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The role of resveratrol in cellular aging

Daria Bieniek, Natalia Skierkowska, Monika Prylińska, Jakub Husejko, Małgorzata Gajos, Hanna Bednarek, Filip Biernacki, Kornelia Kędziora-Kornatowska

Abstract

Resveratrol is a substance present in grapes, blueberries and peanuts. Its concentration in grapes varies depending on the type and strain of the fruit. Resveratrol has a number of health-promoting properties for the body. Researchers most often indicate antioxidant, anticancer and cardioprotective activity, especially in the context of coronary heart disease, as well as anti-inflammatory, inhibiting the proliferation of pro-inflammatory cytokines. Resveratrol plays a neuroprotective role in the body, especially in the context of Alzheimer's disease, has a positive effect on the genes responsible for longevity and is the perpetrator of the so-called "The French paradox". The aim of the work was to present the role of resveratrol in cellular aging.

Keywords: resveratrol; aging; cellular aging

Intrudaction

Resveratrol (3,4 ',5-trihydroxystilbene) has recently attracted great interest from researchers due to its wide pharmacological potential. Is a nutraceutical or food that combines the characteristics of pharmaceuticals and nutritional values. It belongs also to the group of phytoalexins, or organic chemical compounds, which are produced by plants in response to the attack of pathogens (their concentration increases with the occurrence of stress factors) occurring among others in grapes, berries and peanuts [1].

Its antioxidant, cardioprotective, anti-cancer and anti-inflammatory properties open up new treatment options for many disease entities. It has been reported that the use of resveratrol together with anticancer drugs may sensitize cancer cells to standard chemotherapeutic agents [2].

It has been proven that resveratrol also plays a neuroprotective role in Alzheimer's disease (AD). It reverses the cognitive functions and protects against cognitive deficits in normal aging and, above all, inhibits the production of inflammatory cytokines [3].

Years of research suggest that polyphenol-rich foods are associated with age-related diseases. Starting from atherosclerosis, cataracts, type 2 diabetes, cardiovascular disease, hypertension and cancer. It was suggested that resveratrol and pterostilbene as natural nutrients are probable substances as anti-aging agents [4].

1. Occurrence of resveratrol

Resveratrol was found to be biosynthesized from one molecule of p-coumaroyl-CoA by stilbene synthase (STS) [5].

The best natural source of resveratrol are black grape varieties, and red contain more than green grapes. It has been described that in fresh skins of grapes there is about 50 - 100 mg of this compound per 1 g, which is 5 - 10% of their biomass [6,7]. Wines with the highest resveratrol content are: Pinot Noir, St.Laurent, Marzemino, Merlot, Gamay and Blaufränkisch, where the average content of this compound is approx. 1.9 mg / dm3. There is a small resveratrol content in the Agriogitiko species [8].

In comparison to red wines, the concentration of this compound in rosé wines is lower, while in white the lowest. This is due to the white wine production process, during which the pomace is removed immediately after pressing and squeezing the grape juice. In the production of red wines, the crushed fruits are left with the juice to extract the substances that give the aroma and color. That is why the resveratrol content in this type of wine is related to, among others with the duration of the fermentation process [9, 10, 6]. As a consequence, the content of resveratrol in wine is influenced by many factors, including: differences in the production process (especially the contact of the liquid phase with solid parts of grapes), grape variety, year of cultivation, place of cultivation and atmospheric conditions [11].

Another source rich in resveratrol is the root of the knotweed (Polygonum cuspidatum), cultivated mainly in Japan and China. Resveratrol also occurs in berry fruits (mulberry, blueberry, cranberry, cowberry, blueberry, inedible blueberry, blackcurrant, strawberries, raspberries). In fruit bread, apples, as well as in nuts, and in some herbs. Peanuts contain this ingredient in the amount of 0.02 - 1.8 mg / g. [12]. Resveratrol has been identified in the leaves and flowers of the following plants: crimson, white opium, orchid, Scots pine and son. rhubarb. This compound is also synthesized by trees such as eucalyptus or spruce [13]. In addition, the presence of this compound in cocoa, chocolate and tomato skins has been demonstrated [14].

