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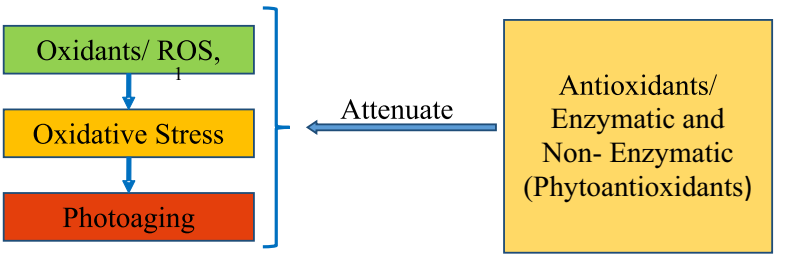
Oxidants, Oxidative Stress and Role of Phytoantioxidants as Photoprotectives - A Review

Chanchal Garg, Munish Garg*

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Graphical Abstract



Abstract

Photoaging is a multifactorial process which is attributed mainly to the degree of sun exposure and the amount of melanin present in the skin. The elemental root of skin aging is the generation of free radicals i.e. reactive oxygen species (ROS) and the oxidative stress. This oxidative stress highly affects the skin as it is rich in lipids, proteins, carbohydrates, DNA etc. Although, it has been well demonstrated that the skin has its own exceptionally effective natural antioxidant defence mechanism which is supported by variety of antioxidant enzymes such as peroxidases, catalases and glutathione, yet, the protection exhibited by them is restricted due to overproduction of reactive oxygen species, leading to skin aging. Antioxidant ability of phytoconstituents extracted from various plants minimise the deleterious effects of reactive oxygen species and restrains the clinical manifestations of skin aging. Antioxidant substances, like vitamin E, ascorbic acid, coenzyme Q10, flavonoidal or polyphenolic compounds present in plant extracts and various combinations of these, when applied topically, helps in retaining the skin antioxidant pool, thereby strengthening the skin antioxidant defence mechanism, thus minimising the deleterious effects of free radicals and oxidative stress. Antioxidant compounds like tetrahydro curcuminoids derived from roots of *Curcuma longa* not only prevents the free radical generation but also counteract the existing free radicals, Acai palm contain anthocyanins which helps in reducing the UVB induced DNA damage. Likewise, polyphenols present in green tea effectively inhibits the free radicals and alter the aging process. Thus, antioxidants, having free radical scavenging potential play a significant role in the prevention and treatment of conditions related to generation of free radicals. This review discusses about the various oxidants (reactive oxygen species or free radicals) formed, oxidative stress caused due to these free radicals and their mechanisms in photoaging. It also reviews the role of various antioxidants particularly, phytoantioxidants in the oxidative stress induced Photoaging and its future potential.

***Key words*:** Photoaging, oxidative stress, phytoantioxidants, medicinal plants.

Introduction

Photoaging is a multifactorial process which is attributed mainly to the degree of sun exposure and the amount of melanin present in the skin. The elemental root of skin aging is the generation of free radicals i.e. reactive oxygen species (ROS) and the oxidative stress. This oxidative stress highly affects the skin as it is rich in lipids, proteins, carbohydrates, DNA etc. This further triggers the occurrence of skin cancer in the individuals (Afaq and Mukhtar, 2001; Goihman-Yahr, 1996). Additional effects on the skin include erythema, hyperplasia, oedema, melanogenesis, sunburn cell formation, immunosuppression, DNA damage and photoaging (Balakrishnan and Narayanaswamy, 2011). Aesthetically, skin aging is a topic of concern, whereas skin cancer is an absolute risk to the health of an individual. UV induced ROS production leads to the modification of signal transduction pathways. The examples are MAPK (mitogen-activated protein kinase), the NF-κB (nuclear factor – kappa beta), the JAK (Janus kinase), STST (signal transduction and activation of transcription) and the 2 Nrf2 (nuclear factor erythroid 2-related factor). Further, ultraviolet radiations remodel the extracellular matrix (ECM) by increasing the matrix metalloproteinases (MMP) and reduce structural collagen and elastin (Bosch et al., 2015). Although melanin pigment present in the skin protects the skin cells by absorbing the

* Corresponding author. Tel: +91- 8059488857

*E-mail address:*mgarg2006@gmail.com,

harmful UV radiations but at times, the quantity of melanin produced may not be adequate to protect the skin from the detrimental effects of the ultraviolet radiations. Hence, other photoprotective strategies need to be adopted which include seizing of incidence of UV photons, DNA repair, and neutralising reactive oxygen species, anti-inflammation and immunomodulation. Now days the use of sunscreen has become most common practice to safeguard the skin from the deleterious effects of UV radiations as it blocks the incidence of UV radiations by absorbing them (Elmets and Young, 1996). Many sunscreen formulations are accessible in the market but they possess certain adverse effects also. One of the effective skin defence mechanisms is use of antioxidants (Kohen, 1999; Shindo et al., 1993)which react directly with thereactive oxygen species, thereby, prohibiting them to reach their biological target (Kohen, 1999). Although, skin epidermis possesses an extremely efficient natural antioxidant defence mechanism such as peroxidise, catalase and glutathione, the protective effect offered by them may not be sufficient due to the overproduction of reactive oxygen species leading to the incidence of cellular oxidative stress occurred as a consequence of disproportion between oxidant species and antioxidant reservoir of living organisms. This leads to skin aging. Thus, antioxidants, having free radical scavenging potential play a significant role in the prevention and treatment of conditions related to generation of free radicals (Chidambaram et al., 2013; Gasca et al., 2013; Kohen and Gati, 2000). The photoprotection provided by the natural substances has become significant in recent years owing to their vast range of biological activities. Antioxidant potential of a variety of phytoconstituents derived from plant extracts minimise the adverse effects of oxidative stress and helps to combat the clinical manifestations of skin aging. This review discusses about the various oxidants (reactive oxygen species or free radicals) formed, oxidative stress caused due to these free radicals and their mechanisms in photoaging. It also reviews the role of various antioxidants particularly, phytoantioxidants in the oxidative stress induced Photoaging and its future potential.

