NON-RADICAL SCAVENGING MECHANISM OF ACTION OF OS MODULATORS-

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ABSTRACT-

Antioxidants and free radicals have attracted attention in cellular biology because of their central functions in many physiological environments and all their implications in various diseases. Exogenous sources (mitochondria, endoplasmic reticulum, peroxisomes, phagocycotic cells etc) & endogenous (pollution, smoke, alcohol, tobacco, heavy metals etc) are sources of free radicals, they both produce reactive species of oxygen and nitrogen. Free radicals can degrade nucleic acids, lipids, and proteins, causing oxidative stress by disrupting the normal redox balance. Diabetes, neurodegenerative disorders (parkinsons, alzheimers, and multiple sclerosis), CVD disorders (artherosclerosis and high blood pressure), and pulmonary disorders have all been related to this. The imbalance between the development and aggregation of reactive species of oxygen in cells and tissues causes oxidative stress and the cellular system's capability to refines these reactive materials. Despite the fact that environmental stressors (such as UV, ionising radiations, toxins, and heavy metals) contribute to accelerate the ROS output, resulting in a discrepancy that leads to cell and tissue damage, ROS may play and do a variety of physiological roles. Several antioxidants which includes vitamin E, flavanoids & polyphenols, have been researched in recent years for their anti-oxidant properties, both actual and suspected. Oxidative Stress (OS) is a characteristic of several disorders, and OS modulators can be helpful in their treatment. Oxidative Stress could be influenced by activating / inhibiting sirtuins and the main receptor of endogenous enzymes of antioxidant, nuclear factor erythroid-2 related factor 2 (Nrf2).Free radicals play a part in physiological processes at low - to - moderate levels, but Oxidative Stress (OS) is induced by an aggregation of free radicals or a reduction in antioxidant levels.. It's a risky process that damages cellular conversations which includes lipids, RNA, proteins & DNA, which results in many diseases. This report discusses the formation, origins, and molecular objectives of free radicals, as well as a short description of pathogenesis of many diseases causes due to ROS.

INTRODUCTION-

MODULATORS- A modulator is a connection that connects two distinct signals so that they can later be separated and data acquired. "A substance that modifies the action of a molecule or a biochemical pathway, especially transmitter modulators," in clinical terms.

FREE RADICAL SCAVENGERS- An antioxidant, for example, is a substance that helps protect cells from the destruction causes by free radicals. Free radicals have the property of high reactivity which are generated by normal metabolism of the cell. In mammalian cells, many defensive mechanisms work to prevent the creation of free radicals or to forage excess amounts that have already formed. Scavengers of free radical either eliminate formation of reactive species of oxygen or destroy them before they can harm the cell's critical parts.

OXIDATIVE STRESS- Oxidative Stress (OS) arises when there is a discrepancy between the accumulation and aggregation of reactive species of oxygen (ROS) in tissues and cells and the system's biological capacity to nullify these reactive compounds.

Reactive species of oxygen (ROS) is produced as a product of metabolism of oxygen & can be used for variety of physiological functions, which includes cell signalling.

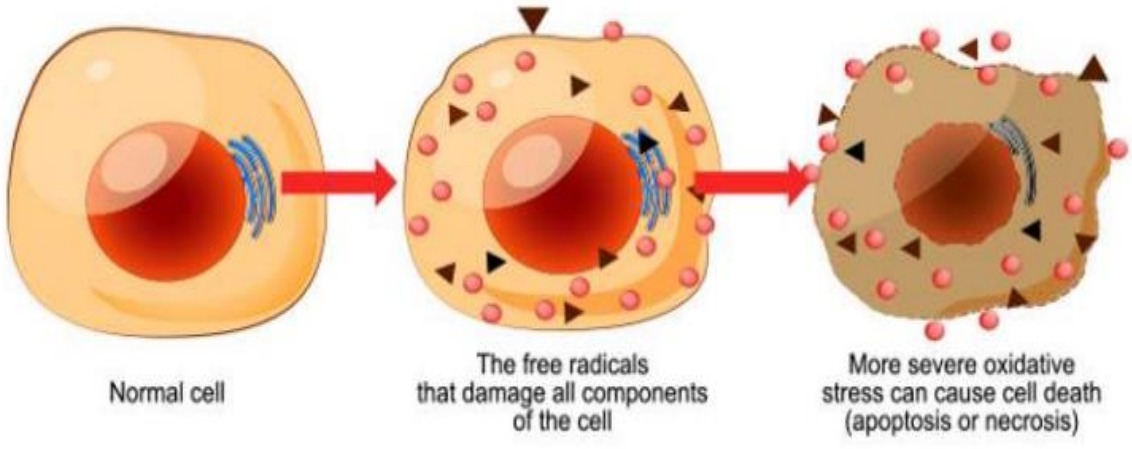

Figure 1

OXIDATIVE STRESS FREE RADICAL SCAVENGING MECHANISM OF ACTION-

OXIDATIVE STRESS-

OS is defined as a discrepancy in ROS quantity and cellular antioxidants endogenous pathways (OS). As ROS plays an important part in immune system & inflammatory signalling by eliminating pathogens [1, 2], their effectiveness of treatments within the multiple physiological network are unknown.

OS is linked to the expansion of several pathological or uncontrolled conditions and disorders includes neurodegenerative diseases, cancer, & ageing, by affecting many essential components of cells. We still don't have a full understanding of OS's various functions in human biology and pathology, despite decades of study. As a consequence, in the comparatively brief history of oxidative medicine, the functions of production of free radicals gets totally changed. [3].

Various methodological difficulties occurs during the process of drug development, a lack of knowledge concerning antioxidant metabolism and its correlations with physiologically related processes in body & a lack of similarity between biological markers of OS are all contributing to the current state of uncertainty about the effectiveness of antioxidant therapy. OS modulation is important for the creation of new therapies for a variety of disorders for which there are currently no successful treatments. This special issue's main aim is to consider different pharmacological and chemical aspects of OS modulation science[4].

Oxidative stress is a feature of several disorders, and OS modulators can be helpful in their treatment. Two pathways for modulating OS are the activation or inhibition of sirtuins and nuclear factors. Unfortunately, a number of clinical trials concerning antioxidant therapies have failed, and the reasons for this have yet to be fully understood.

