JABŁOŃSKA, Wiktoria, WARDĘSZKIEWICZ, Marta, KASPRZAK, Amelia, MARKOWIAK, Szymon, ŚWIERCZ, Maciej, KUBISZ, Magdalena, MAŃKOWSKA, Aleksandra, TRUCHTA, Monika, PEJAS, Anna and KOLANO, Agata. Resveratrol - its properties, occurrence and health benefits. Journal of Education, Health and Sport. 2024;51:116-128. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.51.009
https://apcz.umk.pl/JEHS/article/view/47735
https://zenodo.org/records/10466568

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 17.11.2023. Revised: 30.12.2023. Accepted: 06.01.2024. Published: 07.01.2024.

Resveratrol - its properties, occurrence and health benefits

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ABSTRACT

Introduction and purpose: Wine ingredients relevant to health are polyphenols, which are divided into flavonoids and non-flavonoids. Resveratrol is a non-flavonoid component of wine widely known for its health-promoting properties. This article will discuss its chemical structure, synthesis, metabolism, occurrence in nature and impact on human health.

Review methods: The purpose of this article was to assemble and analyse the available data about resveratrol. The search of articles in Pubmed database was carried out using following keywords: "wine", "resveratrol", "polyphenols", "alcohol". Inclusion criteria: indexed in Pubmed database, published in last 10 years. Exclusion criteria: Case reports, studies in language other than English, studies that seemed to be biased.

Descripiton of the state of knowledge: Resveratrol has a wide range of health-promoting effects. It inhibits some stages of platelet activation by reducing the synthesis of thromboxane A2 and their aggregation caused by agonists i.e. collagen, ADP, cathepsin G or thrombin. Furthermore, it causes a reduction in blood glucose and glycated hemoglobin levels, increases insulin sensitivity and potentially has protective effect on pancreatic cells. It lowers total plasma cholesterol and low-density lipoproteins levels while increasing insulin sensitivity and high-density lipoproteins level. In addition to this, it has neuroprotective, anti-tumour and anti-angiogenic effect proven in specific types of cancer.

Summary: Resveratrol is said to improve the therapeutic outcome in patients suffering from cardiovascular diseases, diabetes type 2, Alzheimer's disease, other neurodegeneration

diseases and in certain cancers. Nevertheless, the issue of resveratrol's effect on the human body requires further research.

Key words: wine; resveratrol; polyphenols; non-flavonoids; alcohol

1. Definition

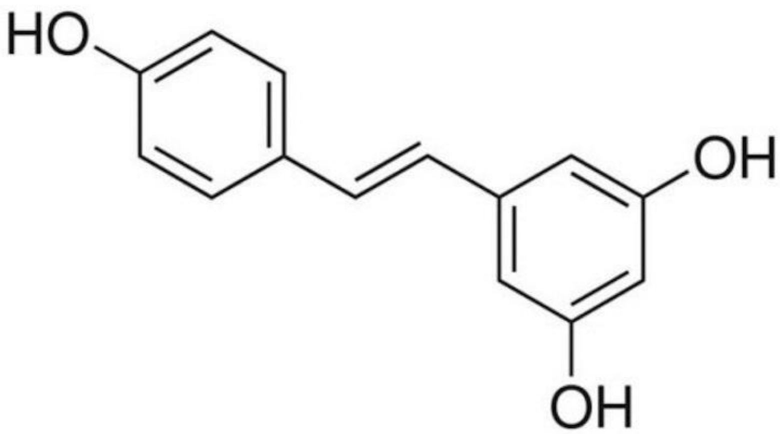

Fig. 1. Chemical structure of resveratrol (source: https://bioinfo.imdik.pan.pl/wiki/Resweratrol)

Resveratrol (3,5,4'-trans-trihydroxystilbene) is a polyphenolic phytoalexin that belongs to the stilbene family. It consists of two phenolic rings linked together by a styrene double bond. It exists in the form of cis and trans isomers, while trans-resveratrol is the more stable and more commonly found form in nature [1].

2. Synthesis

Resveratrol is synthesized in plants in response to unfavorable environmental factors, such as UV radiation, lack of water and, most importantly, fungal infections [2, 3, 4]. The most intensive synthesis of resveratrol takes place in grapes just before they reach maturity. The final enzyme for its biosynthesis is stilbene synthase, activated by the above-mentioned stress stimuli [5]. The concentration of resveratrol reaches its highest level about 24 hours after exposure, and then drops after 42-72 hours due to the action of stilbene oxidase [6].

