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MEDICINAL IMPORTANCE OF CHICHORIUM INTYBUS - A REVIEW

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ABSTRACT

Chicory (*Cichorium intybus* L.) is a perennial herb from the *Cichorium* genus, *Asteraceae* family, and is worldwide cultivated. The aim of this review is to consolidate the nutritional composition and bioactivity of the chicory plant, describe its health beneficial properties and demonstrate *Cichorium intybus* L. plant as a potential food ingredient. Cichoric acid was found to be the main component of the methanolic extract from C. intybus L. Aliphatic compounds and their derivatives are the main fraction, with terpenoids slightly less abundant in the plant Further more, this review collects literature regarding the relationship between nutritional components and their health-related bioactivity, which is the main point of food functionality. 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%. However, further studies, including in vitro and in vivo studies, are needed to confirm this antiviral property of chicory.

KEYWORDS: Chicory, Xylem, Bilirubin, Periocular, Infusion.

INTRODUCTION

Chicory (*Cichorium intybus* L.) is a perennial herb from the *Cichorium* genus, *Asteraceae* family, and is worldwide cultivated. The origin of this species is Europe (Mediterranean region), but it also may be cultivated in all other temperate regions and semi-arid areas (mid-Asia, northern Africa, eastern USA, Australia).[1] Chicory has rich nutritional composition and is potentially a rich source of bioactive substances for human food fortification: inulin, sesquiterpene lactones (especially lactucin, lactucopicrin, 8-deoxy lactucin, guaianolid glycosides, including chicoroisides B and C, sonchuside C), caffeic acid derivatives (chiroric acid, chlorogenic acid, isochlorogenic acid, dicaffeoyl tartaric acid), fats, proteins, hydroxycoumarins, flavonoids, alkaloids, steroids, terpenoids, oils, volatile compounds, vitamins (α-tocopherol, γ-tocopherol), β-carotene, zeaxanthin and minerals.[1,2] In addition to its important nutritive profile, chicory shows many types of biological activity: hepatoprotective, anti-inflammatory, antioxidant, sedative, immunological, cardiovascular, hypolipidemic, antidiabetic, anticancer, gastro-protective, antimicrobial and many others**.**

The importance of plant composition information is reflected in the ability to evaluate the intake of nutrients by consuming chicory enriched food products.**[1,3]**

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.

Scientific classification

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Family: Asteraceae
- Genus: Cichorium
- Species: Cichorium *intybus* L

PHYTOCHEMICAL CONSTITUENTS

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 lactucin and lactucopicrin esculetin, esculin, cichoriin, umbelliferone, scopoletin and 6,7-dihydroxycoumarin from the racemes. The bitter principle is probably a glucoside of fructose and catechuic acid. The presence of stearin, mannites and tartaric acids in the juice of the roots has been reported. Betaine and choline are present in small concentrations.

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 pinnatied. The stems are angled or grooved, with spreading branches, bright blue flowers, short pappus and very long, spreading, negative toddled 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 epicuticular rods of different sizes are deposited on the cuticle.[1,4]

DESCRIPTION OF DIFFERENT PARTS OF CHICORY PLANT

Roots: The roots of chicory are brownish yellow outside and white inside, with a thin bark. It is well developed; the central part is mature and contains a portion of xylem including numerous vessels.

Leaves: 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 long and pinnate.

Stems: The stems are angled or grooved, with spreading branches, bright blue owers, short pappus and very long, spreading,-toddled 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 America, South Africa, Ethiopia, Madagascar, India, Australia, New Zealand.[4]

TRADITIONAL USES

Historically, chicory was grown by the ancient Egyptians as a medicinal plant[5] and it has had a long history of therapeutic use both in areas where it is indigenous and in areas where it has been introduced. The various common or local names describing this plant may be ascribed to the widespread use by different folkloric groups.

