CICHORIUM INTYBUS LINN: A REVIEW OF PHARMACOLOGICAL PROFILE

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ABSTRACT
The use of natural products as medicinal agents presumably predates the earliest recorded history. Cichorium intybus L is a plant which is used in several traditional medicine systems to cure various diseases. Chicory belongs to the family Asteraceae and is a small aromatic biennial or perennial herb. This plant has been known to possess Anti-ulcer, Hepatoprotective, Antibacterial, Cardioprotective, Antioxidant and Free radical scavenging activities. The phytochemical studies reported in the present review confirm the therapeutic value of Cichorium intybus L. Thus the use of this plant for human and animal disease therapy and reinforce the importance of the ethno-botanical approach as a potential source of bioactive substances.

Keywords: Cichorium intybus L, Plant profile, Medicinal agents, Pharmacological activities.

INTRODUCTION
Cichorium intybus L is an erect perennial herb 80±90 cm in height with a fleshy taproot up to 75 cm in length. The genus Cichorium consists of six species with major distribution areas in Europe and Asia. It is cultivated in countries such as the UK, Belgium, France, The Netherlands, Germany, South Africa, the USA and India. It is also known as common chicory, blue-sailor's succory. It is native to the temperate parts of the Old World and is found wild in India in the Punjab and Andhra Pradesh regions. Chicory also cultivated in Bihar, Gujarat, Himachal Pradesh and Tamil Nadu. Chicory has been successfully cultivated in India since 1918 at Coimbatore and subsequently Nilgiris in Tamil Nadu and at Broach, Amalsad and Jamnagar in Gujarat. Chicory forms flowering shoots and seeds after overwintering. Initially, chicory seed was imported into India, but nowadays it is successfully produced locally. Commercial seed production is undertaken in Jamnur and Kashmir, temperate areas of Himachal Pradesh and some hilly regions of Uttar Pradesh. The agroclimatic conditions of these dry temperate areas are conducive to quality seed production. (Bais et al 2001)

PLANT PROFILE
Chicory belongs to the family Asteraceae, Class Magnoliopsida and is a small aromatic biennial or perennial herb. The whole plant contains a number of medicinally important compounds such as inulin, esculin, volatile compounds, bitter sesquiterpene lactones, coumarins, flavonoids and vitamins. The phytochemical or plant constituents are distributed throughout the whole chicory plant, but the main contents are present in the root. Analysis of fresh roots of chicory gave water 77%, gummy water 7.5%, cellulose, inulin and fibre 9% and ash 7.8%. The bitter substances are lacticin and lactucopicrin esculetin, esculin, cichorin, umbelliferone, scopoletin and 6,7-dihydroxycoumarin from the racemes. The bitter principle is probably a glucoside of fructose and catecholic acid. The presence of stearic, mannites and tartaric acids in the juice of the roots has been reported. Betaine and choline are present in small concentrations. (Saxena et al 2011)

The roots of chicory are brownish yellow outside and white inside, with a thin bark. The root is well developed; the central part is mature and contains a portion of xylem including numerous vessels. The leaves are broadly oblong, oblanceolate or lanceolate, crowded at the base, forming a rosette arranged spirally on the stem. The upper leaves are cordate and amplexicaul; the lower leaves are 7.5±15 cm long and pinnate. The stems are angled or grooved, with spreading branches, bright blue flowers, short pappus and very long, spreading, negativetoodled ligules. The fruits are dry, indehiscent, 3 mm long, 2 mm broad and crowned with a ring of 0.5 mm long pappus which is usually white but sometimes half white and half straw coloured. Maturing fruits are brownish black as well as mottled, whereas those which are fully mature are pale. The seeds inside the fruits are 2.5 mm long and ovoid, with pointed apex, brownish tip and white plano-convex cotyledons. The average weight of 100 fruits is 207 mg. In the transverse section of mature fruits the pericarp consists of an outer single-layered, tangentially elongated epidermis with a thick cuticle on the outside. Numerous epidermal rods of different sizes are deposited on the cuticle. (Bais et al 2001)

Description of different parts of Chicory Plant:
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Stems: The stems are angled or grooved, with spreading branches, bright blue owers, short pappus and very long, spreading-todded ligules.

