Review paper

Resveratrol as a factor preventing skin aging and affecting its regeneration

Kamil Leis[1], Karolina Pisanko[1], Arkadiusz Jundziłł[1], Ewelina Mazur[1], Kaja Męcińska-Jundziłł[2], Henryk Witmanowski[1]

[1]Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
[2]Department of Dermatology and Venerology, Faculty of Medicine in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

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Abstract

Resveratrol, a compound belonging to polyphenols, besides its action on the cardiovascular system, affects also wound healing, regeneration, and photoaging of the skin. By interactions with numerous substances and pathways, e.g. MAPK, MAPKK, FOXO3, TGF or metalloproteinase 1, it protects the skin against the harmful effects of type B ultraviolet radiation, which is the main factor in the skin aging processes. It also enhances collagen synthesis by activating the oestrogen receptor and reduces wrinkles. In damaged tissues, it accelerates skin regeneration and healing by activating, among others, VEGF. Based on the review of the literature, there is no doubt that resveratrol has the potential to be used in cosmetology, dermatology and plastic surgery. It can be used as a compound of anti-aging products or as a topical treatment of scars and wounds. In the future this polyphenol might be applied in pharmacotherapy of many dermatoses.

Key words: resveratrol, skin aging, skin regeneration, polyphenols

Introduction

Resveratrol (3,4′,5-trihydroxystilbene) is a compound from the group of polyphenols, phytoestrogens and phytoalexins with a stilbene structure, found in grapes, especially their skin as well as in berries, mulberry, raspberries, tomatoes, strawberries or nuts [1, 2]. The rich source of polyphenols is wines, especially red wines [1]. It has confirmed neuroprotective, anticancer, antioxidant, anti-inflammatory and antiproliferative effects so its activity is very versatile (Figure 1). By reducing lipid levels and inhibiting thrombocyte aggregation, it reduces the risk of cardiovascular incidents [1, 3]. Therefore, it is believed that resveratrol is responsible for the occurrence of so-called "French paradox", i.e. a phenomenon involving relatively low morbidity of cardiovascular disease, despite the French diet, consisting of a high amount of animal fats [2, 3]. Numerous reports confirmed that resveratrol exhibits anti-aging and regenerative effects on the skin.

Slowing down the aging process of the skin

The anti-aging properties of resveratrol are based on its inhibitory effect on the phosphorylation of survivin – the protein responsible for preventing cellular apoptosis and its mRNA as well as blocking Cyclin-dependent kinase 2, 4, 6, nuclear factor kB, cyclin D1, cyclin D2, metalloproteinase matrix , IκB kinase Rα, mitogen-activated protein kinase kinase (MAPKK) and mitogen-activated protein kinase (MAPK). Polyphenol also reduces the severity of skin oedema and its inflammatory processes by inhibiting the (B ultraviolet) radiation-dependent migration of white blood cells [4–7]. It is believed that the most effective form of resveratrol for the skin are isobutyrate and butyrate, having the strongest effect on reducing the concentration of inflammatory cytokines (e.g. interleukin 6 and interleukin 8) as well as on the increase in A1 collagen levels, tissue inhibitor of matrix metalloproteinase 1 or fibrillin 1 (pure resveratrol does not change its level) and decrease in matrix metalloproteinase 9 through