Different preparations of this plant are employed to treat various symptoms and ailments . The juice is said to be a folk remedy for cancer of the uterus and for tumors.[6] In South Africa, although it is considered a widespread weed,leaves, stems, and roots are made into a tea for jaundice and chicory syrup is used as a tonic and purifying medicine forinfants.[7] In Turkey, an ointment is made from the leaves for wound healing.[8]

Prior to the wars in Afghanistan, folkloric reports described the use of aqueous root extracts as a light-sensitive plant remedy for malaria. The flowers of the chicory plant (*Cichorii flos*) are used as a herbal treatment of everyday ailments such as a tonic and appetite stimulant and as a treatment of gallstones, gastroenteritis, sinus problems, cuts, and bruises.[6,9] In Italy, the whorls are made into a decoction and used as a depurative.[10] Chicory seeds are one of the main ingredients of *Jigrine*, a commercial product of India used for the treatment of various diseases of the liver.[11] Other plant parts are also used for liver disorders, namely, aerial parts in Bosnia and Herzegovina[12] and roots in Serbia and India.[13, 14]

BOTANICAL CHARACTERISTICS

Cichorium intybus L. is an annual, biennial or perennial plant belonging to the family Asteraceae (formerly: Compositae).[15] It is winter hardy and usually reaches 20 to 150 cm in height. It forms a long and strong, spindly, thick, brown tapio root. The stem and vein are usually green, although they can take on an occasional red ring. Cichorium intybus can grow from many tall, empty, ribbed stems, each of which can be lifted or rising. It is stiff and has few leaves. At the bottom of the stem there are short, thick hairs, and at the top there are most branches. The buds are branched, stiff and contain no juice. The leaves of C. intybus are green, arranged in a 10–25 cm long rosette. Their shape is narrowly oval, oblong, lanceolate, usually pinnate or serrated. The leaf hair may be present on the lower side of the leaf, mainly on the nerve, on the whole leaf surface or be absent at all. The lower leaves are caudal, with a very wide top segment, while the side segments are triangular, with the apex facing the base of the leaf. The leaves of the stem are green with gray shades,oblong, lanceolate, with an arrow or heart shaped base. The edges are serrated, with teeth decreasing towards the top of the leaf. The upper leaves are whole on the edges and on the surface ciliate. The inflorescence of C. intybus L. consists of numerous, multi-flower anthodiums 2–4 cm in diameter, set on short, thick peduncles either singly or gathered in groups of several people. The color of the marginal flowers is light blue, while the central tube flowers are darker. The flowers open only on sunny days. They are particularly rich in nectar and pollen. The chichory plant gives a light brown shell 2–3 mm long, triangular or pentagonal with short pappus hairs. The stalk is topped with a circle of scales in the upper part. C. intybus grows wild across the temperate climate zone of Europe, southwest Asia, in the Ural and in north Africa.

CHEMICAL COMPOSITION

All morphological parts of chicory (roots, herb, flowers and leaves) contain a large number of various chemical

compounds. Cichoric acid was found to be the main component of the methanolic extract from C. intybus L. Aliphatic compounds and their derivatives are the main fraction, with terpenoids slightly less abundant in the plant. Roots of chicory contain, amongst others, sap, sesquiterpene lactones, such as e.g., germacranolides (lactucin, substitutes, pectins, vitamins B and C.[16,17] Chicory leaves contain inulin, A, B1, B2 and C vitamins, Ca, K, Mg, Na, Fe, Cu, Mn, Zn, phenolic bring about the perianth's blue color.[18] Also present in the plant are: gum, choline, phytosterols, mucus, tannins, copper, latex, lipids, proteins, P and K vitamins, amino acids, -sitosterol, malic acid, oxalic acid, shikimic acid, quinic acid, succinic acid, tannins, saponins, flavonoids, terpenoids, cardiac glycosides, anthocyanins.[19] Essential oils have a large spectrum of activity, especially antiparasitic and antimicrobial. In the available literature, no results were found on the study of the properties of essential oils isolated from chicory.

CHICORY: A MULTI-PURPOSE CROP FOR LIVESTOCK

Chicory is a perennial, deep-rooting herb that can be found as a wild plant in natural grasslands and roadsides and as cultivated varieties in most temperate areas of the world, including Northern Europe.[20,21] In some European, Asian and Middle Eastern countries, chicory has traditionally been used for human consumption and as a medicinal plant to treat several diseases, including malaria and digestive, liver and urinary disorders.[22, 23] Based on its current applications, cultivated chicory can be classified in four types[23]: (i) industrial or root chicory used for the production of inulin-type fructans and as coffee substitute; (ii) Brussels or witloof chicory, for production of etiolated leaves ("chicons"); (iii) leaf chicory for human consumption (fresh salad or cooked); and (iv) forage chicory for animal feeding. In the 1980s, selection of chicory for livestock feeding resulted in the release of the first commercial forage variety, "Grasslands Puna".[24] Since then, several forage chicory cultivars have been developed. The use of chicory diets in livestock nutrition has been previously reviewed

