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Review Article

THERAPEUTIC POTENTIAL OF *CICHORIUM INTYBUS* IN LIFESTYLE DISORDERS: A REVIEW

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ABSTRACT

The genus *Cichorium* (Asteraceae) is comprised six species, widely cultivated in Europe and Asia. *Cichorium intybus* (common name- chicory) is used as a coffee substitute. However, its leaves, flowers, seeds, and roots have been customarily utilized as home grown solution for various ailments since ancient times. Although commercialized as coffee substitute, *C. intybus* is also used in indigenous system of medicine to treat different ailments from wounds to diabetes. Several numbers of chemical constituents of chicory have been identified, and a significant number of these constituents have not been fully investigated for their pharmacological potential. Toxicological information on chicory is also limited. This review targets on the socially imperative medicinal use of chicory in lifestyle disorders. The pharmacological activities of this plant in lifestyle disorders, phytochemical composition (active compounds) isolated from chicory plant with medicinal importance and safety studies are discussed in detail.

Keywords: *Cichorium intybus,* Insulin resistance, Chicory extract, Non-alcoholic fatty liver disease.

INTRODUCTION

The use of natural products, especially of plants origin, for health management is as ancient and universal as medicine itself. The therapeutic use of plants goes back to the Sumerian civilization, and 400 years before the Common Era. It has been recorded that Hippocrates utilized almost 400 diverse plant species for medicinal purposes. Natural products assumed a distinct part in old traditional medicine systems such as, Chinese, Ayurveda, Unani, and Egyptian and are being used even today. The World Health Organization reported that 75% of the world population still depends on plant-based traditional medications for primary health care. Nature has been a source of therapeutic agents for thousands of years, and a large number of modern important medications have originally been obtained from natural sources (vincristine from *Vinca rosea*, morphine from *Papaver somniferum*, Taxol from *Taxol brevifolia, Atropine* from *Atropa belladonna,* etc.) [1]. Lately, the revival of interest in the natural product as a potential hotspot for new solutions has been seen among the academicians and pharmaceutical organizations.

Cichorium intybus L. is a perennial plant with blue or white flowers is easy to grow and can be used for many medicinal purposes (Fig. 1).

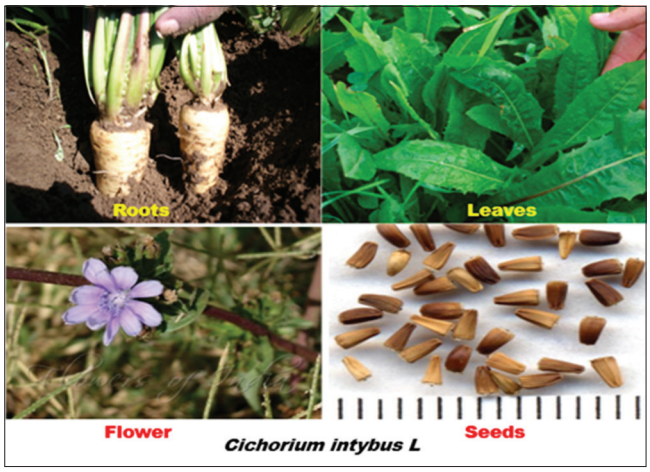

Fig. 1: *Cichorium intybus* L. plant

Cichorium means field and *intybus* are partly derived from the Greek "to cut," because of the leaves, and partly from the Latin *tubus* to indicate the hollow stem [2].

It is best known for the use of its roots as coffee substitute or additives to coffee as it provides bitterness in taste without having any caffeine. Historically chicory had been grown by ancient Egyptians as a medicinal plant, coffee substitute, and vegetable crop and was occasionally used for animal forage. In the 1970s, it was found that root of chicory contained up to 40% inulin, which has a relevant effect on glucose and subsequently is suitable for diabetes [3]. It is an important medicinal herb and has been used in Ayurveda, Unani, and Siddha systems of medicine for the treatment of illnesses of hepatobiliary and renal systems. Oxidative stress plays a key role in the lifestyle disorders such as type 2 diabetes mellitus, obesity, metabolic syndrome, and coronary artery disease. Recent studies have identified several medicinally active constituents in chicory; for example, caffeic acid, caffeoylquinic acid, quercetin, fructooligosaccharides, flavonoids, inulin, and polyphenols. It has been shown to have anti-diabetic [4,5], anti-inflammatory [6], antioxidant [7], and antihepatotoxic activities [8].

