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## Neoplastic Effects of Alcohol in Carcinogenesis Process of Leaver Diseases


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## Abstract

***Purpose***

*In article, the authors proposed to emphasis, at patients diagnosed with alcoholic cirrhosis, number of cases, selected from specialty medical literature, which developed Hepatocellular carcinoma, [HCC], by continued of the abuse alcohol and which presented, at a previous medical control, the diagnosis of steatohepatitis after the chronic abuse of alcohol. The prevention of complicated their diseases the treatment, and/or health outcomes, were remain unknown in these cases.*

***Method***

*This review article encompasses the data selected from articles, written starting from 2018, which analyses the abuse alcohol with effects on a hepatic status. Alcoholic cirrhosis due to long-term chronic alcohol abuse was on the rise, in last years, especially in developed countries. Cirrhosis caused by alcohol required frequent hospitalizations to prevent the complication of transforming liver cancer and at the same time created high costs in the public health system, [1, 2]. Cirrhosis of the liver occurred in about 30% of people who consume alcohol for a long time beyond the allowable daily physiological limits. The disease occurs mainly in men who have consumed large amounts of alcohol daily for more than 10 years, [3].*





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***Results***

*Indirect alcohol biomarkers, which suggest heavy alcohol use by detecting the toxic effects of alcohol, included the following analyses: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl-transferase (GGT), Mean corpuscular volume, (MCV). Carbohydrate-deficient transferrin (CDT) which is a biomarker for chronic alcohol consumption of over 60 g ethanol / day. It was considered that the normal limit value is 31.9 U / l for women and 23.6 U / l for men. Elevated CDT levels have been reported in cases of chronic alcohol abuse, with varying degrees of liver damage. [4].*

***Conclusions***

*The active and rational lifestyle is an essential element in preventing the process of carcinogenesis. Liver disease it's not just how much you drink, but how and when you drink. The treatment of severe alcoholic hepatitis will be necessary in all alcoholic liver diseases centers to prevent hepatic cancer disease.*

**Keywords:** *alcoholic liver disease, cytokines, nutrition, steroids*

## I. Introduction

A blood alcohol level measured after drinking in the last few hours is not a good indicator of chronic alcohol abuse. [5]. Consumption of alcohol at doses up to 10 g / 1 unit / day after the onset of cirrhosis leads to the development of hepatocellular carcinoma. Also, this amount of alcohol is a risk factor for the development of liver cancer if there are other conditions, such as diabetes or viral hepatitis B or C viruses.

Obesity and diabetes also have a synergistic effect. As in other causes of advanced chronic liver disease, it is recommended that patients with alcoholic cirrhosis should be included in HCC surveillance program so that any tumor can be detected at the earliest possible stage: this strategy has been shown to enable the implementation of curative procedures that can increase survival, [6].

A normal drinking is defined as one 12-oz beer, one 4- to 5-oz glass of wine, or one mixed drink containing 1.5 oz of spirits (80 proof), [1 Oz = 29.57 ml]. The relative risk for the noted maladies with consumption of 4 or more drinks daily is as follows: Cirrhosis - for men, 7.5; for women, 4.8. Drinking outside of meal times increases up to 3 times the risk of alcoholic liver disease. Among older patients with alcoholism, from one third to one half develop alcoholism after age 60 years. Alcohol levels are higher in elderly patients for a given amount of alcohol consumed than in younger patients, [7]. Oxidative stress induced by chronic ethanol consumption affects phospholipids and fatty acids in the cell membrane as well as α-linolenic acid with damage to cell structure, [8, 9].

## II. Search Methods Employed

In people with alcoholic hepatitis, promoters of liver cancer, was analyzed as screening method, the ratio of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which were greater than 2: 1. AST and ALT levels were almost always lower than 500. The increased AST / ALT ratio can be done to pyridoxal deficiency and phosphate, which is required for the synthesis of the enzyme ALT. Other laboratory observations included macrocytosis of red blood cells, from peripheral blood, mean corpuscular volume (VEM),> 100) and increases in serum levels of gamma-glutamyl transferase (GGT), alkaline phosphatase and bilirubin, [10].

