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Hepatoprotective activity of medicinal plants: A mini review

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Abstract
A phytotherapeutic approach for the development of modern drug agents can provide various vital drugs from the conventional medicinal plants. Exploration of pure phytocompounds as drug agent is expensive and time taken. Various plants and their herbal formulations are found to be useful for the cure of liver diseases. However, in some cases, the results of treatment are not up to the mark but experimental studies are carried out on a number of valuable plants and their formulations. The therapeutic efficacy is tested against some chemically induced liver damages in liver cancer cell lines and animal models. Antioxidants from the medicinal plants and common dietary sources can provide protection against the liver damages caused by the chemicals and oxidative stress mechanism.

Keywords: Antioxidants, liver diseases, liver cancer cell line, herbal formulation, hepatoprotective, phytotherapeutic

Introduction
In severe cases of liver damage, most of the cells either die or changes to fibrotic state. In such cases, the treatment option includes some agents along with the therapeutic agents which can stimulate the proliferation of liver cell. Human liver cell lines procured from the cancerous tissue or by the genetic engineering of primary liver cells are broadly utilized in *In vitro* studies due to their better availability. The stable metabolism and larger capacity of proliferation of these cells make them an acceptable one for *In vitro* investigation under reproducible and standardized condition. Hepatoma cell line HepG2 is mostly used for *In vitro* studies for the development of cancer therapy. Reports highlighted the importance of cell line for the investigation of metabolic pathways or to test a particular drug candidate solely or in combination for a cancer therapy [1, 2].

For the development of remarkable herbal agent to treat different diseases of liver, medicinal plants have to be validated for their properties such as liver regeneration, antihepatotoxic, and antiviral activity. The plants with above mentioned properties have to be selected. Single plant cannot fulfill all the desired activities. An amalgam of various herbal fraction/extracts can likely to fulfill desired properties to treat liver diseases. Production of these herbal formulations with standards of efficacy, purity and safety can revitalise the treatment of liver ailments. However, plants such as *Aegle marmelos* Correa, *Ficusp seudopalma* Blanco, *Picrorhiza kurroa* Royle, *Cochlospermum angolensis*, *Semecarpus anacardium*, *Humulus japonicas*, *Pleurotus pulmonarius*, *Caesalpinia bonducella*, *Symplocos racemose*, *Berberis vulgaris*, *Urtica dioica L*, *Terminalia arjuna*, *Withania smonifera*, *Punica granatum*, *Morinda citrifolia*, and *Morinda pubescens* (Hyoscyamine) plays an important role in the human wellbeing due to the presence of various primary and secondary metabolites [3, 4, 5, 6]

Around 80% of the globe population is dependent upon the use of conventional medicine which is based on the medicinal plants [7]. The conventional medicine refers to a wide range of natural wellbeing practices including tribal/folk practices as well as Unani, Amchi, Siddha, and Ayurveda. It is determined that around 7,500 plants are utilized in tribal and rural part of India. Out of them, the exact therapeutic value of more than 4,000 plants is still unknown or little known to the large population. The traditional system of medicine such as Tibetan, Unani, Amchi, Siddha, and Ayurveda utilized around 1200 species of plants [8]. A complete investigation of plants applied in local wellbeing traditions and their pharmacognostical evaluation can lead to the production of crucial plant drugs for many untreatable diseases [9].

Liver diseases

Liver plays an important role in the regulation of many of the physiological processes. It is included in various vital functions such as storage, secretion, and metabolism. Detoxification of many xenobiotics and drugs can occur in liver. The bile acid of the liver with some other things directs the digestion process. Liver diseases are one of the severe ailments. It may be categorized as chronic or acute (inflammatory ailment), cirrhosis (results liver fibrosis), and hepatosis (non-inflammatory ailment). They are mainly occurred because of many risk factors which damage the cells of liver by directing peroxidation of lipids and other oxidative damages due to the generation of oxidative stress in liver. Enhanced peroxidation of lipid during the microsomal ethanol metabolism in liver may results in hepatitis and cirrhosis [10].

