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Original Research Article

Oxidative Stress Part in Liver Disorders

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Abstract:

Background: Redox state is a significant contributor to the backdrop of many liver illnesses. Inflammatory, metabolic, and proliferative liver diseases all involve the redox state. The cytochrome P450 enzymes are largely responsible for the production of reactive oxygen species (ROS) in the mitochondria and endoplasmic reticulum of hepatocytes.

Main Body of the Abstract: An imbalance between oxidant and antioxidant agents causes oxidative stress. The main cellular structures that are impacted by ROS and reactive nitrogen species include hepatocytic proteins, lipids, and DNA. Oxidative stress has been recognised as a co-occurring pathogenic process that initiates and advances liver injury. Numerous risk factors, such as alcohol, drugs, environmental toxins, and radiation, can cause the liver to experience oxidative stress, which can lead to serious liver illnesses such alcoholic liver disease and non-alcoholic steatohepatitis.

Short Conclusion: Natural antioxidants found in edible or therapeutic plants frequently have potent anti-inflammatory, free radical scavenging, and antioxidant properties. These properties are thought to form the foundation for additional bioactivities and health benefits.

Keywords: Reactive oxygen species, oxidative stress, liver disorders, anti-oxidants.

Introduction

Oxidative stress is a result of an imbalance between the limited antioxidant defences and the excessive production of reactive oxygen/nitrogen species (ROS/RNS). An immediate effect of excessive ROS generation is the modification of cellular macromolecules like DNA, lipids, and proteins, which can result in cell death. In addition to exogenous sources like ionising radiation, diet, metals, pesticides, or other toxic compounds, ROS are also produced internally as by-products of a number of enzymatic reactions and metabolic pathways that need molecular oxygen and are probably involved in the pathogenesis of various human diseases, such as liver diseases. The liver is one of the most important organs in the body. Importantly, its primary functions which result in ROS as a by-product are the metabolism and detoxification of alcohol and narcotics [1]. Additionally, it is in charge of storing minerals like iron and copper, which are involved in processes that produce ROS, as well as vitamins (A, B, D, E, and K), glycogen, and other nutrients. Unbelievably, regardless of their aetiology, all chronic hepatic disorders have a highly oxidative environment that perpetuates cellular damage and speeds up the development of fibrosis, cirrhosis, and ultimately hepatocellular carcinoma. As a result, all of these conditions could benefit from the same therapeutic approaches meant to strengthen the antioxidant defence system (Figure 1).

Main text

Oxidative substances in humans

Molecules with an unpaired electron in their valence orbital are known as free radicals. The most reactive, and hence harmful, products are thought to be the oxygen based hydroxyl radical and the nitrogen based peroxynitrite anion. Free radicals and their associated reactants are not equally poisonous.

The manifestation of cellular functions, including signal transduction pathways, defence against encroaching microorganisms, gene expression, and the promotion of growth or death, depends on the generation of molecular oxygen in the form of reactive oxygen species (ROS), a natural component of aerobic life. Due to the amount of oxygen in the Earth's atmosphere, redox signalling is crucial. However, an excessive amount of ROS is extremely harmful to cells. Proteins, lipids, and

DNA are the three main parts of a cell that are affected by oxidative stress. In the development of numerous degenerative diseases, such as diabetes, cancer, cardiovascular problems, or neurological diseases, the significance of oxidative stress is frequently emphasised[2](Figure 2).

