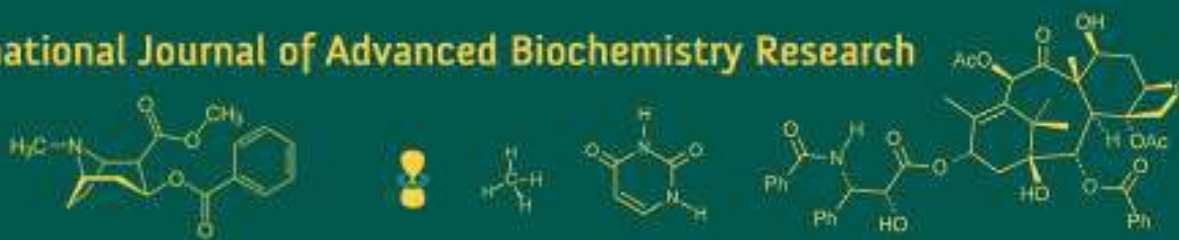


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Cichorium intybus: A bitter herb with remarkable therapeutic benefits

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Abstract

The utilization of medicinal herbs for the treatment of common diseases is an ancient tradition. The plant *Cichorium intybus* (Asteraceae) is used traditionally in India as well as in different parts of the world. It is potentially used in the healing of a wide levels of ailments namely enteric sickness, diabetes, haemorrhoids, malaria, allergies, digestive disorders, and many more. *C. intybus* has been reported to be a reservoir of many bioactive constituents of therapeutic properties such as coumarins, esculin, inulin, flavonoids, bitter sesquiterpene lactones, and vitamins. Although the plant is used extensively in folklore medicine in different parts of the world, there is a limited investigation on the scientific validation of the phytochemical constituents. This review aims at providing collective information on various potential pharmacological activities along with the traditional uses and phytochemical composition of *C. intybus*.

Keywords: *Cichorium intybus*, sesquiterpene lactones, pharmacological activities, phytochemicals

Introduction

The existence of plant-based medicines and their acceptance by people is as old as human civilization. Currently, researchers are paying much attention to the development of plant-based medicines due to their fewer side effects and a long history of use. Besides, ethnomedicinal plants have been reported to be a rich reservoir of many bioactive components with therapeutic potential. The plant *Cichorium intybus* L. or “chicory” belonging to the Asteraceae family is a typical Mediterranean therapeutic plant. *C. intybus* is a tiny (1m height) aromatic, biennial to a perennial herb with large leaves, a fleshy taproot, and bright flowers with blue petals ^[1, 2]. *C. intybus* prefers to grow in open fields, waste places, roadsides, disturbed sites, and railroads ^[3]. *C. intybus* is widely cultivated in different parts of Europe, Asia, North America, and Egypt. The use of the herb in various food preparations dated back to the 16th century. The roots of *C. intybus* var. *sativum*, has been used as a coffee additive in Europe. The roots of the Chicory plants have been reported to contain a significant amount of inulin (up to 40%). Inulin can be consumed as a sweetener, which has been reported to maintain the blood sugar level ^[3].

Flowers and roots of chicory contain various phytoconstituents such as different carbohydrates, methoxy coumarin cichorine, flavonoides, and essential oils ^[4]. The leaves of *C. intybus* are bitter due to the presence of sesquiterpene lactones ^[5]. The chicory herb can be added in the compost heap along with some other herbs to enhance bacterial activity ^[3].

The *C. intybus* herb has been reported to survive in extreme temperatures as well showed to have high adaptability to acidic and alkaline soil conditions, although the extremely high acidic condition is unfavourable for its growth ^[6]. Street *et al.* ^[7] reported four types of cultivated varieties of *C. intybus* based on their uses. The first one is “industrial” or root “chicory”, the taproot of which is rich in inulin. The starch present in the roots of chicory can be used for the industrial production of alcohol. The second one is “forage” chicory which has the potential to be used as feed additives in animals. The third one is “Brussels” or “Witloof” chicory which is grown for commercial production of “Chicon”. The fourth one is “leaf” chicory, which is used as leafy greens in a salad ^[8].

