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REACTIVE OXYGEN SPECIES (ROS) ARE BOON OR BANE

Seema Tripathy * and Prafulla Kumar Mohanty

Post Graduate Department of Zoology, Utkal University, Vani Vihar, Bhubaneswar - 751 004, Odisha, India.

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Correspondence to Author:
Seema Tripathy

Women Scientist-A
Post Graduate Department of Zoology, Utkal University, Vani Vihar, Bhubaneswar - 751 004, Odisha, India.

E-mail: seema.tripathy@yahoo.com

ABSTRACT: Reactive oxygen species (ROS) are inevitable by-products of cellular respiration. These are highly reactive chemical species derived from molecular oxygen (O_2). These include the superoxide (O_2-) and hydroxyl (HO−) free radicals as well as non-radical molecules such as hydrogen peroxide (H_2O_2). These act as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. Redox regulation or controlled ROS generation is the net effect of a subtle balance between ROS generation and neutralization or utilization by cellular antioxidant systems. The most deleterious effect of ROS is "oxidative stress". Oxidative stress plays a major part in the development of chronic and degenerative ailments such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. Several mechanism exists to counteract oxidative stress. This review provides a detailed overview of the influence of ROS on human pathophysiology and novel therapeutic strategies followed to treat ROS mediated diseases or disorders.

INTRODUCTION: Oxygen (O_2) is a crucial element involved to carry out the metabolic reaction like synthesis and degradation of metabolites in aerobic organisms. According to Lavoisier, O_2 plays dual role in living processes by acting as a sustainer and a destroyer. Reactive oxygen species (ROS) are oxygen-derived small molecules. Most ROS that have been described in living organisms are O_2 ions, peroxides and several non-radical oxidizing agents [1]. These include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl ion (OH^-), and nitric oxide (NO).

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ROS are often termed free radicals; this does not apply to H_2O_2 and $ONOO^-$ which are non-radical ROS. These react readily with a variety of chemical structures such as proteins, lipids, sugars, and nucleic acids. Is the generation of ROS really a bane for human beings?

It is demonstrated that excess generation of ROS creates a phenomenon called oxidative stress, a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins and deoxyribonucleic acid (DNA). Oxidative stress mediates several diseases including cancer, atherosclerosis, malaria, chronic fatigue syndrome and rheumatoid arthritis and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, acquired immune deficiency syndrome (AIDS) and aging [2].

This review describes the mechanisms of formation and catabolism of ROS, their concerned role in inducing cytopathologic conditions, the importance of antioxidative defense system in ameliorating the toxicity of ROS and novel therapeutic opportunities provided by antioxidants, plant based products, drugs and stem cell therapies to treat the pathologic conditions induced by ROS.

Nature of reactive oxygen species (ROS): O_2 contains two unpaired electrons and can, therefore, undergo reduction, yielding several oxygen metabolites (**Fig. 1**).

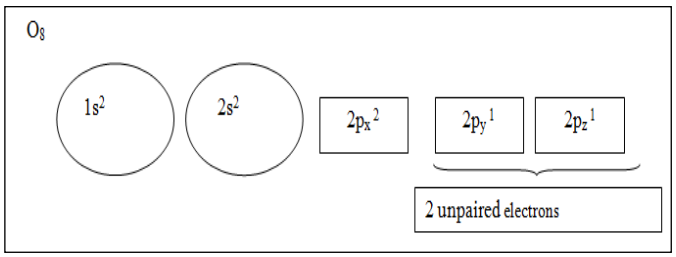


FIG. 1: ELECTRONIC CONFIGURATION OF OXYGEN

Its oxidation number ranges from 0 (O_2) to -2 (H_2O). So, it can execute nucleophilic addition, nucleophilic substitution and chain reaction. ROS react quickly with other compounds and try to capture the required electron to gain stability which itself explains their normal biological activities and damaging effects on cells. During cellular respiration some amount of O_2 escapes from this ordered process and is released as ROS. Mitochondria are not only responsible for production of ROS but at the same time they are also target of ROS to generate diseases [3, 4]. Then why does generation of ROS still remain mitochondrial paradigm? The different factors involved in the intricate generation of endogenous and exogenous ROS by different cell organelles and environment (**Fig. 2**). Once an ROS is initiated, a chain reaction starts with a cascade and finally results in the disruption of a living cell. The ROS are generated via different types of physiologic reactions (**Table 1**).

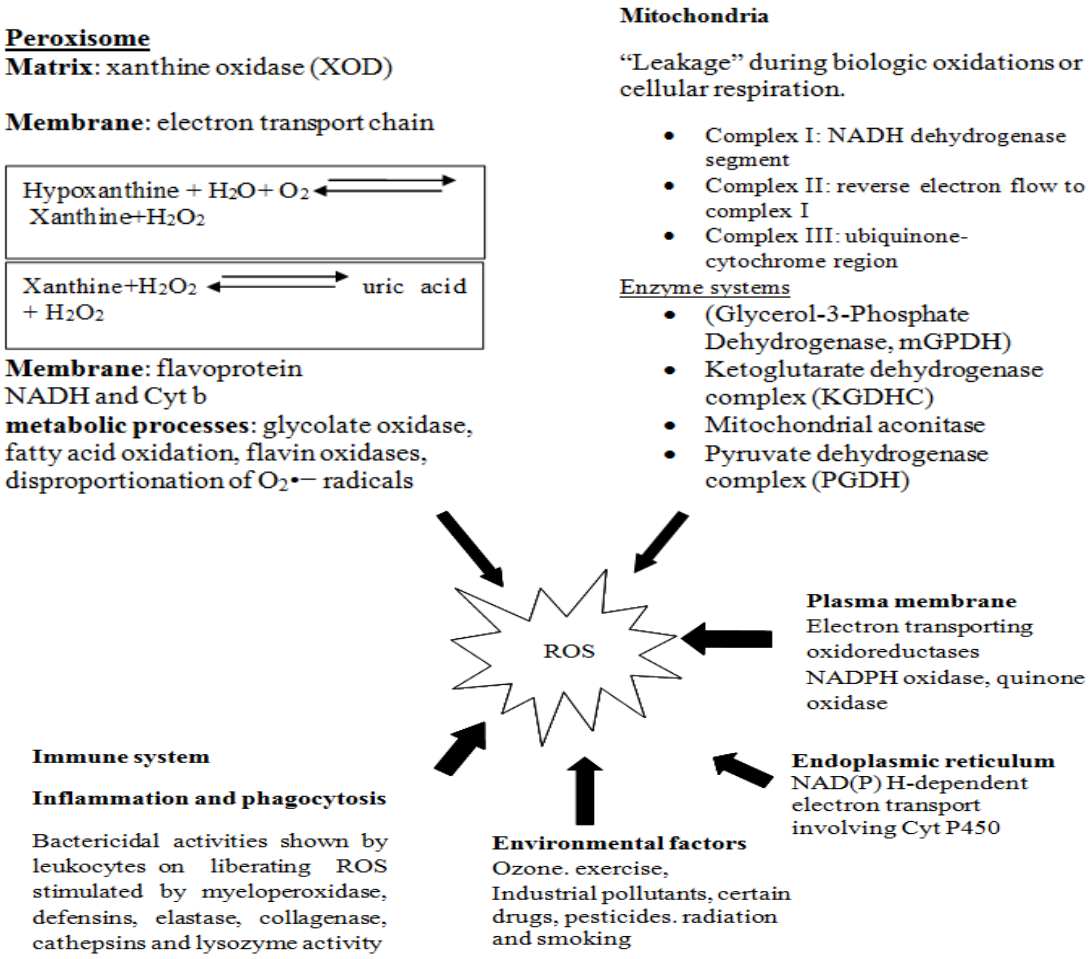
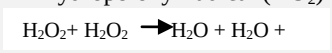
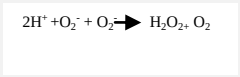
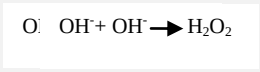


