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Review Article

Cichorium intybus Linn: its Role in Hepatoprotection

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ABSTRACT
Liver plays a major role in detoxification, metabolism and excretion in the body; any impairment in its function may lead to implication's on one's health. Medicinal plants are now considered to be effective therapeutic aids for various hepatotoxicities. In India there are about 33 herbal formulations and *Cichorium intybus* is one of the significant component of some of these formulations. The ethnobotanical studies have reported the widespread uses of this plant in cardiac injuries, diabetes, hyperlipidemic disorders. It is also used for its anti-fungal and anti-cancer properties. This review focuses mainly on the hepatoprotective ability of *Cichorium intybus* and various scientific studies conducted on it. In Laboratory many chemicals have been known to induce hepatotoxicity in experimental animals like carbontetrachloride (CCl4), galactosamine, thioacetamide, paracetamol, antitubercular drugs, d-galactosamine lipopolysaccharide (GalN/LPS), arsenic etc. Scientific studies conducted were studied and analysed. From various scientific studies it was found that the *Cichorium intybus* is effective in imparting hepatoprotection. Various studies reported on *Cichorium intybus* and its presence in various existing formulations proves its role in hepatoprotection. Further, its various parts like stem, leaves, roots, bark etc can be explored for better hepatoprotection alone or in combination with other plants for developing more efficacious and targeted formulations for the treatment of liver disorders.

Keywords: Liver, Hepatotoxicity, Hepatoprotection, chicory, *Cichorium intybus*

INTRODUCTION

The genus Cichorium (Asteraceae) consists of six species with major distribution areas in Europe and Asia[1]. *Cichorium intybus* L., commonly known as chicory is a erect, usually rough and more or less glandular herb.stems 0.3-0.9m, angled or grooved, branches tough, rigid spreading radical and lower leaves 7.5-15 cm, pinatified, lobes toothed, pointing downwards ,upper leaves alternate[2].The flowers blooms from May to the summer time. The colour of the flowers are deep sky-blue. It is a capitate flower and its diameter is about 3-4 cm, and has a brilliant bluish-purple (sometimes pink or white), radially symmetrical bloom. Flowers are singularly arranged along the length of a fibrous and rigid, dark-green stem. This wildflower has two types of leaves: large-dandelion-shaped leaves near the base of the stem and small lanceolate-to-oblong-shaped leaves along the length of the stem.Cichorium intybus is called as Hindubar, Indyba in arabic**,** Zral in baluchisthan, Chicory in California, Bunk, Chicory in English, Kichora, Kikori in greek, Kasani in gujrathi, Kasni in hindi, Kasani in Persian, Gul, Hand in Punjabi, Kasni, Tsikorie, Kashini virai in tamil, Kasini vittulu in telugu, Kasani in urdu[3]. These various common or local names signifies the widespread use of this plant by different folkloric group. Historically, chicory was grown by the ancient Egyptians as a medicinal plant, coffee substitute, and vegetable crop and was occasionally used for animal forage. In the 1970s, it was discovered that the root of *C. intybus* contained up to 40% inulin, which has a negligible impact on blood sugar and thus is suitable for diabetics[4]. *Cichorium intybus* is cultivated for numerous applications and can be divided into four main varieties or cultigroups according to their use[5]:[1] "industrial" or "root" chicory, predominantly cultivated in northwestern Europe, India, South Africa, and Chile, produces the taproot as a coffee substitute or for inulin extraction;[2] "Brussels" or "witloof " chicory is commonly cultivated around Europe as industrial chicory for etiolated buds (chicons) by forcing;[3] "leaf " chicory is used as fresh or cooked vegetables; and[4] "forage" chicory, initially derived from wild chicory commonly found along roadsides and waste areas, has been used since the mid- 1970s to intensify herbage obtain ability in perennial pastures for livestock. The chicory plant is used in Indian medicine as a tonic, curative in acne, emmenagogue and alexiteric. Its various plant parts have beneficial role in treating liver diseases, enlargement of spleen, as bitter tonic effective in jaundice, liver enlargement etc. This review focuses on the various uses of this plant with specific reference to its hepatoprotective capacity, hepatotoxicity inducing agents, Mechanism of Hepatoprotection, various chemical constituents reported, scientific studies conducted on hepatoprotection in this plant in detail.

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Table 1: Hepatoprotective Activity Of *Cichorium Intybus* Against Various Hepatotoxins.

