IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 6, Issue 3 (March 2016), PP. 41-56

Medical importance of *Cichorium intybus* – A review

Prof Dr Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, Thi qar University, Iraq.

Abstract: Phytochemical analysis showed that the different parts *Cichorium intybus* contained sesquiterpene lactones (especially lactucin, lactucopicrin, 8-desoxy lactucin, guaianolid glycosides, including chicoroisides B and C, sonchuside C), caffeic acid derivatives (chiroric acid, chlorogenic acid, isochlorogenic acid, dicaffeoyl tartaric acid), inulin, sugars, proteins, hydroxycoumarins, flavonoids, alkaloids, steroids, terpenoids, oils, volatile compounds, coumarins, vitamins and polyynes. It possessed hepatoprotective, gastroprotective, cardiovascular, antioxidant, hypolipidemic, anticancer, reproductive, antidiabetic, anti-inflammatory, analgesic, sedative, immunological, antimicrobial, anthelmintic, anti-protozoal, wound healing and many other pharmacological effects. This review was designed to highlight the chemical constituents and medical importance of *Cichorium intybus*.

Keywords: *Cichorium intybus, constituents, pharmacology, medical importance*

I. INTRODUCTION

Using of plant for healing purposes started before the mankind's history. Many modern medications were originated from a botanical source[(1)]. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many pharmaceutical drugs[(2-60)]. Phytochemical analysis showed that the different parts *Cichorium intybus* contained sesquiterpene lactones (especially lactucin, lactucopicrin, 8-desoxy lactucin, guaianolid glycosides, including chicoroisides B and C, sonchuside C), caffeic acid derivatives (chiroric acid, chlorogenic acid, isochlorogenic acid, dicaffeoyl tartaric acid), inulin, sugars, proteins, hydroxycoumarins, flavonoids, alkaloids, steroids, terpenoids, oils, volatile compounds, coumarins, vitamins and polyynes. It possessed hepatoprotective, gastroprotective, cardiovascular, antioxidant, hypolipidemic, anticancer, reproductive, antidiabetic, anti-inflammatory, analgesic, sedative, immunological, antimicrobial, anthelmintic, anti-protozoal, wound healing and many other pharmacological effects. This review was designed to highlight the chemical constituents and medical importance of *Cichorium intybus*.

Plant profile:
Synonyms:
Cichorium intybus var. *foliosum* Hegi, *Cichorium intybus* var. *sativum* (Bisch.) Janch[(61)].
Taxonomic classification:
Kingdom: Plantae**; Subkingdom:** Tracheobionta**; Division**: Magnoliophyta**; Class**: Magnoliopsida**; Subclass:** Asteridae; **Order:** Asterales**; Family:** Asteraceae / Compositae**; Genus:** *Cichorium* L. **; Species**: *Cichorium intybus*[(62)].

Common names:
The name of the plant is derived from Greek and Latin. *Cichorium* means field and *intybus* is partly derived from the Greek "to cut", because of the leaves, and partly from the Latin *tubus* to indicate the hollow stem[(63-64)]. Its common names: **Arabic:** shikoryah, hidaba, hindaba bariah; **Chinese:** ju ju; **English:** Belgium endive, chicory, coffee chicory, French endive, succor, witloof**; Franch:** chicon, chicorée, chicorée à café, chicorée de, Bruxelles,chicorée sauvage, endive, endive witloof, witloof**; German:** Chicorée, Fleischkraut, Kaffeezichorie, Salatzichorie, Wegwarte, Wurzelzichorie**; Italian:** cicoria, radicchio; **Japanese**: Kiku nigana; **Spanish:** achicoria de Bruselas, achicoria de café, achicoria de raíz**; Swedish:** cikoria[(61)].

Distribution:
The plant was widely distributed in Africa, Asia-temperate, Asia tropical, Europe, Australia, Northern America and Southern America[(61)].
Description:
Herbs 40-110 cm tall, perennial, with a strong taproot. Stem usually solitary, erect; branches spreading-ascending, subglabrous. Basal leaves rosulate, obovate to oblanceolate, 15-34 × 2-4 cm, attenuate into a petiole-like basal portion, undivided to usually runcinately pinnatipartite, sparsely covered with long multicellular hairs, base attenuate, margin dentate; lateral lobes 3-6 pairs, triangular; terminal lobe distinctly larger than lateral ones,

apex rounded to acute. Stem leaves similar to basal leaves but smaller and less divided, gradually reduced toward stem apex, base clasping, apex acute. Synflorescence of main axis and larger branches spiciform-paniculiform. Capitula axillary and terminal, solitary or in clusters of a few, sessile or on a several cm long, thick, and apically slightly inflated peduncle, with usually 15-20 florets. Involucre cylindric, 0.9-1.4 cm. Phyllaries abaxially sparsely with glandular or simple hairs, apex ± acute; outer phyllaries lanceolate, longest > 1/2 as long as to approaching inner ones in length, spreading-erect, margin ciliate; inner phyllaries linear-lanceolate. Florets blue or exceptionally pink or bluish white. Achene brown, subcylindric to obovoid, 2-3 mm, stout, rugulose, apex truncate. Pappus 0.2-0.3 mm[65].

Traditional uses:

Historically, chicory was grown by the ancient Egyptians as a medicinal plant[66]**.** The dried and roasted roots are used as coffee substitutes and additives, young leaves can be added to salads and vegetable dishes, while chicory extracts are used for the production of invigorating beverages[67].

The plant was used traditionally for the treatment of diarrhea, to strengthen the prostate and other reproductive organs, for the treatment of pulmonary disease and cough, cancer, hangover, for purification of biliary tract, liver complaints, as spasmolytic, to relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion) and temporary loss of appetite[63-64, 68]. Among internally uses areIt was also used in sore throat, hemorrhoids, tuberculosis, abdominal cramps, melancholy, deafness, rashes and as laxative for children[69].

Parts used: Aerial part, flowers seeds and roots[63, 69]**.**

Chemical constituents:

Phytochemical analysis showed that the different parts of the plant contained sesquiterpene lactones (especially lactucin, lactucopicrin, 8-desoxy lactucin, guaianolid glycosides, including chicoroisides B and C, sonchuside C), caffeic acid derivatives (chiroric acid, chlorogenic acid, isochlorogenic acid, dicaffeoyl tartaric acid), inulin, sugars, proteins, hydroxycoumarins, flavonoids, alkaloids, steroids, terpenoids, oils, volatile compounds, coumarins, vitamins and polyynes[69-72].

18 alpha,19 beta-20(30)-taraxasten-3beta,21alpha-diol (cichoridiol) and 17-epi-methyl-6-hydroxyangolensate (intybusoloid), lupeol, friedelin, beta-sitosterol, stigmasterol, betulinic acid, betulin, betulinaldehyde, syringic acid, vanillic acid) 6,7-dihydroxycoumarin, and methyl-alpha-D-galactopyranoside were obtained from the methanolic extract of seeds of *Cichorium intybus*[73-74].

A new guaianolide sesquiterpene glycoside, cichotyboside, which was characterized as 2 alpha, 6 beta, 7 beta, 15-tetrahydroxy-1 (10), 4 (5)-diene-guaian-9alpha, 12-olide-7-O-beta-caffoyl-15-O-beta-D-glucoside, was isolated from the seeds of *Cichorium intybus*[74].

A transformed root culture of *Cichorium intybus* L. was found to produce sesquiterpene lactones of guaiane and germacrane type. Lactucopicrin, 8-desoxylactucin and three sesquiterpene lactone glycosides (crepidiaside B, sonchuside A and ixerisoside D) were isolated from the roots. The yield of 8-desoxylactucin reached 0.03 g/l at the early stationary phase of the culture[75]. Cichoriin-6'-p-hydroxyphenyl acetate, a new coumarin glucoside ester, was isolated from chicory leaves[76].

The phytochemicl screening of different parts (root, stem, leaves and seeds) of *C. intybus* showed the presence of tannins, saponins, flavonoids, terpenoids, cardiac glycosides and anthocyanins in each part. Tannins and saponins content of different parts of *Cichorium intybus* ranged from 0.66±0.02 to 1.51±0.03 and 0.16±0.08 to 0.77±0.27 g/100g dry weight. The total flavonoids (TF) and phenolic acids (TPA) content of different parts of *Cichorium intybus* ranged from 0.05±0.03 to 0.10±0.02 and 0.47±0.07 to 2.52±0.26 g/100g dry weight respectively. A statistically significant difference ($p<0.05$) was observed in phytochemical content of different parts of *Cichorium intybus*. The roots were found to possess comparatively higher content of tannins but low TPA content. Seeds were found to be high in saponins content while leaves were found to possess comparatively high TF and TPA. The total sugars, reducing sugars and non-reducing sugars content in different parts of *Cichorium intybus* ranged from 2.03±0.02 to 4.50±0.37, 0.13±0.02 to 0.44±0.10 and 1.89±0.04 to 4.27±0.37 g/100 g dry weight respectively. The water soluble protein, salt soluble protein and free amino acids content ranged from 5.57±0.58 to14.13±1.50, 6.81±0.51 to 7.94±0.30 and 1.23±0.07 to 8.46±0.24 g/100 g dry weight respectively. A statistically significant difference ($p<0.05$) was observed among various parts of *Cichorium intybus* regarding sugars free amino acids and water soluble protein contents. Leaves were found to be comparatively high in total sugars and non-reducing sugar content while the seeds were found to be high in reducing sugar content. The leaves were also found to posses higher values of free amino acids and water soluble protein content. The roots were found to contain lower amounts of all the studied contents except that of salt soluble protein content[72].

