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IMPACT OF OXIDATIVE STRESS IN CHRONIC DISEASES, THEIR BIOMARKERS, AND THE ROLE OF ANTIOXIDANTS

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ABSTRACT

An imbalance of free radicals and antioxidants in the body leads to a condition called Oxidative Stress. Free radicals produced during the condition of oxidative stress trigger a reaction that can destroy the cell membrane, block the action of major enzymes, and prevent cellular processes necessary for proper functioning. Researchers believe that free radicals are also involved in some cellular signaling processes, known as redox signaling. Free radicals are of many types like $-O_2^-$, -OH, $-ROO^-$, -NO, etc. Various diseased conditions like Atherosclerosis, Cancer, Alzheimer's, Asthma, Myocardial Infarction, and Arrhythmia can occur due to increased accumulation of free radicals. These diseased conditions can be identified by laboratory testing of their increased level of biomarkers in the body. Oxidative stress also plays an important role in the aging of our bodies. To protect from oxidative stressful conditions, Anti-oxidants are produced in our body which stabilize unstable free radicals. Examples of Anti-oxidants are Flavonols, Vit C, Vit E, Superoxide Dismutase, Glutathione peroxidase, etc. Antioxidant phytochemicals exist widely in fruits, vegetables, cereal grains, edible macrofungi, microalgae, and medicinal plants. The promising theoretical and research possibilities of antioxidant prevention and protection against various chronic illnesses are undergoing at present. Nanotechnology and other advanced technological drug delivery of antioxidants seem to have promising outcomes leading to increased therapeutic index and higher drug concentration in tumor tissues.

KEYWORDS: Oxidative Stress, Biomarkers, Antioxidants.

INTRODUCTION

Oxidative stress is an imbalance of free radicals and antioxidants in the body. The theory of oxidative stress as a pathophysiological mechanism can be explained by the concept referred to as the 'oxygen paradox', stating that while oxygen is essential for aerobic life, excessive amounts of metabolic by-products from oxidative stress are toxic.[1] The body's cells produce free radicals during normal metabolic processes. However, cells also produce antioxidants that neutralize these free radicals.

Many natural biological processes in our bodies, such as breathing, digesting food, metabolizing alcohol and drugs, and turning fats into energy, produce harmful compounds called free radicals. They can trigger a reaction that can destroy the cell membrane, block the action of major enzymes, prevent cellular processes necessary for the proper functioning of the body, prevent normal cell division, destroy deoxyribonucleic acid (DNA), and block energy generation.[2] It is in the last two decades that the role of free radicals in the development of diseases was discovered and, thus, the beneficial effects of antioxidants have been widely studied.[3] Multiple tiers of defense exist to protect against these free radicals, including the restriction of their production through the maintenance of a high oxygen gradient between the ambient and cellular environments, their removal by non-enzymatic and enzymatic antioxidants, and the reparation of oxidative damages by structural repair and replacement mechanisms.[4] Free radicals play an essential role in several biological processes. Many of these are necessary for life, such as the intracellular destruction of bacteria by phagocytes, especially by granulocytes and macrophages. Researchers believe that free radicals are also involved in some cellular signaling processes, known as redox signaling. At low to moderate amounts, Reactive Oxygen Species(ROS) are beneficial both in regulating processes involving the maintenance of homeostasis as well as a wide variety of cellular functions.[5]

Excessive ROS production determines the structural modification of cellular proteins and the alteration of their functions, leading to cellular dysfunction and disruption of vital cellular processes. High ROS levels cause lipid, protein, and DNA damage. In particular, ROS can break the lipid membrane and increase

membrane fluidity and permeability. Protein damage involves site-specific amino acid modification, peptide chain fragmentation, crosslinked reaction product aggregation, electric charge alteration, enzymatic inactivation, and proteolysis susceptibility. Finally, ROS can damage DNA through oxidizing deoxyribose, breaking strands, removing nucleotides, modifying bases, and crosslinking DNA-protein.[6]

Free radicals can lead to cell damage and programmed cell death, contributing to diseases like Cancer, Diabetes, Myocardial Infarction, Atherosclerosis, Arrhythmia, Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis, Bipolar disorder, Major Depressive Disorder, Anxiety Disorder, Schizophrenia, and Ageing.

The harmful effects of oxidative stress-induced due by free radicals are negated by achieving a balance between Oxidants and Anti-Oxidants. Therefore, by adequate Anti-Oxidants consumption, we can equalize the deleterious effects of oxidative stress. In pathological or stress conditions, ROS overwhelms antioxidant systems leading to an imbalance, causing oxidative stress and irreversible changes in cell compounds, disrupting normal cellular-signaling mechanisms.[7]

If the intracellular mechanisms of repair of oxidative defects are insufficient or disturbed by the oxidative factors present, there are definitive consequences in the expression of these genes, altering purine or pyrimidine in the structure of cellular DNA, resulting in cancer.[8] In the long term, there is permanent activation of the autoimmune response and the accumulation of local proinflammatory factors, like TNF-alpha, proteases, and kinases, they accelerate tissue growth with the appearance of new modified cells that propagate the initial genetic defects with chaotic and extensive multiplication and also produces structural changes of cell membranes with decreased adhesion, resulting in migration of tumor cells in neighboring tissues or distant blood and lymph.[9]

The expression of self-antigenic types of proteins can be changed by free radicals, resulting in increased immune response which forms the basis for Auto-Immune Diseases. Some plant species have Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH Oxidase) in their pollen grains which induces airway inflammation due to infiltration by TNF-α, Interleukin, Cytokines. Intracellular Pro-oxidant factors like Interferon-γ, Cluster of Differentiation Antigen 14(CD 14), and Tumour Necrosis Factor α, alter the immune response in Auto-Immune diseases.

