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The Role of Resveratrol as Potent Antioxidant for Anti-Aging Formulation Development: A Review

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Abstract
The occurrence of skin aging process is not the same in each individuals. The changes in skin appearance can affect in self-confidence, especially for those who experience the aging process faster than their age called premature aging. Therefore it is necessary therapy to prevent, repair and maintain the structure and function of aging skin. Resveratrol is a potent antioxidant that has activity as skin anti-aging. The limitations of the physicochemical properties of Resveratrol become the focus of attention for formulation of anti-aging development.

Keywords : *Anti-aging, Antioxidant, Resveratrol, Lipid Nanoparticles, Vesicles, Nanocarriers*

I. INTRODUCTION

Skin aging is a complex biological process that will be experienced in every human (1). The aging process is a gradual process of slowing body's tissue ability to repair or maintain its structure and normal functioning. Skin is the most outer layer of the body which several important roles to protect humans body (2). In certain people aging processs can occur according to the ages, but there are some people who experience skin aging process earlier than ages (the process of premature aging) and some are experiencing the aging process more slowly than the ages. This shows that aging process in each individuals depends on many factors affect.

Extracellular matrix (ECM) plays an important role in maintaining skin integrity. ECM has three main components: elastic fibers, collagen and proteoglycans (3). When the aging factor appears, the extracellular matrix will be remodeling (4). The visible changes in skin aging such as dry, coarse, wrinkles accompanied by lines of facial expression can affect appearance showing that the person has entered old age. These changes eventually decline self-confidence, especially in those who experience the aging process faster than their age (5). Therefore, it requires management of both invasive and non-invasive therapy to prevent, improve or maintain the structure and function of aging skin.

II. SKIN AGING

Aging process can be classified by intrinsic factors (chronological aging) and extrinsic factors (premature aging).

1. **Intrinsic aging:** This process also called chronological aging, a natural aging process caused by various physiological factors of the body itself, such as genetic, hormonal, and ethnic In hormonal factors, estrogen has an influence in the synthesis of collagen by fibroblasts, which then stimulate synthesis of hyaluronic acid and increase extracellular matrix. in menopause, there is a condition of hypoestrogenism that affects the elasticity of the skin. While in the ethnic factor, the aging process comes with pigmentation. High levels of melanin pigmentation will protect from the cumulative effect of photoaging. Black ethnic has a greater number of lipids and is compact and so resistant to photoaging. Likewise, the Asian has a slower skin aging ability than the Caucassians. Telomere, a small DNA sequence located at the end of a chromosome is considered an essential element in the intrinsic aging process. Along with the aging process, continuous replication will lead to the shortening of DNA structure that can be repaired by telomerase. Telomere maintenance by telomerase action will inhibit the aging process, but this action can lead to carcinogenesis (6).
2. **Extrinsic aging:** The aging process that occurs due to various factors from the environment is called premature aging. It is caused by several factors such as ultraviolet radiation (UV), air humidity, temperature, polutant . A person can experience aging faster than its age due to the ongoing exposure of these environmental factors. Free radical factor obtained from UV exposure is a major factor that accelerates the aging process called photoaging. Free radicals can cause damage to the skin such as producing Reactive Oxygen Species (ROS) that can cause DNA damage, induce the enzyme matrix metalloproteinase (MMP) that leads to collagen degradation (7).

A. Treatment of Skin Aging: To overcome the problem of skin aging, begins with the prevention of UV exposure. This can be done by using sunblock or sunscreen with chemical or physical filters . The next step that can be done if signs of premature aging have visible:

1. Use active ingredients to reduce signs of premature aging of the skin.
2. If the condition of premature aging on the skin more serious invasive therapy required.
3. To improve the condition of the skin it can use cosmetics such as antioxidants, retinoids, and alpha hydroxy acids that are used routinely to show an improvement in skin conditions (8).

B. Resveratrol as Skin Anti-Aging: Resveratrol is a potent antioxidant that is currently being investigated for a variety of disease conditions. Resveratrol (3,5,40-trihydroxystilbene) (Fig.1) is a naturally occurring phytoalexin antioxidant present in grapes, berries, peanuts and red wine (9). In 1940, resveratrol was first derived from the white hellebore root (Veratrum grandiflorum O. Loes) and nearly 23 years later, it was found in the roots of Polygonum cuspidatum (10). This plant has been used for traditional medicine where it is valued for diverse therapeutic effects (11).

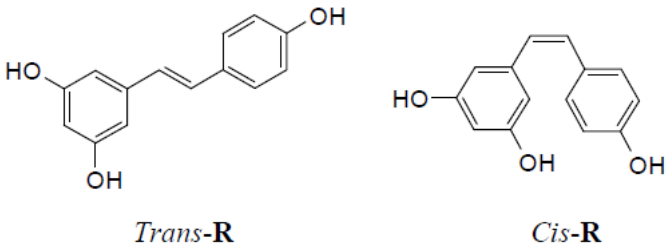

Figure 1. Structures of trans-resveratrol (trans-R) and cis-resveratrol (cis-) (12)

Resveratrol characterized by solid off-white powder with molecular formula C14H12O3, molecular weight of 228.25 g.mol−1, melting point between 253-255 °C, and a fat soluble-compund. Resveratrol consists of two structural isomers: cis- (Z) and trans- (E) (Fig. 1). The trans-resveratrol biologically more active than the Cis-resveratrol (13). Exposure to the sunlight, heat or UV radiation, can turn trans-resveratrol into isomerisation cis form (14). Resveratrol exhibits high membrane permeability and can be considered a class-II compound in the Biopharmaceutical Classification System (15).

