ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Resveratrol: A Unique Antioxidant Offering a Multi-Mechanistic Approach for Treating Aging Skin

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ABSTRACT

Resveratrol is a botanical antioxidant with diverse biologic effects. In this paper we will review the unique antioxidant activity of resveratrol including its effects on mitochondrial function. The molecular signaling of resveratrol and cellular mechanisms that make this botanical active an important anti-aging ingredient for topical application will be discussed.

J Drugs Dermatol. 2013;12(12):1389-1394.

INTRODUCTION

Resveratrol (3,5,4'-trihydroxystilbene) was first isolated from the roots of white hellebore (*Veratrum grandiflorum O. Loes*) and later from the roots of *Polygonum cuspidatum*.(1) This plant has long been used in Chinese and Japanese medicine where it is valued for diverse therapeutic effects. Resveratrol is a natural polyphenolic antioxidant of the stilbene family that is found in more than 70 plant species. Some of the more common botanical sources include berries, peanuts and grapes. Resveratrol is a major constituent of red wine as it is present in the skin of red grapes and concentrates as wine ferments. In nature, resveratrol is a phytoalexin, which functions to protect plants from stress, ultraviolet light and certain fungal infections.

Medical interest in this compound sparked when it was postulated that resveratrol may be responsible for the low incidence of heart disease seen in the French population whose diet is high in saturated fat.[2] This phenomenon, coined by Dr. Serge Renaud and Dr. Michel de Lorgerial as the French Paradox, was attributed to a moderate intake of red wine. Since that time, resveratrol has been the subject of vigorous ongoing research to confirm its health and anti-aging benefits. Studies have shown that resveratrol binds to numerous cell-signaling molecules allowing it to modulate beneficial health effects through multiple pathways.[4] Resveratrol has anti-diabetic, anti-inflammatory and anti-cancer activity.[3-5] It also acts as a

vasodilator, platelet inhibitor and has important cardioprotective effects.[6] Recent studies have suggested that resveratrol may also be effective when applied topically to treat aged skin. In this review we will therefore describe some of the important targets of resveratrol, their clinical implications for treating aging skin and the challenges that have prevented resveratrol from being effectively incorporated into a topical formulation.

Resveratrol as an Antioxidant

Resveratrol is probably most recognized for its potent antioxidant activity. One of the more distinct features of this polyphenol is that it exhibits dual antioxidant capacity. In addition to directly scavenging free radicals resveratrol increases the intracellular expression of other naturally occurring enzymatic antioxidants. Specifically, resveratrol up-regulates expression of nuclear factor-E2-related factor-2 (Nrf2), a transcription factor, which regulates several genes responsible for detoxification of reactive oxygen species.[7] For example, Nrf2 is known to increase the production of glutathione synthetase (GSH), the enzyme that is the rate limiting step in the synthesis of the antioxidant glutathione. Additionally, resveratrol has been shown to boost naturally occurring enzymatic antioxidants including superoxide dismutase, catalase and hemoxygenase-1 thus increasing intracellular antioxidant capacity.[8] The direct free radical scavenging properties of pure resveratrol are well established and appear to be greatly dependent on the structural position of the hydroxyl group.[9] Studies have determined resveratrol to be an effective scaven-

ger of hydroxyl, superoxide and metal induced radicals.[10] Finally, resveratrol prevents lipid peroxidation by chelating copper and by working synergistically with antioxidants such as vitamin E.[11] These combined effects make resveratrol a unique antioxidant capable of both scavenging free radicals on its own and increasing intrinsic antioxidant capabilities.