The pathogenesis of Psychiatric disorders: The brain is considered particularly vulnerable to oxidative damage for several reasons. These include its comparatively high oxygen utilization and hence generation of free radical by-products, its modest antioxidant defenses, its lipid-rich constitution that provides ready substrates for oxidation, and the presence of redox-catalytic metals such as iron and copper.[10] Self-perpetuating damage from oxidative cellular injury or necrosis, via the neurotoxic effects of released excitatory amines (mainly glutamate) and iron, and the activated inflammatory response can also occur. This intrinsic oxidative vulnerability of the brain, together with the growing evidence for neurodegenerative changes associated with many psychiatric syndromes, suggests that oxidative damage may be a plausible pathology for many psychiatric diseases.

In cellular aging, two theories on the mechanisms of cellular aging are currently accepted: the mitochondrial theory and the free radical theory. They support the hypothesis that mitochondria are affected by an increased level of intracellular free radicals, which leads to the alteration of their function and a decreased cellular regenerative capacity. At the same time, the progressive accumulation of intracellular oxidizing factors exceeds the antioxidant capacity. Subsequently, regardless of the mechanism involved, in mitochondrial DNA damage, the cellular stress response will produce an overexpression of proinflammatory genes increasing the levels of prooxidant factors.[11]

Allergic diseases such as Asthma, Atopic Dermatitis, food allergies, and Allergic Rhinitis can be stimulated by oxidative stress. At present, an unhealthy diet, lack of exercise, chemicals from various types of pesticides, and pollution from the air, water, and environment causes oxidative stress which results in many chronic diseases in human as suggested by several experimental and human studies. So, in those patients, supplementation with anti-oxidants can be an appropriate step of treatment and also for promoting healthy aging.

Types of free radicals

Free radical origins(ROS) can be broadly categorized into two types:

1. Exogenous
2. Endogenous

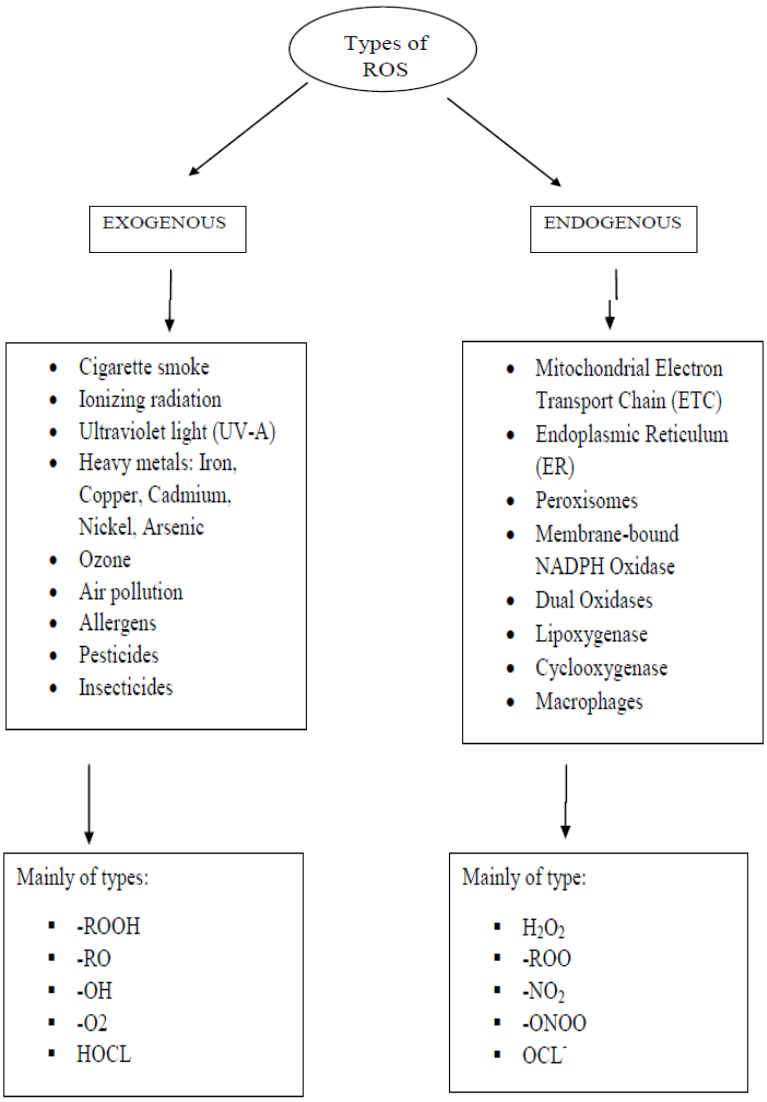

Fig. 1

Exogenous ROS:

They contribute to the increase of ROS production in cells. Ionizing radiation acts by converting hydroxyl radicals, and super-oxides into hydroperoxides and hydrogen peroxide respectively. Subsequently, the peroxides react with Fe and Cu at the cellular level through redox reactions with secondary oxidative activity. Several studies have shown that the exposure of fibroblasts to alpha particles has led to an intracellular increase of oxygen and an accelerated production of peroxide at this level.[12]

Ultraviolet radiation (UVA) by stimulating riboflavin, porphyrins, and NADPH-oxidase, produces 8-oxo-guanine, and decreases glutathione (GSH) level, and results in oxidative stress.[13]

Heavy metals like Iron, Copper, Cadmium, Nickel, Arsenic and Lead can induce free radicals by Fenton or Haber-Weiss type reactions. Lead triggers lipid peroxidation and increases glutathione peroxidase concentration in brain tissue. Arsenic induces the production of peroxides, super-oxides, and nitric oxide and inhibits antioxidant enzymes. The free radicals generated from these reactions can affect DNA, with substitutions of some DNA bases such as guanine with cytosine, guanine with thymine, and cytosine with thymine.[14]

Endogenous ROS:

Mitochondrial electron transport chain(ETC), endoplasmic reticulum (ER), peroxisomes, membrane-bound NADPH oxidase (NOX) isoforms 1–5, dual oxidases (Duox) 1 and 2 complexes, and nitric oxide synthases isoforms 1–5 (NOS1–3) are main sites for cellular redox-reacting species generation. The complexes I and III of mitochondrial ETC produce superoxide anion[15]. Other forms of ROS H_2O_2 are from microsomes and peroxisomes. ROS can also be generated from neutrophils and macrophages by oxygen-dependent mechanisms to fight invading microorganisms. ROS generation within mitochondria (oxidative metabolism) is closely associated with ATP

synthesis (oxidative phosphorylation) and is the main source of energy.[16]

Superoxide radicals are produced by NADPH oxidases and, to a minor extent, as by-products of a wide number of metabolic enzymes such as cyclooxygenase (COX) 1/2, lipoxygenase, Cytochrome P450.[17] Super-oxides have anionic properties, so they can diffuse through lipid membranes and reduces intracellularly to form hydroxyl radical (-OH) and hydrogen peroxide (H_2O_2). Peroxyl and Alkoxyl radicals, Hypochlorite ions can also be formed.

