrf2/HO1signaling pathway	(118)
Resveratrol	Immunomodulatory	Stimulated primary peritoneal macrophages cells	–	Inhibiting NO release via modulating transcription factor Nrf2	(119)
Resveratrol	Immunomodulatory	Human granulocytes and monocytes stimulated with phorbol myristate acetate, macrophages RAW264.7 stimulated with LPS	–	Anti-inflammatory by inhibition of granulocytes and monocytes activation through activation of Nrf2	(120)
Resveratrol	Anti-aging, renal injury in aging	–	C57BL/6 mice	Improved renal function and inflammation via activation Nrf2-HO-1-NOQ-1 and SIRT1-AMPK-PGC-1α signaling	(122)
Synthetic Resveratrol derivatives: stilbenes	Anti-aging	–	Caenorhabditis elegans	Increased the lifespan through decreasing ROS production and accumulation in the presence of daf-16, skn-1 (Nrf2) and sirt-2.1 (sirtuin)	(123)
Resveratrol	Anti-aging	Aged vascular smooth muscle cells	–	Ameliorated mitochondrial O_2^- production and upregulated the transcriptional activity of Nrf2	(124)
Resveratrol	Reproduction protection	–	Placenta of sows and piglets	Elevated the antioxidant content through Keap1-Nrf2 pathway and Sirt1	(125)
Resveratrol	Reproduction protection, placental oxidative stress	HUVECs	–	Ameliorated the placental and endothelial dysfunction through the modulation of Nrf2	(126)
Resveratrol	Reproduction protection, Exposure to di-(2-ethylhexyl) phthalate in the testes	–	Rats	Ameliorated the decreased levels of total antioxidant capacity (TAC) and GSH and elevated MDA levels through activation of expression of Nrf2/HO-1 pathway	(127)
Resveratrol	Reproduction protection	–	Testicular tissue of diabetic mice model	Ameliorated apoptosis through Akt-mediated Nrf2 activation via p62-dependent Keap1 degradation	(128)
Resveratrol	Reproduction protection, exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin	–	Rats	Ameliorated damage on prostate development through activation of Nrf2 pathway	(129)

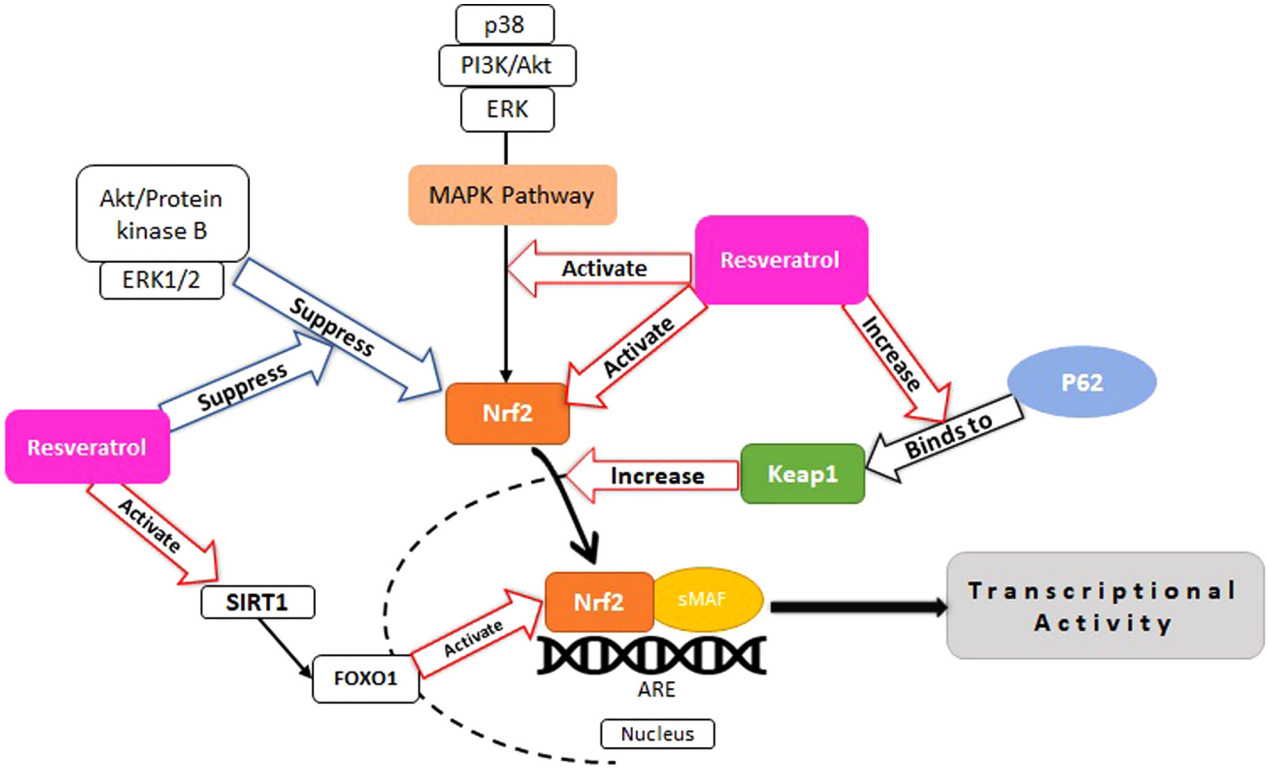

Fig. 2. Mechanisms by which Res activates the transcriptional activity of Nrf2.
As shown, the main mechanism by which Res enhances the Nrf2 expression is the disruption of Nrf2-Keap1 binding and increases the translocation of Nrf2 into the nucleus. Res also dissociates the bindings between Nrf2-Keap1 through increase the interaction between p62-Nrf2. Res also activates Nrf2/ARE through stimulation p38 MAPK and SIRT1/FOXO1 pathways. Res can increase the expression of Nrf2 through suppression of the inhibitory signaling pathway such as Akt/ERK1/2.

