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Review Article
OXIDATIVE STRESS : IMPLICATIONS ON SKIN DISEASES

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Abstract

Earth is abundant with oxygen which used in living system for burning metabolic fuel in order to produce energy. Oxygen is somewhat considered as a toxic agent, due to its ability of formation free radicals. Free radicals are very reactive substances, produced normally in the human body and exhibit a positive effects at normal levels but, in elevated status the development of oxidative injury is inevitable. In order to limit the harmful effects of free radicals, a counter protective system composed of antioxidants have been recognized, these antioxidants arise from endogenous and exogenous sources and work together in a sophisticated system, scavenging free radicals and eliminate their consequences. The skin is known as the largest organ of the human body, and the first line defense of it. It have been reported that many of skin diseases are followed with a remarkable oxidative stress markers. Here in this article we demonstrated some of the pathogenesis of the skin and the association of oxidative stress.
Keywords**:** Oxidative stress, skin diseases, antioxidants, ROS.

Introduction

Free radicals have gained a great attention in medicinal field due to its role in the development and/or association with several diseases (Forman, 2016). Many factors have been linked with the increasing of risks that arise from oxidative stress such as lifestyle, cigarette smoking, drugs, exposure of chemicals, stress, illness, pollution, and many other factors (Aseervatham, Sivasudha, Jeyadevi, & Ananth, 2013). The involvement of oxidative stress have been well established in several diseases such as ischemia-reperfusion injury (Kadhim, Mohammed, & Abbood, 2020; Mohammed, Kadhim, & Abbood, 2020). Antioxidant materials are substances with certain properties which act to scavenge free radicals, therefore reduce the incidence of oxidative stress and its harmful effects (Ozougwu, 2016). It should be pointed out that classical herbal medicines, and diet were the main exogenous sources of antioxidant for ancient peoples which gained them a protection from the free radicals damage consequences (Sen & Chakraborty, 2011). The increasing of free radicals (which overwhelm antioxidants) contribute to the development of cutaneous diseases and disorders. There are many potential targets in the biological system for oxidative damage, one of the most susceptible to these reactions is the skin. The skin is full of biomolecules which comprise very suitable and sensitive substrates for the ROS attack such as proteins, lipids, and DNA (Sen & Chakraborty, 2011). The clarification of oxidative injury mechanisms and illustration of how protection system works will expand our understanding of skin diseases and may lead to further understanding of the mechanisms involved in various pathological conditions of the skin.

1. Free radicals

Free radicals are highly reactive substances which contain unpaired electron(s) at the outer orbit. The absence of full paired electrons in free radical substances lead to common properties shared by most of these substances. Due to the unpaired electron(s) most of free radicals unstable, thus attempt to seek stabilization and therefore, being an oxidative agents (Cheeseman & Slater, 1993; Lobo, Patil, Phatak, & Chandra, 2010).

- Some of the endogenous sources of free radicals (Ebadi, 2001; Lobo *et al.*, 2010):
  - Mitochondria
  - Peroxisomes
  - Inflammation
  - Phagocytosis
  - Arachidonate pathways
  - Hard exercise
  - Ischemia-reperfusion injury
- Some of the exogenous sources of free radicals (Srivastava & Kumar, 2015):
  - Cigarette smoke
  - Environmental pollutants
  - Radiation
  - Certain drugs, pesticides
  - Industrial solvents

1.1. Reactive oxygen species

Reactive oxygen species (ROS) are an entire class of highly reactive substances in which it centered by oxygen. ROS include radicals such as hydroxyl radical, superoxide anion, and nitric oxide (often referred to as RNS, due to the presence of nitrogen), also the term include non-radicals (which are decompose to radicals very easily) such as hydrogen peroxide, hypochlorous acid, and organic peroxides (Krumova & Cosa, 2016). There are numerous sources of ROS in both endogenous and exogenous agents (Phaniendra, Jestadi, & Periyasamy, 2015). Mitochondrial respiration considered as the major generator of ROS in vital cells, through the reduction of molecular oxygen in stepwise reduction in order to achieve the ultimate product H_2O (Eq. 1), appropriate percentage of the non-complete reduced oxygen escape the process yielding ROS (Eq. 2-5) (Poljšak, Dahmane, & Godić, 2012).

$$O_2 + 4e^- + 4H^+ \rightarrow 2H_2O \quad (1)$$

$$O_2 + e^- \rightarrow O_2^{\bullet -} \text{ Superoxide anion} \quad (2)$$

$O_2^{\bullet-} + e^- + 2H^+ \rightarrow H_2O_2$ Hydrogen peroxide (3)

