CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Avalable online at: http://www.iajps.com *Review Article*

A BRIEF OVERVIEW ON LIVER CIRRHOSIS

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Article Received: February 2021 **Accepted:** February 2021 **Published:** March 2021

Abstract:
Cirrhosis is a complication of liver disease and leading cause of morbidity and mortality around the world. Chronic liver diseases represent a crucial health problem across the globe with liver cirrhosis. It is characterized by the formation of regenerative nodules in liver parenchyma enclosed by fibrous septa and loss of liver cells and irreversible scarring of the liver because of chronic liver injury. Cirrhosis of liver always occurs due to necrosis of liver cells followed by fatty liver and fibrosis. The liver structure becomes abnormal and involved with liver blood flow and perform that leads to portal hypertension, Hepatic encephalopathy and impaired hepatocytes performance. Chronic liver diseases represent a crucial health problem across the globe with liver cirrhosis. However, treatment of cirrhosis is designed to prevent further damage to the liver, treat complications of cirrhosis the recent advances within the identification, diagnosis and treatment of chronic liver diseases have changed the treatment history of cirrhosis significantly. Diagnosis of cirrhosis based how badly your liver is injured that includes serological test, and radio techniques like ultrasonography, and magnetic resonance imaging. Ursodeoxycholic acid has anti-apoptotic action that is used for treatment of primary biliary cirrhosis. Silymarin (Silybum marianum) acts as a free radical scavenger, reduces the inflammatory reaction and also modulates enzymes associated with the development of cellular damage, fibrosis and cirrhosis.

Keywords: *Liver cirrhosis, Complications, multiple cell types, Radio Techniques, Ursodeoxycholic acid and Silymarin.*

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Please cite this article in press Shilpa L.S et al., ***A Brief Overview On Liver Cirrhosis.,*** *Indo Am. J. P. Sci, 2021; 08(03).*

INTRODUCTION:

Liver is a large meaty critical hub for numerous physiological processes. The liver is the major organ for the metabolism of three major nutrients: protein, fat, and carbohydrate blood volume regulation, immune system support, endocrine control of growth signaling pathways, lipid,cholesterol homeostasis and regulates most chemical levels in the blood by breakdown of xenobiotic compounds, including many current drugs[1]. It has a central role in detoxification and excretion of endogenous and exogenous substances. High incidence of liver damage is caused by drugs like high doses of acetaminophen or paracetamol, hepatitis infection, alcohol consumption, advanced fatty liver and environmental chemicals/xenobiotics, which lead to liver diseases such as hepatitis. Most of the hepatotoxic chemicals like carbon tetrachloride, produce liver cell damage by inducing an increase in tissue lipid peroxidation, oxidative stress, and serum levels of many biochemical markers such as transaminases, alkaline phosphatase, bilirubin, triglycerides, cholesterol and the effect of toxicity can range from mild, transient changes of the liver [2].

Cirrhosis is a long-term liver disease that characterized by the formation of regenerative nodules in liver parenchyma surrounded by fibrous septa due to chronic liver injury. Cirrhosis occurs due to necrosis of liver cells; liver becomes injured and scarred followed by fibrosis and nodule formation. The liver structure becomes abnormal and slows the normal flow of blood through the liver and function and leads to portal hypertension and impaired 4hepatocyte's function [3]. Cirrhosis represents the common pathway for chronic liver diseases. In 1819, the term cirrhosis (meaning yellowish disease) was introduced by Laennec. It is derived from the Greek term scirrhus.

