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Review

Multiplicity of effects and health benefits of resveratrol

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ABSTRACT

Resveratrol is mainly found in grapes and red wine, also in some plants and fruits, such as peanuts, cranberries, pistachios, blueberries and bilberries. Moreover, nowadays this compound is available as purified preparation and dietary supplement. Resveratrol provides a wide range of benefits, including cardiovascular protective, antiplatelet, antioxidant, anti-inflammatory, blood glucose-lowering and anticancer activities, hence it exhibits a complex mode of action. During the recent years, these properties have been widely studied in animal and human models, both in vitro and in vivo. This paper is intended to present information published during the recent years on the biological activities and multiple effects of resveratrol.

1. Introduction

Studies on natural polyphenolic compounds that are found in plants and known as flavonoids have recently become very popular [1,2]. A vast number of studies on resveratrol, one of such compounds, have been published. Resveratrol was chosen to be analyzed due to a variety of its biological effects, including antioxidant and anticancer properties. The studies have demonstrated that pleiotropic nature is characteristic of this compound. Resveratrol is mainly used as a nutritional supplement; however, the mechanism of its action has not been completely elucidated yet. Structural analogs of resveratrol are also investigated as compounds that could be used in therapy for malignant diseases [3]. An abundance of scientific studies and their novelty challenged us to summarize the existing data on multiple effects as well as mechanisms of action of resveratrol.

2. Structure, sources and tolerability of resveratrol

According to its chemical structure, resveratrol (3,4′,5-trihydroxystilbene) is a polyphenolic compound. It is similar to diethylstilbestrol, a synthetic estrogen [4]. Resveratrol

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presents itself in both *trans*- and *cis*- isomeric forms, and their structures are depicted in Figure. It is found in an abundant amount in red wine, grape berry skins and seeds and, particularly in dried roots of plant *Polygonum cuspidatum* [5]. Content of resveratrol in grapes varies from 0.16 to 3.54 μg/g; dry grape skin contains about 24 μg/g of resveratrol [6]. Resveratrol is also present in other berries and nuts. For example, cranberry raw juice contains about 0.2 mg/L. In other natural foods, the concentration of resveratrol varies in the range of μg/g (peanuts, pistachios) to ng/g (bilberries, blueberries) [6]. It has been documented that red wine contains a much greater amount of polyphenolic compounds than white wine. The concentration of resveratrol ranges from 0.1 to 14.3 mg/L in various types of red wine, while white wines contain only about 0.1–2.1 mg/L of resveratrol [6].

In plants, resveratrol exerts antioxidant function by protecting against sun damage. Food products contain both *cis*- and *trans*-isoforms of resveratrol, mostly in the glycosylated form. Such compounds are called piceids (3-*O*-β-D-glucosides). The *trans*-isoform is more common in plants [7]. Glycosylation prevents enzymatic oxidation, thereby increasing stability and bioavailability of resveratrol [8,9].

It has been reported that this compound has low toxicity as it was well tolerated in the short-term experiments performed in humans [10–12]. Recent clinical trials proved that resveratrol is well-tolerated and pharmacologically safe at doses up to 5 g/day [13]. However, the data [14,15] on toxicity of resveratrol in long-term experiments are scarce. Tome-Carneiro et al. lately found that resveratrol treatment at low dose (8 mg/day) for one year significantly reduced a number of cardiac risk factors [16]. Interestingly, this amounts to 1–3 L of wine, depending on wine sort.

3. Absorption, bioavailability and metabolism of resveratrol

Low solubility of resveratrol in water (<0.05 mg/mL), caused by its chemical structure, affects its absorption [17]. In animals and humans, resveratrol is quickly metabolized in liver; in plasma it binds to lipoproteins and albumin, and this facilitates its entry to cells [18].

Urinary excretion of total metabolites after ^{14}C-labeled resveratrol administration showed that orally or intravenously administered resveratrol had high absorption (at least 70%), but rapid and extensive metabolism [19], leading to formation of conjugated sulfates and glucuronides [20]. Therefore Walle et al. postulated that sulfation of resveratrol might limit the bioavailability of this compound [19]. Reveratrol has curiously high absorption for a compound with poor aqueous solubility [17].