Different parts of *C. intybus* herb are used traditionally in various food preparations and treatment of common diseases in Europe, in some parts of Asia and Africa.

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The chicory plant is rich in different phytoconstituents of medicinal importance. Chicory shows a long history of utilization as a tonic for liver diseases and digestive issues [9]. All imperative parts of this plant possess medicinal properties, mainly the root, seed, leaf, and flower extracts are used in different herbal remedies [10, 11]. The root extracts are used in blood sugar and blood pressure regulation, jaundice, rheumatic, and gout disorders. The root extract is also used in folk medicines as an anti-tumorous agent [9]. There are numerous reports on pharmacological activities of chicory such as anti-cancer, anti-fungal, anti-malarial, anti-diabetic, and free radical scavenging activity [3].

This review aims to investigate various traditional uses and scientific validation of *C. intybus* as well as the phytochemical composition of different parts and their pharmacological potential. The use of chicory in traditional medicine for curing liver and digestive problems has a long history [9]. The roots, leaves and flowers have been used as tonic and appetizers as well as for treatment of a variety of infectious ailments [10, 11].

Traditional uses

Most people of the world are dependent on the indigenous therapeutic plants for their primary health care needs [12]. In India, people living in rural areas mostly rely on herbal medicines for curing common diseases because of easy availability of plants and plant-based formulations in these areas. Herbal medicines are preferred over allopathic medicines by most people because of lesser toxicity and fewer side effects on human health. Ayurveda, Unani and Siddha are the best examples of traditional medicine systems with codified information. However, in folklore or ethno medicine, the therapeutic information is not well documented but are carried forward orally generation after generations. Due to the presence of therapeutically active compounds in medicinal plants, researchers are focusing on integrating folklore medicine with modern medicine system to develop desired therapeutic agents that can provide

alternative remedies to infectious as well as non-infectious diseases.

C. intybus is a multipurpose medicinal herb with antihepatotoxic, antidiabetic, anti-cancerous, antiulcerogenic, and anti-inflammatory properties [13, 7]. In India and South Africa, formulations prepared by using various plant parts are used for plenty of herbal remedies. Mulabagal *et al.* [14] depicted the traditional use of chicory for the curing of various infectious as well as liver diseases. Some reports are available on the use of the roots of chicory plant as 'coffee additives' [5, 15] and aerial parts in various diets in some countries of Western Europe and the United States [16]. In Eastern Anatolia, the powdered form of aerial parts and roots are used for the preparation of decoctions and infusions as a herbal remedy [17]. Tabata *et al.* [18] reported the use of root decoction of *C. intybus* in epilepsy. There is documented data available for use of chicory roots as well as roots/ leaves mixtures in the 'European traditional medication system' for healing some issues such as mild dyspeptic disorders, digestive disorders and as an appetizer [19]. Root decoctions are also used as a tonic and diuretic [20]. The herb is also reported to have shown cholesterol and blood sugar-lowering effects but with a high dose. Bischoff *et al.* [21] reported the remedial activity of aqueous extracts from roots of *Cichorium intybus* (L.) against malaria in Western Afghanistan. The isolated antimalarial compounds were reported to be lactucin and lactucopicrin (sesquiterpene lactones). There are reports on the use of the chicory flowers in the production of dye (Bremness 1998). Decoctions prepared from whorls of the herb are used as a depurative in Italy [22]. The use of chicory seeds as main constituent in "Jigrine", a commercial product for the treatment of liver diseases in India has been reported [23]. In Jordan cooked whole plant is used for the treatment of internal haemorrhage [23]. The prolific exploration of various plant parts in the healing of liver disorders is prevalent in many countries like Bosnia, Herzegovina [24] and Serbia [25]. The traditional uses of *C. intybus* in different regions of the world are represented in Table 1.