S.No	Plant part used	Extract	Hepatotoxic agent used.	Dose	Reference
1.	Roots and root callus		CCl_4		Zafar R. *et al* 1998
2	Seed	Alcoholic extract	CCl_4		Ahmed B. *et al* 2003
3	Leaves	Hydroalcoholic extract	CCl_4	50 mg/Kg and 100mg/Kg	Akram Jamshidzadeh *et al* 2006
4	Root extract		CCl_4 and d-Galactosamine	Pretreatment 800mg/Kg/wt	H.upur *et al* 2009.
5	Whole plant	Ethanol	Thioacetamide	25mg/Kg	Madani H. *et al* 2006, 2008
6	Leaves	Ethanol-Water (1:1,v/v)	CCl_4	200, 400, 500 mg/Kg wt.	Sadeghi Heibatollah *et al* 2008.
7	Liv 52 Formulation	petroleum ether, chloroform, butanol and water (in order)	CCl_4	1 mg of water-extractables per 0.2 ml of liver homogenates(3.2 ± 0.31 mg protein).	Piyush Bardhan *et al* 1985.
8	Whole plant	Ethanolic extract	CCl_4		Göknur Aktay *et al* 2000
9	leaves	Methanol extract	CCl_4	250 and 500mg/Kg	A.H. Atta *et al* 2010.
10.	Whole plant	Ethanol extract	Ethanol	300mg/Kg	Joung-Hoon Kim *et al* 2002
11.	Esculatin, a phenolic compound	-	Paracetamol, CCl_4	Esculatin (6mg/Kg wt)	A.H Gilani *et al* 1998.
12	Seeds	Cichotyboside, a new guaianolide sesquiterpene glycoside.	CCl_4		Bahar Ahmad *et al* 2008.
13	Poly herbal formulation Liv 52, Livokin		CCl_4	2.6ml/Kg Wt, 5.6ml/Kg Wt	C.Girish *et al* 2009.
14	Liv 52(Seeds of *Cichorium intybus* 65mg/tablet)	syrup	CCl_4	0.5 ml of syrup	Goel. A. *et al* 1991
15	Livina	A Poly herbal Liquid Formulation	Ethanol	2 ml of syrup	Darbar S. *et al* 2009
16	Liv 52	syrup	Antitubercular drugs	Different doses for children and adults	Original study by SV Dange.
17.	Liv 52(Seeds of *Cichorium intybus* 65mg/tablet)	syrup	Antitubercular drugs	500mg/kg, p.o	Vijaya Padma *et al* 1998).
18	Roots	Aqueous extract	Oxytetracycline	75mg/Kg by gastric tube	Eman G. Helal *et al* 2011
19.	Liv 100	syrup	Antitubercular drugs	400mg/Kg wt	S.D. Saraswat *et al* 1998.
20	Polyherbal Formulation-PHF-A	Powder suspended in distilled water using 1% Sod.CMC.	Antitubercular drugs (Isoniazide and Rifampicin).	200mg/Kg, 400mg/Kg, 600mg/kg	Desai SK *et al* 2011.

Uses: The chicory plant is used in Indian Medicine in fevers, vomiting, diarrhoea and enlargement of spleen. The seeds are reported to be carminative and cordial, and brain tonic and useful in headache and asthma. A decoction of seeds is used in obstructed menstruation and for checking bilious vomiting. The root is used as a carminative, bitter tonic. It is found to be effective in jaundice, liver enlargement gout and rheumatic complaints[6,7]. The root is reported to be stomachic and diuretic. Roasted roots add a bitter mellow taste to coffee and tea or used as a substitute for coffee[8]. Added to coffee, it counteracts with caffeine and helps in digestion. A tea made from chicory is beneficial in upset stomach. In South Africa, although it is considered as a widespread weed, leaves, stems and roots are made into tea for jaundice and chicory syrup is used as a tonic and purifying medicine for infants[9]. In Turkey, an ointment is made from the leaves for wound healing[10]. The ethnobotanical studies have reported the use of leaves in curing jaundice[11,12]; liver disorders[13,12]; vomiting, loose motion, fever and pleurisy[14]. Leaves and roots are used to disperse the swelling of joints[15].

In recent years many researchers have examined the effects of C.intybus roots and seeds on hepatotoxic damages[16,17,18,19], those of its leaf on cardiac injuries[20], diabetic and hyperlipidemic disorders[21], experimental data also reveals its use as anti-fungal[22], post coital contraceptive[23], and anti cancer[24]. This review focuses mainly on the hepatoprotective ability of Cichorium intybus against various hepatotoxicants.

