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Chicory (*Cichorium intybus L.*) Extracts as an alternative of (glibenclamide) on biochemical parameters in Diabetic Rats

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Chicory plant *(Cichorium intybus L)* has been used as a traditional medicinal plant. This study aimed to investigate the phytochemicals contents in Chicory which extracts compared to Amaryl (glibenclamide) drug for anti-diabetic activity on the serum glucose level in streptozotocin (STZ) diabetic rats. Moreover, fractionation and identification of phenolic and flavonoids compounds in ethanol extract was determined by HPLC, recording catechin as predominant compound. The effect of chicory extract on serum glucose level, high density lipoprotein cholesterol (HDL), Low density lipoprotein cholesterol (LDL), Asptartate transaminase (AST), Alanine transaminase (ALT) and alkaline phosphatase (ALP) comparing with Amaryl in diabetic rats. Results indicate that Ethanol extract gave the highest phenolics and flavonoids compounds of chicory compared with different other extracts recording 121.33 and 88.26 mg/100g, respectively. The highest antioxidant activities were observed using ethanol and aqueous extracts using DPPH method recording 84.32 and 83.12%, respectively. Results indicate that using chicory extract by 500 mg/kg in diabetic rats caused a decrease in blood glucose levels by 288.41 to 170.37 mg/dl. Also, significant increase in HDL (57.18 mg/dl) and decrease of LDL to 31.81 mg/dl with using 500 mg/kg dose. Moreover, (AST) activity in diabetic rats was significantly decreased in all treatmemt compared with (positive Control. On the other hand, the (ALT) and (ALP) activities significantly decreased from 65.33 to 38.67 and 102.94 to 80.08, respectively with oral administration of chicory extract at (500 mg/kg) in diabetic rats. Generally, chicory plants can be used by diabetic patients to decrease complications of diabetes in reducing serum glucose level.

Keywords: Chicory (*Cichorium intybus)* extract, Antioxidant activity, phenols, flavonoids, Diabetic.

INTRODUCTION

Diabetes mellitus is a very common health challenge of the world, in both developed and developing countries and is one of the important causes of death worldwide (Nanditha et al., 2016). Diabetes results in severe complications including hyperlipidemia, neuropathy, retinopathy and cardiovascular disorders, also which impose great costs to the families and countries (Nentwich, and Ulbig, 2015). Diet therapy, exercise, pharmacotherapy and herbal medicines are strategies to treat the diabetic patient. Herbs have been used for diabetes mellitus treatment in ancient Iran, China, Egypt and other countries (Kibiti and Afolayan, 2015).

Cichorium intybus L.; family *Asteraceae*, is commonly known as chicory and is used in the Indian system of traditional medicine as

cardiotonic, anti-inflammatory, digestive, stomachic, liver tonic and diuretic. The photochemical are distributed in the whole plant. These are sesquiterpene lactones, lactucin, 8-deoxylactucin, lactopicrin, cichoriolide A, B and C. Occurrence the genus Cichorium (Asteraceae) consists of six species with major distribution areas in Europe and Asia (Guguloth et al*.,* 2011). Chicory consideredric as rich source inulin and other compounds (Kim and Shin, 1996 and Monti et al., 2005).The chicory roots are a source of many bioactive compounds as fructans, polyphenolic components (5-caffeoylquinic–chlorogenic, dicaffeoylquinic-andchicoric acid), polyphenol glycosides, including derivates of quercetin, apigenin, luteolin and sesquiterpenes. Also, Chicory root contains some phytochemicals such as inulin (starch-like polysaccharide), coumarins, flavonoids, sesquiterpene lactones (lactucin and lactucopicrin), tannins, alkaloids, vitamins, minerals, and volatile oils (Hoste et al., 2006 and Das et al., 2016).

Cichorium intybusis a traditional plant used as food and medicinal plant in edible parts of the ancient world, that finds its application in food and pharmaceutical field as carminative and against cardiac ailments. Chicory is found to be effective in rheumatic complaints, anti-cancer, anti-fungal and anti-malarialanti-diabetic (Lante et al., 2011). Inulin from chicory is being used as a substrate of fiber in health and functional foods. Inulin used as prebiotic helps ininhibiting gastrointestinal infection and boosts the immune system. (Sinkovic et al., 2014).