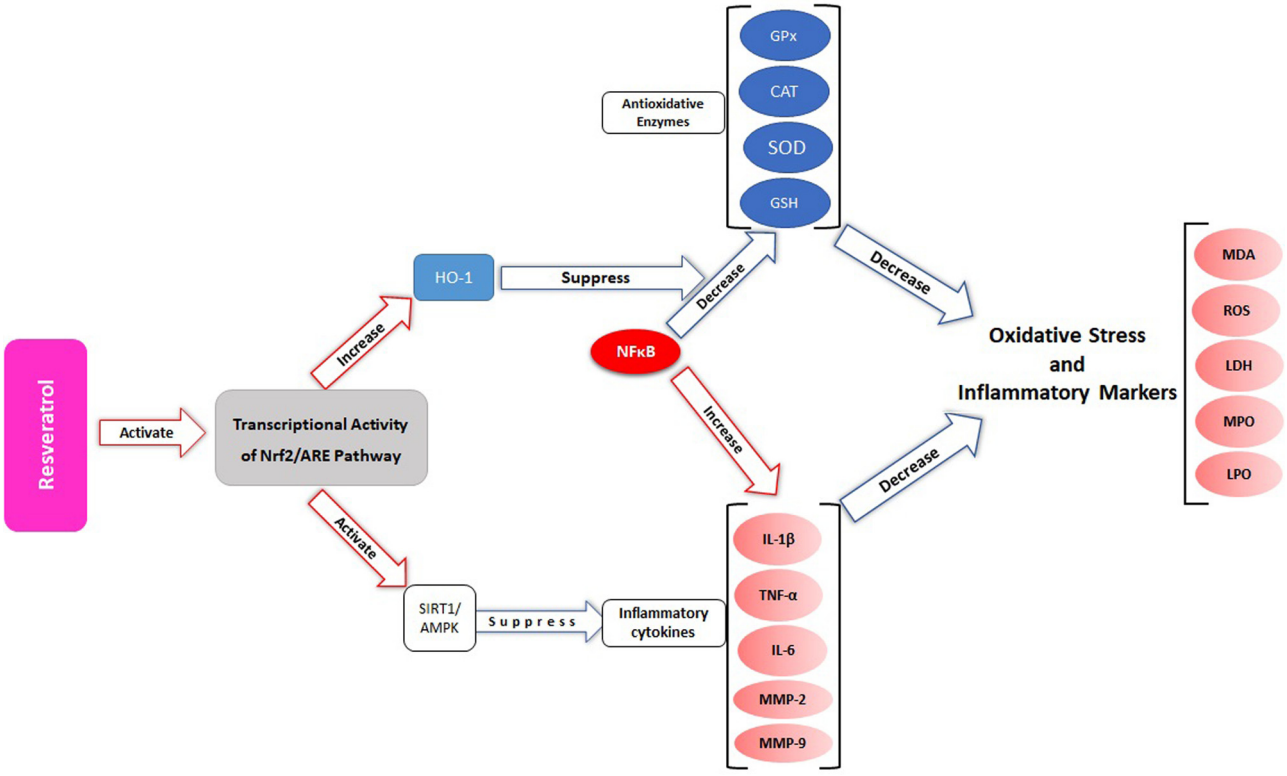

Fig. 3. Res acts as the activator of the Nrf2/ARE pathway and consequent decreases oxidative stress and inflammation. As shown, activation of Nrf2/ARE by Res stimulates the expression of HO-1 and thereby suppresses the inhibitory effect of NF-Kβ on antioxidants and also its stimulatory effect on inflammatory cytokines. Additionally, Nrf2/ARE activation increase the expression of SIRT1/AMPK leading to a decrease in the inflammatory cytokines. Altogether, these events increase the resistance of the cells to oxidative stress.

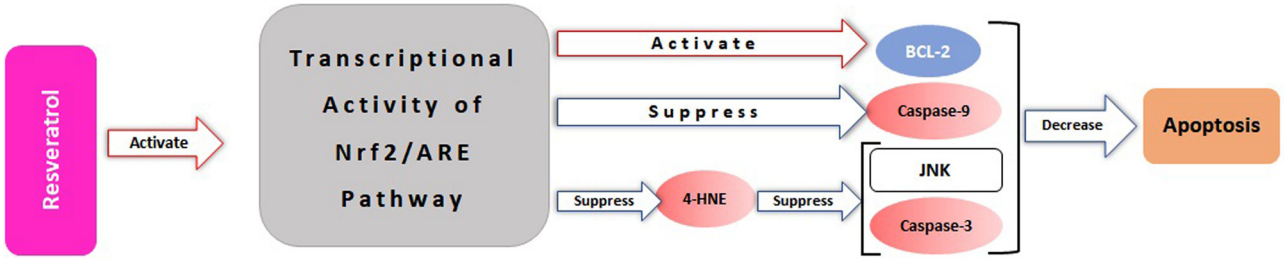

Fig. 4. Res acts as the activator of the Nrf2/ARE pathway and consequent decreases apoptosis.
As shown, activation of Nrf2/ARE by Res stimulates the expression BCL-2 and suppresses JNK-dependent caspase activity and consequent decreases apoptosis.

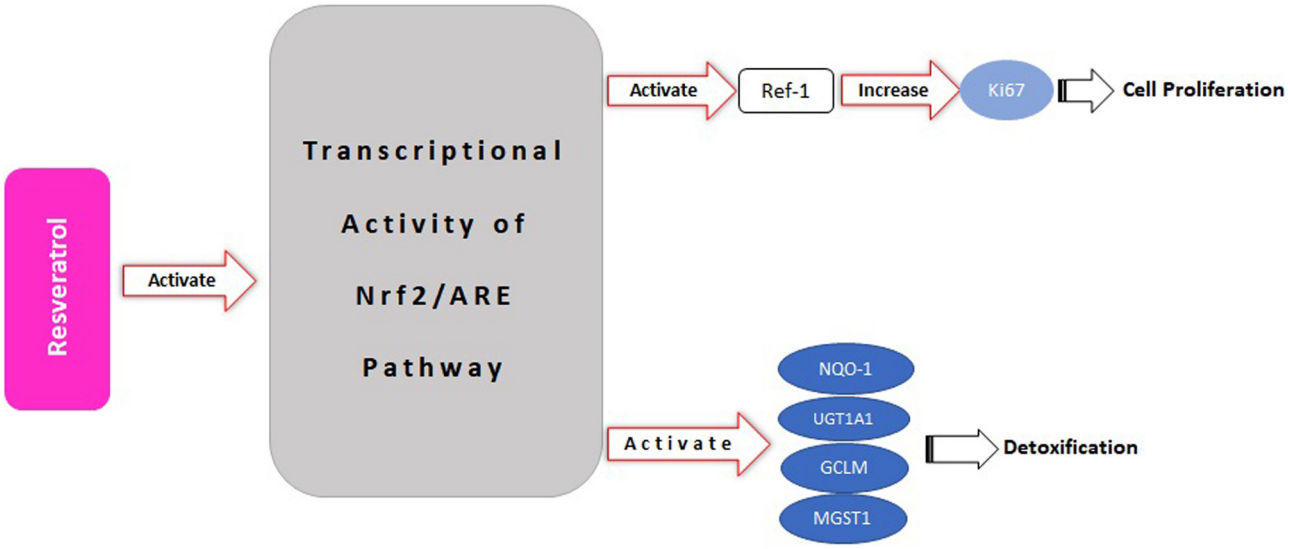

Fig. 5. Res acts as the activator of the Nrf2/ARE pathway and consequently modulates cell proliferation and detoxification.
As shown, activation of Nrf2/ARE/Ref-1 by Res stimulates the expression of NQO-1, UGT1A1, GCLM and MGST1 resulting in detoxification.