PHARMACOLOGICAL PROPERTIES

Health-Promoting Properties

Fresh and dried material is the most commonly used for medicinal purposes. It is one most important therapeutic plant which belongs to family Asteraceae.[25]

Antiviral Properties

The extracts of Cichorium intybus L. showed great anti viral activity against HSV-1and partial activity against adenovirus at higher concentrations.[26] In the study Zhang et al., the anti-hepatitis B property of cichoric acid was evaluated by the D-galactosamine (D-GalN)-induced normal human HL-7702 hepatocyte injury model, the duck hepatitis B virus (DHBV)-infected duck fetal hepatocytes and the HBV-transfected cell line HepG2.2.15 cells, respectively. This study verifies the anti-hepatitis B effect of cichoric acid from C.intybus leaves, therefore cichoric acid could be used to design the antiviral agents.[27] Since the outbreak of the coronavirus disease (COVID-19) caused by SARS-CoV-2 in December 2019, there has been no vaccine or specific antiviral medication for treatment of the infection where supportive care and prevention of complications is the current management strategy using a molecular docking method investigated the potential of using medicinal plants in alleviating the novel SARS-CoV-2 infection. A database comprising more than 16,000 compounds was compiled and docked against the crucial viral proteins; 3-chymotypsin protease (3CLpro), papain-like protease (PLpro) and RNA-dependent RNA polymerase (RdRp) to find potential inhibitors for these enzymes.Nevertheless, chicory was among the plants with potential against SARS-CoV-2.[28]

Reproductive effect

The effect of aqueous extract of chicory on offspring sex ratio in rat was studied. All rats in experimental groups 1 and 2 were ip injected with either 1.0 or 0.7 g/kg body weight (LD50 = 2.244 g/kg) of an aqueous extract of chicory leaves for 30 days at 72 h intervals. After the 8th injection, blood pH, and Na+, K+, Ca2+ and Mg2+ serum levels, were measured in all groups. On day 30, all the rats were mated within and between groups. The results revealed that in comparison with the control group, there were significant increases ($p < 0.01$) in Na+ and K+ levels, as well as the sex ratio of male to female offspring (10.23%).[29]

Hypoglycemic and hypolipidemic effects

The hypoglycemic and hypolipidemic properties of an ethanolic extract of *Cichorium intybus* (CIE) was studied in rats. Male Sprague-Dawley rats aged 9 weeks were administered with streptozotocin (STZ, 50mg/kg) intraperitoneally to induce experimental diabetes. The *Cichorium intybus* whole plant (CIE) was exhaustively extracted with 80% ethanol. Hypoglycemic effects of CIE were observed in an oral glucose tolerance test (OGTT). A dose of 125 mg of plant extract/kg bw 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 induced insulin secretion from pancreatic beta-cells. In addition, hepatic glucose-6-phosphatase activity (Glc-6-Pase) was markedly reduced by CIE when compared to the control group. The authors concluded that 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.[30]

Antibacterial Properties

Chicory plant was active against gram positive and negative bacteria and yeast. C.intybus extracts inhibits Agrobacterium radiobacter sp. tumefaciens, Erwinia

carotovora, Pseudomonas fluorescens, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis, Bacillus thuringiensis, Bacillus subtilis, Salmonella typhi, Micrococcus luteus, Candida albicans, Klebsiella pneumoniae, Enterobacter cloacae and Streptococcus pyogenes.[31,32] The authors of this study suggested that the medicinal plant has significant antibacterial activity and can utilize for the treatment and control of bacterial infections.[33]

Anti-Protozoal and Antiparasitic Properties

C. intybus is a plant with great potential against parasites, both in the context of livestock and humans.[34] This plant synthesizes several bioactive compounds with potential antiparasitic activity, but most studies have been devoted to the role of sesquiterpene lactones (SL). Woolsey et al. demonstrated the efficacy of chicory leaf and root extracts against Cryptosporidium parvum, with the lower SL extract (leaf) showing greater inhibition. Based on the results, the authors suggest that the antiparasitic activity does not appear to be related only to the SL content.[35] Marley et al. conducted a study on lambs that acquired parasites by natural transmission. The effects of chicory on total helminth parasites showed that this forage reduced the number of adult abomasal helminth parasites in lambs.[36]