3. Sources of resveratrol in the daily diet

Its most important sources in the human diet are grape skins and seeds, wine, peanuts, berries and tea [7]. Resveratrol is mainly found in the skin of the grape fruit, and only in marginal amounts in the pulp, so its concentration in different types of wine depends, among other things, on the time of maceration. White wines undergo this process briefly, if at all, which contributes to the low content of this polyphenol compared to red wines [8]. The concentration of resveratrol also varies according to geographical origin, type of wine and oenological practices [9]. Grape skin thickness was not found to correlate with its content. Research conducted on wines of 21 different grape varietals from 18 different regions showed that the highest levels of resveratrol were found in wines made from Pinot Noir from France. Slightly lower concentrations were found in liquors from the same grape variety grown in Spain and Italy. The wine with the lowest labeled resveratrol content comes from the United States and is made from the Zinfandel variety. On average, the five highest levels of trans-resveratrol, regardless of region, were found in wines made from Pinot Noir, St. Laurent, Marzemino, Merlot and Blaufränkisch [10].

4. Metabolism

After oral intake resveratrol is absorbed in the small intestine. The efficiency of this process is 75% and is thought to occur mainly through transepithelial diffusion. This absorption is unusually high for a polyphenol derived from food, especially considering the poor water solubility of this compound. Once absorbed, resveratrol is metabolized very rapidly in hepatocytes with the involvement of cytochrome P450. Metabolic analysis of both plasma and urine indicated that glucoronides and sulfates are resveratrol's main metabolites. Extensive metabolism in the intestine and liver results in bioavailability after oral administration of much less than 1%. Increased dose and repeated administration of resveratrol does not appear to significantly alter this. Currently, there is no evidence of specific receptors for resveratrol, although it is known to accumulate preferentially in tissues compared to plasma. In order to improve its bioavailability, and thus potentially enhance its health-promoting effects, derivatives of resveratrol were introduced. The most common were methylated forms such as pterostilbene and 3,4,5,4′-tetramethoxystilbene. The first had better bioactivity and was proven effective in colon cancer prevention on a rat model, and the latter showed particularly high accumulation in intestinal mucosa [11]. There are also studies evaluating the combination of resveratrol with piperine, which is said to modulate its pharmacokinetic parameters, hence increasing its bioavailability [12].

5. Health benefits of resveratrol

Resveratrol has vast biochemical and physiological properties, including antiplatelet, anti-inflammatory and estrogenic activity which contributy to a wide range of health benefits, from chemoprevention to cardioprotection.

Resveratrol is a strong natural antioxidant, which is due to its ring structure and the possession of conjugated double bonds. The presence of hydroxyl groups in the rings has also proven to be significantly beneficial [13]. By increasing nitric oxide (NO) synthesis, resveratrol captures superoxide radicals, which results in oxidative stress reduction so pivotal in cardiac, cerebral or renal ischemia [3].

Resveratrol inhibits cancer cells proliferation, by increasing the activity of p53, Bax and caspase proteins and by stopping the cell cycle. It also contributes to a decreased expression of cyclins D1 and E, Bcl-2, Bcl-XL(B-cell leukemia/lymphoma) and IAP (inhibitory apoptosis proteins). Furthermore, it has the ability to inhibit the activity of numerous transcription factors, DNA polymerase and protein tyrosine kinases. However, it is possible that resveratrol can induce cell differentiation [13].

Resveratrol’s impact on nervous system also proves to be beyond significant. A study on mice indicated that it reduces neurodegeneration in cerebral cortex, improves cognitive function, learning and memory skills in rats with vascular dementia, and induces neuroprotection in mice models of Alzheimer's disease. It may also have neuroprotective properties in central nervous system injuries, i.e. stroke, or in neurodegeneration of the brain. At this point, however, there are no conclusive results from human studies on this topic [7].

Based on animal models, resveratrol can also be attributed to antidiabetic effects [14]. It causes a reduction in blood glucose and glycated hemoglobin levels, increases insulin sensitivity and potentially has protective effect on pancreatic cells. The exact mechanisms responsible for this action are unknown, but include altering the expression of genes responsible for insulin uptake by target cells, reducing body fat, and lowering oxidative stress.

In studies conducted on patients with impaired glucose tolerance, an increase in insulin sensitivity and a decrease in postprandial glycemia were observed, but without a change in the parameters of pancreatic beta-cell function. On this basis, it can be speculated that resveratrol has potential in supporting the treatment of diabetes, but further studies conducted in this direction are necessary [15].