Table 1: View of various parts of *C. intybus* for traditional uses as 'ethno medicine'

Country	Traditional uses/ethno medicinal uses	Parts used/ Preparations	Reference
India	Fever and blood detoxification	Aqueous extract of leaves	[26]
	Diabetes	Whole plant extract	[7]
	Gastritis and release of gall stone	seed powder extract	[27]
	Jaundice, appetizer, digestive disorders, rheumatism	root powder; decoction	[28]
Turkey	Epilepsy	Boiled root extract; decoction	[18, 29]
	Wound healing	Stem and root latex; applied externally	[30]
	Diabetes	Aerial parts; Ingestion	[31]
	Abdominal pain	Aerial parts; Ingestion	[32]
	Uterus disorders	Whole plant; herbal tea	[30]
Istanbul	Abdominal pain, Ulcer, Gastritis, Liver and spleen disorders	Aerial parts; Infusion	[33]
France	Digestive disorders, renal elimination	Roots; herbal tea	[34]
Germany	dyspepsia and loss of appetite	dried roots	[35]
China	Digestion	Roots/whole herbs	[36]
South Africa	Jaundice	Roots/ stem; herbal tea	[2]

Phytochemical constituents of *C. intybus*

C. intybus is a medicinal plant with a huge source of natural compounds containing broad spectrum of bioactivities. Phytochemical evaluation of different parts of the plant showed the existence of polyphenols, flavonoids, alkaloids, coumarins, phenylpropanoids, triterpenoids and steroids, sesquiterpenoids, nitrogen-contained compounds, and

organic acids [37]. In addition to these, compounds like 'cichorins A, B, C', 'coniferyl aldehyde', 'syringyl', 'coniferyl alcohol', 'coniferin', and 'syringaldehyde', were isolated from the roots and whole plant [38, 39]. The reported bioactive compounds isolated from *C. intybus* were presented in Table 2.