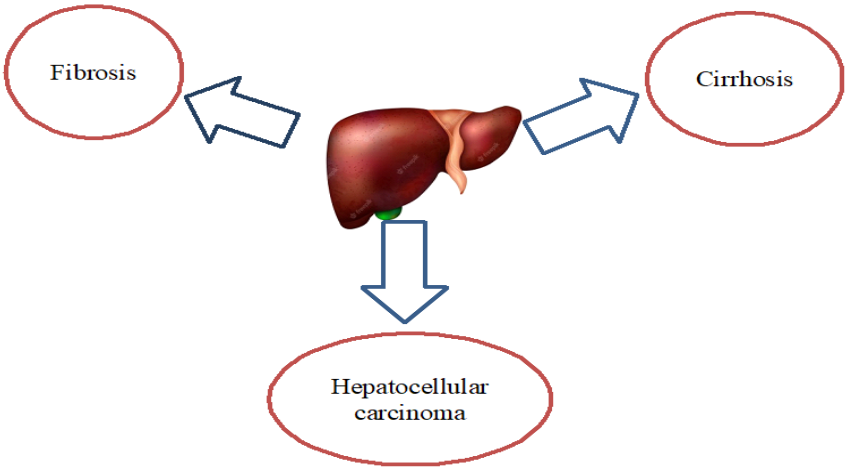

Figure 1: Liver (Cellular damage)

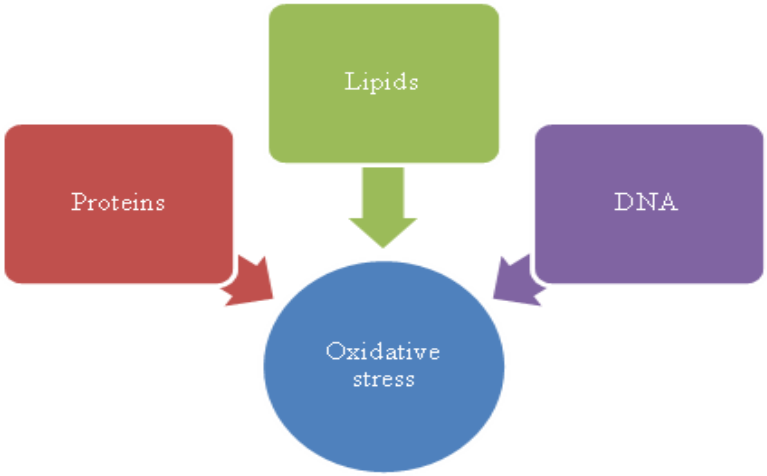

Figure 2: Main parts of oxidative stress

The state of chronic oxidative stress is inextricably linked to the illnesses mentioned. Acute exposure to high amounts of ROS, however, can potentially cause significant harm to the human body, as seen during liver ischemia/reperfusion (I/R). ROS are thought to be molecular secondary messengers that are produced in response to growth factors, hormones, cytokines, and extracellular ATP in addition to their negative effects. As a result, the balance between oxidant and antioxidant particles determines the intricate role that oxidant agents play in cells. Several enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic substances, such as tocopherol, vitamin E, beta-carotene, ascorbate, and glutathione (GSH), conduct protective functions against ROS[3-5]. The amount of inactive ROS increases as this antioxidant system's capacity declines. In the end, a risky redox state is reached, and oxidative agents' negative effects start to show. Numerous amino acids, including tyrosine, tryptophan, histidine, and cysteine in particular, are impacted by these effects. The direct targets of ROS are proteins that contain high concentrations of these particular amino acids. Protein structure and function may change as a result of ROS-mediated alteration. Oxidised proteins are extremely vulnerable to proteasomes' proteolytic assault[2].

Alterations to mitochondrial permeability and transition potential are also brought on by ROS production. These modifications cause pro-apoptotic substances, like cytochrome C, to be released. Furthermore, mitochondrial permeability promotes cellular caspase-3 activation. Reduced ATP synthesis and reduced mitochondrial protein synthesis, modifications to the oxidative phosphorylation system, and damage to

mitochondrial DNA are additional events associated with an elevated redox state[2].

Additionally, sensitive proteins may experience both reversible and permanent alterations as a result of oxidative stress. Usually involving cysteine, reversible changes can both protect a cell from irreparable harm and modify how a protein functions. The permanent loss of function that results from irreversible modifications brought on by ROS, such as lysine and arginine carbonylation, di-tyrosine formation, or protein protein cross-linking, may contribute to both the degradation of damaged proteins and their accumulation into cytoplasmic inclusions. This procedure frequently occurs in conjunction with neurodegenerative diseases[6].