## III. Results of the Reviewed Studies

Most patients with uncompensated liver cirrhosis (70%) had an AST increased by an average of 66 U / L, (N = 5-38U / L). These cases had an AST / ALT ratio of 1.36 (N = 1.33) and the TGP / TGO ratio = 0.95. In the process of liver carcinogenesis, the AST / ALT ratio can be increased by 2.54 and the TGP / TGO ratio decreased by 0.39. Also, was increased in total bilirubin above 5.6 mg / day L, prolongation of prothrombin time (PT), INR above 4.53 mean value and hypo-albumin in sera blood, [11].

Majority of patients with cancer liver disease in hematologic field have had leukocytosis cell [(WBC) count = 13.9 x $10^3$µl, SD = 2.66)] and thrombocytopenia (Platelets, $X^-$ = 133 x $10^3$µl, SD = 1.91), in 70% from total cases. Leukemoid reactions with counts of >100,000 white blood cells (WBC)/$mm^3$ in the absence of infection has been seen in patients with hepatocarcinoma was in percent of 10%. The severity of chronic alcoholism was assessed using the Maddrey (MDF) formula, which is calculated by the equation, [4.6× (PT patient - PT control) + total bilirubin (mg / dl), [[12].

If the result of the calculation exceeds the absolute value 32, mortality over time hospitalization of patients can reach over 50%. In the presented studies, MDF was calculated to have an average value of 20.91, [4.6 x (4.53-1.2) + 5.6]. Mean corpuscular volume (MCV), serum uric acid levels and serum electrolytes are all affected by chronic alcohol consumption. In addition, although symptoms may be nonspecific, increased serum uric acid, hypokalemia, hypomagnesemia and acidosis were indicators that alcohol may play a significant role in liver disease. Alcohol related bone marrow toxicity and/or splenic sequestration might contribute to macrocytosis (increased MCV) and thrombocytopenia. Leukocytosis was frequent in individuals with alcoholic liver cancer, [13].

## IV. Discussion

Hepatocellular carcinoma was the fifth most common neo-plasm and the third most frequent cause of cancer death. Early stages of hepatocarcinoma development, autophagy acts as a suppressor mechanism promoting the recycling of defective organelles and unfolded proteins, prevention of oxidative stress, and maintenance of genome stability. However, autophagy can also favor tumor promotion via oncogene-mediated cancer development, and cellular adaptation to different stress, such as hypoxia or starvation [14, 15].

Although the crosstalk between autophagy and apoptosis not well defined, a relationship has been established due to the interaction


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of different autophagy and apoptosis-related proteins, [16]. Isolated hyperbilirubinemia as a manifestation of alcoholic liver disease without significant liver abnormalities is rarely observed. Bilirubin may gradually decrease when alcohol consumption is stopped, [17]. Acetaldehyde, the result of alcohol metabolism causes liver fibrosis by the deposition of collagen fibers in liver cells. The enzyme alcohol dehydrogenase acts through two molecular mechanisms for ethanol metabolism. The first is the use of a zinc atom used to maintain and position the alcohol group on ethanol and the second is a nicotin-d iamiane cofactor (NAD) that completes the reaction, **[Figure 1**].

