



Hepatoprotective effects of parsley, basil, and chicory aqueous extracts against dexamethasone-induced in experimental rats

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ABSTRACT

Aim: The objective of this study is to investigate the hypoglycemic, hypolipidemic, and hepatoprotective effects of the aqueous extract of parsley, basil, and chicory whole plant in normal and dexamethasone (Dex) rats. **Materials and Methods:** 50 female albino rats were used in this study and divided into 5 groups (for each 10). Group (1) fed basal diet and maintained as negative control group. Group (2) received Dex in a dose of (0.1 mg/kg b. wt.). Groups 3, 4, and 5 were treated with Dex along with three different plant extracts of parsley, basil, and chicory (2 g/kg b. wt.), (400 mg/kg b. wt.), and (100 mg/kg b. wt.), respectively. **Results:** All these groups were treated given three times per week for 8 consecutive weeks. Dex-induced alterations in the levels of serum glucose, triglyceride, cholesterol, low-density lipoprotein-cholesterol levels and cardiovascular indices and serum alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase activities, liver thiobarbituric acid (TBARS) levels increased, while high-density lipoprotein-cholesterol, total protein, albumin, and liver glutathione (GSH) levels decreased. On the other hand, plant extracts succeeded to modulate these observed abnormalities resulting from Dex as indicated by the reduction of glucose, cholesterol, TBARS, and the pronounced improvement of the investigated biochemical and antioxidant parameters. **Conclusions:** It was concluded that probably, due to its antioxidant property, parsley, basil, and chicory extracts have hepatoprotective effects in Dex-induced in rats.

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INTRODUCTION

Dexamethasone (Dex) has potent immunosuppressant and anti-inflammatory properties but therapeutic benefits of this drug limited as it presents several side effects such as insulin resistance and skeletal muscle atrophy and generation of the free radicals which may contribute to oxidative stress as long-term treatment [1]. Natural products have been examined for promising new source pharmaceutical and therapeutic agents in plant secondary metabolites that characterize definite plants [2].

It is thought that the health promoting effect of *Petroselinum crispum* (parsley) may be due to its flavones components as ascorbic acid, carotenoids, flavonoids, coumarins, myristicin, apiol, various terpenoid compounds, phenylpropanoids, phthalides, furanocoumarins, and tocopherol [3].

Ocimum basilicum (basil) had been found to contain linalool, eugenol, methyl chavicol, methyl cinnamate, ferulate, methyl eugenol, triterpenoids, and steroidal glycoside known to exhibit antioxidant, chemopreventive, anti-inflammatory, bactericidal, antiulcer activities, a nervous system stimulant effect,

modulatory effect on glutathione and antioxidant enzymes, antiarrhythmic and hypoglycemic effects [4,5].

Cichorium intybus L. (chicory) own excessive medicinal importance as it has alkaloids, inulin, sesquiterpene lactones, coumarins, vitamins, chlorophyll pigments, unsaturated sterols, flavonoids, saponins, and tannins [6].

The aim of this study was both to investigate the hepatoprotective effect of *P. crispum*, *O. basilicum*, and *C. intybus L.* aqueous extracts against Dex-induced in rats and to explore the antioxidant capability of the extracts.

MATERIALS AND METHODS

Chemicals

Dex ([Fortecortine® 8 mg - Mono ampule) Manufactured by Sigma - Tec Pharmaceutical industries - Egypt - S. A. E. under Licence of: Merck KGaA, Darmstadt, Germany).

Plant Materials

Parsley (*P. crispum*), basil (*O. basilicum*), and chicory (*C. intybus L.*) leaves were collected from herbal medicine market (Cairo, Egypt) and identified by an ecologist in plant department, Faculty of Science, Beni-suef University. The leaves of these plants were cleaned, shade dried for 30 days at room temperature, crushed to a coarse powder and preserved for further processing.

