International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

Reactive Oxigen Species, Antioxidant and Expression of Prostaglandin E2

Liza Deviyanti Hadiwijaya[1], Wimpie Pangkahila[2]

[1]Student of Doctoral Program, Faculty of Medicine Udayana University, Indonesia

[2] Post Graduate Program in Anti-Aging Medicine, Faculty of Medicine, Udayana University, Indonesia

Abstract: ***The aging process will occur in all living things. In the aging process there will be decreased function of various organs and physical changes. According to anti-aging medicine, the process of aging considered a disease that can be prevented, treated, and even treated returned to its optimal state like still young. Oxidative stress plays an important role in the pathophysiology of the aging process and various degenerative diseases such as cancer, diabetes and mellitus its complications, as well as atherosclerosis underlying heart, blood vessel and stroke disease. Free radicals can be produced from the body's metabolic products external factors such as cigarette smoke, the results of ultraviolet irradiation, chemicals inside food and other pollutants. The human body can neutralize free radicals when the amount is not excessive. The body's defense mechanism from free radicals is in the form of antioxidants at the cellular level, membrane, and extra cells. UVA and UVB exposure to the skin can reduce endogenous antioxidants in all layers of skin such as glutathione, Superoxide dismutase, catalase, and ubiquinol. While exposure to UVA and UVB produce free radicals such as Hydrogen Peroxidase, Anion Superoxide, Nitric Oxide can cause reactive oxygen species. Antioxidants are compounds that can absorb or neutralize free radicals so that they can prevent degenerative diseases. Natural antioxidant compounds are generally in the form of vitamin C, vitamin E, carotenoids, phenolic compounds, and polyphenolics which can be in the form of groups flavonoids, derivatives of cinnamic acid, quomarin, tocopherols and organic acids polyfunctional. Flavonoids which have antioxidant activity include flavones, flavonols, isoflavones, catechins, flavones, and chalcons. UV rays stimulate the production of pro-inflamatory factors, namely prostaglandins E2 induced in the presence of cyclo-oxygenase-2, interleukin and platelet-activating factor mediators.***

Keywords: ROS, PGE2, Antioxidant, Skin Aging

1. Introduction

The aging process will occur in all living things. In the aging process there will be decreased function of various organs and physical changes. Aging is complex process and is a process of decline in biological function and cannot be avoided. According to anti-aging medicine / Anti Aging Medicine, the process of aging considered a disease that can be prevented, treated, and even treated returned to its optimal state like still young. Use of knowledge the latest medical knowledge and technology aim to extend live in good health [1].

Based on world population data, an increase in the proportion of the age population advanced (over 65 years) which is quite significant i.e from around 8% in the year 1950 to around 11% in 2009, and is expected to reach the figure 20% in 2050. This will cause related health problems aging, including skin aging which will also increase [2].

Oxidative stress has key role in the pathophysiology of the aging process and various degenerative diseases such as cancer, diabetes and mellitus its complications, as well as atherosclerosis underlying heart, blood vessel and stroke disease. Free radicals can be produced from the body's metabolic products external factors such as cigarette smoke, the results of ultraviolet irradiation, chemicals inside food and other pollutants. The human body can neutralize free radicals when the amount is not excessive. The body's defense mechanism from free radicals is in the form of antioxidants at the cellular level, membrane, and extra cells [3].

The UV radiation exposure causes photoaging which has severe effects on skin tissue, such as wrinkle, decreased of skin elasticity, and thickened epithelium [4]. UV radiation exposure can cause damage to the skin. One mechanism is understood involves the formation of Reactive oxygen species (ROS). Excessive ROS can be dangerous for the skin because it can cause oxidative cell damage, which is the results contribute to collagen damage [5]. UV A radiation (wavelength 320-400 nm) is involved in formation ROS indirectly, which causes damage to the deoxyribonucleic acid (DNA). Whereas UV B radiation (wavelength 290-320 nm), induces DNA damage through direct interaction with epidermal cytokines, which can produce DNA mutation and the formation of cyclobutane dimers and 6-4 photoproducts. UVB rays directly cause damage The form of sunburn and UVA rays slowly and cumulatively causes damage to skin cells that come from immunosuppressed reactions so that damage permanent skin proteins continue, eventually clinically can be seen as wrinkles, dryness, sagging, and skin roughness [5].

The aging process is a complex process that occurs due to exposure to light Chronic UV. In addition, UV light stimulates the production of pro-inflamatory factors namely prostaglandin E2 (PGE2) which is induced in the presence of cyclo-oxygenase-2 (COX-2), platelet-activating factor (PAF) and interleukin-10 (IL-10) mediators [6]. In addition, on UV exposure will also be induces melanin formation in the layers of the skin. This is influenced by the presence of the tyrosinase enzyme which is responsible for the initiation of skin pigmentation [7].

Licensed Under Creative Commons Attribution CC BY

Oxidative stress is a condition of discrepancy between the free radicals with the antioxidants in the body. Free radicals are compounds that have one or more unpaired electrons in their orbitals, so they are very reactive and able to oxidize the surrounding molecules (DNA, proteins, carbohydrates, and lipids). Antioxidants are very easy to oxidize, so Free radicals will oxidize antioxidants and protect other molecules inside cells from damage caused by oxidation by free radicals or reactive oxygen [3].