Oxidants/ free radicals and mechanism of photoaging

The oxidants /free radicals are those species that occur independently having one or more unpaired electrons. These are the metabolic products of oxygen (O_2) in animal tissues formed by successive reduction reactions (Halliwell and Gutteridge, 2007). They are predominantly referred as reactive oxygen species (ROS) which include superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$), which is an excited state of molecular oxygen. $O_2^{\bullet -}$ and $^{\bullet}OH$ are referred to as free radicals as they possess an unpaired electron in their outer shell whereas H_2O_2 and $^1O_2$ are known as non-radicals (Halliwell and Gutteridge, 2007). These reactive oxygen species are extremely reactive and unstable. They tend to return to their stable state by giving electron to the nearby molecules, thus oxidising them and releasing their extra energy. This follows the chain reaction and continues to oxidise the nearby molecules leading to the devastating consequences if not absorbed or quenched by the antioxidants.

The endogenous ROS are predominantly generated in the process of oxidative metabolism in mitochondria as a by-product, where ATP (adenosine triphosphate) is formed from glucose. Along with this reaction the molecular oxygen (O_2) is also converted to Speroxide anion ($O_2^{\bullet -}$)which is a volatile and powerful reactive oxygen species (Dalton et al., 1999). Apart from this, $O_2^{\bullet -}$can also be produced by xanthine oxidase and nitric oxide synthase required for degradation of purine nucleotides and production of nitric acid respectively. $O_2^{\bullet -}$ is highly unstable and is further converted to H_2O_2 either spontaneously or enzymatically in the presence of superoxide dismutase (SOD). Increased concentrations of $O_2^{\bullet -}$may lead to the reduction of transition metals like iron which further react with hydrogen peroxide to produce hydroxyl radical ($^{\bullet}OH$) via Fenton reaction i.e. $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH$ + Hydroxyl ion (Buettner, 1993). $O_2^{\bullet -}$ may also react with nitric acid to form peroxynitrite. Both the $^{\bullet}OH$ and $ONOO^{\bullet -}$ (peroxynitrite) are very strong and highly unstable oxidants and can react with nucleotides (DNA), unsaturated lipids and Proteins (amino acids) leading to DNA mutations, lipid peroxidation and protein oxidation respectively (Sies, 1993). Figure 1 represents the formation of reactive oxygen species (ROS).

The exogenous ROS are generated due to the undue exposure to ultraviolet radiations, environmental pollutants and xenobiotics. UV radiations particularly UVA react with photosensitizers or chromophores in the skin like cytochromes, heme, riboflavin and porphyrin and absorb the energy from UVA. This leads to their transition into highly unstable form. These then return to their stable state by transferring their excess energy to the nearby oxygen molecules thus forming singlet oxygen species ($^1O_2$) and other ROS (Ananthaswamy and Pierceall, 1990; Cadet et al., 2009). Photoirradiation of environmental pollutants such as polycyclic aromatic hydrocarbons like benzopyrene and its intermediates, can lead to the increase in the production of super oxide anion ($O_2^{\bullet -}$) and singlet oxygen ($^1O_2$) (Liu et al., 1998; Saladi et al., 2007; Shyong et al., 2003; Wang et al., 2004; Yu et al., 2006). Detoxification of toxic substances by the body known as xenobiotic metabolism of drugs or toxins obtained by exposure to allergens and toxins such as cigarette smoke, pollution, pesticides and insecticides also leads to an increase in the oxidant species in the body (Ozougwu, 2016).