Several plants have been described in Unani and Ayurveda for lifestyle disorders. However, only a few systemic and well-designed clinical studies have been carried out to develop an effective herbal product for lifestyle disorders.

The plant grows under the wide range of cultivation conditions, in North West India (Punjab, Kashmir, Andhra Pradesh, Karnataka, Gujarat and Maharashtra), Baluchistan, Belgium, France, Germany, Persia, Netherlands, Switzerland, South Africa, Waziristan, West Asia, and the United Kingdom [9].

THERAPEUTIC POTENTIAL OF *C. INTYBUS* PLANT IN LIFESTYLE DISORDERS

Most of the pharmacological studies on this plant have been carried out on aqueous and/or alcoholic extracts.

Anti-diabetic activity

It has been reported that chicory has anti-diabetic activity. The effect of methanolic extract of *C. intybus* (CME) on glucose transport and adipocyte differentiation in 3T3-L1 cells was studied by radiolabelled glucose uptake and lipid accumulation assays,

respectively. CME exhibited a significant increase in glucose uptake with a dose-dependent response. It also inhibited the differentiation of preadipocytes [10]. The polyphenol-rich fraction of chicory roots possesses a strong hypoglycemic potential probably due to their antioxidant activity [11]. Addition of chicory root extract (CRE)/inulin in diet resulted in decreased absorption of glucose in jejunum [12]. These results also suggested that formulation of chicory (e.g., tea) would be beneficial to healthy people as well as to those with diseases such as diabetes, specifically for post-prandial hyperglycemia by decreasing the intestinal absorption of glucose. The ethanolic extract of *C. intybus* was investigated for its anti-diabetic activity on male Sprague-Dawley rats treated with streptozotocin (STZ). A dose of 125 mg/kg body weight influenced oral glucose tolerance test and the same amount given orally for 14 days reduced serum glucose by 20% and cholesterol by 16%. No change in insulin secretion was observed during the investigation [13]. However, contradictory results were reported by Tousch *et al*. [14]. They found that chicoric acid, the caffeoyl ester purified from chicory, increased glucose transport and insulin secretion, suggesting its clinical application as a drug for type 2 diabetes acting on both insulin sensitivity and insulin secretion. The precise reason for these contrary observations is not well understood.

Aqueous extract of chicory seed has both short term (about 2 hrs; on glucose tolerance test) and long-term effects on diabetes. Chicory may be useful as a natural dietary supplement for lowering the pace of diabetes progression [4]. This observation has also been supported by Kaskoos [5]. They reported that continued administration of *C. intybus* seed extract (500 mg/kg BW, 21 days) produced a sustained anti-hyperglycemic effect in STZ induced diabetic rats. Caffeoylquinic acid-rich extract from chicory seeds improved diet-induced metabolic disturbances like type 2 diabetes [7].

An intra-peritoneal injection of *C. intybus* extract to STZ induced diabetic rats resulted in significant reduction in blood glucose and also reduction in lipid profile and malondialdehyde level and increased the reduced glutathione, superoxide dismutase, glutathione-S-transferase, and catalase activities as compared to the rats treated with STZ alone. These outcomes recommended that the *C. intybus* extract has antioxidant properties and averts diabetes complication by modulation of oxidative stress system [15]. Chicory has the capacity to target hyperglycemia, hyperlipidemia, insulin resistance, nonalcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis simultaneously, possibly via modulation of peroxisome proliferator-activated receptor-alpha/sterol receptor element-binding protein-1 ratio [16].

A clinical study was done on 47 adult healthy volunteers divided into a test group that was given CRE orally and a placebo group that drank barley tea containing 10% coffee (ingesting 300 ml daily for 4 weeks) under a randomized, double-blind, placebo-controlled study. The CRE has ideal impacts including antihyperglycemic and antidyslipidemic impacts and additionally improved the bowel movement. Further, the level of adiponectin was significantly improved in the CRE group when the baseline and post-intervention values were compared [17].

Hepatoprotective activity

The folkloric use of chicory as hepatoprotectant has been well-documented. Ethanolic extract of chicory given orally at doses of 6, 18, and 54 mg/kg BW per day showed a significant hepatoprotective effect by reducing the liver enzymes (aspartate transaminase [AST] and alanine transaminase [ALT]). The results were highly significant at the dose of 54 mg/kg BW per day [18].