There are 2 kinds of antioxidant namely endogenous antioxidants, namely enzymes that are antioxidants, such as: glutathione peroxidase (Gpx), catalase (Cat), and Superoxide Dismutase (SOD); as well as antioxidants exogenous, which are obtained from outside the body / food. Various original natural ingredients Indonesia contains a lot of antioxidants with various active ingredients, including flavonoids, vitamins E, C, pro-vitamin A, organosulfur, α-tocopherol, niacin, statins, phycocyanin, and others [3].

Besides preventing or inhibiting oxidative stress and cell tissue damage, Vitamin E play an essential role in inhibits increased production of cytokines such as Tumors Necrosis Factor (TNF-α) or interleukin-6 (Il-6) which is a proinflammatory or inflammatory cytokine [8].

2. Material

2.1 Skin Aging

Aging is a process of decreased biological function that cannot avoided, where the slow pace of decline depends on several factors, namely internal factors such as decreased hormones, free radicals, glycosylation, methylation, genetic factors, decreased immune system, and apoptosis as well External factors such as lifestyle and unhealthy diets, lack of habits good, environmental pollution, stress, and poverty [9-10].

Several theories have been explained about the mechanism of aging including cellular aging and decreased proliferative ability, repair capacity cell DNA reduction, telomere loss in old age, which may be connected with increase oxidative stress and increase the frequency of chromosomal abnormalities [11].

According to anti-aging medicine, the aging process is considered as a diseases that can be prevented, treated, and even returned to their optimal state like still young [1]. Anti-aging medicine is defined as part of medical science based on the use of science the latest medical knowledge and technology to conduct early detection, prevention, treatment, and improvement to the initial state of various dysfunctions, disorders, and diseases related to aging, which is intended for prolong life in a healthy state [1].

The aging process including skin aging is caused by various factors / multifactorial. Based on the cause, skin aging can generally be divided into two, namely, intrinsic aging or chronological aging and aging extrinsic or photoaging. Skin aging experienced by individuals is a combination of skin aging due to intrinsic factors as well as extrinsic factors. Very it is difficult to separate intrinsic skin aging from various external factors affect skin aging [2].

Intrinsic skin aging is a natural process of skin aging that occurs as we get older which starts at the end of the third decade. This process too is a slow process that will cause changes to skin tissue structure. In this intrinsic skin aging, various mechanisms changes occur simultaneously. In the epidermis layer mainly occurs changes in the morphology or structure of the skin, while the dermis layer occurs biochemical changes. Changes also occur in the skin's adnexal organs such as hair, sweat glands and oil glands [12].

The surface of the skin that is experiencing intrinsic skin aging will appear more pale, fine wrinkles arise, layers of the epidermis and dermis atrophy so that the skin looks thinner, transparent, and looks more fragile. The skin also becomes drier and feels itchy. Intrinsic skin aging is also followed by depletion of subcutaneous fat tissue including facial fat, so that will cause a concave and deep cheeks and appearance eye bags. Apart from age factors, other intrinsic factors are related to intrinsic skin aging, including race, variations in skin anatomy in certain areas, and hormonal changes [13].

The process that occurs in intrinsic skin aging is a combination of three processes, including a decrease in the proliferation ability of skin cells, decreased skin extracellular matrix synthesis, as well as increased enzyme activity which degrades collagen in the dermis layer. Skin cells, including fibroblasts, keratinocytes and melanocytes have decreased in number with population age increase. Decreased fibroblast causes decline Collagen biosynthesis in the dermis layer. Proliferation of cutaneous fibroblast cells slowing down will also affect collagen production in the dermis layer causes skin aging and wrinkles. Besides that, there is also an increase in the activity of the matrix metalloproteinase (MMP) enzyme in fibroblasts cells with age which causes increase collagen degradation in the dermis layer [13].

The incidence of intrinsic skin aging is also influenced by the balance between free radical production, especially ROS, the effectiveness of the system free radical antidote, and body repair. In general there are two sources the main free radical, namely mitochondria (plays an important role in the process aging) as well as nonmitochondria. The most common source of intracellular ROS comes from mitochondria. Increased ROS will cause damage to lipids, proteins and DNA cells that will trigger the skin's aging process and non-mitochondria. The most sources of intracellular ROS come from mitochondria. Increased ROS will cause damage to lipids, proteins and DNA cells that will trigger the skin's aging process (Ahmad and Damayanti, 2018). In addition to intrinsic factors, skin aging is also heavily influenced by factors other exogenous (from outside). Some extrinsic factors work together with intrinsic factors that cause skin aging to occur early or premature. External factors that influence, among others, repetitive facial expressions, influence of heat, sleeping position, gravity, lifestyle such as smoking, pollution, and sun exposure, especially UV rays. For example, the force of

Licensed Under Creative Commons Attribution CC BY

gravity causes the tip of the nostrils to go down, the earlobe lengthens, the eyelids fall, the upper lip disappears, and the lower lip looks more real. In addition, the main effect of exposure to light radiation UV both acute and chronic, ie DNA damage, inflammation or inflammation and immunosuppression [14].

