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Review

# Health benefits of resveratrol administration

Sabina Galiniak✉, David Aebisher and Dorota Bartusik-Aebisher

Faculty of Medicine, Rzeszów University, Rzeszów, Poland

**Resveratrol is a polyphenol that is abundant in grape skin and seeds. Food sources of resveratrol include wine, berries, and peanuts. This compound has many properties, including activity against glycation, oxidative stress, inflammation, neurodegeneration, several types of cancer, and aging. Because resveratrol is generally well-tolerated, it is believed to be a promising compound in preventing many diseases, such as diabetes and its complications. Unfortunately, this compound exhibits low bioavailability and solubility. The aim of this review is to summarize the latest information on the multiple effects of resveratrol on health and the benefits of its intake, based on *in vitro* and *in vivo* studies in animals and humans.**

**Key words:** resveratrol, glycation, oxidative stress, polyphenol

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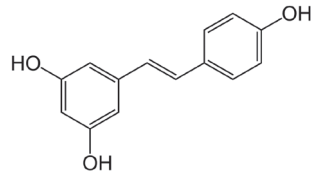
✉e-mail: sgaliniak@ur.edu.pl

**Abbreviations:** AGEs, advanced glycation end products; MGO, methylglyoxal; GO, glyoxal; HSA, human serum albumin; BSA, bovine serum albumin; AOPP, advanced oxidation protein products; ROS, reactive oxygen species; MDA, malondialdehyde; CAT, catalase; SOD, superoxide dismutase; IL, interleukin; TNF-α, tumor necrosis factor α; NFκB, nuclear factor κB; IκB, inhibitor of κB; JAK/STAT, Janus kinases/signal transducer and activator of transcription; PI3K, phosphatidylinositol-3-kinases; Akt, protein kinase B; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein

## INTRODUCTION

Resveratrol (3,5,4'-trans-trihydroxystilbene) is a polyphenolic phytoalexin belonging to the stilbene family. It is a natural dietary plant compound that occurs mainly in grape skin and seeds but is also found in wines and various other types of plant foods, especially peanuts, berries, and tea (Shrikanta *et al.*, 2015). Resveratrol is synthesized by more than 70 species of plants in response to infection, stress, injury, bacteria or fungal infections, and UV-irradiation (Hasan & Bae, 2017). Synthesis of this molecule in plants is catalysed by resveratrol synthase in the phenylpropanoid pathway in a process similar to that of flavonoids (Kapetanovic *et al.,* 2011). Resveratrol was first reported and isolated from white hellebore by a Japanese researcher Takaoka in 1939 (Takaoka, 1939). Resveratrol possesses two phenol rings (monophenol and diphenol) bonded together by a double styrene bond and it exists in both cis and trans isomeric forms. *Trans*-resveratrol (Scheme 1) appears to be the more abundant and stable natural form (Gambini *et al.,* 2015). This molecule has three hydroxyl groups which are involved in free radical scavenging and metal chelation (Caruso *et al.,* 2004; Gülçin, 2010). The presence of hydroxyl groups also facilitates interaction with macromolecules.



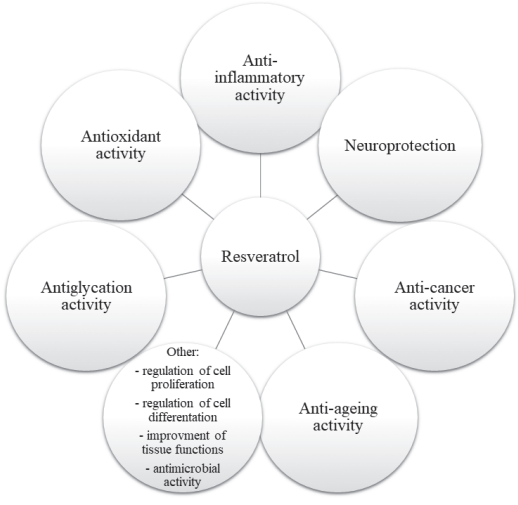

**Scheme 1. Structure of *trans*-resveratrol.**

Resveratrol reveals a wide range of biological properties including anti-glycation, antioxidant, anti-inflammation, neuroprotective, anti-cancer, and anti-aging activity in various *in vitro* and *in vivo* experimental models (Öztürk *et al.*, 2017; Rauf *et al.,* 2017; Jardim *et al.,* 2018; Li *et al.*, 2018; Salehi *et al.*, 2018). Currently, resveratrol research spans a large spectrum of areas and is a subject of considerable scientific attention, in particular, investigations of its biological activity and the effects of resveratrol administration in numerous diseases in both clinical and nonclinical trials (Scheme 2).

