REVIEW

Protective Role of Antioxidants in Alcoholic Liver Disease

Adak Manoranjan*[1]

[1] Department of Biochemistry, College of Medical Science and Teaching Hospital, Bharatpur, Nepal

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ABSTRACT

Excessive consumption of alcoholic beverages is a serious cause of liver disease worldwide. Any abnormality or dysfunction of the liver leads major impairment of the organ function, which in turn, influences the health of the individual. Alcoholic liver disease (ALD) includes fatty liver, hepatic inflammation, liver cirrhosis, fibrosis, alcoholic hepatitis and finally hepatocellular carcinoma. The metabolism of ethanol generates reactive oxygen species, which play a significant role in the deterioration of alcoholic liver disease. Oxidative stress has been considered as a conjoint pathological mechanism, and it contributes to initiation and progression of liver injury.

Antioxidants, phytochemicals, such as polyphenols, regulate the expression of ALD-associated proteins and peptides, namely, catalase, superoxide dismutase, glutathione, glutathione peroxidase, and glutathione reductase. Application of antioxidants signifies a rational curative strategy to prevent and cure liver diseases involving oxidative stress. Although conclusions drawn from clinical studies remain uncertain, animal studies have revealed the promising *in-vivo* therapeutic effect of antioxidants on liver diseases. Natural antioxidants contained in edible or medicinal plants often possess strong antioxidant and free radical scavenging abilities as well as anti-inflammatory action, which are also supposed to be the basis of other bioactivities and health benefits.

Keywords: Alcoholic Liver Disease, Antioxidants. Reactive Oxygen Species

***Corresponding Author:** Dr. Manoranjan Adak, Department of Biochemistry, College of Medical Science and Teaching Hospital, Bharatpur, Nepal, Email: manoranjanadak@rediffmail.com

INTRODUCTION

Liver is a versatile organ of the body and it performs different kind of functions like metabolic, synthetic, excretory, detoxification etc. It also helps to maintain homeostasis and host defense of the body. Mostly the defense mechanisms occur through Kupffer cells, Ito cells, endothelial cells, hepatic cells and neutrophils by directing production of tumor necrosis factor (TNF) and interleukin-1 (IL-1).[1] Any abnormality or dysfunction of the liver leads major impairment of the organ function, which in turn influences the health of the individual.[2] Most common multiple disorders of the liver that can arise from alcohol use, which are collectively referred to as alcoholic liver disease (ALD).[3] Alcoholic liver disease includes fatty liver, hepatic inflammation, liver cirrhosis, fibrosis, alcoholic hepatitis and hepatocellular carcinoma.[4-6] Chronic heavy drinking of alcohol induces liver injury and results in alcoholic liver disease.[7] Since, ALD has no specific clinical features and no specific laboratory tests are available for it, its diagnosis is currently based on drinking history, related laboratory assessments and imaging.[8-10] Alcohol use is rising rapidly in developing regions and is a major concern among indigenous people around the world, showing a

higher prevalence of use and associated problems.[11] But there is still a debate on the safe amount of alcohol consumption, as variability changes with different population worldwide.

How alcohol damages the liver is not completely understood. 80% of alcohol passes through the liver for detoxification. Chronic consumption of alcohol results in the secretion of pro-inflammatory cytokines, Interleukin 6 and 8, oxidative stress, lipid peroxidation, and acetaldehyde toxicity. These factors cause inflammation, apoptosis and eventually fibrosis of liver cells.[12]

Epidemiology of ALD:

Alcoholic liver disease remains one of the most common causes of chronic liver diseases.[13] Studies on alcoholic liver disease have drawn wide attention in the Western world.[14-15] It was reported that ALD should be defined as an alcohol-associated lifestyle disease.[16] In recent years, along with improved living standard and increased alcohol consumption, several epidemiological surveys showed that it has become a serious public health problem in China.[17-19]

Age-specific mortality rates of cirrhosis in Greenland have been shown to 8.9 per 100,000 inhabitants per year for both men and women.[20] In comparison mortality rates in Denmark were 9.4 for men and 8.7 per 100,000 inhabitants per year.[21]

Harmful use of alcohol causes 2.5 million deaths and 69.4 million disability adjusted life years annually worldwide.[22] In fact, ALD and alcoholic pancreatitis constitute the major share, 31.5%, of alcohol related morbidity and mortality. ALD without co-morbidity is the second leading cause of liver fibrosis.[23] Studies conducted in Europe have shown that alcohol is responsible for more than one-third of liver-related hospital stays.[24] Epidemiological investigations conducted in the southern and middle-western provinces at the beginning of present century revealed that the percentage of people with a drinking habit in general population had increased to 30.9–43.4%.[25] The prevalence of ALD in hospitalized patients with liver diseases increased from 4.2% in 1991 to 21.3% in 1996, and the etiology constituent ratio of alcohol abuse in patients with cirrhosis rose from 10.8% in 1999 to 24.0% in 2003.[26]

