

Review Article

ROLE OF ANTI-OXIDANTS IN LIVER

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ABSTRACT

All living organisms utilize oxygen to metabolize and use the dietary nutrients in order to produce energy for survival. Oxygen thus is a vital component for living. Oxygen mediates chemical reactions that metabolize fats, proteins, and carbohydrates to produce energy. While oxygen is one of the most essential components for living, it is also a double-edged sword. Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "Free Radicals." Antioxidant Activity applied to components that can trap free radicals, thereby breaking the chain reaction that normally leads to extensive biological damage. Inhibition of the reactions brought about by oxygen or peroxides. Usually, the antioxidant is effective because it can itself be more easily oxidized than the substance protected.

KEY WORDS

Antioxidant activity, Reactive Oxygen Species, Free Radicals.

INTRODUCTION:

These free radicals are capable of attacking the healthy cells of the body. This may lead to damage, disease and severe disorders. Cell damage caused by free radicals appears to be a major contributor to aging and diseases like Liver Injury, Cancer, Heart disease, decline in brain function, Decline in immune system etc. Since free radicals contain an unpaired electron, they are unstable and reach out and capture electrons from other substances in order to neutralize themselves. This initially stabilizes the free radical but generates another in the process. Soon a chain reaction begins and thousands of free radical reactions can occur within a few seconds.

Control of Free Radicals:

Normally free radical formation is controlled naturally by various beneficial compounds known as antioxidants. When there is deficiency of these antioxidants damage due to free radicals can become cumulative and debilitating. Antioxidants are capable of

stabilizing, or deactivating, free radicals before they attack cells.

Role of Antioxidant in Hepatoprotective Activity:

Hepatocyte Viability and Oxygen Uptake tests

Hepatotoxins reduce the viability of hepatic cells as assessed by trypan blue exclusion and oxygen uptake tests. In liver, CCl_4 is metabolised to $\text{CCl}_3\text{O}^\cdot$ by cytochrome P-450 and the reactive oxidative free radical intermediate generated, $\text{O}^\cdot$ causes further damage. Utilisation of oxygen by hepatocytes gets reduced; therefore, the viability of hepatocytes is reduced.^[10]

Free Radical Scavenging

Free radicals are reactive molecules involved in many physiological processes and human diseases such as cancer, aging, arthritis, Parkinson syndrome, ischaemia, toxin induced reaction, alcoholism, liver injury etc. The damage to hepatic parenchymal cells, leading to hepatic injury, is due to oxidative stress within the cells caused by partially reduced

free oxygen (PRFO) species such as O_2^- (Superoxide anion), H_2O_2 , and $OH^\cdot$ (hydroxy free radical). The elevation of free radical levels seen during the liver damage is due to enhanced production of free radicals and decreased scavenging potential of the cells. A variety of intrinsic antioxidants (reduced glutathione, superoxide dismutase, glutathione-S-transferase etc.) are present in the organism, which protect them from oxidative stress.^[9]

Hepatoprotection by Enzymatic Free Quenching:

Hepatoprotection by enzymatic free quenching is brought about by elevating the levels of antioxidant enzymes in tissues such as the Superoxide dismutase (SOD), Peroxidase and Catalase. The three partially reduced intermediate species between O_2 to H_2O are

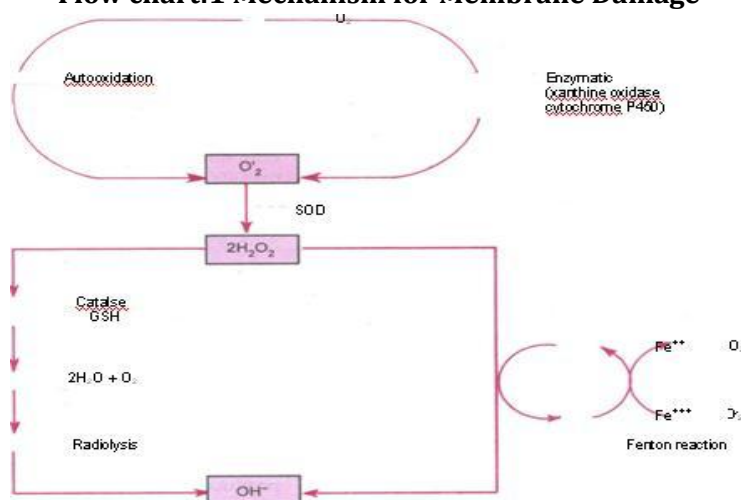
derived from enzymatic and nonenzymatic reaction as under:

Superoxide (O_2^-): superoxide anion O_2^- may be generated by direct autooxidation of O_2 during mitochondrial electron transport reaction. Alternatively O_2^- is produced enzymatically by xanthine oxidase and cytochrome P₄₅₀ in the mitochondria or cytosol. O_2^- so formed is catabolised to produce H_2O_2 by superoxide dismutase.