$H_2O_2 + e^- + H^+ \rightarrow {}^{\bullet}OH + H_2O$ Hydroxyl radical (4)

${}^{\bullet}OH + e^- + H^+ \rightarrow H_2O$ Water (5)

Normal production of ROS *in vivo*, reported that these ROS play significant roles in cell physiology. However, the uncontrolled production reach the harm influence of these ROS, in which an oxidative damage occur from cell membrane to the DNA in the secured core, including peroxidation of membrane lipids, deceased membrane fluidity, and DNA mutations, which all leads to a related pathogenesis such as cancer and degenerative diseases (Li, Jia, & Trush, 2016).

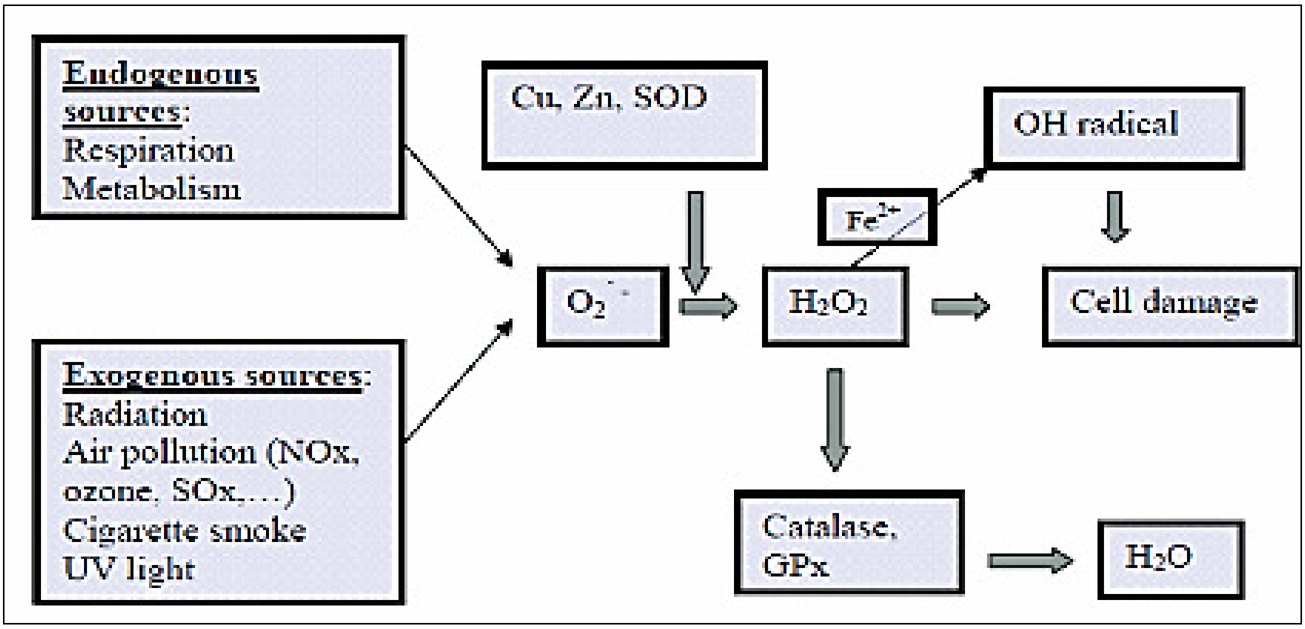

Fig. 1: Cellular generation of reactive oxygen species and antioxidant defense system (Poljšak *et al*., 2012).

In general, the harmful effects of ROS on the cell are most often (Mates, 2000):

1- Nucleic acid damage.

2- Oxidation of polyunsaturated fatty acids in lipids.

3- Oxidation of amino acids in proteins.

4- Oxidative deactivation of specific enzymes through oxidation of cofactors.

2. Antioxidant protection system

The antioxidant molecule distinguished by characteristic properties which enable it to neutralize free radicals (Papas, 2019). Thus, antioxidants delay or reduce cellular damage caused by ROS and other free radicals, it can safely interact with free radicals and terminate the chain reaction previous the damage (Blomhoff, 2004), such antioxidants are glutathione, ubiquinol, and uric acid in which they produced during metabolism processes in the body. The body possesses enzymatic antioxidant system as well (Rizzo *et al*., 2010). Certain diets are rich with antioxidant materials such as vitamin E, vitamin C and β-carotene, these micronutrients can't be synthesized in the human body, rather considered as essential dietary supplements due to their free radicals scavenging function (Frei, 2012).

