Pharmacological and Toxicological Studies on Syrian *Cichorium intybus* plant.

Thesis Presented
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INTRODUCTION

Plants have been used as a source of medicine throughout history and continue have been used traditionally in folk medicine and to serve as the basis for many pharmaceuticals used today. There are at least 120 distinct chemical substances derived from plants considered as important drugs use in one or more countries in the world as antihepatotoxic, antiulcerogenic, antiinflammatory, appetizer, stomachic, liver tonic immunomodulator, antitumor and anticancer properties (Nadkarni 1976 and Angelina, et.al. 1999).

*Cichorium intybus* L. "chicory" is an edible important plant that belongs to the family Asteraceae, growing in Europe, India and Egypt. The plant contains number of medicinally important compounds such as inulin, bitter sesquiterpene lactones, coumarins, flavonoids and vitamins it used as antihepatotoxic, antiinflammatory, liver tonic, cholagogue, depurative, diuretic, emmenagogue, alexeteric and also as tonic, anticancer and other medicinal uses (Nandagopal and Ranjitha 2007).

The leaves of the chicory plant can be eaten in salads or cooked, as well as, the roots are used as coffee (Bremness 1998).

The present work was carried out on Syrian *Cichorium intybus* to investigate the photochemical composition, toxicological properties and pharmacological activities (*In-Vivo & In-Vitro*) as a trial to reach to pharmacologically active, safe and easily applicable natural compound as a source of new drug.
REVIEW OF LITERATURE

*Cichorium intybus* L. known as “chicory” is a medicinally important plant that belongs to the family Asteraceae (Nandagopal and Ranjitha 2007). It has been implemented in folk medicine for several hundred years for treatment of flatulence, colic, gout and burning as well as it has a hepatoprotective effect and blood purifying function (Deshusses 1961).

**A-Historical Overview**

*Chicory* plant was one of the earliest cited in the recorded literature. Ancient Egyptians were known to consume *Chicory* root in large amounts to aid in purifying liver and blood.

Before 4000 years ago, Greeks and Romans began to grow chicory as a vegetable crop to help in cleaning the blood (Deshusses, 1961; Grieve, 1971; Plmuier, 1972; and Munoz, 2004).

For at least 5000 years, *chicory* had been cultivated for its medicinal benefits. The blue color of the flowers and their tendency to close at noon (in England) as if in sleep suggested that: the plant used in treating inflamed eyes.

Nandagopal and Ranjitha (2007) reported that the root extracts had been used as a diuretic and laxative and to treat jaundice.

At second-century the physician Galen called chicory a “friend of the liver”, and it had increasing effect on flow of bile, which could be helpful in cases of gallstones. Laboratory research recorded that the root extracts had antibacterial, anti-inflammatory, slightly sedative effect and
caused hypoglycemia. Also the Leaf extracts had a similar effect but lesser than the root.

**B-Description**

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**Cichorium intybus L.** is a bushy perennial plant with white, blue or pink-blue flowers, can reach 170 cm in height as reported by (lekavičius 1980).

*Chicory* is easy to grow with a long taproot. It grows best in full sun and in well-drained soil. They find the leaves around the base of the stem, which are large, measuring approximately 7.5-15 cm. in length, stalked, lanceolate and unlobe. The flower heads are 2 to 4 cm and usually bright blue, rarely white or pink. There are two rows of involucral bracts; the inner are longer and erect, the outer are shorter and spreading. It flowers from July until October. The flowers fully expand in the morning and close up by noon (Rose and Francis 1981).

Bremer (1994) stated that the Chicory (*Cichorium intybus L.*) is an Asteraceae (Compositae) species belonging to the Lactuceae tribe of the Lactuioideae subfamily. The Food and Agriculture Organization (FAO) reported that the Chicory was a native plant of Western Asia, North Africa and Europe.

Crawford and Sharon (1997) reported that *Chicory* has common names including succory, chicory root, chicory herb, blue sailors, wild chicory, or hendibeh, is well known for its bitter taste and use as a coffee substitute. This form is known as chico’ree in French, Salatzichorie or Chicor’eé in German, radicchio in Italian and archicoria in Spanish. In Belgium it is known as witloof, and in the USA as blue sailor. The words *chicory*, *succory*, *Cichorium intybus* are all derived from Greek or Latin names for the herb.