Resveratrol and Mitochondrial Function

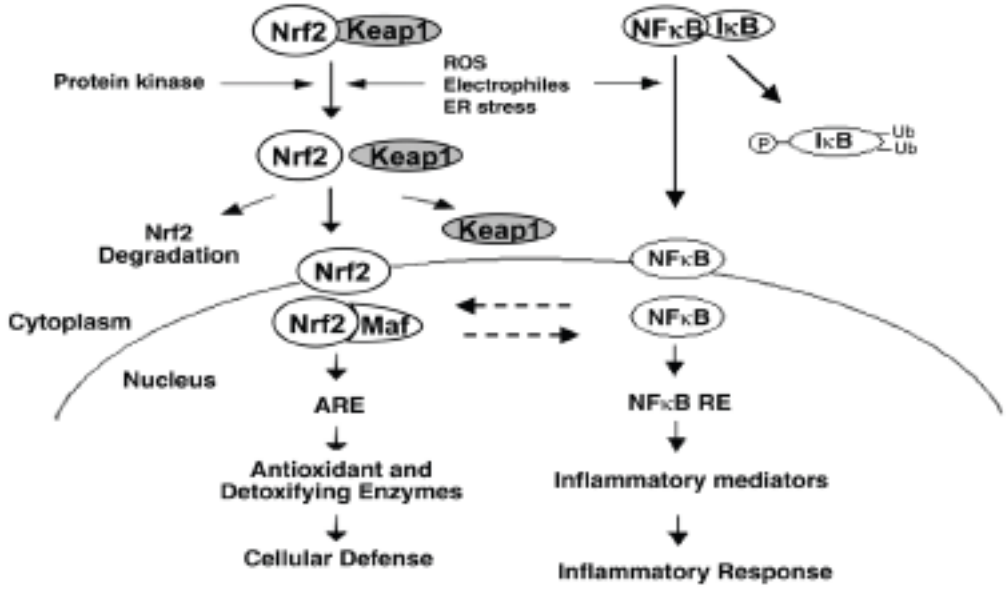
Mitochondria are the organelles primarily responsible for generating cellular energy in the form of adenosine triphosphate (ATP). Production of ATP involves a number of complex redox reactions that generate reactive oxygen species as a byproduct. Multiple features of the mitochondria are unique; in contrast to other cellular components whose DNA is found inside the nuclear envelope, the mitochondria has its own genome localized to its innermost membrane. As of the main sources of endogenous reactive oxygen species, mitochondria are very susceptible to oxidative damage, which can deteriorate the organelle's function and promote apoptosis. Mitochondrial DNA (mtDNA) is especially vulnerable to attack by reactive oxygen species because of its proximity to ROS production, the lack of protection offered by histones and relatively slow repair, as compared with nuclear DNA. Mitochondrial dysfunction is often attributed to various disease pathologies along with the aging process.[12] Resveratrol exhibits multiple properties beneficial for mitochondrial vitality. Specifically, this phytoalexin promotes mitochondrial biogenesis and reduces mitochondrial reactive oxygen species generation.[13,14] Accordingly, there has been extensive research on the use of resveratrol as anti-aging agent. This notion is supported by the fact that resveratrol effects appear to mimic the health benefits of caloric restriction including reducing age related diseases such as cancer, heart disease, diabetes, neurodegenerative disease and enhancing longevity in vitro and in organisms ranging from worms through mice.[15] The SIRT1 and Nrf2 pathways are two of the more widely studied pathways associated with resveratrol's biologic action and continue to be linked with its anti-aging potential.

It is now known that both dietary restriction and resveratrol exert their beneficial effects on health and longevity by activating an important group of enzymes called sirtuins. Landmark resveratrol studies on longevity showed that it was able to extend lifespan in yeast, fruit flies and worms. Sirtuins were first discovered in yeast and have recently been identified in mammals.[16] There are seven mammalian sirtuins the most important of which is sirtuin 1 (SIRT1). SIRT1 is a NAD-dependent deacetylase that turns on and off certain transcription factors that are essential for survival during times of stress. Resveratrol works by activating SIRT1 that deacetylates peroxisome proliferator activator gamma co-activator 1 alpha (PGC-1α) causing an increase in its activity.[17,18] PGC-1α induces transcription of genes that regulate gluconeogenesis and lipid metabolism. In addition, resveratrol through SIRT1 and PGC-1α increases mitochondrial function and has a positive impact on energy homeostasis. Animal research established that resveratrol protects mice against diet induced obesity and insulin resistance by increasing SIRT1 activity.[19] Studies have confirmed that similar mechanisms are in play in humans. One of the noteworthy human studies tested supplementation with resveratrol for 30 days in obese males resulting in improved skeletal muscle mitochondrial function and fat oxidative capacity that was not associated with weight loss. SIRT1 protein levels in skeletal muscle were observed and fasting plasma glucose and insulin levels were decreased in test subjects receiving

resveratrol.[20] In addition, SIRT1 modulates DNA repair, gluconeogenesis, cell-cycle regulation, lipid metabolism, insulin sensitivity, fat mobilization, cell survival and lifespan.[21] Studies of multiple compounds known to affect SIRT1 revealed that resveratrol is among the most potent natural sirtuin activators.[22]