In the US, 67.3% of the population over 18 years of age drinks alcohol each year, with 7.4% of the population meeting diagnostic criteria for alcohol abuse. Liver cirrhosis is the 12th leading cause of death in the United States.[27] Analysis of the global burden of alcohol abuse has prompted researchers to investigate alcohol and disease according to age, gender, socioeconomic status, and race.[28] It is thought that consumption of 80g of alcohol in men for an extended period of time can lead to alcoholic liver disease (ALD), whereas in women only 20g of alcohol can cause the same effects. In addition, many women have a decreased amount of the enzyme alcohol dehydrogenase (ADH), increasing the toxic effects of alcohol on the liver.[29] Recent evidence has shown that estrogen may increase the susceptibility of the liver to alcohol-related damage, rendering women more vulnerable to its toxic effects.[30] The prevalence of ALD, particularly cirrhosis, varies significantly with socioeconomic status and social class. Numerous studies have shown that individuals who are unemployed, have low income, or have low educational background exhibit higher rates of cirrhosis mortality.[31] With regard to race, Native American and Hispanic American men have an increased risk for cirrhosis mortality compared with non-Hispanic white Americans, while African-American women have a higher risk for cirrhosis mortality than non-Hispanic white Americans.[32] The reasons for this race-associated difference can be attributed to lack of access to preventive services, healthcare facilities, and/or alcohol education. In a population- based cohort study of around 7000 peoples in northern part of Italy, only 13.5% patients developed ALD by daily intake of high dose (>120g)of alcohol. In UK, alcohol related deaths have been doubled in last 20 years in both gender and all ages.[33] The survey report on 30000 Denis people suggested that wine ingestion is associated with less liver diseases, rather than beer or spirit consumption.[34]

Risk factors for ALD:

A number of chronic diseases have been identified that influence the progression or aggravation of alcoholic liver injury **(Figure-1).**

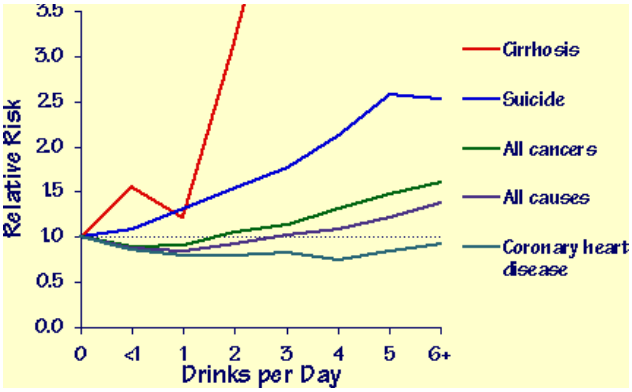


Figure 1: Chronic Diseases and Conditions Related to Alcohol Use[35]

Risk factors of ALD that have been identified in domestic and overseas studies mainly include accumulated alcohol consumption, years of drinking, type of alcoholic beverages consumed, pattern of drinking, female gender, nutritional status, obesity, concomitant viral hepatitis, exposure to drugs or toxins, ethnicity, genetic factors and more. Findings of epidemiological investigations indicate that once a threshold level of alcohol consumption is exceeded, the risk of hepatotoxicity increases dramatically; namely, the risk of liver injury is significantly increased when a certain alcohol intake with a certain number of years of drinking is attained.[35] The pattern of drinking is also a risk factor of liver injury **(Table-1)**.

Table-1: Daily alcohol drinking pattern in men and women[36]

Alcohol drinking level and risk				
Drinking	**Men daily**	**Women daily**	**Men weekly**	**Women weekly**
Very High risk	20+ drinks	15+ drinks	80+ drinks	60+ drinks
High risk drinking	13 - 19 drinks	9 - 14 drinks	50 - 79 drinks	43 - 59 drinks
Medium risk	8 -12 drinks	6 -8 drinks	30 -42 drinks	25-39 drinks
Low risk drinking	5 - 7 drinks	4 - 5 drinks	15 - 27 drinks	8 - 27 drinks
No risk drinking	3 -4 drinks	2 - 3 drinks	11 -14 drinks	10 -14 drinks
Healthy drinking	1 -2 drinks	1 drinks	1 -10 drinks	1 -7 drinks