## SELECTED BIOLOGICAL PROPERTIES OF RESVERATROL

### Antiglycation activity

Glycation is a nonenzymatic reaction between proteins and reducing sugars, leading to the formation of advanced glycation end products (AGEs). Advanced glycation end products accumulate and cause damage at the tissue and cellular level, including lipid peroxidation, endothelial dysfunction, changes in protein structure, and




**Scheme. 2. The activities of resveratrol on health.**

stimulation of inappropriate cellular activity (Singh *et al.*, 2001; Galiniak *et al.,* 2017). Glycation produces highly reactive dicarbonyl compounds such as methylglyoxal and glyoxal, which are key precursors to the formation of AGEs. Methylglyoxal (MGO) is also generated by glycolysis, glucose autooxidation, and lipid peroxidation, while glyoxal (GO) is formed during lipid peroxidation and degradation of monosaccharide and saccharide derivatives. Both MGO and GO are known to enhance oxidative stress in the human body. Recent reports suggest that increased glycation is associated with a higher prevalence of diabetes and related complications (Adamska *et al.,* 2018; Rhee & Kim, 2018), lung (Khan *et al.*, 2018) and breast cancer (Walter *et al.,* 2018), myasthenia gravis (Adamczyk-Sowa *et al.,* 2017), and neurodegenerative diseases (Pinkas & Aschner, 2016).

Increasingly, evidence indicates that compounds of natural origin, especially polyphenols, have antiglycation properties. Among effective glycation inhibitors are phenolic acids, naringin, genistein, rutin, quercitrin, and kaempferol (Sadowska-Bartosz *et al.,* 2014; Yeh *et al.,* 2017). Many reports have confirmed that resveratrol displays antiglycation activity as well.

A high percentage (up to 99%) of resveratrol-induced inhibition of AGE production was demonstrated by Shen and others (Shen *et al.,* 2017) in BSA/fructose, BSA/MGO, and arginine/MGO mixtures. Resveratrol inhibition of AGE and binding to toxic MGO and GO have demonstrated both anti-oxidative and pro-oxidative effects, as resveratrol adducts can lead to the oxidation of amino acids in human serum albumin (HAS) (Arcanjo *et al.,* 2018). Furthermore, resveratrol reveals antiglycation activity against the harmful effect of AGEs or α-dicarbonyls on porcine chondrocytes (Liu *et al.,* 2010), mouse oocytes (Liu *et al.,* 2013), and dendritic cells obtained from peripheral blood mononuclear cells (Buttari et al., 2013).

Yılmaz and others (Yılmaz *et al.,* 2017) has shown that administration of resveratrol in drinking water to chronic MG-treated rats significantly reduces the level of advanced oxidation protein products (AOPP), AGEs, and protein carbonyl in plasma, as well as markers of oxidative stress in the liver. A significant decrease in urine albumin and creatinine and an increase in serum antioxidant enzymes were also observed in patients with type II diabetes and diabetic nephropathy who received resveratrol at the dose of 500 mg per day (Sattarinezhad *et al.,* 2018). Resveratrol prevents opacification and formation of polyols in the bovine lens, as well as ameliorates kidney function due to suppression of AGEs formation, suggesting that resveratrol may be considered as a protective agent against diabetic complications such as cataracts and nephropathy (Ciddi & Dodda, 2014; Hussein & Mahfouz, 2016). Furthermore, resveratrol is a prospective therapeutic agent against diabetic ototoxicity (Erkan *et al.*, 2018), renal fibrosis (He *et al.,* 2016), progression of cataracts (Higashi *et al.,* 2018), and bone density loss in patients with type 2 diabetes (Bo *et al.,* 2018). Likewise, resveratrol is also involved in protection against diabetic cardiomyopathy development *via* improvement of mitochondrial function and inhibition of apoptosis of cardiomyocytes (Diao *et al.,* 2018). Resveratrol preserves pancreatic tissue by reducing inflammatory factors and glucose levels in serum, and ultimately leads to the protection of cardiovascular tissues in diabetic rat models of coronary heart disease (Huo *et al.*, 2019).

