

Possible Treatment of Liver Cancer using Natural Compounds- Review

Akanksha¹, Vandana¹, Komal Kaushik¹, Gunjan Choudhary¹, Runjhun Mathur², Abhimanyu Kumar Jha^{1*}

¹Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, India

²Dr. A.P.J Abdul kalam Technical University, Lucknow, India

***Address for Correspondence:** Dr. Abhimanyu Kumar Jha, Associate Professor, Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, India

E-mail: abhimanyujha630@gmail.com

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ABSTRACT

Liver cancer is the most common tumor of the digestive system with a high mortality rate. Hepatocellular carcinoma (HCC) is the fifth most common cause of malignancy and the third cause of cancer mortality. Apoptosis is instinctive cell death and a highly prearranged physiological machinery to wipe out abnormal cells. Apoptotic cells exhibit remarkable morphological features and trait molecule expression. The introduction of apoptosis in tumor cells is used as the management to control the growth of cells and a remedy for preventing cancer diseases. Accumulating evidence shows that many natural compounds are good sources in the treatment of liver cancer, for example since ancient time natural compounds like plants extracts (fruits and vegetables) and other than that herbs, insects, and animals extracts are common to use in the treating liver cancers or another liver disease. These compounds show both biological and chemical properties in medicines developments and designs. It was diagnosed that various natural compounds are powerful hepatoprotective agents against liver cancer.

Key-words: Apoptosis, Hepatocellular carcinoma, Liver cancer, Plant extracts, Secondary metabolites

INTRODUCTION

Globally 10% of the world population is affected by liver cancer ^[1]. The most commonly observed liver diseases include hepatocellular carcinoma (HCC), chronic hepatitis, alcoholic steatosis, fibrosis, cirrhosis are very harmful health conditions that required the attention of medical professionals, doctors, and scientists. Those patients, who have alcohol addiction or viral hepatitis probably, have a chance to be affected by liver cell damage and cirrhosis, which result in the increase of HCC, which could not have any cure. Although several other treatment options still exist for most liver cancers and there are many drugs, which used as an emergence resistance in the increase of HCC ^[2]. Such treatments essentially used to improve the outcome.

Derivatives of natural products or half natural compounds are agents used in liver therapy nowadays ^[3-5]. Secondary metabolites are related to "natural compounds" that play an important function to protect the mechanism against harmful agents like microorganism's insects, herbivores, and competing plants. Those carry active compounds are in use since ancient's times as essential supplements for the population and are still used as natural supplements as drugs in many countries globally ^[6]. Natural compounds or Natural products are present in huge's amounts as rich sources for basic diverse substances that have variations in biological activities, which are alternative sources use in therapies. Using natural products in diseases preventions is complementary for both treatable and incurable diseases collecting huge compliments worldwide even healthcare centers advised to use natural products to prevent the disease ^[7]. The new therapeutic organization has analyzed the importance of natural products for liver disease. Worldwide, approximately 25% of the drugs arranged from plants and 60% of anti-infectious drugs are under

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clinical investigations that contain Natural origins ^[8]. About 65% of patients with liver cancers who consume herbal medicines in Europe, the US, and Germany are used Silymarin at very high amounts where it cost extent out to \$180 million in desolate ^[9]. Having such a good effect on natural compounds has motivated pharmaceutical experts to determine new drugs.

Apoptosis in Liver disease- Apoptosis can occur in the reaction of viral infections, and contact with any types of hepatocarcinogen, excessive alcohol consumption, or due to genetic mutations. Resident cells express in a high amount of cell death-associated receptors; for instance, hepatocytes, cholangiocytes, activated stellate cells, and Kupffer cells are all express Fas. The expression of the Fas receptor does not only help to manage the liver homeostasis but can also help in the removal of virally infected cells of the liver by the immunocytes ^[10]. Fas/FasL signaling has large implications in liver pathophysiology but also in mitochondria; essential pathways are also involved in liver homeostasis. One of the BH3 proteins subfamily, cleaved by caspase-8, and the truncated Bid then translocates in the mitochondria where it activates the essential apoptosis pathway. It has been revealed that defective mice are show resistance to Fas-induced hepatocellular apoptosis ^[11]. These studies implicated the both extrinsic and intrinsic apoptotic pathways in maintaining healthy liver composition.