OS is also indulged in the physiology of a broad variety of bacteria. It affects DNA replication of bacteria , gene expression, cell division, protein modification & other important functions. OS environments have a favorable or negative impact on the virulence of many bacteria.

Once oxidants & antioxidants in a cellular process are out of control, (OS) occurs. Reactive species of oxygen (ROS) or improper antioxidant system operation cause the imbalance. [5]. It is impossible to overstate the importance of molecular oxygen in biology, as it is required for optimal function of cells and the survival of all the living organisms. As oxygen is essential for life and is indulged in gene transcription, signal changing & other functioning of cells, it also has a detrimental effect on biomolecules in the form of production of species of reactive oxygen (ROS). The univalent metabolic reduction status of oxygen is responsible for the

development of reactive oxygen species, which has a negative effect (ROS). The another very important species, nitric oxide (NO), controls, among other things, vascular smooth muscle cell relaxation and proliferation, angiogenesis, leukocyte adhesion, platelet aggregation, vascular tone, thrombosis & hemodynamics. [6].

Free form of Nitric monoxide (NO•) is toxic for biomolecules. Many of the chemical entities made up of free radicals that include oxygen include the hydroxyl radical (HO•), hydroperoxyl radical (HO2 •), superoxide radical anion (•O2) & peroxyl radicals (ROO•). In this case, word "ROS" applies to both oxygen radicals and easily converted non-radicals. According to Halliwell, a free radical is a genus of one or more free radical that can exist on its own. [11,12]. Free radicals are thought to be part and play a crucial role in a wide range of biological processes as well as biological evolution. When O2 is present in abundance, it is the very vital & important entity for all living organisms on this planet and also used in various biological reactions but if it is present in excess then it has many negative effects.

An imbalance btw the antioxidants & free radicals then it causes oxygen destruction to proteins, fats, carbohydrates & nucleic acids,. [13,14] Antioxidants have tended to shield the body from the harmful effects of free radicals.[15 and 16] Natural antioxidants boost endogenous antioxidants' anti-reactive species of oxygen (ROS) defences & preserve the minimum balance by counteracting ROS. [15–17, 19–20]. To treat various diseases like malignant tumors modern medicines used the combination of both natural and herbal products[19, 20] Several herbal medicines have been shown to be cancer-resistant. Herbal drugs can have antitumor properties by stimulating the immune system, particularly cell differentiation, telomerase inhibition & cancer cell apoptosis according to previous studies. [20, 21 22]

HEALTH OF HUMAN & OXIDATIVE STRESS-

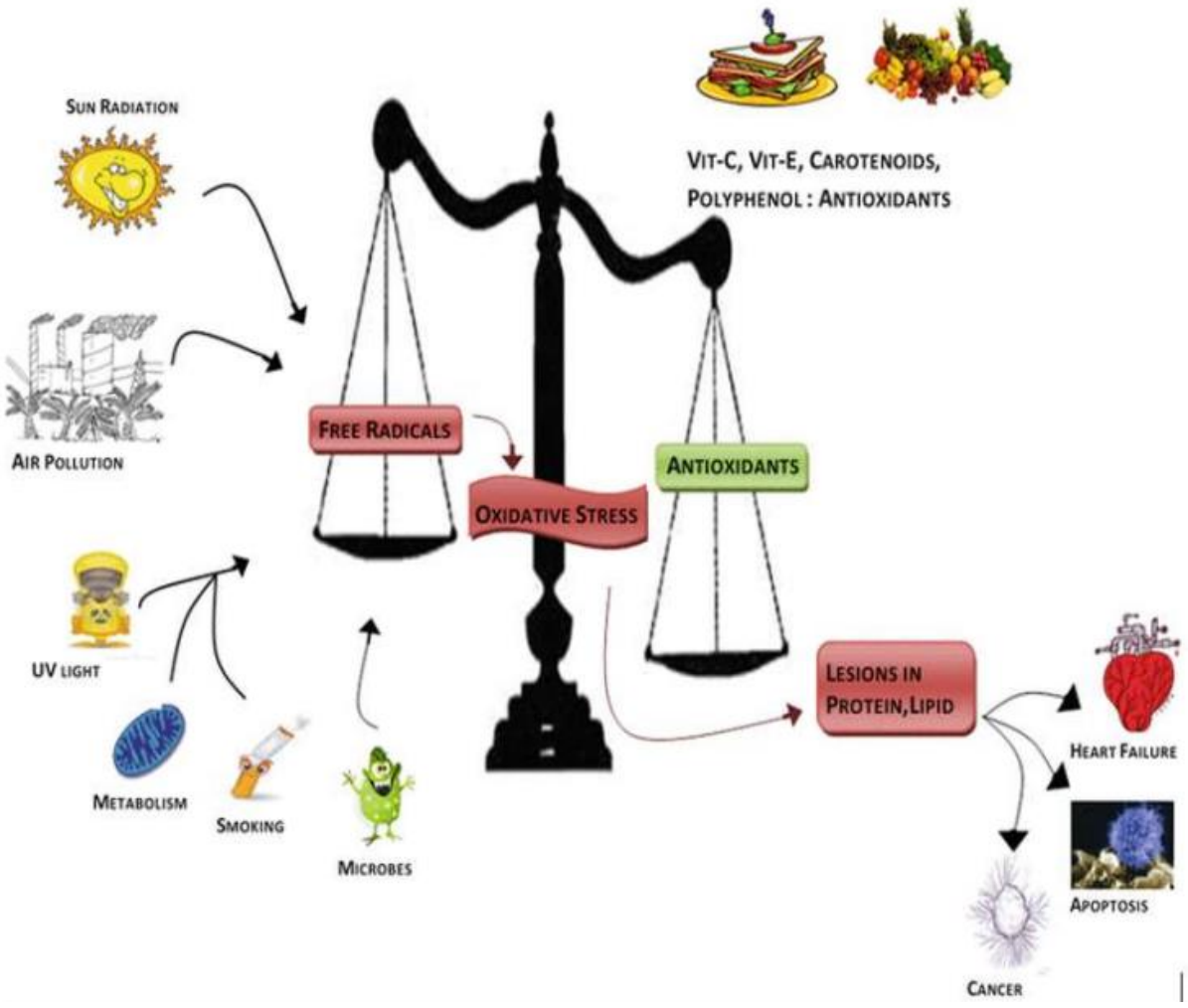

Figure 2

Free radicals are an important part of any biological reaction and are needed for aerobic life and metabolism. The phagocytosis, respiratory chain reaction, prostaglandin synthesis, the cytochrome P450 mechanism & oxidative phosphorylation are all examples of enzymatic and non-enzymatic reactions that occur in the mitochondria (i.e. aerobic respiration).