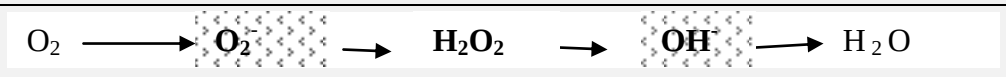
FIG. 2: GENERATION OF ROS BY DIFFERENT INTRINSIC AND EXTRINSIC FACTORS

TABLE 1: GENERATION OF DIFFERENT TYPE OF ROS

Sl no.	ROS	Site of production	Property	Biological reaction	References
1	Hydroperoxyl radical (HO_2) 	Peroxisomes	Protonated form of superoxide, oxidization initiator of lipid.	Release of hydrogen atoms from tocopherol. Polyunstaturated fatty acids in the lipid bilayer.	Kumar [6]
2	Superoxide (O_2^-) 	Phagocyte	Oxidant and reductant, oxidize sulphur, ascorbic acid or NADPH and reduced Cytochrome C and metal ions. In acidic environment at pKa = 4.8, superoxide forms and perhydroxyl radical, which is a powerful oxidant	Dismutation reaction leading to the formation of hydrogen peroxide and oxygen can occur spontaneously or is catalyzed by enzyme superoxide dismutase. Phagocytes generate superoxide anion (O_2^-) for killing of phagocytized bacteria.	Johnston *et al*.,[7]
3	Hydrogen peroxide (H_2O_2) 	Mitochondria Peroxisome	Reduction of superoxide produces hydrogen peroxide (neutral molecule), powerful oxidizing agent, a source of hydroxyl radical	Cellular respiration, numerous enzymes (peroxidases) use H_2O_2 as a substrate in oxidation reactions involving the synthesis of complex organic molecules, e.g., in ß-oxidation, enzymatic reaction of flavin oxidases by disproportionation of radicals.	Kumar [6]
4	Singlet oxygen 	Phagocyte, skin and eye	Non-radical, formed in some radical reactions arising from hydrogen peroxide molecules. On decomposition generates superoxide and hydroxyl radicals. This can trigger on/off many metabolic reactions.	Produced during reduction of O_2 catalyzed by the phagocytic NADPH-oxidase.	Steinbeck *et al*., [8]

Exogenous ROS generated from air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain synthetic drugs such as antibiotics (cyclosporine, tacrolimus, gentamycin, bleomycin). Non-steroidal-anti-inflammatory drugs (NSAIDs) are used widely in the treatment of pain, fever, inflammation, rheumatic and cardiovascular disease but chronic administration of those drugs leads the generation of free radicals which may result gastric erosions, duodenal ulceration and severe complications such as gastrointestinal hemorrhage and perforation. The exogenous compounds like industrial solvents, smoked meat, used oil fat and radiation after penetration into the body by different routes are decomposed or metabolized into free radicals [2, 5]. Different ROS significantly differ from each other in their properties that include reduction potential, half-life and intracellular concentration (**Table 2**).

TABLE 2: DIFFERENT PROPERTIES OF SOME TYPICAL ROS

Property	ROS	ROS		
				
reduction potential (V)	0.94	0.32	2.31	Most inert molecule
Half life (sec)	10^{-6}	10^{-5}	10^{-9}	
In vivo concentration (M)	10^{-10}	10^{-7}	10^{-15}	

"Good" and "evil" of ROS: Miscellaneous ROS are double-edged sword, available abundantly in biological system. Their production may be accidental or deliberated. ROS dose in living system is a critical parameter in determining the ultimate cellular response. At low or moderate concentration, ROS are necessary for cell signaling and maturation process of cellular structures, cell homeostasis, maintenance of tissue architecture and functional integrity [9].

ROS regulate Ras/Raf/MEK/ERK and Ras/ PI3K/ PTEN/Akt transcription factors pathways. The most active ROS like "superoxide" confer immunity directly by showing the mechanisms of "respiratory burst" or indirectly by stimulating various non-oxidative mechanisms that include pattern recognition receptors, signaling, autophagy, neutrophil extracellular trap formation and T-lymphocyte responses [10]. Several evidences suggest that ROS play important role in implantation of blastocysts, disintegration of the structural elements of the sperm cells, iodination of tyrosine in the thyroxine biosynthesis and secretion of mucus in goblet cells [11].

Immunological functions: ROS act as weapons for the host defense system. Indeed, phagocytes (neutrophils, macrophages, monocytes) release free radicals to destroy invading pathogenic microbes [12, 13]. The main enzyme system responsible for ROS production from phagocytic cells is the family of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) which consist of seven members from NOX (1 to 5) and two dual oxidases, Duox1 and Duox2 [14]. These enzymes are responsible for generation of superoxide anion or hydrogen peroxide as primary products and actively exhibit physiological, pathological functions and form confirmative defense against infection [15]. They elicit their defense action by the production of NOX2. NOX2 is responsible for the release of superoxide in the phagocytic vacuole, promotion of bacterial killing and the execution of respiratory burst. Chronic granulomatous disease (CGD) or Quie syndrome is a diverse group of hereditary disease in which certain cells of the immune system are unable to form the reactive O_2 compounds (superoxide radical). So patients of this disease experience multiple and persistent infection. This leads to the formation of granulomata in many organs [16]. CGD affects about 1 in 2, 00,000 people in the United States, with about 20 new cases diagnosed each year [17].

Cellular responses to ROS: ROS tightly regulate a variety of proteins involved in cell proliferation and survival. They either trigger the initial process or direct regulation of signaling molecules at "oxidative interface region". ROS directly interact with key regulatory components of MAP kinases, PI3 kinase, PTEN and protein tyrosine phosphatases signal transduction pathways involved in proliferation and survival. ROS are involved in tissue homeostasis by controlling mitochondrial oxidative stress, apoptosis, and ATM regulated DNA damage response and aging (p66Shc), iron homeostasis through iron–sulfur cluster proteins (IRE–IRP), and antioxidant gene regulation (thioredoxin, peroxiredoxin, Ref-1 and Nrf-2) [18].

