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Resveratrol from diet to topical usage

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Abstract

The stilbene derivative Resveratrol (3,5,4'-trihydroxy-stilbene; RESV) has become the subject of interest of many researchers and pharmaceutical industries due to its well-claimed biological beneficial activities. Although earlier research tended to focus on the effects of RESV on cardiovascular disorders, many others studies have described the beneficial effects of RESV in the area of cancer chemoprevention, inflammation and the interest of researchers on this compound is still increasing. It is now well accepted that the effect of RESV is not just due to its so call "antioxidant" activity but mainly (if not only) to the ability of this compound to trigger cell signaling pathways and gene expression involved in cellular defense systems. Many "in vitro" studies on RESV did not take into account that although its oral absorption is about 75% its goes through a very rapid metabolism and the concentration in the blood stream is almost undetectable. For this reason the interest of the topical usage of RESV by cosmaceutical skin care brands has exponentially raised in the last decade years reporting in general a very promising results on its beneficial effect in protecting the skin from outdoor insults, but there is still some controversy on its topical usage mainly determined by the concentration used. Therefore, more basic research on the topical application of RESV should be performed to better understand its way to prevent cutaenous damage and whether it could be recommended as a preventive skin aging agent for all skin insults.

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Introduction

In recent years, scientifically supported nutritional and medical evidence has allowed nutraceuticals to emerge as being potentially effective for human health, useful to reduce health care costs and to support economic development in rural communities. In this context, plant-derived polyphenols have come out as compounds exerting anti-inflammatory[1]- cancer preventing[2]- photoprotective[3]- and antibacterial- properties. Moreover, many epidemiological studies have correlated polyphenols intake with the prevention of some chronic pathologies such as cardiovascular and neurodegenerative diseases, osteoporosis, diabetes mellitus as well as cancer [4-6].

Polyphenols are a class of natural chemicals characterized by the presence of large multiples of phenol units. The name derives from the ancient Greek word πολύς (polus, meaning "many, much") and the word phenol refers to a chemical structure formed by an aromatic benzenoid (phenyl) ring, an hydroxyl (-OH) group found in alcohols (hence the "-ol" suffix). They form a large group of phytochemicals, which are produced by plants as secondary metabolites to protect them from photosynthetic stress and reactive oxygen species (ROS). These compounds are chemically classified in two groups: *flavonoids* (flavonols, flavones, flavan-3-ols, prothoanthocyanidins, anthocyanidins, isoflavones) and *non-flavonoids* (hydroxycinnamic acids, ellagitannins, gallotannins and stilbenes). Their main dietary sources are fruits and plant-derived beverages such as fruit juices, tea, coffee, and red wine, although cereals, vegetables, chocolate as well as dry legumes could contribute to the total polyphenol intake.

Depending on the chemical structure and redox potential, polyphenols possess an “in vitro” antioxidant properties. Phenolic compounds usually possess low-redox potentials but easily donate one electron to compounds with higher redox potentials, thus being also classified as ROS scavengers. In addition these compounds are strong chelators of metal ions such as Fe^{2+}, Fe^{3+}, Cu^{2+}, Zn^{2+} and Mn^{2+} which contribute to radicals formation and play an important role in generating a redox imbalance also called oxidative stress (OS) able to eventually damage the cell [7]. Being structurally related to many endogenous substrates, phenolic compounds interact with ROS-producing enzymes such as cyclooxygenases, lipoxygenases, peroxidases, nitric oxide synthases, NADPH oxidases and xanthine oxidase[1,8,9]. Moreover, many experimental evidences suggest that their beneficial effects involve decreases in oxidative/inflammatory stress signaling via activation of Nuclear factor (erythroid-derived 2)-like 2 (Nrf2)[10,11], a well-known transcription factor that protects the cells against oxidative damage triggered by injury and inflammation[10]. Polyphenols, in fact, induce many antioxidant enzymes (superoxide dismutase, glutathione peroxidase, gamma-glutamylcysteine synthase) as well as phase II detoxifying enzymes (glutathione-S-transferase,

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hemoxygenase-1, NADPH quinone oxidoreductase). Induction of these enzymes results mainly from transcriptional activation mediated by Nrf2 through its interaction with the antioxidant-response element (ARE) or the electrophile-responsive element (EpRE)[10,11].

Resveratrol

The stilbene derivative (with a C6-C2-C6 structure) Resveratrol (3,5,4'-trihydroxy-stilbene; RESV) has become the subject of interest of many researchers and pharmaceutical industries due to its well-claimed biological beneficial activities.