Free Radicals

Superoxide (O2•) anion, the prototypical ROS that is produced in enzymatic reactions and in the mitochondrial electron transport chain (ETC), as well as other oxidants like hydrogen peroxide (H2O2) or hydroxyl radicals (•OH), are examples of oxygen-derived molecules that are included in ROS. Superoxide anion can be created as a by product of the transfer of electrons to oxygen during the respiratory chain to build ATP in mitochondria, where the majority of ROS are produced [1]. Other heme proteins, xanthine oxidase, peroxisomal fatty acid -oxidation, membrane nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenases, peroxidases, and hepatic P-450 microsomal detoxification are examples of extramitochondrial producers of ROS. Superoxide dismutase (SOD) and the GSH redox cycle are two antioxidants that must be in perfect equilibrium in order to prevent the production of oxidants like hydrogen peroxide, even if oxidative stress results from the alteration of the balance between oxidants (i.e., ROS) and antioxidants[7].

In this sense, the cell exhibits antioxidant defences against ROS of many sources, which include both enzymatic and non-enzymatic elements. Different enzymes that catalyse ROS detoxification processes are part of the enzymatic system. SOD, catalase (CAT), glutathione peroxidase and reductase (GSH-Prx or Gpx), peroxiredoxins, glutaredoxins, thioredoxins, and sulfiredoxins are a few of the most important. Some of these enzymes are positioned in specific locations where free radicals and ROS are produced within the cells to combat them more directly, increasing efficiency in ROS scavenging. For instance, the SOD enzyme has two isoforms, cytosolic (Cu/Zn-SOD) and mitochondrial (Mn-SOD), sometimes known as SOD-1 and SOD-2. Small molecules like glutathione (GSH), ascorbic acid (vitamin C), retinol (vitamin A), and tocopherol (vitamin E), which defend against radical species by accepting electrons in their structure, are examples of non-enzymatic antioxidant components [8].

The nuclear factor E2-related factor 2 (Nrf2), which controls the production of many antioxidant genes, is another important element that is brought on by oxidative stress [9]. Indeed, in many oxidative stress models, pharmacologic stimulation of the Nrf2-dependent antioxidant signalling pathway has been found to protect the liver[10]. Figure 3 shows how each cellular compartment contributes to oxidative stress and how the antioxidant defence system combats ROS production.

Redox Control in the Liver

The efforts to reduce mitochondrial ROS generation will receive attention due to the prevalence of mitochondrial-origin ROS and the involvement of this organelle in liver disorders. Hepatocytes have strong enzymatic and non-enzymatic antioxidant defence mechanisms that combat free radicals. The "first line" of defence in converting superoxide radicals produced in the ETC to H2O2 and O2 is the SOD enzyme. An important enzyme for detoxifying H2O2 is CAT. However, because this enzyme is mostly found in peroxisomes, mitochondrial expression of CAT is nonexistent. Therefore, several antioxidant enzymes perform the task of degrading mitochondrial hydrogen peroxide. The reduction of H2O2 in a chain reaction with GSH as the electron donor is catalysed by mitochondrial glutathione peroxidases (Gpx1) and different hydroperoxides (PrxIII, Trx2), and the subsequent conversion of GSH disulfide (GSSG) back to GSH by the NADPH-dependent glutathione reductase (GR). Since catalase is required for the proper redox maintenance in this organelle, the availability of mitochondrial GSH (mGSH) protects mitochondria from the absence of this enzyme [1].

Since GSH can only be produced in the cytosol, specialised carriers are needed to transport GSH to various compartments, including mitochondria. The 2-oxoglutarate carrier (OGC; Slc25a11), which imports GSH in exchange for 2-oxoglutarate (2-OG), transports GSH into mitochondria in the liver. Dependence of the 2-OG carrier on membrane fluidity is a pertinent GSH transport factor in hepatic diseases.This is based on cholesterol concentration and fatty acid composition. This transport pathway is hampered by increased membrane stiffness, which reduces the availability of mGSH and antioxidant defence. In this regard, earlier research in a variety of alcoholic (ASH) and non-alcoholic steatohepatitis (NASH) models shown that elevated mitochondrial cholesterol led to mitochondrial malfunction, decreased levels of mGSH, and increased vulnerability to cell death. Additionally, mGSH plays a significant role in

regulating cell death pathways via regulating the cardiolipin redox state [11].

