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Review Article

The traditional medicine and phytoconstituents from natural products for liver disease: A review

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ABSTRACT

To combat a variety of liver ailments medicinal plants may serve as a vital source because of presence of pharmacologically active phytoconstituents. It is very interesting to note that there is no drug available in the modern system of medicine for treating hepatic disorders; only certain herbal preparations are available to treat this quite vulnerable disease. A large number of plants with hepatoprotective activity are present but only handful of herbs have such scientific support. Herbal medicines have been used to alleviate liver disorders for many centuries and have currently become a favorable therapy for pathological liver disease.

Keywords: Liver disease, Herb, Hepatoprotective activity

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INTRODUCTION

In the beginning of modern medicine, biologically active agents from plants have played essential role in providing medicine to combat diseases. Medicines derived from plants continue to occupy an important corner in the treatment of disease worldwide¹. In traditional or folk medicine the practices, ideas, beliefs and knowledge not based on scientific evidence is applied to treat, diagnose and prevent disease within a society. It is outlined by culture's knowledge and beliefs and thus is context specific, as are social constructions and negotiations of risk. Modern society when adopts such long existing practices outside of their traditional circumstances, these practices become supportive, alternative or non conventional medicine². With such traditional practice modern medicine may exist side by side, herbal medicines have often continued their popularity for cultural and past reasons. In developed countries such products have become more widely available commercially. In this modern setting, ingredients are sometimes marketed for uses that were never contemplated in the traditional healing systems from which they emerged. An example is the use of ephedra (Ma huang) for weight loss or athletic performance enhancement³. In poor communities traditional medicine has remained the easily approachable and most affordable source of treatment in the primary health care system. The medicinal use of plants is very old⁴. The system of ethno-medicine is safe and is a low cost therapy for treating various ailments. Herbal medicines have been widely used and formed an integral part of primary health

care in India, China, Ethiopia, Argentina and Papua and New Guinea⁵. Traditional Medicines like Ayurvedic, Siddha and Unani are predominantly plant based. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness⁶. According to World Health Organization (WHO), ethno medicine has retained its reputation in all regions of the developing world and its use is rapidly growing in the industrialized countries. Traditional herbal remedies account for 30-50% of the total medicinal consumption in China⁷. In Ghana, Nigeria and Zambia, the first line treatment for 60% of the children with malaria is the use of herbal medicine⁷. With minimum side effects and low cost, people in developing countries like Bangladesh (90%), Myanmar (85 %), India (80%), Nepal (75%), Sri Lanka (65%) and Indonesia (60%) have strong belief in this system of medicine⁸.

LIVER

The largest and most complex internal organ in the body is liver. With the help of its multifarious and several functions, it plays an important role in maintenance of internal environment. Liver is involved in metabolism of fats, carbohydrates and fats in addition liver synthesis number of plasma proteins such as fibrinogen, albumin and in the production of various enzymes, formation and excretion of bile. Some prevalent liver disease is given below:

- ❖ Acute liver disease: the patient is deemed to have acute liver disease if the onset of symptoms does not exceed

six months. Most cases are self-limiting episodes of hepatocyte inflammation or damage, which settle without causing further complications. In some rare cases the damage is so severe that it affects the whole liver leading to acute liver failure. Such rare cases are involved with a high mortality and may require liver transplantation.

