Free Radicals affect Photoaging and Antioxidants Prevention: A Review

Fitria Nugrahaeni[1,*], Dewi Melani Hariyadi[1], Noorma Rosita[1]

Pharmaceutics Department, Faculty of Pharmacy, Airlangga University
Indonesia

[*]*Corresponding author's email: fitrianugrahaenidua [AT] gmail.com*

ABSTRACT---- ***Free radicals play an important part in the process of internal and external aging. Aging is many factor process resulting in several functional and aesthetic changes in the skin. The changes arise from intrinsic as well as extrinsic processes, such as ultraviolet radiation. Antioxidants are substances that can delay or avoid the occurrence of free radical oxidation reactions in lipid oxidation. The focus of this review is the formation of free radicals in skin experiencing photoaging and antioxidants to prevent it.***

Keywords---- Free radicals, photoaging, skin, antioxidants

1. INTRODUCTION

The process of aging is a process of decreasing the body's physiological functions increased weakness. Many factors cause people to grow old through the aging process, which causes pain and eventually brings to death [1]. Various factors that can be grouped into internal factors and external factors. Internal factors are free radicals, reduced hormones, glycosylation processes, methylation, apoptosis, decreased immune systems, and genes [2,3]. The main external factors are unhealthy lifestyles, unhealthy diet, wrong habits, environmental pollution, stress, and poverty. All these factors can be prevented, slowed and even inhibited so that life expectancy can be longer with good quality of life [4]. The skin is a complex and dynamic organ that shows significant signs of aging significantly. The skin is directly related to the surrounding environment because of its aging as well as the consequences of damage to the environment [4,5]. These changes occur as part of the endogenous accumulation of endogenous damage from continuous formation of ROS (reactive oxygen species) formed during cellular oxidation metabolism [2-5].

UV radiation has many adverse effects on the skin, either directly or indirectly. It is estimated that about 50% of damage caused by UV occurs due to free radical formation, whereas direct cellular damage and other mechanisms are the reasons for the rest [6]. The decrease in the amount of collagen and MMP-1 levels due to UV light is substantially mediated by two of the most responsible mechanisms, namely induction of AP-1 and lower TGF-β type II regulation. Where the activation of AP-1 was preceded by the formation of ROS [7]. In this review, we discussed free radicals, antioxidants, skin and their role in photoaging.

2. FREE RADICALS

Free radicals also are known as reactive oxygen species (ROS) are defined as a molecule, atom, or some group of atoms that have one or more unpaired electrons in their outermost orbital. These molecules or atoms are volatile and can quickly form new compounds [1,3,7]. There are various free radicals as a derivative of carbon (C) and nitrogen (N), but the most studied are oxygen radicals. One oxygen paired with electrons is stable; whereas, oxygen with unpaired electrons is reactive because it will seek and generate electrons from vital components and leave damage [8].

Free radicals present in the body can come from within (endogenous) or from outside the body (exogenous). Endogenously, free radicals form as normal responses of the respiratory (breathing) chain in the body. The sources of free radicals in biological materials are superoxide dismutase (SOD) enzymes, cytochrome P-450, xanthine oxidase, lipoxygenase, cyclooxygenase, electron, and quinone transporting proteins [9]. Endogenously, free radicals can arise through several mechanisms such as autooxidation, oxidation activity (e.g.,cyclooxygenase, lipoxygenase, dehydrogenase, and peroxidase), and electron transport systems [10]. Free radicals are produced in cells by mitochondria, plasma membranes, lysosomes, peroxisomes, endoplasmic reticulum and cell nuclei. Exogenously, free radicals are obtained from a variety of sources including pollutants, food, and beverages, radiation, ozone, and pesticides (pesticide residues) [2,5,11].

3. FORMATION OF FREE RADICALS IN SKIN EXPERIENCING PHOTOAGING

The theory of free radicals in the aging process is one of the most accepted theories to explain the causes of aging. Activated Oxygen Species may affect on DNA, cytoskeleton elements, cellular proteins, and cellular membranes. ROS not only has an effect on the aging process as a whole, but is believed to play a cutaneous role in the cause of photoaging, carcinoma, and inflammation [12]. It is well known that UV induces skin breakdowns being relaxed by intermediate reactive oxygen. If antioxidants can absorb some of the free radicals, then there may be a decrease in UV-induced skin damage [3,9,13]. Free radicals also play a role in inflammation which is known to play a role in aging skin. Free radicals are likely to contribute to the development of skin cancer. Many studies explain the role of free radicals and skin diseases [13].