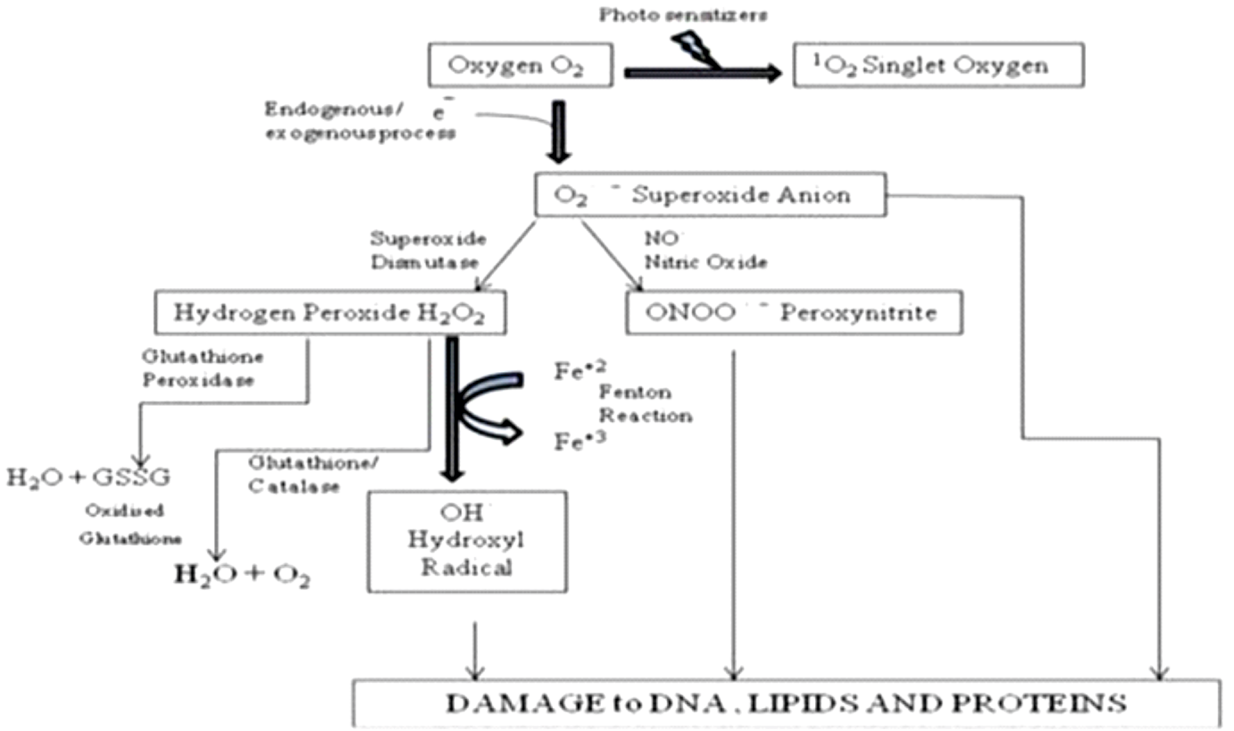


Figure 1: Generation of Reactive Oxygen Species

Oxidative stress

The imbalance between the production of reactive oxygen species in the body and the potential of the biological system to detoxify or repair the damage caused by ROS i.e. the production of antioxidants, is characterised as an Oxidative stress. Reactive oxygen species being in excess leads to oxidative stress. All the reactive oxygen species produced have the potential to combine with the membrane lipids, nucleic acids, proteins and enzymes and other small molecules. This further leads to cellular damage. This oxidative stress can cause deleterious effects on cells and the extracellular matrix. It can also cause damage to nuclear and mitochondrial DNA, membrane lipids and proteins. ROS - induced DNA modifications includes the formation of modified guanine nucleotide (8-hydroxyguanine), oxidised pyrimidine bases and single-strand breaks (Cadet and Douki, 2011; Kielbassa et al., 1997). Inclusion of 8-hydroxyguanine into DNA strands is associated with tumour promotion, indicating that permanent DNA damage leads to mutagenesis and carcinogenesis (Nishigori et al., 2004; Valko et al., 2006). Additionally, the 4977-base pair deletion of mitochondrial DNA, primarily known as 'common deletion', is predominant in human skin exposed to UV rays especially UV A (Birch-Machin et al., 1998). This is attributed to the production of singlet oxygen ($^1O_2$). Mitochondrial damage also leads to a sharp decrease in ATP and cause cell death due to necrosis (Pacher et al., 2007). DNA damage may also lead to cross linkages between DNA and proteins.

UV induced lipid peroxidation have the deleterious effects both structurally and functionally on phospholipids resulting in rigid and permeable membranes. Lipid peroxidation process commences with unstable $^{\bullet}OH$ which draws a hydrogen atom from the neighbouring unsaturated fatty acid leading to the formation of lipid molecule with an extra electron. This, in the presence of molecular oxygen, forms peroxyl radical ($OO^{\bullet}$)(Recknagal and Glende, 1984). If not immediately terminated, this can lead to a chain reaction involving the adjacent lipid molecules and finally disintegrating the cell membrane.

Protein damage induced by reactive oxygen species includes the breaking of the peptide chain and alterations of electrical charge of proteins. It also causes the cross linking of proteins and certain amino acids are oxidised resulting in increased susceptibility to proteolysis by degradation by specific proteases (Kelly and Mudway, 2003). Different amino acids present in the peptides vary in their vulnerability to attack by Reactive oxygen species. Particularly, cysteine and methionine residues containing thiol groups and sulphur are more prone to oxidation by ROS (Dean et al., 1991). Disulphide Bridge is formed when activated oxygen abstracts H- atom from the cysteine residues and forms thiyl radical which further cross-links to second thiyl radical. The protein bound thiol groups are also depleted by several other metals that include metals like Cd, Hg, and Pb (Stohs and Bagchi, 1995). Oxidation of

sulfhydryl groups or methionine residues to form methionine sulphoxide derivative (Brot and Weissbach, 1982) leads to conformational changes, unfolding of proteins and their degradation (Davies, 1987; Dean et al., 1991). Tyrosine is easily cross-linked forming bityrosine in the presence of ROS (Davies, 1987). Iron sulphur centres oxidised by $O2^{\cdot-}$ is an irreversiblechange and leads to inactivation of enzymes (Gardner and Fridovich, 1991).

Antioxidants

Antioxidants are naturally occurring molecules that have an ability to counteract the deleterious effects of oxidative stress. They act by inhibiting the ROS production by directly scavenging them, by decreasing the amounts of oxidants in our body, by prohibiting the ROS to reach their biological target sites, by limiting the propagation of oxidants such as those produced at the time of lipid peroxidation (Kohen, 1999; Shindo et al., 1993).