- ❖ Chronic liver disease: symptoms of liver disease that persist for more than six months causes chronic liver disease. It occurs when permanent structural changes within the liver occur secondarily to longstanding hepatocyte damage⁹.
- ❖ Drug-induced liver injury is a major health problem that affects not only health care persons but also pharmaceutical industry and drug regulatory agencies. According to the United States Acute Liver Failure study group, more than 50% of acute liver failure is due to drug-induced liver injury, including hepatotoxicity caused by overdose of acetaminophen (39%) and idiosyncratic liver injury triggered by other drugs (13%)⁹. Liver diseases accounts for morbidity and mortality in man and animals all over globe and hepatotoxicity due to drug appears to be the most common contributing factors¹⁰.
- ❖ Hepatitis can be caused by the, mushrooms, parasite like amoebas or giardiasis, drugs, viruses, bacteria. Viral hepatitis is caused by infection with any of at least five distinct viruses, of which the three most commonly identified are hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV)¹¹. In India about 40 poly herbal commercial formulations reputed to be active against liver diseases are being used. From 101 plants having hepatoprotective activity 160 phyto constituents have been reported¹². Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenoids, carotenoids, glycosides, and xanthines. Plant extracts of many crude drugs are also used for the treatment of liver disorders.
- ❖ Nonalcoholic fatty liver disease (NAFLD) presents a spectrum of disorders characterized by the accumulation of fat in the liver. This spectrum covers simple steatosis and lobular inflammation with variable degrees of fibrosis leading to cirrhosis and even hepatocellular carcinoma (HCC)¹³. It is strongly associated with the metabolic syndrome and is the leading cause of chronic liver disease worldwide, with a prevalence of 15%–30% in Western populations¹⁴.
- ❖ Liver fibrosis has emerged as a major health problem. It is the outcome of sustained wound healing response to a chronic liver injury from a variety of causes including, drug induced, viral, metabolic diseases and autoimmune cholestatic. In Hepatic fibrosis there is immoderate production and deposition of extracellular matrix (ECM)^{15, 16}.

Hepatic disorders are extreme pain in right shoulder, ribs and right leg, stiffness in the right arm, discoloration of stool, nausea, yellow-blood like urine, anorexia, jaundice, and heartburns. All these can lead to liver abscess. Jaundice is mainly due to pitta dosha and the symptoms are yellowish color of eyes, skin, nails, face and urine, faded skin color like that of a frog, impaired senses, burning pain in the epigastrium, indigestion, asthenia and anorexia¹⁷.

HERBAL DRUGS AS A THERAPY FOR LIVER DISEASES

The Indian Traditional Medicine like Siddha, Unani and Ayurveda are predominantly based on the use of plant materials. Because of safety, efficacy and cost effectiveness of herbal drugs have gained importance and popularity in recent years. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorder. Scientific evaluation of plants has often shown that active principles in these are responsible for therapeutic success. In spite of the phenomenal advances in biochemical, therapeutic and cellular approaches to many diseases, liver diseases remain confusing today. Liver diseases are among the important diseases affecting humans, there is a lack of effective remedies to treat them satisfactorily. None of the available preparations are specific for liver disorders. In India the indigenous system of medicine has abundant data on drugs available for the treatment of liver disorders. For centuries these drugs have been used and have claimed to offer remarkable relief.

For a wide variety of liver disorders several hundred plants have been examined. Just handfuls have been fairly well researched.

1. *Silybum marianum*:

Since the 16th century (Milk thistle) has been used to treat liver diseases. Its major constituents are the flavonoids; silibinin, silidianin, silichristin, and isosilibinin of which silibinin is the biologically most active compound and used for standardization of pharmaceutical products¹⁸. Silymarin is a strong antioxidant that promotes liver cell regeneration, reduces blood cholesterol, and helps in preventing cancer¹⁹. A number of well-designed experimental studies suggest that through antifibrotic properties silymarin might exert beneficial effects in chronic liver diseases. For example, silymarin interferes with leukotriene formation in Kupffer cell cultures and may thereby inhibit hepatic stellate cell (HSC) activation, which is a crucial event in fibrogenesis²⁰. In alcoholic and non-alcoholic fatty liver and steatohepatitis, drug and chemically-induced hepatic toxicity caused by oxidative stress the antioxidant medicine silymarin is the primary therapeutic modality of choice²¹. As a result of its anti-inflammatory, immunomodulating antioxidative, anti-lipid-peroxidative, antifibrotic, and even liver regenerating effects it has been claimed that silymarin has clinical applications in the treatment of cirrhosis, ischaemic injury, radiation toxicity toxic hepatitis, viral hepatitis and fatty liver²². The marketed preparations of silymarin are capsules or tablets containing ethanol extracted silymarin in amounts of 250–750 mg, and purported to be beneficial for liver diseases. It is typically taken 2–3 times daily but daily dosage varies. In Europe Intravenous preparations of purified Silybinin are approved for therapy of Amanita phalloides mushroom poisoning²³.