Antioxidants act as radical scavenger, singlet oxygen quencher, peroxide decomposer, electron donor, hydrogen donor, enzyme inhibitor, and metal-chelating agents. Both enzymatic and non-enzymatic antioxidants exist in the intracellular and extracellular environment to detoxify ROS (Frei, Stocker, & Ames, 1988).

2.1. Mechanisms of action of antioxidants

There are two main mechanisms have been anticipated to explain the antioxidant activity. The first is a chain breaking mechanism in which a donation of an electron from primary antioxidant to the system's free radical is occur. The second one involved the removal of initiators of ROS and RNS through quenching the catalyst that initiate the chain reactions (known as secondary antioxidants) (Krinsky, 1992; Rice-Evans & Diplock, 1993).

2.2. Biological antioxidants

A biological antioxidant has been defined as any substance that when present at low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation of that substrate (Halliwell, 1990). The function of antioxidants involved in decreasing oxidative stress, damage of DNA, and oxidative injury in all targets of both *in vitro* and *in vivo* cells. They also involved in epidemic field as they disturb the development of various cancers and degenerative diseases. Furthermore, when the levels of ROS exceed those of antioxidants, cells would be more vulnerable, and the incidence of cutaneous disorders is inevitable. The defense system involve two major categories of antioxidants, one of which are antioxidants that act to block the generation of ROS, and/or intercept the already generated ROS, which present in the membrane , and aqueous compartments of cells, and divided into enzymatic and non-enzymatic antioxidants. The second category includes natural antioxidants which functionalized in repair processes, which act to remove the damaged molecules before they gathered to give arise to altered cell metabolism or viability (Cheeseman & Slater, 1993; Godic, Poljšak, Adamic, & Dahmane, 2014; Halliwell & Gutteridge, 2015).

The endogenous antioxidants include superoxide dismutases, catalases, and glutathione peroxidases enzymes, uric acid, thiols (e.g. glutathione, and lipoic acid), coenzyme Q10, and bilirubin (Mohammed, Kadhim, Jassimand, & Abbas, 2015).

3. Oxidative Stress in Atopic Dermatitis

The skin is an organ of the body, considered as the largest organ, which perform a protection function against outside attack that include environment pollutants, and chemical materials. Since it defended the body from external agents, it would be the most affect organ from oxidative stress as a result of exogenous ROS sources, additionally to the endogenous sources (Brand *et al.*, 2017). Normal metabolism processes involved in the generation of free radicals which in turn at low levels being an integral piece of normal skin action and are generally of little harm because protection mechanisms can minimize their damaging effects. Excessive free radicals exceed the defense system of antioxidants in the skin and thereby contribute to skin disorders such as skin cancer, dermatitis, and skin aging (Ji & Li, 2016).

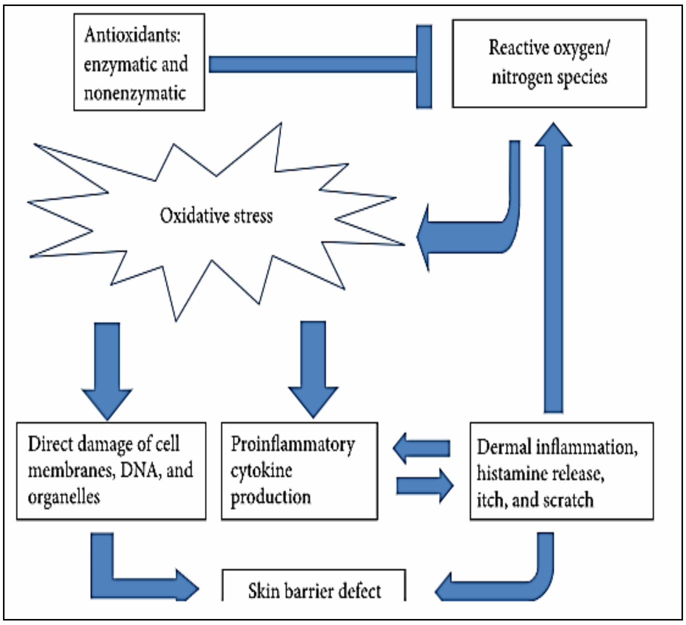

Fig. 2: Cellular generation of reactive oxygen species and antioxidant defense system (Ji & Li, 2016).