Whenever the reactive oxygen species are generated in the body, the body's self defence mechanism comes into action. However, their relative importance is dependent on the type of ROS generated; place of their generation and the possible target of their damage (Halliwell and Gutteridge, 2007). Our body protects itself from these deleterious effects by the use of endogenous enzymatic antioxidants that includes glutathione peroxidise, superoxide dismutase, catalase and low molecular weight antioxidants (LMWAs) called as non-enzymatic oxidants which includes vitamin C, glutathione, vitamin E, coenzyme Q10 (ubiquinone-10) and α-lipoic acid (Beckman and Ames, 1998; Chaudière and Ferrari-Iliou, 1999; Erenel et al., 1993; Fuchs et al., 1989; Halliwell and Gutteridge, 2007; Shindo et al., 1993). Superoxide dismutase (SOD) is an antioxidant enzyme that catalyses the decomposition of superoxide anion to hydrogen peroxide and oxygen (Langseth, 1995). Catalases (CAT) particularly catalyses the decomposition of hydrogen peroxide water and oxygen (Shindo et al., 1993) and glutathione peroxidises are antioxidant enzymes that contain selenium which is essential in reduction of hydroperoxides. With exposure to the sunlight or ultraviolet radiations the amount of naturally occurring antioxidants decreases and leads to aging. Thus, with inadequate antioxidants in the body, the free radicals produced are left unchecked and cause skin aging. This imbalance or insufficiency of the endogenous antioxidants may be restored by the use of exogenous antioxidants. Figure 2 describes the general classification of antioxidants and phytoantioxidants.

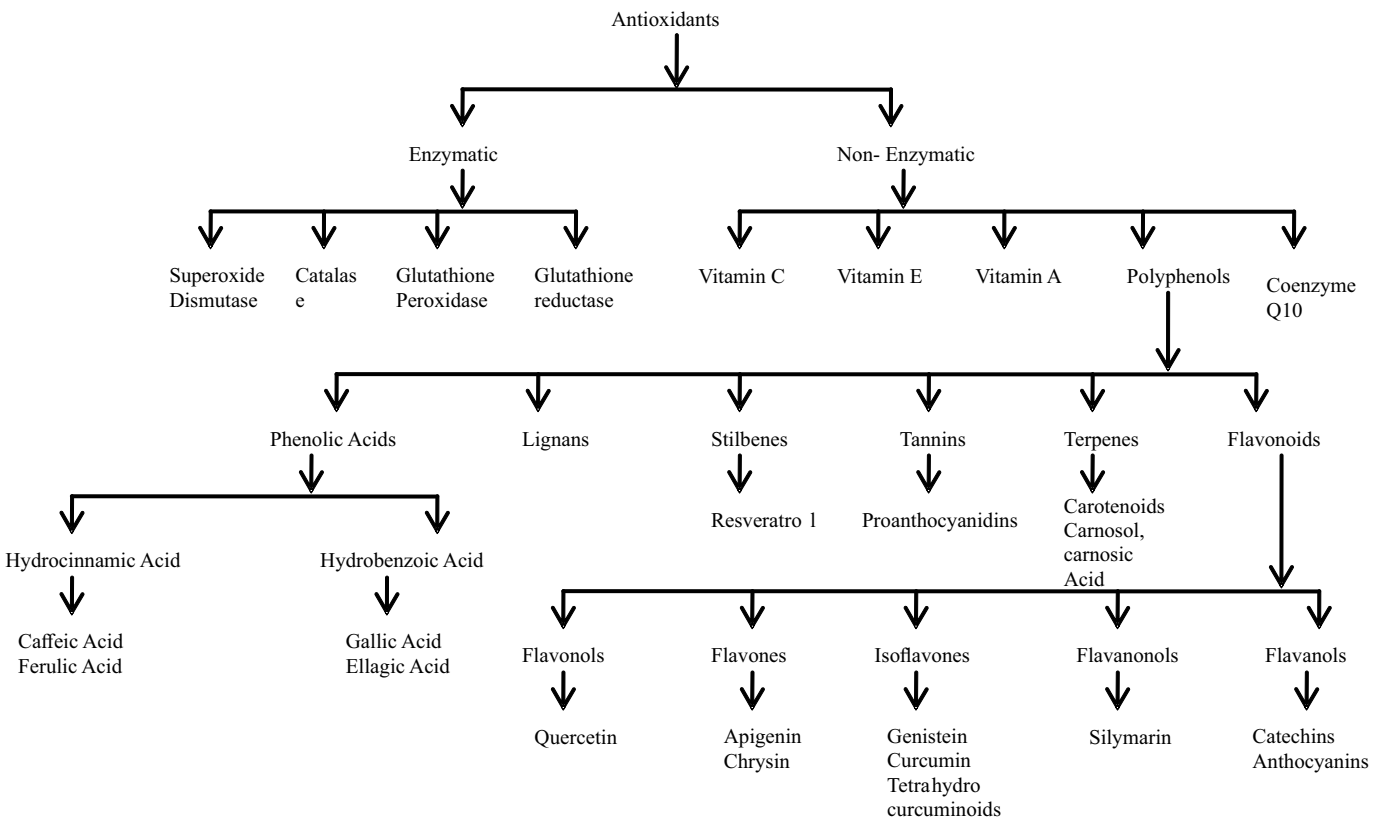


Figure 2: General Classification of AntioxidanNon- enzymatic antioxidants

Non- enzymatic antioxidants

Vitamin C/ Ascorbic acid

Vitamin C is obtained from fruits generally citrus fruits, strawberries, cantaloupe melon etc. and vegetables like tomatoes, leafy greens, cabbage family vegetables such as broccoli and cauliflower (Percival, 1998). It is a water soluble antioxidant in skin which prevents and protects the skin from oxidative stress by neutralising the free radicals in the skin (Percival, 1998). It also acts as cofactor for critical enzymes in synthesis of collagen and inhibits elastin biosynthesis to minimise the accumulation of elastin (Fisher et al., 1996). Vitamin C inhibits tyrosinase and reduces darkening of the pigments and helps in maintaining hydration by shielding the epidermal barrier of the skin (Campos et al., 2008). Vitamin C also exhibits its effect at the molecular level by increasing the synthesis of collagen and reducing MMP-1 expression (Varani et al., 2001). Vitamin C is unstable in the formulations containing water as it is sensitive to light, elevated temperatures, heavy metals and can lead to the decolourisation of the preparation. Thus, derivatives of vitamin C i.e. sodium-ascorbyl-phosphate and magnesium-ascorbyl-phosphate are generally employed. These derivatives release the active ascorbic acid in the presence of phosphatises (Telang, 2013).