Extrinsic skin aging is mainly influenced by UV and also known as photoaging. The incidence of skin aging is mainly photoaging has increased over the past few decades. Not yet many studies on the incidence of skin aging, a study in Australia by Green said about 72% of men and 42% of women in under the age of 30 underwent photoaging [2]. The sun is the main source of UV rays, so it is main contributor of photoaging. The UV rays are composed of UVC, UVB and UVA with different wavelengths. UVA rays can penetrate deeper layers of skin than other types of UV rays and cause more damage. UV radiation that reaches the dermis layer on more bright skin than colored skin dark so individuals with low Fitzpatrick skin types tend to be more vulnerable on photoaging [14].

Skin types are classified by Fitzpatrick based on his reaction to sun exposure and UV radiation. Fitzpatrick's current classification classify the skin into six types of skin color, ranging from very pale (type skin I) to very dark (skin type VI). Natural color or skin pigmentation determined by the amount, type and composition of melanin in the skin. Melanin pigment provides natural protection against UV exposure that is Sun Protection Factor (SPF). Darker skin has a higher natural SPF i.e when compared to Caucasian skin which only has a natural SPF of 3-4 or even less [15].

The clinical picture of photoaging can be dry, pigmented skin irregular skin (varies from getting darker or becoming brighter), skin the pale yellowish, deep and rough wrinkles, atrophic skin, skin become sagging, telangiectasis, solar elastosis, actinic purpura, even up to precancerous lesion formation. Dark skin is more resistant to skin damage due to exposure to UV rays, so the manifestations of skin aging are lighter and lighter occur more slowly 10 to 20 years compared to more skin bright. On skin with Fitzpatrick III and IV types, dispigmented or altered Skin pigments are the main picture of photoaging [15].

The first photoaging classification was carried out by Glogau in 1996. Based on the classification from Glogau, there are 4 types of photoaging starting from type I up to type IV. Glogau type I (mild), which is the initial phase of photoaging, which is usually the case occurs at the age of 20 to 30 years and no wrinkles are found. In Glogau type II (moderate) signs have begun to be found photoaging ie wrinkles on facial expressions. Usually this type II Glogau found at the age of 30 to 40 years. Glogau type III (advanced) shows any further photoaging, usually found at the age of 50, is marked in the presence of wrinkles at rest (resting wrinkle). Photoaging overview severe classified in Glogau type IV (severe) which is usually found at the age of 60 years and is characterized by numerous wrinkles [2].

In addition to the face, manifestations of skin aging also occur in all skin in other areas. Some clinical manifestations that often interfere with aging The skin is senile pruritus, actinic keratosis, seborrheic keratosis, and lentigo solaris. Senile pruritus or complaints of itching in the elderly are mainly caused by dry skin syndrome or often called xerosis cutis. Number the incidence of aging is reported at 30-75%, due to the influence of skin aging which causes a decrease in the ability to maintain skin moisture, increase in transepidermal water loss (TEWL), decrease sweat and sebum production, as well as a decrease in maintaining factors skin moisture [2].

2.2 Ultraviolet Rays and Their Effects on the Skin

Sunlight consists of electromagnetic radiation which is divided into 3 which are visible light (5%), UV (45%), and infrared (50%). The wavelength of UV rays are between 100-400 nm and divided in 3 spectrums namely UVA (320-400 nm), UVB (290-320 nm), and UVC (270-290 nm). UVC exposures will not extent to earth's surface because it is absorbed by ozone and the atmosphere, but UVB and UVA can reach the surface earth and is the biggest environmental influence on skin aging. Although the UVA: UVB ratio is 20: 1, UVB rays have side effects more than UVA [16].

UVA and UVB exposure to the skin can reduce endogenous antioxidants in all layers of skin such as glutathione (GSH), SOD, catalase, and ubiquinol [14]. While exposure to UVA and UVB produce free radicals such as Hydrogen Peroxidase, Anion Superoxide, Nitric Oxide can cause reactive oxygen species [17].

The longer the wavelength, the deeper it will be its penetration into the skin. UVA is not absorbed directly by cell DNA however causes oxidative stress which ultimately induces the occurrence photosensitization and CPD lesions occur. But UVB rays cannot penetrate skin tissue as deep as penetration from UVA rays [18].

The UV light has several health benefits such as the production of vitamin D3, therapy of skin disorders such as psoriasis and vitiligo, but UV rays can also be endangering the skin health both acute and chronic so that it can cause cancer. Among the types of cancer in humans, skin cancer is one of the most common. Development of cancer events throughout the world continues to increase both melanoma and non-melanoma such as basal cells carcinoma and squamous cell carcinoma. The ozone layer efficiently absorbs UV radiation to wavelengths of 310nm including all UVC rays and almost all UVB (95%), but UVA is not absorbed at all. Due to environmental damage and global warming there is a lot of damage to ozone layer and cause increased UVB radiation to the earth [19].

