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## Study of Free Radicals and Antioxidants Status in Cardiovascular Health and Disease

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*Abstract*

*Current hypotheses support the idea that bringing down oxidative anxiety can have a medical advantage. Free radicals can be overproduced or the characteristic cell reinforcement framework protections debilitated, first bringing about oxidative anxiety, and after that prompting to oxidative harm and malady. Cardiovascular infection is one case of this procedure. This issue keeps on being the significant reason for unexpected passing around the world. Oxidation of human low-thickness lipoproteins is viewed as an early stride in the movement and inevitable advancement of atherosclerosis, one of the main sources to cardiovascular brokenness. Convincing backing for the contribution of free radicals in sickness advancement starts from epidemiological reviews demonstrating that an upgraded cancer prevention agent status is related with decreased danger of a few ailments. Dietary nutraceuticals, for example, vitamins C, E and polyphenolics and diminishment of cardiovascular malady frequency are an eminent illustration. This paper surveys the science of ROS/RNS, their pathways through which they identify with the pathology of cardiovascular malady and talks about the putative parts that cancer prevention agents, including phenolics, may play in controlling oxidative anxiety and diminish the frequency of cardiovascular illness.*

**KEY WORDS:** *Oxidative stress, cardiovascular disease, atherosclerosis, inflammation, cell signaling and transduction mechanisms, antioxidants, dietary phenolics.*

## 1. OVERVIEW

Most cardiovascular events are discretionary to atherosclerosis, a disease of the courses including an area thickening of the vessel divider. A stroke or myocardial limited spoil happens when the lumen of the vessel winds up being totally obstructed, overall by a thrombus shaping at the site of a plaque. Atherosclerotic wounds are thought to be begun by relocation of monocytes into the vein internal focus (tunica intima), enlisted by bond particles, possibly in light of vein endothelium damage. An grouping of components have been trapped in bringing on this fundamental mischief, including mechanical damage from stream push declined by hypertension, viral illness (herpes contaminations and cytomegalovirus), introduction to blood borne harms, for instance, xenobiotics from tobacco smoke and lifted levels of common metabolites, for instance, glucose, homocysteine or cholesterol.

## 2. BASIC CONCEPTS OF FREE RADICALS, REACTIVE NITROGEN SPECIES, REACTIVE OXYGEN SPECIES AND OXIDATIVE STRESS:

A free radical is any synthetic species (equipped for autonomous presence) having at least one unpaired electrons, an unpaired electron being one that is separated from everyone else in a nuclear or atomic orbital. Free radicals are framed from atoms through the breakage of a concoction bond with the end goal that each part keeps one electron (free radicals may likewise be shaped by crash of the non-radical species by a response between a radical and a particle - which should then outcome in a radical since the aggregate number of electrons is odd), by cleavage of a radical to give another radical and, at long last by method for redox reactions. Radicals are overall less enduring than non-radical species, regardless of the way that their reactivity changes. Free radicals and responsive oxygen/nitrogen sorts of noteworthiness in living creatures fuse hydroxyl (OH.), superoxide (O<sub>2</sub>), nitric oxide (NO.), nitrogen dioxide (NO<sub>2</sub>.) and peroxy (ROO.). Peroxynitrite (OONO-), hypochlorous destructive (HOCl), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), singlet oxygen (O<sub>2</sub>), ozone (O<sub>3</sub>), nitrous destructive (HNO<sub>2</sub>) and dinitrogen trioxide (N<sub>2</sub>O<sub>3</sub>) are not free radicals but rather can undoubtedly

prompt to free radical responses in living creatures. The term 'receptive oxygen species' (ROS) and 'responsive nitrogen species' (RNS) is an aggregate term that incorporates the radicals as well as the non-radicals. Oxidative anxiety is the term alluding to the awkwardness between era of responsive oxygen species and the movement of the cell reinforcement protections.

People and different aerobes can endure oxygen (O<sub>2</sub>) in light of the fact that, while life forms were advancing electron-transport chains and other chemical frameworks to use this atom, cancer prevention agent resistances to secure against the harmful impacts of O<sub>2</sub> were developing in parallel. ROS/RNS can emerge from unintentional era; this incorporates such components as "spillage" of electrons onto O<sub>2</sub> from mitochondrial electron transport chains; atomic film, endoplasmic reticulum (xenobiotic digestion system, prostaglandin combination) and hepatocytes (detoxification) contain electron transport frameworks, cytochrome P-450 and b5, which create free radicals<sup>6</sup>. Unintentional