Free radicals also play an important part in the process of internal and external aging. Free radicals are commonly formed through normal human metabolism but can be produced as a result of external factors, such as sun exposure, air pollution, cigarettes, radiation, alcohol use, exercise, inflammation, and exposure to particular drugs or heavy metals such as iron [14]. In fact, UV radiation, stress, cigarettes, pollution, drugs and food are sources of ROS such as superoxide, hydroxyl anion, hydrogen peroxide (H_2O_2) and singlet oxygen. Recent data suggest that free radicals can induce most of the transcription factors such as activator-1 protein (AP-1) and nuclear-κβ factor (NF-κβ) [15]. So far, ROS enhances the expression of matrix metalloproteinase (MMP), a particular collagenation, which can degrade skin's collagen. Collagenization formation emerges as a result of activation of c-Jun and c-Fos transcription factors, the combination to produce AP-1, in turn, activates MMP. Also, MAPK pathways (Mitogen-Activated Protein Kinase) are the targets of oxidative stress [4,6,16].

The presence of an oxygen molecule (O2) at the bottom of the epidermis is a major target of UV light waves entering the skin. The oxygen molecule is unique and is an unstable substance, since the electrons in the outer orbit are incomplete, and so tend to attract electrons to supplement their two vacant orbits [17]. The consequence is with the inclusion of UV rays into the skin layer. It can be as an electron donor to oxygen molecules in the epidermis. If UV light gives one electron, then the oxygen atom now has an unpaired electron in its outer orbit. The result is a problem, when the oxygen molecule draws an electron from an average molecule around it, causing the molecule to have unpaired electrons, becoming unstable and becoming aggressive free radicals [17-18]. The oxygen molecule can be converted to singlet oxygen (• O_2) or superoxide anion (O_2-•) and to stabilize it must be self-administered electrically, the superoxide anion will randomly pick up an electron from the nearest molecule. It's not only damages the molecule, but it also converts it into free radicals and causes reactions chain. This type of free radical formation or spreading can damage various components of skin cells, such as enzymes and cell membranes [19].

One of the damages caused by free radicals is the loss of cell membrane control functions. However, skin cells still have enzymatic antioxidants such as superoxide dismutase, which can eliminate and neutralize superoxide anions. Vitamin E present in skin cells can also prevent the formation of some free radicals from superoxide anions [4-7,16,20]. But when skin cells are exposed to high and old UV rays, the antioxidant defense mechanisms in cells are not able to inhibit free radical reproduction, and the resulting damage is unavoidable, all this accelerates the aging process and increases the risk of skin cancer [21].

Superoxide anions are not the only free radicals that are formed by UV exposure. A second electron derived from UV light is given to superoxide anions and creates a union known as peroxidant hydrogen (H_2O_2). This hydrogen peroxide will be a dangerous threat to the cells because these free radicals can enter through the nuclear membrane and occupy and damage the cell's DNA [22]. The presence of iron (Fe^{2+}) and through the Fenton reaction, H_2O_2 can easily convert to aggressive hydroxy radical ($OH^•$) and can react with almost all compounds in the body. Radical hydroxy is known as a destroyer of cellular enzymes, proteins, carbohydrates, lipids and DNA that can cause the chain mutations resulting in cancer and accelerate premature skin aging [23].

4. PATHOGENESIS OCCURS PHOTOAGING

Effect of UV Light Inhibits Collagen Production

UV exposure, in addition to reducing mature collagen in the dermis, also severely damages the synthesis of collagen, primarily through the continued regression of collagen synthesis, mainly by decreasing the regulation of procollagen gene expression of type 1 and type III [24]. Two mechanisms responsible for reducing procollagen gene levels are an induction of AP-1 and lower regulation of TGF-β type II. As previously described, UV rays induce the transcription factor AP-1, by binding and executing elements that are part of the transcriptional complex required for transcription of procollagen, by interfering with the production of collagen. The transcription factor AP-1 has also been shown to decrease collagen synthesis by inhibiting the effects of TGF-β, a major profibrotic cytokine, and one of the executions of these protein signals that activate proteins either directly or indirectly [17-20,24-25].

