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Therapeutic Promise of Natural Antioxidants in Redox Regulation

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ABSTRACT: Phytochemical research has attracted the attention of researchers in the field of biomedical and biotechnological research and explored a new era of drug discovery. Focus of these studies is to minimize or overcome the side effects of synthetic drugs. It aims to find out the equivalent natural molecules that can replace the drugs having harmful side effects on human health.

Advances in the organic and analytical chemistry during last century offered new vision towards the phytochemical research. Investigations of various molecules through different biochemical and biophysical methods can easily reveals the structural and functional properties of the compounds and have opened the new avenues in natural drug discovery. These new techniques are more competent to isolate, characterize and analyze the active principles from these medicinal plants and other natural resources. Thus, the phytochemical research has proved to have a pivotal role in drug discovery.

KEY WORDS: Antioxidants, Oxygen Paradox, ROS, RNS.

INTRODUCTION

Nearly 70-80% of human population including people from tribal, remote areas, as well as semiurban places are, still using the ancient formulations based on the knowledge passed from their ancestors. These practitioners are also using various ethnomedical formulations described in ancient ayurveda unani, and other medical literature. These drugs are in the form of crude extracts, decoctions, powders, tinctures, tea etc. (Ogbonna et al., 2012). Various phytochemicals constituents have proved their role as a drugs or nutrients.

Morphine (a pain killer), an analgesic drug isolated from the plant *Papaver somniferum* was the first-generation drug. Later many more drugs like cocaine (*Erythroxylum coca*), aspirin (*Salix sp.),* digitoxin (*Digitalis purpurea and Digitalis lanata*), quinine (*cinchona officinalis*) etc. having pharmaceutical and medicinal potential were discovered. (Newman, D. J. and Cragg, G. M., 2016).

Medicinal Plant resources are becoming extinct along with decreasing forest land as an impact of increased human population. Hence the requisite for the equivalent abundant resource needs to be searched. Algae is the most abundant source available on the earth and has attracted the attention of researchers to exploit for its medicinal values.

Now a days the reason behind most of the diseases is stress due to the life style, competition, absence of physical exercise, interaction with different disease-causing agents, pollutants and exposure to radiations from various sources.

Biological mechanism behind these diseases is proved as a disturbance in natural antioxidant system, impaired immunity, Inflammation, Radiation interaction, deficiency of nutrients etc. Oxidation of cellular components in absence or defects in antioxidant system which disturbs natural redox homeostasis is responsible for diseases. Immune response which is achieved by the release of various cascade components, that acting as a messenger for various pathways against disease causing agents and disturbances in up and down regulation of the inflammation as a part of immune response are the reasons for progression of diseases. Exposure to radiations from different natural as well as artificial or man-made resources are also contributing in different health problems of human population.

Many of the phytochemicals from different sources such as plant leaves, bark, fruits, flowers, roots, various algae from different habitat, are analyzed for their various constituents to explore their antioxidant, anti-inflammatory and radioprotective properties to be used as a drug.

Oxygen Paradox- Role of Oxygen in aerobic cells

Evolution of photo autotropic organism started producing molecular oxygen (O_2) as a byproduct of their photosynthesis process, and within a very short geological period oxygen became most essential chemical entity for aerobic life.(V. Wadekar et al.2017). Thus, the initial reduced environment without oxygen turned to oxidized environment with oxygen as an indispensable element for living world (McClintock, P. V., 2015).

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Most of the physicochemical metabolic processes rely on oxygen in respiring aerobic cells. It is utilized for the synthesis of various hormones, neurotransmitters etc. and also participate in the xenobiotic detoxification (F.Sibal Pala, K. T. 2007). Reactive Oxygen Species (ROS) is the group of highly reactive chemical entities generated within living cell during different metabolic activities, due to chemical reactions in which oxygen is involved. These ROS have been proved to be toxic to the cell by interfering with other biomolecules to distract their normal physiological function, hence ROS are harmful to living cells. This dilemma towards the role of oxygen in living cell is considered as 'oxygen paradox'.