era likewise incorporates the immediate response of autoxidisable atoms with sub-atomic O<sub>2</sub>, creating superoxide free radical. The major natural process prompting to O<sub>2</sub>-era is the electron transport related with mitochondrial layer; ubiquinone-cytochrome b is the most imperative site of O<sub>2</sub>-creation. It has been evaluated that 1-3% of O<sub>2</sub> inhaled is changed over to O<sub>2</sub> a rate that additions in the midst of times of extended essentialness assimilation framework. O<sub>2</sub>in like manner is conveyed by phagocytic cells (neutrophils, monocytes, macrophages, eosinophils) and helps them to inactivate contaminations and tiny living beings. Right when these cells encounter a phagocytatable atom, their O<sub>2</sub> usage increases gigantically ('respiratory burst') with the start of a layer discovered protein (NADPH-oxidase) which catalyze the diminishment of O<sub>2</sub> into O<sub>2</sub>-O<sub>2</sub>.- appreciate the making of to a great degree responsive compound species, for instance, OH., hypochlorite and chloramines (**Figure 1**).

### ***Unimolecular Radical Reactions***

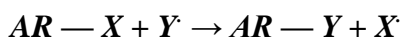
Reactions result from the instability of the first formed radical. The radicals may

completely decompose or rearrange before reaction with other molecules or radicals present.

**Decomposition:** reaction in which the radical decomposes to give a stable molecule and a new radical

**Rearrangement:**

1. Breaking of an adjacent C-C bond in a cyclic system with concomitant formation of a new bond, usually carbonyl and a new isomeric radical
2. Migration of an atom, via intramolecular abstraction by the radical center, thus creating a new, isomeric radical.



Abstraction or displacement:  $S_H2$  reactions<sup>†</sup>

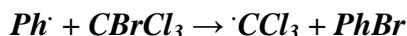
- Biomolecular reaction involving homolytic attack of a radical on a

### **Radical-Molecule Interactions**

#### Addition to unsaturated systems:

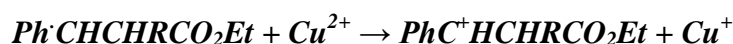
1. Addition of a radical to an olefinic twofold attaches to give another immersed, radical. Regular response is the radical instigated polymerization of olefins.
2. Addition of a radical to a sweet-smelling twofold bond. This moderate stride is far reaching in free radical science, e.g. in the radical substitution of fragrant mixes (homolytic sweet-smelling substitution). The net general response is dislodging of a sweet-smelling substituent by a radical:

molecule. The radical attacks a univalent atom, usually a terminal halogen or hydrogen in an abstraction reaction to give rise to a new radical, e.g.



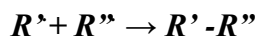
– Homolytic substitution at multivalent atoms also occurs but both do not normally occur at saturated carbon centers.

#### Reaction with oxidizing agents



#### **Radical-Radical Interactions**

##### Dimerization or radical coupling



When  $R' = R''$ , the reaction is dimerization and when  $R' \neq R''$  the reaction is radical coupling or combination.

##### Radical disproportionation

Involves collision of the radicals resulting

Radicals readily undergo 1-electron oxidations with oxidizing reagents of suitable redox potential to give positive ions. Example is the Meerwein reaction, which involves the oxidation of cinnamyl derived radicals by cupric ions:

Localized radicals (methyl, phenyl

radicals) react readily with little chance of dimerization. Only delocalized radicals have a high probability of dimerization in solution. Thus,

in the abstraction of an atom, usually hydrogen, by one radical from the other. This leads to the formation of two stable molecules, with the atom abstracted being  $\beta$  to the radical center:<sup>‡</sup> e.g. the disproportionation of two phenylethyl radicals to give styrene and ethylbenzene.

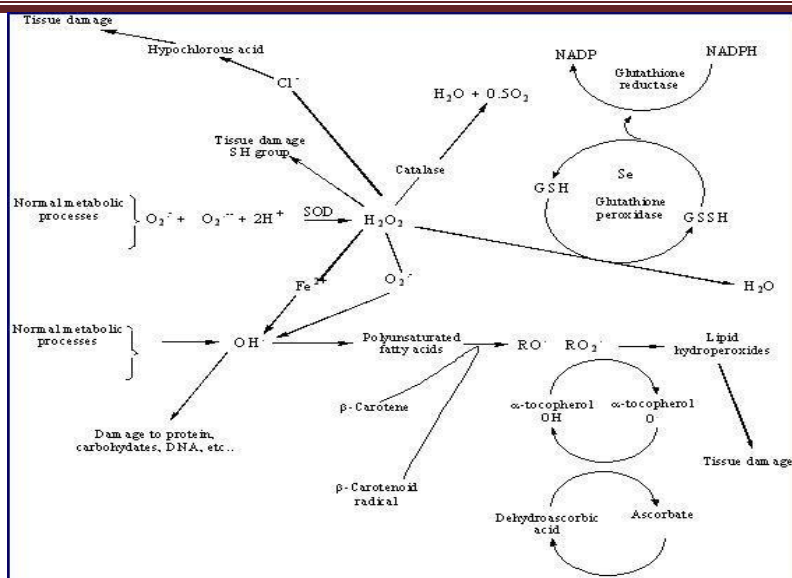


Figure 1: Inter-relationship between reactive oxygen species and antioxidants.