Risk factors for liver cancer

Chronic infection with Hepatitis C and B virus is found to be the common factor responsible for causing liver cirrhosis [11]. Hepatitis C and B viruses can transmit from one individual to another through the use of contaminated needles and blood sharing. This chance of transmission can be reduced via blood test prior to the transfusion of blood [12]. Another risk factor is the alcohol abuse which is the cause of liver cirrhosis leading to hepatic cancer [13]. Tobacco use, obesity, diabetes and smoking can also raise the possibilities of getting liver cancer [14]. Heavy metals exposure through the portable water can also develop a risk in developing some types of hepatic cancer [15]. Further, long-term exposure to thorium dioxide (X-ray chemical), vinyl chloride**,** aflatoxin can raise the chances of cirrhosis and liver cancer in individual [16].

Antioxidant effects of medicinal plants

The whole plant parts of *Tinospora cordifolia*, *Rosmarinus officinalis* L., *Pleurotus pulmonarius*, *Humulus japonicas*, *Cochlospermum angolensis*, *Picrorhiza kurroa* Royle, *Ficusp seudopalma* Blanco, *Aegle marmelos Correa*, *Berberis vulgaris*, *Caesalpinia bonducella*, *and Artemisia annua* L. showed antioxidant activity in liver cancer cell in a dose dependent manner as shown in Table 1[17-35].

Tinospora cordifolia can increase antioxidant enzymes (SOD, CAT, GPx), nonenzymatic antioxidants (GSH) level, and reduce LPO enzyme [27]. *Aegle marmelos C.* attenuated lipid peroxidation (LPO), xanthine oxidase (XO) at 25 and 50 mg/kg concentration given by oral route in mice model. *Berberis vulgaris and Caesalpinia bonducella* increase GPx and SOD activities, lower NO level [24], and reduce lipid peroxidation, increase non enzymatic antioxidants (GSH), and antioxidant enzymes (SOD and CAT) levels [17], respectively. *Artemisia annua* L. also reduced lipid peroxidation and DNA damage [26].

Additionally, the leaves of *Kleinhovia hospital*, *Morinda pubescens* exerted 84% DPPH radical scavenging [28] and 58.40% DPPH radical scavenging [29] activity in DPPH radical scavenging method. The bark of *Terminalia arjuna*, *Urtica dioica* L., and *Symplocos racemosa can* increase GSH, CAT, and SOD, GPx reduce LPO [30, 31, 32]. *Semecarpus anacardium* increase glutathione level at 200mg/kg concentration in male wistar albino laboratory rats. *C. lansium (Lour.)* fruits increase DPPH radical and superoxide anion scavenging activity [33].

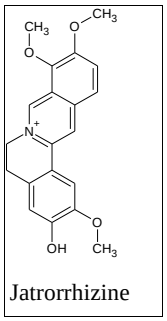
Table 1: Medicinal plant with antioxidant activity in liver cell