The chemical composition of the ethanol extracts of chicory root, peel, seed and leaf has been determined, in particular their inulin and phenolic fractions. The root and peel extracts were characterized by large mass fractions of inulin (60.1 and 46.8 g per 100 g of fresh mass, respectively), predominantly with degree of

polymerization in the range from 3 to 10, while phenolics, determined as caffeoylquinic acids, made up 0.5 and 1.7 g per 100 g of fresh mass, respectively. The leaf and seed extracts had decidedly lower mass fractions of inulin (1.7 and 3.2 g per 100 g of fresh mass, respectively) and higher mass fractions of phenolics (9.6 and 4.22 g per 100 g of fresh mass, respectively), which recognized as caffeoylquinic acids, chicoric acid and quercetin glucuronide[77].

The *Cichorium intybus* seeds extract/fractions contained appreciable levels of total phenolic contents (50.8-285 GAE mg/100g of Dry plant matter) and total flavonoid contents (43.3-150 CE mg/100g of dry plant matter)[78].

The flowers of chicory contain saccharides, methoxycoumarin, cichorine, flavonoids, essential oils, and anthocyanins contributing to the blue colour of the perianth[63, 79].

The aerial parts of *Cichorium intybus* contained 2,6-di[but-3(E)-en-2-onyl]naphthalene, 3,3',4,4'-tetrahydroxychalcone, scopoletin, 4-hydroxy phenylacetic acid, 3-hydroxy-4-methoxybenzoic acid, 4,4'-dihydroxychalcone, 6,7-dihydroxycoumarine, 1-triacontanol, lupeol, beta-sitosterol, as well as beta-sitosterol-3-O-beta-glucopyranoside[80].

The volatile constituents of *Cichorium intybus* were included Octane, Octen-3-ol, 2-Pentyl furan, (2E, 4E)-Heptadienal, 1,8-Cineole, Benzene acetaldehyde, *n*-Nonanal, Camphor, (2E, 6Z)-Nonadienal, (2E)-Nonen-1-al, *n*-Decanal, (2E, 4E)-Nonadienal, *n*-Decanol, (2E, 4Z)-Decadienal, *n*-Tridecane, (2E, 4E)-Decadienal, *β*-Elemene, (E)-Caryophyllene, β-Ylangene, Geranyl acetone, (E)-β-Farnesene, allo-Aromadendrene, dehydro-Aromadendrene, *β*-Ionone, Pentadecane, trans-β-Guaiene, (2E)-Undecanol acetate, Sesquicineole, (2E)-Tridecanol, *n*-Hexadecane, Tetradecanal, Tetradecanol, 2-Pentadecanone, (E)-2-Hexylcinnamaldehyde, Octadecane, *n*-Nonadecane, (5E, 9E)-Farnesyl acetone, *n*-Eicosane, *n*-Octadecanol and *n*-Heneicosane[63, 79].

Sixty four phenolic acids and flavonoids were extracted from several types of *Cichorium intybus* var. silvestre salads. Among the detected compounds, several hydroxycinnamic acid derivatives including 8 mono- and dicaffeoylquinic acids, 3 tartaric acid derivatives, 31 flavonol and 2 flavone glycosides, as well as 10 anthocyanins. Furthermore, several isomers of caffeic acid derivatives were also distinguished by their specific mass spectral data. The compounds isolated from *Cichorium intybus* var. silvestre salads were included: Caffeic acid, 3-Caffeoylquinic acid, 5-Caffeoylquinic acid, 4-Caffeoylquinic acid, *cis*-5-Caffeoylquinic acid, *cis*-Caftaric acid, *trans*-Caftaric acid, 5-Caffeoylshikimic acid, 5-*p*-Coumaroylquinic acid, Quercetin-3-O-glucuronide-7-O-(6-O malonyl)-glucoside, Kaempferol-3-O-glucosyl-7-O-(6 –O malonyl)-Glucoside, Dimethoxy cinnamoyl shikimic acid , Kaempferol-3-O-sophoroside, Isorhamnetin-7-O-(6-O-acetyl)-glucoside, 5-O-Feruloylquinic acid, Dicaffeoyltartaric acid (chicoric acid), Kaempferol-7-O-glucosyl-3-O-(6- malonyl)-glucoside, Delphinidin-3-O-(6-O-malonyl)- glucoside-5-O-glucoside, Cyanidin-3,5-di-O-(6-O-malonyl)-glucoside, Cyanidin- 3- O-(6-O-malonyl)-glucoside, Petunidin-3-O-(6-O-malonyl)-glucoside, Cyanidin , Cyanidin-3-O-galactoside, Cyanidin-3-O-glucoside, Cyanidin-3-O-(6-O-acetyl)-glucoside, Malvidin-3-O-glucoside, Pelargonidin-3-O-monoglucuronide, 4-O-Feruloylquinic acid, Apigenin-7-O-glucoside, Chrysoeriol-3-O-glucoside, Tricin-3-O-glucoside, 1,3-Dicaffeoylquinic acid, 1,4-Dicaffeoylquinic acid, 3,4-Dicaffeoylquinic acid, Quercetin-7-O-galactoside, Quercetin-3-O-(6-O-malonyl)-glucoside, Quercetin-7-O-glucoside, Quercetin-7-O-glucuronide, Quercetin -7-O-(6-O-acetyl)-glucoside, Kaempferide glucuronide, Kaempferol -7-O-glucoside, Kaempferol-7-O-rutinoside, Quercetin-7-O-p-coumaroylglucoside, Isorhamnetin-7-O-neohesperidoside, Kaempferol-7-O-(6-O-malonyl)- Glucoside, Kaempferol-7-O-glucuronide, Kaempferide-3-O-(6-O-malonyl)-glucoside, Kaempferol-3-O-glucuronide, Kaempferol-3-O-glucuronide-7-Oglucoside, Kaempferol-3-O-(6-O-malonyl)-glucoside, Kaempferol-3-O-glucoside, Myricetin-7-O-(6-O-malonyl)-glucoside, Kaempferol-7-O-neohesperidoside, Kaempferol-7-O-(6-O-acetyl)-glucoside, Kaempferol-3-O-(6-O-acetyl)-glucoside, Isorhamnetin-7-O-glucoside and Isorhamnetin-7-O-glucuronide[81].

Pharmacological effects:

Hepatoprotective effect:

The hepatoprotective activity of aqueous-methanolic extract of *Cichorium intybus* seeds was investigated against acetaminophen and CCl_4-induced hepatic damage. Acetaminophen produced 100% mortality at the dose of 1 g/kg in mice while pretreatment of animals with plant extract (500mg/kg) reduced the death rate to 30%. Acetaminophen at the dose of 640 mg/kg produced liver damage in rats as manifested by the significant ($P < 0.01$) rise in serum levels of alkaline phosphatase (ALP), GOT and GPT to 393 ± 28, 767 ± 215 and 692 ± 191 IU/l respectively, compared to respective control values of 198 ± 15, 76 ± 07 and 39 ± 09 IU/l. Pretreatment of rats with plant extract (500 mg/kg) significantly lowered ($P<0.01$) the respective serum ALP, GOT and GPT levels to 228 ± 16, 68 ± 10 and 41 ± 08 IU/l. Similarly, a hepatotoxic dose of CCl_4 (1.5 ml/kg; orally) significantly raised ($P<0.01$), the serum ALP, GOT and GPT levels to 312 ± 20, 503 ± 98 and 407 ± 109 IU/l respectively, compared to respective control values of 215 ± 16, 79 ± 18 and 49 ± 10 IU/l. The same dose of plant extract (500 mg/kg) was able to prevent significantly ($P<0.05$) the CCl_4-induced rise in serum enzymes, the estimated values of ALP, GOT and GPT were 222 ± 27, 114 ± 23 and 68 ± 14 IU/l respectively. Moreover, it prevented CCl_4-induced prolongation in pentobarbital sleeping time which further confirmed hepatoprotectivity[82].

The natural root and root callus extracts of *Cichorium intybus* were studied for their anti-hepatotoxic effects in Wistar strain of Albino rats against carbon tetrachloride induced hepatic damage. The increased levels of serum enzymes (aspartate transaminase, alanine transaminase) and bilirubin observed in rats treated with carbon tetrachloride were very much reduced in the animals treated with natural root and root callus extracts and carbon tetrachloride. The decreased levels of albumin and proteins observed in rats after treatment with carbon tetrachloride were found to increase in rats treated with natural root and root callus extracts and carbon tetrachloride. These biochemical observations were confirmed by histopathological examination of liver sections[83].

Esculetin, a phenolic compound found in *Cichorium intybus* was investigated for its possible protective effect against paracetamol and CCl_4-induced hepatic damage. Paracetamol produced 100% mortality at the dose of 1 g/ kg in mice while pre-treatment of animals with esculetin (6 mg/ kg) reduced the death rate to 40%. Oral administration of paracetamol (640 mg/ kg) produced liver damage in rats as manifested by the rise in serum enzyme levels of alkaline phosphatase (ALP) and aminotransferases (AST and ALT). Pretreatment of rats with esculetin (6 mg/ kg) prevented the paracetamol-induced rise in serum enzymes. The hepatotoxic dose of CCl_4 (1.5 ml/ kg; orally) also raised serum ALP, AST and ALT levels. The same dose of esculetin (6 mg/ kg) was able to prevent the CCl_4-induced rise in serum enzymes. Esculetin also prevented CCl_4-induced prolongation in pentobarbital sleeping time confirming hepatoprotectivity[84].

The hepatoprotective effect of ginger, chicory and their mixture against carbon tetrachloride intoxication was investigated in rats. Carbon tetrachloride treatment significantly elevated the alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyltransferase activities and the serum triglycerides and cholesterol concentration as compared to control group. It also increased RBCs counts, Hb concentration, total and differential leucocytes counts. However it decreased platelet counts, platelet distribution width, mean platelet volume, platelet larger cell ratio. Methanol extract of chicory (250 and 500 mg/kg) alone or mixed with ginger (250 and 500 mg/kg) (1:1 wt/wt) significantly restored the carbon tetrachloride-induced alterations in the biochemical and cellular constituents of blood. No toxic symptoms were reported in doses up to 5 g/kg[85].