The maximum peak plasma concentration of native (nonmetabolized) resveratrol was reached after 30–90 min after oral intake. When single oral dose 25 mg was administered, peak plasma concentrations ranged from 1 to 5 ng/mL (4–20 nM), in case of higher dose resveratrol administration (5 g) the peak plasma concentration was estimated about 2.3 μM [12,19]. Appearance of the second peak 6 h after resveratrol intake indicates that the enteric recirculation of conjugated metabolites by reabsorption takes place. [19]. However, a high accumulation of resveratrol in the intestinal epithelial cells was also demonstrated [20]. The study in vivo performed by Vitrac et al. using ^{14}C-labeled resveratrol showed distribution of resveratrol in urine, bile, duodenum, kidney, lung and liver [21]. It found low bioavailability of native resveratrol, as reflected by its clearance, apparent volume of distribution and urinary excretion. Most abundant metabolite conjugates resveratrol-3-*O*-sulfate, resveratrol-3-*O*-glucuronide and resveratrol-4-*O*-glucuronide in plasma and urine were estimated and their concentrations overpassed that of the native resveratrol approximately 20-fold [22]. Approximate calculations showed maximal plasmatic concentration of native resveratrol <10 ng/mL (40 nM), while total plasmatic concentration (native plus metabolites) was found markedly higher, 400–500 ng/mL (about 2 μM) [19,23]. It demonstrates that bioavailability of native resveratrol is low, however bioavailability of at least one of resveratrol metabolites is significant [17,19,23]. In addition, it was found by Ortuno et al. that bioavailability of resveratrol from wine and grape juice is much higher (sixfold) compared to that from tablets [24].

4. Biological activities and effects of resveratrol

Multiplicity of resveratrol biological effects is mainly caused by the abundance and diversity of molecular targets of this compound like cyclooxygenases/lipooxygenases, a wide range of various kinases, sirtuins [6], transcription factors, cytokines, DNA polymerase, adenylyl cyclase, ribonucleotide reductase, aromatase and others [25]. It is hypothesized that resveratrol provides a complex physiological action because of its capability to modulate different pathways in a micromolar range [25]. Many studies have shown that resveratrol possesses cardiovascular protective [26], antiplatelet [27], antioxidant [28], anti-inflammatory [29], blood glucose-lowering [30] and anticancer [31] activities. By increasing the production of nitric oxide, resveratrol inhibits platelet aggregation and stimulates

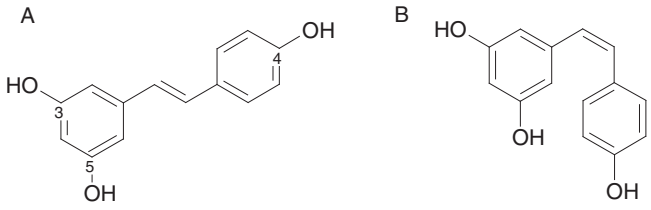

Figure – Chemical structure of *trans*- (A) and *cis*-resveratrol (B).

vasodilation [32]. Recently published data have shown that resveratrol protects against some neurodegenerative diseases, such as Alzheimer's disease [33], and obesity [34,35] as well as is effective in the management of osteoporosis in postmenopausal women without an increased risk of breast cancer [36].

5. Prooxidant and antioxidant activities of resveratrol

It is worth mentioning that the effect of resveratrol depends on its redox status, i.e., if it acts as an antioxidant or a prooxidant. The concentration of resveratrol and cell type are also important [29]. A prooxidant effect of resveratrol has been demonstrated in some studies. Dudley et al. investigated how myocardial infarct size and cardiomyocyte apoptosis were affected in vivo by low and high doses of resveratrol; they found that cardioprotective properties of resveratrol were dose-dependent because at lower concentration (5 μM–10 μM) resveratrol functions as antioxidant, while at higher concentration it acts as prooxidant [37]. In study performed by Ahmad et al. it was observed that administration of low concentrations resveratrol (4–8 μM) to human leukemia cells inhibited caspase activation as well as DNA fragmentation induced by H_2O_2 [38]. However, at higher doses resveratrol induced apoptosis via caspase-3 cascade activation in both normal (60 μM) and leukemic (5–43 μM) hematopoietic cells [39]. The data of many studies indicate that resveratrol was used at high doses ranging between 10–40 μM for cancer prevention [3,6,40]. At low concentration (5 μM) resveratrol increased cell proliferation, while at higher concentrations (15 μM or more) it induced apoptosis in various cancer cells [6]. Besides, it was reported that the cytotoxic effect of resveratrol probably includes mobilization of endogenous copper ions, the concentration of which is markedly elevated in various malignancies [29]. The prooxidant effects of resveratrol were also demonstrated using rat liver microsomal systems. It was found that resveratrol inhibited lipid peroxidation; however, it increased the generation of hydroxyl radicals, indicating that hydroxyl radicals played a minor role in lipid peroxidation [41]. None of the 14 tested in this study naturally occurring polyphenols at up to 40 μM concentration quenched hydroxyl radicals in the Fe^{2+}-ascorbate system. It was concluded that lipid peroxidation by polyphenols was caused by their hydrogen donating properties. Consequently, as mentioned above resveratrol possesses biphasic properties over low to high spectrum of concentrations.