4. Production of ROS in the skin

There are manifold sources of ROS, both enzymatic and non-enzymatic. Enzymes involved in the production of ROS, on purpose or as a byproduct, include the mitochondrial electron transport chain, NADPH oxidases, xanthine oxidoreductase (XOR), several peroxisomal oxidases, cytochrome P450 oxidase family, cyclooxygenases, and lipoxygenases (Milkovic, Cipak Gasparovic, Cindric, Mouthuy, & Zarkovic, 2019).

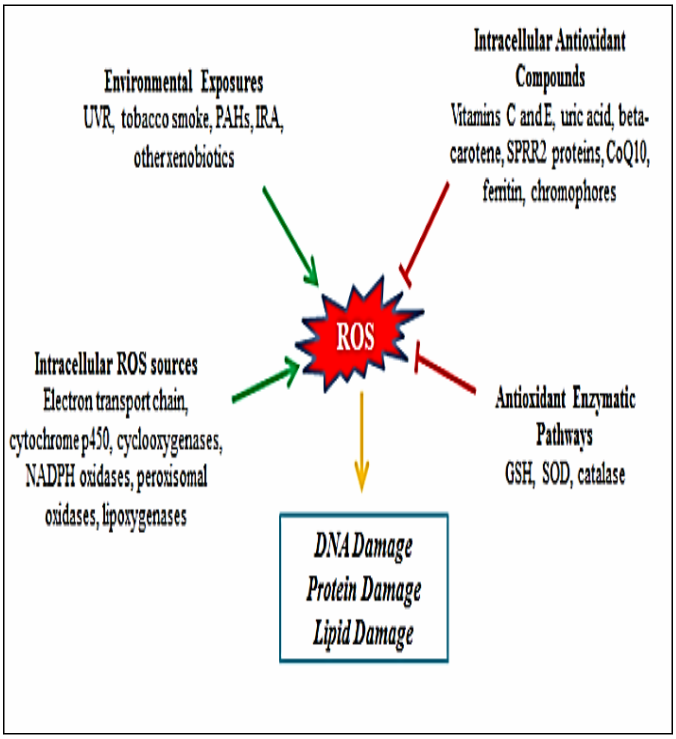

Fig. 3: Summary of ROS and antioxidant sources in the cell. Yellow arrow represent consequence of ROS, green arrows represents both endogenous and exogenous sources of ROS, red arrows for the antioxidant protection (Ahsanuddin, Lam, & Baron, 2016).

4.1. ROS and Skin diseases

It had been confirmed that shorten in the protection system against oxidants leads to ultimate condition of oxidative stress. The development of oxidative stress either from depletion of the defense system or over production of ROS, enhance the development of dermatological disorders (Bickers & Athar, 2006). Polluted environment enhance the generation of ROS, arsenic is one of the most hazard pollution factors which leads to the development of various cancers, and one of them is skin cancer. It have been reported that arsenical skin cancer contributes to over production of mitochondrial ROS in keratinocytes. Arsenic enhance oxidative damage to mtDNA in keratinocytes of these patients (Lee & Yu, 2016). U.V. radiations affects the skin directly as being the front defender of the body, this exposing contributes, through complex pathways, to DNA mutations, in fact it have been said that many non-skin tumors has accumulated less mutations than normal skin cells (Karran & Brem, 2016). The pigment of melanin prevents U.V. rays from damaging skin cell components, the pigmentation increases by the stimulation of U.V. rays. During long exposure to these radiations some of the U.V. rays escape melanin absorption, sequentially lead to the damage of DNA either by generation of ROS or direct break of DNA by chemical reactions (Brand *et al.*, 2017).