The possible potential therapeutic and protective effects of *Cichorium intybus* (chicory) against oxytetracyclin-induced fatty liver was studied in rats. Fatty liver groups showed high significant increase in serum glucose, cholesterol, triglycerides, LDL cholesterol, ALAT, ASAT, GGT, LDH, urea, creatinine and albumin level to globulin level ratio. Total protein, albumin, globulin and HDL cholesterol were significantly decreased compared to control group. These biochemical changes were accompanied with fatty liver histopathological alterations. The treatment with chicory ameliorated most of the evaluated biochemical parameters and improved the induced degenerative histopathological changes. The pretreatment with chicory before the induction of fatty liver, gave some protection against experimentally induced fatty liver[86].

The hepatoprotective activity of aqueous-ethanolic (30:70 %) extract of fresh dried leaves of *Cichorium intybus* at the doses of 100, 200 and 300 mg/kg body weight po, was compared with Silymarin (25 mg/kg, po) treated animals. The significant changes in biochemical parameters (increases in serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alanine phosphatase (ALP) and serum tolal bilirubin (TB) level) in Nimesulide intoxicated rats, were restored towards normal values in *Cichorium intybus* leaves extract (100 mg/kg, 200 mg/kg and 300 mg/kg, po) treated animals. Histopathological examination of liver tissues further substantiated these findings[71].

Cichotyboside isolated from the seeds of *Cichorium intybus* exhibited a significant anti-hepatotoxic activity against CCl_4 induced toxicity in Wistar rats, wherein it reduced the elevated levels of liver enzymes such as serum glutamate oxaloacetate transaminase (SGOT) by 52 units/ml; SGPT 38 units/ml; ALKP 24.97 units/ml, with 7.54 g/dl, 5.48 g/dl increase in total protein and albumin, respectively. It was observed that cichotyboside decreased the level of ALKP comparable with that of standard drug silymarin, exhibiting an 88% decrease in comparison to silymarin (92%) and increased the level of total albumin 85% in comparison to silymarin (89%) against intoxicated control. Whereas, the levels of SGOT and SGPT were also decreased considerably in comparison to standard and intoxicated control[74].

Cichorium root extract therapy normalized some morphofunctional liver features (decreases glycogen content and necrosis and increases the number of cells with pronounced protein synthesis activity in rats with CCl_4-induced hepatitis[87].

The effects of *Cichorium intybus* root extracts at different doses were tested against CCl_4 induced rats liver toxicity. The elevated serum markers and liver tissue microvesicular steatosis were significantly reduced in *Cichorium intybus* groups at 150-450 or 200-500 mg/kg/day[88-89].

The effect of chicory (*Cichorium intybus* L.) seed extract was evaluated in hepatic steatosis caused by early and late stage diabetes in rats, and induced in HepG2 cells (*in vitro*) by BSA-oleic acid complex (OA). Different dosages of *Cichorium intybus* seed extract (1.25, 2.5 and 5 mg/ml) were applied along with OA (1 mM) to HepG2 cells, simultaneously and non-simultaneously; and without OA to ordinary non-steatotic cells. Cellular

lipid accumulation and glycerol release, and hepatic triglyceride (TG) content were measured. The expression levels of sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor alpha (PPARα) were determined. Significant histological damage (steatosis-inflammation-fibrosis) to the cells and tissues and down-regulation of SREBP-1c and PPARα genes that followed steatosis induction were prevented by *Cichorium intybus* seed extract in simultaneous treatment. In non-simultaneous treatment, *Cichorium intybus* seed extract up-regulated the expression of both genes and restored the normal levels of the corresponding proteins; with a greater stimulating effect on PPARα, *Cichorium intybus* seed extract acted as a PPARα agonist. *Cichorium intybus* seed extract released glycerol from HepG2 cells, and targeted the first and the second hit phases of hepatic steatosis[90].

Adding of extracts of *Cichorium intybus* in the reaction mixture containing calf thymus DNA and free radical generating system protect DNA against oxidative damage to its deoxyribose sugar moiety. The effect was dependent on the concentration of plant extracts. However, the effect of *Cichorium intybus* was pronounced. The result revealed that the observed hepatoprotective effect of crude *Cichorium intybus* extract may be due to its ability to suppress the oxidative degradation of DNA in the tissue debris[91].

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 (LD_{50} = 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^+, Ca^{2+} and Mg^{2+} 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%)[92].

Hypoglycemic and hypolipidemic effects:

Ischemic manifestations and cerebral dysfunction have been demonstrated in diabetes. Otherwise, the impairment in the glycemic control is the basic mechanism causing inhibition of neuronal activity. Cerebral extract from alloxan diabetic rats significantly inhibited the brain AChE activity of normal animals, indicating the presence of an inhibiting factor in the cerebrum of diabetic rats. *Cichorium intybus* when fed for 10 days offered neuroprotection in diabetic rats by stimulating AChE activity[93].

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[94].

The effect of *Cichorium intybus* methanolic extract (CME) on glucose transport and adipocyte differentiation in 3T3-L1 cells was investigated by studying the radiolabelled glucose uptake and lipid accumulation assays. By performing detannification (CME/DT), the role of tannins present in CME on both the activitie`s was evaluated. CME and CME/DT exhibited significant glucose uptake in 3T3-L1 adipocytes with a dose-dependent response. CME inhibited the differentiation of 3T3-L1 preadipocytes but failed to show glucose uptake in inhibitor treated cells. The activity exhibited by CME/DT is exactly vice versa to CME. Furthermore, the findings from PTP1B inhibition assay, mRNA and protein expression analysis revealed the unique behavior of CME and CME/DT. Accordingly, the activities possessed by *Cichorium intybus* are highly desirable for the treatment of NIDDM because it reduces blood glucose levels without inducing adipogenesis in 3T3-L1 adipocytes[95].

The direct action of soluble fibers (chicory water-soluble extract and inulin) was investigated on the intestinal absorption of glucose in gut perfused rats. After equilibrium, both jejunal and ileal segments were simultaneously perfused with an isotonic electrolyte solution (pH 7.4) containing glucose (10 mmol/l) and chicory water-soluble extract (chicory extract) or inulin (10 g/l). Each test or control solution was perfused in random sequence, with perfusion times of 30 min. Chicory extract or inulin in the perfusate (10 g/l) inhibited the absorption of glucose from jejunum ($P<0.05$). The observed changes in glucose and water absorption caused by chicory extract or inulin were reversible after switching to a fiber free perfusate. Additionally, net water absorption changed to secretion upon addition of chicory extract or inulin. The authors concluded that the reduction in intestinal absorption of glucose observed after perfusion of chicory extract or inulin may be caused by viscosity-related increases in mucosal unstirred layer thickness[96].

In vitro experiments were designed to compare the effects of two hydroxycinnamic acids, caffeic and ferulic acids, to those obtained with a natural chicoric acid extract (NCRAE) (50 and 100 µg/ml) on the three major

tissues implicated in glycemic regulation (pancreas, muscle and liver). *In vivo* experiments were performed in Wistar rats submitted to a daily intraperitoneal injection of natural chicoric acid extract NCRAE (3, 15 or 30 mg/ kg) for 4 days. On the fourth day, an intraperitoneal glucose tolerance test (IPGTT; 1 g/ kg) was carried out. Results showed that the three compounds used were able each to induce an original response. Caffeic acid mainly promoted a decrease in hepatic glycogenolysis. Ferulic acid elicited a clear increase of insulin release and a reduction of hepatic glycogenolysis. However, this compound induced an inhibition of muscle glucose uptake. NCRAE provoked an increase of insulin release and glucose uptake without any effect on hepatic glycogenolysis. None of these compounds implicated hepatic glucose 6-phosphatase in contrast to chlorogenic acid, known as an inhibitor of glucose 6-phosphatase and which is able to decrease glucose output from hepatocytes. *In vivo* experiments bring evidence that 4 daily ip administrations of NCRAE improve ip glucose tolerance in a dose-dependent manner and mainly via an insulin sensitizing effect[97].

The effects of a high-fructose diet supplemented with rutin and a chicory (*Cichorium intybus* L.) seed extract rich in caffeoylquinic acids (CQA) was tested on gut physiology and the development of disorders related to metabolic syndrome. A 28-days experiment was conducted on 32 young male Wistar rats. In comparison with control rats fed a standard corn starch diet (group C), the experimental group (group E) was fed a diet with an increased content of cholesterol and fructose (to 1% and 66% of the diet, respectively), as well as with oxidized soybean oil. Rats from the other two experimental groups were administered the same diet as group E during the first 2 wks of feeding, whereas at the beginning of the last 2 wks, the diet was enriched with rutin (group ER) or the CQA-rich ethanol extract from chicory seeds (9.6% of CQA, group EC), so the amount of added phenolics was equal in both dietary groups (0.15%). The diet administered in group E caused hyperglycemia and increased blood serum atherogenicity in rats, but did not induce other manifestations of the metabolic syndrome, i.e., dyslipidemia and oxidative stress. Additionally, it affected gut physiology through increasing mucosal sucrase activity and disturbing fermentative processes in the cecum, such as the production of short-chain fatty acids and the activity of microbial enzymes. Similarly to rutin, the dietary addition of the chicory seed extract improved glycemia, which was comparable to that determined in group C. In addition, the extract was found to decrease the atherogenic index to the level observed in group C and to increase blood antioxidant status. Both dietary supplements reduced the content of thiobarbituric acid-reactive substances in kidney and heart tissue when compared with group E[98].

The effects of different chicory extracts on the blood glucose, total cholesterol (TC) and triglycerides (TG) was studied in hyperglycemic mouse model. It was found that the chicory alcohol soluble extract can decrease the blood glucose, TC and TG, which is more effective than the chicory alcohol deposit extracts[99].

