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A COMPREHENSIVE REVIEW ON OXIDATIVE STRESS INDUCED ILLNESS

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ABSTRACT

Oxidative stress, a physiological imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense. This review provides an overview of oxidative stress, delving into its underlying mechanisms, associated consequences, and emerging therapeutic approaches. The first section elucidates the sources of ROS, generation, encompassing endogenous cellular processes and exogenous process that produce oxidative stress. Highlighting the delicate balance between ROS production and antioxidant defenses, we explore how disruptions in this equilibrium trigger oxidative damage to biomolecules, including lipids, proteins, and DNA. The ensuing discussion outlines the multifaceted consequences of oxidative stress, linking it to a spectrum of diseases ranging from cardiovascular disease, Rheumatoid arthritis, Diabetes mellitus, Skin aging, Dermatitis, Auto immune disease, COPD and neurodegenerative disorder. Moreover, the impact of oxidative stress on cellular signaling pathways and inflammation underscores its pervasive influence on health and disease. We illuminate promising therapeutic interventions designed to mitigate oxidative stress. These encompass dietary antioxidants, pharmacological agents, and lifestyle modifications, offering new avenues for preventive and therapeutic strategies. This review, underscores the critical role of oxidative stress in health and disease, emphasizing the need for continued research and innovative approaches to combat its detrimental effects on human well-being.

KEYWORDS: Oxidative stress, Biomarkers, Oxidants and free radicals, Pathophysiology, Drugs.

INTRODUCTION

Oxidative stress is the accumulation of free radicals (reactive Oxygen and nitrogen species) to higher than usual level within cells which leads to cell death or tissue injury. This physiological condition can alternatively described as a severe imbalance between production of free radicals and antioxidant defenses.[1] Free radicals are usually two faced because these radicals are essential to maintain the normal physiological condition. At the same time, when there is an excessive production of free radical it may affect the body physiological process by damaging the cell (Fig.1). Oxidative stress and excessive free radical generation are caused by a number of variables such as diet, lifestyle, metabolism, phagocyte cells and some environmental elements like pollution, exposure to UV or ionizing radiation and so on. Antioxidants are the chemicals that stop the molecules from oxidizing. Antioxidants have an ability to decreases or stops the effects of free radicals.[2,3] This can be achieved by donating an electron to the free radical, which lessens their reactivity. Thus the free radical becomes non-reactive or less reactive and does not produce any unwanted physiological illness. The deviation in this process will lead to oxidative stress.[4]

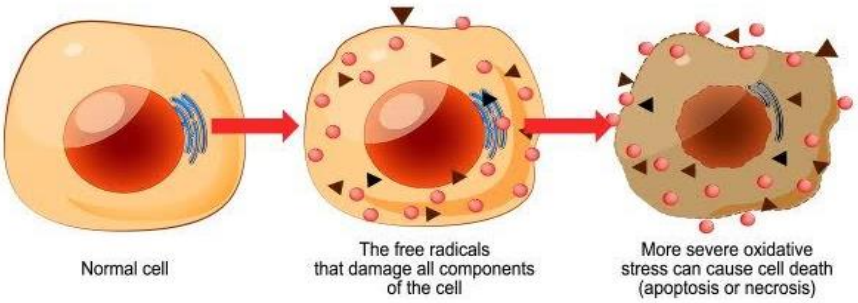

Fig.1: Oxidative damage of normal cell.

OXIDANTS AND FREE RADICALS

Reactive oxygens are classified into oxygen centered radicals and oxygen centered non radicals. The oxygen centered radicals are superoxide anion ($O_2^{\bullet}$-), hydroxyl radical ($OH^{\bullet}$), peroxy radical ($ROO^{\bullet}$) and alkoxyl radical ($RO^{\bullet}$).Oxygen centered non radicals are hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$). Also ozone (O_3), hypochlorous acid (HOCl), nitrous acid (HNO2), dinitrogen trioxide (N2O3), lipid peroxide (LOOH), are not free radicals and generally called oxidants, but can easily lead to free radical reactions in living organisms. In addition, cellular metabolites formed by either endogenous or exogenous

nitrogen can form reactive nitrogen species (RNS), such as nitric oxide ($NO^{\bullet}$), peroxynitrite ($ONOO^{-}$), nitrous acid (HNO2) and nitrite/nitrate.[5]