Vitamin E / Tocopherol

Vegetable oils, seeds/cold pressed seed oils, nuts, and meat/poultry/fish are the potential sources of vitamin E (Percival, 1998). It is a lipid soluble non-enzymatic antioxidant that exists at specific sites in the cell. It neutralises the lipid peroxides produced by the oxidation of the unsaturated fatty acids in the cell membranes, thereby, protecting it from peroxidative damage (Lopez-Torres et al., 1998). Vitamin E reduces photoaging (Bissett et al., 1990; Jurkiewicz et al., 1995), immunosuppression (Steenvoorden and Beijersbergen van Henegouwen, 1999; Gensler and Magdaleno, 1991; Oresajo et al., 2008) and photocarcinogenesis (Burke et al., 2000; Gensler and Magdaleno, 1991). Alcohol form of vitamin E i.e. dl or d α-tocopherol is easily prone to oxidation, thus, its esters are commonly used. d and dl α- tocopherol acetate, linoleate, succinate or nicotinate are the esters of vitamin E that are used and out of these the most commonly used ester is α-tocopherol acetate owing to its stability, efficiency, good compatibility and low cost(Percival, 1998). α- tocopherol reduces MMP-1 and hinders the formation of thymine dimer, thereby obstructing the breakdown of collagen and mutagenesis respectively (Chen et al., 1997; Ricciarelli et al., 1999). *Triticum vulgare* (wheat) oil has plenteous vitamin E and exhibits antioxidant property. In addition, it also helps in nourishing and preventing the loss of moisture content from the skin (Kapoor and Saraf, 2010). Tocopherols are also found in sufficient amount in *Corylus avellana* (hazelnut) oil, *Helianthus annuus* (sunflower) and *Sesamum indicum* (sesame) oil (Bensouilah and Buck, 2006).

Vitamin A

Vitamin A is generally used in two forms i.e. as retinoids or carotenoids in the topical formulations. They are obtained from coloured fruits and vegetables like tomatoes, sweet potatoes. Retinoid are commonly used in sunscreens and other skin care products. The safety concerns of the retinyl palmitate (storage form of retinol) owing to its photocarcinogenic effects on exposure to UV radiations has put it under a careful investigation but clinical medicine studies has demonstrated its safety on prolonged use. Retinol and its other forms like tretinoin, isotretinoin and tazarotene are also known to exhibit antiaging characteristics. They act by binding to the retinoic receptors (nuclear receptors) and retinoid X that inhibits the expression of AP-1 and MMP-1(Fisher et al., 1996) thus leading to the increase in collagen production and epidermal thickness.

Coenzyme Q10 (chemically, 1, 4 - benzoquinone) is a coenzyme predominant in animals and most bacteria. It is generally known as Ubiquinone and the Q and 10 in Co Q10 represents a quinone group and the number of isoprenyl subunits in its tail respectively. It is a fat-soluble substance similar to vitamin which is found mainly in the mitochondria. It takes part in aerobic cellular respiration through electron transport chain, thus generating energy in the form of ATP which accounts to approximately 95% of the human body's energy (Dutton et al., 2000; Ernster and Dallner, 1995). Hence, the organs that require high energy like heart, liver, and kidney possess highest concentrations of CoQ10 (Aberg et al., 1992; Okamoto et al., 1989; Shindo et al., 1994). Coenzyme Q10 exists in three redox states i.e. ubiquinone, semiquinone (ubisemiquinone), and ubsiquinol. It can either behave as a two-electron carrier or a one-electron carrier depending upon the electron moving between the quinone and quinol form and between the semiquinone and one of the other forms respectively. This is attributed due to the presence of iron-sulphur clusters which only accepts one electron at a time. It acts as a free radicalscavenger by neutralizing free radicals, and stabilizing the cell membranes for proper functioning. It is the only known lipid which is produced directly within the body which maintains a redox function by the change of oxidation numbers in atoms during chemical reactions. Foods like broccoli, dark leafy greens, nuts, fish, shellfish, pork, chicken and beef, are good sources of CoQ10 but they provide only about 2 to 5 mg of CoQ10 daily which inadequate to maintain the required blood levels of CoQ10.

