Review article / Artykuł przeglądowy

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Resveratrol as a multifunctional bioactive compound

Resweratrol jako wielofunkcyjny związek bioaktywny

ABSTRACT

Resveratrol is a natural polyphenol found mainly in grape skins, red wine, berries and peanuts. It exhibits a wide range of biological activity, including antioxidant, anti-inflammatory, anti-cancer, neuroprotective and cardioprotective properties.

The article aimed to analyse scientific research focusing on the current state of knowledge on the molecular mechanisms of action of resveratrol, its bioavailability and potential in the treatment of lifestyle diseases, wound healing and skin protection against damage caused by ultraviolet radiation. In addition, the role of resveratrol in the treatment of diabetes, neurodegenerative diseases and cardiovascular diseases was discussed.

In light of the collected data, resveratrol appears to be a promising therapeutic and cosmetic ingredient with multidirectional biological activity. Current limitations in the clinical use of resveratrol are mainly related to its low bioavailability.

Keywords: resveratrol, antioxidants, wound healing, photoaging, prevention of civilization diseases

STRESZCZENIE

Resweratrol to naturalny polifenol występujący głównie w skórkach winogron, czerwonym winie, jagodach i orzeszkach ziemnych, wykazuje szerokie spektrum aktywności biologicznej, w tym właściwości przeciwutleniające, przeciwzapalne, przeciwnowotworowe, neuroprotekcyjne oraz kardioprotekcyjne.

Celem artykułu była analiza publikacji zawierających badania naukowe koncentrujące się na aktualnym stanie wiedzy dotyczącej mechanizmów molekularnych działania resweratrolu, jego biodostępności oraz potencjału w leczeniu chorób cywilizacyjnych, wspomaganiu gojenia ran oraz ochronie skóry przed uszkodzeniami wywołanymi promieniowaniem ultrafioletowym. Ponadto omówiono rolę resweratrolu w terapii cukrzycy, chorób neurodegeneracyjnych oraz schorzeń układu sercowo-naczyniowego.

W świetle zgromadzonych danych, resweratrol wydaje się obiecującym składnikiem terapeutycznym i kosmetycznym o wielokierunkowym działaniu biologicznym. Aktualne ograniczenia w zastosowaniu klinicznym resweratrolu związane są głównie z jego niską biodostępnością.

Słowa kluczowe: resweratrol, antyoksydanty, gojenie ran, fotostarzenie, profilaktyka chorób cywilizacyjnych

INTRODUCTION

Resveratrol is a chemical compound of natural origin with antioxidant properties, found mainly in grapes and red wine. It acts protective against oxidative stress and the negative effects of ultraviolet radiation (UV). It also plays an important role in prevention as well as in therapy of many lifestyle diseases. Resveratrol protects cardiovascular system, inhibits progression of cancer, and supports neurological function and exhibits anti-inflammatory effects. It can also accelerate healing of wounds, promote the treatment of skin infections and prevent photoaging. Due to its properties, it is the subject of numerous studies on applications in medicine as well as in cosmetology.

Resveratrol (3,5,4'-trihydroxystilbene) is a chemical compound, which dissolves well in ethanol, but has limited water solubility. It acts as an antioxidant, so it protects cells against oxidative stress caused by hydrogen peroxide, as well as cell death via UV radiation. It exists in two isomeric forms: cis and trans. In natural conditions trans form predominates, showing greater biological activity than the cis isomer. A particularly rich source of resveratrol is grapes, especially their skins, as well as wine. It occurs in more than 70 plant species and is present in natural food products such as peanuts, tomato peel, cranberry juice or cocoa [1-3]. Resveratrol is absorbed in about 70% in the small intestine, it enters the bloodstream and reaches the to the liver, where it undergoes biotransformation to glucuronate with the involvement of cytochrome P450 (CYP1B1) [4]. It is classified as a phytoestrogen because its chemical structure resembles estrogen which is synthesized in organisms. Plants produce resveratrol in response to fungal infections or severe stress factors, such as water shortage, damage to tissues or UV radiation [5, 6]. It owes its fame to French paradox, which contributed to the study of over the composition of wine and grapes [7].