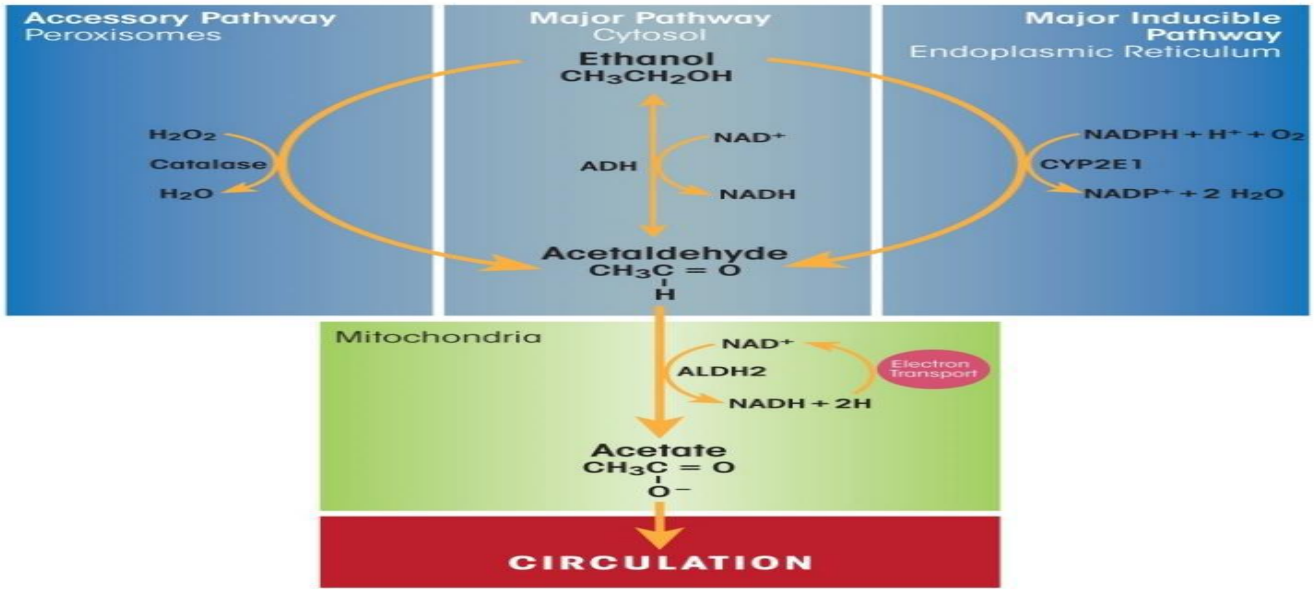


**Figure 1.** This pyruvic acid, as a result of transamination amino acids, is converted to glucose by gluconeogenesis.

People who consume large amounts of alcohol can become overweight through excess NADH which can be used to synthesize glycerol and to synthesize fatty acids with increasing lipid synthesis. NADH in the electron transport chain can also be used for the synthesis of adenosine triphosphate, (ATP), as a source of cellular energy. Ethanol can inhibit the activity of genes for the synthesis of inducible nitric oxide, in response to the stimulation of bacteria by inhibiting the activity of macrophages, contributing to the contribution to the impairment of antimicrobial defense after alcohol consumption. The increase in proinflammatory cytokines, IL-6, IL-17, tumoral necrosis factor, (TNF-alpha), plays a central role in the pathophysiology of alcoholism, **[Figure 2].**

