

Targeting redox system in liver cancer

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Editorial

The liver is one of the most vital visceral organs that aid in the digestion of food, synthesis of essential biomolecules, and transformation of undesirable biomolecules from the body. The liver is the first line of defense against potentially harmful xenobiotics and protects the body by neutralizing hazardous compounds produced during metabolism or introduced in the body from outside.¹ If the liver fails to function properly, it can lead to major health complications in the gastrointestinal system as well as in the whole body. Therefore, it is the most commonly affected target organ by commercially produced chemicals and environmental toxicants. Environmental toxicants especially different pesticides like cyproconazole, fluazinam, dazomet, pyrasulfotole metabolite, hexaconazole, paclobutrazol, flusilazole, acequinocyl, vinclozolin, triadimefon and fluthiacetmethyl were associated with the development of steatosis.² Various liver affecting infections and diseases such as hepatitis B and C virus, alcoholic and non-alcoholic fatty liver disease (NAFLD) caused severe detrimental effects on the liver.³ Amongst them the most common injury is hepatitis which is an inflammatory condition in the liver cells that occurs quickly, yet it can be mitigated by preventive measures. Persistent inflammation can lead to the chronic stage of liver fibrosis which is the replacement of liver tissues with connective tissue fibers. The process of fibrosis can be fast and last for a very long time. The end result of fibrosis is cirrhosis which ultimately leads to hepatocellular carcinoma (HCC).⁴

The diagnostic and prognostic factors for liver diseases primarily comprise the liver function tests (LFT) which are efficient screening tool that effectively detects hepatic dysfunctions.⁵ Bilirubin is a major hepatic marker produced by the lysis of red cells (the haem component) within the reticuloendothelial system. The unconjugated form of bilirubin is delivered to the liver and forms a water-insoluble complex with albumin that cannot be eliminated in urine. Conjugated bilirubin, on the other hand, is water soluble and is eliminated from the body through urine. Serum bilirubin levels are predominantly unconjugated, indicating a balance between production and hepatobiliary excretion. Bilirubin production increases as a result of hemolysis and poor erythropoiesis, and it is then used as a marker of liver function. Other important measures of liver function include aminotransferases, particularly aspartate aminotransferase (AST) and alanine aminotransaminase (ALT), which are excellent indicators of hepatocellular injury. They contribute to gluconeogenesis by catalysing the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid, resulting in the formation of oxaloacetic acid and pyruvic acid. Alkaline phosphatase (ALP) is the next key indicator of liver function, derived from the liver and the bone. ALP increases can be ranged from moderate to severe in the extrahepatic biliary

obstruction, hepato-infiltrative disorders, and liver inflammation and cancer conditions. Glutamyl transferase (GGT) mainly found in hepatocytes and biliary epithelial cells serves as a sensitive test marker for hepatobiliary diseases including HCC. Albumin synthesis is an important function of the liver which serves as the marker of liver dysfunction when serum albumin levels reduce.⁶ In patients with cirrhosis, albumin infusion reduces mortality in patients with spontaneous bacterial peritonitis and improves outcome following large volume paracentesis.⁷ Liver is a major organ attacked by the process of oxidative/nitrosative. oxidative stress induced by various factors including ROS, RNS, inducing irretrievable alteration of lipids, proteins and DNA contents, mitochondrial dysfunction, NADPH-requiring enzyme, the cytochrome P450 enzyme CYP2E1 on liver diseases. A cellular antioxidant function system is required to neutralize the influence of various hazardous cellular agents through the antioxidant system in order to preserve the imbalance of the antioxidant system induced by oxidative stress/nitrosative agent.⁸

Biological cellular antioxidants are natural compounds that can prevent the uncontrolled formation of free radicals and activated oxygen species or inhibit their reaction with biological structures. These compounds include antioxidative enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) and non-enzymatic antioxidants like glutathione (GSH). Antioxidants protect against liver dysfunction via different mechanisms of action for neutralizing the effect of harmful compounds.⁹ Glutathione is one of the most abundant tripeptide non-enzymatic biological antioxidants present in the liver. Its functions include the removal of free radicals such as H₂O₂, superoxide anions and alkoxy radicals, maintenance of membrane protein thiols and as a substrate for antioxidant enzymes GPx and GR, it protects cellular constituents from the damaging effects of peroxides formed during metabolism and other ROS.¹⁰ SOD is an important defense enzyme that catalyzes the dismutation of superoxide anions. It has been suggested that SOD is easily inactivated by lipid peroxides or ROS. This may account for lower SOD and CAT activities in the livers. An increase in the SOD level may favor the formation of deleterious hydrogen peroxide, which if not detoxified by the subsequent antioxidant enzymes (Catalase and GPx) will lead to accumulation of hydrogen peroxide, which can cause DNA damage and mutations and thus, will favor the development and progression of cancer. CAT is a haeme protein that catalyzes the reduction of H₂O₂ and protects the tissue from highly reactive oxygen free radicals and hydroxyl radicals. Catalase along with other antioxidant enzymes plays a key