Various Hepatotoxicants and their Mechanism of Induction: Liver is a vital organ and plays a major role in the metabolism and excretion of xenobiotics from the body. Liver injury or liver dysfunction is the major health problem that challenges not only the healthcare professionals but also the pharmaceutical industry and drug regulatory agencies. Chemicals that cause liver injury are called as hepatotoxins, it is reported that more than 900 drugs are responsible for causing the liver injury and it is the most common reason for a drug to be withdrawn from the market. Many chemicals have been known to induce hepatotoxicity, like Carbontetrachloride (CCl_4), galactosamine, D-Galactosamine lipopolysaccharide (GalN/LPS), Thioacetamide, antitubercular drugs, paracetamol, arsenic etc are used to induce experimental hepatotoxicity in laboratory animals.

Carbontetrachloride (CCl_4)- Carbontetrachloride is metabolized in the endoplasmic reticulum and mitochondria by cytochrome P-450 with the formation of an intermediate CCl_3O^-, which is a reactive oxidative free radical, which initiates lipid peroxidation[25,26].

Galactosamine- Galactosamine produces diffuse type of liver injury simulating viral hepatitis. The intensive inflammatory reaction of periportal areas, the proliferation of cholangioles, the appearance of uni- and multicellular necrosis and of Councilman bodies and the lack of fatty infiltration being the most characteristic features[27]. D-Galactosamine-1-phosphate and UDP-galactosamine were identified as the predominant early metabolites of galactosamine in rat liver. The conversion of galactosamine-1-phosphate to UDP-galactosamine is shown to be catalyzed by UDP-glucose: α-d-galactose-1-phosphate uridylyltransferase. Galactosamine treated livers show a high level of this compound explaining in parts the low affinity of this enzyme for galactosamine-1-phosphate. Due to this galactosamine-1-phosphate accumulation is enhanced by the strongly reduced levels of UDPG. Galactosamine-1-phosphate inhibits the UDPG-pyrophosphorylase reaction, the type of inhibition being mainly competitive with glucose-1-phosphate. In the presence of the concentrations of galactosamine-1-phosphate and glucose-1-phosphate found *in vivo* after galactosamine treatment, UDPG-pyrophosphorylases from rat and calf liver are strongly inhibited *in vitro*. By these mechanisms galactosamine-1-phosphate counteracts its own conversion to UDP-galactosamine. The influence of the strongly diminished UDPG levels on the UDPG-linked synthesis of glycogen, heteropolysaccharides and glucuronides as well as the trapping of uridine phosphates by formation of UDP-hexosamines may play an important role in the induction of galactosamine hepatitis[27]. Galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption, Dose of D Galactosamine is 400 mg/kg, intraperitoneally[28].

Thioacetamide: Thioacetamide is a potent hepatotoxicant that is metabolized by Cytp450 enzymes present in the liver microsomes and is converted to a toxic reactive intermediate called thioacetamide S-oxide due to oxidation process[29,30]. Thioacetamide S-oxide induces oxidative stress in the liver cells[31,32]. This intermediate is responsible for the changes in cell permeability, increase intracellular concentration of Ca^{++}, increase in nuclear volume and enlargement of nucleoli and also inhibiting mithochondrial activity which leads to cell death, severely affecting those cells which are located in the perivenous acinar region[33,34]. Moreover, thioacetamide causes the inhibition of mitochondria and eventually liver necrosis[35]. Damage of liver cell is reflected by an increase in the levels of hepato specific enzymes, these are cytoplasmic in section and are released in to circulation after cellular damage[36].

Alcohol: Alcohol consumption causes various liver abnormalities like fatty infiltration, hepatitis and cirrhosis. Increased lipid peroxidation during microsomal metabolism of ethanol is responsible for Hepatitis and cirrhosis. Fat infiltration is a reversible phenomenon that occurs when alcohol replaces fatty acids in the mitochondria. Alcohol induces *in vivo* changes in membrane lipid composition and fluidity, which may eventually affect cellular functions. The underlying mechanisms responsible for effects of alcohol is associated with increase in hepatic lipid peroxidation which leads to alteration in membrane phospholipid composition. Enhanced generation of oxy free radicals during its oxidation in liver causes the effect of ethanol. The peroxidation of membrane lipids results in loss of membrane structure and integrity. These results in elevated levels of γ-glutamyl transpeptidase, a membrane bound enzyme in serum. Ethanol inhibits glutathione peroxidase, decreases the activity of catalase, superoxide