It can be found in the *cis* or *trans* configuration and both forms occur as glucosides, bounding to a glucose moiety[12]. The glucosides forms are called piceid (Fig.1). If the trans-resveratrol is exposed to sunlight, heated or to UV radiation it can undergo isomerization to the *cis*-form[13-15]. The *trans*-isomer is the more common and it is believed to be more stable [16] and biologically active. For this reason many studies are focused on the effects of trans- resveratrol in different scientific fields (Chemistry, Plant Science, Medicine, Food Science and others) that has resulted in a huge output of in vitro and animal (preclinical) studies. In January 2015, in fact, PubMed (US National Library of Medicine; National Institutes of Health) reports more than 7000 papers on RESV: among these, about 900 correlate RESV to oxidative stress and 50 out of 900 are related to cutaneous tissue.

RESV can undergo polymerization of two to eight units. For instance, ε viniferin is a resveratrol dimer and it was first isolated from *Vitis vinifera* (Vitaceae) [17]. α-Viniferin is a resveratrol trimer and recently research studies highlighted its possible usage for cancer treatment [17-19]. RESV is commonly synthetized by some plants during development and it is known as a phytoalexin because it is biosynthetized as a response to stress factor such as injury, fungal diseases or ultraviolet radiation [15].

Resveratrol food sources

The first reports on RESV bioactivity described its preventive role on cardiovascular health and disease. Renaud and Lorgeril described a phenomenon commonly known as the "French Paradox". The Authors observed that despite French people had a high saturated fat intake with their diet, they presented a lower incidence (about 40%) of coronary heart diseases than the rest of Europe. This was attributed to an increased in red wine intake by the French population [20].

RESV is synthesized in the leaf epidermis and in the grape skins, especially when it is infected with *Botrytis cinerea* [21]. Romero-Pérez et al. [22,23] demonstrated that the amount of RESV varies depending on wine type: it can reach even more than 580 μg/100mL in red wines (Table 1), whereas its content is much lower (~68 μg/100mL) in white wines. This difference can be explained

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by considering that in white wine the skin is removed earlier during wine production, lessening the amount of RESV that is extracted. Furthermore red wine contains more trans-resveratrol than white wine. On the contrary the latter has higher concentration of cis-resveratrol [24], which is extremely light sensitive. The level of RESV and its derivatives present in plants depends on various factors such as environmental conditions, abiotic (light, UV radiation) or biotic stresses (fungal infection, primarily by *Botrytis cinerea*, *Plasmospora viticola*) [15]. Besides wine, RESV is a known constituent of over 72 plant species [25], the main dietary sources of RESV being grape and grape products [26] and peanut products [27]. Also, RESV was detected in cacao, (*Theobroma cacao* L.) [28] hops [29] berries of *Vaccinium* species (blueberries, bilberries, and cranberries) [30,31].

Resveratrol occurrence in food processing and associated agricultural waste materials

The main dietary sources of RESV, grape and peanut products, generate high volume of waste [25]. For instance, winemaking, that is the production of wine from *Vitis vinifera*, is carried out in different steps: grape collection, destemming, crushing and pressing [32]. From this process mainly two different by-products accumulates: grape stems and grape pomace (skins, seeds and lees) [32]. The global amount of grape pomace is approximately 20% of harvested grape [32].

Grape pomace is frequently destined for distillation and production of alcoholic beverages, like grappa in Italy, but there is no real utilization for stems except for composting [32]. From red grape cultivar 'Nerello Mascalese' grape stems, RESV may be obtained in approximate amounts of more than 130 mgs per kilogram of dried stems [32] and from grape seeds, stems, skin and pomace of the Palomino fino grape variety [33].

Grapevine cane, a by-product of vine pruning and summer trimming, usually destroyed by burning, can be also regarded as a widely available potential source of natural RESV [34,35]. Extraction yield of trans-RESV from Vitis vinifera cv. Pinot Noir grape cane was 3.45±0.04 mg g−1 dw and high levels of *trans*-RESV were found in Pinot Noir shoots (15.90 ± 2.99 mg/kg dry matter (DM)), and tendrils [36]. According to Aaviksaar et al. [37], the content of trans-RESV in vine stems varies significantly with cultivar and period of pruning [35]. Autumn-harvested stems contain more RESV, from 1 to 4.7 mg g-1 stems depending on cultivar [35].