Drinking while fasting is more likely to lead to liver injury than drinking with meals.[37] Women have been found to be more sensitive to alcohol-mediated hepatotoxicity and may develop more severe ALD with lower alcohol consumption and shorter durations of drinking than men.[38] The increase in the mortality rate of ALD is related to the degree of malnutrition in the patient.[39] A vitamin A deficiency or a decrease of the level of vitamin E may aggravate liver injury.[40] Obesity or overweight may increase the risk of ALD progression.[35] Drinking alcohol while infected with a hepatitis virus or hepatitis virus infected in the presence of ALD will trigger the development and progression of liver diseases.[41] Following risk factors include:

Quantity of alcohol taken- Consumption of 60–80g per day (about 75–100 ml/day) for 20 years or more in men, or 20g/day (about 25 ml/day) for women significantly increases the risk of hepatitis and fibrosis by 7 to 47%.[42] There was a case – study report that alcohol consumption and duration resulted various type of liver disorder. **(Table-2)**

Table-2: Liver function and alcohol intake[43]

Type of liver function	No. of Cases	Mean alcohol intake in ml/kg body wt/hr	Average alcohol abuse (year)
Normal liver function	70	90	7.7
Uncomplicated fatty liver	118	109	7.8
Steatofibrosis	48	127	10.3
Alcoholic hepatitis	78	125	11.9
Cirrhosis	39	147	17.1

Gender- Women are twice as susceptible to alcohol-related liver disease, and may develop alcoholic liver disease with shorter durations and doses of chronic consumption. The lesser amount of alcohol dehydrogenase secreted in the gut, higher proportion of body fat in women, and changes in fat absorption due to the menstrual cycle may explain this phenomenon.[44]

Diet- Malnutrition, particularly vitamin A and E deficiencies, can worsen alcohol-induced liver damage by preventing regeneration of hepatocytes. This is particularly a concern as alcoholics are usually malnourished because of a poor diet, anorexia, and encephalopathy.[44]

Pattern of drinking- Drinking outside of meal times increases up to 3 times the risk of alcoholic liver disease.[44]

Alcoholic fatty liver-Alcoholic fatty liver is a condition of accumulation of fat in the liver, also known as hepatic steatosis, characterizes a type of liver disease, where vacuoles of triglycerides accumulate in liver.[45] About 90 percent of alcoholics and heavy drinkers develop fatty liver who drink more than 60g/day. In many cases there are no clinical symptoms except for an enlarged liver. Fatty liver can be reversed if alcohol consumption is stopped or significantly reduced, but the condition can lead to death if alcohol consumption is not reduced or stopped.[46] The fatty liver is divided into five grades according to the proportion of hepatocytes with fatty degeneration in the hepatic tissue[47]: (i) presence of fatty degeneration in <5% of the hepatocytes; (ii) presence of fatty degeneration in 5%–30% of the hepatocytes; (iii) presence of fatty degeneration in 31%–50% of the hepatocytes; (iv) presence of fatty degeneration in 51%–75% of the hepatocytes and (v) presence of fatty degeneration in more than 75% of the hepatocytes.

Alcoholic hepatitis- Alcoholic hepatitis is a serious condition where the liver has been severely damaged by the effects of alcohol due to consumption of large quantity of alcohol over a prolonged period of time.[48] The illness is characterized by weakness, fever, loss of appetite, nausea, vomiting and pain over the liver. The liver is often inflamed causing many individual liver cells to die. The rate of mortality in severe cases is about 50 percent. If heavy drinking continues, about 40 percent of cases of alcoholic hepatitis will develop into cirrhosis, multi-organ failure and death.[49] In a large cohort study, it has been observed that in heavy alcoholic patients with post –transfusion hepatitis C , the risk of cirrhosis development increases about 30-folds.[50]The severity of fatty degeneration in alcoholic hepatitis, is also divided into five grades based on the severity of inflammation :(i) no inflammation; (ii) presence of a few balloon-shaped hepatocytes in acinar zone 3 and sporadic isolated spotty acinar necrosis and peri-central vein inflammation; (iii), presence of apparent balloonshaped hepatocytes in acinar zone 3, more spotty acinar necrosis, Mallory bodies and mild to moderate inflammation of the portal area; (iv) extensive balloon-shaped hepatocytes in acinar zone 3, pronounced spotty acinar necrosis, presence of Mallory bodies and apoptotic bodies, moderate inflammation of portal area or periportal inflammation, or both; (v) confluent necrosis or bridging necrosis, or both.