Table 2: Herbal Formulations Containing *Cichorium Intybus* (Kshirsagar Ad *Et Al* 2011)

S.No.	Name of Formulation	Marketing Company
1	Acilvan	Acis laboratories, Kanpur
2	Amlycure	Aimil Pharmaceuticals Pvt. Ltd., Calcutta
3.	Hipex	H. V. Pharmaceuticals, Rajkot (Gujarat)
4.	Liv-52	Himalaya Drugs Co., Bombay
5.	Liv-77	Gobe Pharmaceuticals, Jalandhar City (Punjab)
6.	Livokin	Herbo-Med, Calcutta
7.	Neoliv-100	Bharat Pharmaceuticals, Delhi
8.	Syliv	Systemic Pharmaceuticals, Allahabad
9.	Vimliv	Solumiks, Bombay
10.	G-Liv	Gangakshi Ayur Pharmaceuticals, Uttarakhand.

dismutase, along with increase in levels of glutathione in liver. This decrease in activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase can be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol[37]. The mechanisms underlying alcohol induced liver disease are not clear and several clinical features of alcohol induced damage suggest that autoimmune effector mechanism(s) may be contributing to this damage[38]. Recently, circulating antibodies against Malondialdehyde-Acetaldehyde (MAA) haptenated proteins have been shown to be increased in patients with alcohol induced cirrhosis and hepatitis[39].

Paracetamol: Paracetamol, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. Damage to the liver, or hepatotoxicity, results not from paracetamol itself, but from one of its metabolites, N-acetyl-p benzoquinoneimine (NAPQI) (also known as N-acetylimidoquinone). NAPQI depletes the liver's natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure.

Antitubercular drugs: Tuberculosis is one of the most common diseases in India and has attained epidemic proportions. Tuberculosis and liver are related in many ways. Liver disease can occur due to hepatic tuberculosis or by the treatment with various anti-tubercular drugs. Tuberculosis per se can affect liver in three forms, the most common form is the diffuse hepatic involvement, seen along with pulmonary or miliary tuberculosis. The second is granulomatous hepatitis and the third, much rarer form presents as focal/local tuberculoma or abscess. Antitubercular drugs pose a major problem since they are required to be administered over a prolonged period of time. Adverse effects of antitubercular therapy are sometimes potentiated by multiple drug regimens. Thus, though INH, Rifampicin and Pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is further enhanced. INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P450 leading to hepatotoxicity. Patients on concurrent rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to rifampicin-induced cytochrome P450 enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. Rifampicin shortens plasma half life of AcHz (metabolite of INH) and AcHz is quickly converted to its active metabolites, thus by increasing the oxidative elimination rate of AcHz, there is an increase in the incidence of liver necrosis caused by INH and rifampicin in combination. Rifampicin induces hydrolysis pathway of INH metabolism into the hepatotoxic metabolite hydrazine. It was also observed that some pharmacokinetic interactions also exists between rifampicin and pyrazinamide in tuberculosis patients, when these drugs are administered concomitantly. Pyrazinamide decrease the blood level of rifampicin by decreasing its bioavailability and increasing its clearance. Pyrazinamide, in combination with INH and rifampicin, appears to be associated with an increased incidence of hepatotoxicity[40].

Scientific Studies Conducted on Hepatoprotection: Liver toxicity in experimental animals can be induced by Carbontetrachloride (CCl_4), d-Galactosamine, Paracetamol, alcohol, Thioacetamide, antitubercular drugs, etc. Table 1 enlists some of the scientific studies conducted on Cichorium intybus, which illustrates its role in hepatoprotection against various hepatotoxins.

CONCLUSION

Herbal drugs as hepatoprotective agents provide safety, efficacy, cost effectiveness besides providing protection to the damaged liver from various agents. Allopathic medication alone is not as effective and preferred as compared to the phytotherapeutic approach of modern medication which is more effective, safe and less expensive. Various studies reported on *Cichorium intybus* and its presence in various existing formulations proves its role in hepatoprotection. Further, its various parts like stem, leaves, roots, bark etc can be explored for better hepatoprotection alone or in combination with other plants for developing more efficacious and targeted formulations for the treatment of liver disorders.

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