Resveratrol lowers the risk of cardiovascular diseases such as coronary artery disease, atherosclerosis and myocardial infarction, among others, as a result of inhibiting lipid peroxidation and reducing the penetration of oxidized LDL into blood vessel walls [16]. It also aids in atherosclerosis prevention by inducing NOSs activity. NO production strongly correlates with blood vessels dilation, which balances out endothelin-1 constricting effect. Resveratrol inhibits some stages of platelet activation by reducing the synthesis of thromboxane A2, as well as their aggregation caused by agonists i.e. collagen, ADP, cathepsin G or thrombin [17,18]. It helps to reduce the release of compounds stored in platelet granules and platelet cell adhesion to collagen and fibrinogen, which is the first step in thrombocyte activation [13]. In addition, it inhibits damage to cardiomyocytes while stimulating regeneration of myocardial tissue. In a study on rats in which the myocardium was subjected to brief episodes of ischemia and reperfusion, administration of resveratrol at a dose of 1-2.5 mg/kg/day for 7-14 days resulted in a reduction in the number of apoptotic cells and a reduction in the infarcted area [19].

Furthermore, resveratrol can inhibit inflammation associated with atherosclerosis by regulating COX-2 activity at the transcriptional level, thereby inhibiting PGE2 (prostaglandin E2) production [20]. The anti-glycation effect of resveratrol is also important. Glycation is a non-enzymatic reaction between reducing sugars and proteins that leads to the formation of the final advanced glycation products (AGEs). AGEs accumulate, causing damage at the tissue and cellular levels. They cause, among other things, changes in protein structure, lipid peroxidation or endothelial dysfunction. The glycation process produces highly reactive compounds such as methylglyoxal (MGO) and glyoxal (GO), which increase oxidative stress in the body. It is most likely that increased glycation can lead to neurodegenerative diseases, diabetes or myasthenia gravis. Although studies show that resveratrol inhibits the formation of AGEs, it also binds to MGO and GO, which is an undesirable effect, since adducts can oxidize amino acids in human serum albumin. Studies on MG-treated rats have shown that resveratrol significantly reduces levels of advanced oxidation products of protein (AOPP), carbonylated protein in urine and also markers of oxidative stress in the liver [7].

Angiogenesis is the process of forming new capillaries from an existing vascular network. It is also intrinsically linked to the development of cancer. Angiogenesis is stimulated by growth factors and cytokines. Certain cytokines increase gene expression and proliferation of endothelial cells as well as stimulate these cells to produce proteolytic enzymes which destroy the matrix, causing endothelial cell migration and tissue invasion. The anti-angiogenic properties of resveratrol have been observed mainly in cancers such as lung cancer, gliomas and breast cancer. Resveratrol has been shown to inhibit proliferation, induce apoptosis and block the G1-S phase transition of bovine aortic smooth muscle cells in a dose-dependent manner. It can inhibit the growth and chemotaxis of capillary endothelial cells mediated by the basic fibroblast growth factor receptor (bFGF) and vascular endothelial growth factor receptor (VEGF). In addition to its direct effect on endothelial cells, resveratrol also showed anti-angiogenic effects in vivo, particularly on tumour-induced angiogenesis. A study where mice were subjected to resveratrol showed its great ability to inhibit VEGF-induced corneal neovascularisation. It inhibits the progression and angiogenesis of human ovarian cancer by suppressing the expression of hypoxia-inducible factor-1 and VEGF. It also slows angiogenesis in gliomas by inducing endothelial cell apoptosis, inhibiting VEGF expression in glioma cells and microscopic suppression of angiogenesis manifested by reduced microvessel density. The mechanisms of resveratrol's anti-angiogenic action are thought to be related to a number of factors, including: increased expression of p53 and p21 and impaired cell cycle progression of endothelial or smooth muscle cells, the aforementioned inhibition of VEGF expression, binding of VEGF to endothelial cells and binding of bFGF to its receptor, inhibition of COX-2, matrix metalloproteinase-2 (MMP-2), MMP-9, urokinase-type plasminogen activator, adhesion molecules, cyclin D1 and hypoxia-inducible factor-1 [21].

Summary

Resveratrol has wide-ranging, valuable health effects, especially in cardiovascular, metabolic, neurological or neoplastic diseases - which often fall under the definition of diseases related to contemporary civilisation. Nevertheless, further research is crucial to enable better prevention and improve the therapeutic outcome in patients suffering from aforementioned diseases.

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All authors have read and agreed with the published version of the manuscript.

Financial support: No financial support was received.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

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