Fruits: The fruits are dry, indehiscent, 3 mmlong, 2 mm broad and crowned with a ring of 0.5 mm long pappus which is usually white but sometimes half white and half straw coloured.

Geographical Distributions:
Northern and Central Europe, Siberia, Turkey, Afghanistan, North and Central China, South Africa, Ethiopia, Madagascar, India, Australia, New Zealand. (Saxena et al 2001)

PHARMACOLOGICAL PROPERTIES
Antilucre and Antioxidant Activity
Cichorium intybus L (Asteraceae) roots have been extensively used in Ayurveda medicine. It is variously used as a treatment
for gallstones, gastro-enteritis, sinus problems, diabetes and constipation. Antilucre effect of HACI was evaluated in rats by the oral administration of ethanol 95.5% (dose 1 ml/200 gm b. w.) and pylorus ligation method. HACI was administered at the dose of (50mg/kg and 100mg/kg. p. o.) Antilucre activity was assessed by detecting gastric volume, total acidity, free radical scavenging activity, i.e., in the gastric volume in test group as compared with control group. Ranitidine was used as a standard (50mg/kg. p. o.).

Antioxidant activity of HACI has been assessed by using ABTS radical cation decolorization assay. Maximum ulcer reduction was observed at a dose of 50mg/kg. p. o. of HACI, in ethanol and pylorus ligation induced model, producing a protection index of 46.66% and 43.93% respectively, where as Ranitidine produced greater protection index of 59.99% and 68.29% respectively. A significant reduction in volume of gastric juice and acid output was also observed in ulcer induced animals treated with HACI when compared with ulcer control group. Simultaneously, pH of the gastric fluid was increased significantly. The result of study indicates that the antioxidant properties of HACI may contribute to gastro protective activity probably due to its free radical scavenging activity. These results suggest that HACI root extract possess antilucre activity. (Saxena et al, 2011)

Phytochemical and Antibacterial Activity

Chicory (Cichorium intybus L.) belongs to the family Asteraceae and it is a small aromatic biennial or perennial herb. The whole plant contains a number of medicinally important compounds such as inulin, esculin, volatile compounds (monoterpenes and sesquiterpenes), coumarins, flavonoids and vitamins. In the present study, we evaluated the phytochemical analysis for the presence of various secondary metabolites and antibacterial activity of the root extracts of chicory against pathogenic bacteria like gram positive (Bacillus subtilis, Staphylococcus aureus and Micrococcus luteus) and gram negative (Escherichia coli and Salmonella typhi) bacteria by in vitro agar well diffusion method. The hexane and ethyl acetate root extracts of chicory showed pronounced inhibition than chloroform, petroleum ether and water extracts. Root extracts showed more inhibitory action on Bacillus subtilis, Staphylococcus aureus and Salmonella typhi than Micrococcus luteus and Escherichia coli. (Nandagopal et al 2007)

Hepatoprotective Activity

Effect of chicory root extract (CRE) on the triglyceride metabolism in orotic acid (OA)-fed rats was investigated. Liver weights and hepatic triglyceride concentrations were markedly increased by OA-feeding rats. These results were attributed to the significant increase in the activity of hepatic phosphatidate phosphohydrolase (PAP), diacylglycerol acyltransferase (DGAT), and ratelimiting enzymes for triglyceride synthesis. Supplementation of CRE to OA did significantly reduce the hepatic triglyceride concentrations and DGAT activity without affecting PAP activity. Furthermore, OA treatment was significantly decreased plasma triglyceride (TG) and increased hepatic TG concentrations and reduced microsomal triglyceride transfer protein (MTP) activity without diminishing MTP mRNA expression in rats. However, hepatic TG concentration was significantly decreased and MTP activity was also reduced without diminishing MTP mRNA expression in rats fed simultaneously with OA and CRE diet. The hepatocytes in the OA-feeding rats contained numerous largely fat droplets, but CRE feeding prevented the OA-induced fat accumulation. Present study demonstrates that CRE reduces the liver TG accumulation by reduced DGAT and MTP activities without diminishing MTP mRNA expression by OA administration. (Young Cha et al 2010)