Other internally generated sources of ROS are present in humans, including:

1) Oxidative burst from phagocytes (white blood cells) during bacteria and virus killing and foreign proteins denaturation;
2) Xanthine oxidoreductase (XOR) metabolism;
3) Arachidonate pathways;
4) Peroxisomes metabolism;
5) Detoxification of toxic substances (i.e., vigorous exercise, chronic inflammation, and infection)

Nitric oxide is produced in hypoxic conditions in a respiratory chain reaction, and RNS may trigger reactive species production, such as reactive aldehydes, malondialdehyde (MDA), and 4-hydroxy-2-non-enal.

Stimulated ROS production was first described in phagocytic cells, including neutrophils and macrophages, through NADPH oxidase activation. This was named "the respiratory burst" due to transient oxygen consumption.[18]

Increased level of oxidative stress biomarker in various chronic illness[20,22-26]

Table 1

S. no.	Disease	Oxidative Biomarkers
A	**Cardiovascular system**	
1.	Atherosclerosis	↑Acrolein, ↑ADMA, ↑ Cysteine/cystine, ↑NO_2-Tyr, Iso-LG, ↑ F_2 -IsoP, ↑MDA, ↑HNE, ↑ OxLDL, ↑AGE, ↑3-CL-Tyr
2.	Hypertension	↑ADMA, ↑ Iso-LG, ↑F_2 -IsoP
3.	Myocardial Infarction	↑8-iso-prostaglandin F(2alpha)[20]
4.	Arrhythmia	↑ cysteine, ↑ NOX2 (as known as gp91 phox NADPH oxidase), ↑ NOX4, ↑ small G-protein Rac1 (Rac1 GTPase), ↑ ICAM-1, ↑ ox-LDL, ↑ NF-κB p50, ↑Oxidized CaMKII (ox-CaMKII)[21]
B	**Neurodegenerative disease**	
1.	Alzheimer's disease	↑ADMA, ↓ GSH/GSSG, ↑ NO_2-Tyrosine, ↑F_2-IsoP, ↑Iso-LG, ↑ MDA, ↑ HNE, ↑ AGE, ↑ Nrf-2
2.	Multiple sclerosis	↑Pr-S-SG, GSH/GSSG, ↑ NO_2-Tyrosine, ↑ F_2 -IsoP, ↑MDA, ↑ AGE, ↑ PrCarb
3.	Huntington's disease	↑NO_2-Tyr, ↑F_2 -IsoP
4.	Parkinson's disease	↑Free iron (fe^{2+}) , ↓ GSH/GSSG, ↑ HNE, ↑ PrCarb, ↑ Nrf-2
5.	Amyotrophic Lateral Sclerosis	↓GSH/GSSG, ↑NO_2-Tyrosine, ↑MDA, ↑ PrCarb, ↑ Nrf-2
6.	Depression	↑Thiobarbituric acid reactive substances (TBARS), ↑protein carbonyl content (PCC), ↑free 8-isoprostane, ↑glutathione peroxidase (GPx) activity, ↓ glutathione reductase (GR) activity, glutathione S-transferase (GST)
7.	Schizophrenia	↑Iso-LG, ↑xanthine oxidase
8.	Bipolar disorder	↑Malondialdehyde (MDA), ↑ advanced oxidation protein products (AOPP), ↑ protein carbonyls (PC) and ↑homocysteine (Hcys) concentrations[22] and↑ glutathione peroxidase (GSH-Px)[23]
9.	Anxiety	↑F_2-Isoprostanes (F_2 -IsoP)[24]
C	**Multi-Organs**	
1.	Diabetes mellitus	↑F_2 -IsoP, ↑ Xanthine oxidase
2.	Aging	↑Protein carbonyl (PC), ↑ nitrotyrosine (NT), ↑ trans-4-hydroxy2-nonenal (4-HNE), ↑ malondialdehyde (MDA), ↑ isoprostanes (F2 -IsoPs),[25] ↑hydroimidazolones, ↑ N∈-carboxymethyl-lysine, ↑pentosidine, ↑ glucosepane[26]
3.	Metabolic syndrome	↑MDA, elevated XO activity, ↑ elevated TG and reduced concentrations of HDL-C, ↑ plasma thiobarbituric acid reactive substances (TBARS), ↑protein carbonylation products, and ↑NOx, ↑ advanced oxidation protein products (AOPP)

D	**Cancer**	↑8oxodG/8oxoGuo, ↑ Pr-S-SG, ↓ GSH/GSSG, ↑ NO_2-Tyrosine, ↑ MDA, ↑ PrCarb, ↑ Nrf-2
E	**Rheumatoid arthritis**	↓GSH/GSSG, ↑NO_2-Tyrosine, ↑ F_2 -IsoP, ↑ PrCarb, ↑3-CL-Tyr, ↑ Xanthine oxidase
F	**Chronic renal failure**	↑Cysteine/cystine, ↑ Iso-LG, ↑PrCarb, ↑ 3-CL-Tyr
G	**Cataract**	↑4-hydroxynonenal (HNE), ↑ N-formylkynurenine (Kyn), ↑ 3-hydroxykynurenine (3HK), ↑ calpains (Ca^{2+} dependent cytosolic cysteine proteases), UV rays, lower level of reduced glutathione (GSH), ↑ oxidized glutathione(GSSG), or glutathione disulfide (GSSG), ↑ total antioxidant status (TAS) and ↑interleukin-6 (IL-6)[27]
H	**Asthma**	↑NO_2-Tyrosine, ↑F_2 -IsoP, ↑HNE, ↑PrCarb.
I	**Preeclampsia**	↑MDA, ↓ NOLevels, ↑TBARS, ↑Superoxide anion, ↑H2O2, ↑peroxynitrite, increased catalase and↑ GPx activity, elevated levels of plasma hydrogen peroxide and↑ protein carbonyl with serum uric acid levels[28]