Declaration of Competing Interest

The authors state that there is no conflict of interest.

References

[1] Q. Ma, Role of nrf2 in oxidative stress and toxicity, Annu. Rev. Pharmacol. Toxicol. 53 (2013) 401–426.
[2] C. Tonelli, C. Chio II, D.A. Tuveson, Transcriptional regulation by Nrf2, Antioxid. Redox Signal. 29 (17) (2018) 1727–1745.
[3] J. Dong, K.K. Sulik, S.-y Chen, Nrf2-mediated transcriptional induction of antioxidant response in mouse embryos exposed to ethanol in vivo: implications for the prevention of fetal alcohol spectrum disorders, Antioxid. Redox Signal. 10 (12) (2008) 2023–2033.
[4] E. Kansanen, S.M. Kuosmanen, H. Leinonen, A.-L. Levonen, The Keap1-Nrf2 pathway: mechanisms of activation and dysregulation in cancer, Redox Biol. 1 (1) (2013) 45–49.
[5] M. Nakayama, T. Inoue, M. Naito, K. Nakayama, N. Ohara, Attenuation of the phosphatidylinositol 3-kinase/Akt signaling pathway by Porphyromonas gingivalis gingipains RgpA, RgpB, and Kgp, J. Biol. Chem. 290 (8) (2015) 5190–5202.
[6] F. Medina-Bolivar, J. Condori, A.M. Rimando, J. Hubstenberger, K. Shelton, S.F. O'Keefe, et al., Production and secretion of resveratrol in hairy root cultures of peanut, Phytochemistry 68 (14) (2007) 1992–2003.
[7] Z. Wang, Y. Huang, J. Zou, K. Cao, Y. Xu, J.M. Wu, Effects of red wine and wine polyphenol resveratrol on platelet aggregation in vivo and in vitro, Int. J. Mol. Med. 9 (1) (2002) 77–79.
[8] H.I. Rocha-González, M. Ambriz-Tututi, V. Granados-Soto, Resveratrol: a natural compound with pharmacological potential in neurodegenerative diseases, CNS Neurosci. Ther. 14 (3) (2008) 234–247.
[9] A.M. Rimando, W. Kalt, J.B. Magee, J. Dewey, J.R. Ballington, Resveratrol, pterostilbene, and piceatannol in vaccinium berries, J Agric. Food Chem. 52 (15) (2004) 4713–4719.
[10] C.A. de la Lastra, I. Villegas, Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications, Biochem. Soc. Trans. 35 (Pt 5) (2007) 1156–1160.
[11] D. de Sá Coutinho, M.T. Pacheco, R.L. Frozza, A. Bernardi, Anti-inflammatory effects of resveratrol: mechanistic insights, Int. J. Mol. Sci. 19 (6) (2018) 1812.
[12] E.M. Varoni, A.F. Lo Faro, J. Sharifi-Rad, M. Iriti, Anticancer molecular mechanisms of resveratrol, Front. Nutr. 3 (2016) 8.
[13] W.-M. Chen, L.-H. Shaw, P.-J. Chang, S.-Y. Tung, T.-S. Chang, C.-H. Shen, et al., Hepatoprotective effect of resveratrol against ethanol-induced oxidative stress through induction of superoxide dismutase in vivo and in vitro, Exp. Ther. Med. 11 (4) (2016) 1231–1238.
[14] K. Magyar, R. Halmosi, A. Palfi, G. Feher, L. Czopf, A. Fulop, et al., Cardioprotection by resveratrol: a human clinical trial in patients with stable coronary artery disease, Clin. Hemorheol. Microcirc. 50 (3) (2012) 179–187.
[15] O.R. Oyenihi, A.B. Oyenihi, A.A. Adeyanju, O.O. Oguntibeju, Antidiabetic effects of resveratrol: the way forward in its clinical utility, J. Diabetes Res. 2016 (2016) 9737483-.
[16] L.E. Simental-Mendia, F. Guerrero-Romero, Effect of resveratrol supplementation on lipid profile in subjects with dyslipidemia: a randomized double-blind, placebo-controlled trial, Nutrition 58 (2019) 7–10.
[17] D. Kong, Y. Yan, X.-Y. He, H. Yang, B. Liang, J. Wang, et al., Effects of resveratrol on the mechanisms of antioxidants and estrogen in Alzheimer's disease, Biomed Res. Int. 2019 (2019).
[18] M.-C. Chiang, C.J. Nicol, Y.-C. Cheng, Resveratrol activation of AMPK-dependent pathways is neuroprotective in human neural stem cells against amyloid-beta-induced inflammation and oxidative stress, Neurochem. Int. 115 (2018) 1–10.
[19] Y. Hui, T. Chengyong, L. Cheng, H. Haixia, Z. Yuanda, Y. Weihua, Resveratrol attenuates the cytotoxicity induced by amyloid-β 1–42 in PC12 cells by upregulating heme oxygenase-1 via the PI3K/Akt/Nrf2 pathway, Neurochem. Res. 43 (2) (2018) 297–305.
[20] A. Yadav, A. Sunkaria, N. Singhal, R. Sandhir, Resveratrol loaded solid lipid nanoparticles attenuate mitochondrial oxidative stress in vascular dementia by activating Nrf2/HO-1 pathway, Neurochem. Int. 112 (2018) 239–254.
[21] H.H. Gaballah, S.S. Zakaria, M.M. Elbatsh, N.M. Tahoon, Modulatory effects of resveratrol on endoplasmic reticulum stress-associated apoptosis and oxido-inflammatory markers in a rat model of rotenone-induced Parkinson's disease, Chem. Biol. Interact. 251 (2016) 10–16.
[22] Y.-L. Wu, J.-C. Chang, W.-Y. Lin, C.-C. Li, M. Hsieh, H.-W. Chen, et al., Caffeic acid and resveratrol ameliorate cellular damage in cell and Drosophila models of spinocerebellar ataxia type 3 through upregulation of Nrf2 pathway, Free Radic. Biol. Med. 115 (2018) 309–317.
[23] P.M. Rosa, L.A.M. Martins, D.O. Souza, A. Quincozes-Santos, Glioprotective effect