Address for correspondence: Kaja Męcińska-Jundziłł MD, PhD, Clinic of Dermatology, Sexually Transmitted Diseases and Immunodermatology, Faculty of Medicine, Nicolaus Copernicus University, 9 Sklodowskiej-Curie St, 85-094 Bydgoszcz, Poland, e-mail: kaja_cm@wp.pl
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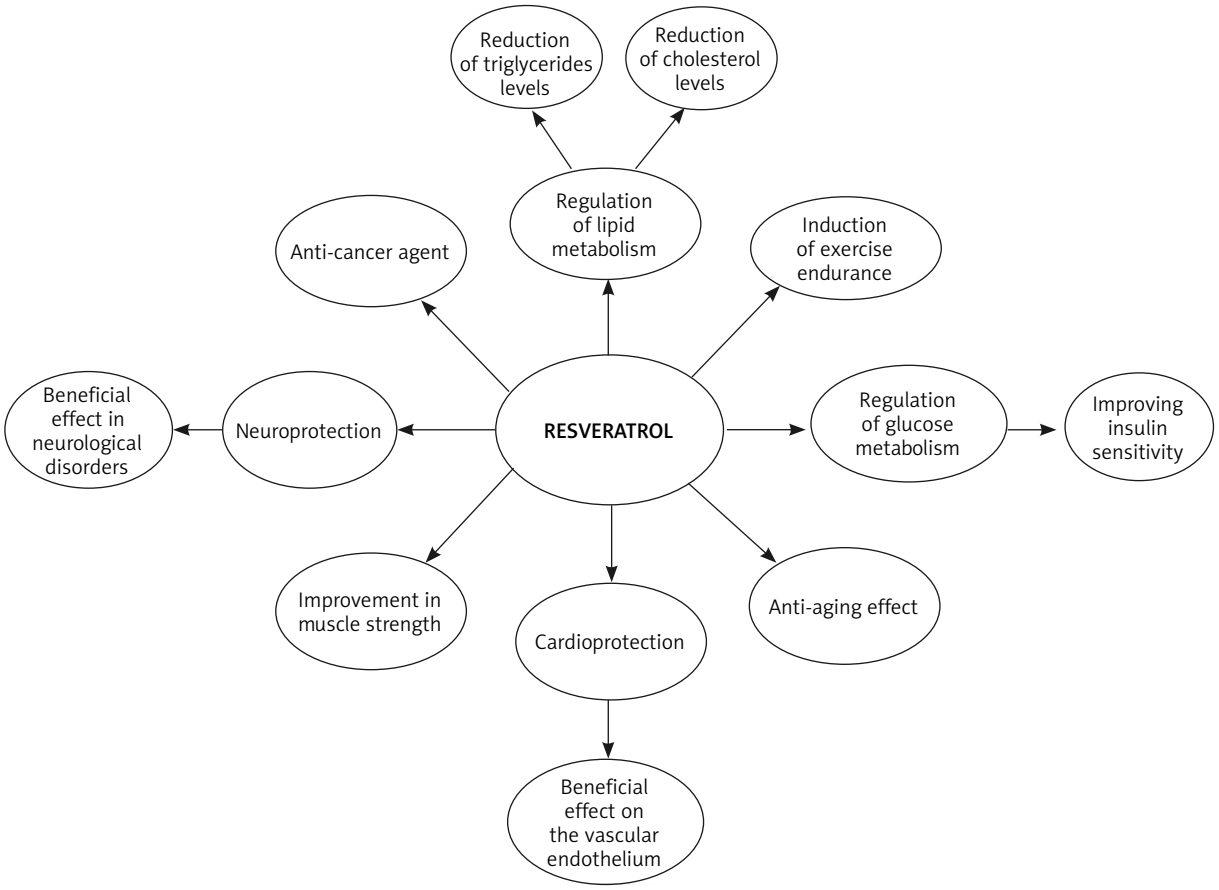

Figure 1. Activity of resveratrol

gene interaction [8]. Also, effects on aging biomarkers have been reported: nerve growth factor, calcium-binding proteins A8, calcium-binding proteins A9, calcium-binding proteins S100, proliferating cell nuclear factor and 5α-reductase [9]. Polyphenol also slows down skin aging through antioxidant activity expressed as inhibition of Bcl-2 phosphorylation processes, reduction of cell adhesion kinase, hydroperoxide as well as B and C protein kinases (Table 1) [10].

The compound, however, does not affect 5α-dihydrotestosterone, 5α-reductase or oestrogen-related gamma receptor without participating in the production of collagen associated with the change in the concentration of these compounds (this happens due to the action on the oestrogen-related α receptor and oestrogen-related β receptor) [11, 12]. Polyphenol inhibits tyrosinase, reducing skin discoloration and smoothes wrinkles through activity against granulocyte-macrophage colony-stimulating factor (GM-CSF) and matrix metalloproteinase 1 (MMP-1) [13–16].