Mobilization of ion transport system: ROS induce modifications in ion transport pathways by the following mechanisms such as oxidation of sulfhydryl groups located on the ion transport proteins, peroxidation of membrane phospholipids and inhibition of membrane-bound regulatory enzymes and modification of the oxidative phosphorylation and ATP levels. These deleterious effects of ROS are due to their interaction with various ion transport proteins underlying the transmembrane signal transduction such as (i) ion channels [Ca^{2+} channels (include voltage-sensitive L-type Ca^{2+} currents, dihydropyridine receptor voltage sensors, ryanodine receptor Ca^{2+} release channels, and D-myo-inositol 1,4,5-trisphosphate receptor Ca^{2+} release channels), K^+ channels (activated K^+ channels, inward and outward K^+ current and ATP-sensitive K^+ channels), Na^+ channels and Cl^- channels)], (ii) ion pumps [sarcoplasmic reticulum and sarcolemma Ca^{2+} pumps, Na^+-K^+ ATPase pump, Na^+ pump, and H^+-ATPase pump (iii) ion exchangers such as the Na^+/Ca^{2+} exchanger and Na^+/H^+ exchanger and (iv) ion co-transporters [K^+-Cl^-, Na^+-K^+-Cl^- and Pi-Na^+ co-transporters].

Alteration in the ion transport mechanism may lead to changes in a second messenger system, primarily Ca^{2+} homeostasis. This further augments the abnormal electrical activity, disrupts signal transduction and promotes cellular dysfunction which may become major cause to induce pathological conditions [19].

Apoptosis: ROS at lower concentration act as signaling molecules. These are responsible for activation of an apoptotic cell signaling cascade by accumulating in the mitochondrial membrane [20]. Cell signaling by ROS would not appear to be random, as previously assumed, but they may target at specific metabolic and signal transduction pathways of some cellular components after generation [21]. ROS lead to intrinsic pathway of apoptosis by permeabilization of the mitochondrial membrane. H_2O_2 causes the release of cytochrome c from mitochondria into the cytosol and also activate nuclear transcription factors like NF-κB, AP-1 and p53. These phenomena may up-regulate death proteins or produce inhibitors of survival proteins. The intrinsic pathway induced through mitochondrial damage leads to many mitochondrial disorders. H_2O_2 also induces extrinsic pathway of apoptosis by up-regulation of the Fas-FasL system. This activation of Fas ligand via phosphorylation is necessary for subsequent steps of apoptosis leading to cell death by releasing cytochrome c outside the mitochondria [22].

Diseases: ROS cause 38 million deaths per year globally with rising prevalence across the world particularly in developing countries. This may be due to the fact that ROS provoke macromolecular damage within the cells and result many chronic and acute diseases **(Fig. 3)**.

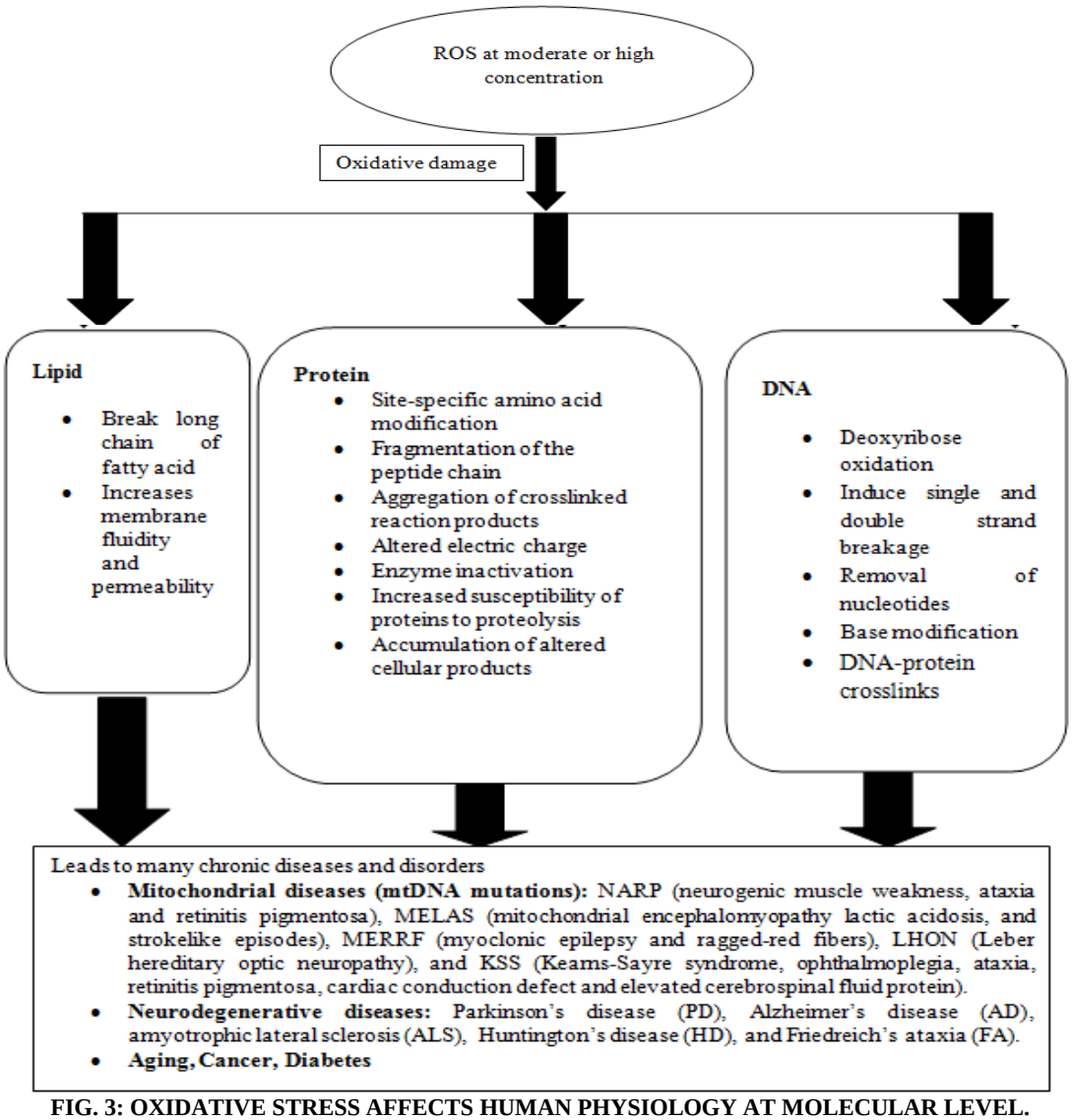


FIG. 3: OXIDATIVE STRESS AFFECTS HUMAN PHYSIOLOGY AT MOLECULAR LEVEL.

Nevertheless, the molecular mechanism by which ROS induce fatal effects on active bio-molecules is not yet fully elucidated. However, the etiology and prognosis of such diseases largely rely on genetic susceptibility of host, environmental factors and personal habits. After entering a cell, virus creates an imbalance in the cell's ROS system. Do ROS generate inside host regulate lysogenic and lytic cycle of virus? Data represented in Reshi *et al*. [23] suggest that patients infected with RNA viruses are under chronic oxidative stress, play a dominant pathogenic role in human immunodeficiency virus (HIV), hepatitis and influenza infection. Here, persistent viral infection is sufficient reason of over production of ROS making the situation more complicated in people suffering from diseases like hepatitis B, hepatitis C and influenza (H1N1).