The characteristics of resveratrol as an effective antioxidant have been demonstrated in studies in vitro [42]; however, it is not clear if it possesses this property in vivo [43]. Acquaviva et al. showed that antioxidant properties of resveratrol (i.e. radical-scavenging capacity) in vitro were increased with increasing concentration of this compound [44]. It has been reported that resveratrol inhibits oxidation of low-density lipoproteins, thus preventing from atherosclerosis [45,46]. Recent studies on isolated liver mitochondria have shown that the addition of resveratrol to the incubation medium significantly increases the activity of manganese-containing superoxide dismutase and diminishes ROS generation [28]. It is known that resveratrol acts as a scavenger of hydroxyl, superoxide and other radicals [46–48]. Thus, it prevents DNA lesions and lipid peroxidation in cell membranes [47,49].

Resveratrol as an antioxidant exerts a dual effect: it can increase the activity of antioxidant enzymes and can act as a scavenger of free radicals [29]. It was shown that resveratrol can maintain the concentration of intracellular antioxidants in biological systems. For example, resveratrol significantly reduced the oxidation of thiol groups in proteins of human platelets [50]. It has also been reported that resveratrol increased the concentration of some antioxidant enzymes such as glutathione peroxidase, glutathione S-transferase, and glutathione reductase [51].

However, in some cancers there were no changes in antioxidant enzymes expression and activities observed or they were even higher. Chung-man et al. reported about different alterations in levels of different antioxidant enzymes in lung cancer tissues and the A549 lung cancer cell line. The levels of SOD were found increased, while glutathione peroxidase levels unchanged and catalase decreased [52]. Consequently, in order to prevent cancer development it is important to maintain the adequate levels of antioxidant enzymatic activities.

6. Antitumor activity of resveratrol

As mentioned above, at lower dose resveratrol acts as anti-apoptotic and cardioprotective agent [26], while at higher dose it elicits proapoptotic properties inducing apoptosis in cancer cells [31]. It is known that resveratrol affects various intracellular mediators, participating in all three stages of oncogenesis: onset, activation and progression [34,42]. Depending on a tumor model, intracellular targets can be NO, tumor suppressor p53, apoptosis regulators, cyclooxygenases, transcription factors, cyclins, calpains, caspases, interleukins, cathepsins, etc. Resveratrol has been shown to suppress proliferation of various tumor cells including myeloid, breast, lung, liver, pancreas, prostate, skin, colon, and stomach [3].

Due to lipophilic nature resveratrol in vivo possibly inhibits phase I enzymes (CYP family) thus preventing the onset of oncogenesis. This polyphenol suppresses recombinant human cytochrome P450 monooxygenase CYP P450 in vitro [53]. Resveratrol has been reported to induce phase II enzymes such as UDP glucuronosyltransferase and NAD(P)H:quinone oxidoreductase in mouse epidermis [54] and to reduce the damage induced by UVB (ultraviolet B) exposure blocking UVB-mediated activation of nuclear transcription factor NK-κB [7,29]. It is known to regulate expression of various genes implicated in inflammation, cytoprotection and carcinogenesis [55].

Moreover, resveratrol induces apoptosis through several different pathways: receptor-mediated or caspase-8-dependent pathway; mitochondrial or caspase-9-dependent pathway or cell cycle arrest and the pathway affecting SIRT 1 (silent information regulators) [56]. Resveratrol was found to induce apoptosis by inducing death receptor Fas, one of the members of tumor necrosis factor TNF superfamily [55]. Dörrie et al. showed that resveratrol induces apoptosis in acute lymphocytic leukemia cells by disrupting the mitochondria membrane potential; it determinates cytochrome *c* release and caspase-9 activation [57].

Due to the ability of resveratrol at higher doses (25–100 μM) to promote S-phase arrest and apoptosis, it inhibited growth of cells in several human cancer lines in a dose-dependent manner (HCE7 esophageal squamous carcinoma, Seg-1 esophageal adenocarcinoma, Bic-1 esophageal adenocarcinoma, MCF7 breast adenocarcinoma, SW480 colon adenocarcinoma, and HL60 promyelocytic leukemia cells) [58]. Many in vitro studies have shown that resveratrol suppresses tumor cell survival by direct activation of apoptosis-triggering cascade and inhibition of antiapoptotic protein expression or signal transduction via phosphoinositidine 3-kinase, mitogen-activated protein kinase, and NF-κB pathways [59–61].