RESV, was extracted, purified, and identified from peanut roots. RESV content of peanut roots is large enough to indicate they are a significant source and add value to this component of the plant, usually left as agricultural waste in the field [38]. Like in the case of grapevine, the growing season affected the RESV contents in the roots, the ones of fall crops were much higher than those of

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spring crops [38]. The highest and lowest RESV contents in the roots of 2000 fall and 2001 spring crops were 1.330 and 0.130 mg/g and 0.063 and 0.015 mg/g, respectively [38]. The observed RESV contents in the peanut roots were higher than the reported contents detected in the wounded cotyledons, edible peanuts, and commercial products [38-41]. Schwarz et al. reported a rapid technique for the isolation and enrichment of RESV and the determination of related polyphenols from peanut press waste using molecular imprinting solid phase extraction technology [25]. Peanut press waste is a byproduct of peanut oil preparation, constituting the remains of the peanut and husk after pressing, and contains a range of bioactive constituents [25]. As this byproduct is regularly disposed of as landfill or stock feed, the value-added benefits of these bioactives often remain underutilized [25].

The tree peony plays an irreplaceable role in the ornamental, medicinal, and food industries [42,43]. The antioxidant activity of tree peony has led to its wide application in medicine [43-45]. In recent years, the tree peony seed has attracted attention in the food industry [43,46,47] because it is a potential resource for edible oil that is rich in a-linolenic acid and has beneficial effects on human nutrition and health [43]. Recognizing its nutritional functions, increasing demand for peony seed oil will produce large quantities of tree peony seed oil extracted residues as a byproduct that will be disposed of as landfill waste or used as a low-value fuel [43]. It has been found that valuable trans-resveratrol and its glycosides exist in the peony seed (Paeonia rockii seeds) [43,48-50]. An efficient and environmentally friendly in situ trans-resveratrol extraction approach was developed and applied in tree peony seed oil extracted residues, for extraction of trans-resveratrol; an yield (5.48 ± 0.14 lmol/g) was obtained under the optimized conditions [43].

Resveratrol Bioactivity

Besides the beneficial effects of RESV on cardiovascular disorders, several others studies have described the ability of RESV to ameliorate inflammation, oxidative stress and it has been even suggested for cancer prevention [51- 66].

Although the general simplistic idea is that the main beneficial effect of RESV is due to its antioxidant activity; this polyphenol has been shown to be involved in a more fascinating defensive cell signalling pathways developing further the interested on its beneficial properties.

The in vitro antioxidant ability of RESV is known to be both potent and efficient although many evidences have been in vitro or at non physiological doses. Baxter and colleagues demonstrated that RESV is more active than vitamin E and vitamin C to prevent lipid peroxidation in a model employing gamma irradiation of liposomes [67].

DPPH is a stable free radical and accepts an electron or hydrogen radical from antioxidant compounds to become a stable diamagnetic molecule, reaction that are spectrophotometric recorded

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by decreases the absorbance at 517 nm. Gülçin [68] evaluated the antioxidant activity of RESV (at different concentrations, ranging from 10 to 30µg/ml) by using several *in vitro* antioxidant assays, including DPPH. The IC_{50} values for RESV was 17.8%, indicates a higher DPPH free radical scavenging activity compared to trolox or α-tocopherol. Murias et al., investigated the antioxidant properties of RESV and its polyhydroxylated resveratrol analogues and shown that exhibits pronounced antioxidant activity [69].

Many studies demonstrated that RESV attenuated oxidative injury in immune-perturbed states and human chronic degenerative diseases [70] and that it induced a significant damage to DNA and protein as well as lipid oxidation [71-73]. Moreover, this polyphenol has been considered as a good candidate against OS in atherosclerosis [74-76]. RESV was found to inhibit iron- or UV- induced lipid peroxidation and to prevent LDL oxidation by copper in Cell cultures of Vihs vinifera and in microsomes preparated from Wistar rats [77,78]. Moreover, experimental evidences suggest that RESV induces Mn-SOD expression via nuclear translocation and activation of sirtuin 1 in vivo [79,80]. Interestingly, Sirtuin 1 is an enzyme that deacetylates proteins contributing to cellular regulation (reaction to stressors, longevity) as well as reduces both nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [81] and xantina oxidase [82] activities, that are endogenous sources of radicals.

