Antioxidants in dermatology

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ABSTRACT

Antioxidants neutralize free radicals produced by various environmental insults such as ultraviolet radiation, cigarette smoke and air pollutants, thereby preventing cellular damage. The role of oxidative stress and antioxidants is known in diseases like obesity, atherosclerosis, and Alzheimer's disease. Herein we discuss the effects of oxidative stress on the skin and role of antioxidants in dermatology.

Key words: Antioxidants, free radicals, oxidative stress

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INTRODUCTION

Aging is a process of progressive decrease in the functioning and reserve capacity of all organs in the body, including the skin (intrinsic or chronological aging). This naturally occurring functional decline in the skin is often compounded and accelerated by chronic environmental insults such as ultraviolet radiation, pollutants, smoking etc., (extrinsic aging).[1]

THEORY OF AGING AND FREE RADICALS

One of the important theories for aging is the free radical theory, which was proposed by Denham Harman in the 1950s, wherein the generation of free radicals results in damage to biomolecules including DNA. This idea was later extended in the 1970s to implicate mitochondrial production of reactive oxygen species (ROS).[2-4] Later this theory was expanded to include other diseases such as malignancies, vitiligo, Alzheimer's disease, atherosclerosis etc.[4,5]

Free radicals are compounds formed when oxygen molecule combines with other molecules yielding an odd number of electrons.[6] The molecules which are oxygen-centred are ROS and those which have nitrogen are reactive nitrogen species (RNS).[5,7] These free radicals with an unpaired electron seek and seize electrons from vital components such as DNA, cytoskeleton, cellular proteins and cell membranes, resulting in cellular damage [Figure 1].[8]

The important ROS are superoxide anion ($O2^-$), peroxide, hydroxyl radical (OH), hydroxyl ion, and singlet oxygen ($^1O_2$).[9] Nitric oxide (NO) and peroxynitrite ($ONOO^-$) are the major RNS in biological systems.[7]

Exogenous sources of ROS are air pollutants, ozone, radiation, chemicals, smoking, toxins, and pathogenic microorganisms.[6] Endogenous source of ROS includes leaks in electron transport chain found in mitochondria during oxidation of food stuffs or inflammatory cells. These produce free radicals by a process of respiratory burst during phagocytosis or enzymes, which indirectly produce free radicals.[10]

SKIN AND FREE RADICALS

In the healthy skin, practically all types of skin cells produce reactive oxygen (ROS) and reactive nitrogen (RNS) species. These free radicals are indispensable effectors in the homeostatic pathways leading to cell proliferation, differentiation, senescence, and death.[7] An elaborate network of endogenous antioxidants maintain homeostasis by neutralizing these free radicals from causing damage to cells. When this fine balance between free radicals and endogenous antioxidants is lost, it results in a phenomenon called oxidative stress. Chronic oxidative stress has been suggested as being the cause or consequence of many acute and chronic human diseases e.g. obesity, cardiovascular diseases, cancer, acute lung injury, retinal degeneration, Alzheimer's disease, Parkinson disease and multiple sclerosis.[4,5] Oxidative stress also play a role in various

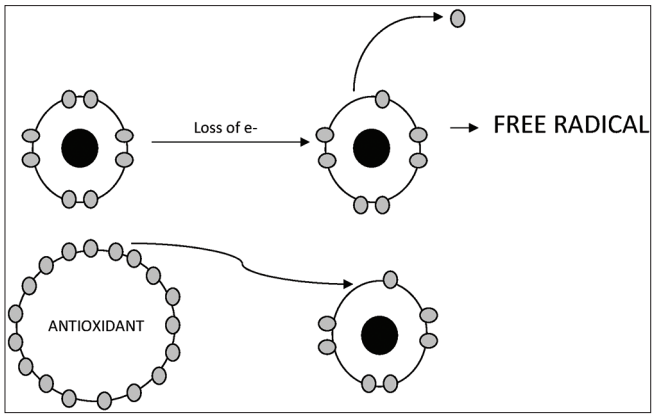

Figure 1: Free radical formation and antioxidant quenching the free radical

dermatological disorders like aging of skin e.g., solar elastosis, deep wrinkles, coarse texture, telangiectasia and pigmentation, psoriasis, allergic contact dermatitis, atopic dermatitis, vitiligo, acne vulgaris, pemphigus vulgaris (PV), lichen planus, alopecia areata, and melanomas.[7,9,11,12]

Various pathogenic mechanisms are responsible for these lesions such as induction of transcription factors that includes Activator protein (AP-1) and Nuclear factor κB (NF-κB) which are responsible for inflammatory changes, metalloproteinase (MMP) like collagenase which causes decreased collagen production, increased collagen breakdown, and increased elastin accumulation resulting in features of aging and lastly mitogenic activated protein kinase (MAPK), which is one of the factor responsible for skin cancers.[6]

ANTIOXIDANTS

Antioxidants are those molecules which are capable of inhibiting the oxidation of other molecules.[5] Oxidation is a process where there is loss of electrons or an increase in oxidation state by a molecule, atom or ion.