Table 2: Bioactive compounds isolated from various parts of *C. intybus*

Types of Phytochemicals	Isolated Compound	Source of isolation	Reference
Phenylpropanoids	'Esculin' (1), 'esculetin' (2), 'Cichoriin' (3), 'umbelliferone' (4) and 'scopoletin' (5)	Flowers	[37, 40]
Flavonoids	'Isoscutellarein' (6), 'apigenin' (7), 'hyperin' (8), 'quercetin' (9), 'kaempferol' (10), 'cichoriin-6-p-hydroxyphenyl acetate' (11), 'apigenin-7-O-L-arabinoside' (12), 'cyanidin-3-O-(600-O-malonyl)- glucoside' (13), 'cyanidin-3-O-galactoside' (14), 'luteolin-7-O-b-D-glucopyranoside' (15), 'cyanidin-3,5-di-O-(600-O-malonyl)-glucoside' (16), 'isorhamnetin-7-O-neohesperidoside', 'isorhamnetin-7-Oglucoside' (17), 'isorhamnetin-7-O-glucuronide' (18), 'cyanidin-3-Oglucoside', 'isorhamnetin- 7-O-(600-O-malonyl)-glucoside' (19), 'quercetin-3-O-(600-O-malonyl)-glucoside', 'quercetin-7-O- (600-O-acetyl)-glucoside' (20), 'quercetin-7-O-p-coumaroylglucoside' 'kaempferol-3-O-glucoside' (21), 'kaempferol-3-O-glucuronide' and 'petunidin-3-O-(600-O-malonyl)- glucoside' (22)	Leaves	[41, 42, 43, 44]
Triterpenoids and steroids	'Taraxerone' (23), 'bauerenyl acetate' (24), 'intybusoloid' (25)	Roots	[37]
	'stigmasterol' (26), and 'campesterol' (27)	Leaves	[45]
Sesquiterpenoids	'Jacquinelin' (28), 'cichoriosides' (29), 'intybulide' (30), 'cichoriolide A' (31) 'crepidiaside B' (32), 'sonchuside A' (33), 'sonchuside C' (34), 'picriside B' (35), 'cichoriosides A' (36), 'cichoriosides B' (37), 'cichoriosides C' (38), 'cichorioside D' (39), 'crepidiaside A' (40), '8-deoxylactucin' (41), 'Ierisoside D' (42), 'lactucopicrin', '11- epiartemin' (43), 'santamarine', 'crepidiaside B' (44), '10a-hydroxycichopumilide' (45), 'magnolialide' (46), '8a-a ngeloyloxycichoralexin' (47), 'artemin' (48) 'Cichotyboside' (49) 'Lactupicrin methyl ester' (50), 'lactucopicrin-15-oxalate' (51), 'chicoralexin' (52), '1a,5a-epoxy-4a-hydroxyl-4b', '10b-dimethyl-7aH', '10aH-guaia-11(13)-en-12-oic acid (138)', '3a-R-santamarine' (53)	Roots Leaves seeds Whole plant	[46]
Nitrogen-contained compounds	'Caffeine' (54), 'theophylline' (55), '8-hydroxyquinoline' (56), 'zeatin' and 'riboside' (57)	Roots	[47, 48, 49, 50]
Organic acids	'tartaric acid' (169), '4-hydroxycinnamic acid' (58), 'oxalic acid' (59), 'quinic acid' (60), 'ascorbic acid' (61), 'citric acid' (62), 'malic acid' (63), '4-Oferuloylquinicacid' (64), '5-O-feruloylquinic acid' (65), '3-caffeoylquinic acid' (66), '4-caffeoylquinic acid' (67), '5-caffeoylquinic acid' (68), 'cis-5-caffeoylquinic acid' (69), 'ciscaffaric acid' (70), 'trans-caftaric acid' (71), '5-caffeoylshikimic acid' (72), '5-p-coumaroylquinic acid' (73), '1,3-di-O-caffeoylquinicacid' (74), '1,3-di-O-caffeoylquinic acid' (75), '3,4-di-Ocaffeoylquinicacid' (76), '3,5-di-O-caffeoylquinic acid' (77), and 'cichoric acid' (78).	leaves	[51]
Volatile components	as 'Octane' (79), '2-Pentyl furan' (80), '(2E, 4E)-Heptadienal. 1,8-Cineole' (81), 'Benzene acetaldehyde' (82), 'Campho, (E)-Caryophyllene' (83), 'β-Ionone' (84), 'Sesquicineole' (85), 'n-Eicosane' (86), 'n-Octadecanol' (87), 'n-Heneicosane' (88)	Aerial part/ roots	[37, 7]
Polysaccharides	'Inulin' (89)	Roots/ seeds	[7]

Pharmacological activities of *C. intybus*

Herein an attempt is made to review and provide information on the reported pharmacological activities of *C. intybus*.

Antioxidant activity

The role of polyphenols such as flavonoids as antioxidants have been well documented [52, 53, and 54]. Phytochemical analysis showed the presence of more than 20 flavonoids in *C. intybus* (Table 2). There are various reports on the antioxidant activity of polyphenolic components isolated from *C. intybus* [7]. Abbas *et al.*, (2015) determined that the hydroalcoholic extract of leaves of *C. intybus* exhibited a significant level of antioxidant activity. Similar results were obtained by Mathur *et al.*, [55] for the hydroalcoholic extract of *C. intybus* showing the restoration of the toxicity effects induced by hydrogen peroxide in HepG2 cell lines. The 'DPPH' assay showed the IC₅₀ value of the leaf extract was very low (67.2 µg/ mL). The investigation carried out by Jancic *et. al.* [56], for antioxidant activity of chicory leaf extracts, showed that the wild type varieties exhibited more antioxidant activity than that of the cultivated varieties. They used 'DPPH', 'FRAP' and 'TEAC' assays to evaluate the trait of antioxidant. Phytochemical based evaluation

showed that the level of phenolic content was more in wild varieties of chicory than that of the cultivated ones with lower antioxidant activity. The experimental study exhibited that the leaf extract of chicory is rich in organic acids, which could be the possible reason for a high level of antioxidant and enzyme inhibitory properties on α-glucosidase [17]. Zeb *et al.* [57] showed that preheating of *C. intybus* with microwave treatment resulted in increased antioxidant activity due to the enhancement of bioactive components.