SOURCES OF FREE RADICALS

Free radicals can also obtained from endogenous and exogenous sources. Endogenous source include immune cell activation, inflammation, ischemia, infection, cancer, excessive exercise, mental stress and aging. some of the exogenous factor like exposure to pollutant, heavy or transition metals, drugs (Cyclosporine, Tacrolimus, Gentamicin, Bleomycin), chemical solvent, foods (smoked meat used oil and fat), cigarette smoke and alcohol are metabolised into free radical with in a body.[6,7]

GENERATION OF FREE RADICALS

Free radicals are generated by enzymatic and non-enzymatic reaction takes place in the body can induce the oxidative stress. The enzymatic reaction like of prostaglandin synthesis, phagocytosis, respiratory Chain and cytochrome 450 system is involved in free radical generations especially reactive oxygen species (Fig.2). The non-enzymatic reaction occurs when cell is exposed to ionizing radiation and also in case of mitochondrial respiration. Superoxide radical generated by NADPH oxidase, xanthine oxidase, peroxidase generates HOCl. H_2O_2 radical is also generated by action of multiple oxidase enzyme (amino acids oxidase and xanthine oxidase). Hydroxyl radical ($OH^{\bullet}$) is most reactive and it is formed by (Fenton reaction) $O_2^{\bullet}$ react with H_2O_2 using Fe^{2+}/Cu^{2+} as catalyst.NO is synthesized from arginine to citrulline oxidation by nitric oxide synthase.[8,9]

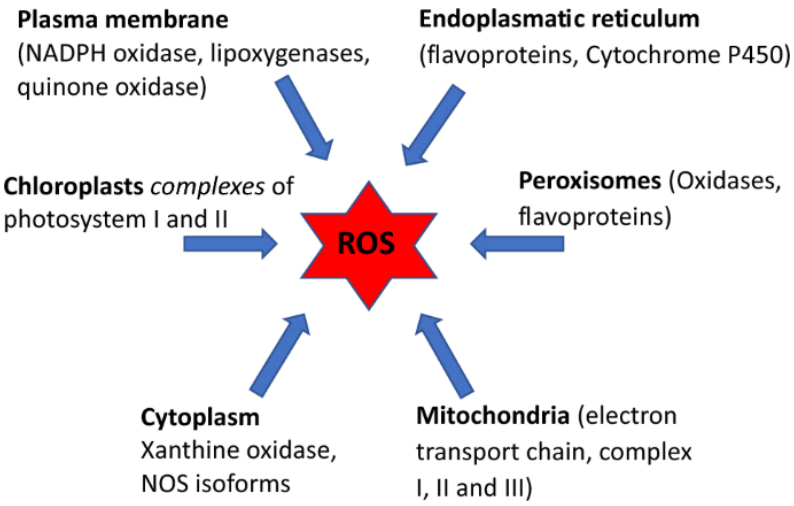

Fig.2: Endogenous sources of ROS formation.

PHYSIOLOGICAL BENEFITS

Free radical and oxidant at low to moderate concentration will produce the physiological benefits like host defence mechanism, cell signalling and so on.

Reactive nitrogen species involved in Cell to cell messenger for proper blood flow modulation, thrombosis, mitogenic process and maintain normal neural activity. Reactive oxygen species is two faced because it acts as secondary messenger in intracellular signalling cascade and maintain oncogenic phenotype and it also induced apoptosis which is anti tumorogenic process.[10]

OXIDATIVE STRESS INDUCED DISEASES

Many studies indicates that free radicals are involved in a both physiological and pathphysiological process.[11,12] The appropriate level of ROS plays a significant role as regulatory mediators in the cell signaling processes of differentiation, proliferation, apoptosis, immunity, defense against microorganism, melanogenesis and aging. Conversely, the high level of ROS is dangerous for living organism as they are detrimental to the major cellular components. When the living organisms stay at oxidative stress state for a long time the free radicals will affect various system in the body(Fig.3).[13-17]