RESVERATROL IN SYSTEMIC DISEASES

CARDIOVASCULAR

Cardiovascular diseases such as atherosclerosis, coronary heart disease or heart attack, are among the most common disorders. Atherosclerosis is a chronic inflammatory disease of arteries and is the main cause of about 50% of all deaths in industrialised societies [8]. In a study conducted in Sweden, found that more than 40% of adults aged 50-64 years without known heart disease had some degree of atherosclerosis [9]. In the United States coronary artery disease is the most common type of heart disease and affects about 5% of adults aged 20 and older. Coronary heart disease caused 371,506 deaths in 2022 in the US [10]. Worldwide, heart attacks affect about 3 million people annually, with more than one million deaths occurring in the United States [11]. In a study of people over the age of 60, the global incidence of heart attack was 9.5%, while in the under-60 group it was 3.8% [12]. One factor in the aforementioned diseases is the high level of cholesterol. Resveratrol may reduce the risk of these diseases by, among other things, inhibiting lipid peroxidation and limiting penetration of oxidised lipoprotein particles such as low-density lipoproteins (LDL) in the walls of blood vessels. Cancer is one of the most common groups of diseases, particularly skin, lung, breast, colorectal, prostate and cervical cancers [13, 14]. Resveratrol plays an important role not only in the prevention of cancers, but also in their treatment. Research indicates that it can inhibit every stage of the tumorigenesis process, including disease initiation, promotion and progression. *In vitro* research showed that resveratrol can increase the effectiveness of chemotherapy by inactivating a protein that acts as a transcription factor *NF-Kb* (*Nuclear Factor kappa B*). NF-κB is produced by cancer cells and controls the expression of many genes, contributing to their resistance to treatment and uncontrolled multiplication. By blocking this factor, resveratrol makes chemotherapeutics work more effectively at the target site [13].

Resveratrol influences the nervous system by its neuroprotective properties. Studies show that it reduces toxicity of β-amyloid in rat hippocampus cells by kinase C activation. In addition, it stimulates the mechanisms of defence against free radicals, among other things, by increasing the glutathione levels, which protects microglia cells. Currently, research studies are underway on its potential use in therapy of neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease [15]. Interesting studies demonstrate the potential effect of resveratrol in the treatment of depression in menopausal women. Perimenopausal depression is a common mental disorder in women. Research on the pathogenesis of depression reveals that dysregulation of metabolic systems, reduced neurogenesis, oxidative stress, as well as the inflammatory response would lead to the progression of depression [16].

RESVERATROL IN WOUND HEALING AND TREATMENT OF INFLAMMATION

Resveratrol plays an important role in regulating inflammation, which has a direct impact on the regenerative processes of the skin. Its wound healing properties result primarily from its effect on signalling pathways in the cytoplasm and cell nucleus, associated with the epidermal growth factor receptor (EGFR). The regenerative mechanism of action of resveratrol is not directly related to its activity as an antioxidant nor the ability to neutralize the free radicals [17]. *In vivo* studies conducted on an animal model has shown that resveratrol could reduce the migration of mast cells to the site of injury, while stimulating the influx of lymphocytes and macrophages. It is also speculated that the compound may modulate the immune response, inhibiting

the reaction-dependent from the antigen (Th1) in favour of a Th2-type response. Importantly, the degree of neutrophil infiltration appears to depend on the type of pathogen [18]. Resveratrol exhibits antimicrobial and antifungal activity, and also supports the immune system at the site of the wound. One study confirmed its effectiveness against pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*, which often complicate the wound healing process. Resveratrol has been proven to be more effective than some popular antimicrobial preparations, such as Levomecol ointment and antifungal Clotrimazole [19]. *Staphylococcus aureus* colonises skin excessively in atopic dermatitis while exacerbations, especially causing dysbiosis of the skin microbiota and a reduction in bacterial diversity. Changes in the microbiome translate into lipid content, pH, hydration and sebum secretion. To this end, treatments are used to reduce staphylococcal colonization [20]. In this context, resveratrol shows potential as a healing aid in skin infections. *In vitro* studies confirm that it inhibits microbial growth in a dose-dependent manner [19].

Resveratrol can also help heal diabetic ulcers. It has a protective effect on the endothelium, preventing its damage caused by high levels of blood sugar. Activates sirtuin 1 (SIRT1, silent information regulator 1), a protein of the sirtuin family playing an important role in the regulation of many biological processes, which promotes angiogenesis and affects the degradation of the transcription factor (FOXO1, *forkhead box protein O1*) after derepression of expression c-Myc [21]. In addition, resveratrol stimulates the overexpression of glyoxalase 1 (GLO1), which promotes the healing process of wounds at various levels, including activation of the enzyme IRE1α (*inositol-requiring enzyme* 1α). All of these mechanisms make resveratrol likely to be a valuable agent in the treatment of hard-to-heal wounds, especially in patients with diabetes [22]. The risk of ulcers, especially associated with diabetic foot, over a lifetime ranges from 19% to 34% and increases with age. Consequences of ulcers are associated with functional deterioration, infections, hospitalisation and even amputation of lower limbs or death. New analyses showed that in some regions the number of amputations has increased by as much as 50% in last years, despite the previous long-term trend of decline. The increase is particularly noticeable among young people and representatives of racial minorities and ethnicities [23].

In vitro studies on resveratrol found confirmation in *in vivo* experiments. In one study on mice, it has been shown that both oral and topical application of the compound inhibited UVB -induced thickening of the epidermis [24]. Additionally, it reduced the expression of enzymes: *matrix* metalloproteinase 1 (MMP-1) and matrix metalloproteinase 9 (MMP-9), which are involved in the degradation of the collagen. The protective effect of resveratrol is due to, among other things, activation of the Nrf2 antioxidant pathway, which protects cells against UV radiation damage [24]. In a rat study, its properties were confirmed photoprotective, especially when applied in the form of lipid nanoparticles, which increased its penetration through the epidermis. The effectiveness of skin protection was higher than with resveratrol alone. Other studies have shown that its combination with β-cyclodextrin (β-CD) effectively reduced oxidative stress. Tests on women aged 45-70 years old showed that after 30 days of use of the product with β-CD, the skin was more hydrated, supple and brightened, and signs of aging have diminished [25].