Hepatoprotective Activity

The indigenous use of *C. intybus* in curing liver disorders in different parts of the world has been well documented. "Liv52" is an Ayurvedic tonic used for liver protection in India and *C. intybus* is one of the major herbal ingredients in it. "Jigrine", another herbal medicine, used in Ayurveda for liver protection is known to contain *C. intybus* leaves. Aqueous- methanolic extract of seeds of *C. intybus* tested against induced liver damage in rats by acetaminophen and carbon tetrachloride (CCL₄) showed a considerable level of decrease in the amount of various elevated liver enzymes such as alkaline phosphatase, glutamyl oxaloacetate transaminase, alanine aminotransferase, hexadecenoic acid and glutamyl pyruvate transaminase in serum [58, 59]. Saggiu

et al. [60] analyzed the ability of *C. intybus* fruit extract to improve biochemical and antioxidant activities in male rats with 4-tert-OP induced oxidative stress.

Elgengaihi *et al.* [61] experimented to study the hepatoprotective potential of *C. intybus* extracts against CCl₄ induced toxicity in male albino rats. For their experiments, one control group, one CCl₄ treated group, one *C. intybus* extract-treated group and one both CCl₄ and *C. intybus* extract-treated group of mice were taken. The fifth group of mice taken was treated with a standard hepatic drug (silymarin). Their results showed significant levels of restoration of the liver damage caused in CCl₄ induced mice when treated with *C. intybus* extracts. Esculetin and cichotyboside isolated from *C. intybus* have been reported to possess a considerable level of hepatoprotective activity [62].

Antimicrobial activity

There have been a few reports on the antimicrobial potential of *C. intybus* extracts against both 'Gram-positive' and 'Gram-negative' bacteria. The methanol extract of *C. intybus* exhibited a higher level of antimicrobial activity than aqueous extract against a wide variety of pathogenic bacterial strains such as '*E. coli*', '*S. aureus*', '*S. epidermidis*', '*Bacillus subtilis*', '*P. aeruginosa*', '*K. pneumoniae*', '*Erwinia carotovora*', '*P. vulgaris*', '*Enterobacter cloacae*' and '*S. pyogenes*' as well as a fungal strain, '*Candida albicans*' [63]. Liu *et al.* [64] revealed that the root extract exerted antibacterial trait against both types of bacterial strains ('Gram-positive' and 'Gram-negative'). *Fusarium solani*, appeared to be the most sensitive against chloroform, aqueous, and ethyl acetate extracts of chicory [65]. Seed extracts were reported to possess antibacterial potentiality towards two bacterial strains ('*P. aeruginosa*' and '*S. aureus*') [66], while on the contrary, leaf extract showed activity towards *Saccharomyces sp.* and *Lactobacillus sp.* [67].

Antidiabetic and hypolipidemic activity

The traditional use of chicory in diabetes leads the researchers to investigate the antidiabetic activity of the whole plant [27, 68]. Chandra *et al.* [69] demonstrated the antidiabetic activity of seed aqueous extract of *C. intybus*. Oral administration of the extract to diabetic rats showed a decreased pattern in the level of blood glucose and triglyceride (TG) levels. *C. intybus* leaf administration to diabetic rats resulted in a considerable decline in the serum glucose level [70].

Phytochemical analysis of chicory showed the presence of large quantities of inulin, especially in its root extracts. Lin *et al.* [71] examined the efficiency of inulin isolated from *C. intybus* in the high fatty diet-induced quail model. They reported a considerable level of increase in lipid metabolism after in the obese quails.