Chen *et al.* used UVA radiation on a 5 J/cm^2 rodent HaCaT cell line while administering resveratrol at doses of 0.1 mmol/l and 0.01 mmol/l. They found that polyphenol enhances the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), while blocking the action of malonic dialdehyde, which reduces the harmful effect of UVA on cells [17].

Similar analyses regarding the inhibitory effect of resveratrol on skin photo-aging processes induced by type B ultraviolet radiation were carried out by Afaq *et al.* and Aziz *et al.* The subjects of their study were SKH-1 cell lines of hairless mice and the radiation intensity was 180 mJ/cm^2. The first team used a polyphenol dose of 25 µmol/0.2 ml acetone per rodent. A lower activity of lipid peroxidation, cyclooxygenase, and ornithine decarboxylase was observed, which indicates a protective effect of the compound on the skin exposed to radiation. The second team, led by Aziz, used resveratrol at a concentration of 10 µmol/200 µl acetone. The compound caused an increase in the activity of the second mitochondria-derived activator of caspases (Smac) apoptotic protein, also found in the literature as DIABLO, lower cellular proliferation (among others due to the effect on the level of Ki-67 protein) and the weakening of survivin-antiapoptotic protein phosphorylation. It also reduced ornithine decarboxylase and cyclooxygenase 2 (COX-2) activity [5, 18].

Bastianetto *et al.* administered resveratrol at a dose of 1–30 µmol to cells from the HaCaT line exposed to

free radical sodium nitroprusside that damages cells and blocks their growth. Polyphenol reduced the drug's harmful effects by inhibiting caspase 3, caspase 9 (full blockade of activity) and regulation of mitochondrial membrane potentials and its protective effect correlated in a dose-proportional manner. However, it did not affect the concentration of reactive nitric oxide or p38 mitogen-activated protein kinases [19].

Subedi *et al.* in 2017 analysed the effect of resveratrol derived from rice on skin exposed to type B ultraviolet radiation at 144 mJ/cm^2. Polyphenol slowed the skin's photoaging processes, including wrinkle reduction by inhibiting the caspase-3-cytochrome C and p-53-Bax complex pathway and the MMP-1 pathway. Reduced inflammation was also observed, due to inhibition of COX-2, interleukin 6, tumour necrosis factor-α (TNF-α) p38 mitogen-activated protein kinases, nitric oxide synthesis or c-Jun N-terminal kinases as well as prevention of decrease in elastin, procollagen 1 and transforming growth factor-β (TGF-β) [20].

A similar study was carried out by Lee *et al.* They administered resveratrol (in pure form or as a rice component) on human UV-B irradiated fibroblasts. It was found that compared to the control group, the skin treated with polyphenol had a higher content of procollagen 1, while lower activity of metalloproteinase 1 [21].

Resveratrol has also been found to have a protective effect on keratinocytes by participating in AMPK (5'AMP-activated protein kinase) activation. Ido *et al.* administered resveratrol at a dose of 25 or 50 µmol to cell culture for 30 min, after which hydrogen peroxide was introduced. Resveratrol in combination with insulin prevented the action of hydrogen peroxide by suppressing proliferative processes, mediated by AMPK and FOXO3 (Forkhead box O3). This in turn, in addition to affecting H_2O_2, also increased cellular insulin sensitivity. It was also observed that the SIRT-1 inhibitor eliminated the protective activity of the polyphenol, and blocking the sirtuin protein alone did not affect (as opposed to AMPK) the increased effect of hydrogen peroxide – resveratrol still showed its protective activity against the skin when inhibiting sirtuin [22].

Resveratrol also stimulates the production of autophagocytes, which are responsible for the elimination of abnormal cells in the body, including the skin. As a result of the supply of polyphenol, cells from the HaCaT line showed a higher concentration of LC3 – II (light chain 3, a protein important for the process of autophagocytosis), as a result of transformations from LC3 – I. Increased LC3 breakdown resulting from lysosome fusion was also observed [23].

Opposite results regarding the effect of resveratrol on skin aging processes were provided by another analysis. Back *et al.* found in 2012 that this compound blocks autolysosomes, reduces the concentration of mTOR Complex 2 RICTOR (rapamycin-insensitive companion of the mammalian target of rapamycin), which in turn reduces the concentration of RHOA-GTPase (GTPase of Ras homolog gene family, member A). This leads to increased levels of β-galactosidase, which is responsible for aging. Researchers believe that resveratrol induces skin aging through this effect, protecting against cancer [23, 24].