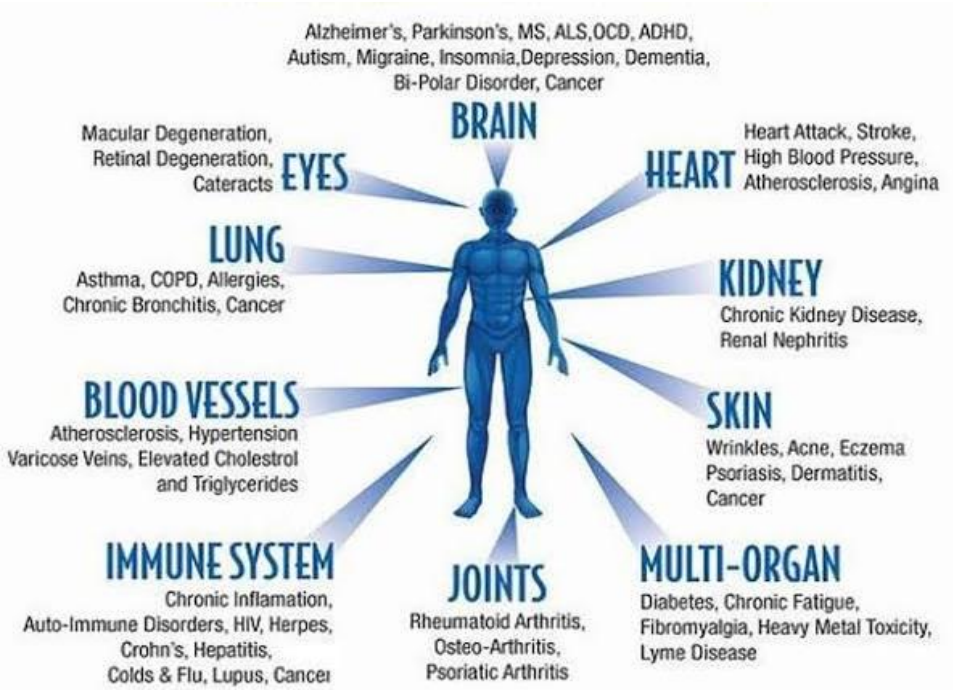

Fig.3: Effect of oxidative stress in our body.

BIOMARKERS OF FREE RADICALS

The WHO defined a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease".

The fluorescent probes are used for the detection of reactive species in blood cells via flow cytometry.[18] (Table: 1)

Table 1: Fluorescent Biomarkers.

Fluorescent probe	Free radicals detected	Fluorescence
Dihydrochlorofluorescein diacetate	$HO^{\bullet}$ $ONOO^{-}$ $ROO^{\bullet}$ $NO_2^{\bullet}$ Indirect H_2O_2	Green
4,5-diaminofluorescein diacetate or 4-amino-5-methylamino-2′,7′-difluorofluorescein diacetate	$NO^{\bullet}$	Green
Dihydrorhodamine 123	HClO H_2O_2 ONOO	Green
Hydroethidine	$O_2^{\bullet-}$	Red

ATHEROSCLEROSIS

Atherosclerosis is the result of hyperlipidemia lipid oxidation the term atherosclerosis consists of two parts atherosis means accumulation of fat component by several macrophages and sclerosis means Fibrosis layer comprising smooth muscle cells leukocyte and connective tissues.[19]

Pathophysiology: Due to alter the shear stress and disturb the laminar flow LDL particle trapped in sub endothelial space of The vessel wall this LDL is oxidised by ROS into oxidized LDL(oxLDL) which in turn stimulates inflammatory response this finally ends with atherosclerotic plaque. Hypercholesterolemia can activate ROS, reduces nitric oxide activity and induces endothelial dysfunction.[20]

Drugs: Statin can reduces cholesterol and acts on the vascular cell NADPH oxidase to increase the endothelial function statin also regulate lipid metabolism and can inhibit NADPH oxidase induced $O_2^{\bullet}$.Statin acts by lowering the lipid, alter intracellular signal

transduction, prevent inflammatory responses, improve endothelial function, block foam cell formation and inhibit platelet aggregation.[21]

Probucol and succinobucol are a class of lipid lowering drugs currently recognised as effective first line antioxidant in treatment of atherosclerosis. Probucol is a potent antioxidant drug, oxidizes and capture the oxygen ions(free radicals) which reduces plasma oxygen free radical concentration and inhibit LDL formation. Succinobucol an analogue of probucol may selectively inhibit redox sensitive endothelial and monocyte inflammatory gene expression.[22-24]

HYPERTENSION

Reactive oxygen species promotes hypertension by causing endothelial dysfunction. Alter The contractility and vascular remodeling. Multiple regulatory systems involving the heart, vessels, kidneys, brain, and immune cells, underpin the pathophysiology of hypertension, and oxidative stress has been considered as a unifying factor linking these elements.[25]

