Resveratrol: An antioxidant for attractive beauty applications

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ABSTRACT

The skin is exposed to many harmful factors. To remain healthy and good-looking, and to be able to resist or recover, balanced regeneration mechanisms are of great importance. One of these is called antioxidant capacity. What happens if the process of removing free radicals becomes saturated and the skin unbalanced? In this scenario, it is extremely beneficial to introduce antioxidants dermally. Resveratrol, a substance found in grapes and red vine, has been proven in vitro and clinically to have a high antioxidative strength. Not only does it play a major role in protection against UV radiation, it also demonstrates significant positive skincare effects in many skin conditions such as acne, wrinkles and pigmentation spots.

Keywords: antioxidant, resveratrol, skin, UV radiation

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INTRODUCTION

Skin layers, especially the epidermis and dermis, are exposed to degradation due to ultraviolet (UV) radiation. The matrix of collagen, elastin and hyaluronic acid fibres is responsible for the elasticity and firmness of the skin. Photo-induced, oxidative or enzymatic degradation of the skin's structures can lead to **premature skin ageing and photo-ageing**, inflammation and other photo-induced diseases, including melanoma and non-melanoma skin cancers (1).

In terms of cosmetic applications, **antioxidants of natural origin** represent one of the most important approaches to counteract the damaging effects of oxidative processes. They act on the skin surface and can also penetrate through the skin barrier, and decelerate ageing. As a part of this group, polyphenols are plant metabolites with many bioactive properties. Besides their action as free radical scavengers, they possess anti-collagenase, anti-elastase and anti-hyaluronidase activities as the most significant skin-relevant effects (1).

Different types of **polyphenols** exist, including simple phenols, phenolic acids and flavonoids (1). A rising polyphenol for beauty applications is **resveratrol**, a stilbenoid or hydroxylated derivative of stilbene in chemical terms. It has gained interest as a cosmetic ingredient because of its antioxidative, anti-inflammatory and antiproliferative activities at the molecular level, and antiwrinkle, photo-protective and skin-whitening properties at the sensory level, to summarise a few of its cosmetic effects (2, 3).

ANTIOXIDANTS OF NATURAL ORIGIN IN COSMETICS

Antioxidative compounds are used to protect human skin against damage caused by **free radicals**, including those that arise from UV radiation (4). To maintain healthy, normally functioning skin, the oxidative and antioxidative processes in both the skin and the whole body must be in balance.

Antioxidants delay, prevent and eliminate oxidative damage. There are many positive effects on skin health related to this mechanism of action, such as diminishing the formation of visual signs of ageing and boosting the (skin) immune system (5).

In cosmetic formulations, natural antioxidants are used as a single, pure compound or a mixture of compounds, both as natural isolates or synthetically produced, i.e. nature-identical compounds, or as plant extracts. They typically function as quenchers of reactive oxygen species or enzyme inhibitors (4).

Due to their instability, concentrations of each antioxidant must be controlled and stability-tested to ensure that a cosmetic product expresses and maintains the claimed activity. This is of particular importance in cosmetic science research and within the concept of active cosmetics. Antioxidative compounds of plant-derived extracts, for example, are very complex. It is thus difficult to determine their activities.

Some of the natural antioxidants used in cosmetic products are resveratrol, which is the focus of this article, α-tocopherol and natural tocopherol mixtures (vitamin E), ascorbic acid (vitamin C), β-carotene and other carotenoids, curcumin, quercetin and other flavonoids, etc. (4).

RESVERATROL AS A COSMETICALLY ACTIVE INGREDIENT

Resveratrol found its place in scientific history back in 1992, in connection with food consumption habits popularly known as the "**French paradox**". The paradox refers to a paradoxical epidemiological observation that French people have a relatively low incidence of coronary heart disease while having a diet rich in saturated fats. This was first explained to be related to alcohol (wine) consumption and later to resveratrol in red wine, which is commonly used in the French diet (6).