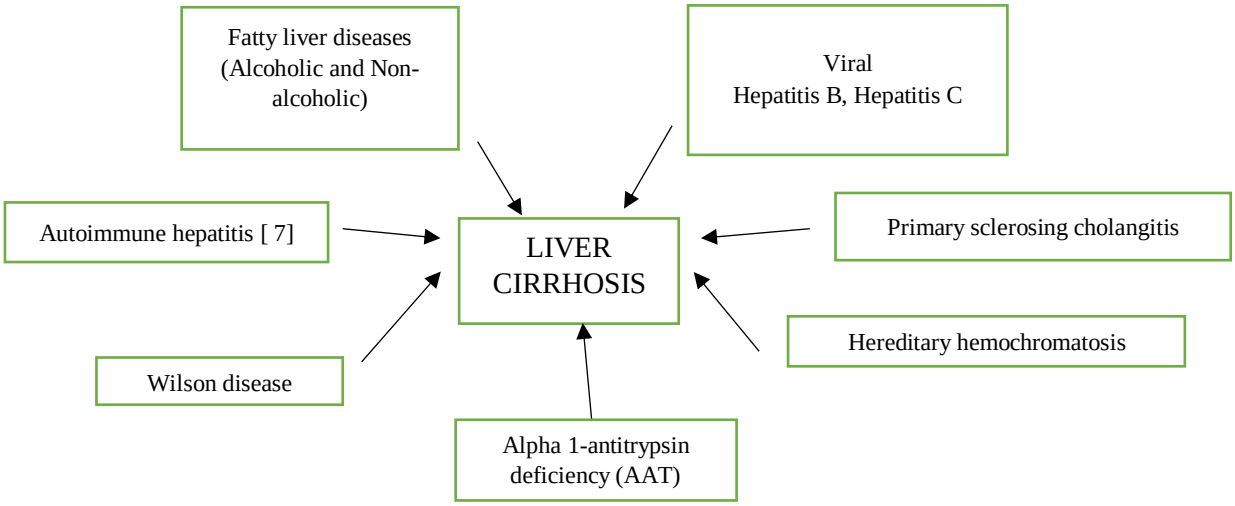
Cirrhosis is a late-stage result of liver disease that defined as a diffuse hepatic process characterized by fibrosis and the replacement of liver tissue by fibrous scar tissue as well as regenerative nodules that lead to the conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis occurs when the normal flow of blood, bile, & hepatic metabolites is altered by fibrosis The progression of liver injury to cirrhosis may occur over weeks to years and leading to progressive loss of liver function[4].The general circulatory abnormalities like in cirrhosis ,splanchnic vasodilation, and hypoperfusion of kidneys and cardiovascular abnormalities including hyperdynamic circulation, cirrhotic cardiomyopathy, and pulmonary vascular abnormalities are intimately linked to the hepatic vascular alterations and resulting portal hypertension[5].

SYMPTOMS AND COMPLICATIONS OF CIRRHOSIS

In early stage of cirrhosis there are usually no signs or symptoms. Progressive condition it causes symptoms like Loss of appetite, tiredness, nausea, weight loss, abdominal pain, anorexia, severe itching, Yellow discoloration in the skin and eyes and various complications are as follows:

1. Impaired metabolic and endocrine functions: Jaundice
2. Asterixis
3. Splenomegaly due to portal hypertension.
4. Haematological derangements such as thrombocytopenia.
5. Gastrointestinal varices.
6. Portal hypertension.
7. Spontaneous bacterial peritonitis.
8. Fetor hepaticus
9. Hepatocelluar carcinoma [6].

CAUSES OF LIVER CIRRHOSIS



MULTIPLE CELL TYPES IN THE PATHOGENESIS OF LIVER CIRRHOSIS

The liver is formed by parenchymal cells. It consists of multiple cell types, primarily defined as parenchymal cells (PCs) 80% these are polygonal cells and 20% of nonparenchymal cells (NPCs). The walls of hepatic sinusoids are specialised endothelial cells that are lined by three different nonparenchymal cells that's are hepatocytes (HCs), Kupffer cells (KCs) and liver sinusoidal endothelial cells (LSECs). Both hepatic PCs and NPCs, are critical for performing organ functions and maintenance and are involved in the initiation and progression of liver fibrosis and cirrhosis [8].

HSCs: It is localized to the perisinusoidal space between hepatocytes and sinusoidal endothelial cells. Activation of HSCs lead to lose of ability to store retinoids and start to proliferate and migration, contraction after transforming into myofibroblasts, generation of a large amount of collagen and another extracellular matrix (ECM). HSC activation assists liver regeneration by producing growth factors and ultimately leading to liver fibrosis.

LSECs: It form the lining of the smallest blood vessels in the liver, also called the hepatic sinusoids. Studies in animals and humans have revealed that LSECs are highly specialized endothelial cells can secrete the cytokine IL-33 to activate HSCs lead to hepatocytes damage and fibrosis stage and promote fibrosis to cirrhosis.