Antioxidant and Free Radical Scavenging Properties

The methanolic crude extracts of traditionally used Indian medicinal plants were screened for their antioxidant and free radical scavenging properties using 2,2’-diphenyl-1-picrylhydrazyl (DPPH) assay and compared with the thiobarbituric acid (TBA) method. Free radical scavenging activity was evaluated using diphenyl picryl hydrazyl (DPPH) radicals. The overall antioxidant activity of Cichorium intybus, showed strong free radical scavenging activity with the DPPH method. Phytochemical analysis of plant extracts indicated the presence of major phytocompounds, including phenolics, alkaloids, glycosides, flavonoids, and tannins. The phenolic concentrations in the above plants ranged from 28.66 to 169.67 mg/g of dry plant extract. The tested plant extracts showed promising antioxidant and free radical scavenging activity, thus justifying their traditional use. (Aql et al. 2006)

Cardioprotective effects

The cardioprotective effects of the aqueous extracts of the leaves of Cichorium intybus (CE) have been examined in the ageing myocardium of albino rats. Shade-dried powdered leaves of C. intybus were fed to the ageing animals for 30 days. The effects of CE on malondialdehyde level on taurine, glutathione and catalase activity of the heart have been studied. Ageing caused peroxidative damage, increase in taurine and glutathione levels in the heart. Catalase activity decreased in the ageing myocardium. CE was found to ameliorate the age induced injury and offered protection to the heart from oxidative damage, suggestive of ageing. (Nayemunnisa et al.)

Antidiabetic activity

Anti-diabetic effects of Cichorium intybus in streptozotocin-induced diabetic rats The present study was designed to investigate the hypoglycemic and hypolipidemic properties of an ethanol extract of Cichorium intybus (CIE) which is widely used in India as a traditional treatment for diabetes mellitus. Male Sprague-Dawley rats aged 9 weeks (160-200 g) were administered with streptozotocin (STZ, 50 mg/kg) intraperitoneally to induce experimental diabetes. The Cichorium intybus whole plant was exhaustively extracted with 80% ethanol, concentrated at 40°C using a rotavapor and freeze dried to get powder. Hypoglycemic effects of CIE were observed in an oral glucose tolerance test (OGTT) in which, a dose of 125 mg of plant extract/kg body weight exhibited the most potent hypoglycemic effect. Moreover, daily administration of CIE (125 mg/kg) for 14 days to diabetic rats attenuated serum glucose by 20%, triglycerides by 91% and total cholesterol by 16%. However, there was no change in serum insulin levels, which ruled out the possibility that CIE induces insulin secretion from pancreatic β-cells. In addition, hepatic glucose-6-phosphate activity (Glc-6-Pase) was markedly reduced by CIE when compared to the control group. The reduction in the hepatic Glc-6-Pase activity could decrease hepatic glucose production, which in turn results in lower concentration of blood glucose in CIE-treated diabetic rats. In conclusion, our results support the traditional belief that Cichorium intybus could ameliorate diabetic state. (Pushpraj et al. 2006)