Exposure to UV light from the sun can trigger the formation of free radicals on the skin. Free radicals that are formed will cause decreased performance of enzymes to maintain cell function, damage the proteins and amino acids which is the main structure of collagen and elastin. Ultra violet radiation has a wide range of acute effects. The effects caused besides sunburn inflammation (erythema) and tanning (melanogenesis) can also be resulting in DNA photodamage, immunosuppression, and vitamin D synthesis [20].

Licensed Under Creative Commons Attribution CC BY

The main effect of UVB and UVA exposure is damage to DNA of skin cells, cell membranes, protein and amino acid degradation enzymes. UV rays are until the skin will be reflected, especially when UV rays arrive at the stratum corneum, where the drier the skin, the harder it is to penetrate UV rays to deeper layers of skin. UV rays will be absorbed more by cells pigmented cells such as melanocytes and corpuscular cells in the blood circulation. UV light with waves below 320nm will be absorbed mainly by the stratum corneum and epidermal layer, and UV rays with wavelengths over 320nm will penetrate to the dermis. [20].

The change immediately after being exposed to UV light is DNA damage which is seen as sunburn cells and the formation of p53 which functions to kill cells that cannot be repaired or are called apoptosis. Clinically this change is seen as erythema which is due to vasodilation blood vessels due to byproducts from cell damage that occurs. Apoptosis is a destructive reaction to the nucleus and cytoskeleton of a cell. Both cellular and biochemical changes in skin are chronological and aging photo damage or extrinsic aging both indicate a reduction fibroblast, decreased regeneration of collagen and other extracellular components compared to the skin of young people [20].

Synthesis of procollagen I and III and other extra cellular components are decreasing and MMP-1 and MMP-9 are increased. Drastic decrease in collagen production also occurs in acute UV light exposure, which explains that aging chronologically goes hand in hand with extrinsic aging by UV light, which is ultimately resulting in the same change namely decreased collagen synthesis and increased degradation of extracellular matrix through the production of MMPs [20].

It is proven that the lesion DNA causes immunosuppression in both mice and humans. UV rays also cause the activation of nitric oxide (NO) synthase, and cause an increase NO production. Similarly, UV light stimulates the production of ROS, which will cause damage to lipids, proteins and DNA so will cause an immunosuppression reaction again. In addition, it is also known that light UV stimulates the production of pro-inflamatory factors, namely PGE2 induced in the presence of cyclo-oxygenase-2 (COX-2), IL-10 and PAF. Immunosuppression starts from exposure to mild UV light which does not cause sunburn [18].

2.3 Reactive Oxigen Species (ROS)

Imbalance of the amount of free radicals with the amount of antioxidants endogenous produced by the body such as SOD, GPx and CAT are called oxidative stress. This situation can be cause cell damage that can cause various diseases. Free radicals can be in the body because of the byproducts of the process oxidation and cell combustion that takes place during breathing, inflammation, physical activity, and exposed to pollution from outside the body such as cigarette smoke, vehicle fumes, food, heavy metals, and solar radiation [8].

Biological molecules basically nothing is radical. When non-radical molecules meet with free radicals, they will form a new radical molecule. Free radicals are unstable and always trying to take electrons from the molecules around them, so free radicals are toxic to biological molecules / cells. Free radicals can interfere DNA production, the lipid layer on cell walls, affects blood vessels, production of prostaglandins, and other proteins such as enzymes found in the body [3].

Free radicals that take electrons from DNA can cause changes in the structure of DNA so as to produce mutant cells. Free radicals too play a role in the aging process, where the reaction of free radical initiation in the mitochondria causing the production of ROS which are reactive in nature [3].

Free radicals are quite many types, but the most abundant in the biological system of the body is oxygen free radicals or ROS. These free radicals are the result of solving homolithic of a covalent bond of a molecule or pair of free electrons atom. ROS is part of the results of normal cell metabolism or cells exposed to other substances that cause inflammation or inflammation. ROS largely a result of physiological responses (endogenous ROS) ie results normal cell metabolism and a small portion is the result of exposure from outside the body (Exogenous ROS), namely reactive oxygen derived from environmental pollutants, radiation, bacterial, fungal and viral infections [8].

Free radicals are molecules, atoms or groups that have 1 or more unpaired electrons in the outer shell so it is very reactive and radicals such as reactive oxygen derived derivatives. Free radicals are quite many types, but the ones that have the most many in the body's biological system are oxygen-derived free radicals ROS and reactive nitrogen species (RNS) [8].

Oxidative stress also occurs due to a decrease in the amount of nutrients and oxygen, giving rise to microvascular damage and ischemic processes (reperfusion injury) (Parwata, 2015).

Reactive oxygen species consist of superoxide ($^{\cdot}O2$), peroxyl ($ROO^{\cdot}$), hydroxyl ($^{\cdot}OH$), hydrogen peroxide (H2O2), singlet oxygen (1O2), peroxynitrite ($ONOO^{\cdot}$), nitric oxide ($NO^{\cdot}$), hypochloric acid (HOCl), and fat oxidation results on food. The common free radicals formed in the body are superoxide. This superoxide will be converted into hydrogen peroxide (H2O2). This hydrogen in the propagation stage will be converted into $^{\cdot}OH$. Hydrosil radicals are what cause fat peroxidation in cell membrane so that the cell is damaged [8].