Table 1. Effect of resveratrol

Induction	Inhibition
• Collagens of group A1 • Inhibitor of matrix metalloproteinase 1 • Fibrillin 1 • AMPK • Autophagocytes • LC3-II	• Survivin • Cyclin-dependent kinase 2 • Cyclin-dependent kinase 4 • Cyclin-dependent kinase 6 • Nuclear factor κB • Cyclin D1 • Cyclin D2 • Matrix metalloproteinase • IκB kinase Rα • MAPK • MAPKK • Leukocytes migration • Matrix metalloproteinase 9 • Nerve growth factor • Calcium binding proteins A8 • Calcium binding proteins A9 • Calcium binding proteins S100 • Proliferating cell nuclear factor • 5α-reductase (?) • Bcl-2 • Protein kinase B • Protein kinase C • Hydroperoxidases • Tyrosinase • Sirtuin

The researchers combined resveratrol with glycolic acid to obtain resveratryl triglycolate. Park *et al.* analysed its melanogenesis inhibitory effect, finding that both pure polyphenol and hybrid are tyrosinase inhibitors. In rodent melanoma cells of the B16/F10 line and epidermal cells of human origin, resveratryl at a dose of 3–10 µmol caused a significant decrease in melanin concentration, blocked microphthalmia-associated transcription factor, tyrosine mRNA as well as l-3,4-dihydroxyphenylalanine chrome tautomerase. This proves that resveratrol and its derivatives can be used to lighten the skin or as a protective agent against melanoma [25].

Resveratrol is also used in the pharmacotherapy of chloasma – a disease characterized by hyperpigmentation on the skin surface, in which etiopathogenesis involves UV type B radiation and reactive oxygen species. It has been proved that the preparation containing flavonoids and proanthocyanidins significantly removed the stain spots without causing any adverse health effects [26].

Bonato Alves Oliveira *et al.* in 2017 conducted a study involving 30 people on the effect of a cream containing resveratrol on the skin. Skin permeability, the presence of skin pores and the level of pigmentation were analysed, and the preparation was used for 45 days. At the end of the study, 24 volunteers remained, 19 of which showed

features of pore involution on the forehead and 14 buccal areas. The skin colour on the forehead and the buccal area decreased in 7 and 4 people, respectively. In some of the patients, pigmentation increased (4 people – the forehead, 5 people – the buccal area). It was found that the cream had no significant effect on wrinkle reduction and water retention, preventing dry skin [11].

Bertuccelli *et al.* compared the skin's anti-aging effectiveness with a mix containing resveratrol with a papaya preparation. Sixty people aged 40–65 took part in the 90-day analysis. One group of patients received 4.5 g of the mixture/day, while the other was supplemented with papaya preparation. Resveratrol was found not to affect the degree of hydration, discoloration and skin elasticity, unlike the papaya preparation [27].

Skin regeneration

Polyphenol also participates in accelerating the processes of wound regeneration and healing, diminishes scarring and reduces scar size. This is due to the increase in the concentration of endothelial growth factors, which consequently leads to the narrowing of the edges of the wound [26].

Zhao *et al.* in 2017 compared the effectiveness of metformin, rapamycin and resveratrol on wound healing in an animal model. Researchers have found that both metformin and polyphenol affect the epidermis and hair follicles, while rapamycin has only a small regenerative effect. They also affect collagen synthesis in damaged areas of the skin, are involved in the process of angiogenesis in the wound area due to the activation of the AMPK pathway, which is quenched as a result of skin aging, and thus the skin's regenerative ability decreases over time. AMPK was induced by an increase in the concentration of p-acetyl-CoA carboxylase. It was also found that only metformin (which has a stronger regeneration effect than resveratrol) supports 'skin integrity'. However, only exposure to resveratrol caused an increase in activity of the pathway associated with Sirt 1, which increases the level of peroxisome proliferator-activated receptor-g coactivator 1α (PGC-1α). However, the results of the effect of resveratrol and metformin on the concentration of S6 kinase (also known as MAPK-activated protein kinase-1) are ambiguous [28].