Reductant $\xrightarrow{\text{oxidation}}$ product + e-

As the number of molecules having antioxidant properties is increasing with each passing day, it is difficult to keep abreast with all of them. Commonly used antioxidants in dermatology are classified as endogenous and exogenous [Table 1].[6,9,13]

Naturally occurring antioxidants work in synergy with each other i.e. if an antioxidant disarms a free radical by eliminating the odd number of electrons it will no longer be able to function as an antioxidant unless it is replenished. This is done by another antioxidant and its synergy is called network antioxidation. The participating antioxidants are referred to as network antioxidants.[6,14]

Table 1: General classification of antioxidants[6,9,13]

Endogenous antioxidants
- Enzymatic -Glutathione peroxidase, glutathione reductase, Superoxide dismutase, Catalase
- Non enzymatic
  - Water soluble antioxidants - ascorbic acid (Vitamin C), glutathione, ubiquinone, uric acid, flavonoids, melanin
  - Fat soluble antioxidants -alpha tocopherols (vitamin E), carotenoids, Coenzyme Q10.
  - Both fat soluble and water soluble -alpha lipoic acid
  - Others – Melatonin, Selenium

Exogenous antioxidants
- Fat soluble - Lycopene , Curcumin
- Water soluble - Green tea, Coffee Arabica , Silymarin, Polypodium leucotomus, Resveratrol , Grape seed extract, Pomegranate
- Others –Pycnogenol, Soy isoflavones

DISTRIBUTION OF ANTIOXIDANTS IN SKIN

Skin is endowed with natural antioxidants as it is exposed to numerous environmental insults. Vitamin E, catalase, superoxide dismutases, glutathione peroxidases are abundantly present in the viable layer of the epidermis. The extracellular space of skin epidermis and dermis, contains large amounts of antioxidants such as ascorbic acid, uric acid, and glutathione. The outer most layer, the cornified envelope of normal human skin contains antioxidants such as glutathione, vitamin C, uric acid, α-tocopherol, squalene, and coenzyme Q10, distributed in a gradient with the highest concentration on the deepest cornified envelope layers.[7]

Summary of important antioxidants is given in Table 2.[6,9,15]

Antioxidant activity

The antioxidant activity of various antioxidants is studied using four parameters - Trolox equivalent antioxidant capacity (TEAC), oxygen radical absorbing capacity (ORAC), ferric reducing antioxidant capacity (FRAP), free radical scavenging properties by diphenyl-1-picrylhydrazyl radical (DPPH).

The antioxidant potency composite index, is based on [(sample score/best score) × 100] that is averaged for all the parameters for each beverage. It was found that pomegranate has the highest antioxidant activity. Following is the list of beverages and their potency index [Table 3].[16]

Since most antioxidants are dietary supplements, their side effects are supposed to be negligible such as presence of irritation with topical vitamin E or retinoids, and occurrence of peripheral vasodilatation or cutaneous flushing with oral niacin.[15]

Table 2: Summary of important antioxidants[6,9,15]