Basic aspects- The liver is a major crisis disease of worldwide proportions in its long history and incorporates with Maladies, which can change the activity of serious life-threatening conditions. These can comprise their inborn metabolic activity, alcoholic cirrhosis, viral hepatitis, and metastatic cancers with drug-induced hepatotoxicity ^[12]. It is considered through morbidity and mortality with social and economic costs. The phytochemicals may be utilizing from some dietary sources by the Amelioration of sickness in the population ^[13]. It is safe and effective in Ameliorating liver disease. Scientists may lead compounds with their specific structures with natural sources of pharmacological effects. The current drug is prescribed directly through isolated plants or artificially modified natural products ^[14]. Such type's of natural compounds can be described as resveratrol, 6,7-dimethyl esculetin, Matrine, Ellagic acid, Silymarin, Wogonin, Curcumin, Glycyrrhizin, Naringenin, Geniposide, Rhein, Mellein, Artemisinin, etc.

Natural Compounds

Wogonin- Viruses like (Hepatitis B virus (HBV) and hepatitis C virus (HCV) epidemic play an important role to threat the worldwide disease. (Chronic hepatitis B and C) can occur in alcoholic as well as in nonalcoholic fatty liver disease, which may be carrying some progressive growth in liver cancer, such as emphasize cirrhosis and it can express final-stage complications, plus bleeding and de-compensating in liver cancer ^[15-17]. While, several types of antiviral drugs were approved for hepatitis B, which causes drug resistance activity and adverse side effects in liver disease. These newly discovered anti-HBV drugs are compulsorily required to treat HBV infections. Wogonin is a collect monoflavonoid *Scutellaria radix* are used from many years ago in Asia for inflammatory diseases and hepatitis ^[18]. The anti-HBV activity demonstrates the capability to suppress hepatitis B surface antigen (HBsAg) secretion in cell culture. In Plasma, HBsAg stages significantly decreasing liver disease though it can be treated with Wogonin, showed some result in histopathological liver boosting. Wogonin has revealed successful cytotoxic effects in hepatocellular carcinoma cells SK-HEP-1; induce by apoptosis, which activates the caspase-3 cascades and induces p53 protein and have involved in the alternative expression of p21 protein ^[19].

Curcumin- Curcumin is a type of active compound which obtain from the plant *Curcuma longa* is already isolated a few centuries ago. Curcumin is using to prevent many diseases for example rheumatism, skin related diseases, intestinal worms, diarrhoea, body ache, dyspepsia, hepatic disorders, inflammations, etc in ancient India. In recent years, Curcumin has been used and does not show any side effects. Curcumin commonly used in inflammatory diseases, including in cancer, Diabetes, Cardiovascular diseases, Arthritis, Alzheimer's disease, and psoriasis throughout the modulation of molecular targets ^[20]. They can inhibit several factors like nuclear factor-kappaB, which can modulate some pro-inflammatory and profibrotic cytokines. They have anti-oxidant properties, which can supply a rational molecular activity in hepatic disorders. Curcumin may attenuate the liver injury, which may be induced by ethanol, subchronic and chronic carbon tetrachloride (CCl4) intoxication that can reverse CCl4 cirrhosis ^[20].

Glycyrrhizin- The Hepatitis C virus is a type of chronic liver cancer; this can be damaged liver and hepatocellular carcinoma. The current treatment may involve interferon plus ribavirin, which has only some profits due to unfavourable side effects for example anaemia, depression, and fatigue ^[21]. The biologically active ingredient plays an important role in liquorice (*Glycyrrhiza glabra*) root, which has pharmacological effects and is used for the treatment of chronic hepatitis. It has anti-inflammatory and antiviral activity in triterpene and drugs used clinically in China for the treatment of tumors and protection of liver function. Glycyrrhizin may protect the effect of non-specific anti-inflammatory, and decrease the frequency of sodium and water retention ^[22]. Glycyrrhizin MMP-9 Articulation has been observed ^[23]. MMP-9 shows the growth of LPS/GalN-HCV occurs in mice liver injury and recommends the inhibition activity by glycyrrhizin in liver injury by down-regulation of MMP-9. Glycyrrhizin may inhibit the hepatocyte apoptosis due to the down-regulating expression of caspase-3 and also inhibit the cytochrome C from mitochondria into their cytoplasm ^[24]. The mRNA phase of heme oxygenase-1 is amplified due to glycyrrhizin treatment. These results show that the CCl₄-induced liver injury is preserving due to induction of heme oxygenase-1.