More recent studies demonstrated that resveratrol prevents mitochondrial dysfunction and confers cytoprotective benefits via the Nrf2 pathway.[23] Since diminished mitochondrial function is associated with reduced longevity, the ability of resveratrol to enhance mitochondrial function may be a key mechanism for its anti-aging effects. At steady state, inactive Nrf2 is associated with Kelch-like erythroid cell-derived protein 1 (Keap-1) in the cytoplasm. Once activated, Nrf2 dissociates from Keap-1 and translocates to the nucleus where it binds the antioxidant response element (ARE) initiating the cellular response to oxidative stress. (Figure 1) While the exact method of Nrf2 translocation is unclear, it has been shown that under conditions of oxidative stress, Nrf2 exhibits greater nuclear accumulation and transcriptional activity.[24] The increase in the Nrf2 induced gene expression will prompt the antioxidant defense response in order to maintain cellular redox homeostasis.[25] Resveratrol is believed to work in similar ways by stimulating the Nrf2 pathway, promoting the subsequent translocation of Nrf2 into the nucleus, leading to downstream increase in expression of Nrf2 target genes, specifically heme oxygenase-1 (HO-1).[26]

FIGURE 1. Schematic representation of Nrf2 and NF-kB activation by reactive oxygen species.[27]



HO-1, along with the other genes, will subsequently activate the antioxidant defense system needed to protect cellular components, especially the mitochondria, from oxidative damage. Studying cultured endothelial cells, Zoltan Ungvari (2009) was able to demonstrate that resveratrol's activation of Nrf2 induced naturally occurring enzymatic antioxidants leading to significant reduction of mitochondrial oxidative stress.[28] Other studies have linked resveratrol action with the Nrf2 pathway by demonstrating its protective role of human epithelial cells.[29]

Resveratrol as a Chemoprotector

Within the last decade, a large portion of resveratrol medical research has focused on its potential as a chemopreventive agent. Resveratrol exerts anti-tumor activity by affecting all three stages of tumor formation including initiation, promotion and progression.[30] The stilbene induces apoptosis of tumor cells by down regulating expression of the inhibitor of apoptosis gene survivin and by inducing expression of the tumor suppressing p53.[31] Furthermore, studies have demonstrated that resveratrol has both in vivo and in vitro cytotoxic activity against melanoma cells.[32] Animal studies have also confirmed that topically applied resveratrol inhibits non-melanoma skin cancer formation. Mice which were irradiated with daily UVB and had

either pre- or post-treatment with topical resveratrol showed a delay in the onset of tumor formation and the incidence of tumors.[33] The fact that post-treatment with resveratrol conferred benefits similar to pre-treatment demonstrates that chemoprevention is not due to the sunscreen effects. Other studies demonstrated that pre-treatment of mouse skin with topical resveratrol reduced UVB-induced edema, erythema and leukocyte infiltration and inhibited COX2 expression and ornithine decarboxylase activity.[34] These studies suggest that resveratrol may confer an added benefit through its anti-inflammatory activity.

"Studies have shown that resveratrol binds to numerous cell-signaling molecules allowing it to modulate beneficial health effects through multiple pathways."

Resveratrol and Skin Aging

Skin aging is a complex sequence of events that reflects the changes occurring in both natural (intrinsic) and extrinsic aging. While the clinical stigmata of natural aging differ significantly compared to extrinsic or photoaging, the cellular and molecular mechanisms are similar. 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.[35] There is also good evidence that intrinsic as well as extrinsic skin aging are associated with a depletion of naturally occurring antioxidants that serve as a defense mechanism against free radical damage.[36] When left unchecked, ROS can directly damage cell membranes, proteins and DNA. In addition, ROS turn on cellular and molecular mechanisms that accelerate skin aging including up regulation of transcription factors such as activator protein 1 (AP-1) and nuclear factor-kB (NF-kB).[37,38] AP-1 is one of the prominent transcription factors responsible for the production of metalloproteinases (MMPs), the enzymes that break down collagen. The essential role of MMPs in promoting premature skin aging has been demonstrated in pivotal scientific studies.[39] Furthermore, multiple studies have shown that the decrease in collagen production is associated with AP-1 and may involve the cytokine transforming growth factor beta (TGF-β).[40,41] This cumulative loss of dermal collagen is believed to be the primary cause of wrinkling. Likewise, NF-kB is paramount in the production of pro-inflammatory mediators that contribute to skin aging.[42,43] In vitro studies have demonstrated that resveratrol effectively down regulates both AP-1 and NF-kB and thus serves a key role in preserving dermal collagen and reducing skin inflammation.[44,45]

The stilbene chemical structure of resveratrol is similar to that of the synthetic estrogen diethylstilbesterol. In view of this it is not surprising that resveratrol is a phytoestrogen and estrogen beta receptor agonist (ERβ).[46] Post-menopausal women are known to lose collagen at a rate of 1% per year causing skin to become thin, wrinkled and fragile.[47] Estrogen replacement therapy mitigates collagen loss and improves the clinical signs of skin aging. The use of phytoestrogens such as resveratrol, are of particular interest since they may provide the skin benefits of estrogen without the associated risks.