AIDS: AIDS is characterized by a decrease in the CD4 lymphocytes. AIDS is the end phase of HIV infection. The fluctuation in the ROS concentration induced apoptosis of CD4 cells and dysfunction of other immune system components seem to contribute to the progression of AIDS. Due to weakening of antioxidant system, the level of glutathione (GSH), cystine, vitamin C and superoxide dismutase (SOD) are decreased and the serum malondialdehyde (MDA) and 4-hydroxynonenal (HNE) levels are elevated in patients infected with HIV-1 [23]. The nuclear transcription factor NF-κB, which is necessary for viral replication, is activated by ROS and combined effects of MA and gp120 disrupt arrangement of tight junction proteins causing irreversible damage to blood brain barrier (BBB). Thus, facilitating the entry of infected monocytes into astrocytes and microglia of central nervous system (CNS) leading to neurodegenerative disorders in case of AIDS patients.

Hepatitis C: Hepatitis C virus (HCV) infection has become pandemic affecting 3% of total world population. HCV is a positive-stranded RNA virus that causes severe liver diseases, such as cirrhosis and hepatocellular carcinoma. HCV uses an RNA-dependent RNA polymerase to replicate its genome and an internal ribosomal entry site to translate its proteins. HCV infection is characterized by an increase in the concentration of ROS. Choi *et al*. [24] reported that ROS can rapidly inhibit HCV RNA replication in human hepatoma cells.

The increased ROS level in hepatitis C patients may, therefore, play an important role in the suppression of HCV replication. The HCV polyprotein precursor when cleaved by viral proteases and host cell signal peptidases results in at least three structural (core, E1 and E2) and six nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B). Reports have shown that HCV gene expresses core protein in the host cell that in turn increases the level of ROS through the mediation of calcium signaling. The NS5A protein of HCV causes alterations in Ca^{2+} homeostasis. The release of calcium from the ER results in an increase in ER stress. The released calcium taken up by the mitochondria results in increased ROS production and oxidative stress. ROS are involved in transcriptional activation of a large number of cytokines and growth factors. This continuous production of ROS acts as fuel for the vicious cycle.

Oxidative stress causes hepatic damage and enhances occurrence of non-reparative damage. Consistent viral infection in hepatitis increases ROS level resulting in decrease in cellular concentration of GSH and increase level of oxidized thioredoxin and lipid peroxidation products. HCV core gene expression has been associated with increased ROS, decreased intracellular and/or mitochondrial GSH content [25]. Thus, viral induced ROS production further exaggerates the problems to hepatocellular carcinoma and other associated liver disorders like fibrosis and cirrhosis, various metabolic alterations including steatosis and insulin resistance associated with fibrosis progression or iron overload and the development of HCC or non-Hodgkin lymphoma.

Influenza (H1N1): Influenza, a virus-induced lung disease caused by influenza A virus (IAV) leads to substantial mortality and economic loss worldwide with 2, 00 000 annual hospitalization in the US and 5, 00, 000 additional deaths globally per year and this figure reaching million number of death. The excessive production of ROS like superoxide and hydrogen peroxide decreases GSH synthesis that plays a pivotal role for influenza virus replication by allowing the folding and maturation of viral haemagglutinin.

Mitochondrial ROS might be responsible for controlling IAV infection and may be potential sources of ROS generation [26]. NADPH oxidase 2 (Nox2), has a prominent role in increasing severity of symptoms of influenza. Thus, it may assume that the use of Nox2 oxidase inhibitors in preparation of antivirals vaccines could suppress influenza.

Fetal growth: Fetal programming occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or 'insult' applied at a critical point in *in utero* development. The 'insults' that alter placental development include hypoxia, oxidative and abnormal maternal nutrient status, to which the placenta may adapt by alterations in transporter expression and activity to maintain fetal growth or by epigenetic regulation of placental gene expression [27, 28]. The increasing metabolic activity of placental mitochondria throughout gestation results in increasing oxidative stress in a normal pregnancy. This oxidative stress is exacerbated in pregnancies complicated by pre-eclampsia or diabetes that can be measured by production of ROS or by decreased level of antioxidant enzymes [29, 30]. Thus, produced ROS include superoxide and nitric oxide, both of which can be produced by trophoblast. Trophoblast and placental villous vascular endothelium express NADPH oxidase (NOX) 1 and 5 isoforms, which are probably the major enzymatic sources of superoxide in the placenta. In pregnancies complicated by pre-eclampsia, increased expression of both NOX 1 and 5 are seen [31].

Cardiovascular diseases: Chronic kidney diseases (CKD) and cardiovascular diseases (CVD) are unified with oxidative stress. These are further provoked by diabetes, obesity, metabolic syndrome, smoking or genetic predisposition, increasing age and acute injury. The progression of CKD to CVD or vice versa is mediated by events like (i) inflammation and the release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β) and IL-8 from activated lymphocytes, (ii) endothelial dysfunction due to increased retention of uremic toxins and decreased L-arginine synthesis which causes alterations in nitric oxide (NO) signalling - dyslipidaemia and associated pro-oxidative/inflammatory state lead to increased oxidised-low density lipoproteins (ox-LDL), a major component in the pathogenesis of atherosclerosis and (iii) redox perturbations [32]. All these factors create imbalance between the production ROS or reactive nitrogen species (RNS) and endogenous antioxidants. This leads to mitochondrial dysfunction and alterations in redox sensitive pathways such as Nrf2/keap1/ARB.

Cancer: The role of ROS in cancer is controversial as it promotes as well as inhibits cell proliferation. ROS make rapid and transient second messenger molecules for signal transduction and signal amplification. Specifically, T cells generate hydrogen peroxide and/or superoxide. In fact, certain cancer drugs aim in increasing the free radical amount in body. Several anticancer agents, collectively termed redox therapeutics act by increasing intracellular level of ROS. It was observed that the combination of doxorubicin and mitomycin C are supra-additive tumor cell killing chemicals *in vitro* in both murine and human breast cancer cells and *in vivo* against murine breast cancer cells [33].

Recently, Singer *et al.* [34] have demonstrated that glioblastoma, a sub-population of tumor cells with stem cell-like properties, glioma stem cells (GSCs), is specifically endowed to resist or adapt to the standard therapies, leading to therapeutic resistance. This is the most common cause of tumor recurrence, which is ultimately fatal in 90% of the patients 5 years after initial diagnosis has been suppressed by redox modulator cannabidiol (CBD). CBD induces a robust increase in ROS, which inhibit cell survival. The regulation of ROS generation may provide a novel strategy to control cancer progression.

Aging: Aging is an extremely complex process that affects most of the biological functions of an organism, generally culminating in disease and death due to the accumulated actions of different types of stresses. Among these stresses, oxidative reactions accelerate aging of an organism that decline physiological functions mimicked aging process by accumulation of damaged products. Although the statement "aging is a disease" remains at paradox, it is perhaps due to involvement of mitochondrial ROS during the process of aging.

mtDNA is constantly exposed to ROS generated by the mitochondrial electron transport chain and mutations may accumulate exponentially with age. The simultaneous increase in lipid peroxidation and oxidation of mitochondrial proteins adds to the oxidative stress effects, initiating the vicious cycle of molecular degeneration [35]. This putative vicious cycle can operate at different rates in various tissues, leading to differential accumulation of oxidative damage, which could explain the differences in functional impairment and deterioration of different tissues in the aging process. A considerable damage happens to mtDNA that progresses with age. Among them, the most significant is the 10-fold increase in an oxidative damage marker (8-hydroxy-2-deoxyguanosine) in mtDNA versus nuclear DNA (nDNA) from human brain [36]. A study of aging in rhesus monkeys by Bowling *et al* [37] has revealed the fact that there is significant decrease in the activities of complex I and IV, as well as in mitochondrial ATP generation with increasing age. Several mtDNA point mutations also increase with normal aging [38]. But are ROS-mediated damages the sole cause of such point mutations?