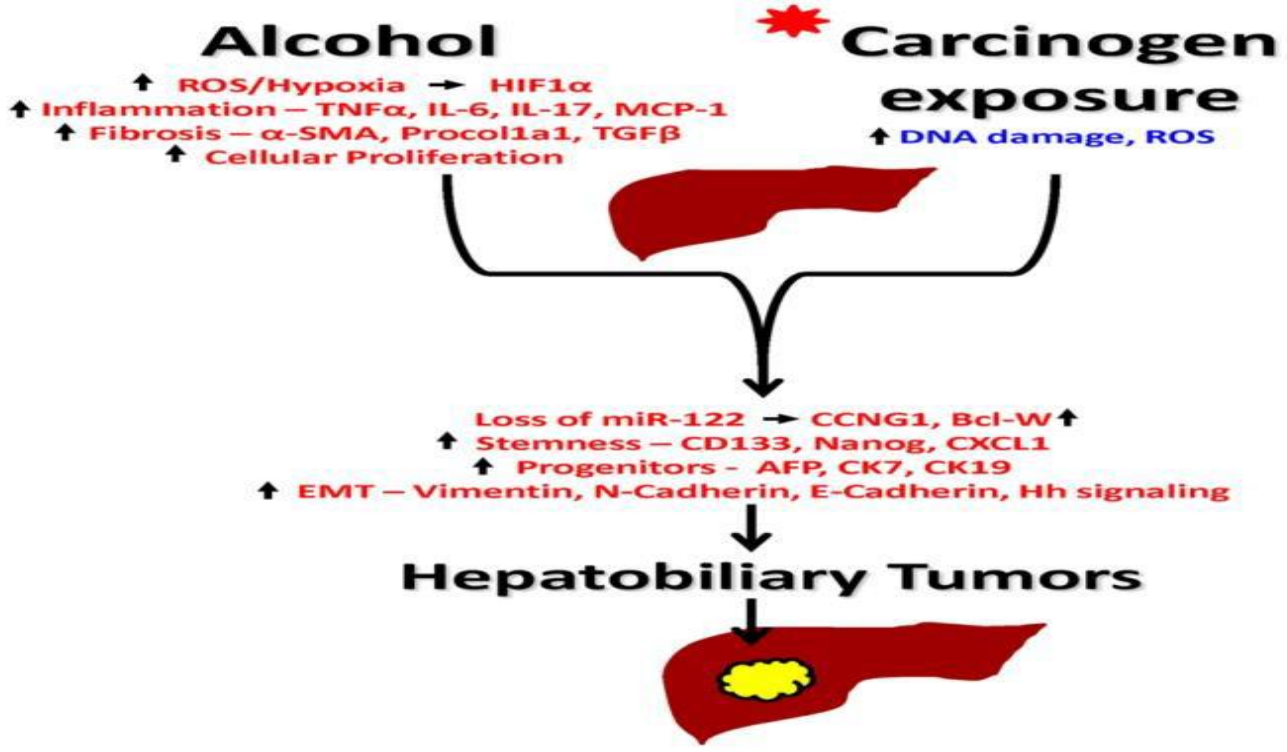


**Figure 2**. Increased proinflammatory cytokines, IL-6, IL-17, particularly TNF alpha, play a central role in the pathogenesis of Alcoholic Liver Disease

In recent years, microRNAs, miR-155, have been found to help increase TNF-alpha production and sensitize liver cells to produce more TNF-alpha in response to liposaccharide activation (LPS).


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[14]. LPS endotoxin is recognized by the Toll-like receptor complex (TLR)-4 on macrophages or Kupffer cells in the liver and contributes to the production of proinflammatory cytokines leading to liver damage. precursors to carcinogenesis. Polymorphisms exist in the enzymes ADH, CYP2E1, and ALDH. Differences in ADH and ALDH certainly contribute to the negative association with ethanol dependence in some Asian populations. HLA phenotypes, a genetic predisposition toward alcoholism and female gender may also contribute to overall risk.

Chronic alcohol abuse increases gut permeability resulting in high circulating endotoxin that reaches the liver via portal circulation. Endotoxin (lipopolysaccharide or LPS) is recognized by the Toll-like receptor (TLR)-4 complex on resident macrophages or Kupffer cells in the liver, leading to production of proinflammatory cytokines, tumor necrosis factor (TNF)-α, and resulting in injury to liver cells (hepatocytes), [15, 16], **[Figure 3].**