2. „A French paradox”

In 1992 Serge Renaud and Michel De Lorgeril published a paper entitled “Wine, alcohol, platelets, and the French paradox for coronary heart disease” [15]. The authors using epidemiological data from MONICA project (a worldwide monitoring project for cardiovascular diseases organized by the World Health Organization - WHO) observed that mortality for coronary heart disease (CHD) among people in France was much lower than in other industrialized countries like the United States of America or the United Kingdom, despite the fact that French diet is known for high consumption of saturated fat. In most countries high consumption of saturated fat was positively related to high mortality from CHD. However that was not the case in France. They called it the “French Paradox”.

The MONICA project results studied by Serge Renaud and Michel De Lorgeril showed that the mortality rate from CHD in France is closer to those in Japan and China, rather than to those the USA and UK, i.e. for women, despite the fact that saturated fat consumption (14-15% of energy) and concentration of serum cholesterol, which are similar to the results from USA and UK.

Serge Renaud and Michel De Lorgeril made a hypothesis that this paradox may be related to high wine consumption in France. The authors indicated that consumption of alcohol as in France (20-30g per day) may reduce the risk of CHD by at least 40%. Newer research also seem to confirm that the habit of wine drinking in moderate quantities lowers the risk of cardiovascular diseases, cerebrovascular diseases and peripheral vascular disease due to reduced platelet aggregation and monocyte adhesion. It lowers also the risk of cancer and slows down some of the neurodegenerative diseases like Alzheimer's disease, protects the skin against damage caused by UV rays [15,16,17,18,19,20,21].

Red grapes and red wine that is produced out of them are a rich source of resveratrol. It is believed that resveratrol is the secret ingredient present in the red wine, that is accountable for the “French paradox” [22]. Resveratrol has many biochemical and physiological properties, including anti-inflammatory effect and inhibiting platelet aggregation [23,24,25,26,27,28]

3. Longevity genes

According to demographic research, most of the longevity communities around the world are located in mountainous areas. Inhabitants of Georgia and Armenia are known for their longevity [29]. Inhabitants of these areas for many generations were isolated from the external influences and progress of civilization, which suggests that genetic factors may be responsible for longevity, isolation and limiting the influx of people in high mountains could lead to gene pool restriction for generations. Additionally, the diet used by the inhabitants of these areas is considered to be pro-healthy, and red wine is its everyday element [29].

In good-quality red wine can be found anthocyanins, which are attributed to health-promoting, anti-inflammatory, anti-atherosclerotic effects. The highest pro-health properties are attributed to resveratrol. 3,5,4'-trihydroxystilbene (the chemical name for resveratrol) is an antioxidant contained in the skins of grapes. It has been shown that in appropriate concentrations it protects cells against apoptosis in states of myocardial ischemia, ventricular arrhythmias and cerebral ischemia [30,31]. In addition, resveratrol stimulates the weight loss of mice fed a high-fat diet through the expression of genes responsible for longevity genes, especially SirT1 and FoxOs [32,33]. An increasing number of research results suggest that resveratrol, increasing the expression of the so-called genes of longevity, it also imitates the restriction of the delivery of calories to tissues, reduces the concentration of insulin and glucose in the blood and IGF-1 factor (insulin like growth factor 1), thus increasing insulin sensitivity and increases HDL cholesterol [32,34]. In the studies of Bluhera et al. Blockade of insulin receptors in adipose tissue prolonged the life of mice by nearly 20% [35]. The expression of the SirT1 gene can be induced not only by resveratrol and red wine [36, 37] but also interestingly also by white wine and its components, tyrosol and hydroxytyrozole [38].