Abbreviation: *asymmetric dimethylarginine (ADMA), reduced glutathione/oxidized glutathione ratio (GSH/GSSG),* F2*-isoprostane(F2-IsoP, malondialdehyde (MDA), protein carbonyl (PC), nitrotyrosine (NT), trans-4-hydroxy2-nonenal (4-HNE), N-formylkynurenine (Kyn), plasma thiobarbituric acid reactive substances (TBARS), advanced oxidation protein products (AOPP), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), oxide (8-oxo-7,8-dihydro-2'-deoxyguanosine), 8-oxoGua (8-oxo-7,8-dihydroguanine), protein carbonil content (PCC), 3-chloro-L-tyrosine (3-CL-Tyr), nuclear factor erythroid 2–related factor 2 (Nrf2), homocysteine (Hcys), glycation end-products (*AGE)

Effect of lifestyle on oxidative stress response:

Various lifestyle factors like:-

- **Overtrained/untrained conditions of the body** contribute to oxidative stress. Skeletal muscle fibers continuously generate reactive oxygen species at a low level, which increases during muscle contraction. They exert multiple direct and indirect effects on muscle activity (contractility, excitability, metabolism, and calcium homeostasis) and are involved in skeletal muscle fatigue during strenuous exercise. Instead, moderate exercise and low-intensity training improve endogenous antioxidant status. Physical exertion produces a hyperregulation of the nuclear factor kappa B and mitogen-activated protein kinase that activates several enzymes and proteins with an important role in maintaining oxidative/antioxidant intracellular homeostasis[19]. Mitochondrial autophagy called Mitophagy helps to adapt the heart to oxidative conditions, stimulated by physical exercise.
- **Alcohol consumption** → decreases GSH → Fatty liver → Alcoholic liver disease
- **Smoking** → increase in quinone/hydroquinone complex (Q/QH2) → interstitial lung disease → Cancer

Oxidative Stress and Its influence on various systems

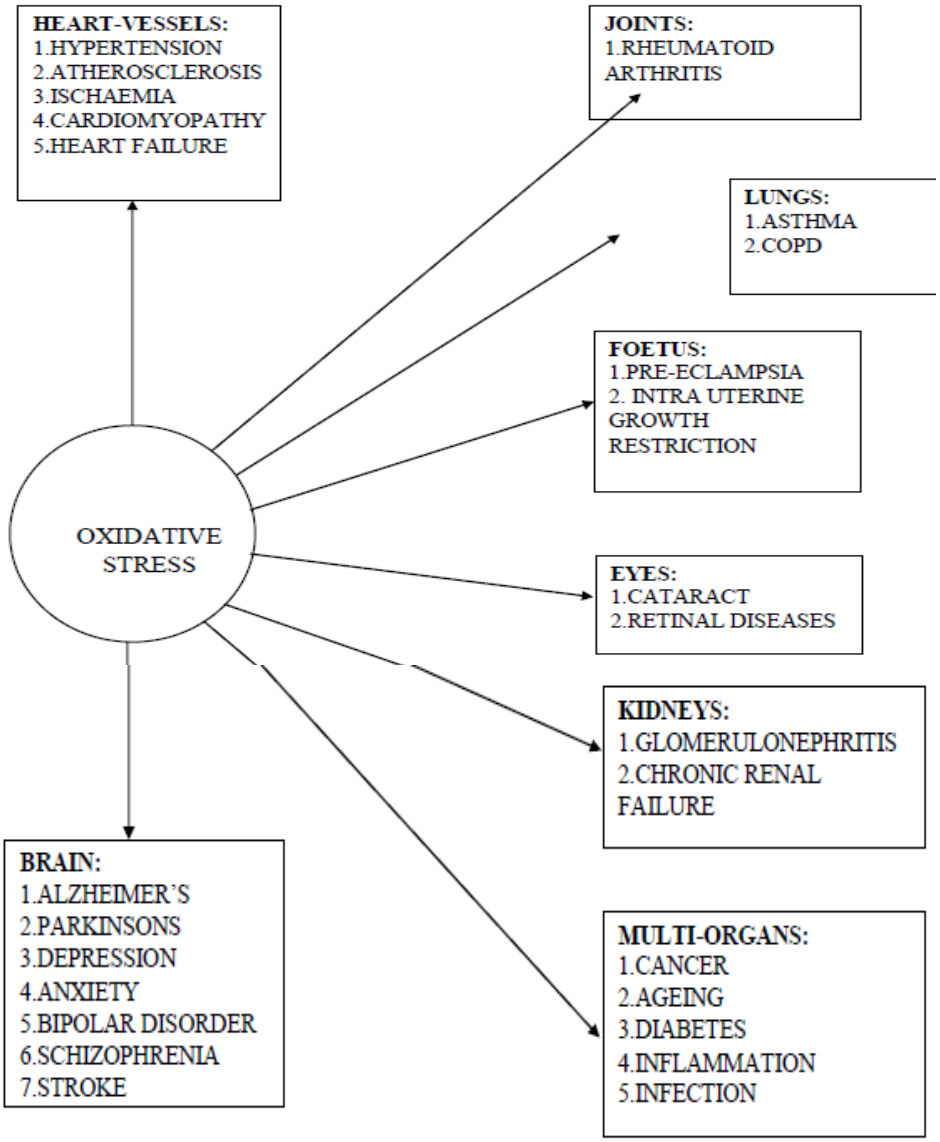

Fig. 2

Oxidative Stress and Cardiovascular diseases

Hypercholesterolemia and Hypertension are two main factors responsible for increasing free ROS. An increased number of ROS leads to loss of cell viability and is involved in the development of CVD like Myocardial ischemia, Atherosclerosis, Arrhythmia, and Heart Failure. Increased ROS levels modulate transcription factor activity, like NF-kB, activator protein-1 (AP-1), and the peroxisome proliferators-activated receptor (PPAR). Phospholipids oxidized through receptor-independent/dependent pathways can induce the expression of endothelial cells, resulting in increased pro-inflammatory gene activity, cytotoxic effects, and cellular growth factors, these provoke platelet aggregation and favour thrombogenesis.