### 3. REACTIVE OXYGEN SPECIES AND THE CARDIOVASCULAR SYSTEM:

Receptive oxygen species have been viewed as injurious to cell work and there is great confirmation to propose that they assume a part in the pathophysiology of heart illness states. In any case, coordinate circumstances and end results connections have not been unmistakably portrayed. The expansion in the era of ROS under a few pathophysiological conditions, that appear to be identified with provocative procedures, is still to be exhaustively comprehended; this might be because of

challenges in characterizing their site of source. Impeded mitochondrial lessening of atomic oxygen might be an intracellular source. Emissions by phagocytic white platelets, broken endothelial cells, or the auto-oxidation of catecholamine might be the extracellular sources. ROS may likewise come about because of cell harm because of presentation to ionizing radiation, bright beams, cigarette smoking or other air toxins. Other than their harmful impacts, ROS are likewise now being perceived as essential controllers of cell capacity and modulators of cell flagging pathways.

***ROS in pathophysiology of Heart disease:***

One of the systems used to evaluate the part of oxidative worry in the pathogenesis of heart brokenness has been to uncover confined cardiovascular tissues to a characterized oxidation stretch condition and study the subsequent impacts. Promote in vivo and ex vivo thinks about have given valuable confirmation supporting the part of oxidative worry in various conditions (atherosclerosis, ischemia-reperfusion damage, hypertension, catecholamine-actuated cardiomyopathy, diabetic cardiomyopathy, heart hypertrophy and congestive heart disappointment etc.) prompting to extreme cardiovascular dysfunctions. In this audit the part of ROS in atherosclerosis is being accentuated as, other than being considered as the significant reason for dreariness and mortality<sup>32</sup> its result is additionally connected to different conditions prompting to cardiovascular issue. The part of ROS in other previously mentioned conditions has been widely checked on and is alluded to various phenomenal reports.

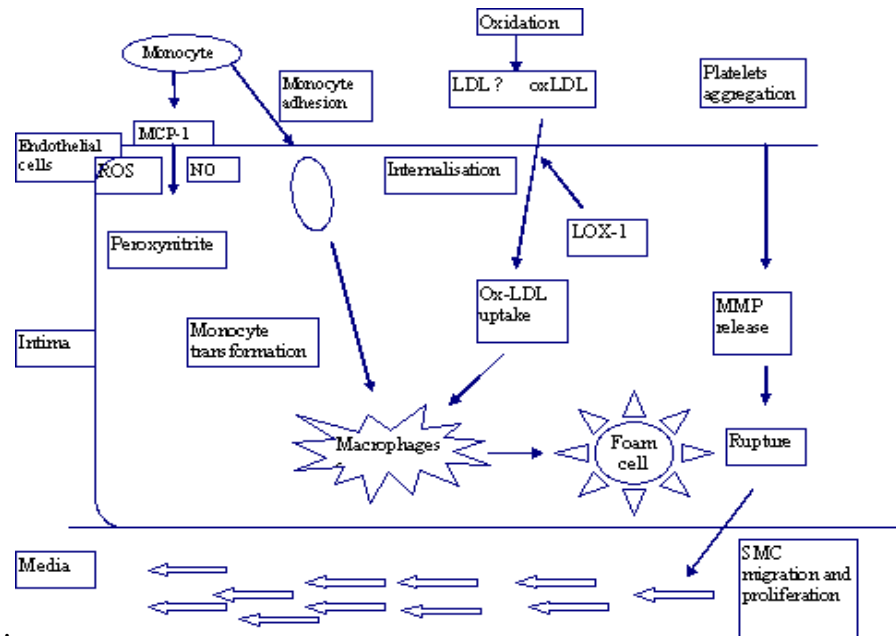
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corridors including a nearby thickening of the vessel divider.