Oxidative stress impacts deleterious effect on organs and causes organ specific diseases (**Fig. 4**). ROS play a key role attributing to pathology of diabetes, cardiovascular diseases, and neurological diseases (**Table 3**). A recent review by Kiranmayi [39] may be referred to detailed understanding of the effect of ROS on human health.

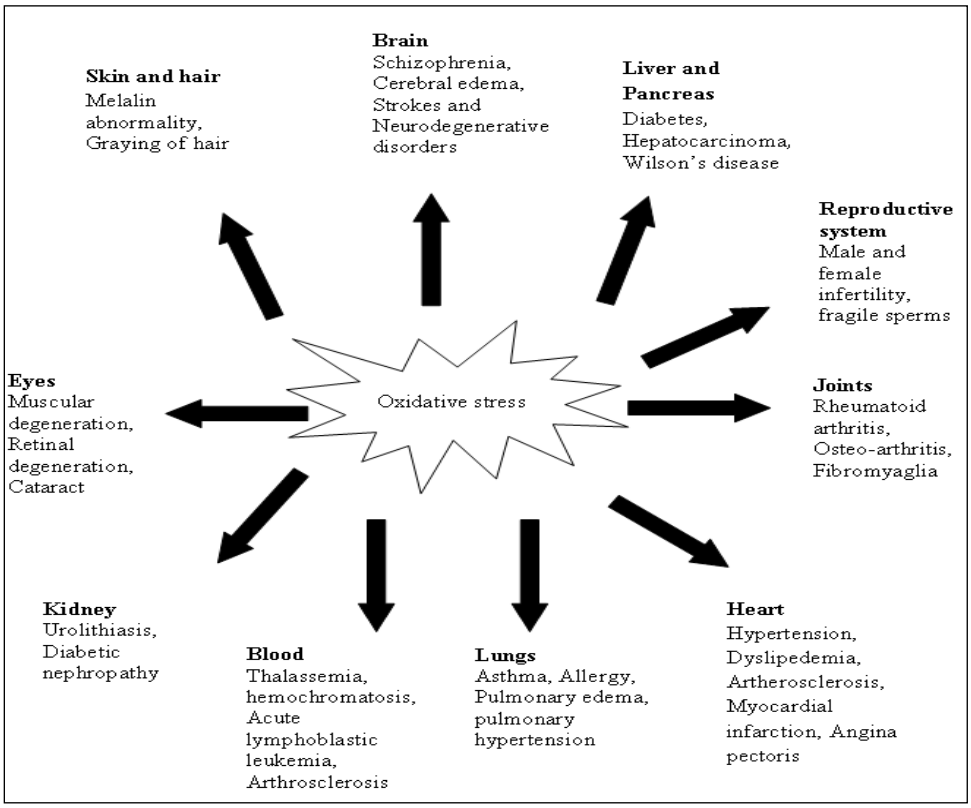


FIG. 4: DELETERIOUS EFFECTS OF OXIDATIVE STRESS ON VARIOUS ORGANS

TABLE 3: SOME OF THE ROS MEDIATED MAJOR DISEASES

Examples of diseases	Clinical manifestation	Mechanisms of involvement of ROS	References
Diabetes-II	High blood glucose level, insulin resistance	Superoxide anion, which is accompanied with generation of a variety of ROS, imbalance in redox state of body, provoked OS causes Insulin resistance (IR) and altered gene expressions. This alternation of gene affects individual through multiple routes. 1. Stimulated polyol pathway where ≤ 30% glucose can be diverted to sorbitol and fructose. 2. Increased transcription of genes for proinflammatory	Singh *et al.*, [40]

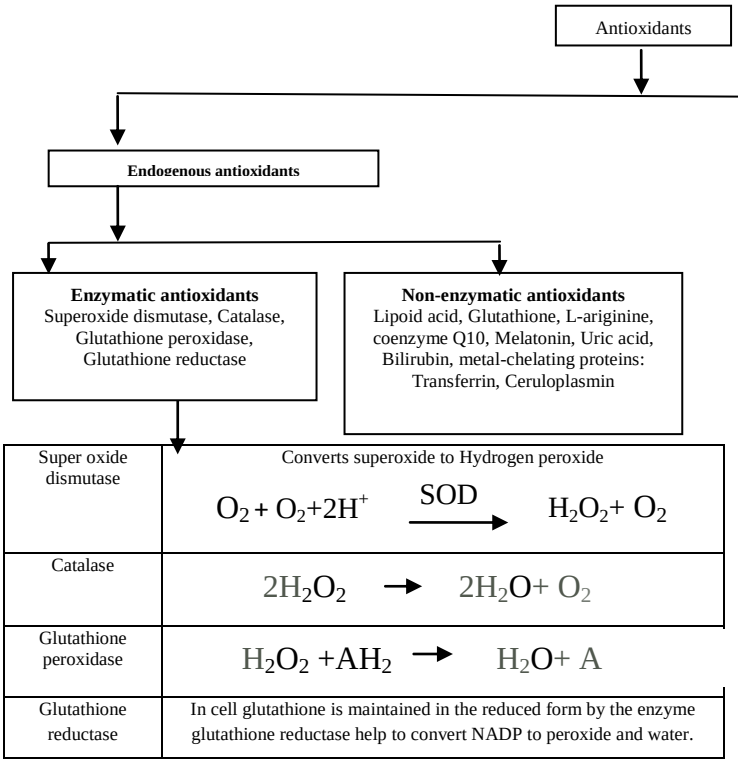
		cytokines and plasminogen activator inhibitor-1 (PAI-1). 3. Activation of protein kinase-C (PKC) leading to several molecular changes. 4. Increased synthesis of advanced glycation end products (AGEs) and autooxidation of glucose with formation of ketoimines and AGEs.	
Hypertension,	Elevated blood pressure	Vascular smooth muscle cell proliferation induced by ROS in both in vitro and in vivo. AngII promotes oxidant production via NADH/NADPH oxidase, Superoxide production-mediated endothelial dysfunction	Wattanapitayakul and Bauer [41]
Coronary artery disease (atherosclerosis)	lesions on the walls of blood vessels, formation of plaque in the vessels and finally rupture of the vessels.	Superoxide production-mediated endothelial dysfunction, Increased oxLDL	
Myocardial infarction (MI)	Formation of edema, acidosis and NO accumulation in the heart following reperfusion.	Ischemia/reperfusion injury driven by ROS formation, Oxidant-derived myocyte necrosis and/or apoptosis.	
Heart failure		Increased NO production induces cardiac dysfunction, Cytokine-derived ROS induces cardiac apoptosis, ROS-induced cardiac apoptosis and/or necrosis.	
Schizophrenia	Increase level of 8-oxo-7,8-dihydro-20 deoxyguanosine and 8-Oxo-7,8-dihydroguanosine (urinary samples)indicating oxidative stress Induced nucleic acids damage decrease SOD, RBC catalase and plasma nitrites,	NOX2 involved in release of.neurotransmitters. NOX2 contributes to changes in interneurons, including the loss of parvalbumin expression and the capacity to secrete GABA. Oxidative stress may change the set of active transcription factors within GABAergic neuron	Brieger *et al.,* [42]
Parkinson's Disease (PD)	degeneration of dopaminergic and nondopaminergic cells affect voluntary movement (bradykinesia), rigidity, and tremor. Cognitive deficits (dementia), i.e. post encephalitic parkinsonism.	The key loss of dopaminergic neurons involves oxidative stress and neuroinflammatory mechanisms through increased level of inducible nitric oxide synthase (iNOS) followed by activated microglia, T-cell infiltration and astrogliosis leading to accumulation of O^{2-} and NO free radicals. Dopaminergic neuronal loss via oxidative stress-mediated inflammation also involves cyclooxygenase-2 (COX2) over-expression. ROS accumulation up-regulates NADPH-oxidase that exaggerate microglial inflammation.	Popa Wagnr *et al.,*[43]
Alzheimer's Disease (AD)	microglial inflammation leads to dementia, progressive deterioration of thought, perception and mood.	Mitochondrial dysfunction and/or aberrant accumulation of transition metals, while the abnormal accumulation of A-beta and tau proteins appears to promote the redox imbalance. Generation Abeta- or tau-induced neurotoxicity. A-beta facilitate the phosphorylation and polymerization of tau, thus forming a vicious cycle that promotes the initiation and progression of AD.	Zhao and Zhao [44]

