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Review Article

Topical use of resveratrol: technological aspects

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Abstract

Resveratrol is a natural polyphenolic phytoalexin found in grapes, berry skins, roots of Japanese knotweed and is reputed as an excellent antioxidant, anti-inflammatory, neuro- and cardio- protective agent. Resveratrol has also beneficial effects in therapy of different skin conditions such as acne, exfoliative eczema, psoriasis and is known to provide a protection against ultraviolet radiation-mediated oxidative stress. However, its low oral bioavailability and short biological half- life compromise its beneficial therapeutic effects; therefore, its topical application is a practical approach in the treatment of various cutaneous disorders. Challenges associated with the development of topical resveratrol drug delivery systems and dosage forms include its low aqueous solubility as well as its poor UV-, pH- and temperature-dependent stability. The purpose of this article is to discuss the mechanism of action, therapeutic effect and physicochemical properties of resveratrol and to present recent technological approaches designed to improve its stability, bioavailability and therapeutic efficiency.

Keywords

antioxidant activity, biologically active compound, drug delivery systems, skin protection

Introduction

Trans-resveratrol (*trans*-3, 4′, 5-trihydroxystilbene) is a non-flavonoid polyphenolic compound, that can be found in various plant species, such as grape berry skins, peanuts and roots of Japanese knotweed *Polygonum cuspidatum* (Pangeni et al. 2014). It is produced in plants as a form of defense mechanism against exogenic stress stimuli like UV-light, fungal infections, exposure to chemical fertilizers (Rabesiaka et al. 2011). Naturally, resveratrol occurs in two isomeric forms (Figure 1). However, the biologically active compound is *trans*-resveratrol, which is the focus of our review (Rabesiaka et al. 2011). The *trans*-isoform can turn quickly into *cis*-isomer under the influence of UV-light and high pH values (Pezzuto et al. 2002). Both forms exist as glucosides with main glucoside derivate resveratrol-3-O-β-glucoside (Pezzuto et al. 2002; Ratz-Łyko and Arct 2018).

Trans-resveratrol is a relatively new chemopreventive agent, as it has been isolated for the first time in 1939 by Takaoka from *Veratrum grandiflorum* O. Loes (Pezzuto 2019). Until the early `90s, there has not been much attention towards its properties, until it was reported about the cardioprotective effects of red wine and is associated with resveratrol content in it (Singh and Pai 2014). Red wine is reported to have highest resveratrol concentration because the resveratrol content found in grape berry skins is more significant in comparison to the flesh, a reason along with the shorter maceration time that explains the lower resveratrol concentration in white wine (Frémont 2000). Resveratrol is known to be responsible for

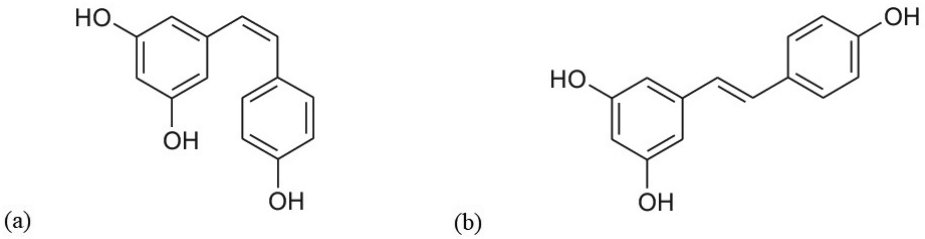

Figure 1. Chemical structures of *cis*- (**a**) and *trans*-resveratrol (**b**). (Adapted from Ratola et al. 2004)

the well-known "French Paradox," claiming that people in France, despite their high consumption of saturated fats, suffer from lower incidences of coronary heart diseases in comparison to people in other countries. This phenomenon is explained by the increased consumption of red wine as a source of resveratrol (Ndiaye et al. 2011; Singh and Pai 2014). Possible mechanisms associated with cardioprotective effects of resveratrol include inhibition of platelet aggregation, arterial vasodilation caused by nitric oxide release, inhibition of low-density lipoprotein, suppressed proliferation of smooth muscle cells and pulmonary aortic endothelial cells, stimulation of angiogenesis and insulin sensitization (Wu and Hsieh 2011; Al-Jumaily et al. 2014).

Besides its cardioprotective properties, resveratrol is widely studied due to its anticancer, antioxidant and anti-inflammatory activity (Pangeni et al. 2014). However, its therapeutic effect by systemic application is limited due to its rapid metabolism and low bioavailability (Pezzuto et al. 2002; Ratz-Łyko and Arct 2018). In recent years, researchers discovered that *trans*-resveratrol is also beneficial for skincare and in skin disease management. Resveratrol in topical formulations is reported to inhibit the proliferation of keranocytes, to stimulate their differentiation and is useful in the treatment of skin diseases such as exfoliative eczema, acne and psoriasis (Pelliccia et al. 2001; Tsai et al. 2016). *Trans*-resveratrol as an excellent antioxidant agent can protect the skin from ultraviolet radiation-mediated oxidative stress and resulting cutaneous disorders, e.g., actinic keratosis and skin cancer (Singh and Pai 2014).