Limitation of food intake, temporary fasting and moderate physical activity prolong the life of the test animals. It has been known for almost 80 years that the consumption of low-calorie, but wholesome food known as a caloric restriction or dietary restriction extends the life of mice and rats by as much as 50% [38]. Studies of recent years indicate the role of sirtuin in this process. The first sirtuin (Sir2) is described in yeast. This is NAD + - dependent histone deacetylase silencing gene activity. The deletion of the Sir2-producing gene resulted in the shortening of the yeast's lifespan and its overexpression of elongation [39]. Moreover, the lack of this gene in yeast cells blocked the beneficial effect of glucose restriction on the body's lifespan, indicating that perhaps the sirtuin activating factors will mimic the calorie restriction unpleasant to humans. A similar effect of prolonging life by about 15% was obtained by chemical or genetic activation of sirtuin in other model organisms, which proves that the regulation of life length by sirtuin is evolutionarily preserved [40]. The mouse compound SIRT1, which is the equivalent of yeast Sir2, indicates that sirt1-deficient mice were not susceptible to caloric restriction and the action of the sirtuin antagonist [41].

Seven sirtuins (SIRT1-7) are known in mammals that differ in enzymatic activity, substrates, and cellular location. Only three sirtuins (SIRT1-3) are exclusively deacetylases. Sirtuins are activated by energy deficiencies that arise during exercise and starvation. This increases the level of sirtuin cofactor such as NAD + and sirtuin substrates are activated, which are not limited to histones only. Of particular interest to researchers is the mitochondrial sirtuin SIRT3. It activates mitochondrial enzymes involved in β-oxidation of fatty acids, amino acid metabolism and electron transport chain, which increases the metabolism of mitochondria. [39] Activation of SIRT3 also prevents mitochondrial apoptosis. Interestingly, two variants of the SIRT3-producing gene showed a relationship to human longevity, but another variant was found, which showed a connection with an increased incidence of metabolic syndrome [42].

Studies have been carried out using their agonists, which include natural polyphenol, resveratrol found among others in red grapes. Indeed resveratrol prolonged the life of model animals such as yeast, C. elegans or fruit fly, however, not all studies confirm this [42]. Resveratrol activates signaling pathways that are cardioprotective and, as shown in mice and rats, balances the negative effects of obesity and insulin resistance [43].

4. Resweratrol *vs* IQ

Resveratrol reduces blood glucose, acts as a protective function of beta-cells of the pancreas, reduces hyperinsulinemia and insulin resistance of tissues, and therefore appears to be a good adjuvant for the treatment of insulin resistance [44].

Resveratrol activates the SIRT-1 protein. This protein has the ability to regulate the transcriptional activity of some genes, increases insulin secretion by pancreatic beta cells and enhances lipolysis in adipose tissue. Resveratrol activates the PGC-1 glucogen inducer in the liver, thus reducing the amount of energy consumed [34]. By imitating the delivery of calories to tissues, it reduces insulin and blood glucose as well as IGF-1 factor. In this way, it increases the sensitivity to insulin [32, 34, 45]. Bluher's research has shown that it has the ability to block insulin receptors in adipose tissue [45]. In a study in which men with diagnosed diabetes were given for 4 weeks twice a day, 5 mg resveratrol increased the insulin sensitivity [45].

In addition, resveratrol reduces glucose and glycosylated hemoglobin [44]. In a study of 10 people over 65 years of age, with diagnosed impaired glucose tolerance, given 1 to 2 g of resveratrol, a reduction in postmeal glucose was observed. It was also found that the higher the dose of consumed resveratrol, the more beneficial the therapeutic effect [46].

Resveratrol stimulates the action of hepatic AMP-activated liver protein. It takes part in the regulation of lipid and glucose metabolism. It leads to the activation of catabolic processes. In addition, it increases glucose uptake by affecting Glut 4 (glucose transporter 4) [44, 47, 48].

After administration of resveratrol, in healthy male rats, a decrease in insulin, glucose and insulin sensitivity were observed compared with the control group, which confirms the facts described above. Hepatic parameters during the study indicated the safety of resveratrol [49].

Studies conducted on mouse lemur trees showed that animals fed for 5 weeks with resveratrol in a dose of 200 mg per kilogram of body weight per day, were weighted five times less than those who were deprived of this compound. Metabolism of these animals increased by 29% despite the smaller amount of food consumed. The studies also showed an increase in the

concentration of enzymes inducing the deposition of stored energy in the form of adipose tissue: pancreatic polypeptide and glucose-dependent insulinotropic peptide [50].
During the studies on resveratrol supplementation in patients with glucose disturbances, no hypoglycaemia was observed in patients. This gives hope for the use of this compound in the therapy supporting the treatment of diabetes in the future [47].