Kiers, et. al. (1999) said that the genus *Cichorium* includes 6 diploid species (2n = 18) native from the Old World, the closely related species are *intybus* (*C. intybus L.*) and endive (*C. endivia L.*) which have been domesticated and are mainly cultivated in Europe.
**C-Active principles**

**Scarpati and Oriente (1958)** isolated from the aqueous extract of *chicory* leaves a new active crystalline substance for which the name chicoric acid. Experimental evidence indicated its structure as a caffeic diester of laevorotatory tartaric acid.

**Bridle, et. al. (1984)** identified that the major anthocyanin of red leaves of *Cichorium intybus* was cyanidin 3-O-β-(6-O-malonyl)-d-glucopyranoside by fast atom bombardment mass spectrometry and NMR spectroscopy.

**Sarah and Jeffrey (1985)** maintained amounts of the sesquiterpene lactones and the major phenolics in the *chicory* plant at different times during the growing season. The levels of the sesquiterpene lactones (lactucin, lactupicrin and 8-deoxylactucin) and the hydroxycoumarin cichoriin were found to be highest in the most actively growing regions of the plant.

**Anil, et. al. (1989)** collected the roots of *Cichorium intybus* at seed maturation stage and they found that the roots contained a considerable amount of free and bound fructose

**Kenji, et. al. (1990)** isolated sesquiterpenoid phytoalexin and cichoralexin from *Cichorium intybus* inoculated with *Pseudomonas cichorii* by spectroscopic methods.

**Krebsky, Geuns and De (1996)** studied the fatty acid (FA) content of polar lipids of Belgian endive (*Cichorium intybus var. foliosum cv.*) They found the major of fatty acid present in these lipids was linoleic (33–62%) followed by palmitic (24–36%).

**Du, Yuan and Jiang (1998)** investigated the chemical constituents of root *Cichorium intybus* by means of solvent extraction and
chromatography on silical gel. They isolated seven compounds; four of them were identified as alpha-amyrin, taraxerone, baurenyl acetate and beta-sitosterol.

Inulin is stored in the taproot of chicory. Long inulin and short oligofructans chains are used by the agro-industry as low calories fat substitute. They are considered as health promoting because it stimulates the growth of beneficial colonic microflora reported by (Causey, et. al. 2000; Delzenne and Williams 2002)

Four pigments including two anthocyanins were isolated from blue perianth segments of Cichorium intybus. The structures were delphinidin 3,5-di-O-(6-O-malonyl-\beta-D-glucoside) (R1=R2=malonyl) and delphinidin 3-O-(6-O-malonyl-\beta-D-glucoside)-5-O-\beta-D-glucoside

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\begin{align*}
&\text{R1=malonyl, } R2=H. \\
&\text{Reported by (Nørbaek, et. al. 2002)}
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He, et. al. (2002) studied the chemical constituents in the root of Cichorium intybus by column chromatography and NMR, IR, MS data. They found twelve compounds were isolated and identified. They were 2, 3, 4, 9-tetrahydro-1H-pyrido-(3,4-b)indole-3-carboxylic acid. While (Janusz, et. al. 2002) isolated from the roots sesquiterpene lactones of guaiane and germacrane type of chicories: Lactucopicrin, 8-desoxylactucin and three sesquiterpene lactone glycosides: crepidiaside B, sonchuside A and ixerisoside D.

Kisiel and Michalska (2002) isolated from chicory leaves
Cichoriin-6'-p-hydroxyphenyl acetate, a new natural product from *chicory* leaves.

**Melliou, et. al. (2003)** isolated from the dichloromethane extract of *Cichorium spinosum* by spectroscopic methods, new alkylresorcinol derivative, cichoriol B, and a mixture of three other ones, cichoriols A, C, and D, but the methanol extract afforded one new sesquiterpene lactone, (4R)-3,4-dihydrolactucopicrin.

The herb *Cichorium intybus* contained: Inulin (up to 58% in the root), sesquiterpene lactones (lactucin and clactucopicirin), coumarins (chicorin, esculetin, esculin, umbelliferone and scopletin) and glucofrutosans, reported by **Khare (2004)**

**Wanda and Klaudia (2006)** isolated phenolic acid and sesquiterpene lactones from roots of *Cichorium endivia var.* by spectral methods. Twelve known sesquiterpene lactones and the new guaianolide 10β-methoxy-1α, 11β, 13-tetrahydrolactucin (10), together with three known phenolic acid esters.