2. *Camellia sinensis* (Green Tea):

An inherent herb from southern China is made from the leaves of the plant *Camellia sinensis*. Green tea is composed of active compounds such as catechin, gallic acid, epigallocatechin, epigallocatechin gallate, and epigallocatechin gallate (EGCG) in which EGCG is considered the most therapeutically significant compound. Apart from the use of green tea in acute liver injury and oxidative stress injury, green tea is proved to be useful in preventing Hepatic C Virus (HCV) entry into the liver cells²⁴. Many studies have shown that the polyphenolic fractions isolated from green tea possess anti-inflammatory activity and inhibit oxidant

stress²⁵. In animal models they have been reported to prevent liver toxicity induced by a number of hepatotoxicants like: carbon tetrachloride, acetaminophen and 2-nitropropane. In both diet induced and genetic animal model dietary green tea has also been shown to prevent fatty liver disease²⁶.

3. *Andrographis paniculata*

In Indian systems of medicine it is extensively used as hepatoprotective and hepatostimulant agent²⁷. Very few studies on the effects of crude extracts of *A. paniculata* on liver function are available. Most studies for hepatic effects have been conducted on either andrographolide or other purportedly active principles. Significant choleric effects of andrographolide in anesthetized guinea pigs and in conscious rats have been reported. Protection of andrographolide against acetaminophen-induced reduction in volume and contents of bile was better than that produced by silymarin²⁸.

4. *Glycyrrhiza glabra*

It has been used in traditional medicine to alleviate bronchitis, gastritis and jaundice and is obtained from aqueous extract of the liquorice root (*Glycyrrhiza glabra*). The major constituents are hydroxycoumarins, flavonoids, glycyrrhetic acid and beta-sitosterol, the latter with probable glucocorticoid and mineralocorticoid properties. An established treatment for chronic hepatitis in Japan is a standardised extract containing glycyrrhizin, cysteine and glycine. A daily dose of 80 mg/day given intravenously for 2 weeks normalised elevated aspartate and alanine transaminase²⁹. This preparation is also available over-the-counter in the United States as a powder, tablet and tablet. The protection against various forms of experimental hepatic injury is due to inhibition of activity of 11-beta-hydroxysteroid dehydrogenase, prostaglandin E2 production by macrophages, and antioxidant properties through the induction of catalase and glutathione-S-transferases³⁰. Some evidence points to an antifibrotic effect in the rat CCl₄ model; possibly through inactivation of NFκB³¹. In an open-label trial including 56 patients with subacute liver failure Glycyrrhizin has also been used. Patients were treated for 30 days with glycyrrhizin 100 ml daily followed by an 8-week period with glycyrrhizin administration every other day. With historical controls from the previous 10 years survival was compared and proved to be better in the glycyrrhizin-treated group³². However, the design of this study does not allow clear conclusions with regard to the usefulness of glycyrrhizin in the treatment of advanced liver disease.

5. *Phyllanthus amarus*

The plants of the genus *Phyllanthus* have long been used to treat chronic liver diseases and are found in most tropical and subtropical countries. Several polyphenoles, hypophyllantins and Phyllantins are major constituents of which chemical and pharmacological properties are well described³³. Experimental data indicate through interference with polymerase activity, mRNA transcription and replication some of the active compounds within *Phyllanthus* may exert activity against hepatitis B virus infection³⁴.

6. Liv-52.

Recognized and registered in more than 45 countries, an Ayurvedic supplement, and a well-known herb prescribed by many physicians worldwide. Introduced in 1955, Liv-52 has been studied since then for the treatment of liver diseases such as fatty liver conditions, protein energy malnutrition, alcohol liver disease, pre-cirrhotic hepatitis, and early cirrhosis conditions, elevated liver enzymes, radiation or chemotherapy-induced liver damage³⁵. Liv-52 contains the following herbs: *Terminalia arjuna*, *Cassia occidentalis*, *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, and *Phyllanthus amarus* and is available as tablets and syrup³⁶. According to the manufacturers, during the process there is contact of the ingredients which could result in both individual and collective action on the liver. Apart from occasional complaints of nausea, Liv-52 has not shown any serious side-effects.