Living cells are evolved to tackle the situation by using this molecular oxygen, in mitochondrial respiration, where this oxygen is utilized as a terminal electron acceptor in electron transport chain (ETC) in mitochondria. In this way the oxygen formed in the process of photosynthesis from the water is again converted back to water molecule and Adenosine Triphosphate (ATP) is synthesized from substrate biomolecules.

Redox Homeostasis:

The total reductional potential (reducing capacity) is the redox state of the cell which is balanced by the redox couples present in cellular organelles, tissues as well as in biological fluids such as NAD+/NADH (the two forms of cofactor Nicotinamide adenine dinucleotide. NAD^+ is an oxidized form and NADH is the reduced form), 2GSH/ GSSG Glutathione/Glutathione disulfide (oxidized form)(Kohen, R., and Nyska, A. (2002).

Oxidative stress shifts redox potential towards less negative values which are more negative for normal physiological conditions. The increased levels of ROS create redox imbalance that affects signal transduction which in turn alters gene expression. It results in redox dysregulation and leads to pathophysiological changes. If cell is unable to maintain the production of free radicals ROS and RNS (Reactive Nitrogen Species) and their utilization, neutralization or removal, it induces the various chronic and degenerative diseases such as diabetes mellitus, hypertension, atherosclerosis, carcinogenesis, aging, ischemic reperfusion injury, neurodegenerative diseases, cardiovascular diseases, muscular damage, renal injury, asthma, liver damage etc.

Both the prokaryotic and eukaryotic cells are evolved to adjust and adopted with the unfriendly coexistence of these free radicals. Cells developed the mechanism to utilize these unfavorable entities for the advantageous processes. Cell can protect itself by re-establishing the redox homeostasis with the help of reducing species present in cell such as GSH, NADH, FADH etc. Different physical, cellular metabolic processes including cell differentiation, Proliferation, apoptosis and necrosis depend on the redox status i.e. steady state level of H_2O_2. The fate of radical within the cell will depend on the concentration, duration and magnitude of its production.

Endogenous sources of Free Radical; Reactive Oxygen Species (ROS) formation

In vivo oxygen free radical production through enzymatic reactions in aerobic cell was first hypothesized by Denham Harman. Mitochondria as a major source of superoxide radical generation was first reported by Loschen, G., and Flohé, L. (1971). The various cell organelles viz, mitochondria, peroxisomes, cytochromes P450, inflammatory cells are the major contributors in free radical formation.

Electron Transport Chain in mitochondria (ETC) where the molecular oxygen is reduced to water produces various free radicles. Superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\cdot}$) are generated as an intermediate byproduct. The various chemical reactions through which the free radicals are generated are summarized as, univalent as well as bivalent reduction of molecular oxygen, protonation and dismutation or disproportion of superoxide anion etc.

Per hydroxyl radical (HO_2.) an extremely reactive species is produced by protonation of superoxide anion (O2.-). Singlet oxygen (O_2') formed by the spin reversal of outer orbit electron is a highly potent oxidant Langseth (1996).

H_2O_2 is considered as a non-radical because of absence of free electrons. It can easily diffuse through biological membranes, can easily pass and spread within all the compartments of the cell. The hemolytic cleavage of H_2O_2 by transition metal yields the highly reactive hydroxyl radical (HO.). Metabolic pathways including NADH oxidase, Xanthine oxidase (XO), NADPH-cytochrome P450 reductase etc. are also contributing the in vivo production of superoxide radicals as a byproduct.

Super oxide radical (O_2.-) are generated by the process of autoxidation of Co-enzyme Q or ubisemiquinone passes through voltage dependent anion channel (VDAC) from mitochondrial membrane into cytosol.