Resveratrol Bioavaibility, Metabolism and Toxicity in Human

The oral absorption of RESV in humans is about 75% and is thought to occur mainly by transepithelial diffusion [83]. Studies of trans-resveratrol bioavailability indicate its absorption and rapid metabolisation with a relatively low excretion in urine and feces [84]. In the plasma the peak of free RESV was registered at 30 min after ingestion, as a consequence of the gastric absorption [84-88]. It is generally agreed that the major plasma and urine metabolites are resveratrol-O-glucuronides and sulfates, with the sulfates being predominant [84,86,89-91]. The following metabolites were found in the plasma of both healthy humans and colorectal cancer patients ingesting 2.2 and 4.4 mmol of trans-resveratrol: resveratrol-3-O-glucuronide, resveratrol-4'-O-glucuronide, resveratrol-3-O-sulfate, resveratrol-4'-O-sulfate, a resveratrol-O-disulfate, and an O-glucuronide-O-sulfate [84].

Some physicians and pharmacologists, suggested that when orally given, RESV cannot have beneficial effects because it is rapidly metabolized in these forms that possess lower pharmacological activity compared to RESV [92-95]. For this reason, studies have been recently performed to increase RESV bioavailability by using encapsulations and novel delivery systems of this compound [96].

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In addition, it should be mentioned that it is difficult to know the exact daily intake of RESV in humans. Red wine intake, in fact, is not the same among subjects, it could varies in the long period in the same subjects and it could be also differ among the wines. A daily intake of about 4 mg/person/day has been supposed, an amount indeed much lower than that one which causes side effects [97, 98].

Another aspect which is worth to mention is RESV toxicity. Some authors have reported the lack of adverse effects when RESV is administered in humans at doses lower than 0.5 g/die for up to 8 days [85,87,99,100]. On the contrary, when higher doses (> 1g) were used, digestive disorders including diarrhea, abdominal pain, nausea, flatulence [99-106] as well as high bilirubin levels [85,99] were observed.

Another RESV effect that has to be considered, is its capacity to act as pro-oxidant in systems containing redox-active metals. In presence of O_2, in fact, transition metals could catalyze the redox cycling of phenols, leading to the formation of ROS which in turn can lead to DNA damage, oxidative base modifications, strand breaks and formation of DNA adducts [107]. Moreover, high RESV doses could inhibit CYPs and interact with ABC transporters resulting in changes in drug bioavailability and causing adverse effects [105,108]. In conclusion, to reach any definitive statements regarding the therapeutic potential of RESV, more studies are needed to establish its safety profile in humans.

Why the skin?

The skin consists of two main layers, the epidermis and the dermis. The dermis is superficial to the subcutaneous fat tissue and is reachable by blood capillaries. Dermal fibroblasts synthesize a complex extracellular matrix containing collagenous and elastic fibers. The epidermis contains mostly keratinocytes that rise to the skin surface as they differentiate progressively to form the non-nucleated corneocytes that consists of the superficial part of the epidermis, the stratum corneum (SC). The SC comprises a unique two-compartment system of structural, non-nucleated cells (corneocytes) embedded in a lipid-enriched intercellular matrix, forming stacks of bilayers that are rich in ceramides, cholesterol, and free fatty acids. The SC is the outermost layer of human skin and is composed of corneocytes (keratinocyte-derived anucleated cells) and a matrix of intercellular lipids. It functions as a physiochemical barrier, to protect and prevent water loss from the epidermis maintaining its integrity, and to provide protection from the environment by producing antioxidant molecules which interact with free radicals or their by-products to either eliminate or to minimize their deleterious effects. The SC supports the absorption of liposoluble compounds and promotes the penetration of lipophilic molecules. Ways for molecules to penetrate the SC: intercellular

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(penetration between the corneocytes), transcellular (penetration through the keratinized corneocytes), intrafollicular (penetration through hair follicles), and/or polar (penetration between polar pores) [109]. Other physiochemical factors which regulate penetration include molecular mass, concentration, solubility, partition coefficient, pH variations, co-solvents, temperature, and enhancers.

Because of its critical location, the SC is a major interface between the body and the environment and provides a biological barrier against an array of chemical and physical environmental pollutants. Due to the constant exposure to oxidants including ultraviolet (UV) radiation and other environmental pollutants such as diesel fuel exhaust, cigarette smoke (CS), halogenated hydrocarbons, heavy metals and O_3, the SC can be defined as our first defence against the outdoor environment [110-112].