Hepatoprotective Properties

The hepatoprotective properties of extracts from various morphological parts of C.intybus have been confirmed in recent years by many authors.[37] One study, which used mice with liver previously damaged with acetaminophen and carbon tetrachloride, demonstrated, that application of a aqueous- and methanolic chicory seed extract to the animals lowered their mortality, as well as serum levels of alkaline phosphatase (AP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Analogous results were obtained for alcoholic extracts of seeds and aqueous extracts of root and root callus–biochemical parameters, as e.g., elevated bilirubin levels, of treated animal health improved, and histological procedures confirmed significant alleviation of liver damage. A number of liver damage markers, including low levels of superoxide dismutase, glutathione peroxidase, catalase and high levels of liver enzymes, were alleviated with a chicory-containing diet. Asadi et al. induced oxidative stress in rat liver with methotrexate . This resulted in dramatic reduction in the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and a significant increase in the levels of total bilirubin (TB) and malondialdehyde (MDA).[38]

Anti-inflammatory effect

Ethyl acetate chicory root extract produced a marked inhibition of prostaglandin E2 (PGE2) production in human colon carcinoma HT29 cells treated with the pro-inflammatory agent TNF-alpha. Two independent mechanisms of action were identified.[39] a drastic inhibition of the induction by TNF-alpha of cyclooxygenase 2 (COX-2) protein expression and[40] a direct inhibition of COX enzyme activities with a significantly higher selectivity for COX-2 activity. The inhibition of TNF-alpha-dependent induction of COX-2 expression was mediated by an inhibition of NF-kappaB activation. A major sesquiterpene lactone of chicory root, the guaianolide 8-deoxylactucin, was identified as the key inhibitor of COX-2 protein expression present in chicory extract. A placebo-controlled, double-blind, dose-escalating trial, was conducted to determine the safety and tolerability of a proprietary bioactive extract of chicory root in patients with osteoarthritis (OA). The results of the pilot study suggested that a proprietary bioactive extract of chicory root has a potential role in the management of OA .Only one patient treated with the highest dose of chicory discontinued treatment due to an adverse effects.[41]

Wound healing effect

Wound healing activity of the aerial parts, leaves, and roots as well as ashes of either leaves or roots were studied in rats. Subsequently, roots of the plant were submitted to further detailed investigations. The wound healing activity of the methanolic extract, its subextracts, and fractions were evaluated by using *in vivo* linear incision and circular excision wound models in rats. The hydroxyproline content of the tissues treated with extracts was also assessed for the activity evaluation. Moreover, in order to find out a possible involvement of antioxidant activity in wound healing, the test samples were also investigated by DPPH radical scavenging activity and total phenolic concentration were also determined. Additionally anti-inflammatory activity was assessed based on the inhibition of acetic acid-induced increase in capillary permeability. Through the bioassay guided fractionation one compound was isolated and its structure was elucidated by spectroscopic methods. For the determination of the activity mechanisms, the fractions were screened for hyaluronidase, collagenase and elastase enzyme inhibitory activities. Methanolic extract of *Cichorium intybus* roots was found to possess potent wound healing activity. When this extract was subjected to successive solvent extraction with n-hexane, dichloromethane (DCM), ethyl acetate and n-butanol. DCM subextract was found to be the most active one and through chromatographic techniques DCM subextract was fractionated into several fractions and β-sitosterol was determined as the active compound responsible for the activity.[42]

Analgesic and sedative effects

Lactucin, lactucopicrin, and 11β, 13- dihydrolactucin (30mg/kg dose) induced analgesic effects in mice by hot plate and tail-flick tests. All three compounds exerted an analgesic effect in the hot plate test, lactucopicrin appeared the most potent. In the tail-flick test, the antinociceptive effects of all the tested compounds

(30mg/kg dose) were comparable to that of ibuprofen (60mg/kg dose). Lactucin and lactucopicrin were also exerted sedative action as evident from the decreased spontaneous locomotor activity in mice.[43]