Preparation of Plant Extract

Preparation of aqueous parsley extract

The 100 gram dried parsley leaves were extracted by adding 1000 ml of distilled water and boiled for 30 min. The extract was then filtered, and then the filtrate was evaporated, using rotary evaporator under reduced pressure to dryness (at 45°C). The extract was dissolved in distilled water before the administration to rats [7].

Preparation of aqueous basil extract

The 300 g ground powder of dried basil leaves was infused for 30 min in 200 ml of distilled water at 100°C followed by filtration. The solution obtained was concentrated rotary evaporator under a vacuum at 65°C. The resulting crude extract was suspended in 30 ml sterile distilled water, and aliquots were stored at -20°C until use [8].

Preparation of aqueous chicory extract

The powdered chicory leaves were added to the already boiling distilled water and infused for 15 min. Then, the infusion (2% w/v) was filtered, and the filtrate was freshly used [9].

Animals

Female albino rats (*Rattus norvegicus*) weighing about 120-150 g were used for the study and were kept in the animal house at 26 ± 2°C with relative humidity 44% to 56% along with light and dark cycles of 12 h. Animals were provided with standard diet and water *ad libitum*.

Animal Groups

For the achievement of the objectives of this study, 50 female albino rats were randomly divided into 5 groups including the normal groups and the diabetic groups each group consists of 10 rats. Group 1: Served as normal control. Group 2 was considered as Dex-control was given Dex subcutaneously 0.1 mg/kg/day [10], and this group was considered as control for the Groups 3, 4, and 5. Group 3 (Dex-treated with parsley): The rats in this group were given Dex and also were administered aqueous parsley at dose level of 2 g/kg/b. wt. [7]. Group 4 (Dex-treated with basil): The animals in this group were Dex and also were given aqueous basil at dose level 400 mg/kg/b. wt. [4]. Group 5 (Dex-treated with chicory): The animals in this group were Dex and also were treated with aqueous chicory at dose level 100 mg/kg/b. wt. [11]. All these groups were treated for three times per week for 8 consecutive weeks and the treatments with parsley, basil, and chicory were performed orally between 7.00 and 9.00 a.m.

Biochemical Assay

At the end of the experimental period (8 weeks), rats were sacrificed under diethyl ether anesthesia. Blood samples were collected from each rat, allowed to coagulate at room temperature then centrifuged at 3000 r.p.m. for 20 min. The clear, non-hemolyzed supernatant sera were quickly removed and kept at -20°C until examined.

The serum samples were analyzed for glucose according to the method of [12] using standard diagnostic kits from Spinreact and serum cholesterol [13], triglycerides [14], high-density lipoprotein-cholesterol (HDL-C) [15], total protein [16], albumin [17] using the commercial assay kit provided from Bioscope Diagnostics, beta lab, Egypt, while very low-density lipoprotein-cholesterol (VLDL-C), LDL-C, and cardiovascular indices were calculated mathematically according to [18,19] using the following formula:

$$\text{VLDL-C} = \text{Triglycerides}/5$$

$$\text{LDL-C} = \text{Cholesterol} - (\text{Triglyceride}/5) - \text{HDL-C}$$

$$\text{Cardiovascular index 1} = \text{Total cholesterol}/\text{HDL-C}$$

$$\text{Cardiovascular index 2} = \text{LDL-cholesterol}/\text{HDL-C}$$

The activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was determined kinetic at 546 nm using

a standard method [20], respectively, using kit provided from Bioscope Diagnostics, betalab, Egypt. Lactate dehydrogenase (LDH) was measured using the kinetic method described by Young [21] using reagent kits obtained from BioSystems, Barcelona, Spain.

Hepatic Oxidative Stress and Antioxidant Enzymes Assay

Liver tissues were homogenized in cold 0.9% NaCl with a glass homogenizer to make up to 10% homogenate (w/v). The homogenates were centrifuged, and the clear supernatants were used for lipid peroxidation (LPO), glutathione (GSH), and antioxidant enzymes. The supernatant was used for the estimation of malondialdehyde (MDA) [22]; GSH [23]; GSH s-transferase (GST) [24]; GSH peroxidase (GPx) [25]; GSH reductase (GR) [26]; and catalase [27] levels using the reagent kits purchased from Biodiagnostic Company, Giza, Egypt.