Plant	Compounds	Plantparts	IC_{50}/ dose concentration	Proposed mechanism	Test system	Reference
Tinospora cordifolia	Jatrorrhizine, Saponarin, Galactoarabinan	Whole plant	300 mg/kg	Increase SOD, CAT, GPx and GSH level and reduce LPO enzyme.	Male wister albino rats.	[27]
Kleinhovia hospita	Eleutherol	Leaves	IC50 = 491.8 lM	Scavenged the radical	DPPH radical scavenging method	[28]
Morinda pubescens	Hyoscyamine	Leaves	IC_{50} = 289.33±62.14 µg/mL.	58.40% DPPH radical scavenging	DPPH method using L-Ascorbic acid	[29]
Terminalia arjuna	Terminoside A	Bark	400 mg/kg	Increase SOD, CAT, GPx and GSH level and reduce LPO enzyme.	Male wistar albino rats	[30, 31]
Rosmarinus officinalis L	Rosmanol, Carnosol	Whole plant	0 to 120 g/mL	50% increased antioxidant activity.	Human liver carcinoma HepG2 cells	[21]
Pleurotus pulmonarius	Ergosta-5, 7, 22-trien-3β-ol		0.25 mg/ml to 4 mg/ml	DPPH scavenging activity	Mice	[25]
Humulus japonicus	Luteolin-8-*C*-glucoside		0.1-2 mg/ml	DPPH radical and hydroxyl radical scavenging activities of methanol extracts of Humulus japonicus were 60% and 35%, respectively	DPPH radical scavenging method	[20]
Semecarpus anacardium	Anacardoside, Galluflavanone	Nut	200 mg/kg	Increase glutathione	Male wistar albino laboratory rats	[34]
Cochlospermum angolensis	Gallic acid, Protocatechuic acid	Whole plant	$EC_{50} \leq 170$ µg/mL	Increase DPPH scavenging activity	Human liver carcinoma HepG2 cells	[22]
Picrorhiza kurroa	Picrorhiza acid		2 µg/mL	Radical scavenging assays (DPPH• and •OH), ferric reducing antioxidant property (FRAP) and thiobarbituric acid (TBA) assay for testing inhibition of lipid peroxidation	Hep3B (human hepatocellular carcinoma)	[19]
Ficus pseudopalma Blanco	Lupeol		DPPH (IC50=331.76 µg/mL), nitric oxide (IC50=19.81 µg/mL) and	DPPH, nitric oxide, and FRAP scavenging activity	Hepatocellular Carcinoma (HepG2) cells	[23]

			FRAP (IC50>53.04 µg/mL).			
Aegle marmelos Correa	*Marmin umbelliferone*		25 and 50 mg/Kg b. wt. orally	Suppressed lipid peroxidation (LPO), xanthine oxidase (XO)	Wistar rats	[18]
Urtica dioica L.	p-coumaric acid	Seeds	2 mL/day	Increased the levels of antioxidants (CAT, GR and SOD) enzyme and increase MDA	Male Sprague–Dawley rats	[32]
Berberis vulgaris	Cannabisin G	Whole plant	0.2-1 mg/ml	GPx and SOD activities increased, lowered NO level	GPx, SOD and DPPH assay	[24]
Symplocos racemosa	Symploquinone A, B, C	Bark	100 and 200 mg/kg	Increase glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD), reduce LPO.	Hepatocellular carcinoma rats	[35]
Caesalpinia bonducella	*5-hydroxyvihaticanal*	Whole plant	100 and 200 mg/kg	Reduce lipid peroxidation, increased nonenzymatic antioxidants (GSH), and antioxidant enzymes (SOD and CAT) levels,	Hepatocellular carcinoma rats	[17]
C. lansium (Lour.)	*8-hydroxypsoralen*	Fruits	For DPPH 25, 50, 75 and 100 µg/ml, and for superoxide anion 12.5, 25, 37.5 and 50 µg/ml	Increase DPPH radical and superoxide anion scavenging activity	DPPH and superoxide anion assay	[33]
Artemisia annua L.	*Gentisic acid*	Whole plant	0.50 mg/g dry matter in 80% (v/v)	Reduced lipid peroxidation and DNA damage	2,7-dichlorofluorescein (DCF) assay	[26]