Resveratrol has been found in almost **70 plant species** such as grape vine (*Vitis vinifera*), peanut (*Arachis hypogaea*), acai (*Euterpe oleracea)*, raspberry (*Rubus idaeus*), Japanese knotweed (*Reynoutria japonica*, formerly known as *Fallopia japonica* and *Polygonum cuspidatum*), etc. The molecule is biosynthesised in plants as the **mechanism of resistance to stressful factors**, including fungal or parasite infections, UV radiation and chemical substances (5, 7).

Resveratrol is a 3,4',5-trihydroxystilbene (Figure 1) with a chemical formula of $C_{14}H_{12}O_3$ and a molecular weight of 228,24 g/mol (3). It appears as white or almost white powder practically insoluble in water. It is **soluble** in ethanol, caprylic/capric triglyceride and alkanediols, such as 1,2-hexanediol, pentylene glycol or propanediol (8). Also, it is soluble in dimethyl sulfoxide and acetone (7), but these reagents are only relevant for scientific research.

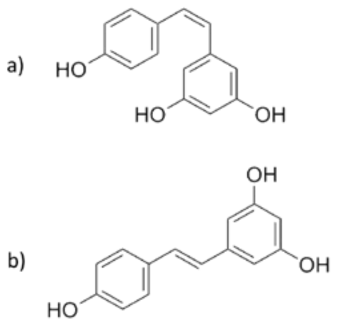

Figure 1: Chemical structures of cis-resveratrol (a) and trans-resveratrol (b).

Furthermore, resveratrol exists in two isomeric forms, *cis* and *trans* (Figure 1); the latter is the **biologically active form**. *In vitro* studies have shown that the *trans*-form is more photo- and thermostable than *cis*-resveratrol. The isomerisation of *trans*-resveratrol to *cis*-resveratrol is influenced by exposure to sunlight or UV irradiation. Some factors that affect this process are irradiation time and wavelength, temperature and pH, and the physical status of the molecule (i.e. solid or in a solution). No increase of *cis*-resveratrol typically occurs at 50 °C if the pH is maintained below 7 and the formulation is kept away from sunlight (9).

In the cosmetic industry, resveratrol (INCI: *Resveratrol*) is mostly used as a pure compound with a **recommended concentration** of 0.1 to 1% (8). Cosmetic labels may also include ingredients that contain resveratrol such as grape extracts (INCI: *Vitis Vinifera Vine Extract* and *Vitis Vinifera Leaf Extract*), products obtained through the fermentation of *Pichia* yeasts (INCI: *Pichia/Resveratrol Ferment Extract*), or filtrates of products obtained through the fermentation of resveratrol and plant extracts using *Lactobacillus* bacteria (INCI name: *Lactobacillus/Camellia Sinensis Catechins/Gelidium Crinale/Laminaria Japonica/Monostroma Nitidum/Resveratrol Ferment Filtrate*). Resveratrol's derivatives are also used under INCI names such as *Hydroxyresveratrol*, *Glucosyl Resveratrol*, *Resveratryl Glucoside*, *Resveratryl Triacetate*, and dimethyl, tributyl and tripentyl ether of resveratrol (INCI: *Resveratrol Dimethyl Ether*, *Resveratrol Tributyl Ether*, *Resveratrol Tripentyl Ether*), and others (3).

BIO-PRODUCTION OF *trans*-RESVERATROL

The increased demand for resveratrol for cosmetic and pharmaceutical applications requires production from sustainable sources (10).

On an industrial scale, the extraction and purification of *trans*-resveratrol from plants remain challenging, expensive and in some cases even incompatible with sustainable approaches. On the other hand, the chemical synthesis of resveratrol leads to difficulties in the purification of the ingredient and may be hazardous when the compound is intended for use in food or medicine (11).

Research has therefore focused on the **fermentation process**. Typically used hosts for resveratrol biosynthesis include *Escherichia coli*, *Lactococcus lactis*, *Streptomyces venezuelae* and *Corynebacterium glutamicum* as prokaryotes, and the yeast *Saccharomyces cerevisiae* as a eukaryote. To obtain a high-quality product, it is crucial to select a suitable host organism and to optimise the fermentation process (11).