Histological Examination of Liver

Liver specimens were fixed in 10% formal saline for 24 h. 5% formic acid was used for decalcification, processed, and embedded in paraffin. Thin paraffin sections (4 μ m) were stained by H and E [28].

Statistical Analysis

The data were analyzed using the one-way analysis of variance [29] followed by least significant difference test to compare various groups with each other. Results were expressed as mean \pm standard deviation (SD), and values of $P > 0.05$ were considered non-significantly different, while those of $P < 0.05$, $P < 0.01$, and $P < 0.001$ were considered significantly, highly, and very highly significantly different, respectively.

RESULTS

Data in Table 1 show treatment of diabetic rats induced by Dex with parsley, basil, and chicory extracts caused considerable positive effects on the investigated parameters as compared to their corresponding control rats where $P < 0.001$ in all compared groups.

Data presented in Table 2 demonstrated that treatment of diabetic rats induced by Dex with parsley and chicory extracts cause a significant increase in serum total protein and albumin while treatment with basil cause a non-significant increase in total protein and a significant increase in albumin level when compared with diabetic rats.

Results showed that the treatment of rats with parsley, basil, and chicory extracts produced a profound, significant decrease of the LPO products in the liver and also, produced an increase of glutathione level and antioxidant enzymes when compared to their control group as shown in Table 3.

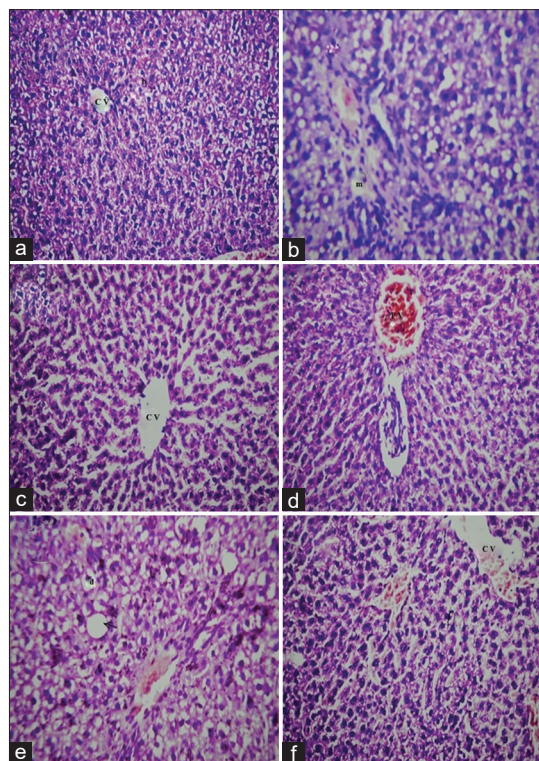


Figure 1: (a-f) Photomicrographs of rat liver sections of different experimental groups stained with hematoxylin and eosin, (a and b) liver sections of normal (G1) and dexamethasone (G2) groups, (c-d) liver sections of diabetic rats treated with parsley extract group (G3), (e) Liver section of diabetic rats treated with basil extract group (G4), and (f) liver section of diabetic rats treated with chicory extract group (G5)

