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Review article

Oxidative stress is bane in chronic liver diseases: Clinical and experimental perspective

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ABSTRACT

Oxidative stress plays an important role in the pathogenesis of various chronic liver diseases (CLD) and increasing evidence have confirmed the contributory role of oxidative stress in the pathogenesis of drugs and chemical-induced CLD. Chronic liver injury is manifested as necrosis, cholestasis, fibrosis, and cirrhosis. Chronic administration of anti-tubercular, anti-retroviral, immunosuppressive drugs is reported to induce free radical generation during their biotransformation in the liver. Further, these reactive intermediates are said to induce profibrogenic cytokines, several inflammatory markers, collagen synthesis during the progression of hepatic fibrosis. Oxidative stress and free radicals are reported to induce activation and proliferation of hepatic stellate cells in the injured liver leading to the progression of CLD. Hence, to counteract or to scavenge these reactive intermediates, several plant-derived antioxidant principles have been effectively employed against oxidative stress and came out with promising results in human and experimental models of CLD. This review summarizes the relationships between oxidative stress and different liver pathogenesis induced by drugs and xenobiotics, focusing upon different chronic liver injury induced by alcohol, antitubercular drugs and hyperactivity of antiretroviral drugs in HIV patients, viral hepatitis infection induced oxidative stress.

Introduction

The liver is vulnerable to many forms of chronic injury due to its unique anatomic location and functions. It has remarkable ability to scavenge the free radicals generated during the metabolism of various drugs and xenobiotics by virtue of its intracellular antioxidant system. The increased generation of free radicals, together with the decreased antioxidant defense in hepatocytes, promotes the progression of oxidative stress leading to various liver dysfunctions. Thus, the oxidative stress is implicated in various forms of CLD *i.e.,* viral hepatitis, necrosis, fibrosis, cirrhosis and hepatocellular carcinoma. Ample experimental and clinical evidence has reported the hepatoprotective principles for their antioxidant potential against myriad hepatic ailments. For instance, silymarin, silibinin, curcumin, resveratrol, green tea etc., have been extensively studied against CLD in experimentally as well as clinically and came out with promising results. Unsurprisingly, these drugs are primarily antioxidants, which indicate the significance of antioxidant therapy in the oxidative stress-induced CLD. Hence, this review summarizes different etiologies of free radical generation and their mechanism of action on inducing oxidative stress in CLD.

Free radicals and oxidative stress

In a biological system, oxidative stress is said to occur due to the physiological imbalance, when the antioxidant defense system is overwhelmed by the excessive presence of reactive oxygen species (ROS) and free radicals [1]. As a result of an imbalance between ROS and antioxidant defense, the consequent damage to potential cellular functions which leads to various pathophysiological alterations in the liver [2]. Several *in vitro* and *in vivo* studies have reported that free radicals especially, ROS intervene and modulate various cellular functions *i.e.,* cell cycle, signaling, adhesion, metabolism, and death [3].

Free radicals are highly reactive species having unpaired electrons in their outermost shell, which are capable of independent existence and the presence of these electrons makes the free radicals highly reactive [4]. A variety of free radicals are produced throughout the body, which is found to be the by-products of cellular metabolism, ongoing stress, and exposure to UV light or X-rays [5,6]. It is an established fact that when a free radical reacts with a non-radical, the later usually becomes a radical and thus a chain of reaction is initiated. Some important free radicals known in biological systems include superoxide ($O_2^{\cdot-}$), hydroxyl ($OH^{\cdot}$), hydrogen peroxide (H_2O_2), hypochlorous acid ($HOCl_2$), nitric oxide

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($NO^{\cdot}$) and singlet oxygen and these radicals have a potential to generate ROS [7].

The highly reactive intermediates are mainly generated in the liver during the biotransformation of various drugs and thus cause oxidative stress by exploiting the intracellular antioxidant system. Increase in intracellular ROS level can cause peroxidation of polyunsaturated fatty acids of membrane phospholipids, which can further react with oxygen to create peroxyl radical. In turn, these radicals can react with adjacent side chains and thus enable the chain reaction of membrane-bound lipids resulting in peroxidation of lipids. Enhanced lipid peroxidation results in the accumulation of conjugated dienes such as malondialdehyde, lipid peroxides etc. Therefore, measurement of lipid peroxidation and intracellular antioxidants activity is taken as direct *in vivo* and *in vitro* reliable indices for the contribution of free radical generation and thereby oxidative stress [8,9].

Oxidative stress in chronic liver diseases

Oxidative stress and associated hepatotoxicity could represent a common link between different forms of CLD predominantly hepatic fibrosis. Excessive levels of ROS released during different forms of CLD and are said to play a pivotal role in various liver ailments [10–13]. The principle causes of CLD have been directly linked with alcoholic liver disease, viral hepatitis, and administration of drugs.