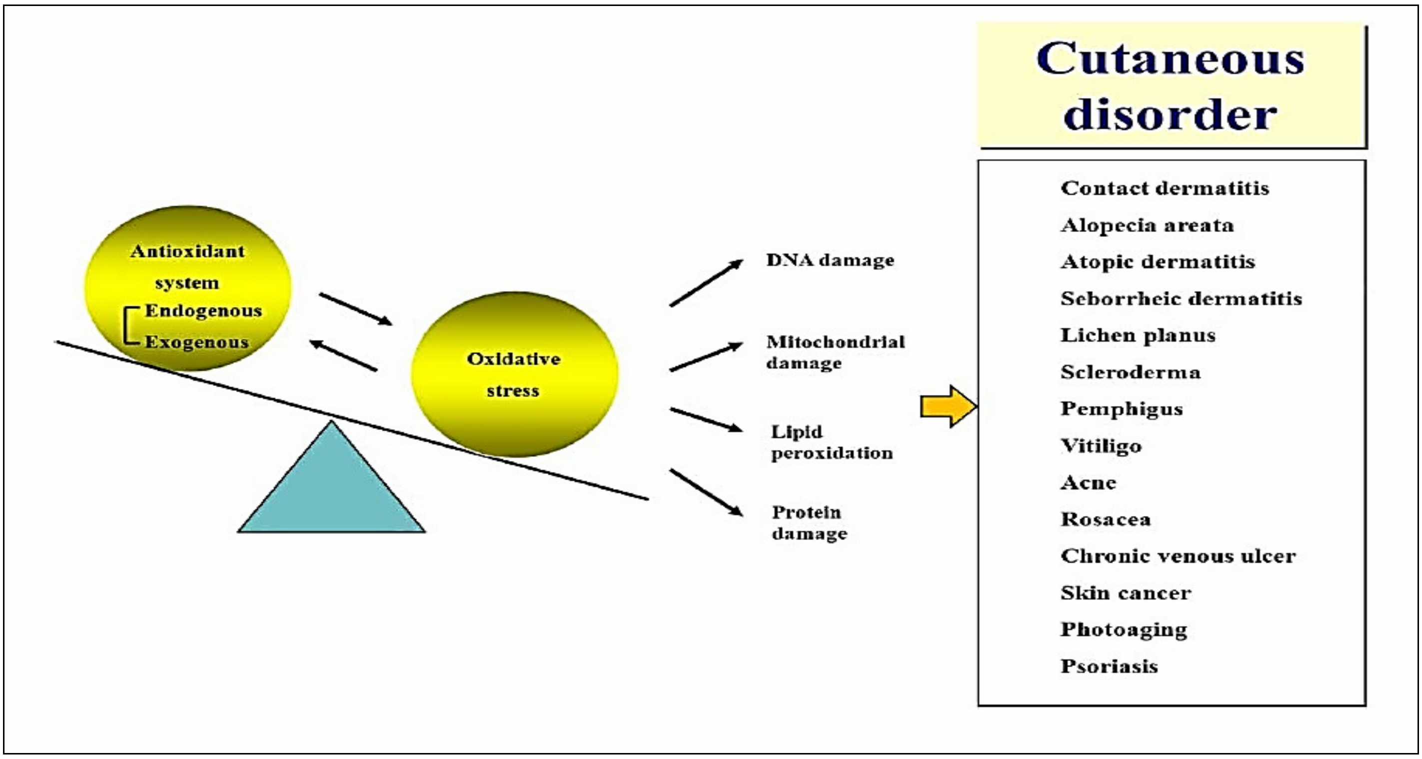

Fig. 4: Oxidative stress and cutaneous disorders (Baek & Lee, 2016).

4.1.1 Autoimmune skin diseases

There is magnificent lack in many autoimmune diseases pathophysiology until today. Recent studies have been investigated oxidative stress in these diseases and attempted to reveal the connection between them. Here we demonstrate briefly the influence of oxidative stress in some diseases (Shah & Sinha, 2013).

4.1.1.1. Psoriasis pathogenesis

Psoriasis is a skin disorder which classified under chronic immune diseases. It is characterized by overexpression of pro-inflammatory cytokines in the skin, including ILs, IFN-γ, and TNF (Zhou, Mrowietz, & Rostami-Yazdi, 2009). Several studies showed an increasing of various ROS such as superoxide dismutase, nitric oxide, and hydrogen peroxide in patients with psoriasis (Cannavò, Riso, Casciaro, Di Salvo, & Gangemi, 2019).

4.1.1.2. Allergic and inflammatory skin diseases

The skin is under continuous exposure to both endogenous and exogenous pro-oxidant agents which leads to the eventual generation of ROS, and consequential development of oxidative stress damages to cell components. Some evidence indicates that allergic and inflammatory skin diseases like atopic dermatitis, urticaria and psoriasis are mediated by oxidative stress (Okayama, 2005).

4.1.1.3. Rosacea

Rosacea is a skin disease that involved genetic and environmental factors, hence the pathophysiology of the disease may involve inflammatory mediators, and ROS (Jones, 2009). The statistics data of peroxide levels, antioxidants, and ferritin in rosacea patients support the development of oxidative stress with the disease (Tisma *et al*., 2009).