Liver is the major site of endogenous source of H_2O_2 generation. Peroxisome in which the fatty acid oxidation results in H_2O_2 generation (M Inoue E.F. et.al. 2023). The enzymatic reactions in peroxisomes catalyzed by fatty acid acyl co-A oxidase, L-hydroxyl

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acid oxidase, D-amino acid oxidase, contribute free radicals' formation. Microsomes at hyperoxia site generates about 80% of H_2O_2. Arachidonic acid and prostaglandin metabolism also result in production of a free radicals Dröge.W.,2002).

Transition metals, that are the cofactors of different enzymatic reactions also produce free radicals. For example, Iron (Fe) as an important catalyst of oxidation–reduction reaction can easily gain or lose electron (Fe2+, Fe3+). Generally, Iron does not remain as a free entity but excess production of super oxide radical results in release of free iron. Different pathophysiological conditions are marked with the release of free iron such as β-thalassemia, hemochromatosis, hemolysis (free radical interaction with RBC membrane bursts RBCs that result in breakdown of hemoglobin to release free iron, which act as pro-oxidants and proved to be detrimental to cellular membrane through Fenton reaction leads to free radical formation. (F. Sibal Pala, 2007).

Endogenous sources of Nitrogen free radicals; Reactive Nitrogen Species (RNS) :

In Eukaryotes, the oxidation of terminal guanido nitrogen of L arginine results in formation of nitrogen free radicals (NO.) and H_2O_2.The reaction is catalyzed by a group of flavoprotein (hemoprotein) the enzyme Nitric Oxide Synthetase (NOS). This enzyme has different isoforms which are present in varying concentration, in different tissues viz, neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) etc. Intracellular Ca ions are the important cofactors for their action.

Different types of reactive Nitrogen Species (RNS) are generated by the activity of Nitrogen Oxidases such as nitroxyl anion (NO^-), peroxynitrite ($ONOO^-$). nitrosonium cation (NO^+). Various intermediate species like S-nitroso- glutathione, S-nitroso-cysteine are chemically active and proved to be a reason for alteration in biomolecular functions and thus affect physiological processes (Dröge, W.,2002).

Different cells of Innate Immunity like activated macrophages, neutrophils and other phagocytic cells also contributes in endogenous production of ROS and RNS. In response to various immune modulator, cytokines macrophages showed the elevated level of NOS. (Schreck R, and Beauerle D.A.,1991).

Exogenous Sources of ROS

Along with above internal /endogenous sources, variety of external sources are also responsible for ROS production. Air pollutants and water pollutants consumed by inhalation, ingestion of alcohol, industrial solvent, heavy metals as well as transition metals (As Cd, Pb, Hg, Fe,) are also contributing free radical formation in aerobic cells. (J. Martnett. L.,2000); and (Valko et al.,2005). Cooking smoke (smoke of oil, fats, smoked meat), cigarette smoke, are equally the reason for free radical formation.

Drugs like cyclosporine, gentamycin, tacrolimus, bleomycin etc. are also having role in free radical generation. Interaction with ionizing radiations promotes free radical formation by initiating chain reactions. Dugan L.L. and Choi D W 1999).

Interaction of ROS with Biomolecules

Damaging role of free radicals within the cell are explained by Denham Harman that free radicals are responsible for cellular degenerative processes. ROS has proved its role in stimulation of oncogene results in oncogenic phenotype and induction of malignancy in cell.

Interaction of free radicals with Nucleic acids, DNA and RNA, causes modification of bases and double or single strand break. All components of nucleic acids, bases, purines, pyrimidines as well as sugar are sensitive to hydroxyl free radical.

Hydroxyl radical (OH.) interact with hydrogen atom from sugar and methyl group of pyrimidine to generate allylic radical resulting in breaking of strand. Mitochondrial DNA is more susceptible as it is not protected by histone.

During oxidative stress, an oxidized DNA product is formed, that tautomerizes to induce mutation. Along with ROS, Reactive Nitrogen Species (RNS) like peroxynitrites and nitrogen oxides NO imparted in DNA damage. (G. C. Brown, and V.Borutaite.,2001). 8- hydroxy guanine (8-OH-G) is a product formed by the oxidation, which through tautomerization induces mutation. Nitrogen oxide plays important role in DNA damage.