KCs: Known as Browicz-Kupffer cells and stellate macrophages cells in the liver that participate in various metabolic states are specialized macrophages located in the lining walls of the sinusoids of the liver that form part of the reticuloendothelial system (RES) play a critical role in maintaining liver functions. KCs can be activated by many injurious factors such as viral infection, alcohol, high-fat diet, and iron deposition and lead to destruction of hepatocytes by producing harmful soluble mediators and serving as antigen-presenting cells during viral infection. KC produce inflammatory cytokines, TNF-alpha, oxygen radicals and protease and mediated hepatic inflammation is considered to aggravate liver injury and fibrosis [9].

STAGES OF LIVER CIRRHOSIS

Liver cirrhosis is defined as an advanced stage of liver fibrosis in here the scar tissue begins to replace healthy tissue in the inflamed liver [10]. The most common primary etiologist for cirrhosis are Chronic alcohol abuse, Chronic viral hepatitis (B, C , D) and non-alcoholic fatty liver disease (NAFLD). Fatty liver disease called hepatic steatosis that caused by accumulation of too much cholesterol and triglycerides [11]. NAFLD condition in which people who drink little or no alcohol. It has been divided into two main histological subtypes: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH)this is much more serious than a simple fatty liver,so the incidence of development to cirrhosis is higher in NASH than in NAFL.[12]

Stages of liver cirrhosis

LABORTORY TESTS AND FINDINGS IN CIRRHOSIS

Table 1: Laboratory tests for liver cirrhosis

LIVER FUNCTION TESTS	NORMAL LEVEL	CHARACTERS
AST, ALT	AST is 5–34 U/L ALT is 0–55 U/L	Normal or moderately raised.
ALP	50–125 U/L	Increased by less than three-fold
Bilirubin	0.0–1.5 mg/Dl	Raised than ALP
Albumin	3.5–5.0 g/dL	Decreased in advanced cirrhosis [13].
BUN	8–26 mg/dL	Detection of nitrogen in your blood
Cr	0.6–1.0 mg/dL (female) 0.7–1.3 mg/dL (male)	Detection of liver disease Elevation of serum creatinine
Platelet	140–440 (103/μL)	Incidence of Thrombocytopenia [14].

RADIO TECHNIQUES

1. Ultrasound Examination

Ultrasound is a safe and relatively inexpensive imaging, tool, allowing annual or biannual tests in chronic hepatitis patients. Initial findings of hepatic fibrosis by US are similar to simple hepatosteatosis [15]. To detect changes in size, shape of the liver and to detect the movement of the liver by ultrasound wave. In cirrhosis, there may be distortion of the arterial vascular architecture and marginal nodularity of the liver surface. The patency of the portal and hepatic veins is evaluated. Elastography is used for diagnosis ultrasound wave help to measure liver its stiffness (or elasticity) is calculated [16].

2. Computerized Tomography Scan (CT Scan)

CT is the most sensitive and non-invasive diagnostic imaging diagnostic tool for evaluating hepatic morphological changes. CT scans of the liver and biliary tract can provide more detailed information about the liver, diagnosis of specific types of jaundice, hepatic morphology and extra-hepatic manifestations related to portal hypertension. Changes in size, volume and used to visualize placement of needles during biopsies of the liver are easily visible in a CT scan [17].

3. Endoscopy

For detection and treatment in the liver, gallbladder, bile ducts, and pancreas. It uses X-rays and a long lighted tube.

4. Magnetic Resonance Imaging (MRI) Scan

For diagnosis of benign tumours (haemangiomas). Magnetic resonance angiography demonstrates the vascular anatomy and Magnetic resonance cholangiography shows the biliary tree.

5. Magnetic resonance elastography (MRE)
MRE is similar to ultrasound elastography, it uses a vibration device to induce a shear wave in the liver. The system consists of an active driver, located outside the magnet room, which generates continuous low frequency vibrations (60 MHz) [18]. MRE has many advantages, it can exam the whole liver, with a lower sampling error than with a biopsy or other imaging modalities, good diagnostic accuracy; and the results are not influenced by hepatic steatosis, obesity, and ascites [19].

URSODEOXYCHOLIC ACID
Ursodeoxycholic acid (UDCA) is a nontoxic, choleretic and hydrophilic endogenous bile acid that has been shown effective in the non-surgical treatment of cholesterol gallstones and primary biliary cirrhosis (PBC). UDCA is reported to have "hepato-protective properties" used to dissolve cholesterol gall stones and to treat cholestatic forms of liver diseases including primary biliary cirrhosis [20]. UDCA is an is an epimer, 3α,7β-dihydroxy-5β-cholan-24-oic acid (Figure 1), which is a secondary bile acid having hydrophilic properties [21]. The clinical properties of UDCA include anti-apoptotic effects, lowering serum TNF-α concentrations, decreasing endoplasmic reticulum stress and improving hepatic insulin sensitivity [22].