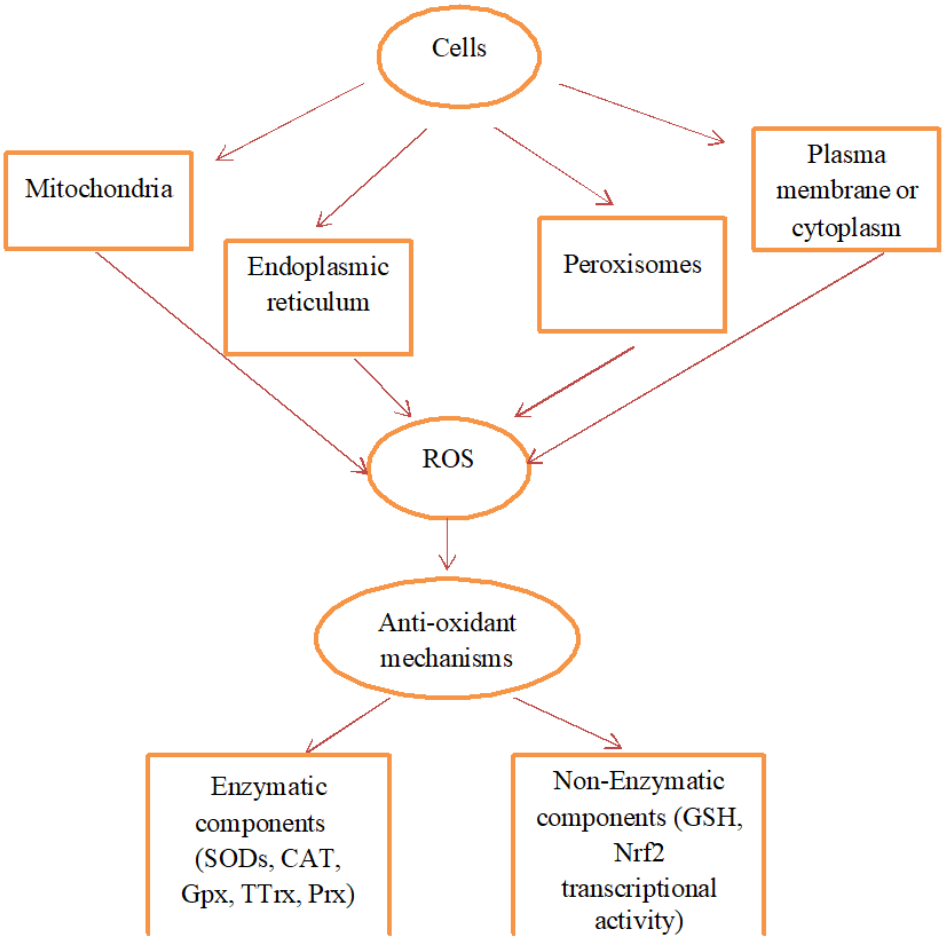

Figure 3: Major sources of ROS

When free radical species avoid the antioxidant defence mechanisms of the cell, they interact with macromolecules to produce harmful adducts that change the function of every cell's component before apoptosis [12]. As potential disease biomarkers, elevated levels of oxidative stress markers, such as the DNA damage marker 8-hydroxy-20-deoxyguanosine (8-OHdG) and lipid peroxidation products (MDA and 4-HNE), have been found in hepatic tissue and plasma of patients with a variety of liver disorders, including NASH, hepatitis C, liver fibrosis, and HCC[1]. Similarly, excessive lipid oxidation alters the physical characteristics of cellular membranes and may be a factor in the deterioration of the Ca2+ buffering ability and mitochondrial membrane potential. Ca2+ excess triggers the opening of the mitochondrial permeability transition (MPT), which, if it persists for a long period of time, causes a secondary burst of ROS and sets off a chain reaction of unfavourable consequences that ultimately culminates in hepatocellular mortality[13-14].