Resveratrol- Resveratrol is a polyphenolic phytochemical, occurs in berries, grapes, and wine, and shows the importance of the therapeutic agent in the treatment of liver ailments. Various types of studies may do and their result has the properties in hepatoprotective of resveratrol. Resveratrol can prevent their hepatic damage by free radicals and inflammatory cytokines, induce anti-oxidant enzymes and elevate glutathione satisfaction, and have various modulate signal transduction pathways in liver cells. They were using for purified enzymes, cultured cells, and laboratory animals, which can be suggested the resveratrol anti-ageing, anti-carcinogenic, anti-inflammatory, and anti-oxidant properties through relevant of chronic diseases in humans ^[25]. Resveratrol can reduce their TNF- α and IL-6 mRNA and can decrease the number of Kupffer cells in the injured liver. It enhanced the fibrosis and promoted the regeneration of hepatocytes recover the survival of BDL mice. Resveratrol was very useful for the treatment of cholestatic liver injury ^[26]. According to long-term management of silymarin may significantly be amplified

and survival of patients during alcohol-induced liver cirrhosis. Based on molecular methods, silymarin can reduce tumor cells by proliferation, angiogenesis, and insulin resistance. It has been seen that in Liver cirrhosis, non-alcoholic fatty liver and steatohepatitis are involved in threat elements of HCC. The chemopreventive result of silymarin on HCC has a good result on cell survival and apoptosis is interfering with cytokines in *in vivo* and in *in vitro* condition.

Naringenin- Naringenin was a naturally occurring citrus flavanone, which occurs in grapes and tomatoes shows pharmacological qualities. Oral administration of naringenin (20 and 50 mg/kg daily) extremely prohibited the DMN-induced loss in the body and their liver weights and can inhibit the elevation of serum alanine transaminase, bilirubin levels aspartate transaminase, and alkaline phosphatase ^[27]. It is verified that naringenin exhibited hepatoprotective and anti-fibrogenic effects against DMN-induced liver injury in *in vivo*. It can also show some antioxidant properties and can be used to decrease the lipid peroxidation against oxytetracycline-induced oxidative pressure in the liver ^[28].

Geniposide- Geniposide is a plant subclass of glycoside from the fruit of *Gardenia jasminoides* Ellis, hyperlipidemia, and fatty liver ^[29]. Nowadays, geniposide can show its effect to inhibit liver fibrosis. Additionally, geniposide may suppress the expression of CYP2E1 and amplified the activity of the peroxisome proliferator-activated receptor- α (PPAR α) phrase. Geniposide can exert protection effects against hepatic steatosis in rats fed with a high-fat diet. The mechanism may be associated with its antioxidant actions or regulation of adipocytokine, which can release and expression of PPAR α . Genipin, and aglycone of geniposide, exhibits the activity of anti-inflammatory and anti-angiogenic. Genipin induced apoptotic cell death in rats due to hepatoma cells and human hepatocarcinoma Hep3B cells ^[30].

Rhein- Rhein is an anthraquinone derivative of rhubarb, which inhibits the proliferation of several human cancer cells. It plays an important role in inducing cell cycle and arrests via downregulation of oncogene c-Myc and apoptosis throughout the caspase-dependent pathway ^[31]. Rhein ameliorates fatty liver disease due to harmful energy balance, hepatic lipogenic regulation, and

immune modulation in diet-induced obese mice^[32]. The protections of rhein against APAP-induced liver and kidney injuries have resulted from the amelioration of Acetaminophen-induced oxidative pressure^[33]. Rhein is protected through hepatocyte while injury and prevented the progress of hepatic fibrosis in rats, which may be linked with a role of antioxidation, anti-inflammation, inhibiting the phrase of TGF-beta1 and it may suppress the activation of hepatic stellate cells^[34]. It has to protect outcomes on liver injury and can inhibit liver fibrosis induced by CCl4/ethanol in rats^[35]. The mechanisms worked for the action of antioxidant and anti-inflammatory activity.