Moreover, the antimicrobial and antiviral effect of *trans*-resveratrol provide skin protection from infections (Baxter 2008). In addition to its pharmaceutical application, *trans*-resveratrol has also become subject of interest for the researchers in cosmetics industries. It can modulate skin turgor and elasticity and improve the overall appearance of dehydrated and wrinkled skin, hence delaying signs of aging (Tsai et al. 2016; Ratz-Łyko and Arct 2018). Besides the positive aspects of resveratrol`s effects on the skin, its formulation into topical dosage forms faces some challenges, associated with its physicochemical properties and UV-dependant isomerization.

The purpose of this article is to discuss the mechanism of action, therapeutic effect and physicochemical properties of resveratrol and to summarize some of the latest technological approaches that overcome its natural limitations, optimizing its effectiveness in topical formulations.

Physicochemical properties of resveratrol

The particular physicochemical properties of resveratrol, which have an impact on its inclusion in different dosage forms, are listed in Table 1 (Robinson et al. 2015; Ratz-Łyko and Arct 2018).

Table 1. Physicochemical properties of resveratrol

Molecular formula	C14H12O3
Molecular mass	228.247 g/mol
Physical state	Solid
Melting point	254 °C
Log P n-octanol/water	3.32
Solubility	Low in water
	High in ethanol
	Very high in PEG-400

Resveratrol is characterized with low aqueous solubility, which determines its low concentration at stratum corneum and hinders its transdermal permeation (Hu et al. 2016). Robinson et al. (2015) conducted pre-formulation studies of resveratrol, testing its solubility in commonly used solvents. Highest solubility of the tested biological compound was established in PEG-400, followed by alcohol. Another critical factor that should be taken into consideration in the formulation process of *trans*-resveratrol is its UV-, pH- and temperature- dependent stability (Zupančič et al. 2015). By conducting solution-state pH stability test, Robinson et al. (2015) established that the polyphenolic compound preserves its initial concentration in acidic and neutral conditions and is least stable in basic media. Regarding its photostability issues, several studies reported that during exposure to light *trans*-resveratrol was converted to its *cis*-isomer within 1 or 2 hr (Gambini et al. 2015). The discussed above properties of resveratrol give the researchers a reason to develop along with the conventional topical dosage forms, novel drug delivery systems (e.g., liposomes, dendrimers, solid lipid nanoparticles, micro and nano-emulsions) in order to overcome its technological limitations.

Mechanism of action of resveratrol

Beneficial effects of *trans*-resveratrol are associated with its antioxidant, anti-proliferative and anti- inflammatory

properties (Rabesiaka et al. 2011; Pangeni et al. 2014; Pezzuto 2019). Resveratrol is known to inhibit platelet aggregation and oxidation of low-density lipoproteins and also to reduce the intracellular formation of peroxide and superoxide radicals in human skin fibroblasts *in vitro* (Stojanović et al. 2001; Ng et al. 2018).

The chemopreventive effect of resveratrol is linked to quinone reductase 2, which in turn increases the expression of cellular antioxidant and detoxifying enzymes to improve cellular resistance to oxidative stress (Amri et al. 2012; Singh and Pai 2014).

Its anti-inflammatory activity is due to inhibition of cyclooxygenase 1 *in vitro* and cyclooxygenase 2 in mouse skin (Ng et al. 2018). The antioxidant activity of resveratrol can be related to its role as a potential scavenger of peroxyl and superoxide radicals or to its ability to decrease oxidation via enzyme inhibition (Alonso et al. 2017). It is found that *trans*-resveratrol acts as a better radical scavenger in comparison to vitamins E and C. However, an improved synergistic effect is achieved in a combination of resveratrol with one of the vitamins (Zupančič et al. 2015). The formation of reactive oxygen species in human skin contributes to different skin pathologies, including cancer (Gokce et al. 2012).

Chronic UV radiation exposure, which can cause DNA damage is another major factor in the pathogenesis of cutaneous disorders (Ndiaye et al. 2011). Chemoprevention refers to the use of agents, which can inhibit, reverse, or retard the effect of UV radiation exposure to the skin (Nichols et al. 2009). Role in the pathogenesis of sunlight-induced cancer along with chromosomal alterations and mutations plays survivin, a member of the inhibitor of apoptosis gene family and critical regulator of survival or death of cells. Aziz et al. (2005) established that resveratrol may ensure skin protection against UVB-mediated damages and potential cancerogenic development, by modulation survivin's expression and activity. According to Osmond et al. (2012) resveratrol may be used in adjuvant therapy of melanoma, since it reduces the viability of melanoma cells and increases the cytotoxicity of temozolomide on malignant cells. Resveratrol is also able to inhibit redox factor 1, making melanoma cells more sensitive to chemotherapy (Ndiaye et al. 2011).