Interaction of fatty acids (RH.) with hydroxyl free radical (OH.) in membrane lipids leads to lipid peroxidation. In this process poly unsaturated fatty acids (PUFA) generates fatty alkyl free radical (ROO.). These fatty alkyl free radicals are having high oxidizing potential, hence can generate hydroperoxide and alkyl radicals. This chain reaction continues till the free radical chain is terminated. Thus, the lipid peroxidation generates reactive, unstable, long lived toxic by-products and the interactions of these with cell membrane and other organelles is one of the reasons of cell dysfunction, which may proceed to cell death.

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The free radicals generated by either source is not balanced, mitigated, neutralized or removed from the cell may lead to serious consequences of this oxidative stress responsible for various pathophysiological conditions and diseases.

Table 1: Oxidative Stress and Human Diseases

Organ affected	Types of Diseases
Lungs	Asthma, Chronic Bronchitis
Kidney	Glomerulonephritis, Chronic renal failure
Heart	Arteriosclerosis, Hypertension, Ischemia Cardiomyopathy, Heart failure
Brain	Alzheimer's, Parkinson's, Memory loss, Depression, Stroke
Joint	Arthritis, Rheumatism
.Eyes	Cataract, Retinal diseases
Multi organs	Cancer, Aging, Diabetes, Inflammation, Infection

Role of Antioxidants

Antioxidants are the natural or synthetic chemical compounds that reduce oxidative stress of the biological cells and prevent organisms from the deleterious effects of free radicals. Free radicals are the unstable chemical entities appeared as a byproduct of metabolic reaction in respiring cells. Antioxidants are capable of slowing down as well as preventing the oxidation of cellular components by terminating chain reaction induced by free radicals' formation. Antioxidant by being oxidized itself removes free radical intermediates thus by inhibiting further oxidation reaction of biomolecules or cellular components. Thus, antioxidants are reducing agents like thiols, polyphenols etc. (Sies H., 1997).

Mechanism of Antioxidant action

Antioxidants combat the free radicals in the following ways (AdwasA.A.et al., 2019) .

1. By inhibiting the production of free radicals.
2. By delaying the production of free radical.
3. By scavenging free radicals.
4. By converting free radicals in less toxic form.
5. By delaying the formation of secondary radicals.
6. By interrupting the chain propagation of free radicals.
7. By boosting the (endogenous) internal antioxidant defense through synergistic effect.
8. By chelating metal ions.

Types of Antioxidants

According to their origin and the mode of action, the antioxidants are classified into two main groups viz. endogenous and exogenous antioxidants. Endogenous antioxidants are further categorized into enzymatic and nonenzymatic antioxidants, while exogenous antioxidants are the antioxidants from food and nutrition as a supplement.

Endogenous Antioxidants

A well-developed endogenous antioxidant system has been evolved to remove or neutralize the free radicals, which are formed as an unavoidable entity during normal cell metabolism. These endogenous antioxidants are classified into two broad categories viz, enzymatic antioxidants and non-enzymatic antioxidants.

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Table 2: Endogenous Sources of Antioxidants:

Source	Antioxidant	Role
Enzymatic Sources	Superoxide dismutase (SOD)	Dismutation of superoxide anion radical ($O2•^-$) into hydrogen peroxide (H_2O_2) by reduction
	Catalase (CAT)	The oxidant formed (H_2O_2) is transformed into water and oxygen (O_2) by catalase (CAT)
	Glutathione peroxidase (GPx)	Removes H_2O_2 by using it to oxidize, reduces glutathione (GSH) into oxidized glutathione (GSSG).
	Glutathione reductase (GRx)	Regenerates GSH from GSSG, with NADPH as a source of reducing power.
Non-Enzymatic Antioxidants	Lipoic acid, Glutathione, L-arginine, Coenzyme Q10, Melatonin, Uric acid, Bilirubin, Metal-chelating proteins, Transferrin	Detoxification of organic peroxides. Xenobiotics metabolism

Endogenous Enzymatic Antioxidants

The antioxidant enzyme system involved here interact directly and detoxify ROS. Black, A. T., J. P. Gray., 2008). These enzymes work in cooperative way to maintain the redox homeostasis of the cell (Rao, G. M. and A.V. Rao.2000).