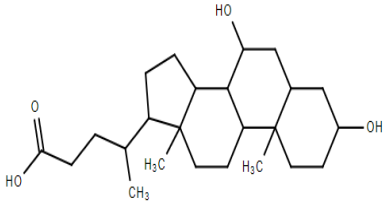


Fig 1: Chemical structure of UDCA

Anti-apoptotic effects: Apoptosis is a `physiological' cell death that deletes damaged and aged cells from the organism. Dysregulation of apoptosis in hepatocytes and bile duct epithelial cells contributes to cholestatic liver injury. Primary biliary cirrhosis, UDCA play role in modulating the apoptotic threshold in both hepatic and non-hepatic cells and improved both symptoms and biochemical parameters of cholestasis (bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase) and inflammation (aminotransferases). UDCA modulating the apoptotic threshold in both hepatic and non-hepatic cells and reduces the need for orthotopic liver transplantation [23].

SILYMARIN
Silybum marianum is the scientific name for Milk thistle has been used for centuries to treat hepatic conditions and reduces liver dysfunction. The plant contains isomeric mixture of at least seven flavolignans and the flavonoid taxifolin. The most important flavolignans present include silybin (silybin A and silybin B), silydianin, and silychristine[24-25].

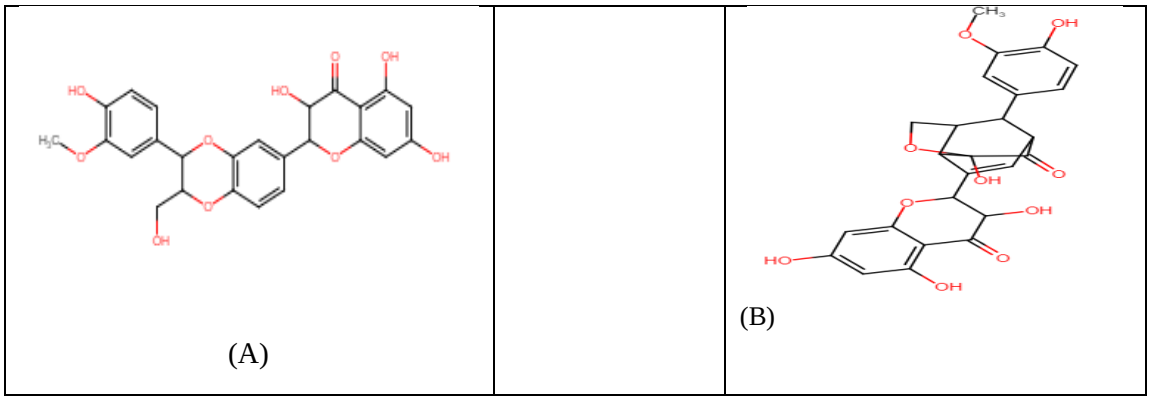


Fig 2: Chemical structure of (A)silybin, (B)silydianin

It used as a natural treatment for things including cirrhosis, jaundice, hepatitis, and gallbladder disorders. Silymarin flavonolignans exhibiting many pharmacological activities that is Silybin represents between 50% and 70% of the extract from silymarin. Silymarin is an powerful antioxidant and preventing free radical formation by inhibiting specific ROS-producing herbal drug which can protect biological systems against the oxidative that protects the liver from the free radical damage and used for the treatment of hepatic diseases worldwide due to its antioxidant, anti-inflammatory, and anti-fibrotic activities. Silymarin Flavonolignans as diastereomeric pairs significantly suppressed autophagy activation and the activity of ERK/p38(figure3) mitogen-activated protein kinase (MAPK) pathway [26].