An intra-peritoneal administration of methanol and water-extract of chicory to albino rats exhibited marked reduction in liver enzymes [19]. Chicory exhibited a hepatoprotective effect and was highly effective in reducing serum ALT and AST even below the normal values of these enzymes could be obtained upon long-term treatment [20]. In addition, the mixture of *C. intybus* and *Cinnamon zeylanicum* extract has shown beneficial effect in NAFLD patients by lowering the liver enzymes [21]. Chicory is the potential wellspring of antioxidant, phenolics, and alkaloids with strong hepatoprotective impact [22].

The hydroalcoholic fraction of the leaves of *C. intybus* was tried against hydrogen peroxide-induced toxicity in HepG2 cells. The harming impact was restored by hydroalcoholic part of *C. intybus* leaf extract in a concentration-dependent manner [23]. The effect of chicory leaves alone or mixed with dandelion leaves aqueous extract was investigated against CCl_4 induced liver intoxication in Wister albino rats and was found to have hepatoprotective activity with significant lowering of liver enzymes [24]. Dietary intake of the mixture of celery leaves, chicory leaves, and barley grains is hepatoprotective and showed hypolipidemic effects by lowering the liver enzymes and improving the lipid profile in hypercholesterolemic rats [25]. While supporting the traditional belief on the hepatoprotective effect of the *C. intybus* leaves extract, Jamshidzadeh *et al*. [26] also reported hepatotoxic effect at a high concentration of extract (200 mg/kg/BW, i.p in rats).

The ethanolic extract of seeds showed a significant hepatoprotective effect against toxicity induced by CCl_4, which may be attributed to the individual or combined effect of phytoconstituents present in them. This outcome affirmed the fables claim for *C. intybus* L. seeds as hepatoprotective cure [27]. A methanol extract of chicory seeds possesses potent anti-hepatotoxic activity and is one of the main ingredients of *Jigreen,* a commercial product in India used for the treatment of various diseases of the liver [28].

The oral administration of aqueous extracts of roots and root callus of chicory *in* albino rats showed hepatoprotective activity. In addition, histopathological examination of the liver demonstrated no fat accumulation or necrosis after the treatment [29]. CRE to orotic acid-fed rats resulted in reduced liver triglyceride accumulation and microsomal triglyceride transfer protein activities as compared to the control group [30]. The hepatoprotective impact of chicory is likely because of the aversion of lipid peroxidation (LPO), supporting of endogenous antioxidant, and overexpression of genes encoding antioxidant enzymes, thus averting DNA damage. This impact has all the earmarks of being intervened by characteristic antioxidant in chicory roots, which fundamentally reduced the oxidative danger and prompted typical hepatic capacities [31].

Antioxidant activity

Chicory has promising potential to be considered as a natural substance for ameliorating oxidative stress and hepatic injury induced by nitrosamine (sodium nitrite, 0.05% in DW) compounds [32]. Red chicory leaf was assessed for its potential as a natural substitute for synthetic antioxidants for the food and feed industry. It's actively remained stable after lyophilization and reduced LPO of different oils in the Rancimat test. In addition, red chicory extract added to yeast culture before oxidative stress induction exhibited a pleiotropic protective effect on stress-responsive genes [33]. Red chicory was also studied for its polyphenol content and the antioxidant activity by using the synthetic 2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl radical scavenging activity. Total phenolic content is correlated with antioxidant activity in both the synthetic radical scavenging activity and the enzyme-catalyzed reactions (xanthine oxidase, myeloperoxidase, and diaphorase) [34]. Vanadium administered in combination with chicory leaves was very effective in modulating glucose metabolism and antioxidant status in diabetic rats [35]. Chicory leaf extract also showed increased activation of the antioxidant system offering protection to the heart [36].

The water extract of *C. intybus* showed an antioxidative effect on low-density lipoprotein (LDL) and inhibitory effects on the production of thiobarbituric acid reactive substance and the degradation of fatty acids in LDL [37]. A high level of anthocyanins, present in the seeds of *C. intybus,* might exert a direct scavenging effect against reactive oxygen species (ROS) formation due to antioxidant activity [38].