**Rollinger, et. al. (2006)** reported that the dichloromethane extract of *chicory* roots (*Cichorium intybus L.*) had a pronounced inhibitory effect (70%) on AChE at a concentration of 1 mg extract/ml. Because the extract contained two sesquiterpene lactone (8-deoxylactucin and lactucopicrin), so they suggested that the plant could be use in Alzheimer's disease treatment.

**Seema (2006)** dealt with the isolation and characterization of chemical constituents from *Cichorium intybus*. Two new compounds, cichoridiol (18α, 19β -20(30)-taraxasten-3β, 21α-diol), and intybusoloid (17-epi-methyl-6-hydroxyangolensate) were also isolated. Some of these
compounds were tested for their enzyme inhibitory activity against prolyl endopeptidase, β-glucuronidase and α-glucosidase. In addition, eleven known compounds, such as friedelin, lupeol, β-sitosterol, stigmasterol, betulinaldehyde, betulinic acid, betulin, vanillic acid, syringic acid, 6,7-dihydroxy-2H-benzapyran-2-one and methyl-α-D-galactopyranoside had also been isolated from this plant.

Nandagopal and Ranjitha (2007) reported that Chicory (Cichorium intybus L.) contains a number of medicinally important compounds such as inulin, esculin, volatile compounds (monoterpenes and sesquiterpenes), coumarins, flavonoids and vitamins.

The seeds of Cichorium intybus L. contained new guaianolide sesquiterpene glycoside, cichotyboside, which were characterized as 2alpha, 6beta, 7beta, 15-tetrahydroxy-1, 4 (5)-diene-guaian-9alpha, 12-olide-7-O-beta-caffoyl-15-O-beta-D-glucoside (Ahmed, et. al. 2008).

Asta and Jurg (2008) found higher amounts of octane and the tentatively significantly in roots than in over ground parts of the chicory, an opposite relation was observed for nonadecane which higher in the aerial parts than in roots.

They also hydrodistillated volatile compounds from the roots and over ground parts of Cichorium intybus L. from dried material and analyzed by GC/MS. They found Octane, n-nonadecane, pentadecanone, hexadecane and a tentatively identified compound (pentenyl salicilate) as principal components among all volatile constituents.

Warashina and Miyase (2008) obtained twelve new sesquiterpene and sesquiterpene glycosides compounds from roots of Cichorium endivia (Compositae) by the spectroscopic methods. The compounds were identified as guaianolide, germacrenolide and elemanolide.
Zidorn (2008) summarized all reports on sesquiterpene lactones and their immediate precursors from the Cichorieae (Lactuceae) tribe of the Asteraceae. These substances belong to three classes of sesquiterpenoids: guaianolides (243 compounds), eudesmanolides (73 compounds), and germacranolides (44 compounds).

Vipaporn and Christian (2010) isolated flavonoids from the Cichorieae (Lactuceae) tribe of the Asteraceae family. The reported compounds are; flavanones (11 compounds), flavanonols (2 compounds), flavones (72 compounds), flavonols (35 compounds), anthocyanidins (9 compounds), isoflavonoids (2 compounds), chalcones (3 compounds), and an aurone. The distribution of the various classes of flavonoids is analyzed with regards to data from the current molecular-based reassessment of the systematics of the tribe.

Zayna, et. al. (2010) quantified the four major active compounds, namely esculetin, lactucin, lactucopicrin and chlorogenic acid in seed, stem and root of the Cichorium glandulosum (by HPLC). They found the percentage recoveries were 98.2%, 99.57%, 100.50%, and 99.46% for chlorogenic acid, esculetin, lactucin, and lactucopicrin, respectively. The correlation coefficients (r) were 1.000, 0.9989, 0.9998, 1.000 and RSD were 1.6%, 1.5%, 0.77%, 2.0% for chlorogenic acid, esculetin, lactucin, and lactucopicrin, respectively. The contents of the chlorogenic acid, esculetin, lactucin and lactucopicrin were 0.0048, 0.0043, 0.6789, 0.7520 mg x g(-1), respectively in the root, and 0.0710, 0.1890, 0.2396 and 0.0520 mg x g (-1) in the seeds of C. glandulosum, respectively.