Oxidative stress in disorders of the liver:

Alcoholic Liver Disease (ALD)

ALD is a common type of chronic liver disease brought on by continued alcohol usage. For the first time, Comporti and colleagues proposed in 1967 that ethanol-induced fatty liver was caused by lipid peroxidation. From the earliest stage of steatosis to alcoholic hepatitis, cirrhosis, and ultimately HCC, the oxidative metabolism of ethanol sets off a broad range of processes that help ALD advance. Unfortunately, there are currently few therapeutic options available because to the incomplete understanding of the pathogenesis of ALD. Alcohol dehydrogenase (ADH), which metabolises ethanol to acetaldehyde in the liver, is the first enzyme involved in the metabolism of alcohol, which leads to an increased ROS formation and the initiation of oxidative stress in hepatocytes [1].

Acetaldehyde dehydrogenase (ALDH) then catabolizes acetaldehyde to acetate. Acetaldehyde is extremely reactive and forms adducts with DNA, causing tissue damage, in contrast to acetate, which is stable. As a result of KCs, endothelial cells, and stellate cells being able to recognise the hybrid adducts formed by acetaldehyde and its product

MDA, an inflammatory response that promotes the development of ALD is triggered. Additionally, ethanol is metabolised by the microsomal system cytochrome P450, CYP2E1, which after alcohol chronic intake transforms alcohol to acetaldehyde.

Due in part to the saturation of ADH with alcohol, which causes ROS to be produced and the initiation of oxidative stress, CYP2E1 is induced and becomes the favoured pathway of oxidative ethanol metabolism. Further evidence for the relationship between oxidative stress and inflammation during ALD comes from the fact that ROS can make hepatocytes more sensitive to LPS produced from the stomach and tumour necrosis factor-alpha (TNF-α), which in turn produces more ROS [15].

The liver is damaged by ALD through a number of mechanisms. The enzymes ADH and ALDH convert NAD+ to NADH. By inhibiting gluconeogenesis and fatty acid oxidation, the changed NAD+/NADH ratio causes fatty liver. Alcohol itself stabilises CYP2E1, which is elevated in chronic alcohol consumption and creates free radicals by converting NADPH to NADP+. CYP2E1-produced ROS have the ability to peroxidize the oxidation related mitochondrial and peroxisomal enzymes, which leads to the build-up of fatty acids and the emergence of hepatic steatosis. Alcohol causes liver damage by promoting a gradient of hypoxia from the portal vein to the central vein. Alterations in ROS metabolism enhance the expression of the hypoxia-inducible factor-1 alpha (HIF-1), which increases the release of TNF-α and affects mitochondrial function, amplifying liver damage through an immunological response. The poor antioxidant defence that contributes to inflammation and the severity of the disease observed in people with ALD also causes oxidative stress to produce hepatocyte apoptosis and mostly necrosis. Alcohol withdrawal reverses the mGSH depletion that alcohol feeding causes by reducing the amount of cholesterol in the mitochondria [1].

The consequences of mGSH depletion and ASH in rats given an ethanol-polyunsaturated fatty acid treatment are also described in recent research; however, betaine cotreatment prevents these effects. Surprisingly, alcohol-induced ER stress increases cholesterol production and changes its trafficking into mitochondria, thus altering mGSH levels. Accordingly, in ethanol-fed rats, TUDCA's ER stress blockade restored the mGSH pool [16]. Furthermore, ROS are involved in the conversion of HSC into myofibroblasts and the activation of matrix metalloproteinases, which results in the remodelling of the extracellular matrix in the liver and the development of cirrhosis and excessive hepatic fibrosis in severe ALD. These consequences are made worse by mature hepatocytes' reduced potential for regeneration [17].