Chicory roots demonstrate some biological activities such as antioxidant, anticancer, antiinflammatory, antiparasitic, antihepatotoxic, which impact positive health effect on humans and livestock. These biological activities are due to the presence of secondary metabolites (flavonoids, tannins, and coumarins) found in chicory. Inulin is a natural polysaccharide possessing unique physicochemical properties which give it a range of uses in food and pharmaceutical industries (Barclay et al., 2010). .Naringin and its aglyconenaringenin are two flavonoid compounds with promising anti-diabetic effects (Mahmoud et al., 2015). Flavonoids are a group of natural polyphenolic compounds with potential benefits in human health (Barnes and Prasain, 2005). Significant anti-oxidant, anti-inflammatory, anti-diabetic, cardio protective and hepatoprotective effects of flavonoids were reported (Kamel et al., 2016).

Due to problems caused by using chemical medicines and its side effects on human health, Herbal medicines, products and therapies are a subject of great public interest both nationally and Worldwide. Use of herbal therapy is common among patients with diabetes.

This investigation was undertaken to study the chemical composition of chicory *(Cichorium intybus)* and the best methods for extracting active ingredients, also the biological effects of chicory, which has been used in a traditional way for anti-diabetic activity, on the serum glucose level in streptozotocin diabetic rats.

MATERIALS AND METHODS

Fresh chicory plants were obtained from Faculty of Agricultural, Cairo University. Male albino rats (Sprague- Dawley strain) weighing 150.17±1.83g. were obtained from the Animal Colony Laboratory, Helwan, Egypt. The rats were kept under a controlled hygienic condition in plastic cages and fed on the basal diet for one week before starting the experiment.

Streptozotocin (STZ) and Biochemical Kits were purchased from El-Gomhoryia Company for Chemicals, Cairo, Egypt.

Preparation of chicory extract

Dried chicory plants were ground into a powder then ethanol and the other solvent (Hexane, Chloroform, ethyl acetate, Acetone, Ethanol, water) were added to obtain concentrated extracts. This extracts were kept for chemical analysis. The ethanol extract was evaporated to get dry film for biological experiments.

Chemical analysis

Moisture, protein, ash, crude fiber contents and total carbohydrate were determined according to the methods described by A.O.A.C. (2005). Determinations of total phenolics, flavonoids and tannins compounds according to Swain and Hillis (1959), (Chang et al., 2002) and Bajaj and Devsharma (1977), respectively. Determination of the antioxidant activity with DPPH by Brand-(Williams et al., 1995). Identification of phenolic and flavonoid compounds by High Performance Liquid Chromatography (HPLC) according to Fernández de Simón et al., (1990). Inulin was determined by HPLC (Wang et al., 2010).

Biological experiments

Thirty-six male albino rats were assigned randomly to six groups each group contain 6 rats:
Group 1: (negative Control -) rats were fed with a

basal diet.
Group 2: (positive Control +) was the diabetic group as the rats were induced by injection of STZ at a dose of 40 mg/kg body weight. After 72 h, (the presence of diabetes was confirmed) glucose blood was higher than 250 mg/dl.
Group 3:Diabetic rats administered of glibenclamide (amaryl) by concentration of 0.05mg/kg body weight.
Group 4: Diabetic rats with chicory extract administration at 300 mg/kg body weight.
Group 5: Diabetic rats with chicory extract administration at 350 mg/kg body weight.
Group 6: Diabetic rats with chicory extract administration at 500 mg/kg body weight.

At the end of the experiment, blood was collected in tubes to serum test preparation. Determination of serum glucose according to Trinder (1969). Determination of high-density lipoprotein cholesterol (HDL) and determination of low-density lipoprotein cholesterol (LDL) were calculated according to Tietz (1976a). Serum aspartate transferase ($_S$.AST) activity was measured calorimetrically according to Tietz (1976b). The method of Serum alanine transferase ($_S$.ALT) activity was measured colorimetrically according to the method of Tietz (1976b). Alkaline phosphatases (ALP) in serum was determined according to Youn *et al.,* (1972).

Statistical analysis

Statistical analysis was carried out according to Snedecor and Cochran (1989). Using analysis of variance and the significance was determined using L.S.D. values at P = 0.05 (Gomez and Gomez, 1984).

RESULTS

In the present study, dried samples of chicory were used to study and assess their chemical composition, antioxidant activity of their extracts and antidiabetic.