Gastroprotective effect and maintenance of gastrointestinal health

The aqueous decoction of *Cichorium intybus* roots showed 95% inhibition of ulcerogenesis when orally administered to Sprague-Dawley rats 15 minutes before the induction of ulcerogenesis by ethanol.[44] The antioxidant, cytoprotective, and antiproliferative activities, of extracts of the whole leaf or only the red part of the leaf of Treviso red chicory (*Cichorium intybus* L.) (a typical Italian red leafy plant) in various intestinal models, such as Caco-2 cells, differentiated in normal intestinal epithelia and undifferentiated Caco-2 cells. The results show that the whole leaf of red chicory can represent a good source of phytochemicals in terms of total phenolics and anthocyanins as well as the ability of these phytochemicals to exert antioxidant and cytoprotective effects in differentiated Caco-2 cells and antiproliferative effects in undifferentiated Caco-2 cells. Compared to red chicory whole leaf extracts, the red part of leaf extracts had a significantly higher content of both total phenolics and anthocyanins. The same extracts effectively corresponded to an increase of antioxidant, cytoprotective, and antiproliferative activities.[45]

Pancreas protective effect

Five intraperitoneal injection of cerulean (50 µg/ kg at 1 h intervals) in mice resulted in acute pancreatitis, which was characterized by edema, neutrophil infiltration, as well as increases in the serum levels of amylase and lipase in comparison to normal mice. Different doses of *Cichorium intybus* root (CRE) and aerial parts hydroalcoholic extract (CAPE) orally (50, 100, 200 mg/kg) and intraperitoneally (50, 100, 200 mg/kg) were administrated 1.0 and 0.5 h respectively before pancreatitis induction on separate groups of male mice (n=6). Control groups treated with normal saline (5 ml/ kg) similarly. Both extracts in greater test doses (100 mg/kg and 200 mg/kg, ip) were effective to decrease amylase (23-36%) and lipase (27-35%) levels. In oral route, the dose of 200 mg/ kg showed a significant decrease in levels of amylase (16%) and lipase (24%) activity while the greatest dose (200 mg/kg, ip) was only effective to diminish inflammatory features like edema and leukocyte infiltration in pancreatitis tissue ($P<0.01$).[46]

Effect on the Immune System

C. intybus is a medicinal plant commonly used in traditional medicine for its benefits in immune-madiated disorders. There are several evidences showing that C. intybus can modulate immune responses.[49] studied the effect of ethanolic extract of chicory root on the immune system by targeting mouse dendritic cells. C. intybus at higher concentrations inhibited proliferation of allogenic T cells and in lower concentrations changed the level of cytokines such that IL-4 decreased and IFN- increased.

Analgesic Properties

The analgesic properties of three particular active substances of chicory—lactucin, lactucopicrin and 11,13-dihydrolactucin—were proven in mice subjected to the hot plate (proving lactucopicrin the most potent) and the tail-flick test. It is noteworthy that a 30 mg/kg dose of any of these compounds used in the tail-flick test produced an effect comparable to that of a 60 mg/kg dose of ibuprofen. Furthermore, lactucin and lactucopicrin provided some extent of tranquilization as observed by reduction in spontaneous motor activity of the animals.[50]

Anti-Cancer Properties

In recent years, cytotoxicity studies of C. intybus extracts have shown its antitumor potential.[51,52] The studies also identified metabolite constituents including guaianolides, 6-methoxyflavone, eudesmanolides, germacranolides, polyacetylene, sterol, anthocyanin, delphinidin, 3,4-dihydroxyphenethyl and other novel compounds. Many of these phytometabolites have shown positive cytotoxic activities in vitro, and antitumor action in vivo and in clinical trials, demonstrating the potential of C. intybus metabolites as antitumor drugs. Structural activity relationship studies have further confirmed these bioactivities.[51] C. intybus extracts have a cytotoxic effect among others on breast cancer (MCF-7), amelanotic melanoma (C32), prostate cancer (LNCaP), renal adenocarcinoma (ACHN), leukemia cells.[52] A study using Ehrlich ascites carcinoma mice proved a significant reduction in tumor progression upon application of raw ethanolic extract of the root. As high as 70% increase in average lifespan was observed upon intraperitoneal administration of 700 mg/kg body mass per day In turn, the aqueous-ethanolic macerate of the leaves suppressed proliferation of the C32 amelanotic melanoma cells.[50]