The byproducts of natural cellular metabolism, ROS and RNS, have both negative and positive effects in the body. [23]. At low to moderate concentrations, certain free radicals have physiological benefits in vivo, such as phagocytosis, infectious agent defence, energy production, cell development, role in various cells signalling processes & the activation of a mitogenic reaction.

As part of their normal function, all cells generate free radicals. Oxygen free radicals damage biological tissue and contribute to injury. Cell structures, lipids, proteins, and nucleic acids are all killed by lipid peroxidation, which is the mechanism of

injury. They cause further tissue damage by rupturing cell membranes and releasing intracellular components. [24]. Antioxidant enzymes and nonenzymatic defence schemes use a range of antioxidant pathways to reduce the adverse impact of reactive oxygen species (ROS).

OS is a harmful situation that arises as reactive species of oxygen (ROS) levels rise & antioxidant levels fall. This could result in tissue degradation as a result of physical, biological, and psychological factors, which shows results of having tissue injury and disease in humans. [25]. Living organisms have evolved a diverse defence system and body that uses a range of defence mechanisms to combat free radical-induced oxidative stress, comprising prophylactic, repair, physical, and antioxidant defences.

The pathogenesis of many human diseases have attributed to free radical reactions resulting from oxygen, including [26, 27, 28]:

• Neurodegenerative diseases include Alzheimer's disease, multiple sclerosis, Parkinson's disease, memory loss , amyotrophic lateral sclerosis & depression.

• CVD disorders includes atherosclerosis, coronary hypertrophy, ischemic heart disease hypertension, trauma & shock.

Pulmonary complications include inflammatory lung diseases like asthma & COPD.

• Infant babies are more likely to have periventricular leukomalacia, bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, and necrotizing enterocolitis. Rheumatoid arthritis is an inflammatory disease that affects the joints.

• Kidney issues including glomerulonephritis and tubulointerstitial nephritis, as well as progressive renal failure, proteinuria, and uremia.

• Maculopathy, as well as cataracts and age-related ratina.

• The mechanism of ageing

• Complications of diabetes.

• Skin tumours • Immunodeficiency

• Pancreatitis and cirrhosis of the liver.

• Infertility • AIDS

THE DESTRUCTIVE EFFECT OF FREE RADICALS AND THEIR MECHANISMS-

A free radical is an entity that has a valence electrons in its outer orbitals and is highly reactive in the body, oxidizing or reducing (giving or taking an electron from) other atoms. Oxygen species that are reactive are generated as waste products of aerobic respiration's electron transport chain and are primarily generated by mitochondria. While the bulk of electrons join the third electron transport pump mechanism, approximately 1% to 3% of them react easily with oxygen, forming the superoxide radical. [29] Free radicals play an important role in the physiological processes of the body, including the development of superoxide and nitric oxide by neutrophils and macrophages, that helps in phagocytosis and the killing of bacteria by these cells. Superoxide radicals generated by phagocytic cells may be viewed as non-selective antibiotics that can destroy any contaminating bacteria (along with neutrophils) while also potentially harming nearby tissue cells, as these radicals leads to the inflammatory response. These free radicals also encourage fibroblast cell proliferation (mitotic division), which promotes scar tissue formation and lymphocyte proliferation during the cloning process. No also helps vascular smooth muscle relax, that leads to dilation of vessels and increased blood flow to the inflammatory site. [30]

Both endogenous and exogenous sources provide ROS and RNS. Endogenous generation of these species includes immune cell stimulation, inflammation pathways, extreme exercise, mental activity stress, ischemia, ageing and cancerous infectious disorders. Exogenous ROS sources include pollution of sewage, air, water as well as alcohol, smoking, opioids, heavy metals, some medications (tacrolimus and cyclosporine), radiation, cooking, and certain solvents like benzene. These substances biodegrade in reactive oxygen species after entering the (ROS). Changes in proteins and nucleic acid are caused by the adverse effects of reactive species of oxygen(ROS) on cell macromolecules like nucleic acids, lipids & proteins. Many diseases, including diabetes, heart disease, atherosclerosis, liver disease, and cancer, start and progress because of free radical development. [31]

LIFESTYLE AND ENVIRONMENTAL FACTORS EFFECTS-

OS may arise when ditetic antioxidant consumption do not meet antioxidant requirements, or when the right balance of nutrients is not includes throughout the diet. If the relative levels of antioxidants are too high, inefficient regeneration of

oxidised vitamins to their reduced state can occur, potentially resulting in the accumulation of vitamin radicals. Hypertensive and coronary disease patient have inadequate levels of vitamin E and C in their blood. [32-37]. High-salt and high-fat diet, which has been related to hypertension and atherosclerosis, have also been linked as a result of a rise in oxidative stress [38, 39]. Smoking & drinking a lot of ethanol, two dietary health conditions for hypertension and atherosclerosis, which improve oxidative stress. [40-41].

OS continues to aid the enhancement of high blood pressure and atherosclerosis. The capacity of ROS to alter proteins and lipids will cause modifications that are common in these two vascular diseases.

Figure 3

FREE RADICAL-

The general concept of free radical is "molecules or molecular fragments that contains one or more unpaired electrons in atomic or molecular orbitals" [42]. Uncharged, highly reactive, and short-lived molecules are known as free radicals. Human bodies contain 10,000–20,000 free radicals, that invade each & every cell. Many of these radicals are beneficial because they collaborate with immune cells to kill bacteria and tone smooth muscles, which regulate blood vessel and internal organ activity. Free radicals produced in our bodies uncontrollably can cause autoimmune disorders, cardiac and neurodegenerative diseases, cancers, and other issues. [43].