5. Advantages of resveratrol

The study suggests that the limitation of LDL lipoprotein oxidation by resveratrol may be related to its ability to inhibit quinone reductase 2 activity, which catalyzes the transformation of adenosine nucleotides and thus increases the activity of cellular antioxidant mechanisms [51]. This compound significantly reduces the generation of reactive oxygen species (ROS), and this effect is likely to exert a synergistic effect along with other polyphenols present in the wine [52].

The strong anti-atherosclerotic properties of resveratrol were confirmed by studies conducted on a mouse model, using animals with a silent gene responsible for the expression of apoE and the receptor for LDL lipoproteins. It was shown that after 8 weeks of using a high-fat diet, animals whose diet was enriched with resveratrol were characterized by inhibition of the rate of thromboembolic changes in the carotid arteries and a significant reduction in atherosclerotic plaque size [53].

The mechanism of anti-inflammatory action of resveratrol is mainly due to its ability to inhibit the synthesis and secretion of inflammatory mediators, including lymphotoxin, granulocyte and macrophage colony stimulating factor (GM-CSF), interleukin 8 (IL-8) and histamine. Inhibition of the inflammatory reaction under the influence of resveratrol is also related to its ability to block the translocation of the NF-κB transcription factor into the nucleus [54].

Resveratrol is of great interest due to its neuroprotective properties, particularly in relation to Alzheimer's disease and Parkinson's disease. An example of such activity may be the protection of hippocampal cells of experimental animals against β-amyloid toxicity, dependent on the activation of protein kinase C (PKC) [55]. In the context of Parkinson's disease, resveratrol has the ability to inhibit the production of proinflammatory cytokines within dopaminergic neurons in animals with disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [56]. In turn, in animals in which Parkinson's disease was induced by means of 6-hydroxydopamine, resveratrol affected the proper ultrastructure of dopaminergic neurons and alleviated the course of the disease, which was causally related to the limitation of the local inflammatory response. These effects were noted already after two weeks of using the compound [57].

The anti-tumor effect of resveratrol lies in the ability to effectively inhibit each stage of cancer, ie initiation, promotion and progression of the disease. It was observed that resveratrol possesses the ability to sensitize tumor cells to commonly used chemotherapeutic agents, including: doxorubicin, cisplatin, cytosine arabinoside and methotrexate. Studies carried out on cervical cancer cells, chronic myeloid leukemia and multiple myeloma have also shown that resveratrol may sensitize cancer cells to X-rays [58]. Antitumor activity of resveratrol has been demonstrated, both in terms of antiproliferative and proapoptotic activity, in relation to many types of tumor cells, including: B-cell lymphatic leukemia, non-Hodgkin's lymphoma, breast cancer, ovarian cancer, prostate cancer, colon cancer and malignant melanoma [59] .

6. Anti-aging effect

This relationship has a very beneficial effect on the lifespan of model organisms. Significant elongation of life under the influence of resveratrol was noted in the case of such organisms as: budding yeast (Saccharomyces cerevisiae), roundworm (Caenorhabditis elegans) and fruit fly (Drosophila melanogaster). An interesting observation, especially in the context of the evolutionary aspects of the aging process, is the fact that extending the lifespan of lower organisms resveratrol did not limit their fertility. The experienced organisms were also successfully completed. For example, studies carried out on Nothobranchius furzeri species have shown that resveratrol extends their life by as much as 56% [60].

Interesting information was provided by the studies of Baur et al. Who showed that resveratrol improves health and reduces the risk of death by 30% in mice on a high-fat diet. This effect is attributed to the effect of resveratrol on a number of metabolic processes, including the increase in tissue sensitivity to insulin, lowering of insulin-like growth factor-1 (IGF1), activation of AMP-activated kinase and increase in the number of mitochondria in the cell [32].

According to reports, the effect of resveratrol on the suppression of cell division loss rate may also be the result of blocking the mROR (mammalian target of rapamycin) signaling pathway, which is one of the most important cellular senescence effector pathways [61].