Hypotensive Effect

According to Sedighi et al. ethanol leaves extract of C. intybus plays a protective role against hypertension. In this study, 32 maleWistar rats were divided into four groups of eight each. Animals in the control group were administered with normal saline and in the C. intybus groups with extract at 25, 50, and 100 mg/kg for two weeks. Median (MAP), systolic (SAP) and diastolic arterial pressure (DAP) significantly decreased in the 50 mg/kg extract-treated group compared to the control and 200 mg/kg extract treated groups.[53]

Anti-Inflammatory Properties

Chicory is used externally in compresses useful for treatment of skin disorders, incl.dermatitis, inflammatory diseases of mucous membranes, ulcers, wounds and trauma. Flower infusion is excellent for treatment of inflammation-irritated skin and eyes, thanks to its antiseptic, anti-inflammatory, moisturizing and nutritious

properties.[54] It also aids treatment of eczema and poorly healing wounds, improves periocular circulation, alleviates periorbital puffiness and symptoms of eye tiredness; it's also excellent for dry skin care.[54] The medicinal materials of C. intybus are usually prepared as mixes with other herbs. Chicory roots demonstrated significant dose-dependent decrease in paw edema in carrageenan-induced paw edema method. Chicory roots diminished the serum TNF-_, IL-6, and IL-1 levels. They also significantly attenuated the malonylaldehyde levels and increased the activities of CAT and GPx in paw tissue.[55] A placebo-controlled, double-blind, dose-escalating trial, was conducted to determine the safety and tolerability of a proprietary bioactive extract of chicory root in patients with osteoarthritis (OA). The results of the pilot study suggested that a proprietary bioactive extract of chicory root has a potential role in the management of OA. Only one patient treated with the highest dose of chicory discontinued treatment due to an adverse effects.[56]

Anti-Neurotoxic Properties

Cichorium intybus contains glycosides and triterpenoids, which inhibit glutamatergic transmission and enhance GABAergic transmission. The present study was aimed at studying the effect of chicory extract on the pyridoxine-induced peripheral neuropathy with a particular focus on glutamatergic and GABAergic systems. In experimental study, a high dose of pyridoxine (800 mg/kg, i.p.) was injected for 14 days to induce neuropathy in male rats. Results showed beneficial effects of chicory extract on pyridoxine-induced peripheral neuropathy. Modulating of the GABAergic system mediated by TNF-_ may be involved in the of chicory extract.[57]

Toxicity and side effects

Cichorium intybus was considered a safe drug as a result of its long use. No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages. There is a slight potential for sensitization via skin contact with the drug.[58] A 28-day (subchronic) oral toxicity study, conducted in rats revealed that there was no extract-related mortality or any other signs of toxicological significance[59] Toxicity evaluation of *Cichorium intybus* extracts was carried out by *Vibrio fischeri* bioluminescence inhibition test. This bacterial test measures the decrease in light emission from the marine luminescent bacteria *V. fischeri* when exposed to toxins. The tested extracts showed less than 20% inhibition of bioluminescence, therefore *Cichorium intybus* was considered safe for human use. A placebo-controlled, double-blind trial was carried out to determine the safety and tolerability of bioactive extract (dose escalation trial) of chicory root in patients with osteoarthritis. The treatment was well tolerated, only one patient treated with the highest dose of chicory discontinued the treatment due to adverse effects[[60]

Tumor-Inhibitory activity

The crude ethanolic extract of mg/kg/day intraperitoneal dose of the tested extract. The aqueous-alcoholic macerate of the leaves 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 500C. intybus also exerted an antiproliferative effect on amelanotic melanoma C32 cell lines. Magnolialide, a 1βC. intybus*-hydroxyeudesmanolide isolated from the roots of , inhibited several tumor cell lines and induced the differentiation of human leukemia HL-60 and U-937 cells to monocyte or macrophage-like cells[61]

Anti allergic activity

The aqueous extract of *C. intybus* inhibited the mast cell-mediated immediate allergic reactions in vitro as well as in vivo *C. intybus* extract. 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 IgE in rats[62]