of resveratrol: an emerging therapeutic role for oligodendroglial cells, Mol. Neurobiol. 55 (4) (2018) 2967–2978.
[24] L.D. Bobermin, R.H.A. Roppa, A. Quincozes-Santos, Adenosine receptors as a new target for resveratrol-mediated glioprotection, Biochim Biophys Acta Mol. Basis Dis. 1865 (3) (2019) 634–647.
[25] C.-Y. Chen, J.-H. Jang, M.-H. Li, Y.-J. Surh, Resveratrol upregulates heme oxygenase-1 expression via activation of NF-E2-related factor 2 in PC12 cells, Biochem. Biophys. Res. Commun. 331 (4) (2005) 993–1000.
[26] A. Daverey, S.K. Agrawal, Pre and post treatment with curcumin and resveratrol protects astrocytes after oxidative stress, Brain Reserch 1692 (2018) 45–55.
[27] A. Kumar, C.K. Singh, H.A. Lavoie, D.J. Dipette, U.S. Singh, Resveratrol restores Nrf2 level and prevents ethanol-induced toxic effects in the cerebellum of a rodent model of fetal alcohol spectrum disorders, Mol. Pharmacol. 80 (3) (2011) 446–457.
[28] R. Shirley, E.N.J. Ord, L.M. Work, Oxidative stress and the use of antioxidants in stroke, Antioxidants Basel (Basel) 3 (3) (2014) 472–501.
[29] J. Yang, J. Huang, C. Shen, W. Cheng, P. Yu, L. Wang, et al., Resveratrol treatment in different time-attenuated neuronal apoptosis after oxygen and glucose Deprivation/Reoxygenation via enhancing the activation of Nrf-2 signaling pathway in vitro, Cell Transplant. 27 (12) (2018) 1789–1797.
[30] G.A. Abdel-Aleem, E.F. Khaleel, D.G. Mostafa, L.K. Elberier, Neuroprotective effect of resveratrol against brain ischemia reperfusion injury in rats entails reduction of DJ-1 protein expression and activation of PI3K/Akt/GSK3b survival pathway, Arch. Physiol. Biochem. 122 (4) (2016) 200–213.
[31] Y. Gao, R. Fu, J. Wang, X. Yang, L. Wen, J. Feng, Resveratrol mitigates the oxidative stress mediated by hypoxic-ischemic brain injury in neonatal rats via Nrf2/HO-1 pathway, Pharm. Biol. 56 (1) (2018) 440–449.
[32] S.V. Narayanan, K.R. Dave, I. Saul, M.A. Perez-Pinzon, Resveratrol preconditioning protects against cerebral ischemic injury via nuclear erythroid 2-related factor 2, Stroke. 46 (6) (2015) 1626–1632.
[33] J. Ren, C. Fan, N. Chen, J. Huang, Q. Yang, Resveratrol pretreatment attenuates cerebral ischemic injury by upregulating expression of transcription factor Nrf2 and HO-1 in rats, Neurochem. Res. 36 (12) (2011) 2352.
[34] V. Kesherwani, F. Atif, S. Yousuf, S.K. Agrawal, Resveratrol protects spinal cord dorsal column from hypoxic injury by activating Nrf-2, Neuroscience. 241 (2013) 80–88.
[35] B. Jian, S. Yang, I.H. Chaudry, R. Raju, Resveratrol restores sirtuin 1 (SIRT1) activity and pyruvate dehydrogenase kinase 1 (PDK1) expression after hemorrhagic injury in a rat model, Mol. Med. 20 (1) (2014) 10.
[36] P. Kaur, S. Sharma, Recent advances in pathophysiology of traumatic brain injury, Curr. Neuropharmacol. 16 (8) (2018) 1224–1238.
[37] M.V. Russo, D.B. McGavern, Inflammatory neuroprotection following traumatic brain injury, Science. 353 (6301) (2016) 783–785.
[38] C. Cornelius, R. Crupi, V. Calabrese, A. Graziano, P. Milone, G. Pennisi, Z. Radak, E.J. Calabrese, S. Cuzzocrea, Traumatic brain injury: oxidative stress and neuroprotection, Antioxid. Redox Signal. 19 (8) (2013) 836–853.
[39] R.M. Guerriero, C.C. Giza, A. Rotenberg, Glutamate and GABA imbalance following traumatic brain injury, Curr. Neurol. Neurosci. Rep. 15 (5) (2015) 27.
[40] L. Zhang, H. Wang, Y. Zhou, Y. Zhu, M. Fei, Fisetin alleviates oxidative stress after traumatic brain injury via the Nrf2-ARE pathway, Neurochem. Int. 118 (2018) 304–313.
[41] W. Dai, H. Wang, J. Fang, Y. Zhu, J. Zhou, X. Wang, Y. Zhou, M. Zhou, Curcumin provides neuroprotection in model of traumatic brain injury via the Nrf2-ARE signaling pathway, Brain Res. Bull. 140 (2018) 65–71.
[42] J. Fang, H. Wang, J. Zhou, W. Dai, Y. Zhu, Y. Zhou, X. Wang, M. Zhou, Baicalin provides neuroprotection in traumatic brain injury mice model through Akt/Nrf2 pathway, Drug Des. Devel. Ther. 10 (12) (2018) 2497–2508.
[43] Z. Shi, W. Qiu, G. Xiao, J. Cheng, N. Zhang, Resveratrol attenuates cognitive deficits of traumatic brain injury by activating p38 signaling in the brain, Med. Sci, Monit. 24 (2018) 1097.
[44] T. Bai, X. Hu, Y. Zheng, S. Wang, J. Kong, L. Cai, Resveratrol protects against lipopolysaccharide-induced cardiac dysfunction by enhancing SERCA2a activity through promoting the phospholamban oligomerization, Am. J. Physiol. Heart Circ. Physiol. 311 (4) (2016) H1051–H1062.
[45] L. Cheng, Z. Jin, R. Zhao, K. Ren, C. Deng, S. Yu, Resveratrol attenuates inflammation and oxidative stress induced by myocardial ischemia-reperfusion injury: role of Nrf2/ARE pathway, Int. J. Clin. Exp. Med. 8 (7) (2015) 10420–10428.
[46] E. Hao, F. Lang, Y. Chen, H. Zhang, X. Cong, X. Shen, et al., Resveratrol alleviates endotoxin-induced myocardial toxicity via the Nrf2 transcription factor, PLoS One 8 (7) (2013) e69452.
[47] W. Zhang, C. Guo, R. Gao, M. Ge, Y. Zhu, Z. Zhang, The protective role of resveratrol against arsenic trioxide-induced cardiotoxicity, Evid. Based Complement. Altern. Med. 2013 (2013).
[48] N. Gurusamy, D. Ray, I. Lekli, D.K. Das, Red wine antioxidant resveratrol-modified cardiac stem cells regenerate infarcted myocardium, J. Cell. Mol. Med. 14 (9) (2010) 2235–2239.
[49] N. Gorbunov, G. Petrovski, N. Gurusamy, D. Ray, D.H. Kim, D.K. Das, Regeneration of infarcted myocardium with resveratrol-modified cardiac stem cells, J. Cell. Mol. Med. 16 (1) (2012) 174–184.
[50] J.W. Kim, S.C. Lim, M.Y. Lee, J.W. Lee, W.K. Oh, S.K. Kim, et al., Inhibition of neointimal formation by trans-resveratrol: role of phosphatidyl inositol 3-kinase-dependent Nrf2 activation in heme oxygenase-1 induction, Mol. Nutr. Food Res. 54 (10) (2010) 1497–1505.
[51] Z. Ungvari, Z. Bagi, A. Feher, F.A. Recchia, W.E. Sonntag, K. Pearson, et al., Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2, Am. J. Physiol.Heart Circ. Physiol. 299 (1) (2010) H18–H24.