The main advantages of **bacterial hosts** are a short life cycle, easy genetic manipulation and handling, a high level of enzyme and protein expression, and a high growth rate. On the contrary, the main disadvantages are the poor expression of large proteins and the low ability of so-called post-translational modifications (11). Post-translational modification is a special process during protein biosynthesis in every living cell and involves, for example, chemical changes and the formation of a native three-dimensional structure, in biochemistry also known as protein folding. Post-translational modifications are crucial for the functional activity of proteins.

The general advantages of the *Saccharomyces cerevisiae* **yeast host** are the intact ability of post-translational modifications and the good expression of large proteins, while the yeast is also easy to grow and genetically manipulate, and has a so-called generally recognised as safe (GRAS) status. The main disadvantage is a lower yield (11).

A brief overview of biosynthetic resveratrol production with yeast as a host starts with glucose, ethanol or glycerol as substrates, which are deemed to be of high sustainability grade. Other fundamental constituents for resveratrol's biosynthesis are the amino acids tyrosine and phenylalanine, and malonyl-CoA. Each of these compounds undergoes various reactions with the ultimate step involving the condensation of three units of malonyl-CoA with *p*-coumaroyl-CoA through an enzyme, stilbene synthase (10, 11).

Despite intensive research, including significant strain engineering, resveratrol production is still considered low. Ibrahim et al. report that resveratrol yield obtained using yeast fermentation reaches no more than 1 g/L of resveratrol and is significantly below industrial needs. They also stress that the path toward sustainable industrial production leads through even more intensive research and the deepening of scientific knowledge (10).

ANTIOXIDATIVE POWER OF RESVERATROL

Air pollution, cigarette smoke, UV radiation and psychological stress are some of the most prevalent harmful factors that lead to oxidative stress in human cells (12). **Oxidative stress** is an imbalance between the production of free radicals and the antioxidant defence system, and leads to tissue damage. Resveratrol has attracted a great deal of attention as an antioxidant, not only because of its protection power but also because it can be used in various applications, including cosmetic, food and even medical.

The **antioxidative power of resveratrol** is closely linked to its chemical structure composed of hydroxyl groups on benzene rings and conjugated with a double-bond ethene system (Figure 1). Research has confirmed that replacing the hydrogen atom in hydroxyl groups with a methyl group ($-CH_3$) or removing the hydroxyl group leads to a significantly reduced antioxidative activity, whereby the 4′ hydroxyl group is essential (13, 14). Resveratrol was shown to be a scavenger for superoxide radical (O^{2-}), hydroxyl radical (OH^-), hydrogen peroxide (H_2O_2), nitric oxide (NO) and nitrogen dioxide (NO_2). The main mechanisms of **scavenging free radicals** are the transfer of hydrogen atoms and sequential electron transfer (13).

Reactive oxygen species attack polyunsaturated fatty acids of cell membranes, resulting in lipid peroxidation. Among the main products of lipid peroxidation, malondialdehyde is considered the most mutagenic, while 4-hydroxynonenal is the most toxic (15). Some studies concluded that resveratrol inhibited lipid peroxidation **more efficaciously** than the antioxidative vitamins C and E, which was attributed to its lipophilic and hydrophilic characteristics (13).

Furthermore, resveratrol also acts as a **chelator**. It binds metal ions such as copper and iron ions, and prevents the entering of a metal ion into an oxidative reaction. This consequently prevents the generation of reactive oxygen species and ultimately oxidation (13).

RESVERATROL IN PHOTO-AGEING AND PHOTOCARCINOGENESIS

The most ubiquitous physical carcinogen in our natural environment is **UV radiation**. Depending on the wavelength, there are short-wave UVC rays, mid-wave UVB and long-wave UVA rays. Because UVC rays are blocked by the ozone layer of the Earth's atmosphere, UVB and UVA rays are responsible for inducing skin disorders, including photodamage and skin cancer (16).