Chemical composition of chicory plant

Results shown in Table (1) demonstrate the analysis of chicory plant. The chicory plant showed that contents of crude protein 13.55% and total carbohydrate 66.66%,also total lipids, crude fiber and Inulin were found to be 5.43, 2.83 and 16.96%, respectively.

It is clear that the ethanolic extract has the highest amount of phenolic compounds (121.33 mg/100g) followed by acetone, ethyl acetate, chloroform, aqueous and hexane extracts (102.44, 82.23, 52.56, 42.13, 14.32 mg/100g., respectively). Data also show that total flavonoids and tannins contents were 88.26 and 26.13 mg/100g, respectively in ethanol extract. Wherever, hexane extract reveals lowest content of flavonoids and tannins recording 10.52 and 5.63 mg/100g, respectively. Results concerning, that the highest antioxidant activity which are 84.32 and 83.12% of ethanol and aqueous extracts, respectively,

Table (1): Proximate analysis of chicory (% on dry weight basis).

Constituents	g/100g
Moisture	83.53±0.51
Ash	11.53±0.74
Crude protein	13.55±0.62
Total carbohydrate	66.66±0.25
Total lipid	5.43±0.28
Crude fiber	2.83±0.78
Inulin	16.96±0.00

Values represent mean ± SD of 3 replicates.

Total phenolics, flavonoids, tannins and antioxidant activity of different extracts (hexane, chloroform, ethyl acetate, ethanol and aqueous extracts of chicory plant were represented in Table (2).

Data in Table (5) found that changes in the serum HDL and LDL cholesterol by using different doses 300, 350 and 500 mg/kg from chicory extracts in diabetic rats. Results revealed that gradually increase of HDL otherwise LDLwas decreased with increasing chicory extract dose. HDL was significantly increase with using 500 mg/kg dose 57.18 mg/dl followed decrease of LDL 31.81 mg/dl .

Data presented in Table (5) show the serum Asptartate transaminase (sAST) activity in diabetic rats. Results found that the best dose was 500mg/kg significantly decrease (sAST) recording 30.50 IU/l followed by use of 350 mg/kg which recorded 36.17 IU/l compared with positive Control +).

The same Table also reveal the serum Alanine transaminase (sALT) activity in diabetic rats. Results indicate that the best dose was 500mg/kg with orally administration of chicory extract which has the lowest level of (sALT) recording (38.67 IU/l), followed by the use of 350 mg/kg which recorded 42.50 IU/l.

Results in Table (3) illustrate the phenolic and flavonoids fractionation by HPLC. Data show that the main compound of phenols was Catechein recording408.39ppm followed by pyrogallol 219.47ppm, while, the lowest contents were

caffeic acid and cinnamic acid recording 2.83 and 2.06ppm, respectively. On the other hand, flavonoids fractionation of chicory extract reveals that a high content of Rutin recording 416.81ppm, naringin 378.02ppm and luteolin 7- glucose 301.03ppm, however, the lowest contents were Quercetin and Narigeninrecording12.93ppm and 5.64ppm, respectively.

Table (2): Total phenolic, flavonoid and tannin, compound contents and Antioxidant activity (DPPH %)in different extracts of Chicory

Constituents	Phenolic Compounds mg/100g	Flavonoids mg/ 100g	Tannins mg/100g	DPPH (%)
Hexane	14.32±5.30	10.52±1.6	5.63±5.6	41.36±2.5
Chloroform	52.56±6.30	48.34±6.22	14.35±4	60.42±4.80
ethyl acetate	82.23±5.37	74.33±5.34	21.12±2.3	65.32±7.10
Acetone	102.44±7.31	81.75±5.47	25.13±5.3	70.4±52
Ethanol	121.33±10.20	88.26±9.23	26.13±2.6	84.32±2.20
Aqueous	42.13±5.30	38.14±3.5	28.22±2.39	83.12±2.70

Values represent mean ± SD of 3 replicates.