Traditional medicines- Traditional medicine or drugs is a very complex mixture of natural products that have several different components and show an important property indispensable role in the prevention and treatment of diseases. A selective and sensitive method was developed to screening the potentially bioactive components *in vivo* with the semi-quantitative determination of multi-components in the plasma membrane of the mouse with only single oral administration of Yin-Chen-Hao-Tang, a prominent property for liver disorders^[36]. The initial option compounds were 6,7-dimethylesculetin considered significantly. Matrine is an active component of traditional medicine with (*Sophora flavescens*), which shows a large spectrum of pharmacological effects. It is attenuated through the endotoxin-induced acute liver injury after hepatic ischemia/reperfusion generally due to its anti-inflammatory and antioxidative activities and shows the inhibitory result on cell apoptosis^[37]. Matrine inhibited MMP-9 expression of SMMC-7721 cells^[38]. To further explore the hepatic stellate cell (HSC) active the results in a protection against ecological insult, that the profile of differentiation of HSC was examined by treatment with ellagic acid^[39].

Table 1: Natural compounds and their uses

Natural compounds	Uses
Silymarin	Acute and chronic viral hepatitis
Wogonin	anti-angiogenesis, anticonvulsant, anti-hepatitis
Curcumin	Muscle soreness, induced inflammation

Glycyrrhizin	Skin disorders, respiratory disorders
Naringenin	Improve skin hydration, soothes irritation
Geniposide	Antioxidant, antitumor
Rhein	Anticancer, antimicrobial
Mellein	Gastrointestinal, bleeding, migraines, pneumonia
Artemisinin	Anti malarial
Resveratrol	High cholesterol, cancer

Clinical studies- The hepato-protective are likely to have a variety of natural products in clinically evaluated^[40-42], which show effectiveness in glycyrrhizin, matrine, and silymarin treatments of hepatitis, alcoholic liver cancers^[43]. In Japan, glycyrrhizin injection was used as a therapeutic drug for chronic hepatitis, since last history 1979^[44]. Glycyrrhizin is inhibited by injection of new glycyrrhizin express and manages during oral, rectal, intranasal, and subcutaneous routes. In the future, new pharmaceutical preparations of glycyrrhizin will be developed by chronic hepatitis patients, who involve in glycyrrhizin therapy. The function of the liver and cellular immunity in children with infectious mononucleosis complex liver impairment (IM-LI) was showed the clinical therapeutic properties in glycyrrhizin^[45]. Glycyrrhizin injection therapy can reduce the chance of hepatocellular carcinoma in patients with IFN-resistant by activation of chronic hepatitis C. the value of average aminotransferase is twice or more of the upper limit of normal after their interferon^[46]. Natural products appear through targets that have a high risk for liver cancer^[47]. HBV infection is one of the worldwide public health problems, which may lead to cirrhosis and HCC in the liver.

CONCLUSIONS

In this review, herbal medicines based on the clinical trial of laboratory analysis, which studies for the treatment of liver disease, highlight the harbour (natural compounds) bioactive molecules. It may have hepatoprotective tracts a significant natural product derived from drugs. A naturally occurring compound has been used in the treatment of liver diseases for several years since pathological liver unbalances. The active phytochemicals

include hepatoprotective properties recognized in various plants. These phytochemicals can be developing as a single ingredient as a drug, with a high-quality control medicine. The drug development industries are now facing challenges like drug discovery methods with extremely expensive, riskier, and critically inefficient.

Natural products are a chief source of new drugs for the pharmaceuticals company are used their extracts today. Natural products have served as material medical, which suggests that they can use for a better result against liver disease.

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CONTRIBUTION OF AUTHORS

Research concept- Runjhun Mathur

Research design- Akanksha

Supervision- Dr Abhimanyu Jha

Data collection- Vandana

Data analysis and Interpretation- Gunjan and Komal kaushik

Literature search- Akanksha and Runjhun Mathur

Writing article- Akanksha

Critical review- Runjhun Mathur

Article editing- Akanksha

Final approval- Dr Abhimanyu Jha

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