Free radicals will react with the surrounding cell molecules to gain an electron pair so that it becomes more stable, but the cell molecule the body that the electron picks up will turn into free radicals. This reaction will take place continuously in the body and if not stopped will cause oxidative stress which causes inflammation, DNA or cell damage and various diseases such as premature aging, heart disease, cataracts, cancer, and other degenerative diseases [8].

Licensed Under Creative Commons Attribution CC BY

Free radicals can be produced in the process of uric acid formation which is catalyzed by the xanthine oxidase enzyme. In this process it will be generated superoxide radicals (˙O2). This metabolic process usually occurs in mitochondria. Free radicals can also be formed from inflammatory process, i.e. the process of changing NADPH to NADP with the NADPH oxidase catalyst. In this process O2 leak occurs which then turns into ˙O2 which can stimulate the formation of proinflammatory cytokines like TNF-α and IL-6. This metabolic process usually occurs in the cytoplasm [8].

The existence of free radicals will not always harm the human body but there are also those that have beneficial effects, such as helping destruction of microorganism cells, cancer and the maturation process of cells inside body. Leukocytes produce free radicals to destroy gingiva, ligaments periodontal and alveolar bone by damaging DNA, disrupting production prostagladin and stimulates the formation of proinflammatory cytokines such as TNF-α and IL-6. However, excessive free radical production and production inadequate antioxidants can cause damage to tissue cells and enzymes. Tissue damage can occur due to oxidative disorders caused by fatty acid free radicals or known as lipid peroxidation [19].

Mitochondrial ROS production can cause oxidative damage against proteins, membranes and DNA from the mitochondria itself, disorders the ability of ATP synthesis and other metabolic functions. Oxidative damage mitochondria can also increase the tendency of mitochondria to releases proteins from intermenbrane space such as cytochrome c to cytosol by Mitochondrial Outer Membrane Permeabilization (MOMP) and later activate cell apoptosis. Oxidative stress / ROS causes damage to the induced dermis by some MMP. Matrix metalloproteinase is a family of proteinases contains zinc which is able to degrade every type of ECM protein. MMP involved in various physiological and pathological processes associated with ECM damage, including ECM remodeling after injury, angiogenesis and development and cancer invasion [20].

2.4 Antioxidant

Antioxidants are compounds that can absorb or neutralize free radicals so that they can prevent diseases degenerative diseases such as cardiovascular, carcinogenesis, and other diseases. Antioxidants are substances that the body needs to neutralize radicals free and prevents damage caused by free radicals to cells normal, protein, and fat. This compound has a molecular structure that can giving electrons to free radical molecules without the same interruption once its function and can break the chain reaction of free radicals [19].

Antioxidants in the chemical sense are electron-giving compounds (electron donors) and biologically antioxidants are capable compounds overcome the negative effects of oxidants. The balance between oxidants and antioxidants is important to maintain integrity and functioning of lipid membranes, proteins, and nucleic acids in cell [21].

Antioxidants outside the body can be obtained in the form of synthesis and natural. Synthetic antioxidants such as buthylatedhydroxytoluene (BHT), and tert-butylhydroquinone (TBHQ), buthylated Hydrocyanisol (BHA) can effectively inhibits oxidation. However, the use of synthetic antioxidants is limited by government rules, due to it carcinogenic effect, so they are needed safe natural antioxidants. Source of natural antioxidants is plants because they contain flavonoid compounds, chlorophyll and tannins [22].

Antioxidants function as compounds that can inhibit reactions free radicals cause carcinogenic, cardiovascular and deep aging diseases human body. Antioxidants are needed because the human body does not have sufficient antioxidant defense system, so that when there is radical exposure excessive, the body needs exogenous antioxidants (derived from outside) [21].

The main function of antioxidants is to reduce the oxidation process fats and oils, minimize the damage process in food, prolong service life in the food industry, increase stability fat contained in food and prevent loss of sensory quality and nutrition. Antioxidants based on the reaction mechanism are divided into three types, namely primary antioxidants, secondary antioxidants and tertiary antioxidants [21].

2.5 Flavonoids as Natural Antioxidant Compounds

Natural antioxidant compounds are generally in the form of vitamin C, vitamin E, carotenoids, phenolic compounds, and polyphenolics which can be in the form of groups flavonoids, derivatives of cinnamic acid, quomarin, tocopherols and organic acids polyfunctional. Flavonoids which have antioxidant activity include flavones, flavonols, isoflavones, catechins, flavones, and chalcons. Cinnamic acid derivative including caffeic acid, ferulic acid, chlorogenic acid, and others. This matter caused by the -OH group and the double bond (> C = C) owned by the compounds above [19].