One should be mindful of the basics when it comes to their own existence. Free radicals are generated at the time of synthesis of ATP in mitochondria. The two most well-known groups are reactive species of oxygen (ROS) and reactive nitrogen species (RNS) (RNS). ROS and RNS are used in both radical and nonradical (oxidant) entities. Radicals are less stable & have a greater reactivity than non-radicals. Non-radical derivatives/ oxidants could easily be transformed to free radicals in living organisms through a variety of reactions. [44]. In mitochondria, the non-enzymatic process of oxidative phosphorylation leads to the development of ROS and RNS. Excessive synthesis of hydroxyl radicals and peroxynitrite, for example, causes lipid peroxidation, which damages cell membranes and lipoproteins. Malondialdehyde (MDA) and other diene derivatives which are mutagenic and cytotoxic compounds are formed as a result. ROS/RNS damage proteins, resulting in structure deformity and enzyme function loss. These species infiltrate DNA, causing oxidative lesions that leads to mutagenesis and impairing functional development. To counteract the damage caused by oxidative stress , the body has variety of antioxidants. [45,46].

THE ANTIOXIDANTS-

Antioxidants are chemical compounds that bound to free radicals & protect biological molecules from destruction. Endogenous antioxidants are included in our bodies that are used to counteract various free radicals. Exogenous antioxidants, also known as dietary antioxidants, are gathered from external sources, mostly via food diet. This kind of antioxidant can be found in brightly coloured plants, fruits, and grains. Dark chocolate, berries &green tea are also good sources of antioxidants. There are currently a plethora of oral supplements marketed as nutritional antioxidants on the market.

By losing their own electrons, antioxidants binds to free radicals.As a result, chain reactions that are oxidative are halted, and free radicals can no more infiltrate the cell. After giving an electron, an antioxidant forms a free radical. They aren't dangerous because they can withstand electron shifts without becoming reactive. Within the cell there are two lines of antioxidant defence. Beta-carotene, Vitamin E & coenzyme Q make up fat-soluble cell membrane, first line. Vitamin E is believed to be the more effective chain-breaking antioxidant inside the cellular membrane. The antioxidant which is water soluble present within the cell. The enzymes involved are, superoxide dismutase (SOD), vitamin C, catalase & glutathione peroxidase. [47].

To nullify free radicals, both endogenous and exogenous in nature, a variety of components function together.

- All of them are antioxidants produced by endogenous enzymes.
- Metabolic, non enzymatic or nutrient based antioxidants.
- Proteins that binds metals include albumin, lactoferrin, ferritin & ceruloplasmin.
- Phytonutrients & phytoconstituents are two types of phytonutrients.

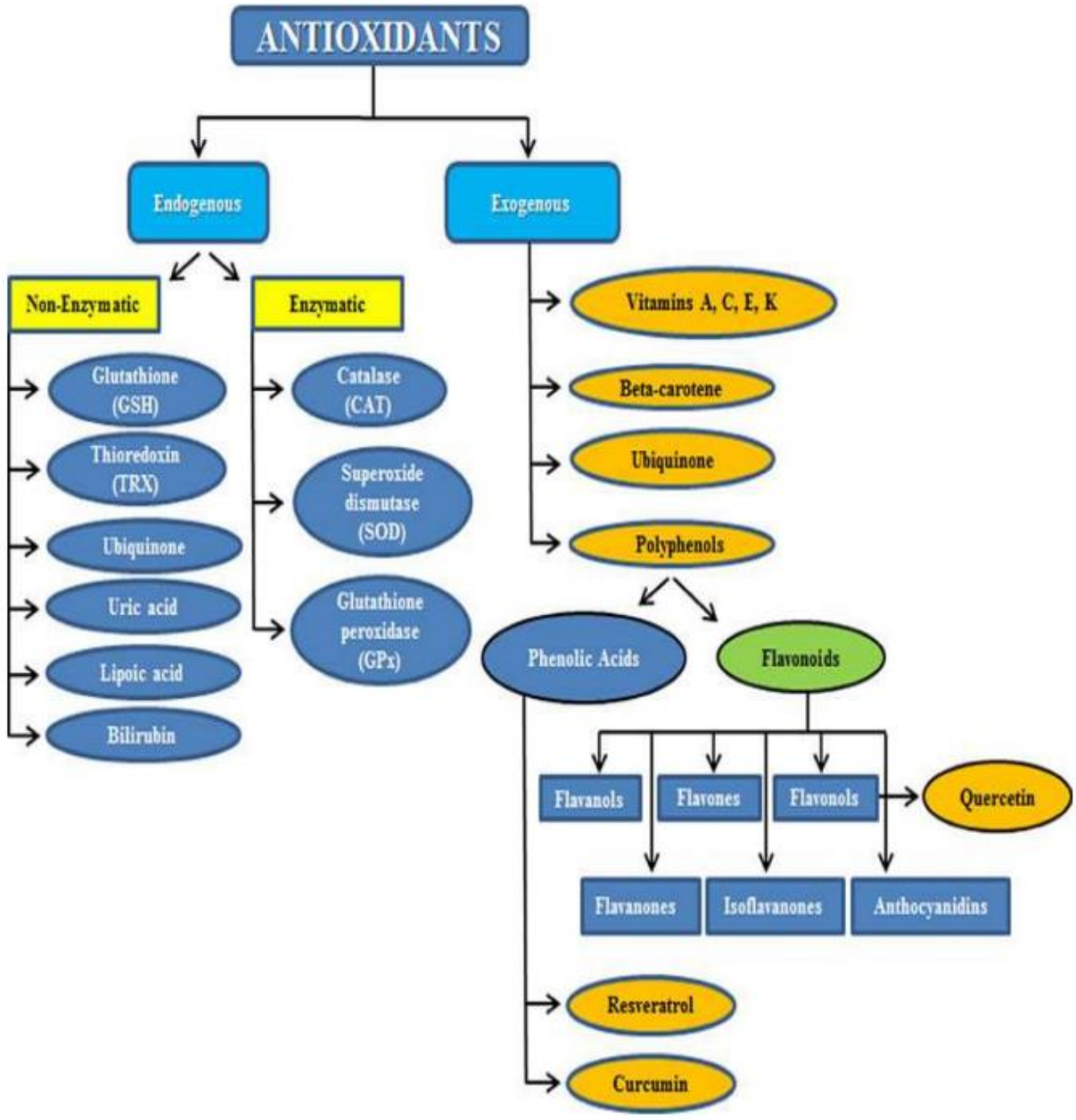

Figure 4

MECHANISM OF ANTIOXIDANT ACTION-

Antioxidants have two modes of action: direct and indirect. In direct action, agents that can kill oxidised compounds are used. Vitamins E and C, as well as thiol compounds such as cysteine, GSH, and dihydrolipoic acid, can both neutralise ROS and lipid peroxides directly. Polyphenols, which are used in fruits and wines, as well as certain antihypertensive and antilipidemic medications like ACE inhibitors and statins, have direct antioxidant function.