Oral absorption of resveratrol

After oral administration, resveratrol undergoes rapid metabolism up to 30–60 min, so the active substance is not able to achieve its therapeutic effect (Ndiaye et al. 2011). Besides its short initial half-life, resveratrol`s bioavailability is reported to be low also due to the rapid hepatic metabolism implemented via human hepatic sulfotransferase and glucoronosyl transferase (Amri et al. 2012). Resveratrol is metabolized in the liver mostly into sulfates, glucuronides, or sulfoglucuronides conjugates followed by elimination in urine (Ratz-Łyko and Arct 2018). During the elimination phase, an increase in the concentration in the terminal part of the profiles is detected may be due to enterohepatic recirculation (Singh and Pai 2014).

Studying the resveratrol absorption in humans it was found that resveratrol concentration in plasma is deficient in the range 1–5 ng.ml (Soleas et al. 2001; Pangeni et al. 2014). In their study, Brown et al. (2010) investigate the safety profile, pharmacokinetics and resveratrol`s effects on insulin-like growth factor-1 and insulin-like growth factor-binding protein-3. According to the authors, resveratrol`s profile is safe. However, administration of doses about 2.5 g and 5 g resulted in mild gastrointestinal problems. Regarding resveratrol`s effect on tested growth factors, a dosage at 2.5 g showed the most significant increase, which may contribute to its cancer chemopreventive properties (Brown et al. 2010).

The influence of oral absorption and rapid metabolism of resveratrol is studied by Niles et al. (2003) who reported in their first research that resveratrol inhibited growth and induced apoptosis in human melanoma cell lines. However, according to their second study, its concentration is ineffective to ensure growth inhibition *in vivo*. One possible explanation is namely due to resveratrol`s rapid clearance or may be due to the existence of resveratrol metabolite piceatannol in the skin, which may stimulate *in vivo* the growth of human melanoma cells (Niles et al. 2006). Different strategies are developed to overcome its poor oral bioavailability. This includes the possibility to combine resveratrol with additives, that can inhibit its *in vivo* metabolism, to synthesize different analogs with improved bioavailability and last but not least, to use different nanotechnological approaches (Ndiaye et al. 2011). Inclusion of resveratrol in various carriers such as β- and hydroxypropyl-β-cyclodextrin complexes, in liposomes and solid lipid nanoparticles, has been reported in the literature (Lucas-Abellán et al. 2007; Caddeo et al. 2008; Gokce et al. 2012). However, its therapeutic effect in skin disease management can be achieved through its topical application.

Effects of topically applied resveratrol on different skin conditions

Topical application is an easy and convenient route of administration, delivering the active substance at the desired site of action, with a lower risk of emerging potential adverse effects. Regarding transdermal bioavailability, it has been assumed that molecules with a molecular weight greater than 500 Da, a high degree of ionization, low (≤-1) and high (≥4) log Po/w values have limitations to overcome the skin barrier (Ratz-Łyko and Arct 2018).

The physicochemical properties of resveratrol (Table 1) suggest its ability to overcome the skin barrier in neutral condition (Ratz-Łyko and Arct 2018).

Topical resveratrol delivery is also an attractive alternative in comparison to its systemic application, therefore it is object of numerous research articles and several patents. Hung et al. (2008) studied transdermal delivery of resver-

atrol from solutions with various pH values, soybean oil and different hydrogel compositions (carbopol, ammonium acryloyldimethyltaurate/vinylpyrrolidone copolymer, hydroxyethyl cellulose, hydroxypropyl cellulose sodium, hydroxypropyl methylcellulose, carboxymethyl cellulose sodium). They established that resveratrol transdermal transport is highly dependent on the type of carrier. In the case of aqueous buffers, the one with lower pH values exhibited good permeability and deposition and in case of hydrogels, their viscosity, not the polarity controlled resveratrol`s permeation and deposition (Hung et al. 2008). Pellicia et al. (2001) patented the use of this natural phytoalexin and its derivates in different topical dosage forms for the treatment of acne, exfoliative eczema and psoriasis.

Acne vulgaris is a disease of the pilosebaceous unit, which is characterized by the appearance of comedones, papules, nodules and different degrees of scarring (Tan et al. 2018). In randomized, double-blind study patients were treated daily for ten weeks with topical resveratrol cream and afterward, their skin condition was evaluated. A marked reduction of erythema, number of acne lesions, and comedones was observed in 96% of the tested patients in comparison to control subject (2%) (Pelliccia et al. 2001).