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 Salmonella typhimurium strains TA97a, TA98, TA100, and TA1535 and Escherichia coli strain WP2 uvrA 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[63] Ames test and subchronic toxicity assessment were conducted. The sesquiterpene-rich extract was evaluated for potential mutagenic properties (Ames test) using. Though cytotoxicity 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[63]

Miscllenеous 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 immunoactive 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.[63]

Anti helminthic activity

Several studies have been conducted on grazing animals to determine the anthelmintic potential of secondary metabolites present in C. intybus. Grossly, it has been concluded that the animals grazing on chicory have a higher performance index and lower incidence of gastrointestinal nematode infestations. In the majority of the experiments, the condensed tannins and sesquiterpene lactones were responsible for anthelmintic activity. Anthelmintic activity of chicory has also been noticed in the case of lambs wherein the total number of abomasal helminths was found to be lesser in the lambs grazing on this plant. The condensed tannin and sesquiterpene-rich extracts of C. intybus were evaluated for their efficacy against the larvae of deer lungworm, Dictyocaulus viviparous and other gastrointestinal nematode larvae using a larval migration inhibition assay. A dose-dependent decrease in the larval motility was observed in both lungworm and gastrointestinal nematodes. The sesquiterpene lactone-rich extracts of C. intybus were also found to inhibit egg hatching of Haemonchus contortus.[64]

Gastroprotective activity

*C. intybus has been used in Turkish folklore for its antiulcerogenic potency. The aqueous decoction of C. intybus*roots was orally administered to Sprague-Dawley rats 15 minutes before the induction of ulcerogenesis by ethanol. More than 95% inhibition of ulcerogenesis was observed in the test group.[65]

Anti-Inflammatory 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.[66]

Analgesic and Sedative activity

Lactucin (1) and its derivatives lactucopicrin (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 given at a dose of 60 mg/kg. Lactucopicrin appeared to be the most potent analgetic of the three tested compounds. Lactucin and lactucopicrin, but not 11beta,13-dihydrolactucin, also showed sedative properties in the spontaneous locomotor activity test.[66]

ALLERGIES TO THE COMMON CICHORY

A rare allergy to the chicory plant has been documented in ~20 cases over the last 100 years. Most of these cases occurred in adults who were in contact with chicory due to their occupation, and only a single case involved a child reacting to inulin. Depending on the individual, allergic symptoms can be systemic and/or local, ranging from rhinoconjunctivitis, to asthma and anaphylactic reactions, to contact dermatitis. As individual as the allergic reactions are, the chicory preparations and routes of exposure are also unique and varied. There are only two reported cases where fresh chicory roots induced an allergic reaction topically. The majority of reactions occurred in response to leaves (raw and cooked) after skin contact or inhalation. Sometimes, reactions were also caused by the inhalation of dried chicory roots and inulin, consumption of inulin-containing products, and once by intravenous inulin administration during a standard renal function test. It is not yet clear exactly how allergic reactions to chicory are triggered. Proteins from chicory or newly formed inulin-protein compounds (arising during production), as well as sesquiterpene lactones could be potential allergens. Sensitization might arise from repeated exposures or from cross-sensitization with birch pollen or lettuce. Due to all this ambiguity, the general advice is that people with allergies or occupational exposure to Asteraceae family members, people with birch-pollen allergies, and people with atopic dermatitis should be cautious when coming into contact or consuming chicory- and inulin-containing foods.[68,69]

DOSAGES

Dose: 3-5 g powdered root in 150-250 ml water. Infusion was prepared by scalding 2 to 4 g drug with boiling water, allowing it to stand for 10 minutes, then straining. A tea is prepared by brewing 2 to 4 g of the whole herb with 150 to 250 ml boiling water and then straining it after 10 minutes.[70]

CONCLUSION

This review discuss the chemical constituent, pharmacological and therapeutic effects of *Cichorium intybus* as promising herbal drug because of its safety and effectiveness. In conclusion, Cichorium intybus L. is a common plant with great potential. It certainly does deserve a wider use in medical prophylaxis and phytotherapy. Individual parts, e.g., leaves or flowers, both in fresh and dried form, can be a valuable addition to daily diet. The multipurpose effects of C. intybus extracts may be a promising alternative source for the pharmaceutical industry. It is interesting to note that chicory was among the plants with potential against

SARS-CoV-2. However, further studies, including in vitro and in vivo studies, are needed to confirm this antiviral property of chicory.

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