Ultraviolet light also disturbs the expression of the type 1 procollagen gene with TGF-β through the down-regulating of TFG-βII receptors for 8 hours of irradiation, indicating the cell is unresponsive to the effects of TGF-β [26].

In fibroblast cultures, UV rays affect the down-regulation of TGF-BII receptors resulting in a loss of TGF-β response which will substantially reduce the expression of the type 1 procollagen gene. This data suggests that TGF-βII receptor down-regulation, and for the repression of transcriptional media AP-1, also plays a role in decreasing expression of procollagen gene observed in vivo after exposure to UV rays [26,27].

The evidence continues to grow from in vitro research that UV radiation triggers the action of ligand receptors through the formation of ROS. It has been assumed that ROS is oxidant and through the oxidation process will decrease the protein-tyrosine phosphatase enzyme[27]. This reduction of the enzyme will cause up-regulation of receptor growth factor and will eventually activate AP-1 [27,28].

Reactive oxygen species (ROS) also affect signal transduction mediated by MAP kinase (MAPKs), p38 and JNK. This enzyme is as good as the ceramide of the cell membrane which further causes the induction of AP-1. Activator protein-1 consists of two subunits, i.e., c-fos expressed constitutively and c-jun which can be induced UV [29]. The excessive expression of c-Jun components of the AP-1 on cultured fibroblasts can reduce the amount of type 1 collagen expression. The protein-1 activator may suppress the expression of the type 1 procollagen genes, procollagen type 3 and TGFβ dermal fibroblast cells resulting in decreased collagen synthesis [28,29]. In humans within a few hours of exposure to UV rays will form MMPs, especially gelatinase and collagenase which ultimately reduce the amount of collagen in the dermis layer [30].

Collagen production is cut in a skin that has photoaging. After UV radiation, the pro-collagen supply is noticeably reduced and absent at 24 hours after exposure in vivo. Activator protein-1 and transforming growth factor β (TGF-β) are involved in UV-mediated down-regulation of collagen synthesis [31].

UV exposure to human skin or mice induces a series of matrix metalloproteinases (MMP), which are involved in the photoaging process [30,31]. The metalloproteinase matrix with proteinase is capable of damaging collagen tissue and other components of the extracellular matrix. Recent studies have shown that UV exposure can reduce collagen in photoaging by blocking receptors TGF-ß type II / Smad signaling [32]. Overall, the effects of ultraviolet on the dermis result in collagen degradation, collagen synthesis barriers, inflammation, and oxidative stress, as well as decreased cell capability and eventually apoptosis [33].

Skin

The skin is the largest organ that covers the entire body. The skin area on the people averages about 2 m^2 by weight 10 kg if weighed with its fat or 4 kg if it is nonfat, or weighs about 16% of a person's body weight [34]. The skin is the organ that was first exposed to pollution by substances contained in our environment, including microorganisms that grow and live in our environment. The skin is also very involved, elastic and sensitive, and varies in climatic conditions, age, sex, race, and body location [35].

Skin Anatomy

The skin is histologically composed of 3 main layers of the epidermis layer or cuticle dermis layer (korium, vera cuticle, actual skin), and subcutis layer (hypodermis). There is no firm line between demists and subcutis. Subcutis is characterized by the presence of loose connective tissue and the cells that form fatty tissue. The epidermal layer and dermis are limited by dermoepidermal links [36].

a. Epidermis

The epidermis is a plated epithelial tissue, with epithelial cells that have a particular layer. This layer consists of 5 layers of stratum germinativum, stratum spinosum, stratum granulosum, stratum lusidum, and stratum corneum [36,37].

b. Dermis

The dermis is a fibroelastic connective tissue, of which there are many blood vessels, lymphatic vessels, nerve fibers, sweat glands and oil glands, each of which has functional meaning for the skin itself [37]. This layer is much thicker than the epidermis, formed by elastic tissue and solid fibrous with cellular elements, glands, and hair as skin adnexa [38].