Flavonols

Quercetin

3,5,7,3',4'- pentahydroxyflavon (quercetin) is most potent and abundant antioxidant found in fruits and vegetables like grapes, lemons, apples, tomatoes, onions, lettuce, broccoli, kale, cotton seeds etc., beverages like tea, redwine, herbs like *Gingko biloba*, *Apocynum venetum*, *poacynum hendersonii*, and

opuntia ficusindica, olive oil and propolis from bee hives (Erden Inal et al., 2001; Sestili et al., 1998). Owing to the antioxidant potential and ability to chelate the metal ions, quercetin is assumed to have photoprotective effect against UV radiations or minimise the harmful manifestations of UV exposure (Sestili et al., 1998). Quercetin also preserves or protects the skin antioxidants i.e. glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase activities and against UV A irradiating damage (Erden Inal et al., 2001). Quercetin is presumed to protect the plants from UV induced damage because of its increased biosynthesis on exposure to UV B radiations (Solovchenko and Schmitz-Eiberger, 2003; Wilson et al., 1998). This flavonol absorbs UV radiations thus pointing towards its probable mechanism of action by direct absorbance of UV radiations and preventing the formation of reactive oxygen species and direct DNA damage (Russo et al., 2000). Quercetin and its derivatives such as quercetin 3-O-acetate, quercetin 3-O-propionate and quercetin 3-O-palmitate were known to inhibit UV C (200-280nm) induced liposomal peroxidation (Saija, 2003). In animals, quercetin is demonstrated to inhibit UV B induced skin damage when applied topically (Casagrande et al., 2006; Widyarini, 2006).

Flavones

Apigenin

Apigenin, chemically 5,7,4'- tri hydroxyflavone, is commonly found flavonoid in herbs like parsley, rosemary and thyme, fruits such as apples, cherries and grapes, vegetables like beans, broccoli, celery, leeks, onions, barley and tomatoes, and beverages such as tea and wine (Afaq and Mukhtar, 2001; Peterson and Dwyer, 1998). Apigenin was demonstrated to show the protective against UV A and UV B induced skin carcinogenesis in SKH-1 mice (Birt et al., 1997). Also, in-vitro use of apigenin resulted in considerable suppression of UV mediated induction of ornithine decarboxylase activity, decreased tumour incidence and enhances tumour free survival (Wei et al., 1990). Apigenin also possess anti-inflammatory (Crespo et al., 2008; Kumazawa et al., 2006; Nicholas et al., 2007; Patel et al., 2007; Smolinski and Pestka, 2003) and free radical scavenging activity (Kim et al., 1999; Raso et al., 2001). UV B induced apoptosis is enhanced by apigenin affecting both intrinsic and extrinsic pathways (Tong et al., 2007).

Chrysin

Chrysin, an analogue of apigenin is chemically 5, 7 dihydroxyflavone. It is natural occurring flavones found in propolis and honey (Gambelunghe et al., 2003). Chrysin is a potent inhibitor of aromatase (Kao et al., 1998), human immunodeficiency virus activation (Weng et al., 2005), anti inflammatory (Critchfield et al., 1996), antioxidant (Woodman and Chan, 2004). Wu et al, 2011 (Wu et al., 2011) signified that chrysin can be potentially used in the prevention of the harmful effects caused by UV radiations. Chrysin is also capable of reducing various detrimental effects of UV A and UV B on the skin which also takes into account the overproduction of reactive oxygen species, induction of COX-2, apoptosis and aquaporin (AQP-3) down regulation. Animal studies have confirmed the efficacy and safety of chrysin as a topical application (Wu et al., 2011).

Flavanonols

Sylimarin

Sylimarin is a flavonoid isolated from the seeds of *Silybum marianum* (milk thistle) (Katiyar et al., 1997). It mainly contains silybin, silidianin, silychristin and isosylibin (Mereish et al., 1991). Of these flavonoids, silybin is the most potent phytochemical which has a remarkable ability to scavenge the reactive oxygen species and prevent lipoprotein oxidation. Silymarin, when applied topically, decreases the formation of UV- induced sunburn cells, reduces pyrimidine dimmers and decreases the skin tumours (Afaq et al., 2002; Katiyar et al., 1997). The high antioxidant potential of silymarin is attributed owing to its polyphenolic hydroxyl groups which exhibits a great ability to form complexes at 3, 4 – or 4, 5 - positions with transition and other metal ions (Soto et al., 2003). Silymarin prevents photocarcinogenesis by inhibiting the UV B induced oxidative stress, inflammation and suppressing the immune system (Katiyar, 2005; Katiyar et al., 2008; Meeran et al., 2006).

Isoflavones

Genistein

Chemically, genistein is 5, 7, 4'-trihydroxyisoflavone, which is mainly found in soybean plant (*Glycine maxi*). It is a potent antioxidant and scavenges the peroxyl radicals and prevents the lipid peroxidation both in vitro and in vivo (Hwang et al., 2000; Wiseman et al., 2000). It is also known to inhibit UV-induced DNA oxidation and decreases the hydrogen peroxide - induced DNA damage in human lymphocytes (Giles and Wei, 1997; Widyarini et al., 2001). Genistein efficaciously prevents the UV B- induced skin burns in humans and UV A- induced photodamage and molecular alterations in mouse skin (Wei et al., 2003). It also prevents the UV B – induced senescence- like characteristics in human dermal fibroblasts through the maintenance of antioxidant enzyme activities and modulation of mitochondrial oxidative stress (Wang et al., 2010).

Tetrahydro curcuminoids **(THC)**

Tetrahydro curcuminoids are derived from curcuminoids present in the rhizome of *Curcuma longa* (turmeric). It is long been used traditionally for its various beneficial interest, especially, for its anti-inflammatory, anti-cancer and anti-oxidant properties (Kocaadam and Şanlier, 2017). Tetrahydo-curcuminoids show high antioxidant potential by scavenging superoxide anion ($O_2^{\bullet -}$), because of its specific molecular structure (Osawa et al., 1995). It prevents the formation of free radicals and neutralising existing free radicals. Curcumin

inhibits chemically induced neoplastic lesions in skin through its antioxidant mechanism (Shah and Netrawali, 1988). Curcumin also prevents lipid peroxidation (Iersel et al., 1996).