In normal conditions, the skin is protected against the oxidative stressors by an enzymatic (SOD, CAT, GPX, etc) and non-enzymatic (tocopherol, glutathione, etc) machineries. One of the main player involved in cellular protection from OS insults is the transcription factor NRF2 (Nuclear erythroid 2-related factor), which is expressed in all types of skin cells including keratinocytes, fibroblasts and melanocytes [113]. Indeed, NFR2 is involved not only in the transcription of defensive enzymes such as glutathione S-transferase (GST), quinone reductase NAD(P)H (NQO1), UDP-glucuronosyltransferases (UGT), epoxide hydrolase (EPHX), c-glutamylcysteine ligase (GCL), heme oxygenase-1 (HO-1), glutathione reductase (GR), thiore-doxin reductase (TrxR), catalase (CAT), and superoxide dismutase (SOD), but also in keratinocytes differentiation, melanocytes maturation and fibroblasts cells cycle [114-116].

When generated in excessive quantities, free radicals can rapidly overwhelm tissue antioxidants, which in turn result depleted by oxidative stress processes. The loss of antioxidant cellular defense correlates with an increase in lipid peroxidation affecting skin barrier function [117]. Free radicals-induced damage, in fact, could lead to collagen fibers breakdown, resulting in fine wrinkles. Moreover, in the skin, the presence of radicals can aggravate inflammatory injury and promote chronic inflammation, resulting in skin disorders.

For instance, the inability to proper activate NRF2 has been associated with the development of dedermatitis, vitiligo, and the higher susceptibility to outdoor stressors induced skin damage[118].

There are more than 3,000 kinds of skin disorders. Some are temporary and easily treated, while others could persist lifelong and cause chronic symptoms, disability and emotional distress. Among the different skin diseases, erythema, edema, hyperplasia, “sunburn cell” formation, skin aging, dermatitis, psoriasis, acne as well as cutaneous neoplasia, seem to be all somehow linked to OS [119-123].

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It is well known that OS induces the production of oxidation products, such as 4-hydroxy-2-nonenal (HNE) [124], which can bind to proteins altering their functions. HNE influences also the release of pro-inflammatory mediators, such as cytokines [125, 126], which in turn may be critical for the development of inflammatory skin related diseases. This evidence is also supported by the fact that radicals can act as second messenger in different biological processes, by activating NF-kB or AP-1, ERK, JNK and p38 MAPK pathways and promote the release of mediators (i.e. cytokines) involved in cell growth, differentiation and in the degradation of dermis connective tissue [123]. According the current understanding about the molecular pathways that mediate skin damage, there is a general consensus about the correlation between OS and skin diseases. Boissy and Manga have shown that melanocytes are more susceptible to OS in patients with vitiligo, a depigmenting disorder [127]. Free radicals may also participate in the pathogenesis of allergic reactions in the skin [128] and trigger cutaneous inflammation [129]. Moreover, skin exposure to a number of irritants or pro-inflammatory agents including UV radiation, generates free radicals by the oxidative burst in infiltrating leukocytes at the site of inflammation [120]. For example, high levels of radicals, that can cause catalase attenuation, might be a critical aspect of the MAPK signaling involved in skin aging and photoaging [130] since, radicals can directly alter kinases, phosphatases, and transcription factors, or modulate cysteine rich redox-sensitive proteins.

Finally, recent evidences suggest that many air pollutants, such as environmental tobacco smoke, volatile organic compounds, formaldehyde, toluene, nitrogen dioxide, and particulate matter and ozone, act as risk factors for the development or aggravation of atopic dermatitis. These air pollutants probably induce OS in the skin, leading to skin barrier dysfunction and/or immune alteration [122]. Recent studies have also demonstrated the direct or indirect involvement of OS in the pathogenesis of skin fibrosis [123] and in cutaneous wound healing [131, 132].

Resveratrol and skin

On the basis of RESV chemical properties and since OS plays a critical role in many cutaneous conditions including skin cancers [133-135], a huge amount of *in vivo* and *in vitro* studies on the effect of RESV on cutaneous tissue have been performed. In general, the topical usage of natural compounds has been suggested since it avoids all the bioavailability issues that derive from consuming polyphenols with the diet. A recent work by Alonso et al. has assessed in both “in vitro” and “in vivo” the permeation of topical application of RESV, showing that the topically applied RESV penetrates into the skin in a gradient fashion and that RESV after its penetration was able to maintain its antioxidant efficiency [136]. RESV permeated the different layers of the skin in an

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average concentration of 11.25 ± 6.56 μg/cm^2 [136]. When applied in the concentration range of 5–55 mM, the amount of skin incorporation of RESV increased with the applied concentration up to 30 mM, whereas skin incorporation efficiency was inversely proportional to the applied concentration and when applied with 10% ethanol, in the epidermis the concentration was 0.02 μM [137]. Hence, RESV must be used at relatively high concentrations (e.g. mM for topical in vivo and μM for in vitro studies) in order for efficacy to be achieved in cutaneous applications.