c. Subcutis

This layer is a continuation of the dermis, consisting of a loose connective tissue containing fat cells in it. Fat cells are round, large cells, with nuclei, pushed to the sides due to the increased fat cytoplasm. These cells form groups separated from one another by trabecular and fibrous. The fat cell layer is called panniculus adiposus, serves as a food reserve [35-38]. In this layer, there are edge nerve endings, blood vessels, and lymph channels. The thickness of fatty tissue is not the same, depending on the location, on the abdomen 3 cm, while in the eyelid and penis area is very thin. This fat layer also serves as a cushion [39].

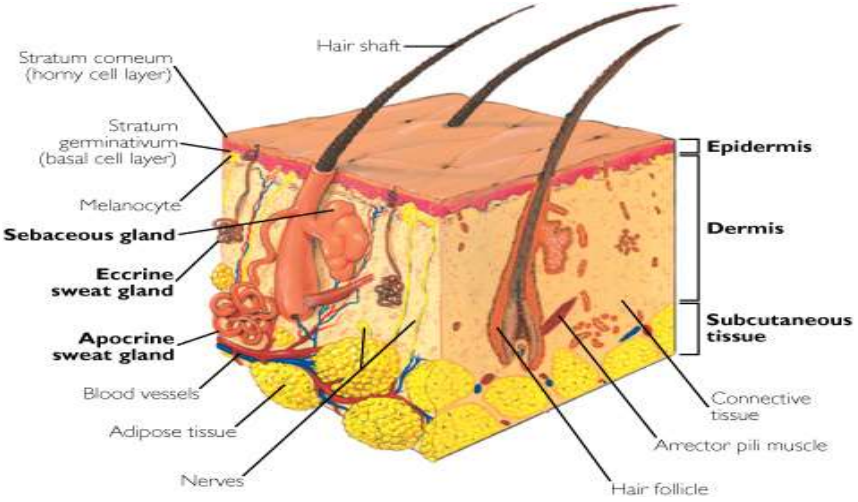

Figure 1. Skin Structure

Skin Physiology

The skin has various functions that are as follows:

a. Protection Function

The epidermis is useful to cover the body's tissues from outside influences [37-39]. The outermost layer of skin is covered with a thin layer of fat that allows the skin to withstand body temperature, resist minor injuries, prevent chemicals and bacteria from entering and dispel physical stimuli such as ultraviolet rays from the sun [40].

b. Absorption function

Healthy skin is not easy to absorb water, solution or solid. But volatile liquids are more likely to be quickly absorbed by the skin, as well as substances that dissolve in oil [39,40]. The ability of skin absorption is affected by the thin thickness of the skin, hydration, air humidity, metabolism and the type of carrier substance that attaches to the skin. Absorption can be through intercellular gap, gland or hair ducts channels [40,41].

c. Excretion function

Skin glands secrete substances that are not useful or residual metabolism in the body such as NaCl, urea, uric acid, ammonia, and less fat. The sebum produced by the skin palm gland protects the skin and retains excessive evaporation so that the skin does not dry [39-41].

d. Sensory function (sensory)

The skin contains sensory nerve endings in the dermis and subcutis. The Ruffini body located in the dermis, receiving cold stimuli and hot stimuli played by Krause's body. Meissner's tactile body found in the dermis papil receives a touch of arousal, as is the Merkel-Renvier body based in the epidermis [42].

e. Function of regulating body temperature (thermoregulation)

The skin regulates body temperature through dilatation and vascular construction as well as through respiration that is affected by the autonomic nerves [41,42]. The skin performs this role by secreting sweat and wrinkle muscle walls of blood vessels of the skin when there is an increase in temperature. With the release of sweat, the body heat also wasted. This thermoregulation mechanism is governed by the sympathetic nervous system that promotes the intermediate acetylcholine agent [38,41,42]

f. The function of pigment formation (melanogenesis)