Not all antioxidants are made equal when it comes to their ability to suppress inflammation. Few antioxidants are more active than others due to chemical compositions. Antioxidants possessing a large capacity to reduce are not only greatly efficacious against stress of oxygen and also produces antioxidants with low reduction potential. To hinder the aggregation of vitamin radicals and continue capacity of physiological antioxidants this is necessary [48]. Some antioxidants also prevent other enzymes from harm.

The solubility of antioxidants in water or lipids influences the location where they act. Lipoic acid is lipid and water solubility, for example lipoic acid is transformed to dihydrolipoic acid within the cell, that can easily travel out of the cell thereby shield both the intracellular and extracellular compartments of oxidative stress [48]. Vitamin E is lipophilic, rendering it ideal for protecting endothelial membrane lipids from oxidative harm. Since vitamin E is present generously in low density lipoprotein holding it in a reduced state is important [49]. CoQ10 is an antioxidant that is lipid soluble that can be used in a wide range of biological membranes. CoQ10 saves vitamin E and defends against lipid peroxidation better than vitamin E as both are found in the same liposomal membrane. [50].

Vitamin C is an antioxidant which is soluble in water possessing anti inflammatory properties. Due to its prevelance in the plasma and ability to reduce , vitamin C retains the vitamin E in low density lipoproteins. [51] it may additionally shield the circulatory system from oxidative stress. Antioxidant balance in the body is expected to play a role in decreasing the stress caused by oxidation anywhere it occurs.

Certain pharmaceuticals have antioxidant effects in addition to their primary function. Indirect antioxidant activity is provided by nonthiol ACE inhibitors, while direct antioxidant activity is provided by thiol-containing inhibitors. [52]. These inhibitors hinders ACE activity, which is their main antihypertensive activity, and therefore decrease all-stimulated NADPH oxidase-induced oxidative stress [53]. Another antihypertensive treatment that decreases oxidative stress is calcium channel blockers which might be a consequence attributed to a reduction in calcium

induced reactive species of oxygen output in the cytosol or a decrease in pressure inducing NADPH oxidases activity resulting in lowering of blood pressure possessing both direct and indirect antioxidant effects.

ROLES OF ANTIOXIDANTS AND FREE RADICALS IN DISEASES-

Free radical destruction has been linked to a host of degenerative diseases, including cardiovascular disease, neurological conditions, asthma, ischemia-reperfusion damage, and ageing, despite the antioxidants' antagonistic activity. Cancer and diabetes, which are caused by reduced glucose tolerance, a disease known as "mitochondrial oxidative stress," and inflammatory oxidative disorders, which contribute to atherosclerosis and systemic inflammation, can be divided into two groups. Free radical exposure has been shown to hasten the ageing process (protein oxidation and lipid peroxidation) (lipid peroxidation and protein oxidation). DNA modification is a critical move of carcinogenesis, & some tumours have high levels of DNA lesions, which correlates with oxidative damage in cancer aetiology. ROS-induced alterations in the heart are linked to, ischemic cardiac disease, cardiomyopathies, , atherosclerosis, hypertension & heart failure. [54].

Many autoimmune disorders are characterised by cell damage caused by free radicals. In comparison to controls, increased levels of isoprostanes and prostaglandins in serums & synovial fluids [55] suggested oxidative damage & inflammation. Increased oxidative stress has been suggested as one of the main causes of hyperglycemia, which may lead to a variety of diabetic complications. [56]. Since oxidative damage worsens with age, it is thought to be a contributing factor in a no. of neurological conditions, such as Parkinson's & Alzheimer’s. [57].

FREE RADICAL SCAVENGERS-

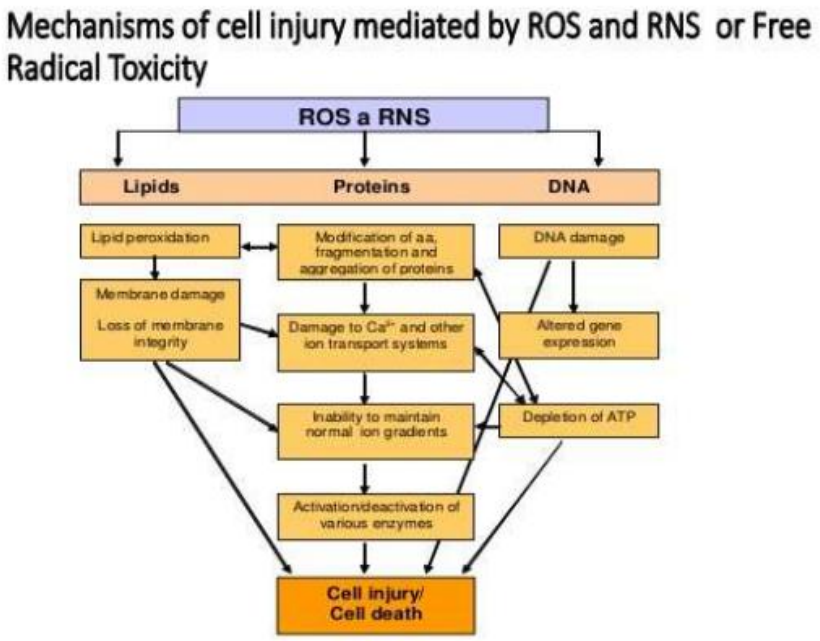

Figure 5

By interacting with free radicals in the polypropylene formulation and transforming them to stable, non-reactive products, free radical scavengers function similarly to secondary antioxidants in preventing thermal oxidation. Free radical scavengers such as HALS (hindered amine light stabilisers) were first used in the 1970s. They may also act as peroxide decomposers or quenchers. They hold a lock on the market for light stabilisers, and they are now also used as thermal antioxidants.