4.1.1.4. Scalp Seborrheic Dermatitis

Seborrhoeic dermatitis (SD) is a common, chronic inflammatory skin disease that mainly affects the scalp. A study of Ozturk *et al.* investigated malondialdehyde levels, and the activities of superoxide dismutase and catalase in scarping samples of SD patients. It showed a significant increasing in malondialdehyde levels as well as superoxide dismutase and catalase activities in SD patients. Oxidative stress hence may play role in the pathogenesis of SD, but further information are required (Ozturk, Arican, Kurutas, Karakas, & Kabakci, 2013).

4.1.1.5. Vitiligo pathogenesis

Vitiligo is classified under depigmentation diseases in which a selective destruction of function melanocytes occur, which cause a depigmentation in skin, and hair (Sarkar, Sethi, & Madan, 2017). It was demonstrated the vitiligo accompanied by over production of ROS (Tang, Li, Fu, Wu, & Xu, 2019). Many evidence have been observed for the induction of oxidative stress in vitiligo patients including low catalase levels, a remarkable increasing of hydrogen peroxide concentration, ultrastructural modifications suggestive of lipid peroxidation in melanocytes, keratinocytes and Langerhans cells in the skin, and high level of methionine sulfoxide (Glassman, 2010).

5. The importance of antioxidants to the skin

Melanin and enzymatic antioxidants provide an endogenous protection against U.V. radiations and the sequential generated ROS. Also, antioxidants in diet have been shown a remarkable role in maintaining oxidative balance homeostasis in the skin, such antioxidants include vitamin E and C, β-carotene, and polyphenols. It had been established that exposing to U.V. rays affect skin capacity of antioxidants, vitamin C, glutathione, superoxide dismutase, catalase, and ubiquinol are depleted in skin during exposure to U.V. in both dermis and epidermis. Also ascorbyl radicals are rising on U.V. exposure of skin. Studies of cultured skin cells and murine skin *in vivo* have indicated that U.V. radiations-induced damage involves the generation of ROS and depletion of endogenous antioxidant systems (Godic *et al*., 2014; McArdle *et al*., 2002).

5.1. Vitamin C

Ascorbic acid or generally known as vitamin C is a water soluble structure with antioxidant properties, presented in various foods and considered as essential dietary supplement for its unique properties (Linster & Van Schaftingen, 2007). The skin contains high level of vitamin C at normal conditions, in which vitamin C perform beneficial functions such as protection against oxidative stress that arise from multiple sources, and stimulation of collagen synthesis. There are clear information of the depletion of vitamin C in skin aging and photo-damage (Pullar, Carr, & Vissers, 2017). A study of Mcardle *et al.* on human skin showed a quite good prevention of oral vitamin C supplement which uptake previous the exposure to U.V. radiations, thus it minimize the induced oxidative stress from these rays exposure (McArdle *et al.*, 2002). Another study investigated the application of vitamin C on aged human skin indicated that skins whom under the application of cream containing vitamin C showed an increasing in density of dermal papillae on the contrary of those whom did not under the application of vitamin C, which declare that vitamin C involved in the enhancement of dermal papillae density (Sauermann, Jaspers, Koop, & Wenck, 2004). Scurvy disease which accompanied by deficiency of vitamin C characterized by symptoms approve the benefit of this vitamin to the skin such symptoms include impaired wound healing, bruising, and bleeding gums, which thought to be arise because of the role of vitamin C as a cofactor hydroxylase enzymes which in turn gave stabilization to the tertiary structure of collagen (Carr & Maggini, 2017).

5.2. Vitamin E

Vitamin E is a group of fat soluble compounds which includes α-, β-, γ-, and δ-tocopherol, and α-, β-, γ-, and δ-tocotrienols. Vitamin E is a respected antioxidant material which act as chain-breaking antioxidant in free radical reactions (Herrera & Barbas, 2001). Upon exposing to U.V. radiations a depletion of vitamin E occurs as part of defense mechanism against U.V. damaging consequences, whereas skin photooxidative damage suffers a very early and sensitive event in which α-tocopherol depleted in stratum corneum (Thiele & Ekanayake-Mudiyanselage, 2007). Numerous reports have been recommended oral supplement of vitamin E in the therapy of vibration disease, claudication, collagen synthesis and wound healing, yellow nail syndrome, cutaneous ulcers, bullosa, epidermolysis and cancer prevention (Thiele, Hsieh, & Ekanayake-Mudiyanselage, 2005). Vitamin E shows to have a chemo-protective characteristics, as it reported to improve some conditions including pigmented contact dermatitis, cloasma, and atopic dermatitis, the most influence has been observed in the area of a photo-protection. Additionally, the application of vitamin E before exposing to U.V. radiations reduces the immunosuppression, and DNA adduct formation (Junkins-Hopkins, 2010).