Similarly, it has been shown that by modulating the switching between apoptosis and autophagy resveratrol has a beneficial effect on cardiomyopathy induced in cardiac myoblast cells exposed to the combination of high glucose and palmitate (Xu *et al.,* 2018). Guzmán and others (Guzmán *et al.*, 2018) noted that resveratrol at a dose of 1, 10 and 100 μM has a protective effect on acute high glucose-induced damage in endothelial cells. Moreover, resveratrol attenuates methylglyoxal induced endothelial damage by promoting the expression and activity of endothelial nitric oxide synthase in thoracic aorta in older rats (Tasatargil *et al.,* 2018). In diabetic mice receiving resveratrol, a decrease in the level of apoptosis of glomerular podocytes and renal tubular epithelial cells was noted (Zhang *et al.,* 2018). The diabetic rats treated with resveratrol had reduced levels of factors related to endoplasmic reticulum stress which underlies the progression of diabetic nephropathy (Yuan *et al.,* 2018).

In summary, the results indicate that resveratrol may be considered as a beneficial anti-glycation agent in *in vitro* and *in vivo* experiments as well as in the treatment of diseases associated with increased glycation.

### Antioxidant activity

Oxidative stress is defined as an imbalance between generation of reactive oxygen species and the antioxidant defence in favor of oxidant production. Enhanced oxidative stress damages macromolecules and impairs their functions, which underlies many age-related diseases including cancer, diabetes, chronic kidney disease, cardiovascular and neurodegenerative diseases (Liguori *et al.,* 2018). Moreover, overproduction of ROS induces inflammation, dysregulation of mitochondria and cell death (Wu *et al.,* 2018). Also, it was shown that autooxidation of glucose may contribute to excessive ROS production and intensification of oxidative stress (Matough *et al.,* 2012). Resveratrol is confirmed to be a powerful antioxidant which activity is associated with presence of three hydroxyl groups in its structure. Resveratrol has an inhibitory effect on excessive ROS production, aberrant mitochondrial distribution, and lipid peroxidation (Liu *et al.*, 2013; Liguori *et al.,* 2018). Treatment of primary epidermal keratinocytes with resveratrol leads to a 1.3-fold increase of endogenously generated glutathione and quantitative reduction of the cellular redox environment and endogenous ROS production (Plauth *et al.,* 2016). In astroglial cells treated with ammonia, resveratrol prevents both an increase in ROS production and a decrease of mitochondrial membrane potential, which indicates a role in maintaining cellular redox homeostasis (Bobermin *et al.,* 2018). In fibroblasts exposed to rotenone, resveratrol decreases mitochondria fragmentation and maintains the potential of the mitochondrial membrane, as well as prevents the attenuation of oxidative phosphorylation, thus exerting a protective effect against the harmful impact of ROS (Sgarbi *et al.,* 2018). Recent study by Cheng and others (Cheng *et al.*, 2019) revealed that resveratrol prevents hepatic steatosis in obese mice fed a high-fat diet by reducing oxidative stress and inflammation. The protective effect of resveratrol against hepatic steatosis is supported by lowering the accumulation of lipid droplets in hepatocytes (Zhou *et al.*, 2018).

Furthermore, resveratrol treatment of the epithelial cells protects them from oxidative damage induced by hydrogen peroxide and promotes the expression and phosphorylation of occludin and other zonula occludens proteins. This protection is caused by reducing MDA and intracellular ROS concentration and increasing expression levels of antioxidant enzymes (Wang *et al.,* 2016). The protective effects of chronic administration of resveratrol against AGE-induced oxidative stress and

apoptosis, together with the improvement of glucose tolerance, are also observed in pancreatic cells in mice with type 2 diabetes (Lee *et al.*, 2012; Ginés *et al.,* 2017).