Flavanols

Anthocyanins

The colour of many fruits, vegetables, cereal grains and flowers is mainly attributed to the presence of anthocyanins which range from yellow to purple except green (Takeda, 2006; Yoshida et al., 2006). The antioxidant potential of anthocyanins is because of their unique chemical structure, being an electron deficient molecule, which makes them highly reactive towards the reactive oxygen species (Galvano et al., 2004). Also, anthocyanins efficiently absorb the UV as well as visible radiations and scavenge the reactive oxygen species (Gould et al., 2002). The most abundant anthocyanin found in naturally is cyanidin-3-glucoside. It exhibits its photoprotective effects against both UV A and UV B radiations in human keratinocytes (HaCaT), procaspase-3 and DNA fragmentation (Cimino et al., 2006).

A red orange complex formed by the mixture of three varieties of *Citrus sinensis* (Moro, Tarocco and Sanguinello) is rich in cyanidin-3-glucoside (Bonina, 1996; Bonina et al., 2005, 2002). It shows its photoprotective effect by exhibiting a good free radical scavenging ability, inhibiting Xanthine oxidase and its antilipoperoxidative capacity (Russo et al., 2002). *Vaccinium myrtillus* L. (bilberry or blueberry) contains anthocyanins which are known to scavenge superoxide; decrease the hydrogen peroxide induced radicals and prevents the lipid peroxidation *in vitro* (Martín-Aragón et al., 1998) and *in vivo* (Milbury et al., 2002). Anthocyanins namely cyanidin-3-glucoside, petunidin-3-glucoside, malvidin-3-glucoside and delphinidin-3-glucoside are mainly present in bog blueberry (*Vaccinium uliginosum* L.) extract. These anthocyanins protect from UVB induced photoaging in skin by obstructing the destruction of collagen and inflammatory responses through transcriptional mechanisms of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signalling (Bae et al., 2009). The photoprotective activity of Strawberry (*Fragaria x ananassa*) is demonstrated mainly due to the presence of anthocyanins that prevents the collagen destruction and inflammatory responses via NF-κB and MAPK signalling (Giampieri et al., 2012). The anthocyanins mainly cyanidin 3-O-glucoside and cyanidin 3-O-rutinoside present in Acai palm (*Euterpe oleracea*) are responsible for its antioxidant activity (Gallori et al., 2004; Lichtenthäler et al., 2005).

Catechins

Catechins, predominantly found in Tea (*Camellia sinensis*) leaves, contain pyrocatechol group and is composed of catechin, epicatechin, galactocatechin, epicatechin-3-gallate and epicgallocatechin-3-gallate (EGCG). In humans, the topical administration of catechins reduce the epidermal changes occurred due to UV exposure, especially the increase in p53 expression and apoptosis (Mnich et al., 2009). Tea polyphenols exhibit their antioxidant potential by scavenging free radicals like singlet oxygen (Higdon and Frei, 2003; Khan and Mukhtar, 2007), hydrogen peroxide (Lambert et al., 2007; Weisburg et al., 2004), superoxide (Harada et al., 1999), hydroxyl (Nanjo et al., 1999) and peroxyl radicals (Grinberg et al., 1997; Guo et al., 2003; Jovanovic and Simic, 2000; Reszko et al., 2010; Shi et al., 2000; Unno et al., 2002). These polyphenols also decreases the UV – induced lipid peroxidation (Kim et al., 2001) and oxidation of proteins in free radical generating system *in vitro* (Nakagawa et al., 2002). Epigallocatechin-3-gallate inhibits various factors encompassing photoaging like UVB induced activator protein-1 activity and MAPK cell signalling pathways (Barthelman et al., 1998; Katiyar et al., 2001). Tea polyphenols also provide protection to the DNA from getting oxidised by hydrogen peroxide and ultraviolet radiations *in vitro*(Wei et al., 1999). When applied topically, tea polyphenols minimise the UVB-induced pyrimidine dimers both in epidermis and dermis (Katiyar et al., 2000) and UV induced erythema and sunburns in human skin (Elmets et al., 2001).

Stilbenes

Resveratrol

Resveratrol, chemically trans-3,5,4'-trihydroxystilbene, is a naturally occurring polyphenolic phytoalexin belonging to stilbenes class of compounds. It is fat soluble and exists in both Cis- and Trans- configurations (Saraf and Kaur, 2010). It occurs in skin of red grapes and in red wine (Siemann and Creasy, 1992). It is also found in derivatives of certain nuts, peanuts (Counet et al., 2006; Sanders et al., 2000), cranberries, cranberry juice (Counet et al., 2006; Wang et al., 2002). Resveratrol, in plants is known to act as protective agent and is synthesised when exposed to stress, infection, or strong UV radiations. It is a potent antioxidant, anti-inflammatory and anti-aging agent. It exhibits is antioxidant potential either by scavenging the existing free radicals or by reducing or prohibiting the formation of new free radicals via chelation of metal ions which catalyses the formation of free radicals. Many *in vitro* and *in vivo* studies reveal the use of resveratrol topically against UV B –induced cutaneous damage and UV A induced oxidative stress (Adhami et al., 2003; Afaq and Mukhtar, 2006; Aziz et al., 2005). It also prevents UV A – mediated damage and abnormal cellular proliferation (Chen et al., 2006).

Terpenes

Carnosol and Carnosic Acid

Carnosol and carnosic acid are the major constituents present in Rosemary (*Rosmarinus officinalis*) and are responsible for about 90% of its antioxidant potential (Afaq et al., 2003a). These polyphenolic compounds prevent lipid peroxidation and inhibit the oxidative damage to skin surface lipids by scavenging the lipid free radicals (Calabrese et al., 2000).