Detection of ROS: Due to high reactive nature, it is very difficult to measure ROS directly in biological systems. So, now-a-days fluorescence probes are being used to detect individual ROS. Electron spin resonance Fluorescence probes are currently being used to provide information about the activity and exact location of free radical reactions where it is takes place. That can provide information about the activity and location of free radical reactions. Considering the technical aspects and cost, the downstream products such as oxidative products or enzyme levels are important parameters for estimation of ROS. Spectrophotometry and chemiluminescence are widely used methods for detection of ROS indirectly. Products like 8-hydroxy-deoxy guanosine (8-OHdG), 8-hydroxy-adenine and 7-methyl-8-hydroxy-guanine resulting from DNA

damage by free radicals can be detected in urine. Lipid peroxidation is an important event mediated in many diseases like atherosclerosis, inflammatory bowel disease (IBD), retinopathy of prematurity (ROP), borderline personality disorder (BPD), asthma, Parkinson's disease, kidney damage, preeclampsia and others. Many assays are available to measure lipid peroxidation, such as MDA by the thiobarbituric acid (TBA) test and diene conjugation. Recently, ferrous oxidation with Xylenol Orange assay coupled with triphenylphosphine has shown to be a reliable marker in determining levels of hydroperoxides (ROOH). 8-epi-prostaglandin-F2α (8-epi-PGF2α) is a marker of oxidative stress derived from oxidation of phospholipids containing arachidonic acid. Oxidative damage to proteins is important as it influences the function of receptors, enzymes and transport proteins. These can be measured by assay specific for -SH oxidation, carbonyls, aldehyde adducts oxidized tyr, trp, his, met, lys, leu, ileu, val, protein peroxides or hydroxides [45].

Mechanisms to nullify ROS: Antioxidants are vital cogs in numerous metabolic reactions and are co-players in redox homeostasis but there are many others cellular molecules of equal importance. The antioxidant defense mechanisms present in animals help to neutralize the generated ROS. The antioxidant defense mechanism act in integrated manner by blocking the initial production of free radicals, scavenging the oxidants, converting the oxidants to less toxic compounds, blocking the secondary production of toxic metabolites or inflammatory mediators, terminating the chain propagation of the secondary oxidants, repairing the molecular injury induced by free radicals or enhancing the endogenous antioxidant defense system of the target [46]. Humans have evolved highly complex antioxidant systems (enzymic and nonenzymic), which work synergistically, and in combination with each other to protect the cells and organ systems of the body against free radical damage (**Fig. 5**).

The antioxidants can be endogenous or obtained exogenously as a part of a diet or as dietary supplements. An ideal antioxidant should be readily absorbed and quench free radicals, and chelate redox metals at physiologically relevant levels. It should also work in both aqueous and/or membrane domains and effect gene expression in a positive way. Endogenous antioxidants play a crucial role in maintaining optimal cellular functions and thus, systemic health and well-being. However, the conditions which promote oxidative stress, endogenous antioxidants may not be sufficient and dietary antioxidants may be required to maintain optimal cellular functions [47].



Exogenous antioxidants or nutrient antioxidants
Vitamins (A, C and E), Minerals (Selenium and Zinc), lycopene, metal chelators, flavinoids, phenolic compounds, carotinoids

Exogenous antioxidants	Sources	Functions
Vitamin A	Milk, butter, fish liver oil, papaya, banana etc., spinach and carrot.	Increases GSH, SOD, GSH peroxidase activity.
Ascorbic acid (vitamin C)	Berries, broccoli, Brussels sprouts, cantaloupe, cauliflower, grapefruit, honeydew, kale, kiwi, mango, nectarine, orange, papaya, sweet potato, strawberries, tomatoes, and red, green, or yellow peppers.	Increases scavenging capacity, reacts with several types of ROS, regenerate by vitamin E.
Tocopherols (vitamin E)	Broccoli, carrots, chard, mustard and turnip greens, mangoes, nuts, papaya, pumpkin, red peppers, spinach, and sunflower seeds.	A fat - soluble antioxidant that stops the production of reactive oxygen species formed when fat undergoes oxidation.

Non-enzymatic antioxidants

Glutathione	Major non-protein thiol. Inhibits excessive peroxidation. Reduced thiols are essential for recycling of antioxidants like vitamin E and vitamin C.
α-lipoic acid (thiol or bi-thiol residue (1,2, dithiolane-3-pentanoic acid)	Forms a part of several multienzyme complexes, such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and the glycine cleavage system having ROS scavenging activity, capacity to regenerate endogenous antioxidants such as glutathione, vitamins C and E, metal chelating activity and repair of oxidized proteins.
Melatonin	Water soluble antioxidant which can cross the blood-brain barrier,
l-argine	Reduces vascular oxidative stress induce by superoxide, main agent to repair cardiac damage by improving endothelium-dependent vasodilator function and systemic NO production, reduces vascular oxidative stress and progression of atherosclerosis.
Q-10	Lipid soluble antioxidant. Acts as an obligatory co-factor, exhibit function of uncoupling proteins and a modulator of the transition pore. In its reduced form, CoQH2, ubiquinol, inhibits protein and DNA oxidation and lipid peroxidation and also that of lipoprotein lipids present in the circulation also show anti-atherogenic effect.
Bilirubin	Bilirubin can suppress oxidation of lysosomes at oxygen concentration that are physiologically relevent
Zinc	Protective antioxidant metalloenzymes. cytosolic mitochondrial SOD require Zn to show its activity.
Transferrin, Ceruloplasmin,	Prevents lipid peroxidation by chelating free unbound iron. Ceruloplasmin convert ferroxidase enzyme by catalyzing the oxidation of Fe^{+2} to the $Fe+^{3}$ state.