[52] Y. Seo, J. Park, W. Choi, D. Ju Son, Y. Sung Kim, M.-K. Kim, et al., Antiatherogenic effect of resveratrol attributed to decreased expression of ICAM-1 (Intercellular adhesion Molecule-1) mechanistic link from focal adhesion to monocyte adhesion, Arterioscler. Thromb. Vasc. Biol. 39 (4) (2019) 675–684.
[53] A. Kode, S. Rajendrasozhan, S. Caito, S.-R. Yang, I.L. Megson, I. Rahman, Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells, Am. J. Physiol. Lung Cell. Mol. Physiol. 294 (3) (2008) L478–L488.
[54] H. Zhang, A. Shih, A. Rinna, H.J. Forman, Exacerbation of tobacco smoke mediated apoptosis by resveratrol: an unexpected consequence of its antioxidant action, Int. J. Biochem. Cell Biol. 43 (7) (2011) 1059–1064.
[55] S. Li, G. Zhao, L. Chen, Y. Ding, J. Lian, G. Hong, et al., Resveratrol protects mice from paraquat-induced lung injury: the important role of SIRT1 and NRF2 antioxidant pathways, Mol. Med. Rep. 13 (2) (2016) 1833–1838.
[56] X. He, L. Wang, G. Szklarz, Y. Bi, Q. Ma, Resveratrol inhibits paraquat-induced oxidative stress and fibrogenic response by activating the nuclear factor erythroid 2-related factor 2 pathway, J. Pharmacol. Exp. Ther. 342 (1) (2012) 81–90.
[57] W.-W. Dong, Y.-J. Liu, Z. Lv, Y.-F. Mao, Y.-W. Wang, X.-Y. Zhu, et al., Lung endothelial barrier protection by resveratrol involves inhibition of HMGB1 release and HMGB1-induced mitochondrial oxidative damage via an Nrf2-dependent mechanism, Free Radic. Biol. Med. 88 (2015) 404–416.
[58] D. Xu, Y. Li, B. Zhang, Y. Wang, Y. Liu, Y. Luo, et al., Resveratrol alleviate hypoxic pulmonary hypertension via anti-inflammation and anti-oxidant pathways in rats, Int. J. Med. Sci. 13 (12) (2016) 942.
[59] J.A. Rubiolo, G. Mithieux, F.V. Vega, Resveratrol protects primary rat hepatocytes against oxidative stress damage:: activation of the Nrf2 transcription factor and augmented activities of antioxidant enzymes, Eur. J. Pharmacol. 591 (1-3) (2008) 66–72.
[60] K. Sahin, C. Orhan, F. Akdemir, M. Tuzcu, C. Iben, N. Sahin, Resveratrol protects quail hepatocytes against heat stress: modulation of the Nrf2 transcription factor and heat shock proteins, J. Anim. Physiol. Anim. Nutr. (Berl) 96 (1) (2012) 66–74.
[61] R. Jia, Y. Li, L. Cao, J. Du, T. Zheng, H. Qian, et al., Antioxidative, anti-inflammatory and hepatoprotective effects of resveratrol on oxidative stress-induced liver damage in tilapia (Oreochromis niloticus), Comp. Biochem. Physiol. Part C Toxicol. Pharmacol. 215 (2019) 56–66.
[62] J.Y. Nan, P.Y. Lin, Z.Y. Ping, C.X. Fei, Z. You, C.C. Li, et al., Comparison of the hepatoprotective effects of the three main stilbenes from mulberry twigs, J. Agric. Food Chem. (2019).
[63] A.E. Wagner, C. Boesch-Saadatmandi, D. Breckwoldt, C. Schrader, C. Schmelzer, F. Döring, et al., Ascorbic acid partly antagonizes resveratrol mediated heme oxygenase-1 but not paraoxonase-1 induction in cultured hepatocytes-role of the redox-regulated transcription factor Nrf2, BMC Complement. Altern. Med. 11 (1) (2011) 1.
[64] X. Tan, L. Li, J. Wang, B. Zhao, J. Pan, L. Wang, et al., Resveratrol prevents acrylamide-induced mitochondrial dysfunction and inflammatory responses via targeting circadian regulator Bmal1 and Cry1 in hepatocytes, J. Agric. Food Chem. 67 (31) (2019) 8510–8519.
[65] H.H. Tsou, W.C. Hsu, J.L. Fuh, S.P. Chen, T.Y. Liu, H.T. Wang, Alterations in acrolein metabolism contribute to alzheimer's disease, J. Alzheimer Dis. 61 (2) (2018) 571–580.
[66] E.H. Bae, S.Y. Joo, S.K. Ma, J. Lee, S.W. Kim, Resveratrol attenuates 4-hydroxy-2-hexenal-induced oxidative stress in mouse cortical collecting duct cells, Korean J. Physiol. Pharmacol. 20 (3) (2016) 229–236.
[67] S. Raghubeer, S. Nagiah, A. Phulukdaree, A. Chuturgoon, The phytoalexin resveratrol ameliorates ochratoxin A toxicity in human embryonic kidney (HEK293) cells, J. Cell. Biochem. 116 (12) (2015) 2947–2955.
[68] I. Arany, S. Hall, A. Faisal, M. Dixit, Nicotine exposure augments renal toxicity of 5-aza-cytidine through p66shc: prevention by resveratrol, Anticancer Res. 37 (8) (2017) 4075–4079.
[69] P. Zhang, Y. Li, Y. Du, G. Li, L. Wang, F. Zhou, Resveratrol ameliorated vascular calcification by regulating Sirt-1 and Nrf2, editors, Transplant. Proc. (2016) Elsevier.
[70] A.A. Javkhedkar, A.A. Banday, Antioxidant resveratrol restores renal sodium transport regulation in SHR, Physiol. Rep. 3 (11) (2015) e12618.
[71] A.A. Javkhedkar, Y. Quiroz, B. Rodriguez-Iturbe, N.D. Vaziri, M.F. Lokhandwala, A.A. Banday, Resveratrol restored Nrf2 function, reduced renal inflammation, and mitigated hypertension in spontaneously hypertensive rats, Am. J. Physiol.Regul. Integr. Comp.Physiology. 308 (10) (2015) R840–R846.
[72] J. Li, L. Li, S. Wang, C. Zhang, L. Zheng, Y. Jia, et al., Resveratrol alleviates inflammatory responses and oxidative stress in rat kidney ischemia-reperfusion injury and H2O2-induced NRK-52E cells via the Nrf2/TLR4/NF-κB pathway, Cell. Physiol. Biochem. 45 (4) (2018) 1677–1689.
[73] V. Krajka-Kuźniak, H. Szaefer, T. Stefański, S. Sobiak, M. Cichocki, W. Baer-Dubowska, The effect of resveratrol and its methylthio-derivatives on the Nrf2-ARE pathway in mouse epidermis and HaCaT keratinocytes, Cell. Mol. Biol. Lett. 19 (3) (2014) 500.
[74] A. Plauth, A. Geikowski, S. Cichon, S.J. Wowro, L. Liedgens, M. Rousseau, et al., Hormetic shifting of redox environment by pro-oxidative resveratrol protects cells against stress, Free Radic. Biol. Med. 99 (2016) 608–622.
[75] J. Kim, J. Oh, J.N. Averilla, H.J. Kim, J.S. Kim, J.S. Kim, Grape peel extract and resveratrol inhibit wrinkle formation in mice model through activation of Nrf2/HO-1 signaling pathway, J. Food Sci. (2019).
[76] Y. Liu, F. Chan, H. Sun, J. Yan, D. Fan, D. Zhao, et al., Resveratrol protects human keratinocytes HaCaT cells from UVA-induced oxidative stress damage by down-regulating Keap1 expression, Eur. J. Pharmacol. 650 (1) (2011) 130–137.
[77] J. Soeur, J. Eilstein, G. Lereaux, C. Jones, L. Marrot, Medicine. Skin resistance to