Anti-inflammatory effect:

Ethyl acetate chicory root extract produced a marked inhibition of prostaglandin E_2 (PGE_2) production in human colon carcinoma HT29 cells treated with the pro-inflammatory agent TNF-alpha. Two independent mechanisms of action were identified: (1) a drastic inhibition of the induction by TNF-alpha of cyclooxygenase 2 (COX-2) protein expression and (2) 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[100].

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[101].

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 from the activity[102].

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[103].

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[104].

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[105].

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 ($P<0.01$)[106].

Effect on energy homoeostasis:

The effect of chicory (*Cichorium intybus*) salad leaves in inhibiting protein tyrosine phosphatase 1B (PTP1B) was studied with evaluation of their role in modulating the key markers involved in insulin cell signalling and adipogenesis using 3T3-L1 adipocytes. Purification studies enlightened the additive effects of chlorogenic acid (CGA) along with other caffeic acid derivatives present in methanolic extract of *Cichorium intybus* (CME). Incubation of CME and CGA with 3T3-L1 adipocytes significantly enhanced the 2-deoxy-d-^{3}[H]-glucose uptake and inhibited adipogenesis through altering the expressions of insulin signalling and adipogenesis markers. The effect of CME was also investigated on insulin sensitivity in high-fat diet with low streptozotocin-induced diabetic rats. Supplementation of CME for 2 weeks reinstated the insulin sensitivity along with plasma metabolic profile. Accordingly, the results demonstrate that the caffeoyl derivatives of chicory salad leaves show promising pharmacological effect on energy homoeostasis via PTP1B inhibition both *in vitro* and *in vivo*[107].

Cardiovascular effect:

Pharmacological study of eight varieties of *Cichorium intybus* on isolated toad's heart showed that the eight varieties have a quinidine like action, but with variable potency. The site of action was determined on a representative sample where it produced effect after blocking the ganglia and after atropinisation[108].

The vasorelaxant activities of chicoric acid from *Cichorium intybus* along with caffeic acid were studied in isolated rat aorta strips. chicoric acid , a diester composed of (S,S)-tartaric acid and caffeic acid, showed slow relaxation activity against norepinephrine (NE)-induced contraction of rat aorta with/without endothelium. These compound did not affect contraction induced by a high concentration of potassium (60 mM K^{+}), while it inhibited NE-induced vasocontraction in the presence of nicardipine. The results revealed that the inhibition of NE-induced vasocontraction is due to a decrease in calcium influx from the extracellular space, which enhanced by NE[109].

The detoxification role of *Cichorium intybus* was evaluated in Cisplatin - induced toxicity on electrolyte balance in rats. At a dose of 500 mg/kg bw of *Cichorium intybus* ethanolic extract pretreatment showed partial counter action on the electrolytes imbalances and Na^{+}-K^{+}-ATPase activity[110].

Caffeine-free chicory coffee is a rich source of plant phenolics, including caffeic acid, which inhibits *in vitro* platelet aggregation, and also phenylpyruvate tautomerase enzymatic activity of the proinflammatory cytokine,

macrophage migration inhibitory factor (MIF). The cardiovascular benefits of chicory coffee consumption were assessed on 27 healthy volunteers, who consumed 300 ml chicory coffee every day for 1 week. The dietary intervention produced variable effects on platelet aggregation, depending on the inducer used for the aggregation test. Whole blood and plasma viscosity were both significantly decreased, along with serum MIF levels, after 1 week of chicory coffee consumption. Moreover, significant improvements were seen in red blood cell deformability. No changes in hematocrit, fibrinogen level or red blood cell counts were detected. The full spectrum of these effects is unlikely to be attributable to a single compound present in chicory coffee, nevertheless, the phenolics, including caffeic acid, are expected to play a substantial role[111].

Immunological effect:

The effects of the ethanol extract of *Cichorium intybus* (CIEE) on the immunotoxicity of ethanol (EtOH) were investigated in mice. CIEE at dose of 300 mg/kg was orally administered to mice daily for 28 consecutive days. The combination of CIEE and EtOH showed significant increases in the circulating leukocytes and the relative weights of liver, spleen and thymus, as compared with those in mice treated with EtOH alone. However, the body weight gain was not affected. Splenic plaque forming cells (PFC) and hemagglutination (HA) titers to sheep red blood cells (SRBC), and the secondary IgG antibody response to bovine serum albumin (BSA) were markedly enhanced by CIEE plus EtOH treatment as compared with EtOH alone. In mice receiving the combination of CIEE and EtOH when compared with EtOH alone-treated mice. There were also significant increases in delayed-type hypersensitivity (DTH) reaction, phagocytic activity, natural killer (NK) cell activity and cell proliferation as well as interferony (IFN-gamma) secretion. Interleukin-4 (IL-4) content showed insignificant induction by CIEE plus EtOH treatment. Accordingly, findings indicate that the immunotoxicity induced by EtOH is significantly restored or prevented by CIEE treatment[112].

The effect of an aqueous extract of *Cichorium intybus* (CIAE) on mast cell-mediated immediate type allergic reactions was studied. CIAE (0.1-1000 mg/kg) dose-dependently inhibited systemic anaphylactic reaction induced by compound 48/80 in mice. CIAE inhibited compound 48/80-induced anaphylactic reaction 100% with the dose of 1000 mg/kg. CIAE 1000 mg/kg, also significantly inhibited local anaphylactic reaction activated by anti-dinitrophenyl (DNP) IgE. When mice were pretreated with CIAE at a concentration ranging from 0.1 to 1000 mg/kg, the plasma histamine levels were reduced in a dose-dependent manner. CIAE (1-1000 microg/ml) dose-dependently inhibited histamine release from the rat peritoneal mast cells (RPMC) activated by compound 48/80 or anti-DNP IgE. When CIAE (1000 microg/ml) was added to RPMC, the level of cAMP in RPMC, increased significantly compared with that of control cells. The results indicate that CIAE inhibits mast cell-mediated immediate-type allergic reactions *in vivo* and *in vitro*[113].

Antioxidant effect:

The *Cihorium intybus* seed extract/fractions exhibited good DPPH radical scavenging activity, with IC_{50} ranging from 21.28-72.14 µg/ml. 100% methanolic extract and ethylacetate fraction exhibited the maximum antioxidant activity. However, the results showed significant ($p<0.01$) variations in the antioxidant activities of *Cihorium intybus* seeds solvent extract/fractions[78].

The efficacy of *Cihorium intybus* leaves powder to minimize the oxidative damage, causing brain dysfunction in diabetes, was studied in rats. Diabetes was induced with alloxan monohydrate. Oxidative damage, impairment of oxidative defense and neuronal activity were investigated in cerebral hemispheres 48 h after alloxan administration. Diabetes caused an elevation ($p<0.001$) of blood glucose, protein carbonyl content (PrC) and lipid peroxidation. The brain level of the antioxidant enzyme, catalase (CAT), reduced glutathione (GSH) and acetyl cholinesterase (AChE) exhibited significant decline in alloxan-diabetes. Feeding with dried powder leaves of *Cihorium intybus* decreased blood glucose level to near normal level and minimize the impairment of oxidative defense[114].

The antioxidant properties of *Cichorium intybus* var. Silvestre, from Italy, were investigated *in vitro*. Vegetable juices were obtained by centrifugation, and (1) filtration at 2 degrees C; (2) filtration at 25 degrees C, and stored for 3 h; (3) boiled for 30 min at 102 degrees C, and then analysed. The antioxidant properties were evaluated *in vitro* as antioxidant activity (AA) (model system beta-carotene-linoleic acid) and ex vivo as protective activity (PA) against rat liver cell microsome lipid peroxidation measured as 2-thiobarbituric acid-reactive substances (TBA-RS) generated by peroxide degradation. All the vegetable juices showed high but very variable AA (> 83%) and PA (> 64%). After dialysis and analysis of fractions it was shown that the vegetable contained both biological antioxidant and prooxidant compounds. The prooxidants had MW < 3000, the most potent antioxidants compound (PA = 100%) had MW > 15000[115].

Statistically significant differences ($p<0.05$) were observed in the DPPH radical scavenging capacities of different parts of *Cichorium intybus* . Leaves were found to possess comparatively good free radical scavenging capacity due to higher DPPH radical inhibition and lower IC_{50} value. However, all parts of *Cichorium intybus* showed lower percentage of DPPH radical inhibition and higher IC_{50} values as compared to those of Trolox and ascorbic acid taken as standard antioxidants[116].

Cell injury associated with reactive oxygen species (ROS) has been reported in various muscular disorders. *Cichorium intybus* extract reduced H_2O_2-induced viability loss in myoblasts, inhibited oxidative stress-induced apoptosis and increased intracellular heat shock protein 70 (Hsp 70) expression. *Cichorium intybus* extract also inhibited the level of intracellular ceramide. These results indicate that *Cichorium intybus* extract may prevent skeletal muscle atrophy by inducing the expression of Hsp 70 and inhibiting the level of ceramide[117].

The Total phenolic compounds increased from 22.34 to 27.87 mg GAE (gallic acid equivalents)/100 g (dry extracts) with increasing solvent polarity. The half inhibition concentration (IC_{50} µg/ml) of the radical scavenging activity of the chicory extracts ranged from 281.00 to 983.33 µg/ml. The content of caffeoylquinic acids of root extract, which was extracted by the optimal combination was 0.104%[118].

Anticancer effect:

Ethanolic extract of chicory root showed a tumour-inhibitory effect against Ehrlich ascites carcinoma in mice. A 70% increase in the life span was observed with a 500 mg/kg/day intraperitoneal divided over 8 doses[119].