Gonçalves *et al.* confirmed the regenerative effect of resveratrol on the skin. Rats after chemical peeling in the form of 50% glycolic acid were given resveratrol for 15 days. It was found that the skin along with the epidermis of polyphenol-supplemented rodents is thicker, which, authors explain, is due to the induction of collagen production [29].

Afshar *et al.* in 2017 analysed the effect of polyphenol on angiogenesis and wound healing. For this purpose, a dorsal wound was created in 60 rodents and then divided into 5 groups, of which 4 were control groups and 1 was supplemented with resveratrol at a concentration of 0.05% and 0.1% (administration twice a day) lasting for 2 weeks. At the end of the experiment, it was found that the polyphenol caused an increase in the concentration

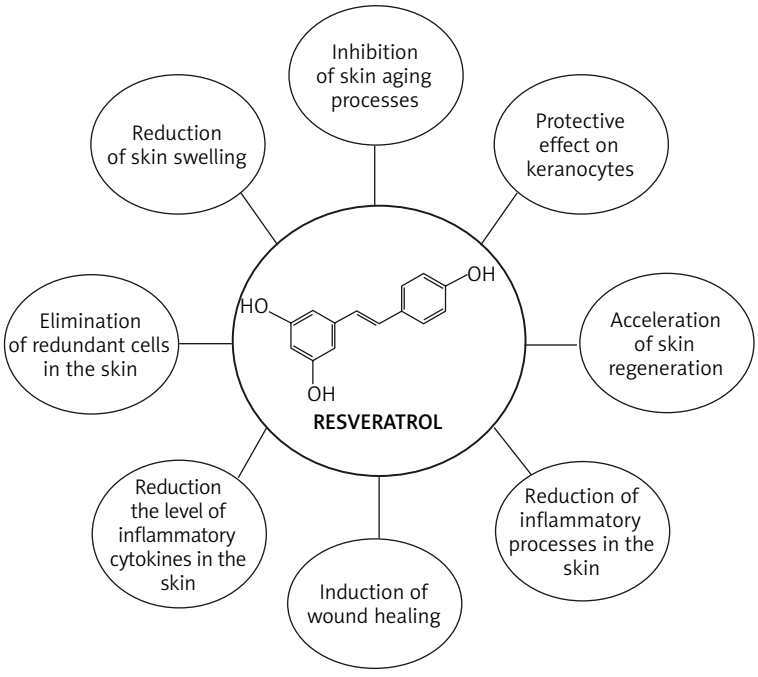

Figure 2. Activity of resveratrol on the skin

and activity of vascular endothelial growth factor (VEGF) and the wounds in the polyphenol treated group healed faster than in other rodents, as well as the angiogenesis processes were more prominent in this study group [30].

Lakshmanan *et al.* conducted a similar study in 2019 with C57BL/6 mice. These researchers concluded that resveratrol caused, in compound-treated mice, an increase in VEGF and Bcl-2 antiapoptotic protein as well as faster wound healing and more effective angiogenesis compared to rodents belonging to other groups [31].

Baca *et al.* also studied the correlation between resveratrol supply and the rate of skin wound healing. More than 20 wounds of the dorsal region were produced in three pigs and then treated with resveratrol in doses: 2 mg/ml, 10 mg/ml and 50 mg/ml. After 6 weeks, the animals treated with the compound showed a reduction in the wound surface (88.4% vs. 86.9% and 77.2%) and the effect was correlated with the dose. Researchers also found that polyphenol reduced the scar size. They noted, however, that this aspect requires further research [32].