Potential of phytochemicals

Many phytochemicals are found to be the potential one against hepatocarcinoma. Structures of some of the phytochemicals is presented in figure 1. Curcumin was found to induce both mitochondrial and nuclear DNA damage [36]. DNA damage was detected previously through the use of comet assay where DNAs were formed as single strand breaks. From those studies, it was also found that the mitochondrial DNA was more damaged than the nuclear DNA. As a result, hepatoma cells are increased by curcumin [37]. Besides, a natural alkaloid named berberine, which is found in plants was previously used to secure the plasmid DNA by destroying the damaging characteristics and oxidative stress of H2O2 [38]. The DNA damaging events in promyelocytic cancer cells (HL-60) are also found through this single phytochemical [39]. Berberine was also responsible for the demonstration of cell cycle arrest and the death of apoptotic cells in the cancer cells [37].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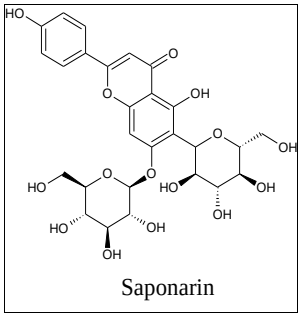
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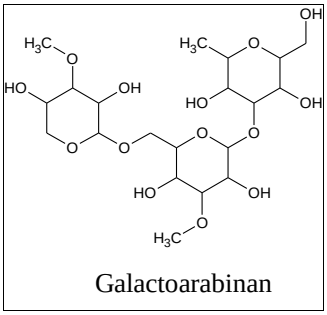
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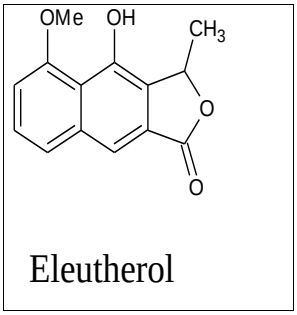
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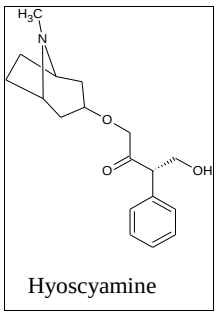
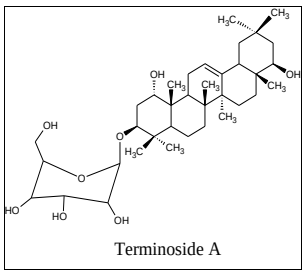
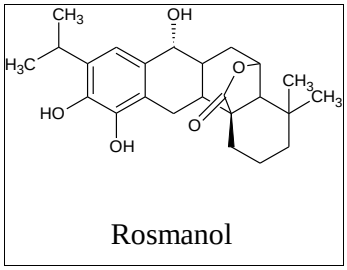
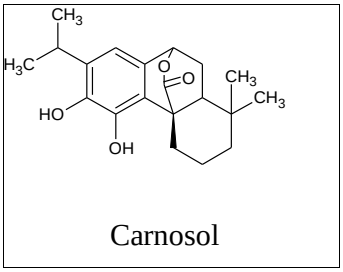
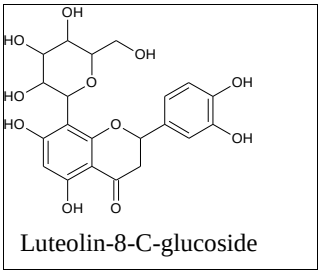
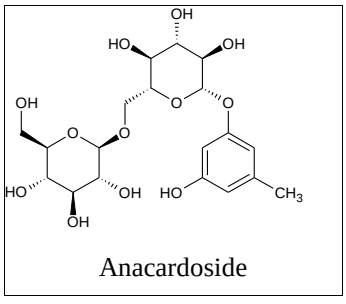

Hyoscyamine

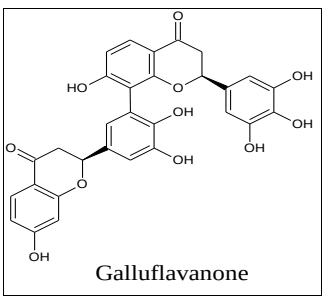

Terminoside A

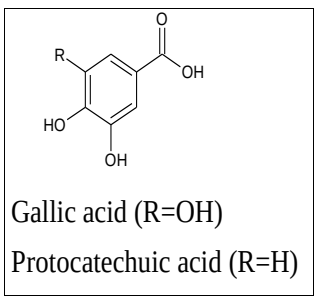

Rosmanol


Carnosol

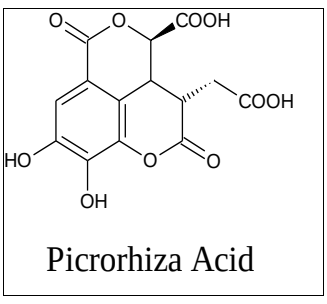

Luteolin-8-C-glucoside


Anacardoside


Galluflavanone


Gallic acid (R=OH)