Table (3): Identification of phenolic and flavonoid compounds using HPLC of chicory ethanolic extracts

Phenolic compounds	ppm	Flavonoid compounds	ppm
Pyrogallol	219.47	Apigenin 6-rhamnose 8-glucose	109.961
Gallic acid	7.84	Luteolin 7- glucose	301.03
4-amino-benzoic acid	11.94	Naringin	378.02
Protocatchoic acid	20.97	Rutin	416.81
Catechein	408.39	Apigenin 7- glucose	54.097
Catechol	73.42	Apigenin 7-o-Neohespiroside	70.09
Chlorogenic acid	19.93	Kampferol 3-7-Diramoside	29.68
Epicatechein	-	Quercetrin	58.52
P-OH-benzoic acid	62.40	Quercetin	12.93
Caffeic acid	2.83	Narigenin	5.64
Vanillic acid	41.98	Acacetin 7-neo Rutinoside	83.96
P-Coumaric acid	5.82	Hespirtin	57.68
Ferulic acid	9.61	Kampferol	19.33
Iso- Ferulic acid	6.27	Apigenin	20.06
Benzoic acid	182.89		
3,4,5-tri methoxy-cinnamic acid	9.97		
Coumarin	4.88		
Salycilic acid	217.12		
Cinnamic acid	2.06		
Caffeine	85.69		

Effect of chicory extract on biological pramter in diabetic rats.

Data in Table (4) explain the effect of chicory extract on serum glucose level in diabetic male rats using different doses of 300, 350 and 500mg/kg. Results indicate that the best dose was 500mg/kg which revealed significant decrease in serum glucose level from 288.41 to 170.37mg/dl followed by the use of 350mg/kg which revealed significant decrease in serum glucose level from 292.77 to 179.92 mg/dl.

Moreover, results in Table (5) also indicate that the serum alkaline phosphatase (ALP) activity was significantly decreased to (85.68, 83.01 and 80.08IU/l at doses of 300,350 and 500 mg/kg), respectively compared with diabetic control (102.94 IU/l).

The root and the leaves of chicory are appetizer, cholagogue, depurative, digestive diuretic, hypoglycaemic, laxative and tonic. Chicory extract contains inulin and fructooligo saccharides. Inulin behaves-like a soluble fiber so increase the viscosity of the stomach content and slow down the rate of gastric emptying of water,

Table (4): Effect of different concentrations from chicory extract on serum glucose level (mg/dl) diabetic male albino rats.

Treatments	Treatment periods experimental diets				
	Before Treatment	Week1	Weeks2	Weeks3	Weeks4
Control (-)	97.61^{d}±7.30	94.64^{d}±6.23	99.45^{f}±6.33	95.26^{h}±7.59	97.38^{h}±7.90
Control (+)	299.45^{q}±16.63	296.49^{a}±11.38	294.35^{a}±9.52	291.04^{a}±5.16	289.70^{a}±6.35
Glibenclamide (*Amaryl*)	298.07^{ab}±11.74	289.50^{ac}±9.94	244.27^{de}±9.64	219.70^{cd}±12.55	194.86^{d}±6.92
Chicory (300 mg/kg)	289.41^{c}±20.95	286.73^{bc}±14.87	237.26^{e}±8.97	213.83^{de}±9.35	199.45^{cd}±8.06
Chicory (350 mg/kg)	292.77^{bc}±12.91	285.34^{bc}±9.11	239.97^{e}±8.96	204.64^{ef}±8.97	179.92^{ef}±8.34
Chicory (500 mg/kg)	288.41^{ab}±9.98	288.70^{ac}±10.44	241.58^{de}±6.05	191.98^{g}±8.42	170.37^{g}±7.80
L.S.D. at 0.05%	17.21	121.42	15.33	12.43	9.31

Table (5): Effect of different concentrations from chicory extracts on serum LDL, HDL (mg/dl) sAST, sALT and ALP (IU/l) in diabetic male albino rats (Orally).

Treatments	HDL (mg/dl)	LDL (mg/dl)	s.AST (IU/l)	s.ALT (IU/l)	ALP (IU/l)
Control(-)	48.35^{bc}±4.02	31.96^{d} ±4.39	25.67^{c}±4.13	34.83^{f}±3.76	79.95^{d}±1.95
Control(+)	32.92^{f}±4.82	115.65^{a}±9.45	59.83^{a}±8.73	65.33^{a}±6.83	102.94^{a}±3.25
Amaryl (1 mg/kg)	41.56^{de}±5.64	74.52^{b}±4.79	36.00^{b}±4.47	53.00^{bc}±3.46	89.08^{bd}±1.78
Chicory (300 mg/kg)	44.69^{cd}±5.25	68.99^{b}±6.60	36.33^{b}±7.09	47.00^{d}±5.14	85.68^{bc}±3.57
Chicory (350 mg/kg)	52.69^{ab}±6.74	53.05^{c}±7.54	36.17^{b}±6.65	42.50^{de}±5.39	83.01^{bd}±0.87
Chicory (500 mg/kg)	57.18^{a}±7.28	31.81^{d}±7.71	30.50^{b}±12.8	38.67^{ef}±4.03	80.08^{d}±3.69
L.S.D. at 0.05%	6.72	10.56	9.12	7.45	4.03