Resveratrol also has potential use as a skin lightener. Studies have demonstrated that resveratrol and other stilbenes have potent tyrosinase inhibitory activity.[48] 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.[49,50] In view of these diverse properties, resveratrol provides a multi-mechanistic approach that makes it a remarkably promising agent for the treatment of various skin aging symptoms.

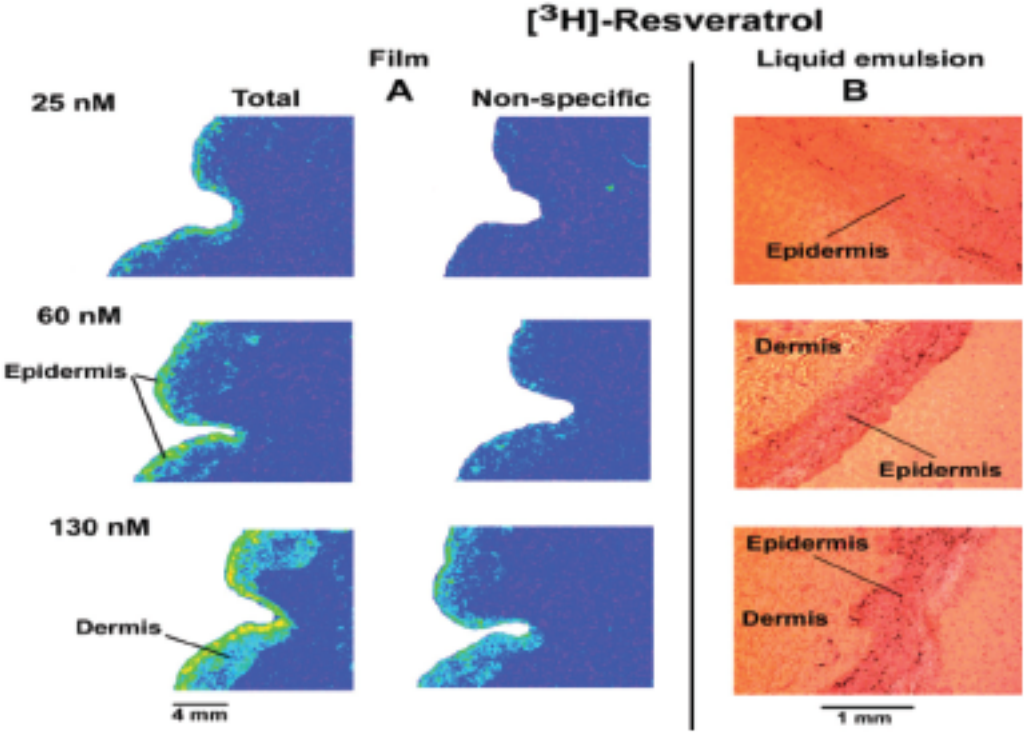
Bioavailability, Formulation and Delivery of Resveratrol

While the inherent potential of resveratrol is undeniable, there are several challenges that prevent its broader utilization in treating skin conditions. Resveratrol is absorbed quickly after oral ingestion with peak plasma levels 30 minutes after consumption. [51] Up to 70% of resveratrol is bioavailable in the plasma after absorption but rapid enterohepatic metabolism significantly reduces that level. Orally ingested resveratrol is

excreted primarily by the kidney and only a small fraction that is ingested reaches the tissues of various bodily organs. This is especially problematic for skin tissue since it is the outermost organ of the body. Multiple studies have attested to the challenges of systemic administration of resveratrol attributing this difficulty to rapid metabolism and an inability to sustain meaningful plasma concentration.[52] Researchers have suggested that both naturally occurring and synthetic derivatives may be utilized to circumvent the issue of rapid metabolism. Nonetheless, comprehensive clinical data on resveratrol derivatives is still under investigation. Targeting resveratrol to the epidermal tissue via oral administration is clearly not the most effective strategy to deliver this phytoalexin to the skin.