5.3. Carotenoids

Carotenoids are group of pigments, they are widespread in nature with more than six hundred identified member, only few carotenoids involved in human health such as β-carotene (Young & Lowe, 2018). The concentration of carotenoids in the skin may reflects the lifestyle of people. Healthy rich diet present high level of carotenoids for individuals such as fruits and vegetables. A reduction of carotenoids concentration arise from stress factors including U.V. radiation exposure, illness, alcohol consumption and smoking. It was demonstrated that people who contain high level antioxidant are less incidence to premature skin aging, where they suffer from a minor dense wrinkles and shallower furrows in the skin comparing with people of low antioxidant level (Lademann, Meinke, Sterry, & Darvin, 2011).

5.4. Retinoids

Retinoids are vitamin A derivatives, which produced naturally and synthetically (Dmitrovsky & Spinella, 2017). Retinoids derivatives are safe and effective agents which used in photodamaged skin treatment (Riahi, Bush, & Cohen, 2016). Tazarotenic acid is the active form of tazarotene, a synthetic acetylenic retinoid. Tazarotene is a modulator of various characteristics of the psoriatic lesion. The treatmen of psoriasis patients with tazarotene showed a decreased expression of keratin 6, keratin 16, skin-associated anti-leukoprotease, MRP-8, involucrin, and small praline-rich protein 2 expression in psoriatic lesions with an increase in filaggrin (Van De Kerkhof, 2006).

5.5. Coenzyme Q10

Ubiquinone or so called coenzyme Q10 is a structure of quinone synthesized in wide species of living organisms, which have an antioxidant characteristic. A study of Choi *et al.* investigated the wound healing and anti-inflammatory effects of Coenzyme Q10 on mice with skin incision, the results showed increasing in collagen-like polymer level in coenzyme Q10 treated mice, as well as an inhibition of myeloperoxidase, thus confirm the cutaneous healing effect of coenzyme Q10 in vivo (Choi *et al.*, 2009).

5.6. Glutathione

Glutathione (GSH) is a powerful antioxidant with anti-melanogenic characteristic, several studies investigated the skin-lighting agent of GSH in various dosage types (oral, intervenes, and cream) the outcome results of these studies proved the significant reduction of melanin index in all types. Furthermore, cream GSH showed an improvement in keratin index, curvature index, and skin moisture (Sonthalia, Jha, Lallas, Jain, & Jakhar, 2018).

5.7. Zn(II)-glycine

It is a coordinated compound composed of Zn^{2+} ion as central metal and glycine. It is a membrane permeable complex which act as an inducer of the expression of metallothionein, Zn(II)-glycine is a skin lightening agent which functionalized to reduce U.V. B induced oxidative stress (Ochiai *et al.*, 2008).

5.8. Polyphenols

Polyphenols are phytochemical compounds expressed in many fruits and vegetables to be the most abundant, and highest activity of known antioxidants in diet (Scalbert, Johnson, & Saltmarsh, 2005). Sevın *et al.* 2006, studied the green tea polyphenolic compound Epigallocatechin-3-gallate (EGCG) effect on rats before and after exposing them to acute U.V. A radiations, the team reported a significant decrease in the sunburn cells in rats whom dosage with EGCG before the exposing, whereas the application of EGCG after the exposing shows no differences (Sevın *et al.*, 2007). Also, numerous flavonoids, a polyphenolic structure containing compounds, have showed great intendancy to prevent or reduce the harmful effects of U.V. A and U.V. B radiations such as DNA damaging, as well as they exert a reduction effects of the development of thymidine dimers, gene mutations and keratinocyte apoptosis (Mucha, Budzisz, & Rotsztejn, 2013). The study of Mahdi *et al* on *Hylocereus* Pitaya fruit (dragon fruit), indicating that the fruit is rich with polyphenolic compound. They applied ointment made of fruit extract on the treatment of wounds for mice, they observed a faster healing for mice whom under the application of ointment (Mahdi, Mohammed, Jassim, & Mohammed, 2018).