Pathophysiology: Altered superoxide production decreases in bioavailability by scavenging the compound creating high reactive peroxy nitrate which oxidizes NO synthesis cofactor which cause NOS and coupling lead to endothelial dysfunction. Altered NO bioavailability leads to impact vasodilatation. Both H_2O_2 and superoxide regulate vasodilatation. These changes leads to hypertension.[26]

Drugs: ACE inhibitor and sartans (angiotensin II receptor blockers).Angiotensin II is a potent stimulus for NADPH oxidase results in ROS generation. Losartan has the ablility to correct endothelial dysfunction of resistance arteries. Captopril and Quinapril reduces PMA stimulated ROS production.[27,28]

ANGINA PECTORIS

Angina pectoris is defined as a substernal chest pain, pressure, or discomfort that is typically exacerbated by exertion and/or anxiety or other emotional or mental stress, lasts greater than 30 to 60 seconds. The pain or discomfort may radiate down the arms, up into the neck, into the lower jaw, into the epigastrium, and sometimes into the back. It typically lasts between 5 and 15 minutes. Sometimes it is described as an ache or a burning. In women and the elderly population, angina may present in a more atypical fashion or as an anginal equivalent and can be characterized by dyspnea, fatigue, weakness, palpitations, or dizziness.[29]

Pathophysiology: NO is an important signaling molecule involved in the maintenance of vascular function. A decreased nitric oxide (NO) bioavailability and an increased oxidative stress play a pivotal role in different cardiovascular pathologies.

The high circulating levels of endogenous methylarginines, that is, symmetric, asymmetric dimethylarginine (SDMA, ADMA) and monomethylarginine (MMA), act as NO-synthesis inhibitors. The disturbance in NO level lead to an impairment of endothelium dependent vasodilation, anti-oxidant condition.[30]

Drugs: Allopurinol can reduce myocardial oxygen consumption for a particular stroke volume. This effect might be related to reduction in oxidative stress because xanthine oxidase is known to use molecular oxygen to produce oxidative stress, and hence blocking the enzyme might prevent oxygen wastage and thereby increase the supply of molecular oxygen in ischaemic tissue and this in turn regulates the NO level.[31]

DIABETES

Oxidative stress plays a significant role in the development of vascular complications in diabetes, particularly type II diabetes. Elevated levels of ROS in diabetes may be caused by a decrease in oxidative damage or an increase in production by the antioxidants catalase (CAT--enzymatic/non-enzymatic), superoxide dismutase (SOD), and glutathione peroxidase (GSH-px). The tissues are vulnerable to oxidative stress due to the fluctuation in these enzyme levels, which promotes the growth of diabetic problems. An increase in vascular illnesses other than hyperglycemia, according to epidemiological research, can be a significant factor in the explanation of diabetic mortality.[32]

Pathophysiology: In diabetes mellitus, oxidative stress is mostly due to the mitochondria. The oxygen used during oxidative metabolism in mitochondria is altered into oxygen free radical (O), a significant ROS is transformed into other reactive species (RS) like ONOO, $HO^{\bullet}$, and H_2O_2. Insulin signaling is influenced by ROS/RNS. The ROS and RNS are produced in response to insulin to carry out their full physiological function, but insulin signaling also controls them negatively, causing them to develop insulin resistance, a risk factor for type II diabetes.[33]

Drugs: Metformin is effective in reducing the level of oxidative stress factors by regulating the antioxidant system of the cell. In response to changes in cellular energy in skeletal

muscle, metformin activates intracellular signaling pathways, which enhances glucose absorption.[34] Metformin's main action, as demonstrated by numerous investigations, is the suppression of mitochondrial complex I (NADH: ubiquinone oxidoreductase). The formation of cellular ROS may be greatly influenced by mitochondrial complex I. It is well known that a blockage of this complex results in a lessened generation of reactive species because less NADH+ can transport electrons. As a result, metformin lowers endogenous ROS levels in mitochondria.[35]

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) results in the breakdown of articular cartilage and bone. It is a chronic autoimmune disease marked by immune cells infiltrating the synovial membrane and causing synovial hyperplasia. It has been established that oxidative stress (OS) contributes to the development of this condition by damaging DNA, lipids, and proteins and causing synovial inflammation.[36]