Protocatechuic acid (R=H)


Picrorhiza Acid

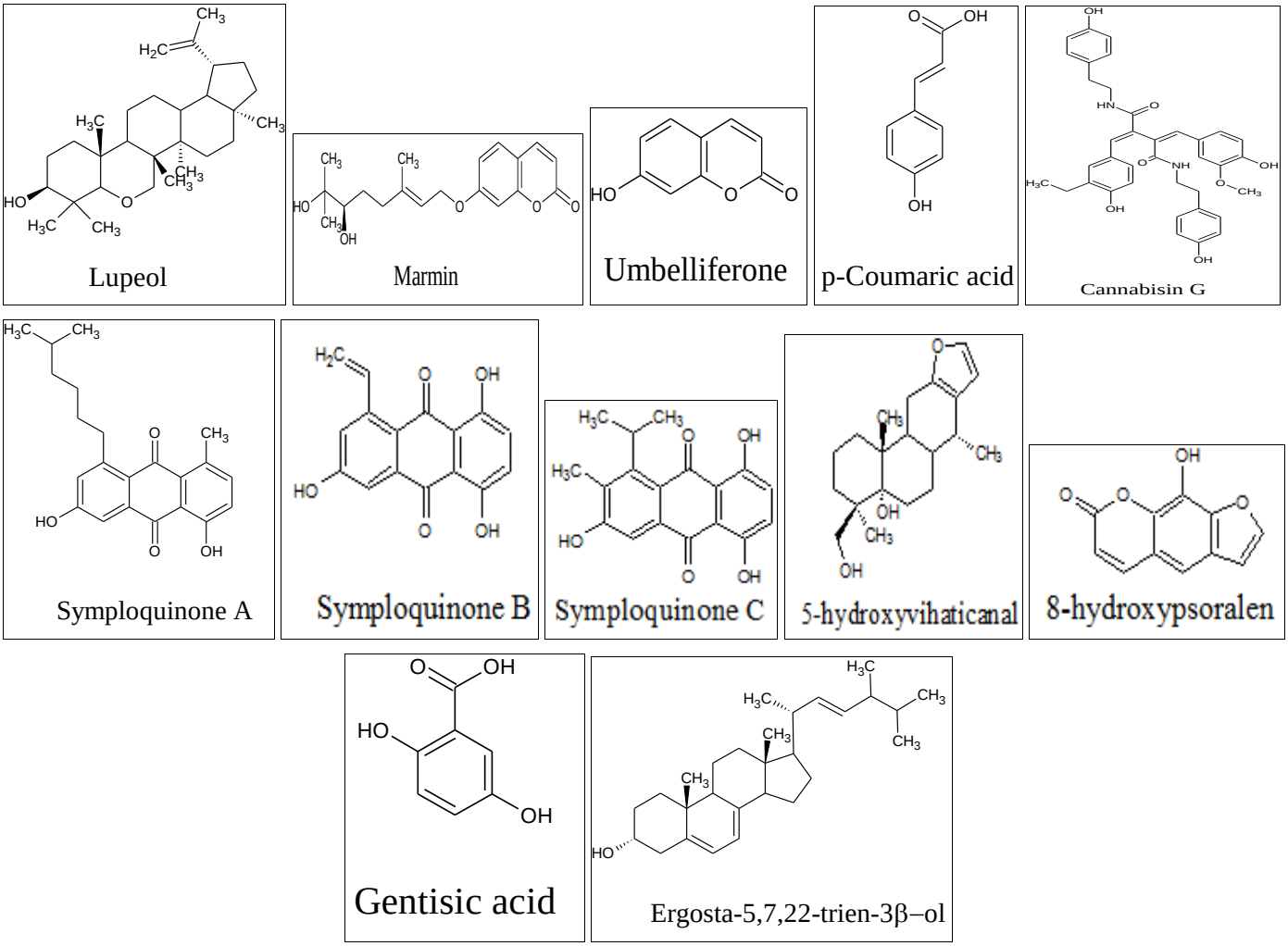


Fig 1: Structures of different phytocompounds

Interaction process of few Phytochemicals

1. Curcumin

Curcumin plays an important role as a phytochemical. Basically, curcumin is a kind of polyphenol found in Curcuma longa plants. The molecular targeting systems and alarming signaling pathways are mainly triggered by the polyphenol of curcumin in order to prevent cancer [40]. From various studies it has been found that the 'inflammatory pathway disorder' increases the risk of cancer growth [41]. There are several pro-inflammatory molecules which are produced and increased by this single inflammation process such as cytokines, ROS, cyclooxygenase (COX-2), transcription factors including nuclear factor κB (NF-κB), protein kinases B (AKT), activator protein 1 (AP1), signal transducer and activator of transcription 3 (STAT3) and so on.

Undoubtedly, all these molecules play an important role in the development of cancer, as these are inflammatory pathways [42, 43]. In this case, curcumin participates in interaction process with the help of some immune mediators through its immunomodulatory characteristics and proves itself as an anticancer drug [40].

2. Campothecin

Camptothecin is known to be a natural alkaloid which is procured from the *Mappia foetida*, *Canzptotheca acirminata*, and many other plant species. It has an antitumor potential and mainly acts upon topoisomerase I, an enzyme responsible for the DNA supercoiling relaxation [44, 45]. Many derivatives of camptothecin are in clinical trial stages. In phase I trial, 20-(S)-9-nitrocamptothecin and 20-(S)-camptothecin were given to 29 and 59 patients having tumor, respectively. These compounds are found to be effective in different patients with skin, prostate, breast, and liver cancer [46].

3. Quercetin

Carbon tetrachloride (CCl_4) directed hepatic carcinoma has been broadly studied in the field of hepatology. The radicals of CCl_3 make covalent interaction with the components of cell and inhibits the secretion of lipoproteins and thus results steatosis. On reaction with oxygen, they lead to the formation of CCl_3-OO, which introduce peroxidation of lipid and results in programmed cell death. Quercetin is known to be a natural flavonoid with various