In order to avoid the degradation of low-density lipoproteins and the development of atherosclerosis, antioxidants and free-radical scavengers have become extremely essential. Antioxidant activity has been reconsidered over time. Cancer, cardiovascular disease, arteriosclerosis, brain conditions, skin irritations, and inflammations are all caused by the concentration of elevated amounts of free radicals in various tissues. These high levels of free radicals will oxidise biomolecules, causing oxidative damage to the lipid membrane. Carbon and peroxy radicals (the source of lipid peroxidation) are generated as a direct effect of its elevated amounts. A single radical trigger a cascade of lipid peroxidation reactions that cause a large number of molecules to be damaged [58]. To mitigate the effects of elevated amounts of free radicals, the body has a defence system that allows free radicals available to copper, superoxide dismutase & iron transport proteins, and also lipid-soluble & water-soluble antioxidants. Any variation in a body's normal physiological conditions causes a variety of diseases, just as any disparity in free radical levels and antioxidant pathways causes a variety of human diseases. The

majority of antioxidants function by blocking oxidation or functioning as antioxidants that split chains.

SOURCES OF FREE RADICALS AND THEIR GENERATION-

ROS might come from both endogenous and exogenous sources. Mitochondria, peroxisomes & the endoplasmic reticulum are endogenous origins of ROS, all of which have a high oxygen intake.

MITOCHONDRIA-

The bulk of intracellular ROS originates from mitochondria. Superoxide radicals are formed at 2 main sites in the electron transport chain: complex I (NADH dehydrogenase) & complex III (superoxide radicals) (ubiquinone cytochrome c reductase). A reduced form of coenzyme Q is formed when electrons from complex I or II are transferred to coenzyme Q or ubiquinone (Q) (QH2). From an unstable intermediate semiquinone anion, the reduced form QH2 regenerates coenzyme Q in the Q-cycle (Q-). The superoxide radical forms as the newly formed Q- passes electrons to molecular oxygen. Since enzymes don't make superoxide, the higher the metabolic rate, the more ROS is produced [59].

Mitochondrial superoxide dismutase converts superoxide anion to hydrogen peroxide (MnSOD). Catalase (CAT) and glutathione peroxidase can also detoxify H2O2 (GPx).

Monoamino oxidase, glycerol phosphate dehydrogenase, ketoglutarate dehydrogenase & p66shc are other mitochondrial elements that lead to the formation of ROS. [60].

The ShcA protein family contains the p46Shc and p52 Shc proteins, as well as the p66Shc protein. The 66-kDa subunit of the growth factor adaptor protein that is involved in apoptotic cell death in mammals is known as p66Shc. It regulates how reactive oxygen species (ROS) are formed in mitochondria. The cytoplasm contains the majority of p66Shc, with a small amount present in the mitochondrial intermembrane region. When introduced to oxidative stress, p66Shc readjusts towards the mitochondria inner membrane, where it binds to Cytochrome-C, causing reactive oxygen species to form (ROS) [61].

PEROXISOME-

The respiratory cycle in peroxisomes involves the transfer of electrons from different metabolites of oxygen, resulting in H2O2, but it is unrelated to oxidative phosphorylation, which produces ATP, rather releasing free heat energy. Peroxisomes also produce H2O2, O2• OH•, and NO•, among other free radicals. The -oxidation of fatty acids is the main biochemical pathway that produces H2O2 in the peroxisomes. Multiple enzymes of peroxisomes, such as D-amino acid oxidase, acyl CoA oxidases, L—hydroxy oxidase, xanthine oxidase, , urate oxidase & D-aspartate oxidase, produces different ROS. [62].

ENDOPLASMIC RETICULUM-

The formation of ROS is aided by enzymes of ER like b5 enzymes, cytochrome p450 & diamine oxidase. [63]. Erop1p, other crucial enzyme of thiol oxidase, catalyses the transfer of electrons from dithiols to molecular oxygen, resulting in H2O2. [64].

Endogenous reactive species of oxygen factors includes prostaglandin synthesis, adrenalin auto-oxidation, phagocytosis, lowered riboflavin, FMNH2, FADH2, cytochrome P 450, regulation of immune cells, emotional fatigue, a number of activity , inflammation, infection, cancer, ageing, ischemia & others [57].

In biological processes, a variety of exogenous species contains ROS as seen in the table below.

ALCOHOL	**ULTRAVOILET LIGHT**
TOBACCO SMOKE	COOKING(oils, fats, meat)
INDUSRTIAL SOLVENTS	DRUGS LIKE-
PESTICIDES	DOXORUBICIN, BLEOMYCINE
AIR AND WATER POLLUTION	METRINIDAZOLE, HALOTHANE
HEAVY METALS LIKE Fe, Cu, Co, Cr	PARACETAMOL, ETHANOL

MOLECULAR TARGETS OF FREE RADICALS-

Where free radicals (ROS/RNS) and antioxidant defences are out of balance , the following will be developed in greater quantities, causing oxidative and nitrosative stress. All three main groups of biological molecules are vulnerable to free radicals: proteins, nucleic acids & lipids [65] due to their high reactivity.

Deoxyribonucleic acids (DNA)-

ROS and RNS are also capable of oxidising nucleic acids.Since it is so close to the source of ROS, mitochondrial DNA is more vulnerable to destruction than nuclear DNA. The OH• radical, in particular, interacts specifically with all the components of DNA, including purine & pyrimidine bases, and also the deoxyribose sugar backbone [66], creating single & double stranded breaks in DNA. As hydrogen atoms are absorbed by the OH radical, a number of modified puines, pyrimidine base by-products, and DNA-protein crosslinks are formed. When OH• targets pyrimidines, it forms uracil glycol, thymine glycol, 5-hydroxydeoxyuridine, 5-hydroxydeoxycytidine, hydantoin & other pyrimidine adducts. Purine adducts produced by hydroxyl radical attack include 8-hydroxydeoxy adenosine, 8-hydroxydeoxy guanosine & 2,6-diamino-4-hydroxy-5-formamidopyrimidine. Other free radical-induced DNA base adducts include cytosine glycol, 5-formyl uracil, 5,6-dihydrothyronine, 5-hydroxy-6-hydro-uracil, 5-hydroxy-6-hydro-cytosine, uracil glycol & alloxan [67]. The key free radical mediated sugar moiety adducts in DNA are 2-deoxytetrodialdose, glycolic acid, erythrose, 2-deoxypentonic acid lactone, and 2-deoxypentose-4-ulose [68]. 8-hydroxy deoxyguanosine is an oxidative DNA damage biomarker that plays a role in carcinogenesis, mutagenesis & ageing process. The concentration of 8-OHdG is less in nuclear DNA than in mitochondrial DNA [69].

