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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

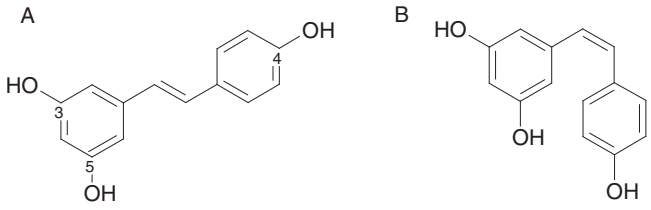

Figure – Chemical structure of *trans*- (A) and *cis*-resveratrol (B).