Purification and properties of a second fructan exohydrolase from the roots of Cichorium intybus-1-FEH II (1-fructan exohydrolase, EC 3.2.1.80) was purified from forced chicory roots (Cichorium intybus L. var. foliosa cv. Flash) by a combination of ammonium sulfate precipitation, concanavalin A (Con A) affinity chromatography and anion and cation exchange chromatography. This protocol produced a 70-fold purification and a specific activity of 52 nkat mg⁻¹ protein. The apparent size of the enzyme was 60 kDa as estimated by gel filtration and 64 kDa on SDS-PAGE. Optimal activity was found between pH 5.0 and 5.5. The temperature optimum was around 35°C. No product other than fructose could be detected with inulin as the substrate. The purified enzyme exhibited hyperbolic saturation kinetics with an apparent Kₘ of 58 mM for 1-kestose (Kes) and 64 mM for 1,1-nystose (Nys). The purified 1-FEH II hydrolyzed the β(2,1) linkages in inulin, Kes and Nys at rates at least 5 times faster than the β(2,6) linkages in levan oligosaccharides and levanbiose. Fructose did not affect the 1-FEH II activity but sucrose (Suc) was a strong inhibitor of this 1-FEH II (Kᵢ=5.9 mM). The enzyme was partially inhibited by Na-EDTA and CaCl₂ (1 mM).

Antimalarial activity

Folklore reports described the use of aqueous root extracts of Cichorium intybus (L) as a light-sensitive plant remedy for malaria. Preparative isolation and bioassay against HB3 clone of...
Cichorium intybus was extracted with ethanol 70% and the methanolic extract was very low against A. niger and R. solani. The antimicrobial activity was determined by the disc diffusion method and minimum inhibitory concentration (MIC) against a panel of microorganisms (four bacterial strains, i.e. P. multocida, E. coli, B. subtilis and S. aureus and three fungal strains, i.e. A. flavus, A. niger and R. solanii). The results indicated that seeds extract/fractions was very low in inhibitory effect on the proliferation of lymphocytes in the presence of PHA (SI range 0.01–0.49). A dose dependent inhibitory effect was obtained in the case of D. kotschyi. Treatment of mixed lymphocytes with 0.1–10 µg/ml of C. officinalis (SI range 1.34–1.80) and C. intybus (SI 2.18 and 1.70, respectively) strongly increased the cell proliferation. In conclusion, this in vitro study revealed the capacity of all extracts to enhance the proliferation of lymphocytes after stimulation with the allogenic cells.

Evaluation of Phenolic content

Fresh aerial parts of different chicory varieties: green chicory two red chicory varieties and Witloof or Belgian endive were analyzed by HPLC/DAD/MS. The chromatographic fingerprint was diagnostic for each variety. A monocaffeoyl tartaric acid, chlorogenic acid, and caffeic acid were detected in all the varieties, while cyanidin 3-O-glucoside, delphinidin 3-O-(6′-malonyl) glucoside, and cyanidin 3-O-(6′-malonyl) glucoside were the main phenolic compounds in the red varieties. The flavonoidic compounds, quercetin 3-O-glucuronide and luteolin 7-O-glucuronide, were absent in the Witloof sample. The phenolic compounds from total leaves were the same as those obtained from only the colored parts; nevertheless, the total amount was remarkably lower with a decrease of up to 80% for Belgian endive. Chemical stability at high temperature was observed for the phenolic fraction from the green variety after decoction at 100 °C for 30 min.

Antioxidant, Antimicrobial and Phytochemical Analysis

This study was carried out to evaluate the antimicrobial and antioxidant effectiveness of methanolic extract and different fractions (n-butanol, ethyl acetate, chloroform and n-hexane) of C. intybus seeds. The antimicrobial activity was determined by the disc diffusion method and minimum inhibitory concentration (MIC) against a panel of microorganisms (four bacterial strains, i.e. P. multocida, E. coli, B. subtilis and S. aureus and three fungal strains, i.e. A. flavus, A. niger and R. solanii). The results indicated that seeds extract/fractions of C. intybus showed moderate activity as antibacterial agent. While Antifungal activity of C. intybus seeds extract/fractions was very low against A. flavus and A. niger while moderate against R. solanii. The C. intybus seeds extract/fractions contained appreciable levels of total phenolic contents (50.8-285 GAE mg/100g of Dry plant matter) and total flavonoid contents (43.3-150 CE mg/100g of Dry plant matter). The C. intybus seed extract/fractions also exhibited good DPPH radical scavenging activity, with IC50 ranging from 21.28-72.14 µg/mL. Of the C. intybus seeds solvent extract/fractions tested, 100% methanolic extract and ethylacetate fraction exhibited the maximum antioxidant activity. The results of the present investigation demonstrated significant (p<0.01) variations in the antioxidant and antimicrobial activities of C. intybus seeds solvent extract/fractions.