Exogenous antioxidants	Sources	Functions
Zinc	Oysters, red meat, poultry, beans, nuts, seafood, whole grains, fortified cereals and dairy products.	Protection of protein sulfhydryl groups against oxidation and inhibit the production of reactive oxygens by transition metals. Show protective effect against general and liver-specific prooxidants.
Selenium	Rice and wheat. Nutrition taken from plants grown in selenium rich soil.	Cofactor of glutathione transferase and glutathione peroxidase (GSH-Px) enzyme system form 2nd line of defense as it can destroy peroxides and hydroperoxides and other selenoproteins.
Carotinoids (ß carotene)	Carrot, green leafy vegetables, banana, sweet potatoes, carrots, cantaloupe, squash, apricots, pumpkin and mangoes. Some green, leafy vegetables, including collard greens, spinach and kale.	Precursor of vitamin A. Prevents initiation of fatty acids peroxidation chain reaction by inactivating singlet oxygen (without degradation) reacting with hydroxyl, superoxide, and peroxyl radicals.
Flavinoids various polyphenol and anthocyanins, (flavonols, proanthocyanidins, isoflavones, hydroxycinnamic acids, catechins), proanthocyanidins, quercetin glucosides),	Parsley, onions, blueberries. grapes, black tea, green tea and oolong tea, bananas, all citrus fruits, Ginkgo biloba, red wine and dark chocolate (70% cocoa) .	Suppressing reactive oxygen formation, by inhibiting enzymes, chelating trace elements involved in free-radical production, scavenging reactive species and up-regulating and protecting antioxidant defences

FIG. 5: MAJOR ANTIOXIDANTS USED TO SCAVENGE ROS.

The antioxidant behavior of polyphenolic compounds, that present in naturally in fruits, vegetables, cereals and beverages show pleiotropic health beneficial effect acting at three different levels (**Fig. 6**). The antioxidants activate three signaling pathways namely GSH, thioredoxin (TXN) and catalase. TXN is a protein that reduces ROS level which can be regenerated by thioredoxin reductase (TXNR) [48]. TrxR in conjunction with Trx generates a ubiquitous oxidoreductase system with antioxidant and redox regulatory roles. TrxR-catalyzed regeneration can activate several antioxidant compounds that include ascorbic acid (vitamin C), selenium-containing substances, lipoic acid, and ubiquinone (Q10). GSH synthesis and regeneration of nuclear factor erythroid 2-related factor 2 (NRF2) mainly affects GSH production and NADPH-related responses, forkead box

O(FOXO) proteins and the tumor suppressor p53 regulate SODs and catalase [48]. At the same time different antioxidant pathways are controlled by NRF2. Many signalling pathways that are linked to tumorigenesis can also regulate the metabolism of ROS through direct or indirect mechanisms [49].

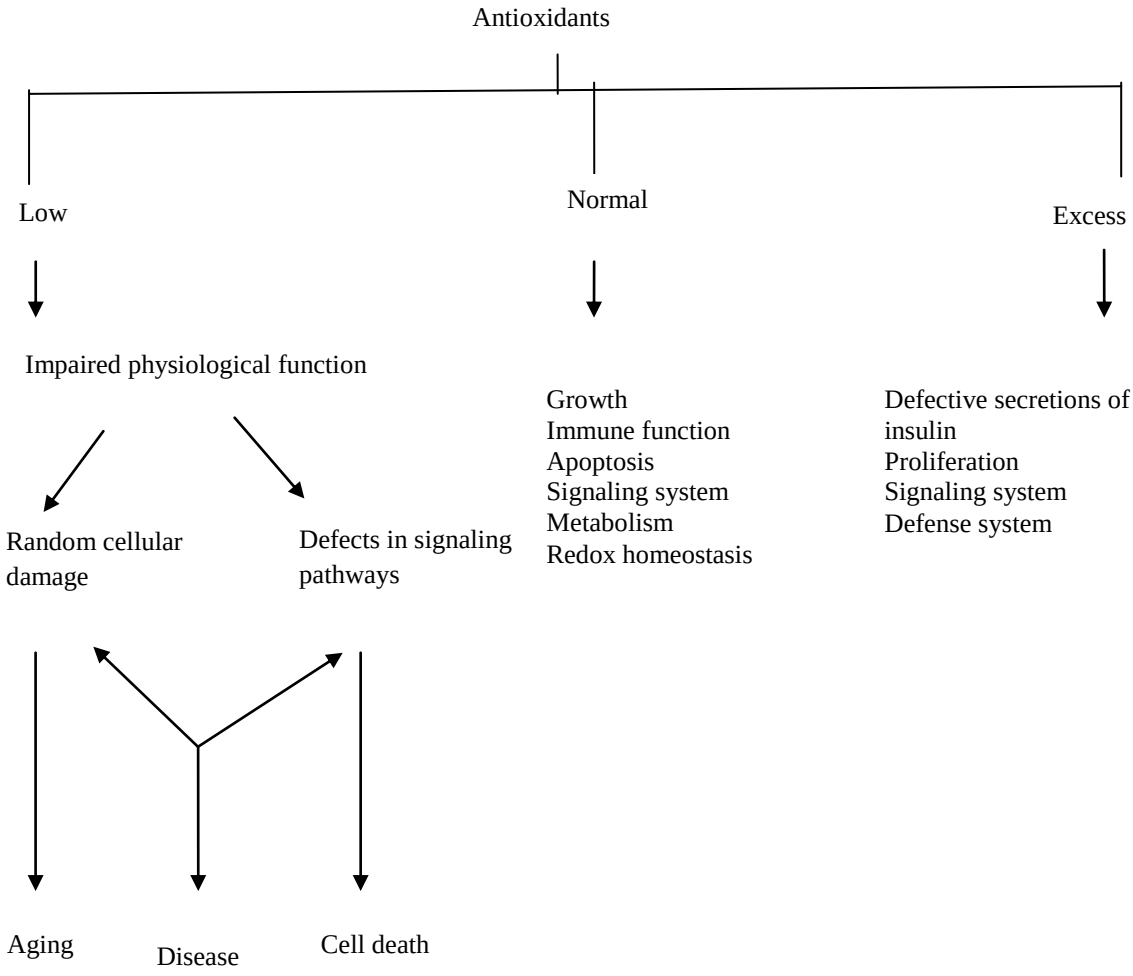


FIG. 6: EFFECTS OF ANTIOXIDANTS ON HUMAN HEALTH

Treatment of ROS mediated disorders: Despite recent advances in basic and applied biotechnology research and association studies, the optimal therapy for treating ROS mediated disorders are still at a preliminary stage. This may be due to several other agents and factors also associated with ROS mediated diseases. Therefore, direct approach of treating such diseases is rare. Some natural products, synthetic drugs, stem cell therapy and ex vivo gene transfer of stem and progenitor cells are currently used to treat ROS mediated diseases. The synthetic drugs used to treat ROS mediated disorders have many side effects. So, antioxidants therapy is most appealing to patients and clinicians due to low cost and the fact that they can be supplemented along with dietary components. Another important benefit is that these have lower side effects. Most experts use a combination of vitamins, optimize patients' nutrition and general health and prevent worsening of symptoms during times of illness and physiologic stress. A study by Zeng et al 50 demonstrates that both the anti- and pro-oxidant treatments dramatically influence the survival, apoptosis and ROS production of human umbilical cord derived mesenchymal stem cells (hUCMSCs) through the MAPK-PKC-Nrf2 pathway *in vitro*.