Gastroprotective activity

The traditional use of 'chicory' as an antiulcerogenic agent is prevalent in many European countries. The scientific investigation demonstrated that prior to ulcerogenesis induction, oral administration of *C. intybus* aqueous root extract (decoction) to Sprague-Dawley rats resulted in 95% of ulcer inhibition as compared to the untreated ulcer induced rats [72]. Wu [73] showed that *C. intybus* root powder administration resulted in improved regulation of imbalances of gut microbiota in cyclophosphamide-induced

immunosuppressive mice. The leaf extract of *C. intybus* has been also reported to show antidiabetic activity, probably due to its high content of anthocyanins [74].

Antimalarial activity

In Western Afghanistan, *C. intybus* aqueous root extracts are used as indigenous medicine for malaria treatment. Bischoff *et al.* [21] validated the traditional belief by reporting an exhibition of antimalarial effectiveness of 'lactucin' and 'lactucopicrin' isolated from roots. In addition to these, 'guaianolide', reported exhibiting antimalarial activity has been derived from the chicory root [7].

Anthelmintic Activity

C. intybus petroleum ether extract has been reported to show anthelmintic activity [75]. Forage chicory extracts showed antilarval activity against *Ostartagia ostertagi* [76] and *Cooperia oncophora* [77].

Antitumour effects

Root ethanolic extract of *C. intybus* depicted considerable high antitumour efficacy [78]. Aqueous-alcoholic leaf extracts of chicory showed antiproliferative activity on malignant C32 cell lines [79]. 'Magnolialide' (1 β -hydroxyeudesmanolide), derived from root portion of chicory, showed significant antitumour activity [80]. Chicory polysaccharide (CPS) isolated from the herb inhibited the growth of sarcoma in mice when CPS was orally administered prior to receiving tumour cells [81].

Immunomodulatory effects

Crude *C. intybus* extracts were reported to show effective immunomodulatory effects [82]. Oral administration of CPS to mice resulted in a significant increase in antibody-forming cells, activity of macrophages and size of the thymus gland and spleen [83]. CPS was also shown to have immunity-boosting effects on human [84].

Anti-inflammatory effects

Rizvi *et al.* [85] attempted to validate the traditional use of *C. intybus* as an effective anti-inflammatory remedy. In their experiment, carrageenan-induced paw edema Albino Wistar rats were administered with root ethanolic and aqueous extracts of *C. intybus* to observe anti-inflammatory potential of the extracts. Both extracts (aqueous and ethanolic extracts) depicted a significant decline in paw edema. There was a decrease in the level of cytokines such as 'TNF- α ' (tumour necrosis factor alpha)', 'interleukin 6 (IL-6)', and 'IL-1' in the serum whereas there was an enhanced action of 'antioxidant enzymes' (especially glutathione peroxidase and catalase) indicating reduced inflammatory effects. The inflammatory effects of *C. intybus* could be due to various phytochemicals such as Sesquiterpene lactones, flavonoids, glycosides and tannins [86, 7]. Flavonoids isolated from Chicory showed inhibitory effects on prostaglandin synthesis which are responsible for acute inflammation [87].

Other pharmacological activities

In addition to the above-mentioned bioactivities *C. intybus* also showed neuritogenesis and neurotrophic effects [88, 89, 90], Antihyperuricemia activity [91, 92, 93, 94, 95, 96, 97] and antiosteoporotic effects [98].

Sesquiterpene lactones: a bitter constituent in *C. intybus*

Sesquiterpene lactones, one of the major bioactive constituents found in *C. intybus* is considered to be the reason for the slightly bitter taste of the plant [99, 100]. Schenck and Graf [101] determined that lactucin and lactucopicrin are two sesquiterpene lactones that could confer bitterness at a considerably low concentration. Five sesquiterpene lactones namely lactucin, lactucopicrin, 8-deoxylactucin, 11(S), 13-dihydro-8-deoxylactucin and 11 (S), 13-dihydro-8-deoxylactucin were isolated from *C. intybus* and assessed for their detection thresholds for the bitter tastes [100]. Out of these five sesquiterpene lactones, 11(S), 13-dihydro-8-deoxylactucin was proven to be most bitter. Price *et al.* [102] measured the sensory threshold for the bitterness of sesquiterpene lactones, lactucin, 8-deoxylactucin and lactucopicrin and their glycosides isolated from red chicory and lettuce. When they compared the quantities of these bioactive compounds with the bitterness level, they found that there was a relation between the increase in bitterness and a higher level of one of these sesquiterpene lactones, lactucin glycoside. Similar data by Peters *et al.* [103] showed a strong correlation between the level of lactucin glycoside and bitterness.