Resveratrol effectively inhibited AP-1 and NF-kB expression (16). AP-1 is a main transcription factor responsible for the production of metalloproteinases (MMP) enzymes that contribute to collagen degradation. Increased collagen degradation is a major cause of wrinkles. While NF-kB produces a pro-inflammatory mediator that also plays a role in skin aging Other studies have shown that resveratrol prevents mitochondrial dysfunction (17). The elevation of mitochondrial function decreases the regeneration of body cells that can accelerate aging (18), and thus application of resveratrol becomes the primary key as anti-aging.

In vivo studies have shown that topical use of resveratrol in hairless mice reduces skin inflammation, inhibits cyclooxygenase (COX) ornithine decarboxylase (ODC) induction, and formation of hydrogen peroxide due to UV-B exposure (19).

Based on its chemical structure, resveratrol has a stillben group similiar to estrogen diethylstilbesterol. Therefore, resveratrol also has activity as phytoestrogens and estrogen beta receptor agonist (ERβ). In postmenopausal women, clinical signs of skin aging will shown due to the loss of estrogen production. The use of resveratrol as phytoestrogens becomes potential to overcome the clinical signs of skin aging in the absence of side risks (20).

C. Topical Formulation of Resveratrol as Anti-Aging

Resveratrol is a polyphenol compound with many several health benefits. Resveratrol has many mechanisms as a powerful antioxidant to improve the functioning of organs systems including the skin. Resveratrol plays an important role as a topical ingredient for treating the skin as it can prevent and correct the clinical signs of aging (21). However, further innovation in the delivery system is needed to overcome the limitations of resveratrol in order to maintain the stability and effectiveness of resveratrol into the skin (22).

1. **Lipid nanoparticles:** Solid Lipid Nanoparticles (SLN) is the first generation of lipid nanoparticles that has developed since 1990 (23). SLN is produced by replacing the liquid lipid component (oil) from oil / water emulsions with solid lipids (24). SLN has ability to protect unstable chemical ingredients and prolonging drug release (25). Nanostructured Lipid Carriers (NLC) is the latest generation of Solid Lipid Nanoparticle (Fig.2). NLC was developed to overcome the weakness of SLN due to its limited loading and the occurrence of drug expulsion during storage. NLC consists of a certain amount of lipid matrix and liquid lipids. The NLC remains in solid formation by controlling the oil content added to the formulation, so that the controlled drug release drug for NLC can be achieved.

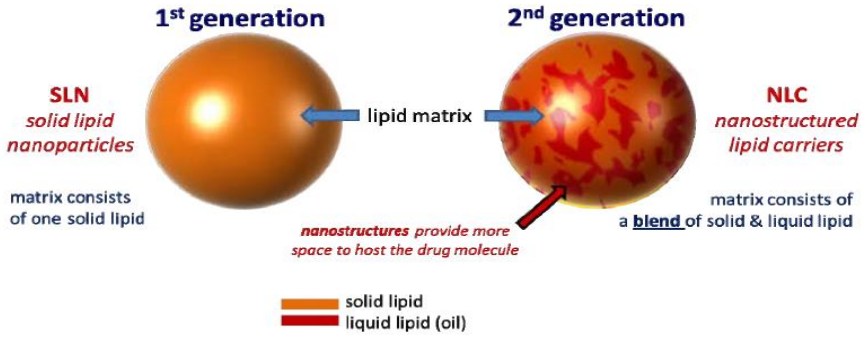

Figure 2. Structure of SLN and NLC (26)

In 2012, Gokce et al (27) conducted a study to determine the effectiveness of resveratrol formulated in SLN and NLC systems with Compritol as solid lipids and miglyol as lipid liquids. The results showed that the use of topical resveratrol in SLN and NLC systems increasing resveratrol penetration into the dermis and protect fibroblasts from exposure to ROS.

2. **Vesicles:** Vesicular carriers can be divided into two main groups, namely liposomes and niosomes (28). Liposomes are vesicular structures consist of a hydrophobic lipid bilayer membrane surrounding an aqueous core. Hydrophobic lipid bilayer membrane composed of a phospholipid and cholesterol (29). Resveratrol loaded by liposomes achieve incorporation percentage higher than 70%, low zeta potential during storage, and increase cell proliferation under the stress condition induced by UV-B light (30). These result showing good capability in incorporation, stability and photoprotective effect. Niosomes are non-ionic surfactants vesicle in aqueous media resulting in closed bilayer structures. Niosomes have more advantages over liposomes because of higher chemical stability and penetration (31). An ex vivo studies conducted by Negi et al in 2017 (32), show high permeation and resveratrol deposition in skin when compared with ordinary resveratrol. In addition, the study also showed that resveratrol entrapped niosomal gel significantly reduced edema in the rat paw induced carragenan model.

3. **Protein based nanocarriers:** Protein-based nanocarriers are being developed due to biodegradability, biocompatibility,high nutritional value, low cytotoxicity, abundant renewable sources and extraordinary binding capacity of various drugs (33) (34). Silk is a protein polymer produced by insects and spiders. Silk protein has several advantages for drug delivery due to its biocompatibility, slow biodegradability, controllable structure and morphology and less inflammatory (35). Silk protein from silkworms degumming consists of two proteins, fibroin and sericin. (36). Fibroin is the core of silk of a fibrous protein, while sericin is a protein that wrap fibroin fibers with a successive sticky layers to help the formation of cocoons (37).
An in vitro cytoyoxic study has been conducted by Sukhtam in 2017, about resveratrol loaded sericin carriers, it is known that there is no cytotoxic effect against normal skin fibroblast cells. This result suggests that resveratrol load sericin is safely applied to the manufacture of therapeutics and cosmetics.

III. CONCLUSION

Based on several studies, it is known that resveratrol can be formulated in various delivery systems to maintain its stability, safety and effectivity as anti-aging. These factors are important in the formulation development of drugs and cosmetics.

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