therapeutic effects. It provides protection to the liver against CCl_4-directed liver injury via anti-inflammation and antioxidative stress. The main mechanism responsible behind the protection leads to the inhibition of MAPK (mitogen-activated protein kinases) phosphorylation and Toll-like receptor 4 (TLR4) and Toll-like receptor 2 (TLR2) activation which ultimately directs the NF-*κ*B (nuclear factor kappa light chain enhancer of activated B cells) inactivation and decreases the production of inflammatory cytokines in liver [47, 48].

4. Berberine

The hepatoprotective activity of berberine was investigated in mice which were administered with doxorubicin to induce hepatotoxicity. Berberine pre-treatment remarkably decreases the histologic damages and functional hepatic tests[49].

The mechanism underlying to reduce the hepatotoxicity was also determined in case of CCl_4-directed hepatotoxicity.

Berberine reduces the nitrosamine and oxidative stress and also changes the inflammatory response in the liver. Further, it prevents the increase in peroxidation of lipid and decrease in the activity of superoxide dismutase (SOD) and contributes in the reduction of iNOS, COX-2, and TNF-α level. Decrease in the level of transaminase provide support in relation to the hypothesis, according to which berberine is found to be effective in maintaining the integrity of liver cell membrane [50, 51].

Conclusion

The aim of ethnopharmacological investigation in case of medicinal plants is not limited to find pure isolated compound as a therapeutic drug. Active fraction, extracts or mixture of extracts can be used as an effective drug option. The drugs obtained from plant (either individual or combination) for hepatic diseases are proved to be sufficient in the cure of hepatic diseases caused because of the intake of alcohol, viruses, and chemicals. Effective formulation is needed to be developed by the use of indigenous variety of plants, with all validation in terms of pharmacognostical experimentation and pre-clinical and clinical trials. In order to make plant drugs globally acceptable, the manufacturing of plant-based drugs should be governed properly according to the standard of efficacy or safety.

Conflict of interest

There is no conflict of interests

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