Flavonoids and sesquiterpenes were subjected to severe water stress; in the second the stress was moderate. Polyphenol content and antiradical activity. Two growing periods were analysed: in the first, the plants were subjected to severe water stress; in the second the stress was absent. The polyphenol content (Folin-Ciocalteu test) was higher in samples from the former than in the latter (about 650 and 420mg of gallic acid/100g fresh sample, respectively), and in any case did not differ between the two growing systems; antiradical activity for the second sampling was higher in the case of the biodynamic system.

Immunomodulatory activity

Chicorium intybus highly appreciated for its bitter taste, were studied to investigate their possible biological activity on fungi from a variety of ecological environments: some are parasites on plants (phytopathogens) or of animals and humans (zoophilic and anthropophilic dermatophytes). The results of the present investigation demonstrated significant (p<0.01) variations in the antioxidant and antimicrobial activities of C. intybus seeds solvent extract/fractions.

Antiinflammatory activity

The inhibition of TNF-α mediated cyclooxygenase (COX) induction by chicory root extracts was investigated in the human colon carcinoma (HT 29) cell line. The ethyl acetate extract inhibited the production of prostaglandin E2 (PGE2) in a dose-dependent manner. TNF-α mediated induction of COX-2 expression was also suppressed by the chicory extract. The results of the present investigation demonstrated significant (p<0.01) variations in the antioxidant and antimicrobial activities of C. intybus seeds solvent extract/fractions.

Antifungal activity

In this work extracts from roots of the common vegetable Cichorium intybus, highly appreciated for its bitter taste, were studied to investigate their possible biological activity on fungi from a variety of ecological environments: some are parasites on plants (phytopathogens) or of animals and humans (zoophilic and anthropophilic dermatophytes). The results of the present investigation demonstrated significant (p<0.01) variations in the antioxidant and antimicrobial activities of C. intybus seeds solvent extract/fractions.

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Analgesic and Sedative activity

Lactucin (1) and its derivatives lactuocopirin (2) and 11 beta,13-dihydrolactucin (3), which are characteristic bitter sesquiterpene lactones of Lactuca virosa and Cichorium intybus, were evaluated for analgesic and sedative properties in mice. The compounds showed analgesic effects at doses of 15 and 30 mg/kg in the hot plate test similar to that of ibuprofen, used as a standard drug, at a dose of 30 mg/kg. The analgesic activities of the compounds at a dose of 30 mg/kg in the tail-flick test were comparable to that of ibuprofen.
Tumor-Inhibitory activity

The crude ethanolic extract of C. intybus roots caused a significant inhibition of Ehrlich tumor carcinoma in mice. A 70% increase in the life span was observed with a 500 mg/kg/day intraperitoneal dose of the tested extract. The aqueous-alcoholic macerate of the leaves of C. intybus also exerted an antiproliferative effect on melanotic melanoma C32 cell lines. Magnolilide, a 1β-hydroxyeudesmanolide isolated from the roots of C. intybus, inhibited several tumor cell lines and induced the differentiation of human leukemia HL-60 and U-937 cells to monocyte or macrophage-like cells. (Hazra et al.)