6. Skin Aging

Aging of skin classified into endogenous aging, exogenous aging (mainly photo-aging), and natural aging. As age rise up, the skin becomes drier, thinner, and more wrinkles, also it suffers from a delaytion in the processes of wound healing, as well as development of uneven pigmenting. This may lead to a negative influence on people life and overlap with social or professional functions. Therefore, the inhibition of skin aging and refinement of wrinkling and pigmentation with lowest adverse effects represents the master goals of skin care and treatments. Continuous exposure to U.V. radiations considered to be a major cause of skin aging, which leads to the development of skin relaxation, wrinkles, and other photo-aging characteristics. An alternations in the structure of skin occur during photo-aging, these alternations include lipidation and hydration, properties of light-absorption, skin color, thickness, and stratum corneum integrity (Ahsanuddin *et al.*, 2016).

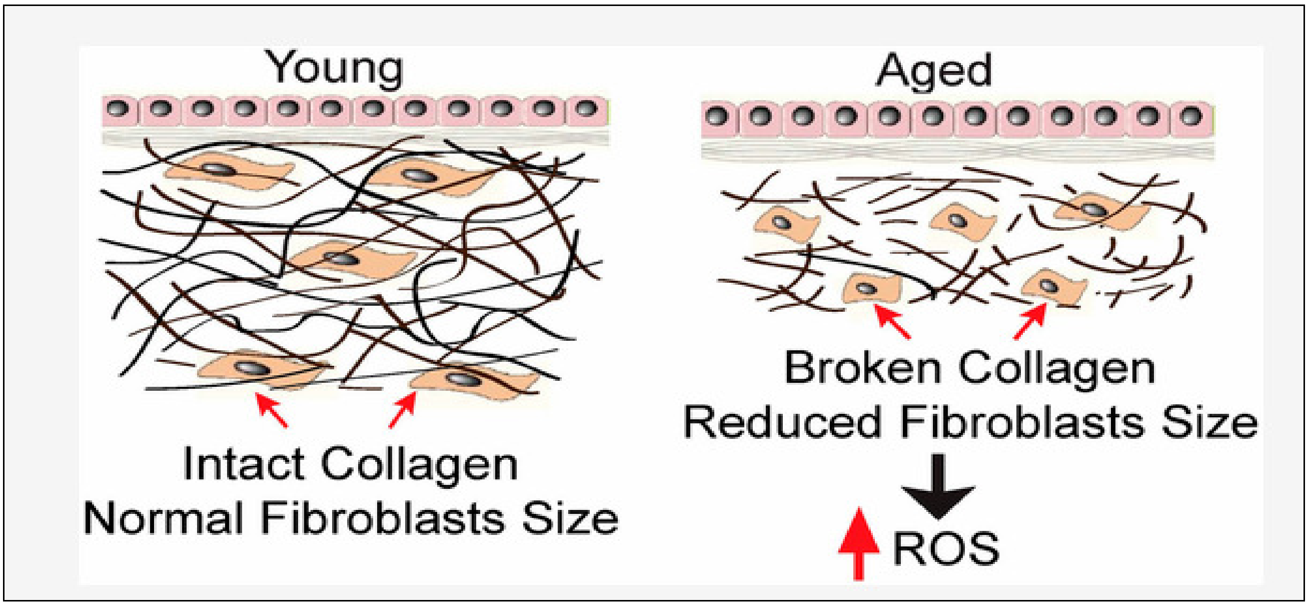

Fig. 5: The difference between young and aged skin tissue (Tu & Quan, 2016).

Conclusion

Free radicals and Reactive oxygen species (ROS) are considered to be important substances for the human body when presented in normal proportions in the body, but over time the body loses its ability to fight these Free radicals and ROS, hence these materials are multiplying in the body, and raises the oxidative stress, thus this lead to a harmful effects to cells, and associated with various diseases. In order to prevent or reduce the harmful effects, and cellular damage caused by this substances, there is a so-called antioxidants, which are the body's defensive system to face these substances. But this system may be influenced by intercepting factors or its production may be not sufficient in the body through generation processes, here antioxidants supplement through diet is necessary (various fruits and vegetables). Since the skin occupies the largest area in the body, skin tissues are exposed to various types of oxidative damage, according to its structure which consists of several layers, each one performs different functions and each layer is equipped with a defense line of antioxidants, thus the susceptibility of pro-oxidant agents in these layers differ from each other and its levels of oxidative stress differ as well. As the skin being surrounded by such oxidant agents any defection of the protection system may associate with the development of the skin disorders, diseases, and aging.

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Abbreviations

ROS : Reactive oxygen species.

RNS : Reactive nitrogen species.

NADPH: Nicotinamide adenine dinucleotide phosphate.

XOR : xanthine oxidoreductase .

SOD : Superoxide dismutase.

GSH : Glutathione.

SD : Seborrhoeic dermatitis.

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