Simultaneously, antioxidant treatment enhances human MSCs anti-stress ability and therapeutic efficacy in an acute liver failure model. It may be due to the fact that antioxidants may activate some

anti-stress gene at the cellular level. Plants produce large amount of antioxidants to prevent the oxidative stress, they represent a potential source of new compounds with antioxidant activity. Some of the products derived from plants are currently used in commercially available drugs to treat several neuronal diseases or disorders mediated by ROS (**Table 4**).

TABLE 4: PLANTS DERIVED PRODUCTS INHIBIT EFFECTS OF ROS GENERATED COMPLICATIONS IN MICE MODEL

Sl no.	Plants	Parts	ROS mediated diseases in mice model	Inhibitory effects	References
1	*Zingiber officinale*	Zingerone	Colitis induced by TNBS (2,4,6-Trinitrobenzenesulfonic acid).	Decreasing NF-κB activity and IL-1β signalling pathway	Hsiang *et al.,*[51]
2	*Phyllanthus fraternus*	Fresh aerial parts of plants	Nephrotoxicity induced by Cyclophosphamide (CPA).	Scavenging potential and antioxidant capacity to ameliorate the CPA-induced toxicity	Singh *et al.,*[52]
3	*Artemisia iwayomogi* Kitamura and *Curcuma longa*	Stem extract	Apoprotein E deficient (apoE(-/-)) mice having atherosclerosis and hyperlipidemia like problems.	Decrease in inflammatory cytokines (tumor necrosis factor-α (TNF-α); and interlukin-6, IL-6)	Shin *et al.,*[53]
4	*Withania somnifera*	Root extract	(1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) MPTP-treated mice induced parkinsonism	Reduced lipid peroxidation and neuroprotective effects.	Shankar *et al.,*[54]

Stem cell therapy: ROS accelerate aging and age related complications like osteoarthritis, cardiovascular diseases and muscle fatigue. Stem cell therapy is a form of biological therapy. Stem cells are uncommitted cells present in multicellular organisms throughout life that have the ability to proliferate, perpetuate and differentiate into specialized cell types upon stimulation by appropriate signals. Stem cells can be derived, cultured and expanded *in vitro* [55]. Due to several ethical controversies, the application of pluripotent embryonic stem (ES) cells is often prohibited for use in biomedical research in certain countries like India. So multipotent adult stem cells (ASCs) derived from several sources like bone marrow, peripheral blood, adipose tissue, umbilical cord blood (UCB) are widely applied for therapeutic purposes. It has been proposed that endogenous antioxidant level of stem cells could influence their fate after transplantation at injured host sites. For example, endothelial progenitor cells are shown to express high level of antioxidant enzymes and to have increased abilities of DNA repair as compared to more differentiated endothelial cells. Therefore, these are less sensitive to oxidative stress–induced apoptosis [56]. Recent reports suggest hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and neural stem cells (NSCs) are ideal candidates to treat ROS induced pathological conditions and disorders (**Table 5**).

TABLE 5: STEM CELLS USED TO TREAT DIFFERENT ROS MEDIATED DISEASES

Sl no.	Adult stem cells (ASCs)	Sources	Differentiated cell types	Treatable diseases	References
1	HSCs	Bone marrow, peripheral blood	Myeloid and lymphoid lineages (neutrophil, macrophage, eosinophil, erythrocyte, and megakaryocyte lineages).	AIDs, Cancer (hepatocacinoma and sarcoma), cirrhosis,	Krishnan and Forman [57]
2	MSCs	Bone marrow and UCB, skeletal muscles, adipose tissues.	Osteocytes chondrocytes and cardiomyocytes	Diseases related to bone, cartilage like rheumatoid arthritis, fracture non union and osteogenic imperfecta and to heart viz., myocardial infarction, reperfusion, cardiac damage.	Bajada *et al.*, [58]; Sheng *et al.*, [59]
3	MSCs	Bone marrow	Neuronal cells, glial cells	Pathogenesis of several	Yim *et al.*, [60]

			and other cells of nervous system	neurodegenerative disorders, including depression, stroke, and Parkinson's disease.	
4	NSCs	Hippocampal and subventricular regions.	Neuronal cells, glial cells and other cells of nervous system.	Alzheimer's disease, spinal cord injury, epileptic seizure, demyelinating diseases, stroke and multiple sclerosis.	Ma *et al*., [61]

MSCs are a prototypical adult stem cell actively involved in tissue homeostasis, wound healing and repair processes. Allogeneic transplants of MSCs do not produce any adverse effect which may be due to their inherent immune-tolerance capacity. They release bio-molecules with anti-inflammatory, immunomodulating and anti-fibrogenic properties [62]. Recent studies have demonstrated that MSCs can be used to treat systemic diseases, local tissue defects or as a vehicle for genes in gene therapy protocols or to generate transplantable tissues and organs in tissue-engineering protocols. Aging is associated with a progressive failing of tissues and organs of the human body leading to a large number of age-related complications [63]. In order to treat degenerative or age-related diseases, infusion of stem cells into patients may lessen the complication of disease due to age.

One of the major obstacles to treat neurological disorders involves the delivery of efficacious levels of the drug to the central nervous system (CNS) as they have to cross blood brain barrier (BBB). The BBB regulates the passage of nutrients, ions, and other substances from the blood into the brain. To cross the BBB effectively the molecular weight should be less than 400 dalton (Da) and the substance should show lipophilic and hydrophilic nature and should not be a substrate for an active efflux transporter at the BBB such as p-glycoprotein. Stem cells such as NSCs and MSCs can be used to delivery drugs or RNA to the brain as stem cells can cross the BBB into the brain [64]. The use of this method to bypass the hurdles of delivering drugs across the BBB is particularly important for diseases with poor prognosis such as glioblastoma multiforme (GBM). Application of stem cell therapy to deliver drugs to neural tumors is currently in early phase clinical trial stage.

CONCLUSION: ROS are necessary evils. However, production and accumulation of ROS is a very slow process. So, future research must progress in the direction to develop new techniques that would identify the source of ROS, the targets of ROS, specific cell types and organs that may be affected by ROS. So that accumulation of excess amount of ROS can be prevented at appropriate time and proper therapeutic strategies may be followed. Further, research must aim at static treatments for neurological disorders and ROS related other complications like cancer and diabetes. At this juncture, it is a concern for all scientific communities to develop novel microbial strains that can be supplemented with pro-biotic food supplements having ability to scavenge excess ROS, so that ROS related complication could be minimized.

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