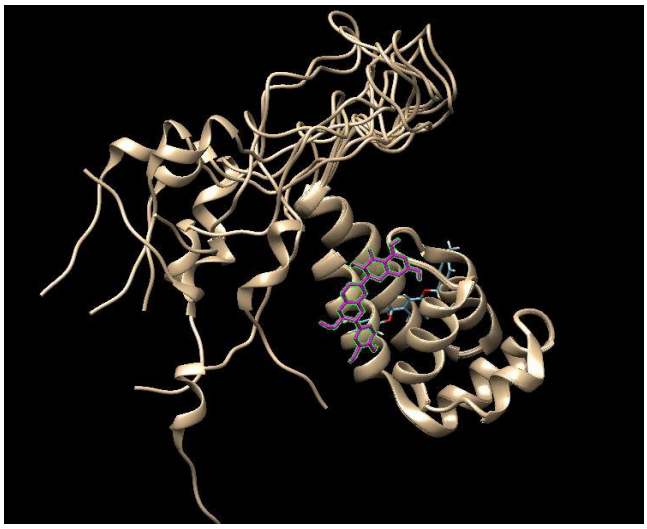


Figure (3) Silymarin undergone docking with ERK receptor (human target)

Antioxidant Properties

Silymarin may enlarge the generation of glutathione in the liver via an increase in substrate availability for its biosynthesis. First, it stabilizes membrane permeability through inhibition of lipid peroxidation, thereby helping the liver to maintain levels of its own powerful antioxidant property which can protect biological systems against the oxidative stress, glutathione [27].

Anti-Inflammatory Properties

Chronic inflammation has been associated with progressive hepatic fibrosis and the development of cirrhosis, and oxidative stress may be the common underlying mechanism in the initiation and progression of hepatic inflammation in various liver disorders.NF-κB is a transcriptional regulator of the inflammatory response and plays an role in regulating inflammatory signaling pathways in the liver. Liver injury induced by hepatic ischemia/reperfusion is characterized by activation of the transcription factor NF-κB, and is activated in virtually every chronic liver disease, including, NAFLD, viral hepatitis B, C, D and biliary liver disease. There is increasing evidence that demonstrates the overall inhibition by silymarin of inflammatory mediators such as NF-Kb (figure4) and inflammatory metabolites.

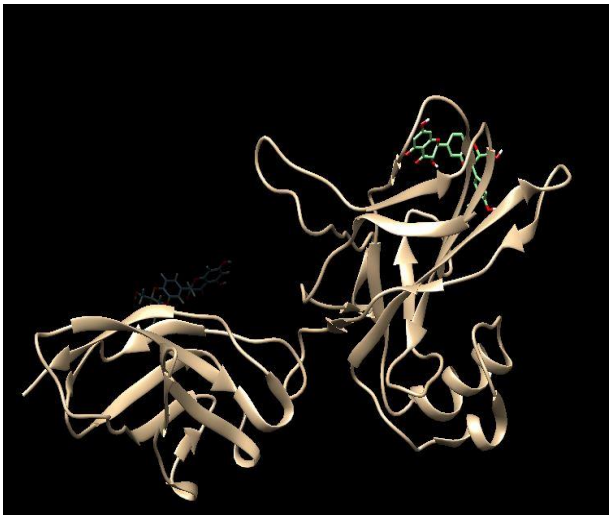


Figure (4) Silymarin undergone docking with NF-κB receptor (human target)

Antifibrotic Effects

Silibinin has exhibited antifibrogenic effects in animal and in vitro models. Hepatic fibrogenesis, which results from chronic liver tissue damage, is characterized by start-up of hepatic stellate cells (HSCs), a liver-specific type of pericyte. Activated HSCs develop into myofibroblasts, lead to the deposition of collagen fibers leading to liver cirrhosis. In an in vitro model of human hepatic fibrogenesis, silibinin demonstrated antifibrogenic properties by dose-dependently, suppresses expression of profibrogenic procollagen alpha1 and TIMP-1 inhibiting the growth factor-induced production of pro-collagen in activated human HSC [28].

CONCLUSION:

In conclusion, the findings from this systematic review indicated that Cirrhosis is the common end stage of a number of chronic liver conditions and a signifcant cause of morbidity and mortality. Cirrhosis is mainly diagnosed by liver biopsy and other serological laboratory test and radio techniques. The progress of new imaging modalities for diagnosing of liver cirrhosis has led to the detection and measurement of minuscule changes. This has ensured accurate diagnosis of liver cirrhosis. Currently, elastography, widely used to measure the stiffness and elasticity of the liver. Silymarin acts as free radical scavenger, anti-inflammatory action, and Antifibrotic effects that has shown positive effects as supportive treatment in most forms of liver disease including cirrhosis. Ursodeoxycholic acid used for primary biliary cirrhosis by decreasing production of cholesterol by the liver and reduces the need of liver transplantation.

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