Anti-inflammatory

Alcoholic extracts of *C. intybus* root have showed an anti-inflammatory effect in the treatment of pyorrhea or gingival inflammation [39]. The inhibition of tumor necrosis factor-alpha (TNF-α) mediated cyclooxygenase induction by chicory root ethyl acetate extract was explored in the human colon carcinoma cells. It repressed the synthesis of prostaglandin E2 in a dose-dependent manner [40].

Chicory roots also showed significant dose-dependent anti-inflammatory activity in carrageenan-induced paw edema model. It decreased the serum TNF-α, interleukin (IL)-6, and IL-1 levels which resulted in increase the anti-oxidant activity in paw tissue. This suggested that anti-inflammatory and anti-oxidant activity of chicory roots may be mediated through the inhibition of cytokines [41].

The herbal mixture of *Origanum majorana* and *C. intybus* extract is useful for the treatment of obesity, shown to reduce food intake and body weight, improve lipid profile, liver function and thyroid action in obese rats [42].

Other pharmacologically important activities

Chicory root aqueous extract decreased cholesterol absorption by 30% in the jejunum and by 41% in the perfused ileum [43]. The n-hexane extract of chicory has potent anti-proliferative and cytotoxic activity (anti-cancer) against the Jurkat cells (Human leukemia cell line) [44]. The ethyl acetate extract of chicory root was tested for T-cell stimulating activity of the dendritic cell. At higher concentration it inhibits T-cell stimulating activity of dendritic cells, whereas at lower concentrations alters cytokine secretion toward TH1 pattern. These observations explain the conventional utilization of this plant in the treatment of immune-mediated disorders [45]. A human pilot study suggested that CRE could play a role in the management of osteoarthritis [46]. The chicory coffee consumption for 1 week significantly reduced whole blood and plasma viscosity, along with serum macrophage migration inhibitory factor (MIF) levels [6].

Active compounds present in *C. intybus* plant and their medicinal importance

C. intybus presents a little-investigated plant in terms of phytochemistry and pharmacology. Approximately, 100 individual compounds have been isolated and identified from this plant, a majority of which are from the roots (Table 1).

TOXICITY STUDY

Chicory has been used since ancient time and seems to be safe for human use. About 28 days study on rats aimed at its toxicological

Table 1: Active compounds isolated from *Cichorium intybus*

Chemical constituents	Part used/Type of extract	Medicinal importance	References
Cyanidin 3-O-p-(6-O-malonyl)-D-glucopyranoside	Leaves/metho-H_2O extract	Not stated	[47]
Cichoralexin	Whole plant	Not stated	[48]
Inulin, sucrose, cellulose, proteins	Root/water extract	Dietary fiber as well as prevent inflammation at GI tract	[12]
Esculetin	Chicory plant	Prevents liver damage induced by paracetamol and *CCl_4	[49]
Putrescine, Spermidine, β-Sitosterol, Campesterol, Stigmasterol	Aerial part of chicory	Alpha glucosidase inhibitory activity [50]	[51]
CQA, DCQA and Chicoric acid	Seeds/ethanolic extract	Anti-obesity effect and improve lipid metabolism [52]	[53]
8-Deoxylactucin, 13-dihydrolactucin, Jacquinelin, Crepidiaside B, 3,4β-Dihydro-15-dehydrolactucopicrin, Magnolialide, Ixerisoside D, Loliolide, Cichorioside B, Artesin, Cichoriolide, Cichorioside, Cichopumilide	Leaves/root/ethanolic extract	Analgesic activity [54]	[55,56]
Chlorogenic acid and Caffeic acid	Root/aqueous extract	Ameliorate glucose metabolism	[57]
Delphinidin 3-O-b-d-glucoside-5-O-(6-O-malonyl-b-d-glucoside) and delphinidin 3,5-di-O-b-d-glucoside (Anthocynine)	Flower/methanol extract	Not stated	[58]
Chicosterol	Chicory seeds/ethyl acetate extract	Not stated	[8]
Kaempferol-3-O-1--d-glucopyranosyl-3-O-1--d-glucopyranoside	Chicory/butanol extract	Anti-ulcerogenic property	[59]
Lactucin and Lactucopicrin	Root/ethanol extract	Anti-malarial and analgesic activity	[60]
Volatile compounds (monoterpenes and sesquiterpenes), Coumarin etc.	Root/ethyl acetate/ n-hexane extract	Antibacterial activity against Gram-positive and Gram-negative bacteria	[61]
Caffeic acid, Chlorogenic acid	whole plant	Increase glucose uptake and increase secretion of insulin	[14]
Hydroxy cinnamic acid	Leaves extract	Anti-oxidant and antidiabetic properties	[10]
Anthocynine, Vitamin A and C as well as potassium, calcium and phosphorus	Leaves	Hepatoprotective, hypoglycaemic, diuretics	[62]
Chicoric acid	Leaves	Stimulate immune system, Anti-inflammatory, Anti-bacterial	[36]
Caffeoylquinic acid, Dicaffeoylquinic acid, Chicoric acid	Seeds, peels, roots and leaves/etanolic extract	Anti-oxidant activity	[63]