Human fibroblasts on pre-treatment with carnosic acid results in the suppression of UV A – induced elevation of metalloproteinase-1 messenger RNA (Offord et al., 2002). Carnosic acid also exhibits photoprotective potential.

Carotenoids

Carotenoids are lipophilic antioxidants that are synthesised in plants. They are mainly found in yellow and orange vegetables and fruits (β-carotene); carrots (α- carotene); tomatoes (lycopene); dark green leafy vegetables, broccoli (lutein and zeaxanthin) etc. They have an ability to detoxify various kinds of ROS (Young, 1991). Carotenoids exhibit their antioxidant potential by scavenging $^1O_2$ and preventing oxidative damage and they also quench the excited chlorophyll (Chl*) molecules as well as chlorophyll in triplet state thus inhibiting the production of $^1O_2$(Siefermann-Harms, 1987). β- Carotene also exhibits its effect on wrinkles and elasticity of skin, procollagen gene- expression and UV- induced DNA damage in human skin (Cho et al., 2010). Lycopene, though not a precursor of vitamin A, it protects the skin from various alterations induced by UV radiations (Rizwan et al., 2011). It is a powerful antioxidant and anticarcinogenic carotenoid which has a strong ability to quench singlet oxygen ($^1O_2$). It helps in scavenging lipid radicals, reduces lipid peroxidation and prevents erythema induced by ultraviolet radiations (Stahl et al., 2006).

Tannins

Proanthocyanidins

These are found in grape seeds and are also known as condensed tannin which form a part of flavonoid family (Vinson et al., 1995). Proanthocyanidins are powerful antioxidants which exhibits excellent free radical scavenging properties (Guo et al., 1996). An antioxidant potential of grape seed proanthocyanidins is owing to the fact that it inhibits the reduction of antioxidant defence components induced by UV B and also augments the sun protecting factor in humans (Afaq et al., 2003b; Mantena and Katiyar, 2006; Mittal et al., 2003). Grape seed proanthocyanidins also have photochemo-preventive effect on UV B induced skin cancer (Perde-Schrepler et al., 2013) and prevents hyperpigmentation (Baumann, 2007). Additionally, UV B-induced oxidative stress and apoptosis was minimised on consumption of grape seed extracts by mice (Filip et al., 2013).

Phenolic Acids

Caffeic and ferulic acids

Coffee beans, propolis, grains, fruits and vegetables contain caffeic acid (3,4- dihydroxycinnamic acid) and ferulic acid (4-hydroxyl-3-methoxycinnamic acid) generally in the conjugation with sugars (Bourne and Rice-Evans, 1998). They provide the protection against UV induced peroxidation and react with nitrogen oxides (Saija et al., 1999). Ferulic acid absorbs the ultraviolet rays more effectively as compared to caffeic acid and is used in many topical skin protective lotions and sunscreens (Saija et al., 2000). Ferulic acid stabilizes the solution of vitamin C and E when incorporated into it and increases its skin photoprotective effect (Lin et al., 2005). *Polypodium leucotomosI* (fern) extract is rich in caffeic and ferulic acids (Koshihara et al., 1984). It inhibits lipid peroxidation, UV induced membrane damage, activation of activator protein- 1 and NF-κB factor (Gonzalez et al., 2010).

Combination of Antioxidants Derived from Natural Sources

Pycnogenol®

Pycnogenol® is a standardised extract from bark of *Pinus pinaster* (French maritime pine). It contains a mixture of various phenolic and polyphenolic flavonoids like procyanidin derivatives, catechin, epicatechin, taxifolin and phenolic acids like caffeic, ferulic, p-hydroxybenzoic, vanillic, gallic, protocatechins etc. (Rohdewald, 2002; Saliou et al., 2001). Pycnogenol® shows marvellous free radical scavenging activity by triggering the production of enzymes like glutathione (GSH) (Rohdewald, 2002). Its supplementation also resulted in the skin hydration and skin elasticity which is mediated by hyaluronic acid and collagen respectively, thus exhibiting is use as anti-aging agent (Marini et al., 2012).

Conclusion

Nevertheless, the basic treatment of photoaging is photoprotection, yet the use of antioxidants can be beneficial to reduce the deleterious effects caused due to excessive exposure to UV radiations. Generally, for the photoprotection of human skin, the oral uptake of selected micronutrients and phytochemicals is suggested by various scientists on the basis of the experiments performed on skin cells *in vitro* and in animal models. However, photoprotection can only be attained if a pharmacologically optimal dose range is reached in the human skin. The use of botanicals is gaining interest now days owing to their safety and efficacy. Moreover, the plant actives are preferred over the synthetic products due to their broad spectrum UV absorption, protection against oxidative stress, modulating several signalling pathways. Natural antioxidants play an important role in these strategies as plants consists of various compounds, mainly the polyphenolic compounds, which cope up with the adverse effects of UV exposure through various strategies like free radical scavenging, skin hydration, stimulating the physiological properties of skin etc. Thus, it has become an urgent need to develop the appropriate antioxidant therapy that is capable of fighting against the oxidative stress and is helpful in reducing the adverse effects of UV exposure. Future prospects in this area can be the use of different antioxidants in combination which may provide the most beneficial defence mechanism to fight against the reactive oxygen species and oxidative stress. The use of phytoantioxidants in cosmetic formulations will facilitate the skin nourishment and its antioxidant replenishment in the similar way as it would be on consuming various fruits and vegetables.

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