Hydrogen peroxide (H_2O_2): H_2O_2 is reduced to water enzymatically by catalase (in the peroxisomes) and glutathione peroxidase GSH (both in the cytosol and mitochondria).

Hydroxyl radical $OH^\cdot$: $OH^\cdot$ radical is formed by two ways in biologic processes-by radiolysis of water and by reaction of H_2O_2 with ferrous (Fe^{++}) ions, the latter process is termed as Fenton reaction. ^[9]

Flow chart:1 Mechanism for Membrane Damage



Mechanism For Membrane Damage:

Free radicals may produce membrane damage by the following mechanisms:

Lipid peroxidation: Polyunsaturated fatty acids (PUFA) of membrane are attacked repeatedly and severely by oxygen-derived free radicals to yield highly destructive PUFA radicals – lipid hydroperoxy radicals and lipid hydroperoxidation. The lipid peroxidase is decomposed by transition metals such as iron.

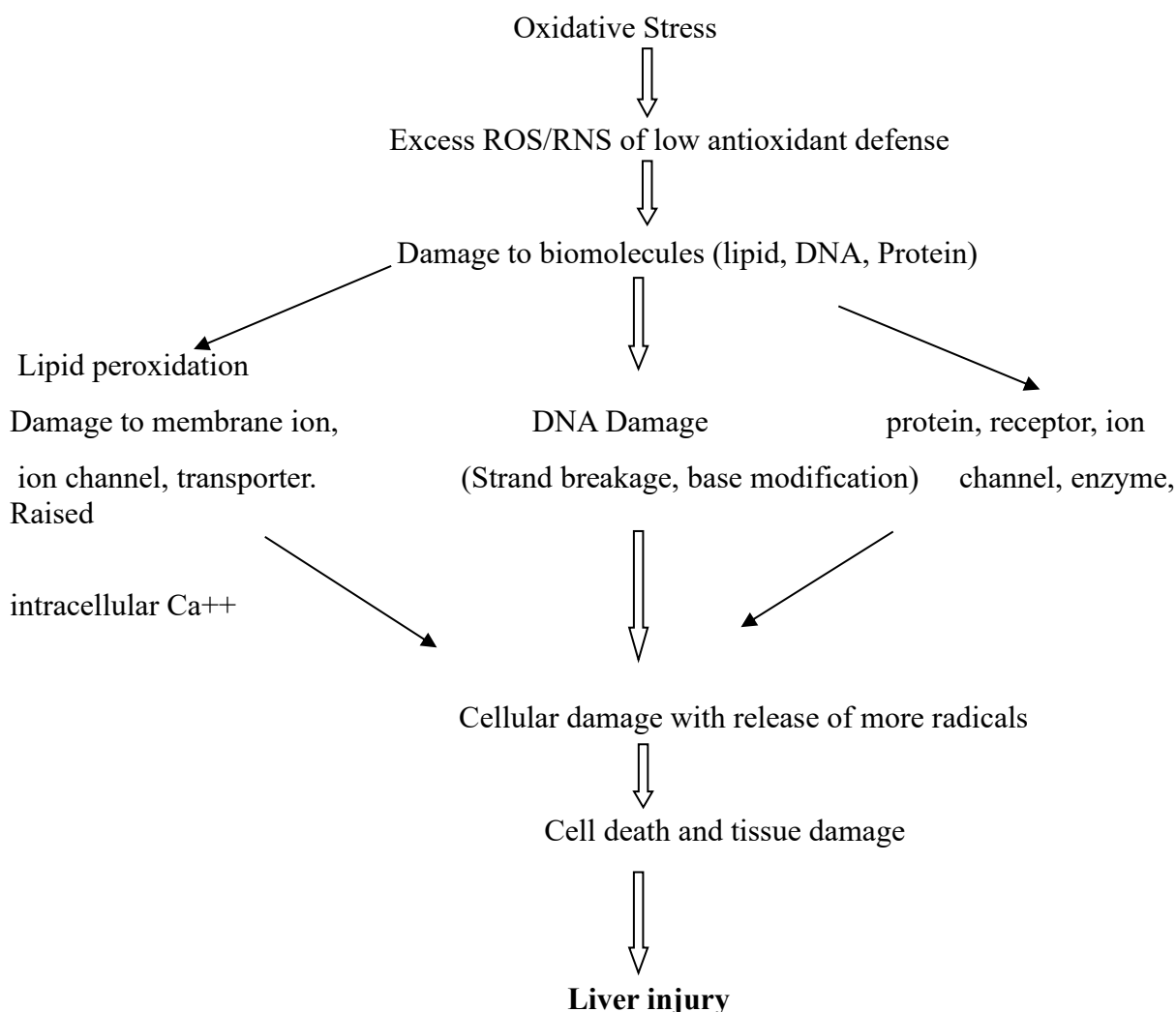
Lipid peroxidation is propagated to other sites causing widespread membrane damage and destruction of organelles.