The plants belonging to the Asteraceae family were reported to be a rich source of sesquiterpene lactones [104]. There are various documented as well as undocumented information on the indigenous use of medicinal plants, rich in sesquiterpene lactones, for the treatment of bacterial infections, stomach ulcers, neurotoxicity, contact dermatitis as well as migraine [105, 106, 107, 108]. Comparative analysis of sesquiterpene lactone, isolated from *Artemisia douglasiana* Besser suggested that the α -methylene- γ -lactone group (α MyL) play a key role in reducing gastric ulcer in mice induced with ethanol. The sesquiterpene lactones are known for their ability to influence α MyL unit by alkylation of thiol groups mostly found in proteins [109]. Lactucin and lactucopicrin are the two most effective sesquiterpene lactones commonly found in chicory and lettuce that have sedative effects [110] (Wesolowska *et al.* 2006). Although the study on the antitumour activity of sesquiterpene lactones is limited, Sweeney *et al.* [111] reported that oral administration of parthenolide, a sesquiterpene lactone to mouse showed significant antitumour activity.

The bitter sesquiterpene lactones presumably protect against herbivores and pathogens [112]. Although sesquiterpene lactones are known to have medicinal properties, due to the bitter taste, their consumption is limited. The level of sesquiterpene lactones in chicory can be lowered by altering the cultivation conditions [113]. However, shortfall of sesquiterpene lactones levels may engender a decrease in resistance patterns of the herb towards biotic stress, thus, affecting the crop yield.

The current transgenic approach in improving medicinal trait

Because of its high medicinal and nutritional value *C. intybus* is predominantly grown in continental Europe, Northern and Southern Africa, southwestern Asia and in some areas of Australia and North America. In order to improve production, as well as the quality of the plant, researchers have paid their attention to developing various breeding techniques [114]. But there is a little investigation on the genetic engineering approach of improving the productivity of *C. intybus* [115, 116]. This review focuses on

providing information on various attempts made for the production of improved varieties of *C. intybus* by using different genetic transformation approaches.

Sun *et al.* [117] first reported the genetic transformation of *C. intybus* using *Agrobacterium rhizogenes*. The transformed plants were able to flower annually without the need for vernalization. Vermeulen *et al.* [118] inserted acetolactate synthase gene isolated from *Arabidopsis thaliana* to produce herbicides resistant *C. intybus*.

Although *in vitro* culture techniques have been attempted for achieving the target of the better production of especillay 'bioactive compounds' in *C. intybus*, the outcome was not as effective as expected [119]. Nowadays, a technique involving either *Agrobacterium rhizogenes* or *A. tumefaciens*- mediated genetic transformation to produce hairy root cultures is gaining considerable interest because of the high level of secondary metabolite yield through this approach [120, 121, 122]. Hanafy *et al.* [119] reported that the genetic transformation of chicory hairy root cultures resulted in increased growth rates as well as more synthesis of inulin as compared to the non-transformed chicory. *C. intybus* growth is adversely affected by various abiotic stresses such as salinity, drought and low temperature. Li *et al.* [123] in his experimental study, inserted a novel betaine aldehyde dehydrogenase (HvBADH1) gene isolated from Tibetan hulless barley into *C. intybus* by *A. tumefaciens*-mediated genetic transformation. Various physiological factors associated with stress tolerance were analysed to study the stress resistance traits of the transgenic chicory plants. They observed that there was better retention of K⁺, a significantly higher amount of glycine betaine (GB) accumulation, reduced oxidative stress and enhanced growth rate in transformed *C. intybus* as compared to non-transformed wild type plants. The results indicated enhanced salinity resistance of transgenic *C. intybus* due to overexpression of HvBADH1 gene in transgenic tissues.