Pathophysiology: Lipid peroxidation (measured by serum levels of malondialdehyde (MDA)) and disease activity (measured by the disease activity score DAS-28) were found to positively correlate with one another, supporting the idea that oxidative stress and disease activity in RA.[37]

Drugs: Infliximab is a crucial anti-oxidant that protects against oxidative DNA damage and lipid peroxidation in RA patients. When infliximab binds to TNF, it prevents TNF from attaching to its receptors and stops the intracellular signaling process that triggers gene transcription and subsequent biological activity. The oxidation of DNA and lipids, as well as the glycosylation of reduced sugar, have all been linked to ROS as potential causes of damage.[38]

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive deterioration of cognitive functions and drastic changes in behavior and personality. Oxidation of proteins, glycation, and lipid peroxidation end products generates toxic species, such as peroxides, alcohols, aldehydes, free carbonyls, ketones, and cholestenone produces oxidative modifications in nuclear and mitochondrial DNA.[39,40]

Pathophysiology: AD pathophysiology emanates from the deposition of amyloid β (Aβ) plaques and the formation of hyperphosphorylated tau proteins (p-tau) causing neurofibrillary tangles (NFTs). The enzymes and signaling mechanisms involved in the control of tau protein can be affected by oxidative stress.[41]

Drugs: Aducanumab- An anti-amyloid antibody intravenous (IV) infusion medication called aducanumab (Aduhelm) is administered once a month. The FDA has given it expedited approval to treat individuals with mild cognitive impairment (MCI) or mild dementia caused by Alzheimer's disease who have elevated beta-amyloid levels in their brains and who are also living with MCI or mild dementia.[39]

SKIN AGING

Aging of the skin is a complicated biological process that is impacted by both external and internal factors. The primary cellular disruption causing senescence in the skin is the change in oxidative equilibrium. Reactive oxygen species (ROS) are primarily formed during cellular oxidative metabolism during the synthesis of adenosine triphosphate (ATP) from glucose and mitochondrial failure in chronological aging. Oxidative stress is linked to increased formation of reactive oxygen species (ROS) and decreased levels of enzymatic and non-enzymatic defenders during the aging process.[42]

Pathophysiology: Extrinsic skin aging, commonly known as photoaging, is mostly caused by exposure to UV light. A complex series of internal reactions in the skin are mostly responsible for the damage to the skin induced by various external elements. They begin with the production of reactive oxygen species (ROS), which oxidatively damages lipids, proteins, nucleic acids, and cell membranes.[43]

Production of reactive oxygen species in excess can lead to chronic inflammation, which can subsequently cause collagen fiber disarray and fragmentation, impair skin cell functions, and aggravate skin diseases such as aging of the skin.[44]

Drug: In humans, extrinsic aging is treated with topical tretinoin. In the US, 0.05% concentrations of tretinoin, a nonaromatic retinoid of the first generation, are authorized for use as anti-aging treatment. It has been demonstrated to be able to lessen wrinkles, skin elasticity loss, and pigmentation-signs of early skin aging brought on by UV radiation.

Tretinoin completely blocks the formation of interstitial collagenase and gelatinases, preventing the breakdown of collagen in UV-exposed excised skin (photoaged).[45]

DERMATITIS

It is an inflammatory disease observed in the skin. Atopic dermatitis is characterized by a chronic and recurring skin disease that typically begins in childhood and has a variable course. The term atopic refers to a tendency to produce more immunoglobulin E (IgE) in response to allergens.

The air pollutants almost certainly cause oxidative stress in the skin, which can lead to skin barrier dysfunction or immune dysregulation. It will not only directly damage the skin's cellular structures but also increases dermal inflammation, weakening of skin barrier function, and allows microbial pathogens to infiltrate the skin.[46]

Pathophysiology: Through lipid oxidation, oxidative stress can damage the deoxyribonucleic acid (DNA) of keratinocytes and interfere with skin barrier function and skin defects, leading to chronic inflammation. Chronic skin inflammation is linked to an increase in reactive oxygen species (ROS) like superoxide ($O_2^{\bullet}$) and hydrogen peroxide (H_2O_2).