Resveratrol-mediated apoptosis is linked to the activation of protein p53 in various human cancer cells, namely breast [62,63], colon [64], esophageal cancer [65], lung adenocarcinoma [66]. p53 is known as a DNA-binding protein which activates the transcription of genes responsible for cell cycle arrest. This protein accumulates in cells as a response to stress and aging [67]. The reported data show that resveratrol activates the induction of p21 (cyclin-dependent kinase inhibitor 1) and p21-mediated cell cycle arrest, which is related to survivin depletion [68]. Survivin, which is one of the inhibitors of apoptosis proteins, is expressed at high levels in cancer cells and directly inhibits apoptosis [69]. Moreover, survivin possibly protects against apoptosis by suppressing caspase activity and inducing mitochondrial dysfunction [70].

Bcl-2 and Bax promoters are known to be regulated by resveratrol, which affects transcription factors p53 and NF-κB in a different way: it enhances the p53-dependent transcriptional activity and reduces the NF-κB-dependent activity [63]. The mechanism of resveratrol action related to reduced NF-κB-dependent activity was found in some cancers, including breast cancer, lung adenocarcinoma and hepatocellular carcinoma [56].

It has been also demonstrated that resveratrol inhibits the invasion and metastasis both in vitro and in vivo through down-regulating the expression of matrix metallopeptidase-9. These enzymes both metallopeptidase-2 and metallopeptidase-9 are overexpressed in malignant tumors and are able to degrade type IV collagen in basement membrane [56].

Some resveratrol analogs have been synthesized to improve the ability of resveratrol to suppress tumor proliferation. One of them HS-1793 exhibited stronger antitumor activity than resveratrol [71]. It was proved that cytotoxicity of the compound depends on its chemical structure, i.e. on inter-position of hydroxy groups; analogs with *ortho*-hydroxy-groups exhibit stronger cytotoxicity than compound without this structure [56]. Moreover, Chalal et al. showed that inhibition effect of analogs on SW480 and HepG2 tumor cells depends on a number and positions of hydroxy and metoxy groups [72]. It was found that some of synthetic resveratrol analogs possess higher activity than *trans*-resveratrol. For example *E*-4-hydroxy-4′-methoxystilbene was found to be one of the most active among studied analogs, while *E*-3-hydroxy-4′-methoxystilbene exhibited the lowest activity. It demonstrates that the position of hydroxy group in the structure of the compound is very important for its activity. In addition, the presence of methoxy group is also relevant, as it decreases the polar character of compound, which leads to an increased lipophilicity.

7. Effects on neurodegenerative diseases

The excess of reactive oxygen species in the brain is believed to be involved in the pathogenesis of various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and stroke. Resveratrol has also been identified as natural therapeutic agent with pharmacological potential against wide range of neurodegenerative diseases including Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and alcohol-induced neurodegenerative disorder.

It was found by Rivière et al. that polymerization of the β-amyloid peptide is markedly inhibited by resveratrol [73], which stimulates the proteosomal degradation of the β-amyloid peptides [74]. Besides, resveratrol exhibits neuroprotective activity against Alzheimer's disease by enhancing glutathione [75] and decreasing malondialdehyde levels [76]. Moreover, resveratrol through SIRT 1 activation reduces NF-κB signaling [77]. It is known that activation of NF-κB in neurons promotes their survival, whereas its activation in glial and immune cells originates inflammatory processes [78]. Supposedly, NF-κB is essential in the transmission of signals from the activated synapse to the nucleus. In addition, NF-κB contributes to neurodegenerative processes including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS-dementia and diabetic neuropathy. It has been proposed by Valerio et al. that NF-κB may regulate the production of Aβ42 oligomer [79]. Inhibition of NF-κB in Parkinson's disease increases susceptibility of dopaminergic neurons to 6-hydroxydopamine [80]. Besides, it was found that activation of NF-κB takes part in pathogenic mechanism of mutant huntingtin [81].

Lee et al. demonstrated that in Parkinson's disease resveratrol used at low doses (5 μM) considerably attenuates dopamine-induced cell death in neuroblastoma cells by activating the antiapoptotic factor Bcl-2 and inhibiting caspase-3 [82]. It was found by Chalimoniuk et al. that resveratrol (0.1 mM) possibly inhibits nitric oxide synthase [83]; nitric oxide is known to participate in the production of superoxide radicals and lipid peroxidation, which causes arachidonic acid release. Both nitric oxide and arachidonic acid are known to be the *inter-* and intra-cellular second messengers. However, released in excess in brain ischemia, Alzheimer's and Parkinson's diseases these compounds are destructive to cell.