Experiments were carried out also on patients suffering from exfoliative eczema and psoriasis. Exfoliative dermatitis or erythroderma is a severe state of skin irritation in which about 90% of skin surface suffers from erythema and scaling (Mahabaleshwa et al. 2016). In this study, patients were divided into two groups and were treated twice daily for six months with resveratrol ointment or a placebo ointment. In resveratrol treated patients, the body area affected by eczema decreased from 69% to 27% and the values for itching as clinical symptom decreased almost four times (from 2.3 to 0.6) (Pelliccia et al. 2001). Psoriasis is a chronic inflammatory disease with complex etiology clinically characterized by discrete, erythematous scaly plaques (Schadler et al. 2019). In a double- blind study, 80% of the patients treated with resveratrol containing ointment showed significant improvement compared to 10% of the control group (Pelliccia et al. 2001).

Resveratrol has also been subjected to patent regarding prevention and treatment of skin conditions associated with inflammation, sun damage and aging (Pezzuto et al. 2002). Farris et al. (2014) conducted a clinical study that evaluates the antiaging effect of resveratrol. Female volunteers aged 40–60 used a night cream containing 1% resveratrol, 0.5% baicalin and 1% vitamin E for three months. Afterward, a marked improvement in skin elasticity and firmness as well as smoothing fine lines and wrinkles was observed in comparison to baseline (Farris et al. 2014).

Technological approaches for the topical formulation of resveratrol

Improving aqueous solubility of resveratrol, providing photoprotection and in the same time preventing the conversion of active *trans*- to an inactive *cis*-isomer are the main reasons for the inclusion of resveratrol in different nanocarriers for topical application (Lv et al. 2018). Nanoscale drug delivery systems such as solid lipid nanoparticles, nanostructured lipid carriers, transferosomes, microemulsions, dendrimers have been developed as a platform for delivery of *trans*-resveratrol (Scognamiglio et al. 2013; Pentek et al. 2017; Lv et al. 2018). All these nanocarriers are known to improve stability and bioavailability of the incorporated active substances to facilitate skin permeation and to provide controlled drug release at the desired site of action (Tsai et al. 2016).

In their study, Gokce et al. (2012) prepared solid lipid nanoparticles and nanostructured lipid carriers loaded with resveratrol and established that both nanoscale delivery systems exhibit antioxidant activity decreasing reactive oxygen species accumulation. However, nanostructured lipid carriers are characterized by better dermis accumulation and deeper skin penetration in comparison to solid lipid nanoparticles (Gokce et al. 2012).

Vesicular carriers such as transferosomes and ethosomes were also studied as resveratrol delivery system (Scognamiglio et al. 2013). Scognamiglio et al. (2013) established that the formulation components have an influence on cytotoxicity and resveratrol skin penetration and only soy phosphatidylcholine based ethosomes were capable of providing *trans*-resveratrol skin permeation in *ex vivo* experiments. In their study, Lv et al. (2018) prepared essential oil-based microemulsions capable of improving solubility, photostability and antioxidant activity of *trans*-resveratrol. Furthermore, the developed microemulsions increase trans-resveratrol skin permeation compared to an aqueous solution (Lv et al. 2018). Enhanced transdermal bioavailability of resveratrol was also achieved from a nanostructured emulsion, prepared from isopropyl myristate and caproyl 90 as oil phases and developed dendrimer-resveratrol complex (Tsai et al. 2016). Inclusion of resveratrol in poly(amidoamine) (PAMAM) dendrimer formulations is also reported to improve resveratrol solubility and stability in water and semisolid dosage forms (Pentek et al. 2017).

Conclusion

Resveratrol is a natural polyphenolic phytoalexin that is an object of numerous research articles and patents due to its beneficial health-promoting effects. Its powerful antioxidant, antimicrobial, anti-inflammatory, cardioprotective, antimicrobial and antiaging properties make it an attractive compound in the treatment of different health disorders. However, its poor oral bioavailability is a significant limiting factor to achieve the desired therapeutic effects. Topical administration of resveratrol is a convenient application route for treatment of different cutaneous disorders. Resveratrol is known for its beneficial effects in the therapy of proliferative skin diseases and it is an efficient anti- and photoaging agent. In recent years many efforts have been made to improve its low ab-

sorption, aqueous solubility and UV- dependent stability. Significant role in this process plays nanotechnology using different drug delivery systems, e.g., microemulsions, liposomes, solid lipid nanoparticles, dendrimers to improve resveratrol`s stability, bioavailability and to ensure controlled drug release.

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