Photo-ageing or the disruption of the dermal structure and skin's connective tissue (especially collagen) caused by UV radiation harms many skin functions. Matrix metallopeptidase enzymes (MMPs) are assumed to be responsible for the degradation of collagen and other extracellular matrix proteins. These proteins are also targets for relieving skin photo-ageing. Sirt1 is a putative anti-ageing enzyme that decreases MMP-9 transcriptional expression in the skin. Recent *in vitro* scientific research indicates that Sirt1 could have a therapeutic value, which was also shown on a mice skin model after UV-mediated photo-ageing. Natural Sirt1 agonists, such as resveratrol, may thus have potential as novel therapeutic or cosmetically active ingredients for use in age-related skin conditions, such as photo-ageing (17).

UV radiation may cause mutagenic effects. Initially, it can cause sunburn, which typically increases the risk of skin cancer later in life, particularly in terms of long-term excessive exposure. However, the risk of skin cancer can be increased by years of sun exposure during outdoor activities, even without sunburn. Other factors that increase the **risk of skin cancer** are skin type, family and personal history of skin cancer, frequent use of tanning beds, multiple moles, etc. (7).

Skin cells respond to UVB-induced damage both by tolerating and repairing it via the activation of antioxidants and DNA repair mechanisms or, ultimately, by undergoing programmed cell death when the damage is irreversible. Unfortunately, some damaged cells escape apoptosis, lose mitotic and differentiation control and become cancerous cells (18).

Available experimental data suggest that resveratrol has the potential as a **chemopreventive agent** for UV radiation-mediated skin damage. Numerous studies have investigated its various molecular mechanisms of action (Figure 2). Resveratrol is involved in the regulation of cell cycle phases, cell proliferation, apoptosis, autophagy, tumour promotion and various cancer-related gene expressions, and in the level of production of reactive oxygen species (7).

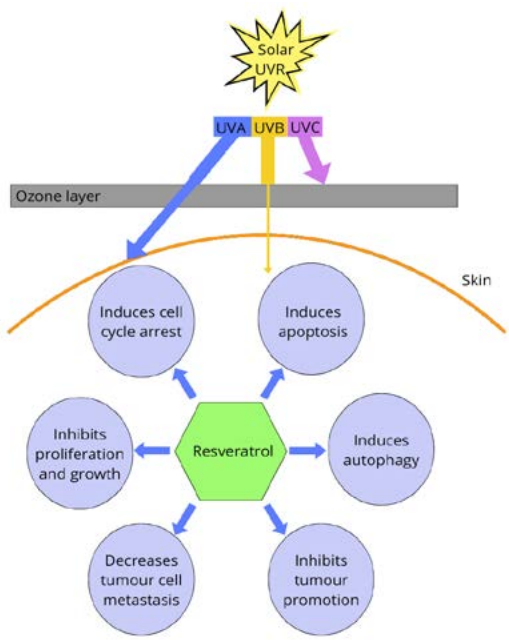

Figure 2: Molecular mechanisms of resveratrol in UV radiation-induced skin cancer; adopted from (7).

SKIN-WHITENING, ANTI-WRINKLE AND ANTI-ACNE BENEFITS OF RESVERATROL

Antioxidants also control oxidative stress correlated with pigmentation disorders, extrinsic skin ageing and inflammation (19).

In vitro and *in vivo* studies have shown that resveratrol may be used as a **whitening ingredient** in cosmetic preparations (3). Dermally applied, *in vivo* investigation with 1% resveratrol dissolved in ethanol and propylene glycol (3:7, V/V) showed a reduction in pigmentation induced by UV radiation in guinea pigs. It decreased cellular melanin synthesis through the inhibition of tyrosinase and inhibition of processes such as tyrosinase gene expression, tyrosinase protein maturation and autophagy (19, 20). It can also be used as an additive compound, especially with a *Morus alba* extract in skin-whitening cosmetics: an *in vitro* study showed a significant synergistic effect. The mixture inhibited 50% of tyrosinase activity, while a single substance (resveratrol or plant extract) inhibited about 25% of activity (21).