Polyphenol secondary metabolite compounds such as flavonoids, polyenes and compounds that contain lots of -OH group are multifunctional and can act with free radicals as reducing agents, free radical scavengers, metal chelating, and silencer formation of oxygen singlets [23]. Antioxidant compounds found in extracts of a plant are thought to be its function can inhibit and neutralize the oxidation reaction involves free radicals, both exogenous and endogenous. Reaction oxidation involving free radicals especially free radicals * OH can damage the normal cell membrane around it and damage the composition of DNA so can cause a mutation. Mutation or composition damage a DNA can cause several degenerative diseases such as cancer, heart, cataracts, premature aging and others [19].

Flavonoids can provide antioxidant effects by preventing the generation of ROS, directly capture ROS or indirectly increase enzyme. Flavonoids can directly capture superoxide and peroxynitrite. Through superoxide capture, flavonoids increase NO bioavailability and inhibits the formation of peroxynitrite [23]. Flavonoids can inhibit DNA damage due

Licensed Under Creative Commons Attribution CC BY

to HO * reaction with nitrogen bases from DNA and stimulating the formation of antioxidants enzymatic such as SOD, catalase and GPx. Flavonoid can protect our body from further reactions of ROS and RNS by capturing ROS, blocking propagation reactions and stimulate the formation of endogenous antioxidants such as GPx, SOD and catalase and reduce MDA levels because they do not occur fat peroxidation (PUFA) and decrease 8-OHdG levels due to HO * yang usually entering into DNA has been captured by flavonoids (Akhlaghi, 2009). Flavonoids can function as anti-inflammatory because flavonoids can inhibit the formation of proinflammatory cytokines such as TNF-α, IL-6, IL-1β and interferon-γ [23].

2.6 Expression of Prostaglandin E2 (PGE2)

Imbalance between ROS production and neutralization with the system natural antioxidants in the body, produce oxidative stress. Reactive oxygen species promote peroxidation of lipid components of cell membranes, altering structure and function of several enzymatic systems, and increase oxidation of carbohydrate. The incidence of UV radiation is a major cause of oxidative stress on the skin and histological differences between exposed UV radiation and areas of the skin that are not exposed [24].

The UV rays stimulate the production of pro-inflamatory factors, namely PGE2 induced in the presence of COX-2, IL-10 and PAF mediators. Immunosuppression begins from exposure to mild UV light which does not cause sunburn [18]. The photoaging and photocarcinogenic mechanism through UV radiation causes ROS and DNA damage, and cell damage, inflammation, immune suppression and ECM remodeling / angiogenesis [24].

Important mediator of photoaging and photocarcinogenesis are inflammation which released mediators from leukocytes, fibroblasts, keratinocytes, tumor cells, and endothelial lining of blood vessels. The mediators include lipid mediators (leukotrienes, prostaglandins and activation factors platelets), plasma mediators (bradykinin, fibrin, plasmin), and inflammatory cytokines such as IL-6, and TNF -α. Lipid mediator, COX-2 and PGE2 is also activated by ROS (Figure 1) [24].

The activation of the enzyme ornithine decarboxylase, which is decreases the activity of different polyamines that regulate cell proliferation also activated by UV radiation. This process triggers production of ROS and RNS, which lead to production of peroxynitrite and eventually triggers DNA deletion and rearrangement [24].

Chronic skin exposed to the sun, showing the presence of wounds like reddish / sunburn. Healing from the injury process is indicated by decreased prostaglandin and leukotrin production resulting from inhibition of the cyclooxygenase pathway, COX-2. Emphasis on prostaglandins will cause reduced pain, edema and vasodilation of the vessels blood. Furthermore the inflammatory reaction can enter a marked proliferation phase with fibroblast cell proliferation [25].

The process of DNA repair, cell cycle and apoptosis is changed to support tumor development. Furthermore, UV radiation changes the expression of factors b-growth transformation (TGF-β), which is the main regulator of the matrix metalloproteinase which remodel the extracellular matrix for skin photoaging and tumor spread [24]. Induction of COX-2 expression by UV irradiation results in an increase PGE2 production. PGE2 binds and activates four receptors are combined with protein G, which are EP1, EP2 and / or EP4 important for the effect of PGE2 on skin damage from UV rays and carcinogenesis [26].

Prostaglandin E2 can bind to and activate four G protein receptors - coupled called EP1-EP4. Each EP receptor is combined into a protein Different G which can activate various downstream mediators. Activation EP1 causes increased intracellular calcium and activation of phospholipase C. EP2 and EP4 are both combined to adenylate cyclase which causes an increase cyclic AMP levels, and EP3 can activate or inhibit adenylate cyclase or increase intracellular calcium levels. In human skin SCC, fourth The EP receptor is demonstrated by immunostaining, with the expression EP1, EP2 and EP4 mRNAs. On the other hand, in both human and rat skin, there is little or no immunostaining was detected from one of the EP receptors [26].

Signaling through EP receptors results in the induction of various genes, including oncogenes, cytokines and growth factors, which then cause inflammation with infiltration and activation of inflammatory cells in the dermis, induction angiogenesis, increased vasodilation and vascular permeability, causes edema. The proliferation of keratinocytes causes epidermal hyperplasia and apoptosis reduction which is otherwise mediated by UV induction of stress oxidative, DNA and p53 damage. Chronic UV light exposure causes mutations p53 and other DNA damage, chronic inflammation and chronic regulation of expression COX-2 and its downstream effects, which can then cause skin carcinogenesis [26].