7. Disadvantages of resveratrol

In addition to numerous pro-health properties, resveratrol also has negative features.
This compound has low absorption. Decomposes quickly in the lumen of the gut and the liver. It is rapidly metabolised by hepatocytes with the participation of cytochrome P450. Its half-life is from 8 to 14 minutes [62]. Its plasma content is low due to the rate of transformation [63]. From the moment it appears in the bloodstream for about 30 minutes, it is converted to sulphite derivatives. These compounds are present in the bloodstream for about 9 hours, then are excreted through the kidneys and the faeces [64, 6].

In animals receiving resveratrol at a dose of 3 g per kilogram of body weight per day for 4 weeks, loss of appetite and weight loss were observed. Serum levels of creatinine, alkaline phosphatase, alanine aminotransferase, total bilirubin, albumin as well as decrease in hemoglobin, hematocrit and erythrocytes count and leukocytosis were found in the blood serum. Histopathological examination of kidneys and gallbladder showed hyperplasic changes.

At a dose of 1 g per kilogram of body weight per day for 4 weeks, only female body weight loss and leukocytosis in males were found. [65]

Discussion

Interest in resveratrol is noticeable in many health care professionals who want to use the compound in their clinical practice, as well as in non-medical people who want to improve their health. The reason for this are numerous published studies indicating the importance of resveratrol in the prevention of cardiovascular diseases, which are still important factors that lower the quality of life and shorten its length. As an antioxidant and a compound with anti-inflammatory effect, it inhibits the processes initiating pathological changes in the blood vessels, which leads to heart and vascular diseases [66].The growing popularity of resveratrol is therefore justified, and the task for scientists is to develop knowledge about the substance in question, because that, along with the increase in its consumption, systematically increase the data on resveratrol, as well as its possible side effects

Due to the detection of a relatively high concentration of resveratrol in dry red wine, research has begun which indicates that a small intake of red wine reduces the risk of cardiovascular diseases. The protective effect of this drink is associated with many mechanisms: an increase in HDL cholesterol, a decrease in platelet abundance, anti-aggregation and rebuilding of the endothelium of blood vessels [67]. It should be remembered, however, that red wine is a drink containing alcohol - a substance that predisposes to many cancers, leading to cirrhosis of the liver or causing fatal accidents. According to statistical data, in 2010 as much as 2.8% of all deaths were caused to a greater or lesser extent by alcohol [68]. In most cases, these were situations associated with frequent drinking of large amounts of alcohol, and supplementation of resveratrol is associated with the recommendation of consuming small doses of wine, however, continuous contact with this type of stimulant, under favorable circumstances, may increase the amount of alcohol consumed and addiction [69].

In order to exclude the risk associated with the presence of alcohol in red wine, there are activities aimed at finding other sources of resveratrol, and without the mentioned stimulants. The promising solution is drinking Itadori tea, traditionally consumed in Japan and in China. The concentration of the antioxidant in question is particularly high, but the number of studies on the effects of resveratrol consumed in the form of Itadori tea on the body is still insufficient [70]. For this reason, it is necessary to continue research in this topic before promoting the consumption of this tea in society. Resveratrol can also be supplemented in the form of pharmaceuticals. The advantage of this solution is to take the compound in question without having to eat the resveratrol accompanying substances in natural products, such as alcohol. However, many side effects, related to the intake of the mentioned antioxidant in this form, have been described, and the bioavailability of resveratrol in this form is not satisfactory [71]. Therefore, measures should be taken to reduce the risk of resveratrol supplementation in the form of pharmaceuticals.

As the work presented shows, resveratrol has many beneficial properties for the human body. Its wide range of activity causes many pro-health responses of the body. Among them, antioxidant and anti-inflammatory effects are distinguished, which is important in cardiovascular diseases, cerebrovascular diseases, cancers or neurodegenerative diseases. Resveratrol slows down the aging process of the body and can affect life expectancy. Thanks to his polyphenolic form, he is credited with the theory of the French paradox. Naturally, resveratrol can be found in food products, among others wine and fruit.

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