Oxidation of proteins: Oxygen-derived free radicals cause cell injury by oxidation of protein macromolecules of the cells, cross linking of labile amino acids as well as by fragmentation of polypeptides directly. The end result is degradation of cytosolic neutral proteases and cell destruction.

DNA damage: Free radicals cause breaks in the single strands of the nuclear and mitochondrial DNA. This results in cell injury; it may also cause malignant transformation of cells.

Cytoskeletal damage: Reactive oxygen species are also known to interact with cytoskeletal elements and interfere in mitochondrial aerobic phosphorylation and thus cause ATP depletion. [9]

Flow Chart: 2

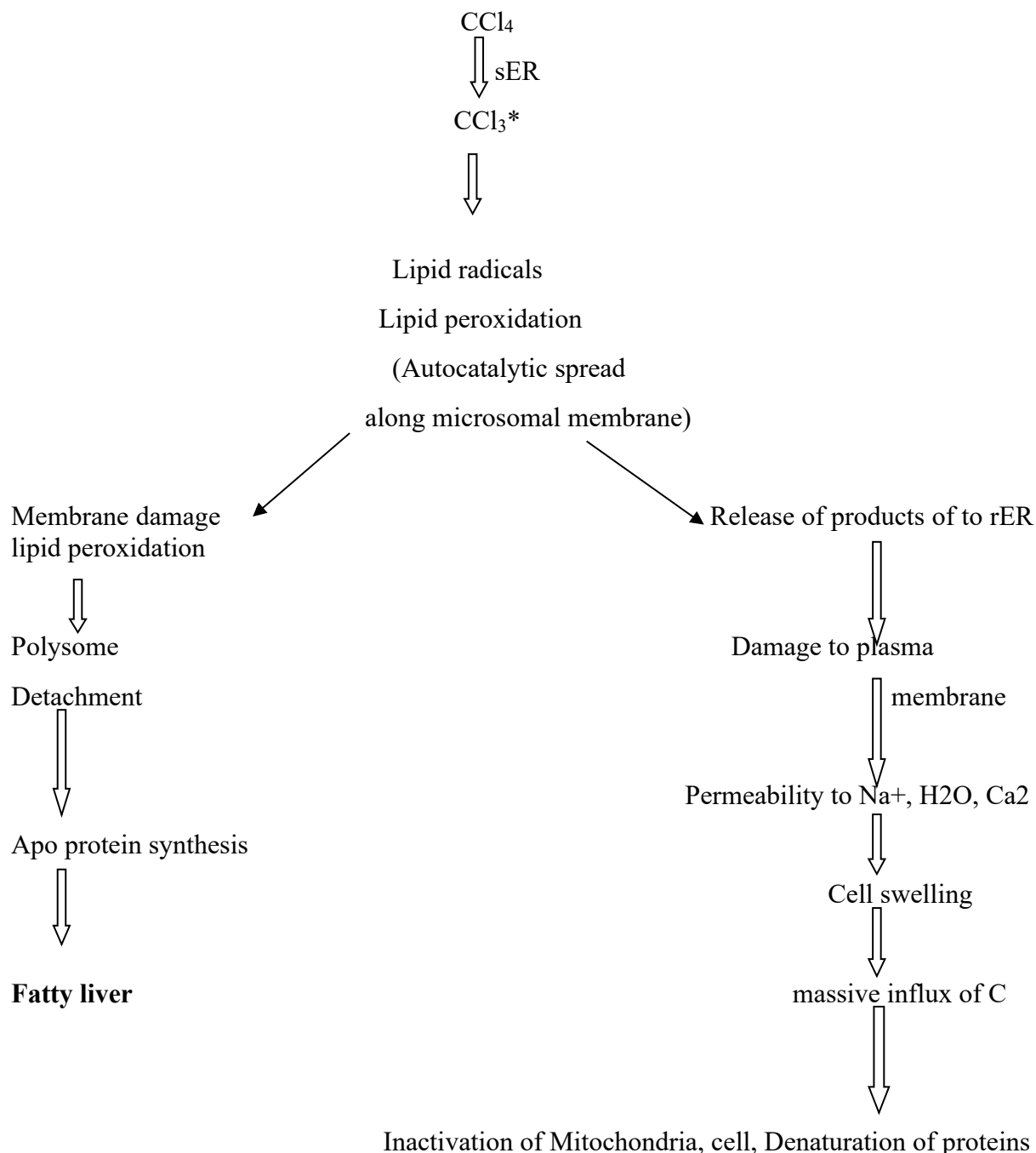


Superoxide dismutase (SOD)