Prostaglandin E2 is a pleiotropic lipid signaling molecule which is synthesized from arachidonic acid with sequential action of cyclooxygenases (COX1 and COX2) and prostaglandin E synthases (PTGES1, 2, and 3). COX2 which increases often coincides with PTGES1 induction in various tumor lesions, and in response to inflammatory stimulation. COX1, PTGES2 and PTGES3 are usually not induced or involved in the overproduction of PGE2 which is seen in abnormal conditions [27].

The main prostaglandin in human skin is prostaglandin E2 which is usually synthesized at a low level, but markedly increased at skin cancer and inflammatory conditions, such as burning due sun exposure.

Licensed Under Creative Commons Attribution CC BY

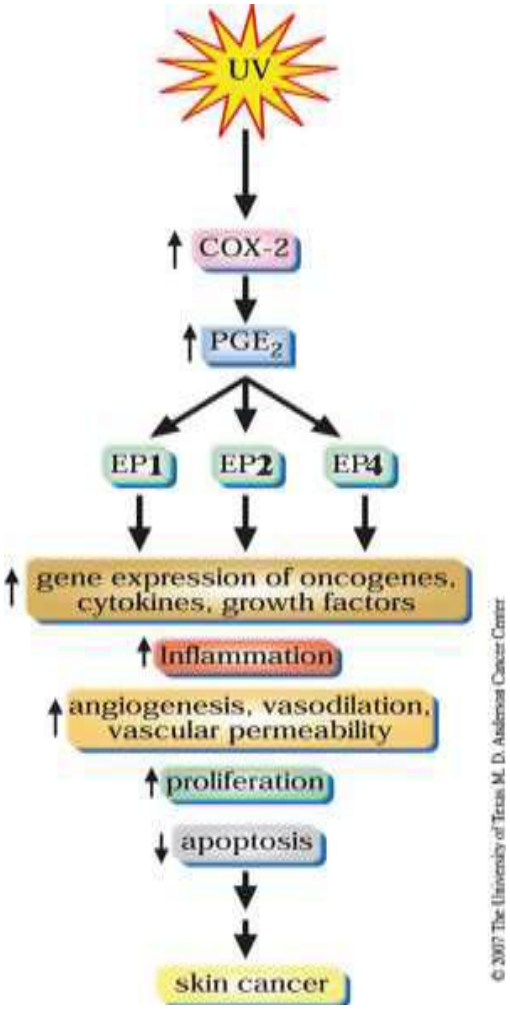

Figure 1: Effects of UV Rays on PGE2 [26]

In cell culture, PGE2 inhibits collagen production fibroblasts, in part by inhibiting the action of TGF-β. Inhibitory effect PGE2 in collagen synthesis has been shown to play a protective role against lung fibrosis, where the disruption of production and action of PGE2 is involved in excessive deposition of collagen fibroblasts. A study reported that PTGES1 mRNA expression is increased during aging and the role of PGE2 in decreasing type I collagen production which is related to the age of human skin [27]. Besides the possible contribution to collagen deficiency, the PGE2 derived from fibroblasts can be a risk factor for other skin disorders.

Prostaglandin E2 can damage the function of adjacent and immune cells keratinocyte epidermis through the paracrine mechanism [27].

3. Conclusion

Natural antioxidant compounds are generally in the form of vitamin C, vitamin E, carotenoids, phenolic compounds, and polyphenolics which can be in the form of groups flavonoids. UV rays stimulate the production of ROS and PGE2. Antioxidant can revent production of ROS and PGE2.