Inulin, a type of fructan in plants is acknowledged for depicting a noteworthy function in providing resistance to abiotic stresses [124]. The inulin isolated from *C. intybus* herb is used in a variety of food items such as in fat-free yoghurt and bread to get a better taste [125, 126]. Inulin is also known to increase gut health [127]. The quality of inulin produced in industrial scale is affected by its polymer length [128].

'1-SST' (Sucrose-sucrose 1-fructosyltransferase) enzyme commences an imperative job in the production of inulin (particularly 'long-chain inulin') in *C. intybus* [129]. In chicory, 1-SST activity was suggested to decline at harvest time, therefore, affecting the polymer length of inulin [130]. Vijn *et al.* [131] attempted to produce transgenic chicory, overexpressing fructan 6-fructosyltransferase (SST) enzyme. The transformed plants were known to synthesise a new type of long-chain fructan in addition to the endogenous inulin. Maroufi *et al.* [132] produced *C. intybus* plants overexpressing '1-SST enzyme' under the regulation of the 'CaMV 35S promoter'. Their study revealed that overexpression of 1-SST resulted in accumulation of long-chain inulin in the roots of transgenic *C. intybus*.

There have been a few reports on the enhancement of sesquiterpene lactone through biotechnological approach in chicory. Malarz *et al.* [133] could successfully enhance the production of '8-deoxylactucin' in the roots of chicory by the use of elicitors and growth condition optimization. Costunolide is an instantaneous precursor of parthenolide and costunolide synthase gene producing enzyme for the

conversion of germacrene acid to costunolide was derived and derived from chicory^[134, 135]. There are also reports on the application of metabolic engineering method to improved accumulation of 'sesquiterpene lactone' in chicory roots by inhibition of its modification into another compound^[136]. Transient co-expression of a 'germacrene A synthase' from feverfew^[137], a 'germacrene A oxidase' from chicory^[138], and 'costunolide synthase' from chicory^[134] in *N. benthamiana* leaves resulted in the synthesis of two costunolide conjugates, 'costunolide-cysteine' and 'costunolide-glutathione'. Germacrene A synthase from 'chicory'^[139] and a germacrene A synthase from 'feverfew' (GenBank JF819848.1)^[137] in *S. cerevisiae* exhibited a noteworthy disparity in the production of 'germacrene A'. From feverfew, the Germacrene A synthase, was found to be more efficient in germacrene synthesis. So, overexpression of germacrene A synthase from feverfew in 'hairy roots' of chicory would be a prolific tactic to acquire huge scale yield of parthenolide for commercialization

Conclusion and future prospects

A comprehensive analysis of the published literature for *C. intybus* supported its various ethnomedicinal uses as well as its popularity as a coffee substitute. This versatile plant is a rich source of many nutritive elements and bioactive components^[140]. The inulin isolated from the roots of this plant has been proven to possess many health benefits^[141]. The traditional uses of this plant as therapeutic agents have been validated by scientific investigation of the bioactive potentials of the isolated phytoconstituents. But there is scope for more research to understand the biological activity against diseases of various unexplored phytochemicals isolated from chicory^[140]. In recent years, various research strategies have been implemented for the generation of transgenic chicory with improved phenotypes. Through genetic engineering technique, researchers have successfully attempted to enhance the accumulation of secondary metabolites in *in vitro* hairy roots^[122] and also to produce stress-resistant varieties^[123]. There are ongoing researches on producing chicory with newer bioactive potentials through genetic manipulation of various pathways of phytochemical synthesis. In future, crop improvement through genetic engineering approach will increase the economic benefit potentials of *C. intybus*.

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