SOD is a ubiquitous cellular enzyme, which dismutates superoxide radical to hydrogen peroxide and oxygen. Dismutation is a reaction in which a single reactant is converted into two different products. Superoxide dismutase, one of the chief cellular defense mechanisms, scavenges superoxide radicals by catalyzing the conversion of two of these radicals into hydrogen peroxide and molecular oxygen. [5]

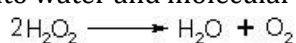
Lipid peroxidation: Lipid peroxidation can be defined as the oxidative deterioration of lipids. Lipid hydroperoxides are non-radical intermediates derived from unsaturated fatty acids, phospholipids, glycolipids, cholesterol esters and cholesterol itself. These are formed in enzymatic or non-enzymatic reactions involving free radical. [2]

Flow chart: 3



Catalase

The hydrogen peroxide formed by superoxide dismutase and other processes is scavenged by catalase, a ubiquitous heme protein that catalyzes the dismutation of hydrogen peroxide into water and molecular oxygen. [4]



Glutathione (GSH)

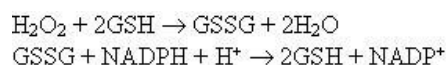
GSH is a tripeptide of glycine, glutamic acid and cysteine. Glutathione is an important naturally occurring antioxidant as it prevents the hydrogen of sulfhydryl group to be abstracted instead of methylene hydrogen of unsaturated lipids. Therefore, levels of glutathione are of critical importance in tissue injury caused by toxic substances. The antioxidant enzymes

superoxide dismutase and glutathione form the first line of defense against free radical induced damage, offer protection against free radicals and thereby, maintain low levels of lipid peroxides.

The primary biological function of glutathione is to act as a non-enzymatic reducing agent to help keep cysteine thiol side chains in a reduced state on the surface of proteins. Glutathione is also used to prevent oxidative stress in most cells and helps to trap free radicals that can damage DNA and RNA.^[3]

Glutathione peroxidase

Glutathione peroxidase (GPx) is an enzyme which catalyzes the reduction of hydroperoxides, including hydrogen peroxides, and functions to protect the cell from peroxidative damage. It is a selenium containing enzyme and reduces H_2O_2 to H_2O by oxidizing glutathione (GSH). Rereduction of the oxidized form of glutathione (GSSG) is then catalyzed by glutathione reductase



GPx activity can be measured indirectly by a coupled reaction with glutathione reductase. Oxidized glutathione (GSSG) produced upon reduction of an organic hydroperoxide by GPx, is recycled to its reduced state by glutathione reductase and NADPH. The oxidation of NADPH to $NADP^+$ is accompanied by a decrease in absorbance at 340 nm. The rate of decrease in the A340 is directly proportional to the GPx activity in the sample.^[1]

Studies on Oxidative Stress in Liver diseases: Important Future Trends in Liver Research

Oxidative stress has recently been shown to play an important role in various liver diseases. Therefore, further studies on oxidative stress in liver diseases are urgently required

Oxidative Stress in Obstructive Jaundice-

The intestinal mucosa in jaundiced rats was

atrophic with significantly decreased villous density and total mucosal thickness. Determination of biochemical parameters of oxidative stress in the intestine showed increased lipid peroxidation and protein oxidation in BDL-rats. Thiol redox state revealed the presence of intestinal oxidative stress in jaundiced rats, indicated by a decrease in GSH.^[6]

Oxidative stress in alcoholic liver injury-

Oxidative stress plays an important role in pathogenesis of alcoholic liver injury. The main source of free oxygen species is cytochrome P450-dependent monooxygenase, which can be induced by ethanol. Reactive oxygen species produced by cytochrome P450 enzyme are more important in intracellular oxidative damage compared to species derived from activated phagocytes. Free radicals lead to lipid peroxidation, enzymatic inactivation and protein oxidation which leads to liver injury.^[7]

Oxidative stress and molecular changes in liver fibrosis-

Clinical and experimental data suggest that oxidative stress (OS) mediates the progression of fibrosis, and that OS-related molecules may act as mediators of molecular and cellular events implicated in liver fibrosis. The generation of reactive oxygen species (ROS) plays an important role in producing liver damage and initiating hepatic fibrogenesis which further lead to liver fibrosis.^[8]

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