Resveratrol intake by diabetic rats at a dose of 5 mg/kg/day leads to normalization of antioxidant status, exacerbated by oxidative stress induced by hyperglycemia (Hussein & Mahfouz, 2016). Administration of resveratrol at a dose of 10 or 20 mg/kg for 4 weeks in rats with a streptozotocin-induced diabetes results in a reduction in the content of AOPP and MDA as well as catalase (CAT) and superoxide dismutase (SOD) activity in the lens compared to untreated diabetic rats (Sedlak *et al.,* 2018). Resveratrol-treated animals have reduced production of ROS, elevated membrane potential, and inhibition of cytochrome c release from the inner mitochondrial membrane (Zhang *et al.,* 2018). Wang and others (Wang *et al.,* 2018) observed that resveratrol counteracted the accumulation of 3-nitrotyrosine and generation of 4-hydroxynonenal during the development of diabetes mellitus-induced cardiomyopathy. Resveratrol-treated rats with diabetes have a significant decrease in the MDA level and total oxidant level, as well as an increase in total antioxidant capacity (Moridi *et al.,* 2015; Khazaei *et al.,* 2016) when compared to untreated groups. Moreover, resveratrol protects the spinal cord from ischemic damage in rats by reducing plasma levels of nitrite, AOPP and MDA, and increasing the enzymatic activity of SOD and CAT (Fu *et al.,* 2018). Resveratrol also attenuates oxidative stress in rats with experimental periodontitis (Corrêa *et al.,* 2018), induced early Alzheimer's disease (Lin *et al.,* 2018) and chronic obstructive pulmonary disease (Wang *et al.,* 2017).

The studies mentioned above indicate that resveratrol has a therapeutic effect in cell and animal experiments involving increased oxidative stress, which is associated to the limitation of ROS generation and stimulation of compounds that act as an antioxidant barrier.

## OTHER BIOLOGICAL ACTIVITIES OF RESVERATROL

### Anti-inflammatory activity

Resveratrol suppresses IL-6 transcription and translation, resulting in attenuation of its secretion by macrophages (Ohtsu *et al.,* 2017). Likewise, the administration of resveratrol to monocyte cultures leads to a reduction in the expression of inflammatory mediators: TNF-α and IL-8, without inducing cytotoxicity (Pinheiro *et al.,* 2018). Resveratrol significantly inhibits the production of extracellular matrix proteins by pancreatic stellate cells, which are involved in the development of pancreatic fibrosis (Xia *et al.,* 2018). Furthermore, resveratrol is involved in the inhibition of toll-like receptors, which in their active form can induce proinflammatory cytokines and chemokine expression and stimulate the activation of innate and adaptive immunity (Chen *et al.,* 2018). Resveratrol reduces matrix-metalloprotease expression and supresses the production of IL-1, IL-6 and TNF-α in a dose dependent manner in chondrocytes with induced osteoarthritis (Li *et al.,* 2018). Moreover, resveratrol treatment in patients after oral implantology reduces serum levels of IL-1β, IL-17A and TNF-α while the levels of IL-2, IL-6 and IL-10 are elevated (BaGen *et al.,* 2018). Ma and others (Ma *et al.,* 2015) observed that resveratrol effectively suppresses NF-κB signaling through inhibiting the activities of NF-κB and IκB kinase, as well as by suppressing the phosphorylation of JAK/STAT signalling pathways. Resveratrol shows protective activity against intestinal ischemia-reperfusion injury by inhibiting mast cells from degranulation and decreasing apoptosis of intestinal epithelial cells, which prevents overall organ dysfunction (Zhao *et al.,* 2018).

Anti-inflammatory activities of resveratrol are observed also in case of hyper-acute small intestinal inflammation (Bereswill *et al.,* 2010) as well as in immune-mediated diseases (Švajger & Jeras, 2012). Moreover, it prevents acceleration of cholesterol accumulation and disturbances of macrophage lipid homeostasis after induction by glycation products (Zhang *et al.,* 2010).