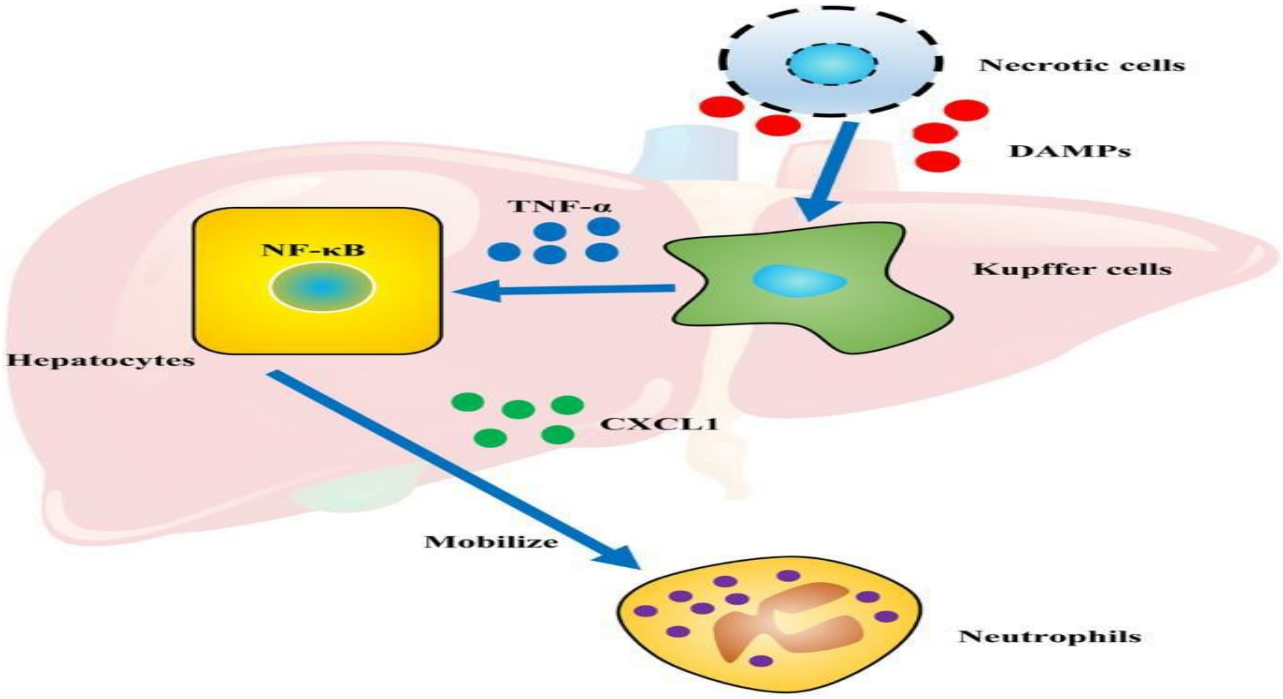


**Figure 3.** The typical inflammatory cytokines, such as TNF-α, IL-1, and IL-6, are primarily produced by inflammatory monocytes, macrophages

Chronic alcoholics have elevated levels of immunoglobulins, especially in IgG and IgA classes with B cell dysfunction. produce inflammatory cytokines. Recent studies have also shown that decreased T cell proliferation after chronic alcohol abuse could be caused by impaired monocyte function by producing inflammatory cytokines. [17, 18], **[Figure 4].**

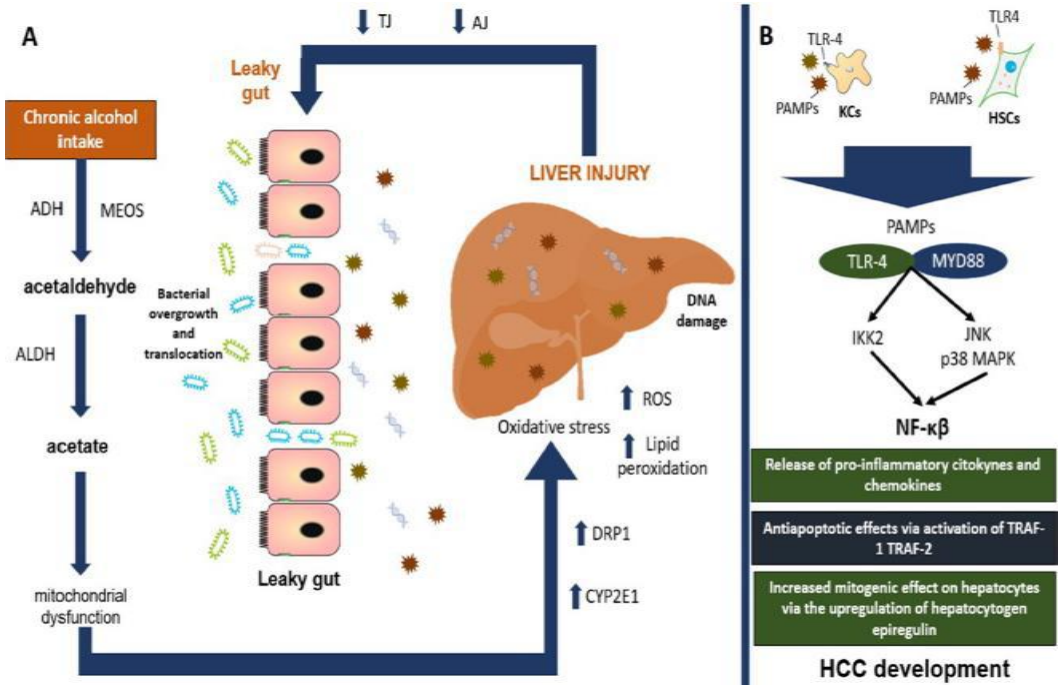


**Figure 4.** Alcohol-induced steatohepatitis is tightly associated with LPS-TLR4 signaling. Among BM-derived cells, Kupffer cells/macrophages highly express TLR4 and produce inflammatory cytokines


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The enzyme ALDH is mainly involved in liver cancer. Overexpression of ALDH enzymes, such as ALDH-1, ALDH-3A1 and ALDH-18A1, gives cancer cells a survival advantage because oxidative stress from high metabolic activity leads to free radical generation (ROS), lipid peroxidation and aldehyde accumulation. toxic, which can inhibit the proliferation and survival of cancer cells. As an antioxidant, the enzyme ALDH can decrease apoptosis of immunogenic cells and limit tumor progression by reducing the stress of the endoplasmic reticulum and the production of ROS. The reduced activity of ALDH-, B1, was found to be protective in patients with hepatocellular carcinoma (HCC), by influencing the oxidation of short-chain aldehydes, including acetaldehyde and propionaldehyde, against hepatocellular proliferation induced liver neoplasm, [19], **[Figure 5].**