Magnolialide, a 1β-hydroxyeudesmanolide isolated from the roots of *Cichorium intybus*, inhibited several tumor cell lines and induced the differentiation of human leukemia HL-60 and U-937 cells to monocyte or macrophage-like cells[120].

The aqueous-alcoholic macerate of the leaves of *Cichorium intybus* exerted an antiproliferative effect on amelanotic melanoma C32 cell lines[121].

The anticancer properties of aqueous extracts of *Cichorium intybus* was studied against cell lines including human prostate cancer PC-3 cells, human breast carcinoma T47D cells and colon cancer RKO cells. Extract of *Cichorium intybus* demonstrated a modest cell growth inhibition in all three cancer cell lines. *Cichorium intybus* (seeds) exhibited 5-24% inhibition in cell viability at 1.0 to10% concentration for 24 hours[122].

Chicory contained photosensitive compounds such as cichoriin, anthocyanins, lactucin, and lactucopicrin. The protective effect of sun light-activated chicory against dimethylbenz[a]anthracene (DMBA) induced benign breast tumors was investigated in female Sprague-Dawley rats. Chicory's extract was significantly increased P. carbonyl (PC) and malondialdehyde (MDA) and decreased the hepatic levels of total antioxidant capacity (TAC) and superoxide dismutase (SOD) in benign breast tumors-induced group compared to control. It also significantly decreased the number of estrogen receptors ER-positive cells in tumor masses[123].

Antimicrobial effect:

The antibacterial effect of *Cichorium intybus* extracts was examined against Gram Positive (*Bacillus subtilis*, *Staphylococcus aureus* and *Rhizobium leguminosarum*) and Gram negative (*Vibrio cholerae*, *Escherichia coli* and *Pseudomonas fluorescens*) bacterial species & two fungal (*Aspergilus niger* and *Sachharomyces cerevisiae*) species. The ethyl acetate extract of chicory root showed antibacterial effects against Gram positive and Gram negative bacteria. Hexane extract of chicory on the other hand showed no such antibacterial effect[124].

The low molecular mass (LMM) extract of *Cichorium intybus* var. Silvestre (red chicory) has been shown to inhibit virulence-linked properties of oral pathogens including *Streptococcus mutans, Actinomyces naeslundii* and *Prevotella intermedia*. HPLC-DAD-ESI/MS(2) was used to investigate the compounds contained in this extract for their anti-virulence activity. The extract contained a number of components, including oxalic, succinic, shikimic and quinic acids, which interfere with the growth and virulence traits (i.e., biofilm formation, adherence to epithelial cells and hydroxyapatite) of oral pathogens involved in gingivitis and tooth decay. Succinic and quinic acid seem to be the most potent, mainly by interfering with the ability of oral pathogens to form biofilms (either through inhibition of their development or promotion of their disruption). The authors poastulated that one or more of these compounds may modulate plaque formation *in vivo*, which is a prerequisite for the development of both caries and gingivitis[125].

The antibacterial activity of the root extracts of chicory was examined against pathogenic bacteria, Gram positive (*Bacillus subtilis, Staphylococcus aureus* and *Micrococcus luteus*) and Gram negative (*Escherichia coli* and S*almonella typhi*) bacteria by *in vitro* agar well diffusion method. The hexane and ethyl acetate root extracts of chicory showed pronounced inhibition than chloroform, petroleum ether and water extracts. Root extracts showed more inhibitory action on *Bacillus subtilis, Staphylococcus aureus* and S*almonella typhi* than *Micrococcus luteus* and *Escherichia coli*[70].

The root and leaf extracts (methanol, distilled water, chloroform, petroleum ether and acetone) of *Cichorium intybus* were investigated for antibacterial activity against Gram negative pathogenic bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The extracts showed a wide spectrum of inhibition against the test pathogens. Methanolic extract of root and leaf proved to have the strongest antibacterial activity. Antibacterial activity of the test extracts at different inhibitory concentration varied significantly at 0.05 level of significance. The maximum activity was recorded at 200mg/ml concentration, the activity decreased with the decreasing of the concentration of the extract[126].

Several extracts displayed antibacterial activities against *Escherichia coli*, *Staphylococcus aureus, Bacillus thuringiensis, Bacillus subtilis*, and *Salmonella typhi*, while *Penicillium* sp. and *Aspergillus* sp. resisted all the extracts[118].

Synergistic activity of *Cichorium intybus* extracts and commonly used antibiotics, amoxicillin and chloramphenicol, were evaluated. Interactions between plant extract and antibiotics were tested against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and clinical isolates *Staphylococcus aureus*, *Bacillus subtilis*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus mirabilis*. The combinations of acetone and ethyl acetate extract from *Cichorium intybus* and antibiotics resulted in additive effects against the tested bacteria[127].

The antimicrobial effectiveness of methanolic extract and different fractions (*n*-butanol, ethyl acetate, chloroform and *n*-hexane) of *Cichorium intybus* seeds was studied *in vitro*. The antimicrobial activity was determined by the disc diffusion method and minimum inhibitory concentration (MIC) against four bacterial strains (*P. multocida, E. coli, B. subtilis* and *S. aureus*) and three fungal strains(*A. flavus, A. niger and R. solani*). The results indicated that seeds methanolic extract and its fractions showed moderate activity as antibacterial agent. While Antifungal activity of *Cichorium intybus* seeds extract/fractions was very low against A. *flavus* and *A. niger* and mild against *R. solani*[78].

The ethyl acetate extract of chicory root had antifungal effect against *Aspergillus niger* and *Sachharomyces cerevisiae*[124].

Guaianolides-rich root extracts of *Cichorium intybus* have shown antifungal properties against anthropophilic fungi *Trichophyton tonsurans, T. rubrum,* and *T. violaceum*[128].

The antiviral activity of protein extracts from transgenic plants of *Cichorium intybus* was investigated against vesicular stomatitis virus. It was shown that the extracts from the hairy roots of chicory possess antiviral activity[129].

II. ANTHELMINTIC AND ANTI-PROTOZOAL EFFECTS

It appeared that the animals grazing on chicory have a lower incidence of gastrointestinal nematode infestations, the total number of abomasal helminths was found to be lesser in the lambs grazing on this plant. The anthelmintic activity of the plant attributed to the condensed tannins and sesquiterpene lactones[130-131].

The effects of condensed tannins (CT) and an extract containing crude sesquiterpene lactones (CSL) from chicory (*Cichorium intybus*) on the motility of the first-(L1) and third-stage (L3) larvae of deer lung worm *Dictyocaulus viviparus* and the L3 larvae of gastrointestinal nematodes was studied *in vitro*, using the larval migration inhibition (LMI) assay. The CT and CSL had a profound effect on the motility of the larvae displayed by their ability to inhibit larval passage through nylon mesh sieves. Incubation of lungworm L1 larvae in rumen fluid (collected from deer fed pasture) containing 100, 400 and 1000 microg CT/ml, inhibited 12, 28 and 41% of the larvae from passing through the sieves, respectively, while the incubation of L3 larvae with rumen fluid (pH 6.6) containing the same concentrations inhibited 26, 37 and 67% of L3 larvae from passing through the sieves, respectively. Gastrointestinal larvae seem more susceptible to CT than lungworm larvae especially at higher concentrations. CT inhibited 27, 56 and 73% of gastrointestinal larvae from passing through the sieves when used at a concentration of 100, 400 and 1000 microg/ml, respectively. CT were more effective ($P<0.001$) at reducing the motility of lungworm L1 and L3 larvae when added to the rumen fluid than when added to the abomasal fluid (pH 3.0). Addition of 2 microg polyethylene glycol/microg CT eliminated the inhibitory effect of CT against L1 and L3 larvae especially during incubation in rumen fluid, confirming the effect as due to CT. The CSL extract also showed similar inhibitory activity against L1 and L3 lungworm and L3 gastrointestinal larvae in both fluids, indicating that this extract was not affected by the pH of the fluid, and was more effective against L3 than L1 lungworm larvae. Condensed tannins appeared to be more effective than CSL at inactivating L1 and L3 lungworm and L3 gastrointestinal larvae in rumen fluid, but CSL were particularly effective against L3 lungworm larvae in abomasal fluid[132].

To determine whether the individual sesquiterpene lactone compounds of *Cichorium intybus* [lactucin (LAC), 8-deoxylactucin (DOL), and lactucopicrin (LPIC)] differ in anthelmintic activity, their effects were studied on the hatching of a predominantly *Haemonchus contortus* egg population. The dominant constituents in the Puna and Forage Feast extracts were DOL and LAC, respectively; LPIC concentrations in the two extracts were similar. Extracts from both cultivars inhibited egg hatching at all concentrations tested ($P<0.001$), but there were significant differences in egg responses to the two extracts ($P<0.001$). With Puna, egg hatching decreased sharply in a linear fashion when the combined LAC, DOL, and LPIC concentrations ranged from 0 to 5.0 mg/ml. A biphasic effect on egg hatching occurred with the Forage Feast extract. The fraction of eggs that hatched decreased gradually to 65% as the sesquiterpene lactone concentrations increased from 0 to 6.7 mg/ml. Treatment with higher concentrations resulted in a sharp decline in egg hatchability. Concentrations of sesquiterpene lactones required for 50% lethality were determined by probit dose-effect analysis to be 2.6 mg/ml (95% confidence interval: 2.4-2.8 mg/ml) for the Puna extract and 6.4 mg/ml (95% confidence interval: 5.9-7.2mg/ml) for the Forage Feast extract ($P<0.0001$). These concentrations provided 1.3 and 1.5mg/ml of DOL and 0.8 and 3.9 mg/ml of LAC for Puna and Forage Feast extracts, respectively. However, the results showed that LAC has minimal effect on egg hatching[133].