### Neuroprotection

Resveratrol is also involved in the reduction of neuronal damage and apoptosis and the improvement of the central nervous system function. Resveratrol has been shown to reduce neurodegeneration in the murine cerebral cortex and enhance memory recovery after exposure to fluoride (Sharma *et al.,* 2018). Also, the administration of resveratrol improves cognition, learning and memory in rats with vascular dementia (Ma *et al.,* 2013). Report by Corpas and others (Corpas *et al.*, 2018) indicates that resveratrol also improves cognition and induces neuroprotection in amyloid and tau pathologies in mice models of Alzheimer's disease. However, results of resveratrol supplementation in human are inconsistent. A meta-analysis of randomized controlled trials suggests that resveratrol may be beneficial (Marx *et al.,* 2018) or may have no significant impact on the selected measures of cognitive performance (Farzaei *et al.,* 2018). Several neuroprotective properties of resveratrol have been suggested in the studies of its effects in the intracerebral hemorrhage (Bonsack *et al.,* 2017), cerebral neurodamage (Nalagoni & Karnati, 2016), and central nervous system injuries such as stroke (Lopez *et al.,* 2015). Likewise, resveratrol shows a neuroprotective effects in cerebral ischemia/reperfusion injury in rat brain by reducing the cerebral infract volume and stimulating the expression of components of the intracellular signaling pathway including kinases such as JAK2, PI3K or Akt and anti-apoptotic molecules, while downregulating the expression of pro-apoptotic caspase-3 and Bax (Hou *et al.,* 2018).

Resveratrol also alleviates neuropathic pain in mice through repressing the expression of proinflammatory cytokines and increasing the expression of anti-inflammatory IL-10 (Tao *et al.,* 2016). Similarly, the observed beneficial effect of resveratrol on hyperalgesia in rats with chronic neuropathic pain is due to the inhibition of the expression of glial fibrillary acidic protein and the P2X7 receptor, a key player in nervous pathological pain (Xie *et al.,* 2017). In addition, resveratrol at the dose of 10-80 mg/kg per day may be an effective treatment for depression in animal models (Moore *et al.,* 2018). There is also evidence that the neuroprotective effect is also enhanced by the antioxidant and anti-inflammatory properties of resveratrol.

### Anti-cancer activity

Many *in vitro* and *in vivo* studies suggest that resveratrol has anti-cancer properties due to its wide range of activities, including antioxidant effects and regulating the expression of pro-apoptotic proteins, as well as molecules underlying tumor development. Resveratrol is known to reduce the incidence and development of various types of cancer, such as cervical (Zhou *et al.*, 2018), pancreatic (Zhao *et al.,* 2018), gastric (Wu *et al.,* 2018), breast and colorectal (Lucas *et al.,* 2018), as well as thyroid cancer

(Zheng *et al.,* 2018). Research results indicate that resveratrol has protective effect on the normal cells, while inducing death in cancer cells. This can be associated with different cellular targets and metabolic pathways of resveratrol in healthy and cancerous cells. In addition, this dual pattern of resveratrol action depends on the dose. Lower concentrations increase expression of cell survival proteins, whereas higher doses stimulate cell apoptosis or necrosis regardless of whether the cell is healthy or pathological (Szende *et al*., 2010; San Hipólito-Luengo *et al*., 2017). Resveratrol at a high dose inhibits synthesis of nucleic acids and proteins, leads to impairment of chromatin structure, and finally, causes cell death (Mukherjee *et al*., 2010).

Monteillier and others (Monteillier *et al*., 2018) showed that intranasal administration of 60 mg/kg resveratrol to mice with induced lung cancer caused a notable decrease in the tumor multiplicity and volume via enhanced apoptosis. Moreover, treating gastric cancer cells with resveratrol elevated the levels of pro-apoptotic proteins such as Bax, while the levels of anti-apoptotic proteins such as Bcl-2 were decreased compared to untreated controls (Wu *et al.,* 2018). Treatment of osteosarcoma cells with 20 μM resveratrol results in reduction of cell viability, decrease in self-renewing and tumorigenesis via inhibition of intracellular STAT3 signaling and cytokine synthesis (Peng & Jiang, 2018). In general, the anti-cancer activity of resveratrol is based on the suppression of the expression of proteins involved in carcinogenesis, such as phospholipid scramblase 1 (Zhou *et al.,* 2018), stimulation of caspase 3 cleavage (Lucas *et al.,* 2018) and activation of the mitochondrial ROS signaling pathway (Zheng *et al.,* 2018). Furthermore, resveratrol inhibits the cell cycle by inducing S-phase arrest in gastric cancer cells in a dose- dependent manner (Wu *et al.,* 2018). Resveratrol has also been found to increase the effect of anticancer drugs and decrease drug resistance in cancer cells (Hallajian *et al*., 2018; Pouyafar *et al*., 2019). Taken together, *in vivo* and *in vitro* studies confirm the beneficial antitumor effect of resveratrol.