One study on the model of photoaging induced by UVA in mice confirmed the key role of resveratrol in the prevention of this process. The results indicate that long-term UVA exposure led to inhibition of autophagy, and reduction in this process contributes to the aging of the body. Additionally, it has been shown that administration of resveratrol subcutaneously improved skin roughness, reduced erythema and wrinkles in mice with UVA radiation-induced skin damage. In addition, it helped decrease excessive keratosis of the epidermis and hyperpigmentation, and reduced inflammatory processes and slowed the breakdown of collagen fibers [26].

Although clinical studies on the effect of resveratrol on photoaging skin are few, one of which showed an improvement in its condition after 12 weeks of using a cosmetic with 1% resveratrol, 0.5% baicalin and 1% vitamin E. The preparation caused transdermal absorption and changes in gene expression, such as hemoxygenase-1 (HO-1), vascular endothelial growth factor - A (VEGFA) and collagen type 3 (COL3A1). Clinical analysis showed a significant improvement in terms of fine lines and wrinkles, firmness, elasticity and skin tone, as well as reduced hyperpigmentation, increased radiance and diminished roughness compared to the initial values. Ultrasound studies in the eye area revealed an average increase in skin thickness of 18.9%, which indicated that it was clearly undergoing remodeling [27].

In contrast, a 2019 study confirmed that resveratrol not only improved skin tone, but also skin hydration. In the study, 20 volunteers took part, who were observed for six weeks. After only two weeks of use, the level of hydration increased by 20%. Regular application of resveratrol strengthened the hydrolipid barrier of the skin and reduced the water loss through the epidermis, which had a beneficial effect on its condition [28]. For this reason, resveratrol has been successfully used in cosmetics to regenerate the skin.

USE OF RESVERATROL IN THE TREATMENT OF SCARS

Resveratrol has a wide field of action; its application was also found in the treatment of hypertrophic scars (HSFB). They are created due to excessive collagen deposition and disorders in proliferation and apoptosis of fibroblasts. The role in this

process is played by the growth factor TGF-β1. The research study showed that resveratrol inhibited the proliferation of fibroblasts of HSFB, blocked the cell cycle and induced apoptosis - this effect was dose - and time-dependent. After just 24 hours of treatment with resveratrol, its antiproliferative effect was observed, which intensified with prolonged therapy and increased concentration [29]. In addition, resveratrol decreased the expression of genes responsible for the production of type I and III procollagen, which led to reduced collagen deposition. Similar properties of resveratrol in the context of scar reduction have been confirmed by other researchers [24].

Studies involving the injection of resveratrol have shown that in hypertrophic scar tissues, the expression of SIRT1 was downregulated compared to healthy skin. SIRT1 can inhibit the transformation of fibroblasts into myofibroblasts induced by TGFβ1, as evidenced by reduced expression of α-SMA, collagen I (Col1) and collagen III (Col3) after the application of resveratrol. In addition, resveratrol therapy in a skin wound model in mice improved the organization of the structure of the skin, leading to the formation of thinner and better-ordered collagen fibers. In the future research will focus on detailed molecular mechanisms involved in the action of the anti-fibrotic SIRT1 [30].

RESVERATROL IN THE ELIMINATION OF HYPERPIGMENTATION

It is believed that resveratrol can inhibit tyrosinase, an enzyme crucial in the process of melanin synthesis, which makes it an active ingredient in preparations designed to lighten skin discoloration [31]. For this reason, the study used resveratrol cream; 21 patients with melasma used the product for 4 weeks. In the patients' self-assessment, moderate to significant improvement was observed in 8 patients (38.1%) in the second week and in 11 patients (52.3%) in the fourth week. Changes in the melanin index were significantly lower in the second and fourth weeks compared to the baseline value [32].

SUMMARY

Resveratrol is a natural chemical compound with powerful antioxidant and anti-inflammatory properties. It is found mainly in grapes, wine, peanuts and cocoa. Due to its ability to neutralize free radicals and modulate cellular processes, it is widely used in the prevention and treatment of lifestyle diseases. Resveratrol may reduce risk of cardiovascular disease by inhibiting lipid peroxidation and reducing oxidative stress. In oncology, it shows potential in inhibiting tumorigenesis and increasing the effectiveness of chemotherapy. Its neuroprotective properties make it a promising ingredient in the treatment of neurodegenerative diseases such as Alzheimer's or Parkinson's diseases. In cosmetology, resveratrol promotes healing of wounds and skin regeneration, has antibacterial and antifungal effects and protects against photoaging. It can be used in the treatment of hard-to-heal wounds, such as diabetic ulcers, by improving angiogenesis and protecting the vascular endothelium. *In vitro* and *in vivo* studies confirm its effectiveness in many areas, but more clinical trials are required to fully understand its therapeutic potential.

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