Lin *et al.* in 2015 analysed the effect of resveratrol supply on burn wounds (doses of 1 ng/ml, 100 ng/ml and 500 ng/ml). As in the studies described above, the compound had a positive effect on wound healing. It reduced

Table 2. Summary of studies confirming the resveratrol's beneficial anti-aging and regenerative effect on the skin. The research papers are presented as they appear in the article

Study	Purpose of the study	Effects
Chen *et al.* 2006	Investigation of resveratrol's anti-aging and UV protective properties	Resveratrol activated superoxide dismutase and glutathione peroxidase, which reduced the harmful effects of ultraviolet radiation on the skin
Afaq et al. 2003	Investigation of resveratrol's anti-aging and UV protective properties	Resveratrol reduced the activity of lipid peroxidation, cyclooxygenase, and ornithine decarboxylase, which protected the skin against ultraviolet radiation damage
Azis *et al.* 2018	Investigation of the anti-aging properties of resveratrol	Polyphenol upregulated second mitochondria-derived activator of caspases (Smac) but inhibited proliferation processes and COX-2 activity
Bastianetto *et al.* 2010	Investigation of the anti-aging properties of resveratrol and protection against free radicals derived from sodium nitroprusside	The natural compound inhibited caspases, thus reducing free radical damage
Subedi *et al.* 2017	Investigation of resveratrol's anti-aging and UV protective properties	Resveratrol inhibited the skin aging-related pathways, maintaining the concentration of e.g. elastin and procollagen and decreased pro-inflammatory factors
Lee *et al.* 2016	Investigation of resveratrol's anti-aging and UV protective properties	Resveratrol helped to maintain the proper concentration of procollagen and weakened the action of metalloproteinases
Ido *et al.* 2015	Investigation of the resveratrol's protective effect against hydrogen peroxide on keratinocytes	Resveratrol reduced skin proliferation caused by free radicals
Soleymani et al. 2019	Investigation of the beneficial effect of resveratrol in the pharmacotherapy of chloasma	Polyphenol contributed to the reduction of skin lesions formed in the course of the disease
Oliveira *et al.* 2017	Investigation of the beneficial effect of resveratrol on human skin	Resveratrol minimized pores and normalized the level of pigmentation
Zhao *et al.* 2017	Investigation of the resveratrol's regenerative properties on the skin and in the treatment of wounds	Resveratrol promoted wound healing by i.e. activating the Sirt-1 pathway, stimulating collagen synthesis, or regulating angiogenic processes
Gonçalves *et al.* 2017	Investigation of the resveratrol's protective effect on the skin against 50% glycolic acid	By inducing collagen synthesis resveratrol contributed to the increase in skin thickness – and thus less skin damage
Afshar *et al.* 2017	Investigation of the resveratrol's regenerative properties on the skin and in the treatment of wounds	Resveratrol induced VEGF activity, thus regulating angiogenesis and accelerating wound healing
Lakshmanan *et al.* 2019	Investigation of the resveratrol's regenerative properties on the skin and in the treatment of wounds	Resveratrol induced VEGF activity, thus regulating angiogenesis and accelerating wound healing
Baca *et al.* 2016	Investigation of the resveratrol's regenerative properties on the skin and in the treatment of wounds	Resveratrol accelerated the wound healing process and contributed to the formation of smaller scars
Lin *et al.* 2015	Investigation of the resveratrol's regenerative properties on the skin and in the treatment of burns	Polyphenol stopped leukocyte migration and activated interleukin 1

leukocyte migration and also caused an increase in the concentration of interleukin 1 (however less effectively than the aloe vera preparation), Monocyte Chemoattractant Protein-1 and VEGF [33].

Summary

The widespread use of resveratrol, in addition to its cardioprotective or neuroprotective effects, also includes skin regeneration, accelerated wound healing and prevention of skin aging caused mainly by type B ultraviolet radiation (Figure 2). Several studies confirming this effect are available, both on an animal and a human model (Table 2). This gives hope that resveratrol will be widely used in cosmetology as an anti-aging agent or in many medical disciplines such as surgery or dermatology as a healing accelerator.

Currently, there is an ongoing study on how to combine the compound with hyaluronan [34], the use of lipid nanosystems containing resveratrol [35], organogels [36] or nanoparticles containing resveratrol. The latter are characterized by higher efficiency, among others in reducing wrinkles or inflammation of the skin compared to the classic form of polyphenol supply [37]. It is also used in many skin diseases such as acne vulgaris or atopic dermatitis [26, 38]. There are also reports in the literature about the protective role of a compound against radiation therapy-induced skin damage.

Conflict of interest

The authors declare no conflict of interest.

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