Alcoholic cirrhosis- Cirrhosis is a late stage of serious liver disease marked by inflammation (swelling), fibrosis (cellular hardening) and damaged membranes preventing detoxification of chemicals in the body, ending in scarring and necrosis (cell death). It causes hepatocellular dysfunction and increased inter-hepatic resistance to blood flow, which results in hepatic insufficiency and portal hypertension respectively.[51] Between 10% to 20% of heavy drinkers (>40g/day) will develop cirrhosis of the liver.[52] Several studies have also suggested that despite quitting alcohol the chances for develop cirrhosis and fibrosis for alcoholic patients are about 5-15%. [53]

Hepatic cancer- Hepatocellular cancer (HCC) is the fifth most common cancer, with an annual incidence of 564,000 cases due to very long term alcohol consumption. In North America and European nation, HCC develops from more than 80% cases of liver cirrhosis , whereas about 50% in Asian countries.[54] Alcoholic patients with history of hepatitis C virus resulted more chances to develop HCC when they continue alcohol consumption 120 g/day.[55]While being hepatitis B virus or hepatitis C virus -positive, or drinking more than four standard drinks perday increases risk for HCC up to eightfold, the combination of alcohol and either of these viruses results in a 50-fold greater risk.[56]

Genetic and Hereditary- It has been found from current report about ALD that the decrease ability to metabolize alcohol to acetaldehyde due to polymorphisms in alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH).[57] Other studies have shown that the more active forms of these alleles could be protective against alcoholism, due to

a decreased alcohol tolerance from the accumulation of acetaldehyde at a quicker rate.[58] The association between ADH and ALDH polymorphisms and ALD is compelling support for the role of acetaldehyde in the development of ALD. Because of its role in the generation of ROS resulting in hepatocyte damage, the CYP_2E_1 allele has been widely investigated for allelic polymorphisms that may contribute to ALD.[59] Further research into glutathione-S-transferase isoenzymes has revealed numerous polymorphic variants that can alter enzyme activity and could possibly increase the levels of toxic intermediates generated through chronic alcohol consumption.[60]

Pathophysiology of ALD: Alcohol is metabolized by a number of different enzymes in the liver, including alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), and the microsomal ethanol oxidizing system (MEOS). ADH converts ethanol to acetaldehyde when alcohol is present in low concentrations in the blood whereas MEOS performs at moderate to high level of alcohol. During the conversion of ethanol to acetaldehyde by ADH, a fraction of ethanol undergoes first-pass metabolism through the liver. This changes the functional properties of the hepatocellular membrane resulting ALD.[61]**(Figure-2)**

Fatty acids accumulation in liver has been noticed in chronic ethanol use due to inhibitory activity of peroxisome proliferator-activated receptor alpha (PPAR-α) on β – oxidation.[63] Eventually these fatty acids are converted to triglycerides, which are exported from the hepatocyte via low-density lipoprotein (LDL). However, in alcoholics this exportation process is defective, leading to the accumulation of triglycerides, or steatosis.[64]

Oxidative stress generated by ethanol metabolism is believed to be a major driver of alcohol-induced liver damage. Chronic alcohol consumption activates the MEOS pathway, generating reactive oxygen species (ROS) through the cytochrome P450 complex (particularly CYP2E1). ROS initiate lipid peroxidation, damaging the plasma and intracellular membranes. Eventually, the mitochondria become susceptible to tumor necrosis factor-alpha (TNF-α), and apoptotic death of hepatocytes ensues. In patients with ALD, the cytokines TNF-α, interleukin-1 (IL-1), IL-6, and IL-8 are increased. In particular, studies have shown that both TNF and soluble TNF receptors are associated with the extent of liver disease.[65]