A. Atherosclerotic plaque

In Atherosclerotic plaque, increased metalloproteinase triggered by oxidative stress can rupture plaques and cause thrombosis. Oxidized LDL is the main reason for Atherosclerosis, Increase in ROS, leads to a decrease in NO bioavailability resulting in decreased endothelial-dependent relaxation. ROS in myocytes trigger cardiac injury oxidizing essential proteins and reducing NO bioactivity.[29]

B. Myocardial infarction

In Myocardial Infarction(MI), ETC is imbalanced, so there is depletion of ATP, mitochondrial depolarization, and intracellular Ca^{2+} overload leading to apoptosis, also mitochondrial DNA is damaged due to oxidative stress on mitochondria leading to CVD. In MI, hypoxia, and reoxygenation increase free radical concentration in cardiac tissues.[30]

C. Heart failure

Using both direct oxidative damage via reoxygenation and indirect damage via localized inflammation ROS

plays an important role in Heart Failure by prolonged endoplasmic reticulum stress and oxidative stress derived from mitochondria. F2-isoprostanes might not only be just biomarkers of myocardial infarction but may also contribute to its pathogenesis and its complications due to thrombotic etiology.

D. Arrhythmia

In Arrhythmia**,** as a result of oxidative stress, there is abnormal release and uptake of Ca^{2+}. Disturbances in mitochondria or endoplasmic reticulum results in activation of signaling pathways which alters the function or expression of cardiac ion channels and promotes arrythmogenesis.[31] Increased plasma levels of ROS result in loss of myocytes/myofibrils, ballooning of mitochondria, and distension of sarcoplasmic reticulum.

Oxidative Stress and Cancers

Cancer develops in humans via a complex process involving both exogenous and endogenous stimuli.[32] Oxidative stress leads to DNA damage (a common form of damage is the formation of hydrolyzed bases of DNA). Activation of proto-oncogenes and chromosomal defects by free radicals are factors for cancer initiation and promotion. An excessive amount of free radicals can lead to cell damage and apoptosis, and free radicals affecting DNA can lead to mutation. ROS overproduction has an impact on cancer cell proliferation and metastatic potential, and it is associated with invasiveness and poor prognosis. ROS contributes to cancer cell migration through various mechanisms:

i. Matrix degradation,
ii. Cell-cell contact,
iii. Cytoskeleton remodeling, regulation of gene expression,
iv. Invadopodia formation

ROS derived from mitochondria have an impact on the initial extracellular matrix, NOX-derived ROS are involved in invadopodia formation, and cytosolic ROS play important role in cytoskeleton remodelling[33]. The effect of cancer depends on the grade of disease progression and also the organ involved. Eg: Skin cancer and UV-A: UV-A has the potential to generate oxidative stress in cells, so antioxidants in various creams strongly negate the biological effects of UV-A. Other than carcinogenesis, repeated exposure to UV rays can also lead to DNA damage→premature wrinkles→photo aging of the skin.

Chain of events in cancer:

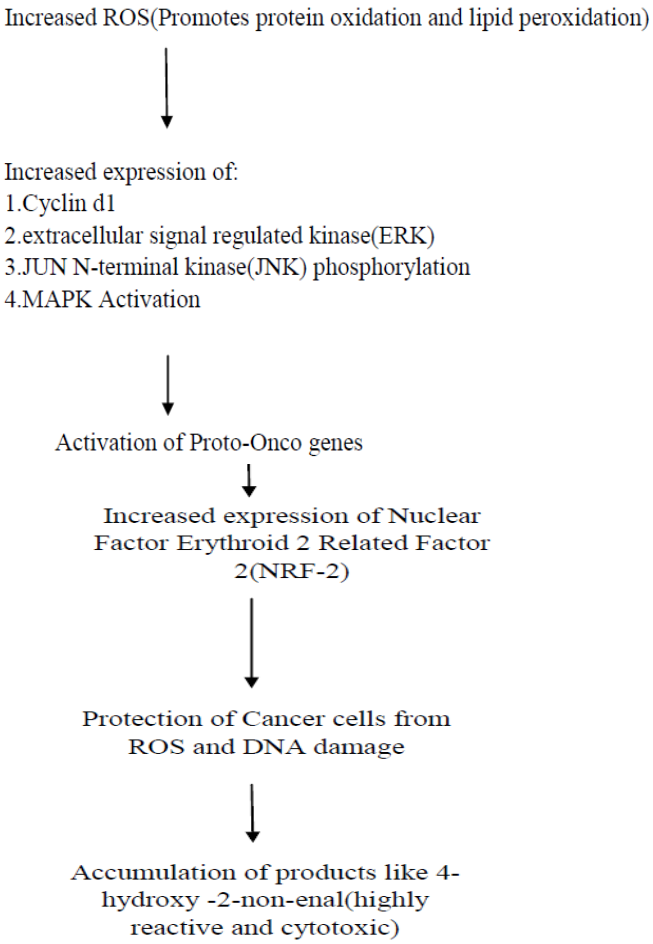

Fig. 3

Oxidative Stress and Rheumatoid arthritis[34]
In Rheumatoid Arthritis, there is infiltration of macrophages and activated T-cells resulting in Chronic Inflammation, and generation of ROS, and RNS in case of Rheumatoid arthritis which is evident in increased levels of isoprostanes and prostaglandins in serum and synovial fluid of patients compared to normal people.