dichotomous role in cancer progression and thus therapies have aimed at either restoring the increased catalase or further rising catalase levels as an effective strategy.¹¹ GR is a cytosolic hepatic enzyme involved in the detoxification of a range of xenobiotic compounds by their conjugation with GSH.¹² GPx is an enzyme with selenium that catalyzes the reduction of H₂O₂ and hydroperoxides into non-toxic products. GPx overexpression was shown to restore tumor cell growth as well as altered the cellular antioxidant components and intracellular ROS.¹³ Decline in the level of hydrogen peroxide might be responsible for exerting antiproliferative effects in HCC. GST is a family of enzymes that are known to catalyze the conjugation of GSH to a number of substrates, ultimately resulting in detoxification. It plays a critical role in cellular detoxification against xenobiotics and toxic compounds as well as against oxidative stress and reactive metabolites of carcinogens. A decline in the level of GST in HCC will prevent the detoxification of harmful reactive metabolites of carcinogens leading to the promotion of carcinogenesis. GST demonstrates an efficient detoxification and promotion strategy for anticancer activity.¹⁴

Different antioxidant therapies could offer the preventive and therapeutic response in liver illnesses including chronic viral hepatitis, alcoholic hepatitis or cirrhosis, and NAFLD. Antioxidant and anti-inflammatory drugs include MK-447 (2-amino-methyl)-4-tert-butyl-6-iodophenol), lipoic acid, indirubin, cinnamides, N-cyclo-alkyl benzamides and indole-3-carboximides which have exhibited broad anticancer and anti-inflammation activities due to their ability to scavenge and inactivate free radicals.¹⁵ Well-known anticancer agents like vinblastine, vincristine, leurosine, leurosidine, ellipticine, rohitukine and variants of podophyllin could suppress or prevent the progress of carcinogenesis.¹⁶ Curcumin has shown numerous pharmacological effects including antioxidant activity, anti-inflammatory activity, anticarcinogenicity, wound healing, anti-fibrogenicity, and anti-microbial activity. Curcumin has shown potent hepatoprotective properties in both acute and chronic liver damages by reducing the production of cytokines such as TNF- α , IL-1, and IL-6 and inactivating the nuclear factor-B (NF- κ B) pathway. It was also shown to lower the oxidative stress caused by carbon tetrachloride (CCl₄) metabolism.¹⁷ Resveratrol possesses different antioxidant, anti-inflammatory, anticarcinogenic, and anti-fibrogenic properties which exerted hepatoprotective effects by preventing hepatic fibrosis through reduction of inflammatory cytokines, NF- κ B activation, and TGF- β level.¹⁸ Quercetin has shown biological benefits such as antioxidant, anti-inflammatory, anticarcinogenic, cardioprotective and bacteriostatic, and exerted hepatoprotective capabilities via reducing the fibrogenic production of TGF- β and regulating the antioxidant system.¹⁹ Silymarin altered the level of phosphatidylethanolamine that reduced oxidative stress, fibrosis, cirrhosis, and lipid peroxidation.²⁰ Naringenin exerted antioxidant, anti-inflammatory, hypolipidemic, antihypertensive, and anti-fibrotic qualities, and liver injury by downregulating TNF- α , iNOS, and COX-2 and boosting Nfr2 and HO-1 expression.²¹

Conclusion

Summarily we present that the antioxidant system in the body and liver has capabilities to combat the disease occurrence. As comprehended in the Figure 1, antioxidant system gets modulated under the influence of inflammatory carcinogenic steps and the protective mechanism is compromised. An altered antioxidant system in the liver leads to an altered biochemical and liver function profile that serves as an indicator of chronic liver dysfunction and cancer. Synthetic and alternative medicines have notably targeted the redox

systems in the liver and exerted protective mechanisms, which need further extensive elaboration for establishing mitigation strategies.

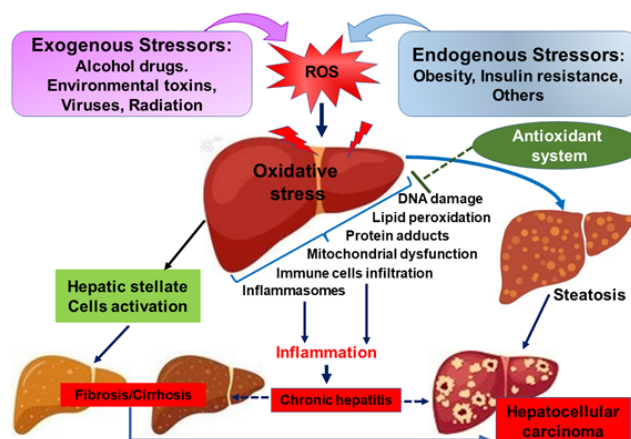


Figure 1 A comprehensive summary of the oxidant stressors and their mechanism of action in the liver.

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Conflicts of interest

We declare there are no conflicts of interest.

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