References

[1] Pangkahila, W. Anti-Aging Medicine: Memperlamat Penuaan, Meningkatkan Kualitas Hidup. 2007, Jakarta, Kompas.
[2] Ahmad, Z., Damayanti. Penuaan Kulit: Patofisiologi dan Manifestasi Klinis. Periodical of Dermatology and Venereology, 2018, Vol. 30 / No. 3 / Desember 2018.
[3] Werdhasari, A. Peran Antioksidan Bagi Kesehatan. Jurnal Biotek Medisiana Indonesia, 2014, Vol.3: 59-68.
[4] Tu, Y., Quan, T. Review: Oxidative Stress and Human Skin Connective Tissue Aging. Cosmetics, 2016, 3, 28; doi:10.3390.
[5] Poon, F., Kang, S., Chien, AL. Mechanisms and Treatments of Photoaging. Photodermatology Photoimmunology Photomedicine; 2015, 31: 65–74.
[6] Halliday, G.M., Honingsman, H. Sunscreen, Photoimunosupression and Photoaging. In: Lim, H.W., Draelos, Z.D., Editors. Clinical Guide to Sunscreens and Photoprotection. New York: Informa. 2009, pp 101-111.
[7] Lin, J.W., Chiang, H.M., Lin, Y.C., Wen, K. Natural Products with Skin-Whitening Effects. J. Food Drug Anal. 2008, 16.
[8] Parwata, O.A. Antikosidan. Buku Ajar Uji Bioaktivitas. Udayana, Bali, 2015.
[9] Pangkahila, W. Tetap Muda dan Sehat. First Edition. Jakarta: Kompas. 2011, p 11-37.
[10] Pangkahila, W. Effect of Hormonal Contraception In Melasma Occurrence, (Presnted at Central Java Seminar in Aesthetic Medicine Update 2014, Semarang June 13-14, 2014).
[11] Makranotaki, E., Brink, TC., Zampeli, V., Elewa, RM., Mlody, B, Hossini, A.M., Hermes, B., Krause, U., Knolle, J., Abdallah, M., Adjaye, J., Zouboulis, CC. Identification of Biomarkers of Human Skin Ageing in Both Genders. Wnt Signalling - A Label of Skin Ageing? www.plosone.org , November 2012, Volume 7, Issue 11.
[12] Masnec I.S., Situm M. Skin Aging. Acta Clin Croat, 2010, 49:515-9.
[13] Poljsak B., Dahmane G., Godic, A. Intrinsic Skin Aging: The Role 0f Oxidative Stress. Acta Dermatovenerol Alp Pannonica Adriat; 2012, 21: 33-6.
[14] Pandel, R., Poljsak, B., Godic, A., Dahmane. Skin Photoaging and The Role of Antioxidants in its Prevention. ISRN Dermatol: 2013, 1-11.
[15] Sachdeva, S. Fitzpatrick Skin Typing: Applications in Dermatology. Indian J Dermatol Venereol Leprol; 2009, 75: 93-6.
[16] Alam, M., Harvey, J. Photoaging. In: Draelos, Z. D., editor. Cosmetic Dermatology Product and Procedures. New Jersey: Wiley-Blackwell. 2010, p 13-20.
[17] Ichihashi, M., Ando, H., Yoshida, M., Niki, Y., Matsui, M. Photoaging of the Skin. Journal of Anti Aging Medicine, 2009, 6, 6: 46-59.
[18] Panich, U., Sittithumcharee, G., Rathvibbon, N., Jirawatnotai, S. Ultraviolet Radiation-Induced Skin Aging: The Role of DNA Damage and Oxidative Stress in Epidermal Stem Cell Damage Mediated Skin Aging. Hindawi Publishing Corporation Stem Cells International, Volume 2016.
[19] Chang, E.J., Kundu, J. K., Liu, L., Shin, J. W., and Surh, Y. J. Ultraviolet B Radiation Actives NF-KB and

Licensed Under Creative Commons Attribution CC BY

Photoprotective Strategies with Phytochemicals. Antioxidant, 2011, 4(2): 248-268.
[20] Rhein, L.D., and Fluhr, J.W. Aging Skin; Current and Future Therapeutic Strategies. Alluredbooks. USA. 2010.
[21] Winarsi, H. Antioksidan Alami dan Radikal Bebas. Yogyakarta: Kanisius. 2007, Hal. 189-90.
[22] Jin, L., Zhang, Y., Yan, L., Guo, Y., Niu, L. Phenolic Compounds andAntioxidant Activity of Bulb Extracts of Six Lilium Species Native toChina. Molecules, 2012, 17, 9361-9378; doi:10.3390.
[23] Akhlaghi, M., Brian, B. Mechanisms of Flavonoid Protection Against Myocardial Ischemia–Reperfusion Injury. Journal of Molecular and Cellular Cardiology. 2009, 46: 309–17.
[24] Bosch, R., Philips, N., Perez, J., Juarranz, A., Devmurari, A., Khaosaat, J.C., Gonzalez, S.. Mechanisms of Photoaging and Cutaneous Photocarcinogenesis, and Photoprotective Strategies with Phytochemicals. Antioxidant, 2015, 4(2): 248-268.
[25] Prasetya, R.C. Ekspresi dan Peran Siklooksigenase-2 dalam Berbagai Penyakit di Rongga Mulut. Stomatognatic (J. K. G Unej) 2015, Vol. 12 No. 1: 16-19.
[26] Rubin, M.G., Logan, A.C., and Levy P.M. Secrets to Naturally Younger Skin. Advantage Quest Publications Rundhaug, J.E., Fischer, S.M. 2008. Cyclo-Oxygenase-2 Plays a Critical Role in UV-Induced Skin Carcinogenesis. Photochemistry and Photobiology, 2010, 84: 322-329.
[27] Li, Y., Lei, D., Swindell, W.R., Xia, W., Weng, S., Fu, J., Worthen, C.A., Okubo, T., Johnston, A., Gudjonsson, J.E., Voorhees, J.J., Fisher, G.J. Age- Associated Increase of Skin Fibroblast-Derived Prostaglandin E2 Contributes to Reduced Collagen Levels in Elderly Human Skin. J Invest Dermatol; 2015, 135(9): 2181–2188. doi:10.1038

Author Profile

Liza Deviyanti Hadiwijaya Student of Doctoral Program, Faculty of Medicine, Udayana University

Licensed Under Creative Commons Attribution CC BY