Non-alcoholic fatty liver disease

The most prevalent chronic hepatic pathology is NAFLD. A third of the population in affluent nations is thought to be affected. Simple hepatic steatosis, NASH, cirrhosis with all the symptoms of portal hypertension, and ultimately HCC are all part of the clinical spectrum of NAFLD. The disruption of fatty acid absorption, production, oxidation, and export is the pathophysiology of NAFLD. The result of this imbalance is an abnormal build-up of fat in the liver. Several predisposing factors, including obesity, diabetes, dyslipidemia, jejunoileal bypass, medications, and parenteral feeding, are associated with NAFLD. The activation of hepatic stellate cells and potential development to cirrhosis and severe fibrosis are also plausible. The second lesion in NAFLD is portal chronic inflammation, but it is yet not sufficiently characterised[2]. Numerous studies have demonstrated that the renin-angiotensin system (RAS) and oxidative stress mediate liver damage in the course of NAFLD[18].

The control of blood pressure and cardiovascular homeostasis depends on the RAS mechanism. Cardiovascular diseases and hypertension are caused by RAS overexpression. The liver is one of many tissues and organs where the RAS is found. It's interesting to note that cirrhosis, chronic hepatitis HCV, and NAFLD have all been associated with increased systemic and local RAS activity. The molecular mechanism of ALD pathogenesis appears to begin with increased angiotensin II levels. This substance has been found in Ren2 transgenic Ren2 rats with an elevated amount of endogenous angiotensin II, and it exhibits pro-oxidant, pro-inflammatory, and pro-fibrotic actions in the liver. Hepatic ROS are significantly produced when angiotensin II is overused[19-20]. Oxidative stress specifically damages mitochondria, impairing gene expression, altering protein synthesis, reducing the amount of mitochondria, and impairing beta-oxidation in the mitochondria.

Additionally, NAFLD produces an increase in mitochondrial CYP2E1 expression, which results in a redox state. Unquestionably, disrupted beta-oxidation is a key factor in the development of NAFLD. It causes fatty acids to build up inside the hepatocytes, which then results in the disease. This hypothesis has been supported by studies showing that valsartan, an angiotensin type 1 receptor blocker, and tempol, a superoxide dismutase/catalase mimic, reduced oxidative stress in Ren2 rats. NADPH oxidase activity is elevated while cytosolic Cu-ZnSOD activity is downregulated as a result of increased ROS

production during ALD. Lipid peroxidation involves an overabundance of reactive agents, which also increases mitochondrial permeability and changes their function[21]. Additionally, ROS are in charge of releasing reactive aldehydes like 4-HNE, which deactivate the mitochondrial respiratory chain and obstruct electron flow from the respiratory chain. As a result, mitochondrial ROS production and oxidative stress rise. It has been crucial to identify the relationship between angiotensin II, oxidative stress, and poor betaoxidation in NAFLD[2].

Hepatic encephalopathy

An intellectual, psychomotor, and cognitive impairment associated with acute or chronic liver illnesses is known as hepatic encephalopathy (HE). Due to the fact that it causes astrocytic swelling in the brain, ammonia has been identified as a main toxin in this type of pathology. N-methyl-D-aspartate (NMDA) receptors are also activated by ammonia-stimulated astrocytes.

The generation of ROS is increased, and antioxidant enzyme activity is decreased when ammonia-induced NMDA receptors are stimulated. However, it is extremely challenging to determine whether astrocyte swelling itself generates oxidative stress through NMDA receptor and calcium-dependent pathways [2] or whether oxidative stress induces astrocyte swelling. Key players in astrocyte swelling are cerebral endothelial cells. They are essential in initiating an aberrant redox state since they are the first resident brain cells to be exposed to hazardous chemicals (like ammonia)[22].