The bitter compounds in the plant, namely, lactucin, lactucopicrin, and the guaianolide sesquiterpenes, isolated from aqueous root extracts of chicory were concluded to be the antimalarial components of the plant. Lactucin and lactucopicrin completely inhibited the HB3 clone of strain Honduras-1 of *Plasmodium falciparum* at concentrations of 10 and 50 μg/ml, respectively[134-135].

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[69].

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[136].

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[121].

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[101].

III. 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[69].

IV. CONCLUSION

This review discuss the chemical constituent, pharmacological and therapeutic effects of *Cichorium intybus* as promising herbal drug because of its safety and effectiveness.

REFERENCES

1-Vickers A. and Zollman C. ABC of complementary medicine herbal medicine.BMJ 1999; 319: 1050-1053.

2- Al-Snafi AE. Chemical constituents and pharmacological importance of *Agropyron repens* – A review. Research Journal of Pharmacology and Toxicology 2015; 1 (2): 37-41.

3-Al–Snafi AE. Pharmacology and medicinal properties of *Caesalpinia crista* - An overview. International Journal of Pharmacy 2015; 5(2): 71-83.

4-Al-Snafi AE. The chemical constituents and pharmacological effects of *Calendula officinalis* - A review. Indian Journal of Pharmaceutical Science & Research 2015; 5(3): 172-185.

5-Al-Snafi AE. The constituents and pharmacological properties of *Calotropis procera* - An Overview. International Journal of Pharmacy Review & Research 2015; 5(3): 259-275.

6-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with hypolipidemic, hemostatic, fibrinolytic and anticoagulant effects (part 1). Asian Journal of Pharmaceutical Science & Technology 2015; 5(4): 271-284.

7- Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their effect on reproductive systems (part 1). Ind J of Pharm Sci & Res 2015; 5(4): 240-248.

8-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their gastro-intestinal effects (part 1). Ind J of Pharm Sci & Res 2015; 5(4): 220-232.

9-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their antiparasitic, antiprotozoal, molluscicidal and insecticidal activity (part 1). J of Pharmaceutical Biology 2015; 5(3): 203-217.

10-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with antidiabetic effects (part 1). J of Pharmaceutical Biology 2015; 5(3): 218-229.

11-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with antifungal activity (part 1). Int J of Pharm Rev & Res 2015; 5(3):321-327.

12-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their dermatological effects (part 1). Int J of Pharm Rev & Res 2015; 5(4):328-337.

13-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with anticancer activity (part 1). Int J of Pharmacy 2015; 5(3): 104-124.

14-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with anti-inflammatory, antipyretic and analgesic activity (part 1). Int J of Pharmacy 2015; 5(3): 125-147.

15-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their immunological effects (part 1). Asian Journal of Pharmaceutical Research 2015; 5(3): 208-216.

16-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their antibacterial activity (part 1). International Journal of Pharmacology and Toxicology 2015; 6(3): 137-158.
17-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with antioxidant activity (part 1). International Journal of Pharmacology and Toxicology 2015; 6(3): 159-182.
18-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their respiratory effects (part 1). International Journal of Pharmacological Screening Methods 2015; 5(2):64-71.
19-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their antiviral activity (part 1). International Journal of Pharmacological Screening Methods 2015; 5(2): 72-79.
20-Al-Snafi AE. Galactagogue action of the crude phenolic extracts of grape seeds (*Vitis vinifera*). International Journal of Biological & Pharmaceutical Research 2015; 6(8): 577-580.
21-Al-Snafi AE. Mammary gland stimulating effects of the crude phenolic extracts of green tea (*Camellia sinensis*). International Journal of Biological & Pharmaceutical Research 2015; 6(7): 573-576.
22-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with cardiovascular effects (part 1). Int J of Pharmacology & Toxicology 2015; 5(3): 163-176.
23-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of medicinal plants with central nervous effects (part 1). Int J of Pharmacology & Toxicology 2015; 5(3): 177-192.
24-Al-Snafi AE. The pharmacological Importance of *Antirrhinum majus* - A review. Asian J of Pharm Sci & Tech 2015; 5(4): 313-320.
25-Al-Snafi AE. Chemical constituents and pharmacological effects of *Astragalus hamosus* and *Astragalus tribuloides* grown in Iraq. Asian J of Pharm Sci & Tech 2015; 5(4): 321-328.
26-Al-Snafi AE. The Pharmacological Importance of *Ballota nigra* –A review. Ind J of Pharm Sci & Res 2015; 5(4): 249-256.
27-Al-Snafi AE. Chemical constituents and pharmacological importance of *Bidens tripartitus* - A review. Ind J of Pharm Sci & Res 2015; 5(4): 257-263.
28-Al-Snafi AE. The pharmacological importance of *Brassica nigra* and *Brassica rapa* grown in Iraq. J of Pharm Biology 2015; 5(4): 240-253.
29-Al-Snafi AE. The chemical constituents and pharmacological importance of *Celosia* cristata – A review. J of Pharm Biology 2015; 5(4): 254-261.
30-Al-Snafi AE. The pharmacological importance of *Centaurea cyanus*- A review. Int J of Pharm Rev & Res 2015; 5(4): 379-384.
31-Al-Snafi AE. The chemical constituents and pharmacological importance of *Chrozophora tinctoria*. Int J of Pharm Rev & Res 2015; 5(4): 391-396.
32-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants affected smooth muscles functions (part 1). Int J of Pharmacy 2015; 5(2): 90-97.
33-Al-Snafi AE. Medicinal plants with anti-urolithiatic effects (part1). Int J of Pharmacy 2015; 5(2): 98-103.
34- Al-Snafi AE, Allahwerdi, IY. and Jawad IA. Using of topical 5% urtica dioica ointment in treatment of psoriasis. European Journal of Biomedical and Pharmaceutical Sciences 2015; 2(4):103-111.
35-Al-Snafi AE. The pharmacological importance of Capsicum species (*Capsicum annuum* and *Capsicum frutescens*) grown in Iraq. Journal of Pharmaceutical Biology 2015; 5(3): 124-142.
36-Al-Snafi AE. Therapeutic properties of medicinal plants: a review of their detoxification capacity and protective effects (part 1). Asian Journal of Pharmaceutical Science & Technology 2015; 5(4): 257-270.
37-Al-Snafi AE. Cardiovascular effects of *Carthamus tinctorius*: A mini-review. Asian Journal of Pharmaceutical Research 2015; 5(3): 199-209.
38-Al-Snafi AE, Wajdy JM and Tayseer Ali Talab. Galactagogue action of *Nigella sativa* seeds. IOSR Journal of Pharmacy 2014; 4(6): 58-61.
39-Al-Snafi AE. The chemical constituents and pharmacological effects of *Adiantum capillus-veneris* - A review. Asian Journal of Pharmaceutical Science and Technology 2015; 5(2): 106-111.
40-Al-Snafi AE. The pharmacological and therapeutic importance of *Agrimonia eupatoria*- A review. Asian Journal of Pharmaceutical Science and Technology 2015; 5(2): 112-117.
41-Al-Snafi AE. The chemical constituents and pharmacological effects of *Ammannia baccifera* - A review. International Journal of Pharmacy 2015; 5(1): 28-32.
42-Al-Snafi AE. The chemical constituents and pharmacological importance of *Carthamus tinctorius* - An overview. Journal of Pharmaceutical Biology 2015; 5(3): 143-166.
43- Al-Snafi AE. Clinically tested medicinal plant: A review (Part 1). SMU Medical Journal 2016; 3(1): 99-128.
44-Al-Snafi AE. The pharmacological importance of *Artemisia campestris*- A review. Asian Journal of Pharmaceutical Research 2015;5(2): 88-92.
45-Al-Snafi AE. Chemical constituents and pharmacological effects of *Asclepias curassavica* – A review. Asian Journal of Pharmaceutical Research 2015; 5(2): 83-87.

46-Al-Snafi AE. The pharmacological importance of *Asparagus officinalis* - A review. Journal of Pharmaceutical Biology 2015; 5(2): 93-98.
47-Al-Snafi AE. The medical importance of *Betula alba* - An overview. Journal of Pharmaceutical Biology 2015; 5(2): 99-103.
48-Al-Snafi AE. Bioactive components *and* pharmacological effects of *Canna indica*- An overview. International Journal of Pharmacology and toxicology 2015; 5(2):71-75.
49-Al-Snafi AE. The chemical constituents and pharmacological effects of *Capsella bursa-pastoris* - A review. International Journal of Pharmacology and toxicology 2015; 5(2):76-81.
50-Al-Snafi AE. The pharmacological importance of *Ailanthus altissima*- A review. International Journal of Pharmacy Review and Research 2015; 5(2):121-129
51-Al-Snafi AE. *Alhagi maurorum* as a potential medicinal herb: An Overview. International Journal of Pharmacy Review and Research 2015; 5(2):130-136.
52-Al-Snafi AE. The pharmacological importance of *Aloe vera*- A review. International Journal of Phytopharmacy Research 2015; 6(1) : 28-33.
53-Al-Snafi AE. The constituents and biological effects of *Arundo donax* - A review. International Journal of Phytopharmacy Research 2015; 6(1): 34-40.
54- Al-Snafi AE. The nutritional and therapeutic importance of *Avena sativa* - An Overview. International Journal of Phytotherapy 2015; 5(1): 48-56.
55-Al-Snafi AE. The Pharmacological importance of *Bellis perennis* - A review. International Journal of Phytotherapy 2015; 5(2): 63-69.
56-Al-Snafi AE. The chemical constituents and pharmacological effects of *Capparis spinosa* - An overview. Indian Journal of Pharmaceutical Science and Research 2015; 5(2): 93-100.
57-Al-Snafi AE. The chemical constituents and pharmacological effects of *Carum carvi* - A review. Indian Journal of Pharmaceutical Science and Research 2015; 5(2): 72-82.
58-Al-Snafi AE. The pharmacological importance of *Casuarina equisetifolia* - An Overview. International Journal of Pharmacological Screening Methods 2015; 5(1): 4-9.
59-Al-Snafi AE. The chemical constituents and pharmacological effects of *Chenopodium album* - An overview. International J of Pharmacological Screening Methods 2015; 5(1): 10-17.
60- Al-Snafi AE. Chemical constituents and pharmacological effects of *Clerodendrum inerme*- A review. SMU Medical Journal 2016; 3(1): 129-153.
61-USDA, ARS, National Genetic Resources Program. Germplasm Resources Information Network-(GRIN). National Germplasm Resources Laboratory, Beltsville, Maryland. URL: http://www.ars-grin.gov.4/cgi-bin/npgs/html/taxon. pl?10543 (18 June 2015)