Resveratrol action against Huntington's disease and amyotrophic lateral sclerosis has been postulated not simply through its antioxidant activity but rather by SIRT activation mechanism [84].

8. Other effects of resveratrol

In animal models [85,86], resveratrol was found to activate NAD^+-dependent proteindeacetylases sirtuins. These proteins deacetylate histones and thus increase the lifetime. Deacetylation results in a stronger interaction between histones and DNA, and in such a way, the expression of regulatory gene p53 is inhibited [87]. It has been reported that SIRT1 regulates metabolism and stress response by affecting histones, several

transcription factors and cofactors, other chromatin proteins, and DNA repair system. SIRT 1 interacts with and deacetylates peroxisome proliferator-activated receptor γ coactivator PGC-1α consequently increasing its activity [88]. PGC-1α is known to control mitochondrial biogenesis and function and can influence fiber-type switching in skeletal muscle and activate adaptive thermogenesis in brown adipose tissue [89]. Recent studies provide evidence that resveratrol acts against various malignant diseases by modulating proliferation of tumor cells as well as protein translation via SIRT1-dependent AMPK (AMP activated protein kinase) activation [90]. AMPK is known as a main regulator of metabolism in the body.

It has recently been reported that resveratrol directly inhibits phosphodiesterase (PDE), leading to increased cAMP levels [91,92]. cAMP is known as a key mediator of metabolic regulation. Resveratrol mimics some aspects of calorie restriction. Calorie restriction causes an increase in glucagon and catecholamine signaling and a decrease in insulin/IGF-1 signaling. Accordingly, cAMP level raises [93]. Resveratrol may trigger some of the pathways that are induced during calorie restriction, namely by increasing cAMP levels, which activates two parallel pathways. In one of them, the increased cAMP levels activate PKA (protein kinase A), which directly phosphorylates and activates SIRT1 [92]; in other, the increased cAMP leads to activation of cAMP-regulated guanine nucleotide exchange factor 1 (Epac1), elevation of intracellular calcium, and AMPK activation. Downstream of AMP and an increase in NAD^+ levels result in activation of SIRT1. Through these two pathways, SIRT1 promotes many beneficial metabolic changes, such as an increase in fatty acid oxidation, gluconeogenesis, mitochondrial respiration and a decrease in triglyceride synthesis, glycolysis, ROS production, inflammation, and genome instability.

It is known that the EPAC1–AMPK–SIRT1 pathway takes place in muscle and white adipose tissue. It is still unclear if it operates in other cell types. Many of participants in this signaling cascade also perform anti-inflammatory and neuroprotective functions. Quite a few sirtuin-activating compounds have been developed as viable therapeutic agents. Highly selective PDE inhibitors are recently being investigated while applying them in a variety of diseases such as inflammatory and neurodegenerative diseases [94]. Identification of PDEs as direct resveratrol targets may open the door to new applications of pharmacologic agents being identified previously.

9. Concluding remarks

Thousands of basic science experiments in vitro and in animal models suggest low toxicity and many positive effects of resveratrol. As mentioned above, continued research of its bioavailability and effectiveness in humans is obviously essential, especially when resveratrol is supplemented for a long time. It is important for future clinical investigations that doses for up to 5 g/day, taken for a month, were well tolerated and safe. However, dose-dependent mild or moderate side effects found in some studies might limit the dosage in clinical trials to <1 g/day.

Due to poor bioavailability of resveratrol, another perspective field could be synthesis of resveratrol structural analogs with improved beneficial effects. Such analogs could be useful in prevention and treatment of various diseases including cardiovascular diseases, cancer, obesity, neurodegenerative pathologies, etc. Application of phytochemical substances such as resveratrol in therapy for malignant diseases in combination with conventional chemotherapeutic preparations can open new perspectives in this field. It is also important to reveal additive/synergistic effects of resveratrol in combination with other therapies.

Resveratrol has also been entitled as a natural therapeutic agent with pharmacological potential in various neurodegenerative impairments including Alzheimer's, Huntington's, Parkinson's diseases, amyotrophic lateral sclerosis and alcohol-induced neurodegenerative disorder.

Consequently, more research is needed to confirm multiple effects of resveratrol and other both natural and synthetic polyphenols, and disclose mechanisms of their action.

Conflict of interest

The authors state no conflict of interest.

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