### Anti-ageing activity

Resveratrol has been reported to extend life span in several different subjects including the fish species *Nothobranchius furzeri* (Valenzano *et al.,* 2006) and *Nothobranchius guentheri* (Liu *et al.,* 2015), as well as *Drosophila melanogaster* (Wang *et al.,* 2013), honey bee (Rascon *et al.,* 2012) and mice (Baur *et al.,* 2006). Roggerio and others (Roggerio *et al.,* 2018) observed that administration of resveratrol (500 mg/day) in healthy and slightly overweight subjects resulted in higher gene expression and serum concentration of sirtuin-1. Sirtuins exhibit a broad spectrum of activity, including anti-ageing and anti-inflammatory effects, inhibition of degenerative disorders such as liver steatosis, as well as improvement of endothelial function, and prevention of cancer (Wątroba & Szukiewicz, 2016). Recent report shows that short-term injection of resveratrol in postovulatory oocyte delayed the aging process of oocytes in middle-aged mice by promoting the expression of sirtuin-1, reducing ROS generation, and ameliorating mitochondrial function (Liang *et al.* 2018). Generally, the mechanisms of resveratrol prolongevity activity are similar to caloric restriction (Bass *et al.,* 2007).

Despite a number of studies that demonstrate the life-extending activity of resveratrol, its anti-ageing properties are still controversial due to the growing number of reports to the contrary. Recently, Ramos-Gomez and others (Ramos-Gomez *et al.,* 2017) described that resveratrol caused mitochondrial dysfunction and reduction in the chronological life-span of *Saccharomyces cerevisiae*. Similarly, it is known that dietary resveratrol does not extend the life span of the mosquito *Anopheles stephensi* (Johnson & Riehle, 2015) nor *Drosophila melanogaster* and does not influence gene expression of longevity-associated and antioxidant enzymes (Staats *et al.,* 2018). Wang *et al.* (2013) suggested that the life-extending effect of resveratrol depends on dietary composition, dose and gender. Their results indicate that resveratrol at a dose of 400 μM has a prolongevity effect on females of *Drosophila melanogaster* fed a high fat diet. However, a lower resveratrol (or fat?) concentration had no effect on the lifespan of female flies fed a (fat? calorie?) restricted diet or diet rich in sugar and protein. Similarly, it was indicated that the life-extending activities of resveratrol depended on the model organism and its genetic background (Pallauf *et al*., 2016).

Besides the aforementioned effects of resveratrol, it exhibits additional beneficial activities on other targets at the cellular and tissue levels. A report by Hara and others (Hara *et al*., 2018) suggests that resveratrol attenuates changes induced in bovine embryos composed of 8–12 cells by vitrification due to degradation of damaged mitochondria, without affecting ATP content and activation of further embryonic development. Gorga and others (Gorga *et al*., 2018) observed that resveratrol decreased expression of cyclins and activated sirtuin 1, which lead to regulation of immature Sertoli cells proliferation. Resveratrol also acts as an activator of Notch signalling and an inhibitor of endothelial cell proliferation and migration (LaFoya *et al.,* 2019).