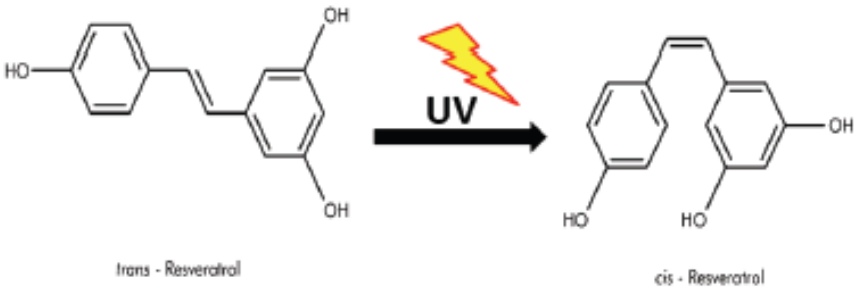
Topical application of resveratrol represents a promising alternative to oral ingestion for use in treatment of skin aging. In fact, while studying human keratinocytes cell lines, a collaboration of scientists at McGill University and L'Oreal Open Research were able to confirm the existence of resveratrol binding sites located in the epidermis.[53] (Figure 2) Since topical applications are delivered directly to the affected area, this may be an effective approach to combat resveratrol's rapid metabolism and allow skin tissue to attain a therapeutic concentration. However, utilizing a topical delivery system presents additional challenges. One of the problems is specific to resveratrol's strong photosensitivity. The polyphenol exists predominantly as two isomers, cis-(Z)-resveratrol and trans-(E)-resveratrol. In this regard it is important to note that the trans-isomer is more stable and biologically active.[54]

FIGURE 2. Photomicrograph of the autoradiographis distribution of [3H]-resveratrol binding sites in human skin. Higher level of silver grain is observed in the epidermis as compared to the dermis.[53]



So to maximize the effect, resveratrol needs to be maintained as a trans-structural isomer. However, Waterhouse et al 2009 demonstrated that UV irradiation (306 nm) caused approximately 90% isomerization of trans-resveratrol to its less desired cis-isoform.[55] (Figure 3) Resveratrol's promise as a topical skin care formulation may be severely limited by the consistent UV exposure of human skin. Unless protected from UV rays by a broad-spectrum sunscreen or used exclusively in the evening, this instability caused by UV irradiation will substantially diminish resveratrol's biological activity.

FIGURE 2. UV induced conversion of trans-Resveratrol to cis-Resveratrol.



Furthermore, the physico-chemical properties of resveratrol have restricted its use in topical formulations. One particular challenge is the stilbene's relatively low water solubility, estimated around 0.05 mg/mL.[56] This property prevents incorporation of high concentrations of pure resveratrol into topical products. This is supported by the fact that the leading topical resveratrol products often contain less that 1% of pure resveratrol in the final formulation. Various solvents are often employed to increase the hydro-solubility of solid ingredients. However, solubilizing agents may potentially introduce unknown and unwanted side effects. Furthermore, resveratrol's protonation state is integral to understanding the complexity of its biological role. Studies have established that transport of resveratrol to the skin is limited by the type of vehicle used in the formulation.[57] Proper formulation parameters are essential since the ingredient is required to both escape from its vehicle and penetrate the initial barrier to exert biologic action in the skin. Overcoming these impediments is an area of ongoing resveratrol research that is essential for the development of effective topical formulations.

CONCLUSION

Resveratrol is an important polyphenol with numerous known health benefits. Working through multiple pathways this powerful antioxidant can improve the function of multiple organ systems including the skin. Resveratrol holds great promise as a topical ingredient for treating skin as it can both prevent and improve the clinical signs of aging. Many of its scientifically proven properties show great potential to ameliorate the aesthetic problems of skin aging. However, further innovation is required to overcome the challenges to effectively deliver resveratrol into the skin in order to transform this omnipotent extract into a proven therapeutic product.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Christina Steel PhD for the critical reading and editing of this manuscript.

DISCLOSUREs

P.F. serves on the advisory board and has received consultancy fees from Beiersdorf, LaRoche Posay/L'Oreal, L'Oreal Paris, NeoStrata Company, Skinceuticals/L'Oreal, and Skin- Medica; and is a speaker/trainer for Allergan, Medicis. D.M. has grants/pending grants from Cynosure/Palomar, Fibrocell Science, LifeSpan Extension, Skinceuticals/L'Oreal, US Cosmecuetechs, NorthCell Pharmaceutical, Allergan, Priori SkinCare, Dr. Brandt® Skincare, Ulthera, BTL Aesthetics; has received consultancy fees from Allergan, SkinCeuticals/ L'Oreal, Fibrocell Science; paid lectures fees from Fibrocell Science; and patents with LifeSpan Extension, Cynosure/ Palomar, Light BioScience, Hampton University. J.K. has received consultancy fees from SkinCeuticals/L'Oreal and paid lectures for SkinCeuticals/L'Oreal. Y.L. has received consultancy fees from SkinCeuticals/L'Oreal. Y.K. is employed by SkinCeuticals/L'Oreal.

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