A stroke or myocardial dead tissue happens when the lumen of the vessel turns out to be totally blocked, as a rule by a thrombus framing at the site of a plaque. Atherosclerotic injuries are thought to be started by resettlement of monocytes into the blood vessel inward center (tunica intima), selected by attachment particles, perhaps in light of blood vessel endothelium harm. An assortment of elements have been ensnared in bringing about this underlying harm, including mechanical harm from stream stretch compounded by hypertension, viral contamination (herpes infections and cytomegalovirus), presentation to blood-borne poisons, for example, xenobiotics from tobacco smoke and raised levels of typical metabolites, for example, glucose, homocysteine or cholesterol<sup>36</sup>. In spite of the fact that an abnormal state of plasma cholesterol is considered to trigger atherosclerosis, the oxidation of cholesterol is by all accounts a fundamental stride. Actually, take-up of oxidized low-thickness lipoprotein (oxLDL) was

appeared to be an early occasion prompting to the advancement of atherosclerosis (Figure 2). oxLDL and oxidized lipoproteins have been accounted for to invigorate O<sub>2</sub> development prompting to apoptosis of cells in the umbilical vascular divider; this was avoided by treatment with cancer prevention agents SOD and catalase. In refined human coronary supply route smooth muscle cells, low levels of oxLDL animate the extracellular grid combination demonstrating the

contribution of oxidative worry in the pathogenesis of atherosclerosis. Elevated amounts of oxLDL were apoptotic involving the added substance part of ROS in expanded plaque defenselessness; this impact was diminished by probucol and catalase. Patients with atherosclerosis and hypercholesterolemia demonstrated higher helplessness of LDL to oxidation in contrast with patients treated with lipid-bringing down operators, for example, lovastatin and probucol.



**Figure 2: ROS and atherosclerosis: (i) oxidation of LDL to oxLDL; (ii) endothelial cell dysfunction; (iii) vascular smooth muscle cells migration and proliferation as well as MMPs release; (iv) monocyte adhesion and migration as well as foam cell development due to uptake of ox-LDL.**



***ROS in Mediated Signal Transduction Pathways in Cardiovascular disorders:***

The cardiovascular framework is an exceptionally mind boggling, efficient framework in which flag transduction plays basic physiological and pathophysiological parts (Figure 3). The cell components of the heart and vascular divider are furnished with a variety of particular receptors and with complex intracellular hardware that encourages and drives proper reactions to extracellular boosts. All vascular cell sorts, including endothelial cells, smooth muscle cells, adventitial fibroblasts, and occupant macrophages, deliver ROS<sup>51-55</sup>. Of specific significance in the vasculature are superoxide (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), since these ROS go about as between and intra-cell flagging particles. The real wellspring of ROS in the vascular divider is non-phagocytic NADPH oxidase, which is controlled by vasoactive operators (Ang II, ET-1, thrombin, serotonin), cytokines (IL-1, TNF $\alpha$ ), development variables (PDGF, IGF-1, VEGF) and mechanical powers (cyclic extend, laminar and oscillatory shear

push). Elevated amounts of low-thickness lipoprotein (LDL), particularly as oxidized low-thickness lipoprotein (oxLDL), have likewise been appeared to increment intracellular ROS era. Under physiological conditions, vascular creation of ROS and the subsequent enactment of redox-ward flagging pathways and enlistment of redox-toughy qualities are firmly controlled. Be that as it may, in obsessive conditions, for example, in hypertension, atherosclerosis, hyperlipidemia, hyperhomo-cysteinemia, and diabetes, where era of ROS is expanded and the renin angiotensin framework might be upregulated, these redox-delicate occasions may add to cell forms required in vascular brokenness and basic renovating.

**4. ANTIOXIDANTS AND THEIR RELEVANCE TO CARDIOVASCULAR DISEASE:**

A cell reinforcement has been characterized as "any substance that, when present at low focuses contrasted and those of an oxidizable substrate, altogether delays or anticipates oxidation of that substrate"<sup>38</sup>. Whenever ROS/RNS are created in vivo, their activities are

contradicted by mind boggling and facilitated cancer prevention agent lines of safeguard systems. These incorporate enzymatic and non-enzymatic cancer prevention agents that hold under tight restraints ROS/RNS level and repair oxidative cell harm (Figure 3). The real chemicals, constituting the main line of resistance, straightforwardly required in the balance of ROS/RNS are: superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) (Figure 1). Turf is a cytoplasmic and mitochondrial chemical, which quicken the dismutation of superoxide. There are three types of SOD: an extracellular and an intracellular copper/zinc (Cu/Zn) and a mitochondrial, manganese (Mn) SOD. Every one of the

three structures catalyze the dismutation of  $O_2^-$  to  $H_2O_2$ . Since SOD chemicals produce  $H_2O_2$ , they work in a joint effort with  $H_2O_2$ -expelling proteins. Feline, an only peroxisomal catalyst in many tissues, changes over  $H_2O_2$  to water and  $O_2$ . Be that as it may, the most vital  $H_2O_2$ -expelling catalysts are the selenoprotein GPx proteins. GPx chemicals evacuate  $H_2O_2$  by utilizing it to oxidize decreased glutathione (GSH) to oxidized glutathione (GSSG). Glutathione reductase, a flavoprotein compound, recovers GSH from GSSG, with NADPH as a wellspring of diminishing force (Figure 3). Glutathione peroxidase likewise catalyzes the decrease of flimsy hydroperoxides to the detriment of GSH.