7. *Ocimum sanctum*

Ocimum sanctum L. (Labiatae; popularly known as "Tulsi" in Hindi and "Holy Basil" in English). In various traditional and folk systems of medicine, including traditional Chinese medicine, Roman, Siddha, Ayurveda, Unani and Greek Tulsi is known herb which is an important hepatoprotective plant³⁷. The various activities of analgesia, hepatoprotection, hypolipidemia, immunomodulation, anti-diabetes, anti-inflammation, antipyresis, anti-neoplasia and antistress is due to presence of many important phytochemicals³⁸. For the treatment of liver diseases, some studies have shown that the combination use of holy basil and silymarin demonstrated synergistic hepatoprotective activity.

PHYTOCONSTITUENTS FROM PLANTS HAVING HEPATOPROTECTIVE POTENTIAL

Several chemically defined molecules have been isolated from crude plant extracts with proven hepatoprotective activity. A list of these compounds is shown in Table 1 with information on family and part of plants used.

Table 1: Phytoconstituents from plants having hepatoprotective potential

Phytoconstituents	Scientific name	Common name	Family	Part used	Ref
Silymarin	<i>Silybum marianum</i>	Milk thistle	Asteraceae	Ripen seeds	39
Andrographolide and neoandrographolide	<i>Andrographis paniculata</i>	Bhuinimb	Acanthaceae	Leaves & tender shoot	40
Curcumin	<i>Curcuma</i>	turmeric	Zingiberaceae	rhizomes	41
Picoside and kutkoside	<i>Picrorrhiza kurroa</i>	Kutki	Srophulariaaeae	Dried rhizomes	42
coumarinolignoids, cleomiscosins A, B, and C	<i>Cleome viscosa</i>	tick weed	Capparidaceae	seeds	43
Oleanolic acid triterpenic acid	<i>Lantana camara</i>	big-sage	Verbenaceae	weed	44
Ursolic acid	<i>Ocimum basilicum</i>	Basil	Lamiaceae	leaves	44
Berberine	<i>Berberis aristata</i>	Chutro	Berberidaceae	roots, rhizomes and stem bark	45
Saikosaponin C, Saikosaponin b2	<i>Bupleurum marginatum</i> Wall. ex	Jangli zeera	Apiaceae	root	46
Beta-elemene	<i>Curcuma aromatica</i> Salisb	Wild turmeric	zingiberaceae	Root and rhizome	47

Ombuine	<i>Gynostemma pentaphyllum</i>	Sweet tea	cucurbitaceae	Whole plant	47
Wogonin	<i>Scutellaria baicalensis</i>	Baikal skullcap	lamiaceae	roots	48
Monomethyl fumarate	<i>Fumaria indica</i>	fumitory	fumariaceae	Whole plant	49
Kinsenoside	<i>Anoectochilus formosanus</i> Hayata		orchidaceae	Whole plant	50
Acanthoic acid	<i>Acanthopanax koreanum</i> Nakai		araliaceae	Root bark	51
Indigtone	<i>Indigofera tinctoria</i> L.	neel	fabaceae	Aerial parts	52
Anastatin A	<i>Anastatica hierochuntica</i>		brassicaceae	Whole plant	53
Anastatin B	<i>Anastatica hierochuntica</i>		Brassicaceae	Whole plant	53

These compounds can serve as important leads, for the discovery of new drugs in the treatment of liver diseases. However, for many of these compounds, the clinical data are very limited. Clinical efficacy and potential toxicity of active compounds in larger trials requires further assessment, before recommendations concerning their routine use can be identified.

CONCLUSION

The current review provides a detailed and updated description of the most widely used herbal medicine in treatment of chronic liver disease. Herbal drugs can treat various liver ailments by inhibiting oxidative damage, suppressing fibrogenesis, eliminating virus infection, and preventing or inhibiting tumor growth. Herbal medicine has become a major contributor to the treatment of liver diseases. The future of the treatment of liver diseases with herbal medicines depends on our understanding of each and every chemical compound and their interactions with each other. Currently, a handful of herbal drugs, such as *Glycyrrhiza glabra*, *Silymarin* and *Liv52*, have been studied thoroughly. These drugs and the other drugs mentioned in the presented study have shown the scientific community their significance and possible usage as major treatment modalities for liver diseases.

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