Resveratrol and Skin aging

Skin aging consists of two didactically independent, clinically and biologically, distinct processes [138]. The first is intrinsic skin aging, which represents chronological aging and affects skin in the same pattern it affects all internal organs [139]. The second is extrinsic skin aging, which we view as aged skin and is the result of external factors and environmental influence, mainly chronic sun exposure and ultraviolet (UV) irradiation but also smoking, pollution, sleep deprivation and poor nutrition [140]. While the clinical stigmata of natural aging differs significantly compared to extrinsic or photoaging, the cellular and molecular mechanisms are similar [141]. Skin aging is thought to be driven by an increased in-situ production of reactive oxygen species (ROS), which result from both a disturbance of mitochondrial function and acute stress responses to different environmental insults including solar radiation [141,142]. There is also good evidence that intrinsic as well as extrinsic skin aging are associated with a depletion of naturally antioxidants that serve as a defense mechanism against free radical damage [141,143].

Traditionally, antioxidant products are exogenously provided to neutralize pro-oxidant species [144]. However, another approach based on stimulation of endogenous antioxidant defense pathways is more original and the beneficial effects of RESV on skin, beyond its direct antioxidant properties, by upregulation of a cutaneous endogenous antioxidant pathways as shown by Soeur et al. 2015 [144]. In primary culture of normal human keratinocytes (NHKs) or in full-thickness reconstructed humans kin, RESV activated the NRF2 pathway at non toxic doses [144].

Among the NRF2 downstream genes, glutamyl cysteinyligase and glutathione peroxidase-2 were induced at their RNA and protein levels. NRF2 gene silencing experiments performed in NHKs confirmed that NRF2 was involved in RESV-induced modulation of cellular antioxidant status, in part by increasing cellular glutathione content [143]. Improvement of endogenous defenses induced in RESV-pretreated reconstructed skin ensured protection against the toxic oxidative effects of cumenehydroperoxide (CHP) and cellular alterations at the dermal–epidermal junction were clearly prevented [144]. Furthermore, several other studies have suggested a not so protective role of RESV, for instance: RESV has been shown to aggravate an *in vivo* ulcer model by NO mediated

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mechanisms [145]. In addition, induction, in human keratinocytes challenged with LPS, of the pro-inflammatory cytokine IL-8 have been reported [146].

Considering that NO is a key mediator implicated in a broad range of age related skin damages, Bastianetto et al suggest that RESV could delay and even prevent the normal course of skin aging by blocking apoptotic events and mitochondrial dysfunctions NO mediated. RESV has been demonstrated to act on cellular signaling mechanisms related to UV-mediated photoaging, including MAP kinases, NF-kB, and matrix metalloproteinases [67]. Topical application of RESV in a SKH-1 hairless mouse model prior to UV-B radiation results in significant inhibition of cellular proliferation, mRNA survivin expression, and survivin phosphorylation [67], protein involved in the apoptotic process. In vitro studies have demonstrated that RESV effectively down regulates both AP-1 and NFkB and thus serves a key role in preserving dermal collagen and reducing skin inflammation [74, 141,147].

Resveratrol prevent UVA-inudced radicals formation in exposed HaCaT, in a dose-dependent manner, in addition, electron microscopy approach confirmed that RESV can also prevent UVA induced ultrastructural cellular changes [67,148]. Furthermore, Giardina et al. reported that in skin fibroblasts treated with RESV there was a dose-dependent increase in the rate of cell proliferation and inhibition of collagenase activity [149].

Resveratrol also has potential use as a skin lightener. Studies have demonstrated that RESV and other stilbenes have potent tyrosinase inhibitory activity [141,150]. This activity has been shown to be a function of chemical structure of the stilbenes including a double bond that is present in the parent molecule [141,151].

In addition, RESV has been demonstrated to ameliorate age-associated phenotypes such as cellular senescence and proliferative dysfunction [152] by showing that human keratinocytes expressed relatively high levels of Forkhead box O3 (FOXO3), a downstream target of both AMPK and SIRT1 and that treating keratinocytes with RESV led to FOXO3 activation and increased expression of its target genes including catalase. Skin from humans over 50 years old had lower AMPK activity than skin from individuals under 20 years old [152], and this strongly suggest that RESV-mediated effects on keratinocyte senescence and proliferation are regulated by AMPK-FOXO3 pathway besides than by SIRT1.