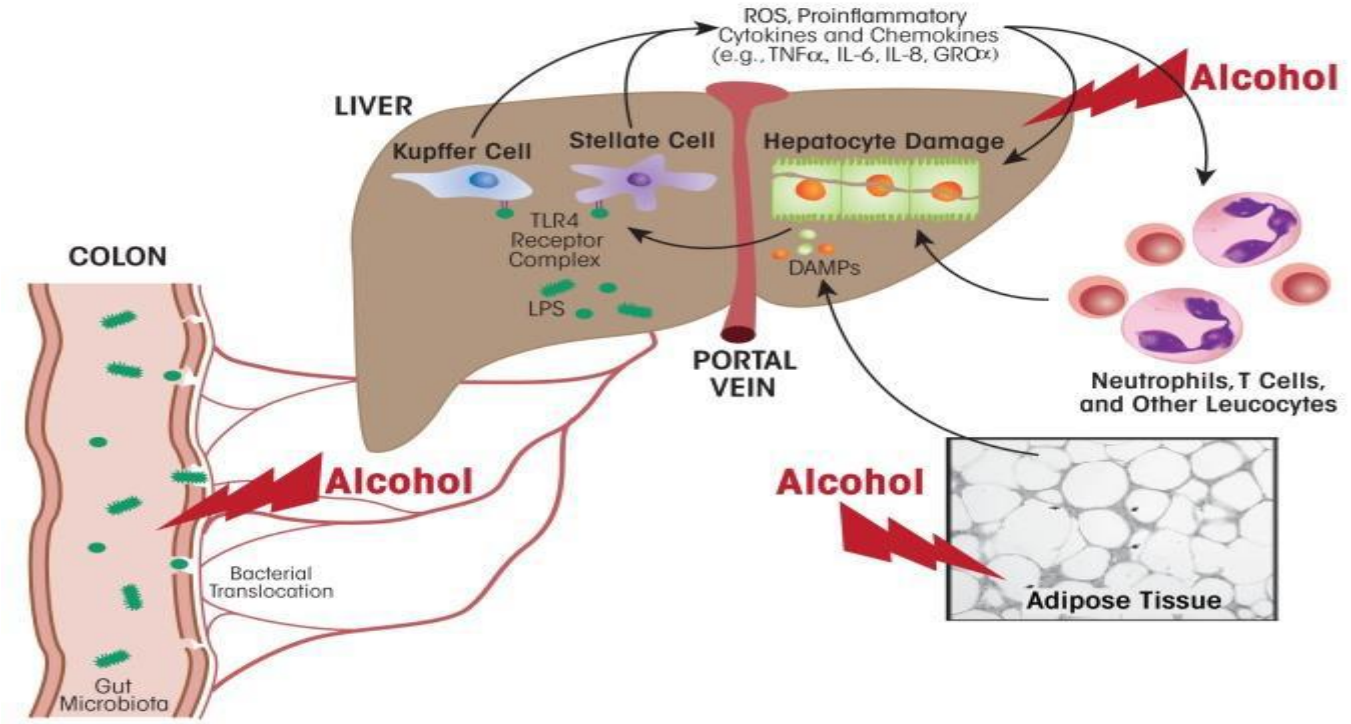


**Figure 5**. Decreased T cell proliferation after alcohol use might be due to impaired accessory cell/monocyte function

Epigenetic changes in cycle cells include histones by acetylation, phosphorylation, hypomethylation of DNA. Dysregulation of miRNA biogenesis has been found in non-viral HCC subtypes, and oxidation of ethanol influences the expression of miR-217, miR-155 and miR-212, [20, 21].

Folate levels are low in alcoholic patients due to decreased intestinal absorption, increased need for folate in the bone marrow in the presence of alcohol, and increased urinary loss. Leukocyte depletion reflects the severity of liver damage. Histological features may include Mallory bodies, giant mitochondria, hepatocyte necrosis, and neutrophil infiltration into the area around the blood vessels {22,23] with the progression in liver carcinogenesis. For most patients with advanced disease, the drug sorafenib was the only treatment option for systemic therapy for these patients. Currently, the standard of care for patients with advanced HCC involves a combination of immunotherapy between the control point inhibitor, atezolizumab, and the antibody bevacizumab [24].