Reduced antioxidant levels and elevated lipid peroxidation are the root causes of oxidative stress in dermatitis. oxidative stress will raises the production of pro-inflammatory cytokines, activates natural killer T cells, cellular dermal infiltration, and results in dermatitis. When defense systems are undermined and threatened during an oxidative imbalance, free radical damage results. The skin has an antioxidant system, but too much ROS can overpower it. Uncontrolled generation of ROS is a major factor in several skin conditions.[47]

Drug: Tacrolimus ointment is a topical calcineurin inhibitor (TCI) that was developed specifically for the treatment of atopic dermatitis (AD). Topical tacrolimus is helpful for several inflammatory skin disorders, including vitiligo, psoriasis, alopecia areata, contact allergy, and skin grafting/transplant. Tacrolimus mainly inhibits T-cell activation and the release of proinflammatory cytokines by acting on T cells in inflammatory skin.[48]

MULTIPLE SCLEROSIS

Loss of the myelin sheath encasing CNS axons is the fundamental physiological abnormality in multiple sclerosis. When the ratio of oxidants to antioxidants is out of balance, favoring

oxidative stress. Chemical, physical, or microbiological factors in tissues and cells can also lead to oxidative stress.[49]

Pathophysiology: Acute lesions exhibit loss of oligodendrocytes, extensive macrophages, demyelination, and axonal destruction. But an ill-defined margin with minimal astrocytic proliferation. Less inflammatory lymphocytes, on the other hand, are present in more persistent lesions, which also shows persistent macrophage deposition, hypertrophic astrocytes, and oligodendrocytes with active remyelination.[50]

Drug: Glatiramer acetate (GA) is a specific MS immunomodulator that induces the synthesis of Th2 cytokines and reduces the frequency of relapses and the formation of active brain lesions. Proinflammatory cytokines play a role in free radical production in the peripheral immune system as well as in the central nervous system (CNS). The effect of GA on iNOS, superoxide radicals (O2–), and 3-nitrotyrosine production by peripheral blood adherent mononuclear cells (PBAMs) was assessed. It is demonstrated that *in vitro* GA reduced spontaneous and LPS-induced iNOS, 3-nitrotyrosine, NO, and O2– production, and that similar inhibition can be demonstrated *ex vivo* in mononuclear cells obtained from GA-treated patients. The inhibition of the production of free radicals in PBAMs may represent a new therapeutic mechanism against inflammation during MS.[51,52]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The long-term respiratory lung illness known as chronic obstructive pulmonary disease (COPD) has major systemic symptoms, related comorbidities, and a detrimental effect on quality of life. It can be characterized by obstruction of airflow and is linked to tissue destruction and lung inflammation. Oxidative and carbonyl stress have been linked to cell death and damage observed in the COPD airways, with smoking and air pollution being recognized as important initiators.[53]

Oxidants impede cilia function and cause epithelial cells in culture to produce more mucus (high-molecular-weight glycol conjugate). Additionally, oxidants damage fibroblasts, decrease surfactant activity, promote thromboxane formation, and have other effects that may impair pulmonary lung mechanics and lung repair mechanisms in COPD patients.[54]

Pathophysiology: COPD is caused by oxidative stress, which activates multiple mechanisms such as the proinflammatory transcription factor nuclear factor-KB (NF-κB), p38 mitogen -

activated protein kinase (MAPK), production of autoantibodies to carbonylated proteins, decreased sirtuin-1 expression, DNA damage, decreased histone deacetylase (HDAC)-2 expression, decreased activity of antiproteases, and increased release of transforming growth factor (TGF)-β.[55]

Drug: L-carbocisteine, a mucolytic agent exhibits antioxidant properties. Lcarbocisteine was tested in human airway epithelial cells to see if it could inhibit oxidant-induced cell damage. The percentage of apoptotic cells following hydrogen peroxide exposure was decreased by L-carbocisteine treatment. Antioxidant effects of L-carbocisteine may also be seen in the respiratory system.[56]

Carbocisteine-induced elevations in thiol-GSH levels promote HDAC2 recruitment and inhibit H4 acetylation of the IL-8 promoter, thereby amplifying dexamethasone activity even in models with elevated oxidative stress.[57]

CONCLUSION

Oxidative stress plays a critical role in most of the diseases caused due to lifestyle changes. Oxidants and free radicals are responsible for oxidative stress and they induce major disease in our body. Various biomarkers are used to determine the excessive free radical production but it is not applicable for all the diseased states. These biomarkers cannot be used to test in vivo. Certain biomarkers mainly target the deadly cardiovascular disease induced by free radicals. This review provides new insight into research on stress induced diseases in different system in our body and their treatment.

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