Foster, et. al. (2011) attributed the anthelmintic activity of chicory leaves (C. intybus L.) to a significant amount of sesquiterpene lactones. These lactons were lactucin (LAC), 8-deoxylactucin (DOL), and lactucopicrin (LPIC).
Hussain, et. al. (2011) isolated one new benzo-isochromene, named cichorin A, together with three known compounds, oleanolic acid, β-sitosterol, and β-sitosterol glucopyranoside, from *Cichorium intybus*.

Saied, et. al. (2011) investigated the Phytochemical properties of the aerial parts of *Cichorium intybus* L. resulted in isolation and identification of two new natural metabolites, 2,6-di[but-3(E)-en-2-onyl]naphthalene (1), and 3,3’,4,4’-tetrahydroxychalcone (2), along with nine known compounds. Their structures were determined by spectroscopic techniques including 1D and 2D NMR. The known compounds were identified as scopoletin (3), 4-hydroxyphenylacetic acid (4), 3-hydroxy-4-methoxybenzoic acid (5), 4,4’-dihydroxychalcone (6), 6,7-dihydroxycoumarine (7), 1-triacontanol (8), lupeol (9), beta-sitosterol (10), and beta-sitosterol-3-O-beta-glucopyranoside (11). Compounds 4-6 and 8 are reported for the first time from *C. intybus*. Compounds 2 and 3 showed weak inhibitory activities against urease and alpha-chymotrypsin enzymes, respectively.

**D-Pharmacological action**

**Hepatoprotective and Antioxidant effect:**

Sultana, et. al. (1995) studied the effect of *Solanum nigrum* and *Cichorium intybus* extracts on DNA against oxidative damage to its deoxyribose sugar moiety. They found the effect of *Cichorium intybus* was much pronounced as compared to the effect of *Solanum nigrum*.

Gilani, et. al. (1998) investigated esculetin, a phenolic compound found in *Cichorium intybus* and *Bougainvllra spectabilis* for its possible protective effect against paracetamol and CCl4-induced hepatic damage. Oral administration of paracetamol (640 mg kg-1) produced liver damage in rats as manifested by the rise in serum enzyme levels of ALP, AST and ALT. Pre-treatment of rats with esculetin (6 mg kg-1) prevented the
paracetamol-induced rise in serum enzymes. The hepatotoxic dose of CCl4 (1.5 ml kg$^{-1}$; orally) also raised serum ALP, AST and ALT levels. The same dose of esculetin (6 mg kg$^{-1}$) was able to prevent the CCl4-induced rise in serum enzymes. Esculetin also prevented CCl4-induced prolongation in pentobarbital sleeping time confirming hepatoprotectivity. These results indicated that esculetin possesses anti-hepatotoxic activity and the presence of this compound in *Cichorium intybus* and *Bougainvillea spectabilis* may explain the folkloric use of these plants in liver damage.

**Zafar and Mujahid (1998)** compared the natural root and root callus extracts of *Cichorium intybus* for their anti-hepatotoxic effects in Albino rats against carbon tetrachloride induced hepatic damage. They found that, the *Cichorium intybus* root callus extract and the natural root extract had protective effect against carbon tetrachloride induced heptocellular damage but the *Cichorium intybus* root callus extract could afford a better protective effect as compared to the natural root extract.

**Gazzania, et. al. (2000)** evaluated the antioxidant properties of water extract of *Cichorium intybus var. Silvestre*. The antioxidant properties *In vitro* as antioxidant activity (AA) and *In vivo* as protective activity (PA) against rat liver cell microsome lipid peroxidation. They found that the plant contained both biological antioxidant and pro oxidant compound and the (AA), (PA) showed high, but very variable AA (>83%) and PA (>64%)

**Kalantari and Rastmanesh (2000)** tried to find out the most effective dose and suitable time of administration for optimum results by orally administration of *Cichorium intybus* at doses of 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 125 mg/kg and 150 mg/kg. They found that the maximum effective dose was 75 mg/kg. As well as, the
histopathological findings and enzyme levels showed that the best protective effect was seen when given within 30 minutes after CCl4 toxicity.