Oxidative stress in alcoholic liver diseases

According to World Health Organization (WHO), alcoholic liver diseases (ALD) are the third most cause of morbidity and mortality worldwide [14]. Chronic alcohol exposure can lead to hepatitis, cirrhosis and hepatocellular carcinoma (HCC) and chronic inflammation are reported to cause systemic illness [15,16]. Ethanol oxidized predominantly in the liver via the cytochrome *P*-450 (CYP2E1) mediated enzyme and this enzyme is responsible for the biotransformation of various drugs in the liver and thus plays a critical role in the generation of ROS and nitrogen species [17–19], which disrupt the normal oxidant-antioxidant homeostasis in the liver. Alcohol-induced oxidative stress mainly mediated via production of reactive acetaldehyde (primary metabolite of ethanol), induction of cytochrome enzymes, formation of O_2^{-}, $OH^{\cdot}$, 1-hydroxyethyl radicals [20] and nitrosative stress through induction of inducible nitric oxide synthase [21]. Additionally, in mitochondria $NO^{\cdot}$ radical reacts with O_2^{-} to produce peroxynitrite radical together mediates various cellular dysfunction. Further, this $NO^{\cdot}$ radicals is said to inhibit respiratory chain complexes by nitrosylating/oxidizing protein thiols or removing iron from iron-sulfur clusters in cytochrome complexes [22]. Clinically, it has reported that ALD patients develop fatty liver initially and then more severe consequences such as fibrosis and alcoholic hepatitis mainly mediated via oxidative stress [23]. Studies have also documented the molecular mechanism behind the alcohol-induced oxidative stress and hepatic fibrosis. Ethanol-induced lipid peroxidation triggers the nuclear factor kappa B (NF-kB), transactivation of the collagen 2(I) gene promoter in hepatic stellate cells by stimulating kinase cascades, including protein kinase C, phosphoinositide 3 kinase, and protein kinase B/Akt [24,25]. These studies undoubtedly showed that the ethanol derived free radicals are responsible for the activation of HSCs, which lead to the progression of hepatic fibrosis via NF-kB signaling. For this reason, antioxidants such as silibinin, silymarin, ebselen, vitamin-E, superoxide dismutase, and precursors of glutathione have been employed in experimental and clinical studies against alcohol-induced oxidative stress [26–28].

Oxidative stress in chronic hepatitis

The WHO in its recent report has pointed out that more than 500 million people have chronic liver infections and over 780,000 people die every year due to acute or chronic consequences of hepatitis [29]. Chronic hepatitis infections cause liver inflammation and may result in fibrosis/cirrhosis or HCC. Several studies have concretely reported that in chronic hepatitis, immunity initiates the production of ROS and nitrosative stress [2,3,30] and variation of ROS generation among different types of hepatitis-infected patients have also been reported. Patients infected with hepatitis C virus (HCV) produces more ROS than other types of hepatitis viruses [31] and chronic hepatitis C infected patients have over 80% chances of developing CLD as compared to patients of hepatitis A, B and E [32]. Clinically, two to five folds increase in the ROS generation in liver tissue of CLD patients have been reported previously [33]. Interestingly, it was found that excess iron deposits in the liver samples from some of the HCV infected patients and this has been attributed due to the generation of free radicals in these individuals [34]. The mRNA expressions of tumour necrosis factor-α and CYP2E1 enzymes was found to increase ROS production in HCV infected patients [35]. Owing to the role of oxidative stress in HCV pathogenesis, antioxidants have been proposed to treat HCV patients and came out with promising results. For instance, normalization of liver enzymes and oxidative stress was observed in chronic HCV patients with elevated pretreatment levels, using antioxidant therapy. Clinical studies have confirmed this by the supplementation antioxidants conferred attenuation of oxidative stress in HCV patients [36,37].

Oxidative stress in drug-induced CLD

The pathology of drug-induced CLD covers a broad spectrum, from acute hepatic necrosis, chronic hepatitis, hepatic fibrosis and vascular injury to cholestasis and carcinogenesis. For instance, chronic use of antitubercular drugs in HIV (Human Immunodeficiency Virus)–TB (Tuberculosis) co-infected patients have been shown to develop oxidative stress-induced hepatotoxicity in recipients of these patients. Administrations of antitubercular drugs such as isoniazid (INH), rifampicin and pyrazinamide have been reported to cause oxidative stress in human subjects in therapeutic doses and toxic doses in experimental animals [13]. During biotransformation in the liver reactive metabolites of these drugs are released, which in turn disrupt hepatocellular membrane and cause oxidative stress-induced necrosis. Fall in the status of glutathione and their conjugating enzyme upon administration of ATDs reported previously and it denotes an impairment of the antioxidant defense mechanism [38]. Isoniazid and other ATDs are metabolized primarily in the liver and during the metabolism, INH is reported to release highly reactive electrophilic species, which could bind to tissue macromolecules resulting in hepatic necrosis [13,39,40]. As we seen earlier, cytochrome enzymes are the major contributor for the formation of ROS for a variety of drugs and this process plays a very important role in the propagation of hepatic injury [41]. Genetic studies conducted in human have shown the involvement of CYP2E1 and its relationship with INH-induced hepatotoxicity [42]. Further, studies conducted in humans and rats have shown that administration of INH and hydrazine could induce CYP2E1 activity, thererby increase in oxidative stress [43–45].

Highly active anti-retroviral therapy (HAART) has been reported to induce oxidative stress and free radicals in the HIV infected patients [46]. HAART-induce oxidative stress has been demonstrated to interfere with the mitochondrial function by decreased mitochondrial membrane potential and an increased mitochondrial O_2^{-} production, followed by a reduction in GSH content. These

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