The system includes following enzymes-

- Superoxide Dismutase (SOD)
- Catalase (CAT)
- Glutathione peroxidase (GPx)
- Glutathione reductase (GRx)

A] Superoxide Dismutase (SOD):

This enzyme system is a first line of defense against free radical. The free Superoxide radical ($O2•^-$) is a toxic and unavoidable product of oxidative stress in aerobic respiring cells. The enzyme catalyzes the reduction of superoxide anion radical ($O2•^-$) into hydrogen peroxide (H_2O_2) and molecular oxygen. The process is called as dismutation (Perry, J. J. and D. S. Shin.2010).

Categorization of SOD according to the spatial distribution of SOD enzyme within cell includes The copper -zinc SOD (Cu-SOD) present in cytoplasm, the manganese SOD (Mn-SOD) present in mitochondria and extra cellular SOD present in extracellular fluids are involved in the dismutation of superoxide radicals at different cell compartments (Suntre Z.E.,2002).

B] Catalase (CAT):

The oxidant formed (H_2O_2) is transformed into water and oxygen (O_2) by catalase (CAT). CAT is major antioxidant enzyme responsible for catalyzing the decomposition of H_2O_2 to water and oxygen (Lukasiewicz-Hussain 2008). (Packer L.,2001).

C] Glutathione peroxidase (GPx):

This enzyme is considered as a member of primary enzyme antioxidant system that removes H_2O_2 by using it to oxidize, reduced glutathione (GSH) into oxidized glutathione (GSSG). GPX4 is the only known enzyme that efficiently reduces lipid-hydro peroxides within biological membranes.

D] Glutathione reductase (GRx):

This enzyme is an important enzyme system needed to maintain the intracellular level GSH (reduced form). This is an enzyme classified under the flavoprotein disulfide oxidoreductase family. It is a homodimer enzyme having four domains in each subunit. These subunits are FAD-binding domain towards its N terminus, an NADPH domain, a Central Domain and an interface domain. An Enzyme is most active in its dimeric form only (Bashir, A., R. N. Perham1995).

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Endogenous non-Enzymatic Antioxidants

A] Glutathione (GSH):

Most important endogenous antioxidants involved in detoxification and xenobiotic metabolism (Valko M L. D., 2007) Glutathione is the nonenzymatic endogenous metabolic antioxidant synthesized with in the cell by its constituent amino acids. It is a cysteine containing peptide. The thiol group of cysteine is a reducing agent. GSH itself get oxidized to GSSG. It serves as an antioxidant and react with free radicals as well as organic peroxides in the process of amino acid transport. Glutathione can oxidize and reduced reversibly. Enzyme Glutathione reductase maintains glutathione in its reduced form. Relatively high concentration of glutathione helps cell in maintaining its redox state (Meister A, and Anderson M.,1983).

B] Melatonin:

It is an indoleamine produced within body is lipid soluble antioxidant. Melatonin once get oxidized does not reduce back. Upon oxidation it converted to more stable end products by interacting with free radicals, hence considered as terminal or suicidal antioxidant. Reitor R.Jet al.,1997), and (Tan DX, et al.,2000).

Other endogenous Metabolic antioxidants are the byproducts of metabolism inside body, such as coenzyme Q10, lipoid acid, uric acid, L-arginine, bilirubin, metal-chelating proteins, transferrin, etc. (Halliwell B, and Gutteridge J.M.1995) & (Jacob R.A.1995).