The anti-proliferative and anti-inflammatory effects of RESV on the skin have been already demonstrated on SKH-1 hairless mice, in which topical applications of trans-resveratrol resulted in a significant inhibition of UVB-mediated skin edema, inflammation and OS [153,154] as well as anti-proliferative effects via modulation of cki–cyclin–cdk and MAPK-pathway [154]. Furthermore, RESV

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has strong chemopreventive effects against UVB exposure-mediated skin carcinogenesis that might be mediated, at least in part, by modulating surviving [155].

In vitro study demonstrated that RESV induces G1-phase arrest of the cell cycle and apoptosis in both human epidermis carcinoma- (A431) [65] and melanoma-cells [156] and that decreases the viability of melanoma cell lines (DM738 and DM443) without affecting fibroblast cells [157]. Moreover, Adhami et al., [64] showed that RESV blocks UVB-mediated activation of NF-kB pathway in normal human epidermal keratinocytes, suggesting that NF-kB pathway plays a critical role in the chemopreventive effects of RESV against UV radiation including photocarcinogenesis.

Recently, our research group has shown that RESV hampered carbonyls and HNE protein adducts formation as well as the induction of TRPA1 (transient receptor potential ankyrin 1) expression (mRNA and protein levels) induced by CS in human keratinocytes [158,159]. TRPA1 is a non-selective cation channel permeable to calcium which is involved in cellular differentiation and inflammation and it is activated by HNE [159]. In addition we found that RESV pretreatment induced an increase of the expression of MsrA, an enzyme involved in cell defense against oxidative protein damage [160]. RESV however prevents CS-induced post-translational modification of SR-B1, a well-known receptor involved in cholesterol uptake. Taken together, these findings further confirm the hypothesis according which RESV could provide skin with a defense against exogenous stressors by acting at different levels [158,159].

Beside the ability of RESV to induce phase II enzyme, as mentioned above, it has been shown that RESV is able to stimulate the expression of a panel of proteins representing structural subunits or assembly factors mitochondrial respiratory chain in skin fibroblasts. RESV treatment increases the amount of mutated proteins and stimulates residual enzyme activities. The up-regulation of mitochondrial respiratory chain enzyme activities induced by RESV translates into increased cellular O_2 consumption rates and increase mitochondrial capacities. It has been suggested that RESV stimulates mitochondrial functions mainly via estrogen receptor (ER) and estrogen-related receptor alpha (ERRα) signaling pathways [161]. ER is well expressed in skin cells, and the decrease of estrogen levels is also involved in the cutaneous features present during chronological aging. Especially in women, during menopause, skin becomes thinner with decreased collagen content, decreased elasticity, increased wrinkling and increased dryness. Many of these effects can be reversed by estrogen replacement or treatment with its agonists. RESV, thanks to its structural similarity with diethylstilbestrol, a synthetic estrogen, can be considered a phytoestrogen. At concentrations (≈3–10 μM) RESV activated transcription of estrogen-responsive reporter genes and was inhibited by specific estrogen antagonists [162]. This, estrogen –like effect, can increase

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epidermal hydration, skin elasticity and skin thickness as well as reducing skin wrinkles and augmenting the content and quality of collagen and the level of vascularization [163-167].

A recent immunohistochemical study has shown that while there is no difference in the expression of ERα and ERβ between male and female human skin, the expression of ERβ is significantly decreased in the epidermis of those above 70 years of age [166].

Conclusion

In this review, our attention have been focused on the occurrence, effects of RESV and the mechanisms underlying these effects in cutaneous tissues.

It should be mentioned that RESV metabolism in the skin is different from the one in the GI tract although the disparate responses present in the literature can be a consequence of the dose and models utilized, as mentioned above.

Concerning skin disorders treatment, the issues of absorption and fate of ingested RESV is moot, since RESV can be applied topically to the skin, although its permeability and metabolism through the skin is not clear and need to be more studied. There is a plethora of literature on absorption and gut and liver metabolism of RESV after oral administration, but few reports have studied its metabolism through the skin. A recent paper by Murakami et al. [95], showed that transdermal application of RESV, more than oral administration, inhibited ear edema in mouse, suggesting that transdermal preparations may be effective in the treatment of acute skin diseases in humans. However, more research is warranted to develop future clinical formulations. Indeed, in the last years, several topical formulations of RESV are being developed, such as hydrogel patches or RESV microparticles contained in the creams or oils that seem prolong its release into the skin [168]. Moreover, the surfactant use was found to produce a stable nano-suspension of RESV that improves its transport across the membrane as well as increases solubility. Furthermore, phospholipid vesicle-based nanoformulations were developed to deliver antioxidant RESV to the skin [56]. The above formulations may be a potential therapeutic alternative to treat skin disorders associated with oxidative stress. Last but not the least, several papers have clearly reported that the use of RESV analogs can be even more effective than RESV. For instance, Ryu et al. were able to provide evidenced in human subject that Resveratryl triacetate (RTA) is not only more stable than RESV but less irritant and has a better skin-whitening properties[169-]. On this topic is worth it to also mention the work by Lephart, where the effect of skin gene expression of several RESV analogs (4′ acetoxy resveratrol, *R*-equol and racemic equol) have been discussed, concluding that many of them have a better skin-antiaging, -antinflammatory and –proliferative effect than RESV itself [170].