Oxidative Stress and Pulmonary diseases[34]
As a result of oxidative stress→ Activation of different kinases and redox transcription factors such as NF-kappa B and AP-1 → there is a systemic and local chronic inflammation that results in narrowing and remodeling of airways ultimately resulting in conditions like Asthma and COPD.

Oxidative Stress and Its effect on foetus[34]
Oxidative stress results in the generation of free radicals like lipid peroxidation products F2-isoprostanes, and MDA which can result in pre-eclamptic pregnancy and intrauterine growth retardation. Major enzymatic sources of superoxide(helps in the generation of ROS) NADPH oxidase 1 and 5 isoforms are also noted in pre-eclampsia.

Oxidative Stress and Ocular diseases[34]
Under the action of free radicals produced due to oxidative stress, the crystalline proteins in the lens can cross-link and aggregate, leading to the formation of biomarkers like 4-hydroxynonenal, N-formylkynurenine, and calpains in **Cataracts**. Lipid peroxidation occurring due to long-term radiation exposure can inhibit mitosis in choroids and retinal pigment epithelium leading to **Macular Degeneration**.

Oxidative Stress and Renal diseases[34]
Oxidative stress can lead to lipid peroxidation which can lead to nephrotoxic conditions like Chronic kidney failure, Glomerulonephritis. Heavy metals (Cd, Hg, Pb, As) and transition metals (Fe, Cu, Co, Cr)-induced different forms of nephropathy and carcinogenicity are strong free radical inducers in the body. Certain drugs such as cyclosporine, tacrolimus (FK506), gentamycin, bleomycin, and vinblastine are activators of lipid peroxidation and thus can be nephrotoxic, so better avoided in chronic kidney diseases.

Oxidative Stress and Its role in Diabetes and Metabolic syndrome
The signaling mechanism between insulin receptors and the glucose transporter system is inactivated by ROS leading to Insulin Resistance.[35] Hyperglycaemia, which occurs as a consequence of diabetes induces the generation of superoxide ions at mitochondria leading to a stage of oxidative stress. Production of Superoxide ions also leads to inhibiting the function of the mitochondria leading to decreased ATP synthesis.

Glucose and Free Fatty Acids (produced from Glucose metabolization) can initiate free radical formation with help of ETC in mitochondria or NADPH oxidase in muscles, and adipocytes. Diabetes by generating ROS impairs micro/macrovascular function leading to conditions like diabetic hypertension, coronary atherosclerotic disease, diabetic nephropathy, and diabetic retinopathy.[36]

Metabolic Syndrome has several risk factors like Insulin resistance, abdominal obesity, atherogenic dyslipidemia, high blood pressure, and hypercoagulability. Oxidative stress results due to a combination of two or more factors leading to cellular function dysregulation.

Oxidative Stress and Its role in neurodegenerative diseases
Neurodegenerative conditions like Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral Sclerosis are the most common conditions. With increasing age, mitochondrial DNA accumulates, the function of ETC decreases, and there is dysregulation of cytosolic calcium.

A. Alzheimer's disease
Oxidative stress leads to the formation of free radicals which form mutant proteins that fail to bind properly to metal ions, by reacting in counter mechanism neurons produce an increased quantity of anti-oxidants including modified forms of amyloid-beta(in case of Alzheimer's) which then act as pro-oxidant amplifies oxidative disasters.[37]

B. Familial amyotrophic lateral sclerosis
Mutation of Super-oxide Dismutase 1(SOD1) protein has been linked to Familial Amyotrophic Lateral Sclerosis. The mutated form of SOD1 fixes a much smaller amount of metal resulting in the formation of excess peroxynitrite(-$ONOO^-$) causing motor disorder.

C. Parkinson's disease
In the case of Parkinson's, Monoamine-oxidase is the source of ROS, which targets the mitochondrial permeability transition pore(MPTP), Poly(ADP-ribose) Polymerase(PARP), and mitochondrial DNA.[38] Other sources of ROS are NADPH Oxidase present in Astrocytes, Microglia, and Neurons. Protein misfolding and aggregation, abnormal Signal Kinase pathway, Neuronal Calcium Dysregulation, and Impaired Synaptic Transmission can be effects of ROS induces damage. Mis aggregated proteins can don't have the ability to inhibit Proteasomes thus resulting in stimulation for more ROS formation.

Oxidative stress mechanisms have been implicated in the pathogenesis of psychiatric disorders as well, as the brain is considered particularly vulnerable to oxidative damage. Reasons being high oxygen utilization and hence generation of free radical by-products, its modest antioxidant defenses, its lipid-rich constitution that provides ready substrates for oxidation, the reducing potential of certain neurotransmitters, and the presence of redox-catalytic metals such as iron and copper.

D. Schizophrenia

The evidence behind oxidative stress mechanisms in Schizophrenia are studies involving blood assays of intrinsic antioxidants that have collectively demonstrated significantly altered antioxidant activities, Deficiency of glutathione, the major intracellular antioxidant. The antioxidants uric acid, albumin, and bilirubin, and the plasma total antioxidant status (TAS) have also been reported to be lower in patients with schizophrenia.[39]

E. Bipolar disorder

A single-nucleotide polymorphism of the TRPM2 gene, which encodes for a calcium channel receptor, has been strongly associated with Bipolar Disorder and is understood to cause cellular calcium dysregulation in response to oxidative stress, Innate dysregulation of the apoptosis and oxidative processes has been suggested by a recent study, in which the hippocampal expression of genes encoding DNA repair and antioxidant enzymes were found to be down-regulated in bipolar disorder, while many apoptosis genes were up-regulated.[40]

F. Depression

Oxidative Stress leading to enhanced oxidation of Apolipoprotein B correlates with the severity of major Depression.[41] As oxidation of lipoproteins and low paraoxonase activity has been implicated in atherogenesis and coronary artery disease, these results may be relevant in understanding the link between major depression and cardiovascular disease.