62-United State Department of Agriculture, Natural resources conservation Service. Plant Database, *Cichorium intybus* L.**,** chicory, http://plants.usda.gov/core/profile? symbol=ciin
63-Street RA, Sidana J and Prinsloo G. *Cichorium intybus*: traditional uses, phytochemistry, pharmacology, and toxicology. Evidence-Based Complementary and Alternative Medicine 2013, http://dx.doi.org/10.1155/2013/579319
64-European Medicines Agency. Assessment report on *Cichorium intybus* L., radix. EMA/HMPC/113041/2010, 2013.
65-Flora of China, www. efloras.org, http://www.efloras.org/florataxon.aspx?flora _id=2 &taxon_id=200023652
66-Wang Q and Cui J. Perspectives and utilization technologies of chicory (*Cichorium intybus* L.): a review. African Journal of Biotechnology 2011; 10(11): 1966-1977.
67-Bais HB and Ravishankar GA. *Cichorium intybus* L. – Cultivation, processing, utility, value addition and biotechnology, with an emphasis on current status and future prospects. J Sci Food Agric 2001; 81:467-484.
68-Judzentiene A and Badiene JB. Volatile constituents from aerial parts and roots of *Cichorium intybus* L. (chicory) grown in Lithuania. Chemija 2008; 19: 25-28.
69-PDR for Herbal Medicines. Medical Economics Company, Inc. at Montvale, 2000: 181.
70-Nandagopa S and Ranjitha Kumari D. Phytochemical and antibacterial studies of chicory (*Cichorium intybus* L.)- a multipurpose medicinal plant. Advances in Biological Research 2007; 1 (1-2): 17-21.
71-Mushtaq A, Ahmad M and Jabeen Q. Pharmacological role of *Cichorium intybus* as a hepatoprotective agent on the elevated serum marker enzymes level in albino rats intoxicated with nimesulide. Int J Curr Pharm Res 2013; 5(3): 25-30.
72-Shad MA, Nawaz H, Rehman T and Ikram N. Determination of some biochemicals, phytochemicals and antioxidant properties of different parts of *Cichorium intybus* L : A comparative study. The Journal of Animal & Plant Sciences 2013; 23(4): 1060-1066.
73-Atta-ur-Rahman, Zareen S, Choudhary MI, Akhtar MN and Khan SN. Alpha-glucosidase inhibitory activity of triterpenoids from *Cichorium intybus*. J Nat Prod 2008;71(5):910-913.

74-Ahmed B, Khan S, Masood MH and Siddique AH. Anti-hepatotoxic activity of cichotyboside, a sesquiterpene glycoside from the seeds of *Cichorium intybus*. J Asian Nat Prod Res 2008;10(3-4):223-231.
75-Malarz J, Stojakowska A and Kisiel W. Sesquiterpene lactones in a hairy root culture of *Cichorium intybus*. Z Naturforsch C 2002; 57(11-12):994-997.
76-Kisiel W and Michalska K. A new coumarin glucoside ester from *Cichorium intybus.* Fitoterapia 2002;73(6):544-546.
77-Jurgonbski A, Milala J, Jusbkiewicz J, Zdunbczyk Z and Król B. Composition of chicory root, peel, seed and leaf ethanol extracts and biological properties of their non-inulin fractions. Food Technol Biotechnol 2011; 49 (1) 40-47.
78-Mehmood N, Zubaır M, Rızwan K, Rasool N Shahid M and Ahmad VU. Antioxidant, antimicrobial and phytochemical analysis of *Cichorium intybus* seeds extract and various organic fractions. Iranian Journal of Pharmaceutical Research 2012; 11 (4): 1145-1151.
79-Judzentiene A and Badiene JB. Volatile constituents from aerial parts and roots of *Cichorium intybus* L. (chicory) grown in Lithuania. Chemija 2008; 19: 25-28.
80-Saied S, Shah S, Ali Z, Khan A, Marasini BP and Choudhary MI. Chemical constituents of *Cichorium intybus* and their inhibitory effects against urease and alpha-chymotrypsin enzymes. Nat Prod Commun 2011;6(8):1117-1120.
81-Carazzone C, Mascherpa D, Gazzani G , and Papetti A. Identification of phenolic constituents in red chicory salads (*Cichorium intybus*) by high-performance liquid chromatography with diode array detection and electrospray ionisation tandem mass spectrometry. Food Chemistry 2013; 138(2-3):1062-1071.
82-Gilani AH and Janbaz KH. Evaluation of the liver protective potential of *Cichorium intybus* seed extract on acetaminophen and CCl_4-induced damage. Phytomedicine 1994;1(3):193-197.
83-Zafar R and Mujahid Ali S. Anti-hepatotoxic effects of root and root callus extracts of *Cichorium intybus* L. J Ethnopharmacol 1998;63(3):227-231.
84-Gilani AH, Janbaz KH and Shah BH. Esculetin prevents liver damage induced by paracetamol and CCl_4. Pharmacol Res 1998; 37(1):31-35.
85-Atta AH, Elkoly TA, Mouneir SM, Kamel G, Alwabel NA and Zaher S. Hepatoprotective effect of methanol extracts of *Zingiber officinale* and *Cichorium intybus*. Indian J Pharm Sci 2010;72(5):564-570.
86-Helal EGE, Abd El-Wahab S, Sharaf AMM and Zedan G. Effect of *Cichorium intybus* L. on fatty liver induced by oxytetracycline in albino rats. The Egyptian Journal of Hospital Medicine 2011; 45: 522-535.
87-Krylova SG, Efimova LA, Vymiatina ZK and Zueva EP. The effect of cichorium root extract on the morphofunctional state of liver in rats with carbon tetrachloride induced hepatitis model. Eksp Klin Farmakol 2006;69(6):34-36.
88-Fallah Huseini H, Mahmoudabady Z, Ziai SA, Mehrazma M, Alavian SM, Mehdizadeh M and RadjabianT. The Effects of *Cynara scolymus* L. leaf and *Cichorium intybus* L. root extracts on carbon tetrachloride induced liver toxicity in rats. Journal of Medicinal Plants 2011; 10 (37): 33-40.
89-Heibatollah S, Reza NM; Izadpanah G and Sohailla S. Hepatoprotective effect of *Cichorium intybus* on CCl_4- induced liver damage in rats. African Journal of Biochemistry Research 2008;2 (6): 141-144.
90-Ziamajidi N, Khaghani S, Hassanzadeh G, Vardasbi S, Ahmadian S, Nowrouzi A, Ghaffari SM and Abdirad A. Amelioration by chicory seed extract of diabetes- and oleic acid-induced non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) via modulation of PPARα and SREBP-1. Food Chem Toxicol 2013;58:198-209.
91-Sultana S, Perwaiz S, Iqbal M and Athar M. Crude extracts of hepatoprotective plants, *Solanum nigrum* and *Cichorium intybus* inhibit free radical-mediated DNA damage. J Ethnopharmacol 1995;45(3):189-192.
92-Behnam-Rassouli M, Aliakbarpour A, Hosseinzadeh H, Behnam-Rassouli F and Chamsaz M. Investigating the effect of aqueous extract of *Chicorium intybus* L. leaves on offspring sex ratio in rat. Phytother Res 2010;24(9):1417-1421.
93-Ahmed N and Tarannum S. Acetylcholinesterase activity in the brain of alloxan diabetic albino rats: Presence of an inhibitor of this enzyme activity in the cerebral extract. Int J Diabetes Dev Ctries 2009;29(4):174-177.
94-Pushparaj PN, Low HK, Manikandan J, Tan BK and Tan CH. Anti-diabetic effects of *Cichorium intybus* in streptozotocin-induced diabetic rats. J Ethnopharmacol 2007; 111(2):430-434.
95-Muthusamy VS, Anand S, Sangeetha KN, Sujatha S, Arun B and Lakshmi BS. Tannins present in *Cichorium intybus* enhance glucose uptake and inhibit adipogenesis in 3T3-L1 adipocytes through PTP1B inhibition. Chem Biol Interact 2008;174(1):69-78.
96-Kim M and Shin HK. The water-soluble extract of chicory reduces glucose uptake from the perfused jejunum in rats. J Nutr 1996;126(9):2236-2242.