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In conclusion, the role of RESV in the future of skin disorders such as skin aging prevention and treatment is promising since oxidative damage that skin cells come under frequently well responds to RESV treatment. One possible way to circumvent the problem of bioavailability for skin disorders is to apply RESV topically to the skin. This would allow resveratrol to come into direct contact with the area of interest, without the side effects associated with systemic metabolism.

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Fig.1. Chemical structure of *trans*- and *cis*-resveratrol and its glucosides forms (piceid)

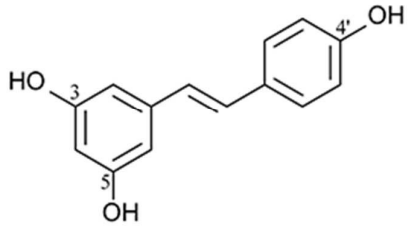
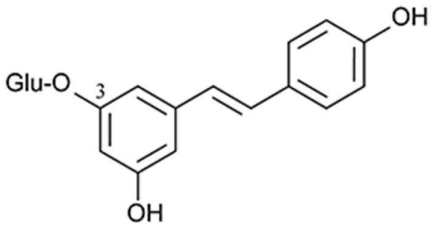
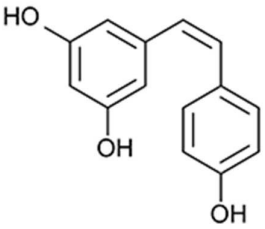
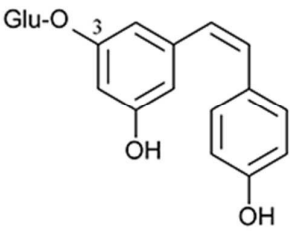
	
trans-resveratrol	*trans*-resveratrol-3-*O*-β-glucosides (*trans*-piceid)
	
cis-resveratrol	*cis*-resveratrol-3-*O*-β-glucosides (*cis*-piceid)

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Table 1 Content of resveratrol and its derivatives in different source (nd-not detected; nc-not calculated)

Food/raw material	*trans*-resveratrol	*cis*-resveratrol	*trans*-piceid	*cis*-piceid	References
Beverages-Red wines (µg/100 ml)					
Pinot Noir, 1994 (California)	1057 ±60	746 ±9	nd	nc	[12]
Cabernet Sauvignon, 1996 (Bulgaria)	672 ±*10*	520±*16*	189±*5*	nc	
Cabernet Sauvignon, 1995 (California)	53±1	45±1	nd	nc	
Merlot, 1994 (Chile)	48±1	152±5.3	nd	nc	
Pinot Noir, 2010 (Romania)	294.3±0.04	261.5±0.03	nd	nc	[15]
Cabernet Sauvignon, 2010 (Romania)	366.4±0.05	229.3±0.04	nd	nc	
Merlot, 2010 (Romania)	718.8 ±0.04	388.2±0.04	nd	nc	
Other beverages (µg/100 ml)					
Itadori tea	68±1	nd	906±3	nc	[12]
Grape (µg/g)					
Merlot	0.5±0.0		7.3 ± 0.4		[12]
Cabernet Sauvignon	0.5±0.0		2.2±0.4		
Peanuts Products (µg/g fw)					
peanuts (boiled)	5.1 ± 2.8	nc	nc	nc	[12]
peanut butter	0.3 ± 0.1	nc	nc	nc	
Hop Variety (mg/kg)					
Nugget	1		5.50	2.76	[29]
Vanguard	0.22		5.21	2.99	
Cocoa Powder (µg/g)					
Natural cocoa powder	1.85 ±0.43	nc	7.14 ±0.80		[28]
Blueberry or bilberry (pmol/g)					
Raw highbush Michigan blueberry	140.0 ± 29.9	nc	nc	nc	[31]

Molecular pathways involved in Resveratrol mediates skin protective effects against environmental insults