The water extract of *Cichorium intybus* (WECI) showed a remarkable antioxidative effect on Low-density lipoprotein (LDL) and inhibitory effects on the production of thiobarbituric acid reactive substance and the degradation of fatty acids in LDL. They concluded that LDL oxidation is inhibited *in vitro* by the addition of WECI, and that LDL is protected by WECI from oxidative attack who reported by (Kim and Yang 2001).

**Krylova, et. al.** (2006) found that the root extract of *cichorium intybus* leaded to normalization of some morphofunctional liver features (decreases glycogen content, cell necrosis and increases the number of cells with pronounced protein synthesis activity) in rats with CCl4-induced hepatitis.

**Heimler, et. al.** (2007) investigated for their polyphenol contents through the Folin-Ciocalteu test in ten genotypes belonging to Lactuca sativa, one of them is *Cichorium intybus*. The antiradical activity was determined by the reaction with the stable DPPH* radical. A cultivated *C. intybus* cultivar exhibited the highest polyphenol content, while a wild *C. intybus* genotype exhibited the highest antiradical activity.

**Ahmed, et. al.** (2008) reported that the seeds of *Cichorium intybus L.* contained Cichotyboside which exhibited a significant anti-hepatotoxic activity against CCl4 induced toxicity in Wistar rats, it decreased the level of ALP, ALTand AST with an increasing in the level of total albumin comparable with that of intoxicated control.
Also, Bahar, et. al. (2003) studied the compound AB-IV of seeds of *Cichorium intybus Linn* of alcoholic extract for antihepatotoxic activity on carbon tetrachloride (CCl4) -induced liver damage in Albino rats. The compound AB-IV had a potent antihepatotoxic activity comparable to the standard drug Silymarin. The histopathological showed almost complete normalization of the tissues as neither fatty accumulation nor necrosis was observed by AB-IV compound.

Lavelli (2008) studied Red chicory products (*Cichorium intybus L. var. silvestre*) for their polyphenol content and evaluated antioxidant activity by using the synthetic 2,2-diphenyl-1-hydra%yl radical and three model reactions catalyzed by relevant enzymatic . However, red chicory phenolics had a much higher inhibitory activity than Trolox (the reference compound) in the model enzymatic systems.

Madani, et. al. (2008) investigated the protective effects of polyphenolic extracts of *Silybum marianum* and *Cichorium intybus* at dose of 25 mg\kg on thioacetamide- induced hepatotoxicity in rat. They noticed a significant decrease in the activity of aminotransferases, alkalin phosphatase and bilirubin in the groups treated with extracts. The protective effect of this extracts can be due to the presence of flavonoids compounds and their antioxidant effects.

Upur, et. al. (2009) showed noticeable antioxidant activity through its ability to scavenge several free radicals (DPPH, O(2), NO) and efficiency against lipid peroxidation. So they suggested that *Cichorium glandulosum* root extract (CGRE) and methanol extract of *chicory* is potent hepatoprotective agent. It could protect liver against the acute injury and its ability might be attributed to its antioxidant potential.

Also they evaluated the hepatoprotective and antioxidant properties effect of CGRE using two experimental models, carbon tetrachloride
(CCl4)- and galactosamine (GalN)-induced acute hepatotoxicity in mice. (800 mg/kg/day, p.o.) was administered for seven days and the results showed significantly reduced (AST), (ALT) and (ALP). While (Atta, et al. 2010) administrated ginger, chicory and their mixture at doses (250 and 500 mg/kg) alone or mixed (1:1 wt/wt) to investigate the hepatoprotective effect against carbon tetrachloride intoxication in rats. The result showed that the extract of chicory had a significant reduction in (AST), (ALT) and (ALP), so the plant was considered as a liver protective against acute injury.

Hassan and Yousef (2010) studied the Cichorium intybus L. as a supplemented diet for hepatoprotection against nitrosamine. The results showed that the rats which received nitrosamine showed a significant increase in liver, total lipids, total cholesterol, bilirubin, and enzymes activity (AST, ALT, ALP and gamma-GT) in both serum and liver. While a significant decrease in the levels of GSH, GSH-Rx, SOD, catalase, was recorded in group. Also hey found the plant succeeded to modulate the observed abnormalities resulting from nitrosamine, indicated by improvement of the investigated biochemical and antioxidant parameters compounds. So they concluded that chicory ameliorating the oxidative stress and hepatic injury.