Embolization can be used to block the flow of blood to a tumor, so that the cancer cells die. Recent studies have confirmed that moderate consumption of red wine is associated with high plasma levels of omega-3 polyunsaturated fatty acids, decreased blood viscosity, increased insulin sensitivity, decreased platelet count and aggregation, and altered plasma coagulation protein levels. HDL-cholesterol, cardio-protector [25]. As for the types of alcoholic beverages, especially wine with a variety of polyphenols, including phenolic acids, tannins, resveratrol, flavonoids, have an anti-carcinogenic antioxidant and anti-inflammatory effects, in contrast to the carcinogenic ethanol [26].

Recent studies have confirmed that moderate wine consumption is associated with high plasma levels of omega-3 polyunsaturated fatty acids, decreased blood viscosity, increased insulin sensitivity, decreased platelet count, altered plasma coagulation protein levels, increased HDL-cholesterol. about 50% with the cardio-protective effect and inhibition of the carcinogenic process in 12 types of cancer, [27].

## V. Conclusions

An active and rational lifestyle is an essential element in preventing the process of carcinogenesis. Liver cancer is not due to the amount of alcohol which a person is consuming, but of the quality alcohol consumed. Treatment of severe alcoholic hepatitis will be required in all alcoholic liver disease centers to prevent liver cancer.

**Abbreviations:** ALDH2 - acetaldehyde dehydrogenase 2; ALD - alcoholic liver disease; AMPK-AMP - activated protein kinase; AGS - acetaldehyde-generating system; ALC - alcoholic liver cirrhosis; CYP2E1 - cytochrome p450; ECM - extracellular matrix; HCC - hepatocellular carcinoma; HBV - hepatitis B virus; HCV - hepatitis C virus.

**Legend table and figures**

**Table 1**. Results of liver enzymes in alcoholic Hepatocarcinoma

**Figure 1**. Major pathways of alcohol metabolism in hepatic cells


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**Figure 2**. Increased proinflammatory cytokines, IL-6, IL-17, particularly TNF alpha, play a central role in the pathogenesis of Alcoholic Liver Disease

**Figure 3.** The typical inflammatory cytokines, such as TNF-α, IL-1, and IL-6, are primarily produced by inflammatory monocytes, macrophages.

**Figure 4.** Alcohol-induced steatohepatitis is tightly associated with LPS-TLR4 signaling. Among BM-derived cells, Kupffer cells/macrophages highly express TLR4 and produce inflammatory cytokines