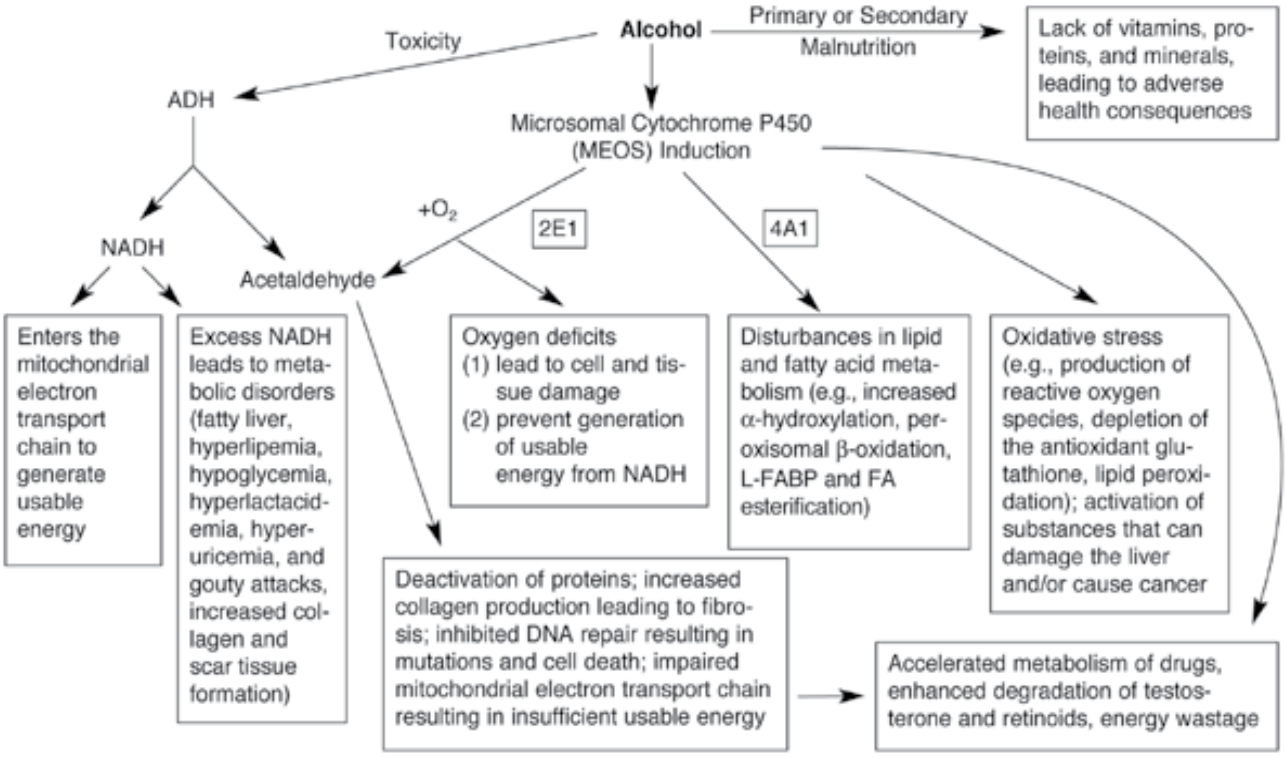


Figure 2: Pathogenesis of alcohol induced liver injury [62]

The mechanisms being involved in the pathogenesis of alcoholic liver disease (ALD) has demonstrated that ALD is a result of complex pathophysiological events involving various types of cells, such as neutrophils, endothelial cells, Kupffer cells, and hepatocytes, and a variety of injurious factors such as endotoxins, oxidative stress, cytokines, and proteases **(Figure-3).** A striking observation is that endo-toxaemia and endotoxin-mediated alteration of liver cell functions play a crucial role in the pathogenesis of ALD. Evidence suggests that there are three possible mechanisms involved in the alcohol-induced endotoxemia: (a) dysfunctional Kupffer cells with reduced ability to detoxify endotoxins, (b) bacterial overgrowth in the gut leading to excessive generation of endotoxins, and (c) disruption of intestinal barrier function and increase in permeability to endotoxins and bacteria.[66] The third possibility has recently gained increasing attention. Alcohol consumption appears to increase intestinal permeability to macromolecules asevidenced by both clinical and experimental studies.[67] Therefore, the action of ethanol at the level of gastrointestinal mucosa appears to be the first site of injury that leads to the development of a complex cascade of cellular responses resulting in hepatocellular injury.

Antioxidants: Oxygen is an element indispensable for life to generate energy ATP (adenosine triphosphate) by the mitochondria. The reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) are also generated during the cellular redox process. These species play a dual role as both toxic and beneficial compounds. At high concentrations, they generate oxidative stress, a deleterious process that can damage all cell structures.[69,70] The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Endogenous and exogenous antioxidants act as "free radical scavengers" by preventing and repairing damages caused by ROS and RNS and therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases.[71]When produced in excess, free radicals and oxidants generate a phenomenon called oxidative stress, a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and deoxyribonucleic acid.[72]

Oxidative stress is thought to play a key role in the pathogenesis of ALD. Alcohol mediates oxidative stress in a number of ways including