When RNS interacts with guanine then it produces nitrative and oxidative lesions like 8-nitroguanine & 8-oxodeoxyguanosine [70]. 8-nitroguanine which is formed during the process , it spontaneously can be eliminated because of formation of apurininc site [64]. When adenine mixed with 8-nitroguanine at the time of DNA synthesis, it results in G-T transversions [71]. 8-nitroguanine is a carcinogenic DNA lesion that causes mutations.

Ribonucleic acids (RNA)-

Reactive species of oxygen can target a variety of RNAs that are formed in the human body. RNA is most vulnerable to oxygen destruction than DNA because of its single stranded nature, lack of an effective conformational change for oxidised RNA, and lack of protein defence. Furthermore, these RNA of cytoplsms are nearer

to the mitochondria of cell, which produce a lot of reactive oxygen species (ROS). RNA is more susceptible to oxidative degradation in humans than DNA [72]. 7, 8-dihydro-8-oxo-guanosine (8-oxoG), the more widely researched RNA harmful by-product, is elevated in a varieties of pathological disorders, including Alzheimer's disease [73], Parkinson 's disease [74], atherosclerosis [75], hemochromastosis [76] & myopathies [77].

Lipids-

Lipids of membrane are more susceptible to free radical oxidation, especially polyunsaturated fatty acid residues in phospholipids. Due to its use in a varities of pathological conditions, lipid peroxidation is very dominant factor. Membrane dysfunction, such as low fluidity & deactivation of membrane-bound receptors & enzymes, is caused by lipid peroxidation [78]. Lipid peroxidation happens as a free radical attacks and extracts (H) from a Methylene group (CH2) in a fatty acid (LH), resulting in development of a carbon derived lipid radical (L•). When a radical of lipid interacts with oxygen molecule, a lipid peroxyl radical (LOO•) is created. The lipid peroxyl radical (LOO•) which is formed is cyclized to form endoperoxides, which then form malondialdehyde (MDA) and 4-hydroxyl nonenal (4-HNA), these by-products are very toxic in nature and can damage DNA and proteins[79]. The radicals of lipids peroxidase speed up the peroxidation process by sucking (H) atoms from another molecules of lipids. Isoprostanes (prostaglandin-like compounds that are developed in one's body by the esterification of arachidonic acid) are a byproduct of arachidonic acid lipid peroxidation and are believed to be the source of oxidative lipid harm [80].

Proteins-

Oxidation of protein may be caused by various species of radicals like O2•, OH•, aloxyl, peroxyl & hydroperoxyl, and also non-radical species such as O3, H2O2, HOCl, singlet oxygen & OONO- [81]. Protein–protein crosslinking occurs resulting ROS oxidising various Amino Acids(AA) in proteins, resulting in protein denaturing and loss of structure, as well as loss of enzyme activity, receptor, and transport protein function [82]. Methionine and cysteine, which contain sulphur, are more susceptible to ROS oxidation, resulting in disulphides &methionine sulphoxide. In cellular systems, however, only 2 enzymes, disulfide reductases and methionine sulfoxide reductases, can convert these 2 oxidised forms of proteins to their original form.

As ROS attacks various amino acids, such as tryptophan, nitrotryptophan, kynurenine, and formylkynurinine, different oxidation products are produced. Although phenylalanine produces 2,3-Dihydroxyphenylalanine, 2-, 3-, and 4-hydroxyphenylalanine, tyrosine produces 3,4-Dihydroxyphenylalanine, 2-, 3-, and 4-hydroxyphenylalanine. Tyr-O-Tyr, cross-linked nitrotyrosine; tyrosine–tyrosine cross-linkages; histidine derivatives include 2-Oxohistidine, asparagine, and aspartic acid. Arginine produces glutamic semialdehyde. Lysine produces a-aminoadipic semialdehyde. Proline is reduced to 2-pyrrolidone, 4- and 5-hydroxyproline pyroglutamic acid, and glutamic semialdehyde, threonine to 2-amino-3-ketobutyric acid, and leucine and valine residues to hydroxyl residues. [83-87]

As reactive species of oxygen causes damage of O2 for residues of amino acids like proline, threonine, lysine & carbonyl, arginine derivatives are produced. Carbonyl classes in proteins have long been believed to be a symptom of oxidation of protein mediated by reactive species of oxygen (ROS) [85]. Other essential markers of protein oxidation include O-tyrosine (a hydroxyl radical marker) and 3-nitrotyrosine (a marker for RNS). Protein carbonyl levels rises in Alzheimer's disease, muscular dystrophy, cataractogenesis, diabetes, Rheumatoid Arthritis, progeria, atherosclerosis, werner's syndrome, respiratory dystrous syndrome, Parkinson's disease & ageing, among other diseases and disorders.

FREE RADICAL REACTIONS-

Chain reactions also contain free radicals, in which a series of reactions results in the revival of a radical, which may then initiate a fresh chain of reactions

Free radical reactions have 3 different stages that can be described. [86]

• The very first stage of the process is to create radicals.

• The final step is the reduction of radicals, in which the necessary free radical is periodically rejuvenate a consequence of chain reaction, taking the response to a close.

ROLES OF ANTIOXIDANTS-

Oxidative stress is induced by lack of antioxidants or suppression of antioxidants resulting in damage of cells. Antioxidants are being extensively studied in pharmacology, especially as treatments for strokes and neurodegenerative diseases, because chronic inflammation may play a vital role in a variety of humans disorders.

It is not clear that, oxidative stress is responsible for it or not.