G. Anxiety

Anxiety was thought earlier to be associated with increased production of -ONOO$^-$. The report of elevated lipid peroxidation and anti-oxidant changes has been found in Obsessive-Compulsive Disorders,[42] Panic Disorders,[43] and Social Phobia,[44] but not with Post-Traumatic Stress Disorder.[45]

Oxidative Stress and Its role in ageing

The basic principle for most theories of aging includes oxidative processes. The major systems involved in excess production of oxidative stress are Mitochondria and NOX. In process of aging, there is an aggregation of high molecular weight proteins in cells and the central point of protein degradation is Proteasomes, they recognize only unfolded proteins as degradation targets.[46]

The proteasomes become dysfunctional during aging. Therefore While Proteasomal Dysfunction correlates with aging, activating proteasomes increases longevity as unfolded proteins which are formed mainly as products of oxidative stress are removed efficiently, thereby reducing the effects of oxidative stress.[47]

Antioxidants

A substance that protects cells from the damage caused by free radicals which are unstable molecules made by the process of oxidation during metabolism. Eg:- vitamin E, vitamin C, carotenoids, selenium, glutathione, L-arginine, and Coenzyme Q10.

Types of antioxidants:- enzymatic and non-enzymatic antioxidants.

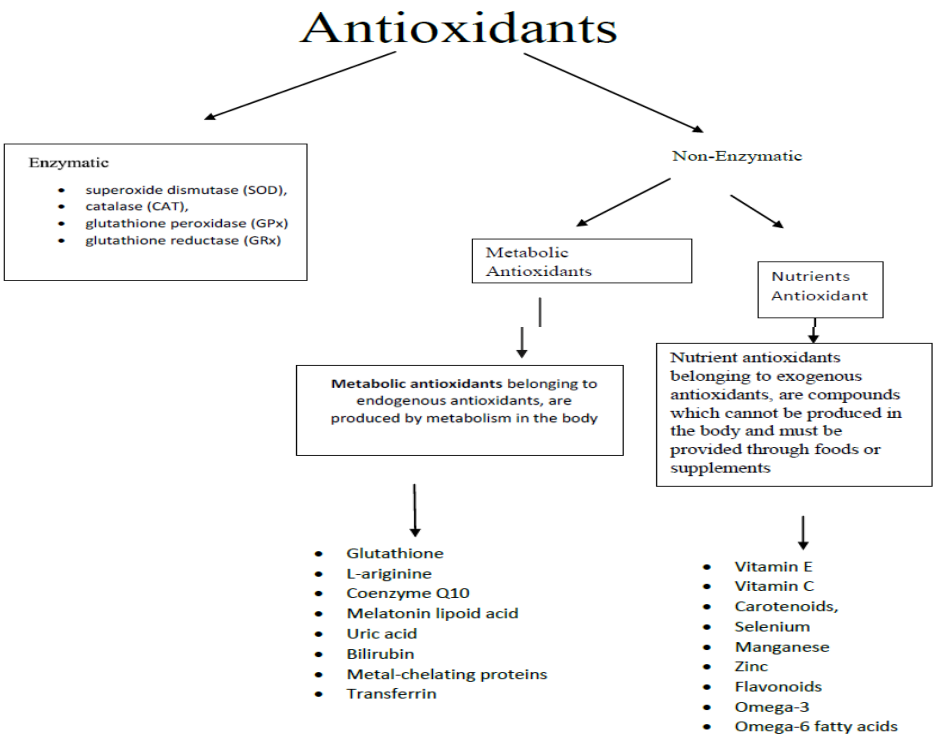

Fig. 4

Antioxidants phytochemicals

Antioxidant phytochemicals exist widely in fruits, vegetables, cereal grains, edible macrofungi, microalgae, and medicinal plants. Common fruits, such as berries, grapes, pomegranate, and guava are rich in antioxidant phytochemicals. Besides, fruit wastes (peel and seed) also contain high contents of antioxidant phytochemicals, including catechin, cyanidin 3-glucoside, epicatechin, gallic acid, kaempferol, and chlorogenic acid. Some vegetables, such as a penile leaf, cowpea, caraway, lotus root, sweet potato leaf, soybean (green), pepper leaf, ginseng leaf, chives, and broccoli are found to have high antioxidant capacities and total phenolic contents. Among cereal grains pigmented rice, such as black rice, red rice, and purple rice, possesses high contents of antioxidants and phytochemicals (flavones and tannins) Among selected Chinese medicinal plants the highest antioxidant capacities and phenolic contents are found in Dioscorea bulbifera, Eriobotrya japonica, Tussilago farfara, and Ephedra sinica, and several flowers including edible and wild ones.

Polyphenols, carotenoids are the two main kinds of antioxidant phytochemicals in foods/plants. For example, β-carotene, quercetin, myricetin, and kaempferol are the main antioxidant phytochemicals found in Cape gooseberry, and anthocyanins and ellagitannins are the major phytochemicals antioxidant compounds of strawberry. Flavonoids isolated from Euterpe oleracea pulp have important antioxidant activity. Natural polyphenols are the most abundant antioxidants in human diets, and their radical scavenging activities are related to the substitution of hydroxyl groups in the aromatic rings of phenolics. The plant variety, geographic region, growing season, and storage can all influence the concentrations of polyphenols in food. Dietary polyphenols could be classified into five classes: flavonoids, phenolic acids, stilbenes, tannins, and coumarins. Flavonoids can be further categorized as flavonols, flavones, flavanols, flavanones, anthocyanidins, and isoflavonoids. When the fruits contain higher total phenolic contents, they possess stronger antioxidant activity. For example, the scavenging activity of grape seed extract against ABTS radical. Carotenoids are a group of phytochemicals that are responsible for the yellow, orange, and red colors of foods. α-Carotene, β-carotene, lycopene, lutein, and cryptoxanthin.[48]