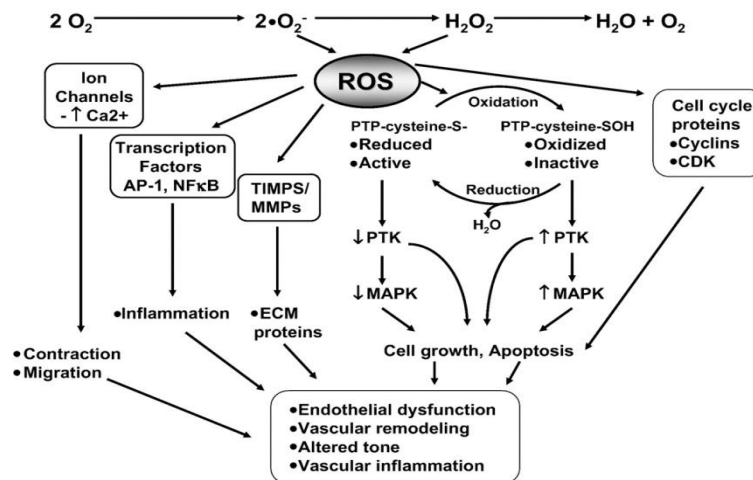


Figure 3: Redox-dependent signaling pathways in vascular smooth muscle cells

The expansion ROS which is delivered from NSDPH oxidase may adjust the action of tyrosine kinases, for example, Src, Ras, JAK2, Pyk2, PI3K, and EGFR, and also mitogen-actuated protein kinases (MAPK), especially p38MAPK, JNK and ERK5. ROS may hinder protein tyrosine phosphatase movement, additionally adding to protein tyrosine kinase initiation. ROS additionally impact quality and protein expression by actuating translation components, for example, NF B activator protein-1 (AP-1) and hypoxia-inducible element 1 (HIF-1). ROS invigorate particle channels, for example, plasma film Ca<sup>2+</sup> and K<sup>+</sup> channels, prompting to changes in cation focus. Actuation of these redox-touchy pathways brings about various cell reactions which, if uncontrolled, could add to hypertensive vascular harm.

The second line of barrier is spoken to by radical rummaging cancer prevention agents, for example, vitamin C, vitamin An and plant phytochemicals like phenolics (underscored later in this audit) repress the oxidation chain start and avoid chain spread. This may likewise incorporate the end of a chain by the response of two

radicals. The repair and anew proteins go about as the third line of guard by repairing harm and reconstituting films. These incorporate lipases, proteases, DNA repair proteins and transferases.

The HMG-CoA reductase inhibitors, otherwise called statins, are intense lipid-changing specialists. There is overpowering proof from clinical reviews that diminishing plasma LDL levels with statins, brings about a particularly bring down danger of cardiovascular occasions identified with atherosclerosis. Late reviews in patients with built up CAD demonstrate that these specialists can bring about an unobtrusive relapse of atherosclerotic sores. It has been recommended that the antiatherosclerotic impact of statins might be autonomous of their LDL-bringing down impact.

## 5. CONCLUSION

The ramifications of oxidative worry in the etiology of a few incessant and intense degenerative issue recommends that cell reinforcement treatment speaks to a promising road for treatment. Procedures for the intercession and counteractive

action of cardiovascular infection require a comprehension of the essential atomic system (s) by prophylactic operators (manufactured cancer prevention agents, dietary cell reinforcement variables from sustenance plants and therapeutic plants) that may possibly anticipate or invert the advancement or movement of the sickness. It stays unequivocal that developing logical support for wellbeing cases and distinguishing proof of dynamic utilitarian fixings should be adjusted by tending to toxicological concerns. The genuine evidence of viability for existing or novel mixes/concentrates ought to exude from a show of clinical adequacy on characterized restorative classifications. In this regard, the result of one such trial led on the Mauritian populace on the impacts of Mauritian dark tea on markers of oxidative anxiety prompting to cardiovascular ailment is as of now abundantly anticipated.

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