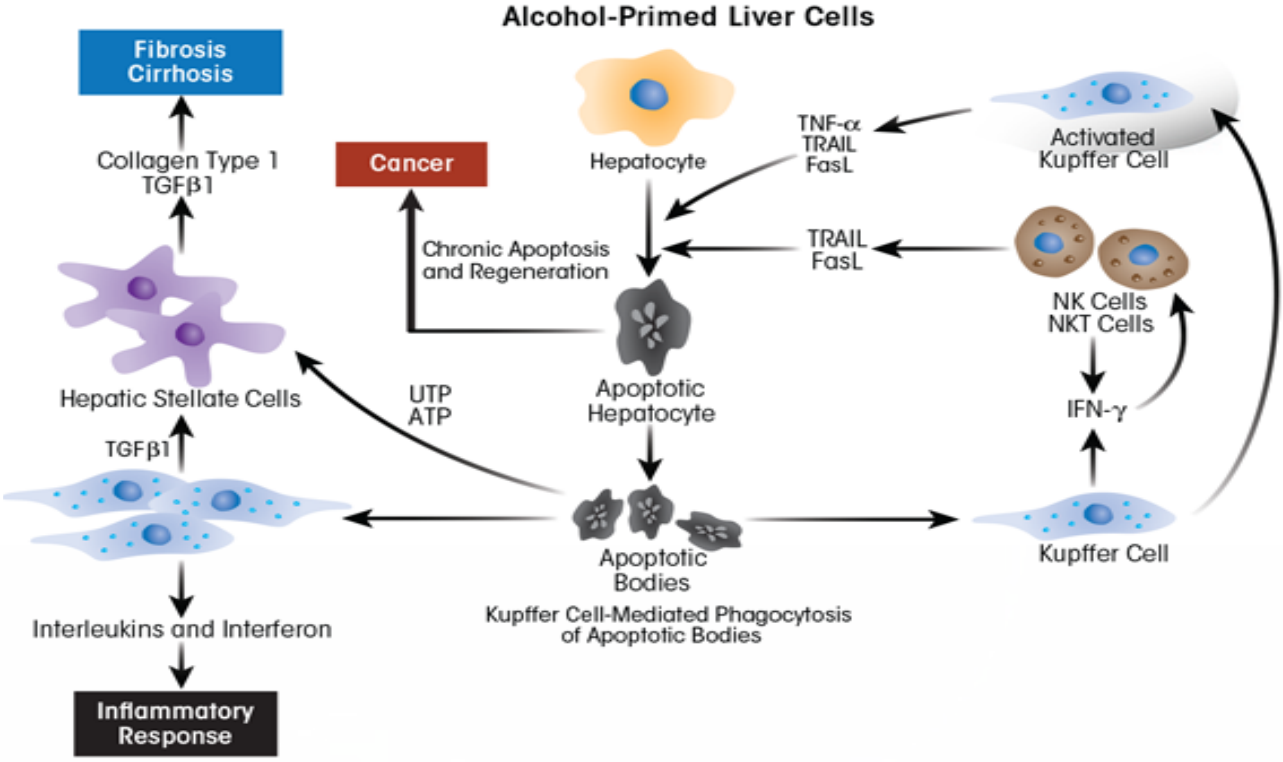
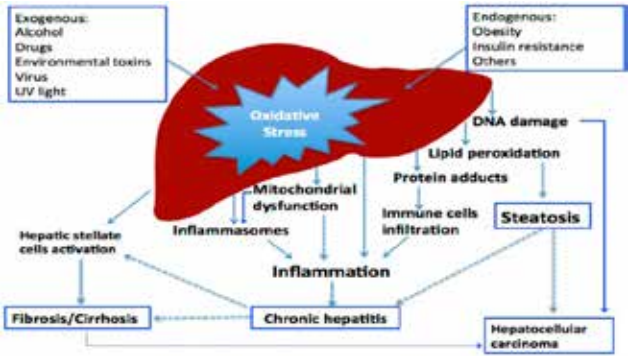


Figure-3: Mechanism for alcoholic liver disease[68].

lipid peroxidation, the production of reactive oxygen species, and depletion of endogenous antioxidant capabilities.[73]On this basis, it has been theorized that aggressive antioxidant therapy would improve outcomes in ALD. The general mechanism scheme of oxidative stress induced by various factors on liver disease.[74]



The body has several mechanisms to counteract oxidative stress by producing antioxidants, either naturally generated in situ (endogenous antioxidants), or externally supplied through foods (exogenous antioxidants). The roles of antioxidants are to neutralize the excess of free radicals, to protect the cells against their toxic effects and to contribute to disease prevention.Antioxidant supplements are compounds obtained either by extraction from natural foods or by chemical synthesis. Of course, they do not have the same composition as natural antioxidants in foods. Therefore, opinions are divided over whether or not antioxidant supplements offer the same health benefits as antioxidants in foods. Following natural antioxidants in foods are highlighted for beneficial effect on ALD:

Silymarin: The active extract of milk thistle is silymarin[75], a mixture of flavolignans, including silydianin, silychristine, and silybin, with silybin being the most biologically active.[76] Silymarin has proven to be one of the most potent liver-protecting substances. Its main routes of protection appear to be the prevention of free-radical damage, stabilization of plasma membranes, and stimulation of new liver cell production. Early studies show that silymarin has the ability to stimulate protein synthesis, resulting in production of new liver cells to replace older, damaged ones.[77] One human randomized double-blind control evaluating placebo *versus*silymarin in alcohol- and non-alcohol-induced cirrhosis showed a 39% *versus* 58% 4-year survival, respectively.[78]

S-adenosylmethionine- Elevated methionine and decreased methionine clearance represent a possible therapeutic target for ALD. In human studies of alcoholic hepatitis and cirrhosis, abnormal hepatic gene expression in methionine and glutathione metabolism occurs and often contributes to decreased hepatic S-adenosylmethionine (SAM), cysteine, and glutathione levels.[79] S-adenosylmethionine appears to attenuate oxidative stress and hepatic stellate cell activation in an ethanol-LPS-induced fibrotic rat model.[80] Most importantly, a randomized, double-blind trial was performed in 123 patients with alcoholic cirrhosis treated using SAM (1200 mg/day, orally) or placebo for 2 years.[81]

Phosphatidylcholine - Phosphatidylcholine, one of the most important fat substances for liver protection and health, is a primary constituent of cell membranes. It acts by several mechanisms:(1) exerting potent antioxidant effects, (2) inhibiting the tendency of stellate cells to progress to cirrhosis, (3) decreasing apoptotic death of liver cells and thereby prolonging the life of liver cells, (4) stabilizing the cell membrane, thus improving the integrity and function of the liver cell, and (5) exerting an antifibrotic effect related to the breakdown of collagen.[82]

Branched chain amino acids - The branched-chain amino acids can enhance protein synthesis in liver and muscle cells, help restore liver function, and prevent chronic encephalopathy.[83]

Lipoic acid - It has been shown to effectively scavenge harmful free radicals, chelate toxic heavy metals, and help prevent mutated gene expression.[84]

N-acetyl-cysteine - N-acetyl-cysteine (NAC) is an amino acid that acts as an antioxidant or free-radical scavenger. NAC is frequently used in liver disease.[85,86] Patients receiving antioxidant combination therapy (N-acetylcysteine, vitamin A, vitamin E, biotin, selenium, zinc, manganese, copper, magnesium, folic acid and coenzyme Q) had improved survival of 1 and 2 months, but this did not translate into longer-term survival at 3 or 6 months.[87]

Acetyl-L-carnitine - Acetyl-L-carnitine is the biologically active form of the amino acid L-carnitine that has been shown to protect cells throughout the body from age-related degeneration.[88]

Coenzyme Q10- Coenzyme Q10 (CoQ10) is an antioxidant that is protective for a liver that has been damaged by alcohol. It protects the mitochondria and cell membrane from oxidative damage and helps generate ATP, the energy source for cells.[89]

Vitamin B complex–They are involved in the metabolism of carbohydrates and fats, functioning of the nervous and digestive systems, and production of red blood cells. The B vitamins have a protective role in alcoholic liver disease.[90] Alcoholic liver disease (ALD) is typically associated with folate deficiency, which favors the progression of liver disease through its effects on methionine metabolism with consequences for DNA synthesis and stability and the epigenetic regulation of gene expression involved in pathways of liver injury.[91]

Vitamin C - Vitamin C is a potent antioxidant found naturally in many fruits and vegetables. Vitamin C has protective effects against liver oxidative damage, particularly when used in combination with vitamin E. The protective effects of vitamin C on iron metabolism-related genes expression and liver protection from drinking alcohol.[92]

Vitamin E -Vitamin E protects the lipid membrane from oxidative damage. Hepatocytes incorporate vitamin E into lipoproteins, which then transport it to various tissues in the body. The evidence that oxidative stress is involved in the pathogenesis of ALD and Vitamin E deficiency being well documented in patients of ALD, an antioxidant like Vitamin E could likely be beneficial in patients with ALD. Recent findings suggest that Vitamin E given in adequate dose will be a useful addition for treating alcoholic liver disease.[93]

Selenium –Selenium is a trace element that acts by several mechanisms, including detoxifying liver enzymes, exerting anti-inflammatory effects, and providing antioxidant defense. The presence of selenium helps induce and maintain the glutathione antioxidant system.[94]

Zinc –Zinc is an essential dietary nutrient used in numerous protective drugs and preparations. Zinc deficiency/altered metabolism is observed in many types of liver disease, including alcoholic liver disease (ALD) and viral liver disease. Some studies suggest improvement in liver function in both ALD and hepatitis C following zinc supplementation, and 1 study suggested improved fibrosis markers in hepatitis C patients. The dose of zinc used for treatment of liver disease is usually 50 mg of elemental zinc taken with a meal to decrease the potential side effect of nausea. [95]