oxidative stress induced by resveratrol: from Nrf2 activation to GSH biosynthesis, Free Radic. Biol. Med. 78 (2015) 213–223.
[78] S. Pastore, D. Lulli, A. Pascarella, R. Maurelli, E. Dellambra, A. Potapovich, et al., Resveratrol enhances solar UV-induced responses in normal human epidermal keratinocytes, Photochem. Photobiol. 88 (6) (2012) 1522–1530.
[79] L.M. Nelson, Primary ovarian insufficiency, N. Engl. J. Med. 360 (6) (2009) 606–614.
[80] A.W. Loren, P.B. Mangu, L.N. Beck, L. Brennan, A.J. Magdalinski, A.H. Partridge, et al., Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update, J. Clin. Oncol. 31 (19) (2013) 2500.
[81] M. Wu, L. Ma, L. Xue, W. Ye, Z. Lu, X. Li, et al., Resveratrol alleviates chemotherapy-induced oogonial stem cell apoptosis and ovarian aging in mice, Aging (Albany NY). 11 (3) (2019) 1030.
[82] O. Kutuk, G. Poli, H. Basaga, Resveratrol protects against 4-hydroxynonenal-induced apoptosis by blocking JNK and c-JUN/AP-1 signaling, Toxicol. Sci. 90 (1) (2005) 120–132.
[83] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.
[84] K.R. Martin, Targeting apoptosis with dietary bioactive agents, Exp. Biol. Med. 231 (2) (2006) 117–129.
[85] A.M. Kabel, A. Atef, R.S. Estfanous, Ameliorative potential of sitagliptin and/or resveratrol on experimentally-induced clear cell renal cell carcinoma, Biomed. Pharmacother. 97 (2018) 667–674.
[86] X. Zhou, Y. Zhao, J. Wang, X. Wang, C. Chen, D. Yin, et al., Resveratrol represses estrogen-induced mammary carcinogenesis through NRF2-UGT1A8-estrogen metabolic axis activation, Biochem. Pharmacol. 155 (2018) 252–263.
[87] B. Singh, R. Shoulson, A. Chatterjee, A. Ronghe, N.K. Bhat, D.C. Dim, et al., Resveratrol inhibits estrogen-induced breast carcinogenesis through induction of NRF2-mediated protective pathways, Carcinogenesis. 35 (8) (2014) 1872–1880.
[88] G. Rai, S. Mishra, S. Suman, Y. Shukla, Resveratrol improves the anticancer effects of doxorubicin in vitro and in vivo models: a mechanistic insight, Phytomedicine. 23 (3) (2016) 233–242.
[89] A. Chatterjee, A. Ronghe, B. Singh, N.K. Bhat, J. Chen, H.K. Bhat, Natural antioxidants exhibit chemopreventive characteristics through the regulation of CNC b-Zip transcription factors in estrogen-induced breast carcinogenesis, J. Biochem. Mol. Toxicol. 28 (12) (2014) 529–538.
[90] T.-c Hsieh, X. Lu, Z. Wang, J.M. Wu, Induction of quinone reductase NQO1 by resveratrol in human K562 cells involves the antioxidant response element ARE and is accompanied by nuclear translocation of transcription factor Nrf2, Med. Chem. (Los Angeles) 2 (3) (2006) 275–285.
[91] A. Bishayee, K.F. Barnes, D. Bhatia, A.S. Darvesh, R.T.J.C. Carroll, Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. 3 (6) (2010) 753–763.
[92] S.-K. Kim, Y. Joe, M. Zheng, S.-K. Kim, J.-K. Yu, G.J. Cho, et al., Resveratrol induces hepatic mitochondrial biogenesis through the sequential activation of nitric oxide and carbon monoxide production, Antioxid. Redox Signal. 20 (16) (2014) 2589–2605.
[93] Y. Li, Y. Guo, Z. Feng, R. Bergan, B. Li, Y. Qin, et al., Involvement of the PI3K/Akt/Nrf2 signaling pathway in resveratrol-mediated reversal of drug resistance in HL-60/ADR cells, Nutr. Cancer 71 (6) (2019) 1007–1018.
[94] L. Cheng, B. Yan, K. Chen, Z. Jiang, C. Zhou, J. Cao, et al., Resveratrol-induced downregulation of NAF-1 enhances the sensitivity of pancreatic cancer cells to gemcitabine via the ROS/Nrf2 signaling pathways, Oxid. Med. Cell. Longev. 2018 (2018).
[95] C. Zhang, K. Chen, X. Zhao, Z. Geng, Protective effects of resveratrol against high ambient temperature-induced spleen dysplasia in broilers through modulating splenic redox status and apoptosis, J. Sci. Food Agric. 98 (14) (2018) 5409–5417.
[96] Y.-S. Chiou, M.-L. Tsai, K. Nagabhushanam, Y.-J. Wang, C.-H. Wu, C.-T. Ho, et al., Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway, J. Agric. Food Chem. 59 (6) (2011) 2725–2733.
[97] G. Bhattarai, S.B. Poudel, S.-H. Kook, J.-C. Lee, Resveratrol prevents alveolar bone loss in an experimental rat model of periodontitis, Acta Biomater. 29 (2016) 398–408.
[98] N. Tamaki, R.C. Orihuela-Campos, Y. Inagaki, M. Fukui, T. Nagata, H.-O. Ito, Resveratrol improves oxidative stress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defense pathways in a rat periodontitis model, Free Radic. Biol. Med. 75 (2014) 222–229.
[99] X. Zhang, A. Jiang, B. Qi, Z. Ma, Y. Xiong, J. Dou, et al., Resveratrol protects against helicobacter pylori-associated gastritis by combating oxidative stress, Int. J. Mol. Sci. 16 (11) (2015) 27757–27769.
[100] J. Zahlten, Y.-J. Kim, J.-M. Doehn, T. Pribyl, A.C. Hocke, P. García, et al., Streptococcus pneumoniae–induced oxidative stress in lung epithelial cells depends on pneumococcal autolysis and is reversible by resveratrol, J. Infect. Dis. 211 (11) (2014) 1822–1830.
[101] Y. Wang, X. Wang, L. Zhang, R. Zhang, Alleviation of acute lung injury in rats with sepsis by resveratrol via the phosphatidylinositol 3-kinase/nuclear factor-erythroid 2 related factor 2/heme oxygenase-1 (PI3K/Nrf2/HO-1) pathway, Med. Sci. Monit. 24 (2018) 3604.
[102] H.K. Vincent, A.G. Taylor, Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans, Int. J. Obes. 30 (3) (2006) 400.
[103] P.R. Avila, S.O. Marques, T.F. Luciano, M.F. Vitto, J. Engelmann, D.R. Souza, et al., Resveratrol and fish oil reduce catecholamine-induced mortality in obese rats: role of oxidative stress in the myocardium and aorta, Br. J. Nutr. 110 (9) (2013) 1580–1590.
[104] M.E. Rubio-Ruiz, V. Guarner-Lans, A. Cano-Martínez, E. Díaz-Díaz, L. Manzano-Pech, A. Gamas-Magaña, et al., Resveratrol and quercetin administration improves antioxidant DEFENSES and reduces fatty liver in metabolic syndrome rats, Molecules. 24 (7) (2019) 1297.