Skin pigment-forming cells (melanocytes) are located in the basal layer of the epidermis. This cell is derived from the nerve rigi; the amount is 1:10 of the basal cell. The amount of melanocyte and the amount and amount of melanin formed to determine the color of the skin. Sun exposure affects melanin production. When exposure increases melanin production will increase [39-42].

g. Function of keratinization

Keratinization starts from the basal cell that cuboid, mitosis upward changes the more polygonal shape of the spinonum cells, lifted upward becomes flattered, and granular into granulosa cells [40-42]. Then the cell is lifted up more flatly, and the granule and its core disappears into spinosum cells and eventually reaches the skin surface into dead cells, its protoplasm dries to hard, flat, without a nucleus called horn cells. This process is continuous and useful for skin rehabilitation functions to perform its functions well [43].

h. The production function of vitamin D

The skin can also make vitamin D from raw materials seven dihydroksicolesterol with the help of sunlight. But this production is still lower than the body's need for vitamin D from outside food [42,43].

Fibroblasts

Fibroblasts are the primary cells in the dermis layer, spindle-shaped with an irregular branching branch cytoplasm, a large, pale oval nucleus with clear nucleoli [41-43]. The fibroblast cells are responsible for the production of collagen, reticulin fibers, elastic fibers and the buffered tissue of the dermis. Also, fibroblasts can also remove these fibers by secreting enzymes such as collagenase (MMP-1) and elastase [44].

Fibroblasts play a significant role in the process of wound healing (wound healing process). The presence of a tissue damage can stimulate fibrocytes and fibroblast mitotic cells [43,44]. So it can be said that the main function of fibroblasts is to maintain the integrity of connective tissue structure and regulate the turnover of connective tissue by producing enzymes that can degrade collagenase, elastin (elastase), proteoglycans and glycosaminoglycans (stromelysin and lysosomal hydrolase) [45]. From one study it was stated that fibroblast cells have stronger resistance to UV-B exposure than other cells such as keratinocytes and melanocytes with cytotoxic doses of UV-B narrowband exposure (100,200 and 400 mJ /cm^2) or UV-B broadband (5.10, and 25 mJ / cm^2) [46].

Matrix Metalloproteinase

The metalloproteinase matrix is a zinc-dependent endopeptidase. MMP gene family in humans consists of 28 types with different structure and specificity. MMPs are associated with physiological and pathological processes related to extracellular matrix turnover, wound healing, angiogenesis, and cancer [45,46]. Many MMPs are capable of causing degradation of type I collagen, i.e., MMP-1, 8.13, MT1-MMP (MMP-14), MT2-MMP (MMP-15), and MT3-MMP (MMP-16). In the skin, only MMP-1 is most often triggered by ultraviolet light exposure and appears to be most responsible for the breakdown of collagen due to sun exposure [44-46]. MMP-1 levels will increase with age, which is estimated as a result of fragmentation of collagen fibers and disorganization of collagen fiber arrangement in the dermis [47].

Activator Protein -1 (AP-1), which is a nuclear transcription factor, consists of two sub-units, c-jun, and c-fos, to control the transcription of metalloproteinases matrices (MMPs) [46,47]. MMPs is an enzyme responsible for the degradation of the extracellular matrix, including MMP-1 (collagenase), MMP-3 (stromelysin), and MMP-9 (92-kD gelatinase). Metalloproteinase is also responsible for the occurrence of collagen degradation [48].

MMP can occur immediately with minimal doses of ultraviolet light, below the dose required to cause erythema. There are a dose and response relationship generated between UV exposure and MMP induction [46-48]. Exposure to insufficient UV rays to cause sunburn can facilitate collagen degradation, and eventually lead to photoaging [49]. Repeated minimal exposure with a dose equivalent to 5-15 minutes of exposure to the sun at midday is sufficient to increase the MMP leveL. From several studies that have been done on fibroblast cultures showed that UV-B light radiation capable of triggering MMP expression at a dose that varied between 10 mJ/cm^2 - 100 mJ/cm^2 [45-50].