Ilaiyaraja and khanum (2010) evaluated the antioxidant In vitro of various solvent extracts of (Cichorium intybus) leaves. They found the aqueous extract possesses a marked radical scavenging properties and significant protection against protein oxidation and DNA damage which could be attributed to the presence of phenolic compound.

Abd El-Mageed (2011) investigated the effect of diet supplementation with celery chicory, and barley powder on liver enzymes and blood lipids in rats fed with cholesterol-enriched diet. He
separately added to the basal diet at 10% concentration each of them or in combination of three plants at 15% for four weeks. He found the diet supplemented with 10% of each them lower the elevated serum level of liver enzymes and blood lipids but the plant combination was more effective in decreasing the elevation of liver enzymes and blood lipids. Finally he recommended that the dietary intake of plant mixture of celery, chicory, and barley at 15% (5% of each) concentration can be beneficial to patients suffering from hypercholesterolemia and liver disease.

**Chao-Jie, et. al. (2011):** found that Cichorium endivia L extract (CEE) significantly blocked the oxidative stress and cytotoxicity induced by tert-butyl hydroperoxide (t-BHP) in HepG2 cells. The results exhibited a markedly protective effect by lowering serum levels of (ALT and AST) and inhibiting the changes in liver biochemistry including MDA, SOD, GSH and GST. So they suggested that the CEE safe remedy to cure liver disease may be due to its phenolic substances

**Effect on intestine:**

**Kaur and Gupta (2002)** stated that the inulin and oligofructose belong to carbohydrates known as fructans which extracted from Chicory and Jerusalem artichoke. Inulin and oligofructose affect on the physiological and biochemical processes in rats and human. They cause reduction in the risk of many diseases by stimulating the immune system of the body, decreasing the pathogenic bacteria in the intestine, relieving constipation, decreasing the risk of osteoporosis, lowering the synthesis of triglycerides and fatty acids in liver and serum.

**Lobo, et. al. (2006)** evaluated the effects of fructooligosaccharides (FOS) on the intestinal absorption of Ca and Mg, as well as on bone
parameters in healthy growing rats. They found that (after feeding of diets with FOS) a higher Ca & Mg absorption was observed in FOS group through all experimental periods when compared with the control group. This effect resulted in a greater and healthy bone.

**Slavin and Feirtag (2010)** examined the effect of 20 g /day supplement of *chicory (inulin)* on stool weight, intestinal transit time, stool frequency and consistency, selected intestinal microorganisms and enzymes as well as, short chain fatty acids and ammonia produced as by-products of bacterial fermentation. They found that significant increase in total anaerobes and Lactobacillus species and a significant decrease in ammonia levels and β-glucuronidase activity. Flatulence increased significantly with the inulin treatment. Thus, inulin is easily incorporated into a food product and has no negative effects on food acceptability. So twenty grams of inulin was well tolerated, but had minimal effects as a laxative in healthy human.

**Raninen, et. al. (2011)** stated that the dietary fiber had beneficial physiological effects such as laxative effects, fermentability. Grain fibers are a major natural source of dietary fiber while inulin, soluble indigestible fructose polymer isolated from *chicory*. It shows many of the same functionalities of grain fibers in the large intestine, in that they are fermentable, bifidogenic, and laxative,

**Anti cancer:**

**Hazra, et. al. (2002)** studied the tumour-inhibitory effect of ethanolic extract of *chicory* root at doses from 300 to 700 mg/kg on mice; they found that it has a significant effect against Ehrlich ascites carcinoma.
Pool-Zobel, et. al. (2002) stated that Inulin (extracted from the chicory root) has significant anticarcinogenic properties. It acts chemopreventively by reducing the incidence of azoxymethane (AOM)--induced aberrant crypt foci and tumours in the colon, these effects may be due to the stimulation of bifidobacteria, which have antigenotoxic in the colon and to reduce AOM-induced tumours. Also fermentation products, including the short-chain fatty acid butyrate, could contribute to the protective effects. In this case a mechanism may be the induction of apoptosis of already transformed cells.