Anti allergic activity

The aqueous extract of C. intybus inhibited the mast cell-mediated immediate allergic reactions in vitro as well as in vivo. This extract restrained the systemic anaphylactic reaction in mice in a dose-dependent manner. It also significantly inhibited passive cutaneous anaphylactic reaction caused by anti-dinitrophenyl IgG in rats. Other markers of allergic reaction, namely, plasma histamine levels and histamine release from rat peritoneal mast cells, decreased significantly whereas the levels of CAMP increased after the treatment with C. intybus extract. (Kim et al 1999)

Toxicological Studies

Although C. intybus has a long history of human use, the high levels of secondary metabolites have shown potential toxicological effects. To evaluate the safety of the root extract of C. intybus, Ames test and subchronic toxicity assessment were conducted. The sesquiterpene-rich extract was evaluated for potential mutagenic properties (Ames test) using Salmonella typhimurium strains TA97a, TA98, TA100, and TA1535 and Escherichia coli strain WP2uvrA. Though cytoxicity was observed at high extract doses in some strains, mutagenicity was not noted. A 28-day (subchronic) oral toxicity study, conducted in CRL: CD (SD) IGS BR rats, concluded that there was no extract-related mortality or any other signs of toxicological significance. The toxicity evaluation of C. intybus extracts has also been done by Vibrio fischeri bioluminescence inhibition test (Microtox acute toxicity test). This bacterial test measures the decrease in light emission from the marine luminescent bacteria V. fischeri when exposed to organic extracts. The tested extracts showed less than 20% inhibition of bioluminescence and hence were concluded to be safe for human use. (Schmidt et al. 2007)

MISCELLANEOUS ACTIVITIES

The ethanol extract of the roots of C. intybus is reported to prevent the immunotoxic effects of ethanol in ICR mice. It was noted that body weight gains were markedly decreased in mice administered with ethanol. However, the body weight was not affected when ethanol was coadministered with the ethanol extract of C. intybus. Similarly, the weights of liver and spleen were not affected when ethanol extract was given along with ethanol. A considerable restoration in the other markers of immunity, namely, hemagglutination titer, plaque forming cells of spleen, secondary IgG antibody production, delayed-type hypersensitivity reaction (in response to subcutaneous administration of sheep red blood cells to paw), phagocytic activity, number of circulating leucocytes, NK cell activity, cell proliferation, and production of interferon-γ, was registered. The immunomodulating potential of an aqueous-alcoholic extract of the roots was established by a mitogen proliferation assay and mixed lymphocyte reaction (MLR). The extract showed an inhibitory effect on lymphocyte proliferation in the presence of phytohemagglutinin and a stimulatory effect on MLR.

Chicoric acid has shown vasorelaxant activity against nor-epinephrine-induced contractions in isolated rat aorta strips. A pronounced anticholinesterase activity of the dichloromethane extract of C. intybus roots was seen in the enzyme assay with Ellman's reagent. Two sesquiterpene lactones, namely, 8-deoxyxalactucin and lacticopirin, also exhibited a dose-dependent inhibition of anticholinesterase. The methanolic extract displays wound healing effect and β-sitosterol was determined as the active compound responsible for the activity, possibly due to its significant anti-inflammatory and antioxidant effects, as well as hyaluronidase and collagenase inhibition.

CONCLUSION

Worldwide Cichorium intybus has a long tradition use. Historically, chicory was grown by the ancient Egyptians as a medicinal plant, coffee substitute, and vegetable crop and was occasionally used for animal forage. This plant contains high amounts of proteins, carbohydrates, and mineral elements. Inulin from chicory roots is considered as a functional food ingredient as it affects physiological and biochemical processes resulting in better health and reduction of the risk of many diseases.

At present chicory remains an extremely versatile plant, amenable to genetic manipulation, and there is interest shown in genetically engineered chicory to obtain higher yields and create new potentials. The documented indigenous knowledge relating to the various medicinal uses of chicory has been supported by phytochemical isolation and investigations into biological activity. Nonetheless, many of its constituents have not been explored for their pharmacological potential and further research is necessary to gain better understanding of the phytochemicals against various diseases. Toxicological data on C. intybus is currently limited; however, considering that the Asteraceae family is a known source of allergic problems, a contraindication for hypersensitivity should be included in the safety data. Recent studies suggest the use of C. intybus as a biomonitor for heavy metals; considering that chicory enters the food chain, this plant should be used with caution.

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