Additionally, during HE, mitochondria are exposed to high glutamine levels, which results in an extra rise in oxidative stress in astrocytes. Additionally, HE is the cause of neutrophil activation and the increased generation of ROS and is inextricably linked to both local and systemic inflammation and infection. More extensive oxidative agents can oxidise RNA, according to other studies, which impairs protein synthesis and causes biochemical disturbances in the brain[23-24]. Animal models and investigations in cell culture supported this hypothesis. Heat shock protein-27, 8-hydroxyguanosine, and protein tyrosine-nitrated proteins all had significantly higher amounts in the postmortem cortical brain tissue of patients with HE, according to the investigation. These proteins serve as indicators of RNA oxidation and provide more evidence of the role that redox status plays in the pathophysiology of HE. The alternative explanation based on the function of oxidative stress in the development of HE is known as the "two-hit" hypothesis. Hyperammonemia and liver damage serve as the "initial hit," and as a result, astrocyte swelling and ROS production develop. Then, an infection, dehydration, hyponatremia, or upper gastrointestinal haemorrhage results in a "second hit," such as an ammonia load. As astrocyte destruction increases, ROS levels also climb. The strong relationship between oxidative stress and astrocyte swelling leads to an auto-amplifying signalling loop, which is reflected in the decline in neurocognitive function [2].

Viral Hepatitis

Over 500 million people are chronic viral hepatitis carriers worldwide. Hepatitis A virus, Hepatitis B virus, and Hepatitis C virus are the three main kinds of viral hepatitis. The latter two are becoming more common, and 12% of all cancers are caused by them, including the hepatitis delta virus (HDV), which can speed up the course of the illness[25]. In viral hepatitis, oxidative stress also has a harmful effect. In human diseases caused, among other things, by viruses, ROS and free radicals are produced. Viruses enter cells by endocytosis and replicate inside them as intracellular parasites exploiting the host cell's natural processes[26]. These activities have an impact on how the ER and mitochondria produce ROS and deplete the antioxidant system (GSH, GSHPx).

Increased levels of a wide range of oxidative stress markers in the liver and blood of infected patients are one of the hallmarks of HBV and HCV infections. These indicators, which are responsible for the activation of inflammatory pathways, include MDA, lipid peroxides, protein carbonyl concentration, oxysterols, and thioredoxin. CYP2E1, ERo1a, and NADPH oxidases are also elevated in HCV. Additionally, Zn shortage in HCV results in oxidative DNA damage, lipid peroxidation, and loss of mitochondrial energization. The prognosis of individuals with HCV has been demonstrated to be improved by its supplemental therapy. Antioxidant therapy, on the other hand, is not always successful because, if administered incorrectly, antioxidants can easily transform into pro-oxidants [27]. Therefore, to create effective treatments, a thorough examination of the processes by which viral proteins generate oxidative stress is required.

Liver Fibrosis

Extracellular matrix (ECM) accumulates excessively and progressively in fibrosis, affecting the physiological architecture of the liver between hepatocytes and sinusoids. In chronic inflammatory illnesses, it is linked to disease progression. In addition, the primary factor causing clinical problems, bleeding incidents and hepatic encephalopathy is persistent portal hypertension brought on by liver fibrosis[1].

The vicious cycles of steatosis, lipid peroxidation, ROS formation, anti-oxidant reduction, modified

mitophagy, and mitochondrial danger signal-induced expression of inflammatory cytokines, which result in hepatocyte apoptosis and necrosis, are what cause steatohepatitis from all aetiologies to be linked to an increase in ROS. Hepatocytes, HSCs, and macrophages produce pro-fibrotic mediators like superoxide, H2O2, and other hydroxyl radicals [28].

The ROS-producing enzymes NAPDH oxidases (NOXs) stimulate angiotensin II, PDGF, and TGF in HSCs and macrophages, activating collagen-producing myofibroblasts that are responsible for the excessive build-up of ECM. DAMPs are released by necrotic hepatocytes, which cause neighbouring cells (HSCs and KCs) to send out warning signals. In this respect, NF-B is regarded as a crucial modulator of the development of liver fibrosis and plays a significant role in the control of inflammation. Its activity is connected to the growth of HSCs. A significant risk factor for HCC development, fibrosis development primarily impacts the quality of life and prognosis associated with liver function[29].