Management of various diseases with the help of anti-oxidants

Table 2

Sr. no.	Disease	Antioxidant management
A	Cardiovascular diseases	Phenolics, flavonoids, Cu, Zn, Mg, Mn, and Se. Dehydroglyasperin C (an antioxidant compound of licorice), Stilbenoids (isolated from Gnetum macrostachyum), phlorizin (a polyphenol found in apple), anthocyanins, crocin, lycopene, and allicin[26]
1	Atherosclerosis	Mito Q[49] β-carotene, vitamin C, vitamin E, Coenzyme Q10 (CoQ10), selenium (Se), Quercetin[26]
2	Hypertension	Aliskiren[50] vitamin A, vitamin C, vitamin E[51]
3	Myocardial infarction	vitamin E, vitamin C, vitamin A[52]
4	Arrhythmia	vitamin C, vitamins E, polyunsaturated fatty acids[21]
B	Neurodegenerative diseases	
1	Alzheimer's disease	Idebenone, Flavonoids **[**quercetin, rutin, coumarin, gallamine, resveratrol, scutellarin, anisidine, hesperidin, epicatechin**]** and other molecules (melatonin, trolox)[53,54]
2	Multiple sclerosis	PUFA (Ω-3 and Ω-6 at 1:1)[55]
3	Huntington's disease	(1) Flavones (7,8-DHF, Chrysin) (2) Flavonol (Fisetin, Kaempferol, Quercetin, Rutin) (3) Flavanones (Hesperidin) (4) Anthocyanidins (Anthocyanins) (5) Isoflavones (Genistein)[54]
4	Parkinson's disease	(1) Flavones (7,8-DHF, Apigenin, Baicalein, Chrysin, Luteolin, Morin, Nobiletin) (2) Flavonol (Fisetin, Myricetin, Myricitrin, Quercetin, Rutin) (3) Flavanols (Catechin, Epicatechin, ECGC) (4) Flavanones (Hesperetin, Hesperidin, Naringenin, Naringin)[54]
5	Amyotrophic lateral sclerosis	(1) Flavones (7,8-DHF) (2) Flavonols (Fisetin) (3) Flavanols (ECGC)[54]
6	Depression	(1) CoQ10, vitamin E, vitamin C, HDL, Selenium, and Zinc) (2)Enzymatic (SOD, glutathione peroxidase, Catalase,

		paraoxonase-1)[56]
7	Schizophrenia	N-Acetyl Cysteine, Glutathione (GSH)[57] Galantamine; Memantine[58]
8	Bipolar disorder	polyunsaturated fatty acids, N-acetylcysteine, vitamin D, folic acid, and zinc[23]
9	Anxiety	Melatonin, ascorbic acid Endophytic fungi-Passiflora incarnate (phenols, flavonoids, tannins, and/or saponins).[24]
C	Multiorgan disease	
1	Diabetes mellitus	(1) Enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase) (2) Vitaminic antioxidant (Vitamin C, Vitamin E, Vitamin D, Vitamin B9) (3) Other antioxidants (coenzyme Q10, N-acetylcysteine, GSH, lipoic acid) (4) dietary phytoestrogen- isoflavones - genistein and daidzein Lignans -Flaxseed, whole grains, legumes, and vegetables[59]
2	Metabolic syndrome	Reduced glutathione[60] Ginkgo biloba- terpene lactones (bilobalide and ginkgolides A, B, and C) and flavone glycosides (isorhamnetin, quercetin,[61] and kaempferol),[62] *Boswellia* species[63]
3	Chronic renal failure	Vitamin C, Vitamin E, Vitamin D, Magnesium, Selenium, Vitamin A, Vitamin B1[64] Quercetin, Curcumin, Resveratrol (3,5,40 -trihydroxy-trans-stilbene), Cordycepin (30 -deoxyadenosine), Flavonoids of C. tinctoria, Flavonoids and polyphenol of P.niruri, Ursolic acid
4	Cataract	Carotenoids- lutein, zeaxanthin, Vitamin C[65] N-acetyl carnosine (NAC)[66]
5	Rheumatoid arthritis	Mediterranean Diet (MD), vitamin D and probiotics, polyunsaturated fatty acids[67]
D	Ageing	coffee, methanol extract of Elaeis guineensis leaves, tetrahydroxystilbene glucoside, epigallocatechin gallate (EGCG), stilbenes (tetrahydroxystilbene), polyphenols (curcumin, resveratrol)[26]
E	Asthma	Vitamin C, Vitamin E, Carotenoids, selenium[68]
F	Preeclampsia	Vitamin A, Vitamin C, Vitamin E[28]
	Cancer	**(1)** Enzymatic antioxidant- **(**superoxide dismutase (Cu, Zn-SOD, Mn-SOD), catalase, glutathione peroxidase**)**[69] **(2)** Nonenzymatic antioxidants- Vitamin C, Vitamin E, carotenoids, thiol antioxidants (glutathione, thioredoxin, and lipoic acid), flavonoids, selenium,**)** Grape seed proanthocyanidin extract (GSPE), Omega-3 fatty acids, quercetin, cyanidin, kaempferol, and genistein[41] (3) saponins and sapogenins (Diosgenin, Dioscin, Polyphyllin D, Oleandrin, Ginsenoside Rg3, Ginsenoside Rh2, Saikosaponin A, Saikosaponin D, Polyphyllin D, Timosaponin AIII (TAIII)[70]

CONCLUSION AND FUTURE ASPECTS

The promising theoretical and research possibilities of antioxidant prevention and protection against various chronic illness is undergoing at present. Previous preventive trials, as well as newly discovered pharmacological and molecular biological effects of antioxidants, are reviewed. Tough present knowledge and treatment method have many limitations and there is a scope for improvement for antioxidant therapy through the various technological advancement method.

In the future, medical science is focusing on more disease-specific, target-directed, and highly bioavailable antioxidants because one of the major obstacles is in the delivery of these agents to their intended site of action. Nanotechnology and other advanced technological drug delivery of antioxidants seem to have promising outcomes leading to increased therapeutic index and higher drug concentration in tumor tissues.

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