Antioxidants

Antioxidants are defined as compounds that can delay, slow down and prevent lipid oxidation processes. In a particular sense, antioxidants are substances that can delay or avoid the occurrence of free radical oxidation reactions in lipid oxidation [51]. Antioxidants work by donating an electron to an oxidant compound so that the activity of the oxidant compound can be inhibited. According to Meydani, and friends, the balance of oxidants and antioxidants is critical because it is related to the function of the body's immune system [50,51]. The unsaturated fatty acid compounds are the largest components that make up cell membranes, which are known to be very sensitive to changes in the balance of oxidants-antioxidants. Thus, immune cells require antioxidants in greater quantities than other cells. Antioxidant deficiency in the form of vitamin C, vitamin E, Se, Zn, and glutathione, Q-10 significantly affect the immune system [50-52].

5. ANTIOXIDANTS AND THEIR SKIN PROTECTION EFFECTS IN PHOTOAGING PROCESS

Free radicals have a significant role in the mechanism of skin damage due to UV exposure. There are four ways to reduce skin damage from free radicals due to UV exposure, i.e., 1) avoid excessive sun exposure, 2) wear sun protective clothes, 3) use sunscreen cream or lotion which contains antioxidants, 4) using antioxidants both systemically and topically [53].

The natural aging process of our body does not work maximally useful when there is an increase in ROS production [52,53]. It makes the imbalance and some free radicals that damage DNA, cytoskeletal elements, cellular proteins, and cellular membranes. UV and visible light inhibit most of the body’s antioxidant defense mechanism [54].

Damping of the harmful effects of oxidants is done in 2 ways: 1) preventing the occurrence and over-accumulation of oxidant compounds, and 2) preventing the ongoing chain reaction. The antioxidants are divided into two groups: antioxidants prevention (preventive antioxidants) such as SOD enzymes, catalase, glutathione peroxidase, glutathione, cysteine; and chain breaking antioxidants that are differentiated from exogenous and endogenous [54,55]. Exogenous antioxidant groups such as vitamin C, vitamin E, lycopene, while endogenous are glutathione, cysteine. Vitamin E, β carotene, and lycopene are lipophilic in that they may contribute to cell membranes to prevent lipid peroxidation, whereas vitamin C, glutathione and cysteine are hydrophilic and play a role in the cytosol and extracellular fluid [51-55].

Glutathione (γ-glutamyl-cysteinylglycine) has a low molecular weight, soluble in water, thiol-tripeptide formed by three amino acids namely glutamate, cysteine and glycine [56]. The sulfhydryl group makes it possible to interact with various biochemical systems so that its active form is abbreviated as "GSH." Glutathione is one of the most active antioxidant systems in human physiology [57]. Glutathione is considered a highly valued cell protector through its direct effects on neutralizing reactive hydroxyl radicals and other oxygen-free radicals. Mitochondria are a source of fuel cell energy and consume more oxygen than other organelles in the cytosol [56-58]. It will produce reactive oxygen species (ROS) that cause oxidative stress, this is the reason mitochondria are used as primary targets for neutralizing ROS glutathione and reducing oxidative stress, so glutathione is essential for function mitochondria and also energy production [59]. Glutathione acts as a protective cell, which can help slow down signs of aging by fighting against radiation damage that can occur to the skin, the retina, the cornea, and the lens of the eye. Also, it also plays a role neutralize free radicals that can accelerate signs of aging [57-59]. Glutathione levels in the body rapidly decrease at around age 20 or depend on exposure to environmental toxins [60].