Contd...

Table 1: Contd...

Chemical constituents	Part used/Type of extract	Medicinal importance	References
*CQA, DCQA	Seeds/ethanolic extract	Improve glycemic, Atherogenic index and Antioxidant status	[7]
Chicoric acid, Cinnamic acid and Caftaric acid (trace)	Seeds/aqueous extract	Amelioration of diabetes and *NAFLD	[16]
Caffeic acid, Quinic acid, Caffeoylquinic acid, Caftaric acid, Quercetin-, Kaempferol, 5-O-feruloyquinic acid, Dicaffeoyltartaric acid (chicoric acid), Cyanidin, 4-O-feruloyquinic acid, Apigenin-7-O-glucoside, Chrysoeriol-3-O-glucoside, -Dicaffeoylquinic acid, Myricetin-7-O-(600-O-malonyl)-glucoside, Dimethoxycinnamoyl shikimic acid, Kaempferol-3-O-sophoroside, Isorhamnetin-7-O-glucoside, Chlorogenic acid, Malic acid	Leaves/methanolic extract	Caffeic acid and cinnamic acid ameliorate glucose metabolism[31] Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism [64]	[65]
Oxalic, Succinic, Shikimic and Quinic acids	Leaves/aqueous extract	Inhibit virulence - of oral pathogens including *Streptococcus mutans, Actinomyces naeslundii* and *Prevotella intermedia*	[39]
(7S, 8R)-3O-Demethyl-, dehydrodiconiferyl alcohol-3-O-β-glucopyranoside, 3,5-Crepidiaside A	Root	Not stated	[66]
Chicoric acid	Aerial part of chicory/ hydro-alcoholic extract	Anti-hyperglycemic effect due to enhance the insulin release and glucose uptake	[67]

*CCl_4: Carbon tetra chloride, CQA: 5-Caffeyolquinic acid, DCQA: Dicaffeyolquinic acid, NAFLD: Nonalcoholic fatty liver disease

evaluation showed that CRE had no mutagenic activity in Ames test as well as in clinical observations, body weight, food consumption, clinical pathology, gross necropsy, and histology. This study confirmed that there was no toxic or adverse effect of orally administered CRE [68]. The leaves extract did not show any toxic effect at acute and sub-chronic toxicity level and was found to be free of any cytotoxicity towards rats [69]. Chicory extract is generally regarded as safe by FDA and has been included in the 'Everything Added to food in the United States' (EAFUS) list. However, the edibility of the chicory seeds and the possible toxicity has yet to be fully established.

CONCLUSION

C. intybus is a coffee substitute and its leaves, flowers, seeds and roots are traditionally used as herbal medicines since ancient times. Pilot studies have shown that CRE is beneficial in osteoarthritis [46] has antithrombotic and anti-inflammatory effects [6] and is beneficial in non-alcoholic fatty liver disease [25]. Experimental studies on *C. intybus* seed extract in animal models showed hepatoprotective, antioxidative, antithrombotic, and antidiabetic properties. However, no systematic clinical study has been conducted to elucidate the role of chicory seeds in different disorders. The documented indigenous knowledge relating to various medicinal uses of chicory has been supported by phytochemical isolation and investigations of its biological activities. Nonetheless, many of its constituents have not been fully explored for their pharmacological potential and further research is necessary to gain the better understanding of the phytochemicals and mechanism of their action against various diseases. There is a lack of established Allopathic medicines for prevention of common lifestyle disorders. The inclusion of the plant in therapeutic regimen may be beneficial in developing a holistic approach involving indigenous and Allopathic systems for management of lifestyle disorders.

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