Betaine- Betaine (trimethylglycine) is a key nutrient for humans and is obtained from a variety of foods and nutritional supplements.[96] In the liver, betaine can transfer one methyl group to homocysteine to form methionine. This process removes toxic metabolites (homocysteine and S-adenosylhomocysteine), restores SAM levels, reverses steatosis, prevents apoptosis and reduces both damaged protein accumulation and oxidative stress.[96,97] Betaine also appears to attenuate alcoholic steatosis by restoring phosphatidylcholine generation via the phosphatidylethanolaminemethyltransferase pathway.[97] Studies suggest that betaine offers hepatic protection against ethanol-induced oxidative stress by decreasing sulfur-containing amino acid breakdown as well.[98]

Sumac - Sumac is a high-tannin variety of sorghum, a numerous species of grasses, one of which is raised for grain and many of which are used as fodder plants either cultivated or as part of pasture. The plants are cultivated in warmer climates worldwide. Species are native to tropical and subtropical regions of all continents in addition to the southwest Pacific and Australasia.[99]

Cloves - Cloves are the aromatic dried flower buds of a tree in the family Myrtaceae. Cloves are native to the Maluku islands in Indonesia and used as a spice in cuisines all over the world..

Eugenol comprises 72-90% of the essential oil extracted from cloves, and is the compound most responsible for the cloves' aroma. Eugenol, a methoxyphenol component of clove has been reported for a number of pharmacological effects, including the antioxidant, anti-inflammatory, analgesic, anesthetic, antipyretic, antiplatelet, antianaphylactic, antidepressant, anticonvulsant, antihyperglycemic, antibacterial, antifungal and antiviral effects. Study reports the curative and antiproliferative effect of eugenol-rich fraction of clove in rats treated with a liver cirrhosis protocol and attributes the inhibitory effect to the decrease in production of free radicals.[100]

Acai berry - The acai berry is the fruit of the acai palm, native to tropical Central and South America. Freeze-dried acai powder was found to have antioxidant activity in vitro against superoxide and peroxyl radicals, and mild activity for peroxy nitrite and hydroxyl radicals. The powder was reported to inhibit hydrogen peroxide-induced oxidation in neutrophils, and to have a slight stimulatory effect on the reactive radical, nitric oxide. Acai berries shows specific protective effect on alcoholic hepatic injury. Its mechanism may be correlated with the inhibition of such inflammatory factors as TNF-α and IL-6.[101]

Cocoa powder - Cocoa powder is rich in flavonoids, a type of phenolic. The amount of flavonoids depends on the amount of processing and manufacturing the cocoa powder undergoes, but cocoa powder can contain up to 10% its weight in flavonoids. It has been suggested that the flavanols may take part in mechanisms such as nitric oxide and antioxidant, anti-inflammatory, and antiplatelet effects.[102]

CONCLUSION

Alcoholic liver diseases (ALD) are very common in lower socio-economical group due to heavy drinking habits and multiple nutritional deficiencies. ALD is a major cause of advanced liver disease worldwide and it is significantly spreading among the young generation. Chronic heavy drinking induces liver injury and results in alcoholic liver disease. Alcohol use is rising rapidly in developing regions and is a major concern among indigenous people around the world, showing a higher prevalence of use and associated problems. Major advances in understanding its mechanisms of pathogenesis have been made at the experimental level using animal models. But till date it is a big challenges for the researchers to established new therapeutic tar gets. However, translation of basic and translational research findings into new therapies has been modest.

Anti-oxidative therapy, mainly using natural and synthetic antioxidants, represents a reasonable therapeutic approach for the prevention and treatment of liver diseases. However, although concept of anti-oxidative therapy has been raised for decades and intensive efforts have been paid, there is a long way to go for the application of antioxidants in liver disease. Clinical trials, by drugs or compounds treat liver disease might partly attribute to anti-oxidative ability, but plain antioxidants mainly used as dietary supplement to prevent the progress of disease or improve the outcome of patients might also be effective. In current studies, intervention of antioxidants is explored widely in prevention models rather than treatment model, without elaborated underlying mechanism investigation.

Additionally, since liver is a central organ for metabolism, oxidative stress in liver diseases interacts with many other diseases. These limitations in current study might result in antioxidants that showed desirable effects for prevention or treatment in animal models, but in humans they do not appear to be effective for the treatment of established disease, which is a barrier for the development of anti-oxidative therapy in clinic. Therefore, translational research is of great importance for anti-oxidative therapy.

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