Coenzyme Q10 serves as an antioxidant that protects the body from damage caused by harmful molecules known as free radicals. Coenzyme Q10 can neutralize free radicals and can reduce or even help prevent some damage resulting from free radicals, such as cell membrane damage, DNA damage, and cell death [61]. The antioxidant properties of CoQ10 are derived from the carrier function of energy. As an energy carrier, Coenzyme Q10 molecules will continuously pass through the redox cycle [62]. When receiving electrons, it will be reduced, and when giving electrons, it becomes oxidized. In the reduced form, the CoQ10 molecule holds a somewhat loose electron [61,62]. Then this Coenzyme Q10 molecule will only pick up one or both of the electrons, and thus act as an antioxidant [63]. CoQ10 inhibits lipid peroxidation by preventing the production of peroxyl lipid radical. Ubiquinone is a quinone derivative that dissolves in lipids with an isoprenoid side chain [61-64]. Homologous ubiquinone contains 1-12 isoprene units. The dominant form of ubiquinone in humans is ubiquinone-10 (includes ten isoprene units). In liver cells, 40-50% of the total cellular ubiquinone is located in the mitochondria, 25-30% in the core, 15-20% in the endoplasmatic reticulum, and only 5-10% in the cytosol [65]. In vitro tests, ubiquinol (reduced form of ubiquinone) has antioxidant activity 2-3 times more potent. The role of ubiquinol/ubiquinone as a redox carrier in the respiratory chain, by participating in the transfer of protons across the inner mitochondrial membrane [66]. Ubiquinol can react with ROS and prevent direct damage to biomolecules and initiation of lipid peroxidation [64-66]. Although ubiquinone cannot prevent autocatalytic free radical reactions by donating a phenolic hydrogen atom, ubiquinone binds singlet oxygen and inhibits lipid peroxidation in the membrane model [67].

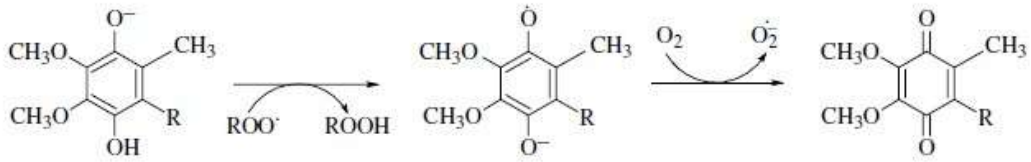

Figure 2 Antioxidant and Probiotic Reactions Ubiquinone

Coenzyme Q10 has a chemical formula C59H90O4 with molecular weight 863.37. Coenzyme Q10 is crystalline powder, yellow to orange. Coenzyme Q10 has a melting point of about 48°C, soluble in ether, very soluble in dehydrated alcohol, practically insoluble in water [66-67]. Coenzyme Q10 should be stored in a dry place, in tightly closed containers and protected from light [67-68]. Chemically, the structure is 1.4, - benzoquinone where Q represents the quinone chemical group and 10 indicates the number of isoprenyl subunits on the side chain. Coenzyme Q10 is present in most eukaryotic cells, especially in human mitochondria. Coenzyme Q10 serves as an antioxidant that protects the body from damage caused by harmful molecules known as free radicals [69]. CoQ10 can neutralize free radicals and can reduce or even help prevent some free radical damage, such as cell membrane damage, DNA damage, and cell death. The antioxidant properties of CoQ10 are derived from the carrier function of energy [68,69]. As an energy carrier, Coenzyme Q10 molecules will continuously pass through the redox cycle. When receiving electrons, it will be reduced, and when giving electrons, it becomes oxidized [70]. In a reduced form, the CoQ10 molecule holds a somewhat loose electron; then this CoQ10 molecule will simply take one or both of the electrons, and thus act as an antioxidant. CoQ10 inhibits lipid peroxidation by preventing the production of peroxyl lipid radicals [69-71].

Recently, researchers have studied the use of exogenous antioxidants used to reduce the damage caused by free radicals [72]. Many believe that topical application and oral consumption of a combination of antioxidants can maintain antioxidant capacity in the skin, due to the synergistic action of a combination of antioxidants [73]. Topical antioxidants are currently being marketed to prevent aging and skin damage due to skin-damaging UV therapy given to wrinkles and erythema caused by inflammatory factors [74]. The free radical theory of the aging process explains why antioxidants can prevent wrinkles, but this theory does not can prove the use of antioxidants can cure existing wrinkles. Many manufacturers claim that their antioxidant products contain products that can cure wrinkles [72-75]. It is important to emphasize to patients that antioxidants can prevent wrinkles but cannot cure wrinkles [76].

6. CONCLUSION

In the future, researchers needed a strategy to get easily obtained antiaging applied to the skin. Especially photoaging not only trying to remove the remaining time on the skin but also play a significant role in the prevention, regeneration, and delay of skin aging that combines knowledge of possible local and systemic therapies, filling the lack of scientific inquiry and becoming one of the principal focuses of aging research.

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