[105] P.K. Bagul, H. Middela, S. Matapally, R. Padiya, T. Bastia, K. Madhusudana, et al., Attenuation of insulin resistance, metabolic syndrome and hepatic oxidative stress by resveratrol in fructose-fed rats, Pharmacol. Res. 66 (3) (2012) 260–268.
[106] N.A. Baker, V. English, M. Sunkara, A.J. Morris, K.J. Pearson, L.A. Cassis, Resveratrol protects against polychlorinated biphenyl-mediated impairment of glucose homeostasis in adipocytes, J. Nutr. Biochem. 24 (12) (2013) 2168–2174.
[107] I. Zagotta, E.Y. Dimova, J.-B. Funcke, M. Wabitsch, T. Kietzmann, P. Fischer-Posovszky, Resveratrol suppresses PAI-1 gene expression in a human in vitro model of inflamed adipose tissue, Oxid. Med. Cell. Longev. 2013 (2013).
[108] B. Wang, J. Sun, L. Li, J. Zheng, Y. Shi, G. Le, Regulatory effects of resveratrol on glucose metabolism and T-lymphocyte subsets in the development of high-fat diet-induced obesity in C57BL/6 mice, Food Funct. 5 (7) (2014) 1452–1463.
[109] V.P. Singh, A. Bali, N. Singh, A.S. Jaggi, Advanced glycation end products and diabetic complications, Korean J. Physiol. Pharmacol. 18 (1) (2014) 1–14.
[110] M.B. Pektas, H.B. Koca, G. Sadi, F. Akar, Dietary fructose activates insulin signaling and inflammation in adipose tissue: modulatory role of resveratrol, Biomed Res. Int. 2016 (2016).
[111] A.-S. Cheng, Y.-H. Cheng, C.-H. Chiou, T.-L. Chang, Resveratrol upregulates Nrf2 expression to attenuate methylglyoxal-induced insulin resistance in Hep G2 cells, J. Agric. Food Chem. 60 (36) (2012) 9180–9187.
[112] R. Gregory, H. Cheng, H.A. Rupp, D.R. Sengelaub, J.R. Heiman, Oxytocin increases VTA activation to infant and sexual stimuli in nulliparous and postpartum women, Horm. Behav. 69 (2015) 82–88.
[113] A.-S. Cheng, Y.-H. Cheng, T.-L. Chang, Resveratrol protects RINm5F pancreatic cells from methylglyoxal-induced apoptosis, J. Funct. Foods 5 (4) (2013) 1774–1783.
[114] G. Sadi, D. Bozan, H.B. Yildiz, Redox regulation of antioxidant enzymes: post-translational modulation of catalase and glutathione peroxidase activity by resveratrol in diabetic rat liver, Mol. Cell. Biochem. 393 (1-2) (2014) 111–122.
[115] M.M. Hussein, M.K. Mahfouz, Effect of resveratrol and rosuvastatin on experimental diabetic nephropathy in rats, Biomed. Pharmacother. 82 (2016) 685–692.
[116] B. Jiang, L. Guo, B.-Y. Li, J.-H. Zhen, J. Song, T. Peng, et al., Resveratrol attenuates early diabetic nephropathy by down-regulating glutathione s-transferases Mu in diabetic rats, J. Med. Food 16 (6) (2013) 481–486.
[117] P. Palsamy, S. Subramanian, Resveratrol protects diabetic kidney by attenuating hyperglycemia-mediated oxidative stress and renal inflammatory cytokines via Nrf2-Keap1 signaling, Biochim. Biophys. Acta Mol. Basis Dis. 1812 (7) (2011) 719–731.
[118] H.B. Koca, M.B. Pektas, S. Koca, G. Pektas, G. Sadi, Diabetes-induced renal failure is associated with tissue inflammation and neutrophil gelatinase-associated lipocalin: effects of resveratrol, Arch. Biol. Sci. 68 (4) (2016) 747–752.
[119] S. You, J. Qian, C. Sun, H. Zhang, S. Ye, T. Chen, et al., An Aza resveratrol–chalcone derivative 6b protects mice against diabetic cardiomyopathy by alleviating inflammation and oxidative stress, J. Cell. Mol. Med. 22 (3) (2018) 1931–1943.
[120] G. Wang, X. Song, L. Zhao, Z. Li, B. Liu, Resveratrol prevents diabetic cardiomyopathy by increasing Nrf2 expression and transcriptional activity, Biomed Res. Int. 2018 (2018).
[121] L. Wang, H. Li, Effects of resveratrol on the Nrf2 and HO-1 expression in diabetic vascular endothelial cells, Int. J. Clin. Exp. Med. 10 (1) (2017) 684–691.
[122] K. Iwasaki, P.D. Ray, B.-W. Huang, K. Sakamoto, T. Kobayashi, Y. Tsuji, Role of AMP-activated protein kinase in ferritin H gene expression by resveratrol in human T cells, Biochemistry. 52 (30) (2013) 5075–5083.
[123] Y. Zhang, G. Wang, T. Wang, W. Cao, L. Zhang, X. Chen, Nrf2–Keap1 pathway–-mediated effects of resveratrol on oxidative stress and apoptosis in hydrogen peroxide–treated rheumatoid arthritis fibroblast-like synoviocytes, Ann. N. Y. Acad. Sci. (2019).
[124] Y. Wei, J. Jia, X. Jin, W. Tong, H. Tian, Resveratrol ameliorates inflammatory damage and protects against osteoarthritis in a rat model of osteoarthritis, Mol. Med. Rep. 17 (1) (2018) 1493–1498.
[125] C.-C. Wu, Y.-S. Huang, J.-S. Chen, Y.-S. Huang, S.-L. Su, K.-C. Lu, et al., Resveratrol ameliorates renal damage, increases expression of heme oxygenase-1, and has anti-complement, anti-oxidative, and anti-apoptotic effects in a murine model of membranous nephropathy, PLoS One 10 (5) (2015) e0125726.
[126] C.A. Adiabouah Achy-Brou, B. Billack, A comparative assessment of the cytotoxicity and nitric oxide reducing ability of resveratrol, pterostilbene and piceatannol in transformed and normal mouse macrophages, Drug Chem. Toxicol. 40 (1) (2017) 36–46.
[127] E. Bigagli, L. Cinci, S. Paccosi, A. Parenti, M. D'Ambrosio, C. Luceri, Nutritionally relevant concentrations of resveratrol and hydroxytyrosol mitigate oxidative burst of human granulocytes and monocytes and the production of pro-inflammatory mediators in LPS-stimulated RAW 264.7 macrophages, Int. Immunopharmacol. 43 (2017) 147–155.
[128] H.E. Yoon, E.N. Kim, M.Y. Kim, J.H. Lim, I. Jang, T.H. Ban, et al., Age-associated changes in the vascular renin-angiotensin system in mice, Oxid. Med. Cell. Longev. 2016 (2016).
[129] E.N. Kim, J.H. Lim, M.Y. Kim, T.H. Ban, I.-A. Jang, H.E. Yoon, et al., Resveratrol, an Nrf2 activator, ameliorates aging-related progressive renal injury, Aging (Albany NY). 10 (1) (2018) 83.
[130] N. Fischer, C. Büchter, K. Koch, S. Albert, R. Csuk, W. Wätjen, The resveratrol derivatives trans-3, 5-dimethoxy-4-fluoro-4′-hydroxystilbene and trans-2, 4′,