97-Azay-Milhau J, Ferrare K, Leroy J, Aubaterre J, Tournier M, Lajoix AD and Tousch D. Antihyperglycemic effect of a natural chicoric acid extract of chicory (*Cichorium intybus* L.): a comparative *in vitro* study with the effects of caffeic and ferulic acids. J Ethnopharmacol 2013;150(2):755-760.
98-Jurgoński A, Juśkiewicz J, Zduńczyk Z and Król B. Caffeoylquinic acid-rich extract from chicory seeds improves glycemia, atherogenic index, and antioxidant status in rats. Nutrition 2012; 28(3):300-306.
99-Yunyan G, Bing Z, Peifen J, *et al.* Research on the pharmacological activities of chicory alcohol soluble and alcohol deposit extracts. J Beijing University of Traditional Chinese medicine 1999; 22(3): 43-44.
100-Cavin C, Delannoy M, Malnoe A, Debefve E, Touché A, Courtois D and Schilter B. Inhibition of the expression and activity of cyclooxygenase-2 by chicory extract. Biochem Biophys Res Commun 2005;327(3):742-749.
101-Olsen NJ, Branch VK, Jonnala G, Seskar M and Cooper M. Phase 1, placebo-controlled, dose escalation trial of chicory root extract in patients with osteoarthritis of the hip or knee. BMC Musculoskeletal Disorders 2010; 11, article 156.
102-Süntar I, Küpeli Akkol E, Keles H, Yesilada E, Sarker SD and Baykal T. Comparative evaluation of traditional prescriptions from *Cichorium intybus* L. for wound healing: stepwise isolation of an active component by *in vivo* bioassay and its mode of activity. J Ethnopharmacol 2012;143(1):299-309.
103-Wesołowska A, Nikiforuk A, Michalska K, Kisiel W and Chojnacka-Wojcik E. Analgesic and sedative activities of lactucin and some lactucin-like guaianolides in mice. Journal of Ethnopharmacology 2006; 107(2): 254–258.
104-Gurbuz I, Ust¨un O, Yes E¸ilada, Sezik E and Akyurek N. *In vivo* gastro-protective effects of five Turkish folk remedies against ethanol-induced lesions. Journal of Ethnopharmacology 2002; 83(3): 241-244.
105-D'evoli L, Morroni F, Lombardi-Boccia G, Lucarini M, Hrelia P, Cantelli-Forti G, and Tarozzi A. Red chicory (*Cichorium intybus* L. cultivar) as a potential source of antioxidant anthocyanins for intestinal health. Oxid Med Cell Longev 2013; doi: 10.1155/2013/704310
106-Minaiyan M, Ghannadi AR, Mahzouni P and Abed AR. Preventive effect of *Cichorium intybus* L. two extracts on cerulein-induced acute pancreatitisin mice. Int J Prev Med 2012;3(5):351-357.
107-Muthusamy VS, Saravanababu C, Ramanathan M, Bharathi Raja R, Sudhagar S, Anand S and Lakshmi BS. Inhibition of protein tyrosine phosphatase 1B and regulation of insulin signalling markers by caffeoyl derivatives of chicory (*Cichorium intybus*) salad leaves. Br J Nutr 2010;104(6):813-823.
108-Balbaa SI, Zaki AY, Abdel-Wahab SM, El-Denshary ESM and Motazz-Bellah M. Preliminary phytochemical and pharmacological investigations of the roots of different varieties of *Cichorium intybus*. Planta Med 1973; 24(6): 133-144.
109-Sakurai N, Iizuka T, Nakayama S, Funayama H, Noguchi M and Nagai M. Vasorelaxant activity of caffeic acid derivatives from *Cichorium intybus* and *Equisetum arvense*. Yakugaku Zasshi 2003;123(7):593-598.
110-Noori S and Mahboob T. Role of electrolytes disturbances and Na^+-K^+-ATPase in cisplatin - induced renal toxicity and effects of ethanolic extract of *Cichorium intybus*. Pak J Pharm Sci 2012;25(4):857-862.
111-Schumacher E, Vigh E, Molnár V, Kenyeres P, Fehér G, Késmárky G, Tóth K and Garai J. Thrombosis preventive potential of chicory coffee consumption: a clinical study. Phytother Res. 2011; 25(5):744-748.
112-Kim JH, Mun YJ, Woo WH, Jeon KS, An NH and Park JS. Effects of the ethanol extract of *Cichorium intybus* on the immunotoxicity by ethanol in mice. Int Immunopharmacol 2002;2(6):733-744.
113-Kim HM, Kim HW, Lyu YS, Won JH, Kim DK, Lee YM, Morii E, Jippo T, Kitamura Y and An NH. Inhibitory effect of mast cell-mediated immediate-type allergic reactions by *Cichorium intybus*. Pharmacol Res 1999;40(1):61-65.
114-Ahmed N. Alloxan diabetes-induced oxidative stress and impairment of oxidative defense system in rat brain: neuroprotective effects of *cichorium intybus*. Int J Diabetes & Metabolism 2009;17:105-109.
115-Gazzani G, Daglia M, Papetti A and Gregotti C. *In vitro* and ex *vivo* anti- and prooxidant components of *Cichorium intybus*. J Pharm Biomed Anal 2000; 23(1): 127-133.
116-Shad MA, Nawaz H, Rehman T and Ikram N. Determination of some biochemicals, phytochemicals and antioxidant properties of different parts of *Cichorium intybus* L.: A comparative study. The Journal of Animal & Plant Sciences 2013; 23(4): 1060-1066.
117-Lee YH, Kim DH, Kim YS and Kim TJ. Prevention of oxidative stress-induced apoptosis of C2C12 myoblasts by a *Cichorium intybus* root extract. Biosci Biotechnol Biochem 2013;77(2):375-377.
118-Liu H, Wang Q, Liu Y, Chen G and Cui J. Antimicrobial and antioxidant activities of *Cichorium intybus* root extract using orthogonal matrix design. J Food Sci 2013; 78(2): M258-263.
119-Hazra B, Sarkar R, Bhattacharyya S and Roy B. Tumour inhibitory activity of chicory root extract against Ehrlich ascites carcinoma in mice. Fitoterapia 2002; 73(7-8):730–733.
120-Lee KT, Kim JI, Park HJ, Yoo KO, Han YN and Miyamoto KI. Differentiation-inducing effect of magnolialide, a 1β-hydroxyeudesmanolide isolated from *Cichorium intybus*, on human leukemia cells. Biological and Pharmaceutical Bulletin 2000; 23(8): 1005-1007.

121-Conforti F, Ioele G, Statti GA, Marrelli M, Ragno G and Menichini F. Antiproliferative activity against human tumor cell lines and toxicity test on Mediterranean dietary plants. Food and Chemical Toxicology 2008; 46(10): 3325-3332.
122-Nawab A, Yunus M, Mahdi AA and Gupta S. Evaluation of anticancer properties of medicinal plants from the Indian sub-continent. Mol Cell Pharmacol 2011; 3(1): 21-29.
123-Al-Akhras MA, Aljarrah K, Al-Khateeb H, Jaradat A, Al-Omari A, Al-Nasser A, Masadeh MM, Amin A, Hamza A, Mohammed K, Al Olama M and Daoud S. Introducing *Cichorium pumilum* as a potential therapeutical agent against drug-induced benign breast tumor in rats. Electromagn Biol Med 2012; 31(4): 299-309.
124-Koner A, Ghosh S and Roy P. Isolation of antimicrobial compounds from chicory (*Cichorium intybus* L.) root. International Journal of Research in Pure and Applied Microbiology 2011; 1(2): 13-18
125-Papetti A, Mascherpa D, Carazzone C, Stauder M, Spratt DA, Wilson M, Pratten J, Ciric L, Lingström P, Zaura E, Weiss E, Ofek I, Signoretto C, Pruzzo C and Gazzani G. Identification of organic acids in *Cichorium intybus* inhibiting virulence-related properties of oral pathogenic bacteria. Food Chem 2013;138(2-3):1706-1712.
126-Verma R, Rawat A, Ganie SA, Agnihotri RK, Sharma R, Mahajan S and Gupta A. *In vitro* Antibacterial Activity of *Cichorium intybus* against some pathogenic bacteria. British Journal of Pharmaceutical Research 2013;3(4): 767-775.
127-Stefanović OD, Stanojević DD and Comić LR. Synergistic antibacterial activity of *Salvia officinalis* and *Cichorium intybus* extracts and antibiotics. Acta Pol Pharm 2012; 69(3):457-463.
128-Mares D, Romagnoli C, Tosi B, Andreotti E, Chillemi G and Poli F. Chicory extracts from *Cichorium intybus* L. as potential antifungals. Mycopathologia 2005; 160 (1): 85–91.
129-Matveeva NA, Kudriavets IuI, Likhova AA, Shakhovskiĭ AM, Bezdenezhnykh NA and Kvasko E. Antiviral activity of extracts of transgenic cichory and lettuce plants with the human interferon alpha-2b gene. Tsitol Genet 2012;46(5):28-35.
130-Miller MC, Duckett SK and. Andrae JG. The effect of forage species on performance and gastrointestinal nematode infection in lambs. Small Ruminant Research 2011; 95(2-3): 188-192.
131-Marley CL, Cook R, Keatinge R, Barrett J and Lampkin HN.The effect of birdsfoot trefoil (*Lotus corniculatus*) and chicory (*Cichorium intybus*) on parasite intensities and performance of lambs naturally infected with helminth parasites. Veterinary Parasitology 2003; 112(1-2): 147-155.
132-Molan AL, Duncan AJ, Barry TN and McNabb WC. Effects of condensed tannins and crude sesquiterpene lactones extracted from chicory on the motility of larvae of deer lung worm and gastrointestinal nematodes. Parasitol Int 2003;52(3):209-218.
133-Foster JG, Cassida KA and Turner KE. *In vitro* analysis of the anthelmintic activity of forage chicory (*Cichorium intybus* L.) sesquiterpene lactones against a predominantly *Haemonchus contortus* egg population. Vet Parasitol 2011;180(3-4):298-306.
134-Leclercq E. Determination of lactucin in roots of chicory (*Cichorium intybus* L.) by high-performance liquid chromatography. Journal of Chromatography A 1984; 283: 441-444.
135-Bischoff TA, Kelley CJ, Karchesy Y, Laurantos M, Nguyen-Dinh P and Arefi AG. Antimalarial activity of lactucin and lactucopicrin: sesquiterpene lactones isolated from *Cichorium intybus* L. Journal of Ethnopharmacology 2004; 95(2-3):455–457.
136-Schmidt BM, Ilic N, Poulev A and Raskin I. Toxicological evaluation of a chicory root extract. Food and Chemical Toxicology 2007; 45(7): 1131-1139.