**Figure 5**. Decreased T cell proliferation after alcohol use might be due to impaired accessory cell/monocyte function

-Acknowledgments: Not applicable; Disclosures: Not Applicable

## References


1. Shravani R. Reddy, Mohamad Mouchli, Robert Summey, Chirstopher Walsh, Adil Mir, Lindsey Bierle, Marrieth G. Rubio, Outcomes of Young Patients with Alcoholic Cirrhosis After First Hospitalization for Cirrhosis: A Carilion Clinic Experience, Cureus.2021; 13 (7): e16695. 10.7759/cureus.16695.
2. Sandoval JL, Leão T, Theler JM, et al.: Alcohol control policies and socioeconomic inequalities in hazardous alcohol consumption: a 22-year cross-sectional study in a Swiss urban population. BMJ Open. 2019, (9): e028971. 10.1136/bmjopen-2019-028971.
3. Arteel GE. Oxidants and antioxidants in alcohol-induced liver disease. Gastroenterology 2003; 124(3):778–90.
4. Szabo G, Mandrekar P. Focus On: Alcohol and the Liver. Alcohol and Health 2010, 33(1/2): 25-33.
5. Lieber C.S. The metabolism of alcohol. Sci Am 1976; 234(3):25-33.
6. Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. Ligue Contre le Cancer. 8 October 2018 1AP-HP, Hôpital Jean Verdier, F-75010 Paris, France.
7. Guan X, Xing F, Li Y. Alcohol consumption increases the incidence of hepatocellular carcinoma in patients with hepatitis B cirrhosis but not in patients with hepatitis C cirrhosis. Eur J Gastroenterol Hepatol. 2021;33(9):1218-21.
8. Szachowicz-Petelska B. Changes in the Lipid Composition of Biological Membranes under the Influence of Endogenous and Exogenous Factors. Biochemistry (Mosc). 2019;84(2):164-70.
9. Anderson P. WHO Reports 3 Million Alcohol-Related Deaths in 2016. Medscape Medical News. Available at https://www.medscape.com/viewarticle/902614. September 27, 2018; Accessed: January 2, 2022.
10. Kang YJ, Zhou Z. Zinc prevention and treatment of alcoholic liver disease. Mol Aspects Med. 2005; 26(4-5):391-404.
11. Sharma P. Value of Liver Function Tests in Cirrhosis. J Clin Exp Hepatol. 2022; 12(3):948-964. doi: 10.1016/j.jceh.2021.11.004.
12. Sullivan MK, Daher HB, Rockey DC. Normal or near normal aminotransferase levels in patients with alcoholic cirrhosis. Am J Med Sci. 2022; 363(6):484-89. doi: 10.1016/j.amjms.2021.09.012.
13. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023; Published online ahead of print. doi:10.1097.
14. Gan, C., Yuan, Y., Shen, H. et al. Liver diseases: epidemiology, causes, trends and predictions. Sig Transduct Target Ther. 2025; (10}, 33. https://doi.org/10.1038/s41392-024-02072-z
15. Hong FK, Tian WH, Jaruga ZB. Elevated interleukin-6 during ethanol consumption acts as a potential endogenous protective cytokine against ethanol-induced apoptosis in the liver: involvement of induction of Bcl-2 and Bcl-x(L) proteins. Oncogene. 2002; 21(1):32-43.
16. Moreau, Richard et al. EASL Clinical Practice Guidelines on acute-on-chronic liver failure Journal of Hepatology, 2025; (9) 2; 461 – 91.
17. Muhammad Rajib Hossain, Ramesh Kumar Pandey, Mohammad Faridul Islam, Praveen Datar, Vijay Gayam, Pradeep Puri, and Thwin Malar, Acute Isolated Hyperbilirubinemia as a Presentation of Alcoholic Liver Disease: A Case Report and Literature Review. Published 12 Feb 2018
18. Nicholas JL, Kelly BL. Suppression of LPS-induced inflammatory responses in macrophages infected with Leishmania. Journal of Inflammation. 2010; 7: 8: 8
19. Vassalli G. Aldehyde Dehydrogenases: Not Just Markers, but Functional Regulators of Stem Cells. Stem cells international. 2019; 2019:390-45
20. Miranda RC, Pietrzykowski AZ, Tang Y, Sathyan P, Mayfield D, Keshavarzian A, Sampson W, Hereld D. MicroRNAs: master regulators of ethanol abuse and toxicity? Alcohol Clin Exp Res. 2010;34: 575–87.
21. Loyd, Dr. Stephen ."What are the early signs of liver damage?". journeypure.com. Retrieved 11 June 2020.
22. Frazier HT, Stocker MA, Kershner AN, Marsano LS. Treatment of alcoholic liver disease. Therap Adv Gastroenterol. 2011; (1): 63–81.
23. Wang N, Feng Y, Zhu M, Tsang CM, Man K; Tong Y et al. Berberine induces autophagic cell death and mitochondrial apoptosis in liver cancer cells: the cellular mechanism Journal of Cellular Biochemistry. 2010; (6):1426-36.
24. Di Castelnuovo A, Costanzo S, Donati BM, Iacoviello L. Prevention of cardiovascular risk by moderate alcohol consumption: epidemioloic evidence and plausible mechanisms. Internal and Emergency Medicine. 2010; 5(4): 291-97.
25. Siloși 1, Boldeanu MV, Andrițoiu A, Cojocaru M, Boldeanu L, Avramescu C. The benefits versus potential side effect of post chemoembolization for hepatocarcinoma. Medico Oncology. 2020; 1(9):1-9.
26. Rehm J. The Risks Associated with Alcohol Use and Alcoholism. Alcohol Research & Health 2007; (34); 2: 4-8.
27. Dinavahi SS, Bazewicz CG, Gowda R, Robertson GP. Aldehyde Dehydrogenase Inhibitors for Cancer Therapeutics. Trends Pharmacol Sci. 2019; 40(10):774-89.



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