DISCUSSION

Chemical composition of chicory plant

These results are in agreement with the results obtained by (Monti et al., 2005) who found that the ash content ranged between 9.58 to 13.75% and the crude protein was 13 % in chicory plant. The results were near to those obtained by(Zarroug et al., 2016). (Hui et al., 2002) reported that Inulin is a polymer of fructose with β (2 -1) glycosidic linkage; the major compound of chicory root, inulin is used as a food ingredient for fat and sugar replacement as a low calorie bulking agent.

Our results are close to (Christova-Bagdassarian et al., 2014) and Dzharova *et al.,* (2016) who found that total phenolics, total flavonoids, rutin and tannin contents are significant components in aqueous ethanol extract of dry leaves of *Cichorium intybus*L..

Phenolics, flavonoids, rutin and tannins as total phenolic compounds offer lots of protection opportunities against oxidative stress in *Cichorium intybus L as* an important role in the antioxidant capacity (Zhang and Kim 2015).

(Pieroni et al., 2002) found the presence of caffeic acid derivatives and flavonoids (quercetin and kaempferol glycosides) which have very high antioxidant activity. These results partially agree with those obtained by Kocsis *et al*.,(2003) who stated that chicory extract contain flavonoids as hyperoside, polyphenols as pyrogallol and caffeic acid derivatives as caffeic acid. These components may be responsible for the *in vitro* antioxidant property of the natural extract.

Effect of chicory extract on biological parameter in diabetic rats

This results may be due to inulin is a dietary fiber with limited calorie value, consequently, suitable for diabetics and is considered to be beneficial to health for its prebiotic properties. Inulin has been identified as an ingredient that substitutes fat or sugar to be suitable for diabetics (Li et al., 2008).

(Nowrouzi et al., 2017) reported that the effect of chicory may be due to inhibiting of glucose absorption in the intestine or by enhancing beta cell for insulin secretion due to increased glucose transport into cells in peripheral tissues mechanisms such as inhibiting endogenous glucose production through the gluconeogenesis and glycogenesis pathways. Furthermore, (Alipour, et al.,2018) concluded that catechins can be effective in controlling hyperglycemia. The observations confirm that Chicory extract of the leaf and stem has anti-diabetic activity and is also involved in correction of altered biological parameters mainly Cholesterol metabolism. In this plant so as to elucidate their mode of action (Hardeep et al., 2013).

Gaafar *et al., (*2010) found that inulin increased serum HDL and decreased serum LDL by inhibition of hydroxyl methyl glutaryl-Co. A reductase which responsible for cholesterol biosynthesis (Deleznne and Kok 2001).

Moreover, (Abdel-Rahim et al., 2016) showed that feeding on chicory leaves causes decreasing in blood glucose levels, improvement in the lipid profile and management of the disturbance in kidneys and liver functions in diabetic ratsAlso, Catechin dose dependently reduced the serum levels of TC, TG, LDL-C, and increased the serum levels of HDL-c (Samarghandian et al., 2017).

Nutrients and lipids. (Urias-Silvas et al., 2007) concluded that inulin-type fructans extracted from chicory regulate appetite and lipid/glucose metabolism. It has also promising effects on the body weight and fat mass development. (Malabu et al., 1994) and (Kurt et al., 2011). It is known that chicory contains iso flavones, polyphenols and other antioxidants that can reduce the elevation of serum ALT and AST. Antioxidants in chicory extract have protective activity and improve liver function (Gazzani et al., 2000). (Yassin et al., 2007) reported that chicory extract improve lipid profiles by lowering plasma total cholesterol and triglyceride concentrations and elevating HDL-c concentration due to presence of inulin. It could be concluded that feeding with chicory causes decreasing in blood glucose levels, improvement in the lipid profile and management of the disturbance in kidneys and liver functions in diabetic rats (Abdel-Rahim et al., 2016).

CONCLUSION

In conclusion, observations confirm that ethanolic extract of Chicory plant has antidiabetic activity and affects lipids metabolism.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

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