Exogenous Nutritive Antioxidants

These are the compounds not synthesized within body but provided through food and supplements. Table-3 explains different type of exogenous antioxidants, their sources and its respective role as antioxidants. (Miller A.L.1996),(Willcox J.K.,2004), (Li. Y, and Schellhorn H.E.,2007).

Table 3: Exogenous molecules, Sources and their role as antioxidants

Molecule	Source	Antioxidant mechanism
Vitamin E (α-tocopherol)	Fruits, whole grains, vegetable oils, wheat germ oil, cereals, nuts, eggs, poultry, meat etc.	Inhibits lipid peroxidation
Vitamin C (Ascorbic acid)	Citrus fruits, green leafy vegetables, tomatoes etc.	Hydroxyl radical, superoxide radical Scavenging Quenching of other free radicals.
Beta-carotene	Fruits, grains, oil and vegetables	Quenching of singlet oxygen
Lycopene	Tomatoes	Neutralization of singlet oxygen
Flavonoids (Polyphenolic compounds)	Green tea, grapes (red wine), apple, cocoa (chocolate), ginkgo biloba, soybean, curcuma, berries, onion, broccoli, etc.	Scavenging of free radicals
Omega-3 and omega-6 fatty acids	Fish fats, krill, algae, walnut, nut oils and flaxseed etc.	Inhibits lipid peroxidation

Synthetic Antioxidants

Synthetic antioxidants are generally considered as a drug. These are the artificial chemical phenolic compounds. These are added in processed foods to increase its useful life by preventing oxidation. They are cost effective, active in low concentration and nontoxic. These compounds are stable and easily permeable through cell membrane. Some of them are characterized by high melting point, solubility in fats and alcohols (Andre C. et al.2019). These artificial synthetic compounds are used as an antioxidant in food industry, cosmetics, vegetable oils, confectionary products, bakery products etc. (Ndiamaka H Okorie,2019).

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Table 4: Synthetic Antioxidants

Name of artificial / Synthetic antioxidant	Chemical structure
Butylated hydroxy toluene (BHT)	2,6-di-tert butyl-4-methylphenol
Butylated hydroxy anisole (BHA)	mixture of 2- tert butyl-4 methoxyphenol and 3-tert-butyl 4-methoxyphenol
(TBHQ)	Tertiary-butylhydroquinone
(NDGA) Nordihydro guaretic acid	2,3-dimetyl-1,4-bis (3,4 dihydroxy phenyl) butane
(PG)	Propyl gallate
OG-DG	Octyl gallate and dodecyl gallate
EDTA	Ethylenediaminetetraacetic acid

Synthetic antioxidants and their effects:

Synthetic antioxidants are generally used in food and cosmetic industry to increase the durability of the product. Many of these proved to be harmful when used in excess. BHA has proved to induce stomach tumors in rodents and found to interfere with endocrine hormones by interacting with receptors & affects reproductive health of the animals, (Halliwell B, and Gutteridge J.M.1995) While Liver and Lung Tumor inducing property of BHT has been observed in the studies in laboratory animals. High doses of BHT causes Lung Liver and Thyroid toxicity. While TBQA has been proved its role in DNA damage (Miller A.L.1996). These chemicals have low biodegradability and hence persists for longer time in environment possibly travel through food chain in ecosystem. Some are tagged with allergic properties causes respiratory irritation, organ toxicity etc.

CONCLUSION

To overcome the disadvantages of the synthetic antioxidants the natural phytochemicals are promising alternative. More medicinal plants, algae are the richest sources of bioactive molecules viz, carotenoids, flavonoids polyphenols and many glycosylated compounds having activity to scavenge free radicals with different mechanisms. Natural compounds proved to have the property of upregulation of Endogenous antioxidant systems. Exploration of various natural resources are explored by isolating, characterizing active biological ingredients are possible with the advances in biomedical and biotechnological techniques. Thus, opening the new safer avenues for minimum side effects & effective therapeutics.

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