5-trihydroxystilbene decrease oxidative stress and prolong lifespan in *Caenorhabditis elegans*, J. Pharm. Pharmacol. 69 (1) (2017) 73–81.

[131] A. Csiszar, D. Sosnowska, M. Wang, E.G. Lakatta, W.E. Sonntag, Z. Ungvari, Age-associated proinflammatory secretory phenotype in vascular smooth muscle cells from the non-human primate Macaca mulatta: reversal by resveratrol treatment, J. Gerontol. A Biomed. Sci. Med. Sci. 67 (8) (2012) 811–820.

[132] Q. Meng, T. Guo, G. Li, S. Sun, S. He, B. Cheng, et al., Dietary resveratrol improves antioxidant status of sows and piglets and regulates antioxidant gene expression in placenta by Keap1-Nrf2 pathway and Sirt1, J. Anim. Sci. Biotechnol. 9 (1) (2018) 34.

[133] S. Gurusinghe, A.G. Cox, R. Rahman, S.T. Chan, R. Muljadi, H. Singh, et al., Resveratrol mitigates trophoblast and endothelial dysfunction partly via activation of nuclear factor erythroid 2-related factor-2, Placenta. 60 (2017) 74–85.

[134] A.A.A. El-Fattah, A.T. Fahim, N.A.H. Sadik, B.M. Ali, Resveratrol and curcumin ameliorate di-(2-ethylhexyl) phthalate induced testicular injury in rats, Gen. Comp. Endocrinol. 225 (2016) 45–54.

[135] Y. Zhao, W. Song, Z. Wang, Z. Wang, X. Jin, J. Xu, et al., Resveratrol attenuates testicular apoptosis in type 1 diabetic mice: role of Akt-mediated Nrf2 activation and p62-dependent Keap1 degradation, Redox Biol. 14 (2018) 609–617.

[136] L.T.R. Silveira, T. de Mello Santos, L.F. Camora, C.F. Pinho, J.A. Anselmo-Franci, R.F. Domeniconi, et al., Protective effect of resveratrol on urogenital sinus and prostate development in rats exposed in utero to TCDD (2,3,7,8-tetra-chlorodibenzo-p-dioxin), Reprod. Toxicol. 83 (2019) 82–92.