Nevertheless antioxidants are included in dietary supplements to avoid oxidative stress.

In order to prevent cancer or coronary heart disease , antioxidants are being extensively used in dietary supplements.

Natural products have such a wide variety of industrial uses, including food and cosmetic preservatives, as well as preventing rubber and gasoline degradation. As chemists have understood for many years, free radicals leads to oxidation which inturn can be avoided by usage of antioxidants.

THERAPEUTIC PROPERTIES OF ANTIOXIDANTS-

Fried Reich ataxia is a unique neurological condition that requires antioxidants for treatment. It is induced via autosomal recessive fashion, meaning that both parents cannot consist the recessive gene which further results in the disorder. Medical studies aren't really accurate in determining how far an illness has progressed. Diseases are assessed using standard neurological scales. Several medical conditions are exacerbated by abnormally elevated levels of oxidative damage to cells, including hemorrhagic shock, rheumatoid arthritis, coronary system illness, cystic fibrosis, gastrointestinal, ulcerogenesis, , metabolic disorder and acquired immunodeficiency. In radio immunotherapy and photodynamic treatment, leutinide is used pharmacologically.[87]

MEDICINAL PROPERTIES OF ANTIOXIDANTS-

Usage of anticancers agents in chemistry- : The usage of anticancer agents in chemistry is increasing eg- LANTHANIDES. Hospital practise is also being influenced by novel therapeutics and diagnostic metal complexes. Advances in bio-coordination chemistry are important for refining compound architecture to decrease the toxic side effects and better acknowledge how they work. Metal-based medications are widely used to cure cancer. Cisplastin and other metal complexes are not being favoured due to high toxicity and development of tolerance. There has been an extensive research to discover novel coordination compounds with less toxicity and better pharmacological aspects. One technique for designing new anticancer agents is to include carrier groups that can target tumour cells with high specificity. The formation of complexes that conform to DNA in a drastically different way toward cisplatin, in an attempt to overcome the drug's resistance mechanism, is also a source of concern.

Importance of antioxidants in red blood cells- Erythrocytes have a greater tendency for blood cells and abnormal haemoglobin. 20 people were induced in the study to find the action of erythrocyte antioxidant system who were suffering from sickle cell anaemia possessing a strong tendency towards red blood cell. The following patients have low glutathione levels, higher levels of superoxide dismutase & decreased catalase operation. The following results clearly tells us that an antioxidant system which is not balanced will not be able to protect from the dangerous effects by the increased production of radicals.

Antioxidants therapy in acute central nervous system injury- Normal metabolism results in the production of highly metabolized chemical species called free radicals. Oxidative stress (OS) can be described as a mismatch of free radicals and the ability of the cells to protect themselves from them (Gutter, 1991). The production of reactive species of oxygen can increase considerably due to various pathways resulting in damage to the tissue. Radicals can be injurious to various important parts of the cell like protein, lipids and nucleic acids inducing necrosis or apoptosis, which results in cell death. The harm can become more common as a result of weakened cellular antioxidant defence mechanisms. Because of the brain damage, the quantity of various chemicals like glutamate which further results in production of ROS causing more parenchymatous damage. Several antioxidants with greatly differing chemical properties were studied to produce beneficial effect on the CNS damage,but only a handful of them have shown any effectiveness in animal models or limited clinical trials. Improved antioxidant architecture should consider the specific and acceptable harmful free radical. The precise key priorities for drug intervention can be determined by a greater understanding of the clinical mechanisms of acute CNS injury.

INVITRO STUDIES OF OS MODULATORS-

INVITRO CELL LINE MODELS-

Eukaryotic studies are surprisingly straightforward and inexpensive thanks to cell culture techniques. Cell culture is a popular technique for researching pathologic and natural processes in cell biology, as well as for testing potential new medicines for diseases like cancer. For the smooth cell functioning and in order to continue to experimentation in vitro, one should use proper primary culture from a licenced provider and proper culture medium. We should use sufficient supplements and growth factors for proper functioning. We use immortalized cell lines in invitro

experimental control but we can also use the normal cell lines for this purpose. For the new drug development and drug discovery related to oxidative stress diseases cell line models have extensively used. Since its identification 50 years ago, procarbazine, an azo precursor, has been used in cancer treatment. The oxidation of the molecule and the release of intracellular hydrogen peroxide are involved in procarbazine's anticancer activity. [88]

Cell homeostasis and normal function are dependent on the regulation of reactive species of oxygen (ROS). Many reports have conducted on this dynamic series of events. Schlenker et al., for example, assessed OS and determined the advance results of RS in cell injury using a bile duct epithelial cell (BDE) model. According to the researchers oxidative stress relatively lowers the volume of cell and affects various cell processes like ion channel activation, apoptosis and ion permeability. [89] compared catalase expression in two cell line models (250MK standard mammary epithelial primary cells and MCF-7 breast adenocarcinoma cells) and evaluated OS resistance to elevated hydrogen peroxide concentrations over time. The MCF7 model was found to overexpress catalase, suggesting that chromatin remodelling would control. [90,91]

CONCLUSION-

This article suggests that Oxidative Stress (OS) induces irreparable damage to cell macromolecules, leading to the onset of number of diseases which includes artherosclerosis, ischemic heart disease, liver disease, diabetes, and carcinogenesis. The dangers of oxidative stress and free radicals to human wellbeing are well documented. Free radicals are used in the commencement and progression of various types of illnesses, from cardiovascular disease to cancer, according to several reports. Antioxidants work by free radicals scavengers and preventing the formation of reactive oxygen species. ROS, or radical derivates of oxygen, is the most common free radical in biological environments. Reactive species of oxygen are dangerous products formed at the time of normal cellular processes (ROS). Rising natural antioxidant consumption may help maintain a tolerable antioxidant status whilst still supporting regular physiological activity. In vitro, antioxidant compounds form one-electron reactions with free radicals, preventing oxidative damage. Due to the importance of OS in the aetiology of many chronic and degenerative diseases, antioxidant therapy tends to be a viable therapeutic choice. Meanwhile, note that eliminating oxidant factors (alcohol, tobacco, unhealthy food, stress, etc.) is just as critical as consuming an antioxidant-rich diet. Our way of life does, in reality, have an effect on our happiness.

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