Hepatocyte injury during hypoxia/reoxygenation

Following hepatic surgery (such as the removal of big hepatic tumours or vascular reconstructions) or transplantation, I/R is a significant mechanism of liver harm. Chronic hepatic infection or inflammation may also be linked to it. A redox state that is caused by oxidative agents that are formed very quickly after reperfusion of ischemic tissue is the primary factor in cellular harm. ROS levels rise as a result of mitochondrial electron transport chain changes brought on by hypoxia. Additionally, ischemia changes xanthine de hydrogenase's physiological form into xanthine oxidase. When this altered enzyme interacts with molecular oxygen, ROS are created. Kupffer cells are in charge of this redox state, which may be found in the extracellular space of the liver where there is the highest level of oxidative stress in I/R. The other cells contributing to ROS production following reperfusion include neutrophils. Neutrophils emit oxidative stress indicators principally 6–24 hours after the start of I/R as a result of NADPH oxidase. The most crucial receptor for neutrophil activation and redox status is Mac-1 (CD11b/CD18). During reperfusion, this receptor's suppression greatly lessens liver damage[2]

Antioxidants as therapeutic agents for liver disease

Antioxidants are justifiably regarded as a good therapeutic approach for the treatment of liver illnesses given the critical role that oxidative stress plays in liver diseases. Although the study results are still debatable and unclear, the therapeutic effectiveness of some antioxidants has been established. Numerous studies have shown that curcuminoids assist hepatocytes during damage and cirrhosis and defend DNA against ROS[31].

Studies on chronic HCV have shown improvement following antiviral medication assisted by silymarin, an extract from milk thistle that protects GSH within hepatocytes. In individuals with chronic HCV infection, ascorbic acid, lipoic acid, quercetin (a flavonoid antioxidant), and mitoquinone (a mitochondria-targeted antioxidant drug) also have positive effects. Resveratrol's antioxidant qualities boost GSH levels in the liver, reduce hepatic lipid peroxidation, and scavenge ROS. Its actions are active when hepatotoxins, such as ethanol, cause liver injury. Additionally, ebselen (a glutathione peroxidase analogue) functions as a therapeutic drug in the early stages of alcohol-induced liver damage. According to research, vitamin E reduces TGF beta gene expression in rat models of NASH and lowers HBV replication[32-33]. The development of NAFLD can also be stopped by vitamin E, according to more studies. The use of vitamin E for NASH currently provides the strongest clinical evidence of effective antioxidant therapy in liver illnesses [34]. The effectiveness of antioxidative medicines in hepatology, however, is incredibly challenging to comprehend and describe despite countless research using both human and animal models[35].

Conclusions

Free radical species, as is widely known, are physiological signalling molecules that, when produced in excess or when they build up as a result of an imbalance with antioxidants, cause oxidative stress. This stress results in significant alterations in cell function and even cell death.

We also discussed the most significant pathogenic mechanisms that contribute to the onset of liver illnesses, emphasising the role that oxidative stress plays in the pathophysiology of these diseases. Despite the recent increase in interest in the use of antioxidants for the treatment of liver diseases, when the benefits of antioxidant compounds have been evaluated in clinical trials, mixed and contentious results have been reported, and many of the promising results obtained in animal models failed to be replicated when translated into human disease. If clinical trial designs are improved, the data derived from them may offer important information igniting interest in the potential future of antioxidants in liver illnesses.

List of abbreviations

ALD	Alcoholic Liver Disease
ATP	Adenosine triphosphate
CAT	Catalase
DNA	Deoxyribonucleic acid

ETC	Electron transport chain
GSH	Glutathione
H2O2	Hydrogen peroxide
I/R	Ischemia/reperfusion
NADPH	Nicotinamide adenine dinucleotide phosphate oxidase
Nrf2	Nuclear factor E2-related factor 2
NASH	Non-alcoholic steatohepatitis
NMDA	N-methyl-D-aspartate
ROS/RNS	Reactive oxygen/nitrogen species
ROS	Reactive oxygen species
SOD	Superoxide dismutase

TNF-α tumour necrosis factor-alpha

Declarations

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