Antioxidant	Properties	Functions as an antioxidant	Dietary source	Clinical benefits studied
Vitamin C	1. Cofactor for critical enzymes in collagen synthesis 2. Recycling photoxidized α-tocopherol, thereby regenerating vitamin E.	1. Increases collagen synthesis 2. Reduces MMP (collagenase) expression 3. Inhibits activation of the transcription factor NFκB 4. Inhibits tyrosinase 5. Decreases sunburn cells by 40%to 60%.	Citrus fruits, black currants, leafy green vegetables, and red pepper	Photodermatoses Post laser-erythema Melasma Stretch marks Antiinflammatory
Vitamin E	Four pair of sterio isomers of which α-tocopherol has the highest activity	Protects the cell membranes from oxidative stress.	Vegetable oil, seeds, nuts, meats	Photoaging Antiinflammatory Anticarcinogenic Wound healing
Vitamin A	Two forms Retinoids Carotenoids (β carotene and Lycopene)	Carotenoids scavenge $^1O_2$ and quench lipid peroxidation. Retinoids bind to the nuclear receptors, retinoic acid receptors, thereby inhibitingAP-1 and MMP-1 expression.	Found in red fruits and vegetables like carrot, sweet potatoes, pink grape fruit, tomatoes.	Antiageing Anticarcinogenic
Coenzyme Q10 (ubiquinone) Synthetic analog is Idebenone	Fat soluble compound present in all cells as a part of energy transfer chain	Scavenge ROS	Fish, shell fish	Antiageing Anticarcinogenic
Green tea extract	High level of polyphenols like gallocathechin-gallate, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG). EGCG is the most active ingredient	Scavenges ROS Stabilises glutathione peroxidase, glutathione, catalase Inhibits AP-1and MAPK expression	Isolated form from camellia sinensis (tea) plant	Antiinflammatory Anticarcinogenic Photoprotective
Silymarin	Naturally occurring polyphenolic flavonoids. It has 3 flavonoids, silybin, silydianin and silychristin. Silybin has the highest biologic potency	Scavenges ROS Prevents lipoprotein oxidation.	Milk thistle plant Silybum marianum	Antiinflammatory Anti carcinogenic
Coffee arabica propriety name-Coffee berry	Contains polyphenols like cholorogenic acid, pro anthocyanidins, Quinic acid, Ferulic acid, caffeic acid	Suppresses UVB radiation-induced IL-10 and MAPK expression	Coffee beans and fruit of the plant	Antiinflammatory Anticarcinogenic
Resveratrol	Polyphenolic phytoalexin compound	Inhibits UV-B activation of NFκB and MAPK pathway	Skin and seeds of grapes, red wine, berries	Antiinflammatory Anticarcinogenic
Polypodium leucotomos	Contains polyphenols like dihidrobenzoic acid, Ferulic acid, caffeic acid, vanillic acid, caffeic acid	Scavenges ROS	Extract from the fern plant Polypodium leucotomos	Photoprotective Anticarcinogenic
Grape seed extract (vitis vinifera)	Rich in polyphenol like proanthocyanidins	Inhibits UVB induced lipid peroxidation, protein oxidation and DNA damage	Extract from grape seed	Antiageing Antiinflammatory
Pomegranate (punica granatum)	Native fruit of Indian subcontinent. Contains two polyphenolic compounds: anthocyanins and tannins	Potent antioxidant Inhibits UV-B activation of NF κB and MAPK pathway	Extract from peel, juice and seed of the fruit	Antiageing Photoprotective Anticarcinogenic

contd

Table 2: Contd

Antioxidant	Properties	Functions as an antioxidant	Dietary source	Clinical benefits studied
Alpha lipoic acid	It is an octanoic acid, an essential cofactor in mitochondrial dehydrogenases.	Metal chelation, Scavenge ROS Regenerate endogenous antioxidants Repairs oxidative damage	Endogenously produced, also found in red meat and Brewer's yeast	Antiageing Post laser erythema
Curcumin (Curcuma Longa, turmeric root, haldi)	Consists of water soluble component turmerin and lipid soluble curcumin	Scavenge ROS Downregulate IL-1 and TNF α Inhibits activation of NF-κB and AP-1 pathway	Tuber of tropical turmeric plant	Antiinflammatory Anticarcinogenic Wound healing
Selenium	Essential trace element for GSH peroxidase activity, cofactor for vitamin E regeneration.	Inhibits UV induced photodamage Scavenge ROS	Walnut, shellfish, fish	Photoprotective Antiinflammatory Anticarcinogenic Acts on P. ovale
Pycnogenol (Pine bark extract from pinus pinaster)	Rich in polyphenol like proanthocyanidins	Inhibits UVB induced lipid peroxidation, protein oxidation and DNA damage	Also found in grape seed, cranberry, black currant	Antiageing Antiinflammatory
L carnosine/ carcinine	Dipeptide of aminoacid B alanine and histidine	Inhibit UV induced lipid peroxidation	Fish and meat	Antiaging
Soy isoflavones	Contain isoflavones like genistein and diadzein	Scavenge ROS	Soya beans, ginko biloba	Antiinflammatory Anticarcinogenic

ROS: Reactive oxygen species, UVB: Ultraviolet B, DNA: Deoxyribose nucleic acid, GSH: Glutathione, UV: Ultraviolet, MAPK: Mitogenic activated protein kinase, EGCG: Epigallocatechin-3-gallate

Table 3: Beverages and antioxidant composite index

Beverage	Antioxidant composite index
Pomegranate juice	95.8
Red wine	68.3
Grape juice	61.7
Blueberry juice	50.9
Black cherry juice	46.5
Cranberry juice	38.0
Green tea	24.2
Orange juice	19.1
Apple juice	14.6
Black tea	12.2

Though there is a lot of interest about the role of antioxidants available for the treatment of various dermatoses, it is important to know that most of the studies have demonstrated an *in vitro* role of these molecules as antioxidants. There is paucity of clinical trials regarding their role to prevent aging of skin.[6,15] Also, there are certain problems in combining these molecules with creams such as sunscreens as it is found that many of these molecules are unstable and if stabilized, they tend to have lesser antioxidant capacity to neutralize the free radicals.[9] On the positive side, few recent studies have also shown that combining various antioxidants can have a synergistic action.[17]

CONCLUSION

Free radicals can damage the DNA, lipid membrane, collagen structures, and also play a role in photo aging and skin cancer. Oral and topical antioxidants have the ability to provide benefits from free radical damage, but long term studies are necessary to validate these findings.

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