Because of its chemical instability, **resveratrol derivatives** have also been evaluated for cosmetic use. *In vitro*, resveratryl triacetate was found to be more resistant to oxidative discolouration and it was less cytotoxic, while a high level of anti-melanogenic activity was retained compared to the effects of resveratrol alone (22). Later, the skin-whitening effects of resveratryl triacetate were examined on 22 human subjects (23). A cosmetic product containing 0.4% of resveratryl acetate or control (i.e. without resveratryl acetate) was applied on one face side twice daily (mornings and evenings). Significant depigmentation occurred in the test group compared with the control group after eight weeks of application.

One scientific *in vivo* study on 42 rats included the application of 50% glycolic acid gel first, followed by the application of a 0.7% resveratrol gel for 15 days. It was concluded that resveratrol increases dermal and epidermal thickness, and has the potential to improve skin with wrinkles (24).

In **acne-prone skin**, resveratrol's antibacterial properties against *Propionibacterium acnes* are believed to make a significant contribution (3, 25). A clinical study with 20 acne vulgaris patients was conducted using a 0.0001% resveratrol gel and a vehicle alone as the placebo (26). A 60-day application on the right side of the face (vehicle on the left side) resulted in a clinically relevant and statistically significant decrease in acne lesions.

SAFETY AND USE OF RESVERATROL IN COSMETICS

In vitro and *in vivo* studies concluded that resveratrol is a **safe and well-tolerated ingredient** for dermal use (3). Ingredient manufacturers recommend 0.1% to 1% of resveratrol in cosmetic formulations (8), while significantly lower (0.0001%) concentrations were also tested in clinical studies (26). The **optimum pH range** is from 3 to 7. Higher pH values or contact with strong oxidising agents may lead to the discolouration of cosmetic products (8).

Cosmetic formulators need to be aware of the resveratrol concentration and vehicles used in products that were tested for safety in scientific research. A case report of a 69-year woman using a cream with resveratrol was reported. Allergic contact dermatitis was confirmed after patch testing with 10% resveratrol in paraffin (27). In another study, dermally used resveratrol and resveratryl triacetate as 0.1 and 0.5% solutions in squalane were used for patch testing (22). Concentrations of 0.1% resveratrol, and 0.1 and 0.5% resveratryl triacetate did not induce any skin reactions in any of the subjects, while 0.5% resveratrol induced slight spotty or diffuse erythema in four subjects. The skin reaction induced by the 0.5% resveratrol solution was classified as **mild irritation**.

RESVERATROL IN MODERN COSMETIC SCIENCE – ADVANCED DELIVERY SYSTEMS

Small hydrophilic polyphenols incorporated into cosmetic products are typically released faster and penetrate into the skin better. In addition, emulsions with a low-lipid content accelerate polyphenol diffusion due to lower viscosity, therefore providing higher release and permeation rates. Those molecules concentrate in the epidermis and dermis, which are the main targets for anti-ageing formulations (1).

In contrast, more hydrophobic molecules, such as resveratrol, are located inside the dispersed lipid phase of oil/water emulsions and they must overcome this interface corresponding to slower diffusion into the skin (1). Because of the poor skin permeation and photodegradation that reduces the activity of resveratrol, it is a major challenge to develop a suitably formulated cosmetic product that facilitates the beneficial effects of resveratrol. As a result, many advanced delivery systems have been created, such as **liquid crystals**, **liposomes**, **nanoparticles**, **nanocapsules**, etc. (5).

CONCLUSION

Based on current evidence, resveratrol acts as a preventive ingredient in many skin conditions, making it a useful compound for cosmetic and dermatological applications. Because of its low water solubility and photo-instability, it is challenging but not discouraging to develop a suitable cosmetic product that facilitates the **beneficial effects of resveratrol as a cosmetically active antioxidant**.

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