Resveratrol induces neuronal differentiation in murine neuroblastoma cells (Namsi *et al.,* 2018) and differentiation of monocytes to macrophages (Vasamsetti *et al.,* 2016). Recent reports show that resveratrol increases self-renewal and maintains the pluripotency of human and mouse embryonic stem cells (Li *et al.,* 2017; Safaeinejad *et al.,* 2017). Intragastric administration or resveratrol causes activation of cardiac stem cells, an increase of capillary density, and reduction of apoptosis of cardiomyocytes, which may be beneficial in myocardial regeneration after acute myocardial infarction (Ling *et al.,* 2017). Furthermore, by reducing the expression of perilipin 5, resveratrol accelerates lipid hydrolysis in brown adipose tissue, which may cause a decrease in weight and myocardial steatosis of heart tissue (Mehdi *et al.,* 2018). Resveratrol also exhibits antimicrobial activity against *Haemophilus influenzae* (Euba *et al*., 2017), *Escherichia coli* (Subramanian *et al*., 2014), *Propionibacterium acnes* (Taylor *et al.,* 2014), and *Staphyloccocus aureus* (Wu & Huang, 2017). Toniolo *et al.* (2018) observed that supplementation with 0.04% resveratrol for six months also improves the resistance to fatigue and functional-mechanical properties of skeletal muscles in aged mice. Furthermore, resveratrol at a dose of 500 mg per day attenuates joint pain and improves functional activity of patients with knee osteoarthritis (Hussain *et al.,* 2018; Marouf *et al.,* 2018). Farrokhi and others (Farrokhi *et al.,* 2018) demonstrated that 120 μM resveratrol reduced production of matrix metalloproteinase 9, which makes it a potential therapeutic agent in atherosclerosis. Resveratrol also has a beneficial effect in counteracting allergic asthma (Alharris *et al*., 2018), as well as anxiety and depression disorders (Liu *et al*., 2019). Moreover, resveratrol improves testosterone levels and sperm parameters by reducing apoptosis in testes (Shatti, 2018).

Unfortunately, despite numerous reports presenting a beneficial effect of resveratrol treatments on many diseases or pathological states, it has poor bioavailability and water solubility (less than 0.05 mg/ml). Reports indicate that a 25 mg intake of resveratrol resulted in plasma concentrations lower than 10 ng/ml, while concentrations of 500 ng/ml in plasma were measured after a high dose of 5000 mg (Walle, 2011). Sergides and others (Sergides *et al.,* 2016) showed that intake of 500 mg of resveratrol in the form of tablets was well-tolerated and led to plasma concentrations of about 70 ng/ml. Other studies also confirm that administration of resveratrol is generally well-tolerated and safe (Sergides *et al.,* 2016; Berman *et al.,* 2017), although some adverse effects were reported when resveratrol was given in high doses (Novelle *et al.,* 2015). Diarrhoea, nausea, anemia, vomiting, flatulence, abdominal discomfort as well as renal failure via cast and crystal nephropathy and acute tubular damage are among the most common side effects of resveratrol, however, the nephrotoxic effect of resveratrol occurred only in patients with multiple myeloma (Brown *et al*., 2010; la Porte *et al*., 2010; Popat *et al*., 2013). A recent study showed that incubation of human placental explants with resveratrol at a dose up to 100 μM led to impairment of fatty acid uptake and oxidation of placental tissue, which may negatively affect fetal development (Landau *et al*., 2017). Kumaran and others (Kumaran *et al*., 2018) also demonstrated that oral resveratrol tablet taken once a day induced thrombocytopenia in woman with melasma.

Resveratrol has a short half-life of approximately 1.5 h due to rapid absorption in the intestine and degradation in the liver (Marier *et al,* 2002). After consumption, 77–80% of resveratrol is absorbed into the blood stream by active transport via intestinal epithelial cells, after which it binds to albumin and lipoproteins. This polyphenol is easily released from the complexes and can be transported into cells. About 49–61% of resveratrol is excreted in the urine (Soleas *et al*., 2001).

To improve the bioavailability of this compound, more complex formulations have been prepared, including nanoparticles and nanostructured lipid carriers containing resveratrol (Gokce *et al.,* 2012; Peñalva *et al.,* 2018). Enhancing resveratrol bioavailability was also attempted in rats by treating them with 3,5,4'-tri-O-acetylresveratrol (TARES), an acetylated resveratrol prodrug that can be enzymatically hydrolyzed to free trans-resveratrol in cells (de Vries *et al.,* 2018).

## CONCLUSION

Overall, resveratrol has potential benefits for human health and exhibits protective effects against glycation, free radicals' production, neurodegeneration, inflammation, and tumor development. Life-extending properties of resveratrol are still controversial, however, there is evidence suggesting anti-ageing activity. The main mechanisms of resveratrol activity are based on the prevention of apoptosis and ROS production by downregulation of expression of anti- or proapoptotic proteins involved in antioxidant barrier systems, and improvements in mitochondrial function.

Nonetheless, more research, especially clinical trials on large number of patients are still needed for unambiguous confirmation of its positive action. Future research should also focus on improving resveratrol bioavailability and counteracting any adverse effects after administration.

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