Conforti, et. al. (2008) evaluated Sixteen edible plants (Cichorium intybus, Mentha aquatica) for their antiproliferative properties. They found that the Mentha aquatica showed a selective antiproliferative activity on breast cancer. While significant activity was exerted by Cichorium intybus on melanoma. Because the Mentha aquatica and Cichorium intybus contained the highest amount of phenolics.

Ali and Hafez (2011) examined the anticancer activity of the plant root extract of Cichorium endivia, L. on three different cell lines (hypatocarcinoma cells, breast cancer cells and colon cancer cells). The degrees activity of extract was measured by determining cytotoxicity for the three cell lines compared with anticancer drug 5 FU (5-fluorouracil). The gene expression for the DNA cancer markers; P53, Bcl2. The expression of the P53 was high both in cells treated with FU and root extract but the expression in colon cancer was lower than liver cancer and breast cancer in successive manner. Expression of Bcl2 was high in cell lines treated with root extract compared with the FU, yet this expression still was low compared with the control ones. Thus, Cichorium endivia, which contains a combination of phenolic compounds, represents an enjoyable means of anticancer especially for hepatocarcinoma.
Akbar, et. al. (2011) reported that the aqueous extract of plants Artemisia vulgaris, Cichorium intybus, Smilax glabra, Solanum nigrum and Swertia chirayta has anticancer properties against various human cancer cell lines. Exposure of aqueous extract of Solanum nigrum and Artemisia vulgaris exerted an inhibitory effect on cell growth and colony formation of the prostate, breast and colorectal cells. Other plant extracts exhibited a modest inhibition in cell proliferation for all three cell lines by induction of apoptosis in cancer cells as measured by internucleosomal DNA fragmentation. They suggested that consumption of the components of these plants or ingestion of extract as tea may impart anticancer effects especially in the colon, breast and the prostate.

Effect on uterus:

Keshri, et. al. (1998) evaluated the ethanolic extract of seeds of Cichorium intybus and aerial parts of Guetterda andamanica, Memcylon lushingtonii, and Solanum crassypetalum for postcoital contraceptive efficacy in adult female Sprague-Dawley rats. The activity in these fractions was invariably associated with a significantly reduced number of implantations.

Ernest (2002) stated that chicory root is classified as an abortifacient and emmenagogue herb. Excessive consumption of abortifacient or emmenagogue herbs stimulates the start of a menstrual period, which may lead to miscarriage. Because of this potential side effect, expectant mothers should avoid chicory root in vegetable or supplement form throughout pregnancy.

Anti-inflammatory

Cavin, et. al. (2005) investigated that the anti-inflammatory activity of ethyl acetate chicory roots extract. They found a marked
inhibition of prostaglandin E(2) and PGE(2). Also they reported that the major sesquiterpene lactone of *chicory* root is guaianolide 8-deoxylactucin. This compound is identified as the key inhibitor of COX-2 protein expression. Thus indicated that the *chicory* root act as a promising source of functional food ingredient, combining prebiotic and anti-inflammatory properties.

**Olsen, et. al. (2010)** studied the properties of *chicory* root extract on 40 patients with osteoarthritis (OA). The patients were treated with escalating *chicory* doses of 600 mg/day, 1200 mg/day and 1800 mg/day for 1 month. They concluded that a proprietary bioactive extract of *chicory* root has a potential role in the management of OA (anti-inflammatory).

**Schumacher, et. al. (2011)** found that Caffeine-free *chicory* coffee was a rich Source of plant phenolics, including caffeic acid, which inhibited *In vitro* platelet aggregation, and also phenyl pyruvate tautomerase enzymatic activity of the proinflammatory cytokine, macrophage migration inhibitory factor (MIF). They found after 1 week of daily admenstration of 300 ML of *chicory* coffee resulting in decreasing of the blood and plasma viscosity; improvements in red blood cell deformability. No changes in (hematocrit, fibrinogen level or red blood cell counts) .So they offered an encouraging starting-point to delineate the antithrombotic and antiinflammatory effects of phenolic compounds found in chicory coffee.

**Immunotoxicity**

**Kim, et. al. (2002)** studied the effects of the ethanol extract of *Cichorium intybus* (CIEE) on the immune toxicity of mice, they noticed a marked enhanced phagocytic activity, natural killer (NK) cell activity,