Table 1: Serum biochemical parameters in control and different treated groups

Parameters	Norm	Dex	Dex+parsley	Dex+basil	Dex+chicory	P_{ANOVA}	LSD at 5%	LSD at 1%
Glucose (mg/dl)	123 \pm 12.3 ^d	218 \pm 11.7 ^a	170 \pm 4.48 ^b	143 \pm 21.8 ^c	160 \pm 1.95 ^b	$P < 0.001$	14.92	20.19
Triglyceride (mg/dl)	44.7 \pm 4.43 ^c	90.1 \pm 7.51 ^a	61.1 \pm 7.37 ^b	54.1 \pm 8.60 ^b	53.0 \pm 7.46 ^{bc}	$P < 0.001$	8.575	11.60
Cholesterol (mg/dl)	101 \pm 10.2 ^c	189 \pm 7.96 ^a	118 \pm 2.83 ^{bc}	135 \pm 3.52 ^b	153 \pm 11.7 ^{bc}	$P < 0.001$	30.54	41.32
VLDL-C (mg/dl)	8.94 \pm 0.88 ^c	18.0 \pm 2.05 ^a	12.2 \pm 1.47 ^b	10.8 \pm 1.72 ^b	10.6 \pm 1.49 ^{bc}	$P < 0.001$	1.714	2.319
LDL-C (mg/dl)	47.8 \pm 10.5 ^e	139 \pm 8.97 ^a	63.5 \pm 5.71 ^d	84.9 \pm 4.78 ^c	107 \pm 14.7 ^b	$P < 0.001$	11.46	15.50
HDL-C (mg/dl)	44.2 \pm 3.59 ^a	32.0 \pm 3.35 ^d	42.3 \pm 3.06 ^{ab}	39.3 \pm 3.81 ^{bc}	36.0 \pm 4.01 ^c	$P < 0.001$	4.269	5.775
Cardiovascular index 1	2.28 \pm 0.24 ^d	5.90 \pm 0.69 ^a	2.78 \pm 0.23 ^d	3.43 \pm 0.39 ^c	4.25 \pm 0.76 ^b	$P < 0.001$	0.608	0.823
Cardiovascular index 2	1.08 \pm 0.25 ^d	4.39 \pm 0.65 ^a	1.50 \pm 0.22 ^d	2.16 \pm 0.35 ^c	2.90 \pm 0.71 ^b	$P < 0.001$	0.573	0.775

Data are expressed as mean \pm SD $n=6$ animals per group. LSD: Least significant difference, mean with the different letters in the row are significantly different, VLDL-C: Very low-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, SD: Standard deviation

Table 2: Serum liver function markers in control and different treated groups

Parameters	Norm	Dex	Dex+parsley	Dex+basil	Dex+chicory	<i>P</i> _{ANOVA}	LSD at 5%	LSD at 1%
Total protein (g/dl)	10.4±0.90 ^a	7.54±0.28 ^c	8.86±0.98 ^b	8.47±1.33 ^{bc}	8.72±1.09 ^b	<i>P</i> <0.01	1.223	1.654
Albumin (g/dl)	6.63±0.37 ^a	4.52±0.19 ^d	5.58±0.33 ^b	5.31±0.44 ^{bc}	5.48±0.46 ^c	<i>P</i> <0.001	0.600	0.812
ALT (IU/L)	52.4±5.74 ^c	76.5±10.3 ^a	61.7±6.37 ^b	58.1±4.19 ^{bc}	58.3±3.28 ^{bc}	<i>P</i> <0.001	7.654	18.50
AST (IU/L)	179±10.4 ^c	240±20.9 ^a	187±11.7 ^c	190±17.7 ^c	214±14.8 ^b	<i>P</i> <0.001	18.51	25.03
LDH (IU/L)	2481±332 ^d	3530±258 ^a	2813±246 ^c	2925±211 ^{bc}	3143±165 ^b	<i>P</i> <0.001	295.4	399.7

Data are expressed as mean±SD *n*=6 animals per group, mean with the different letters in the row are significantly different, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase, LSD: Least significant difference, SD: Standard deviation

Table 3: Liver oxidative stress marker and antioxidant parameters in control and different treated groups

Parameters	Norm	Dex	Dex+parsley	Dex+basil	Dex+chicory	<i>P</i> _{ANOVA}	LSD at 5%	LSD at 1%
TBARS (nmol/g T)	18.2±1.41 ^d	29.6±2.19 ^a	21.6±2.11 ^b	19.7±1.77 ^{bc}	18.7±2.13 ^c	<i>P</i> <0.001	2.313	3.127
GSH (mg/g T)	27.3±3.86 ^a	13.1±2.64 ^c	21.6±2.11 ^b	20.9±3.40 ^b	19.9±3.79 ^b	<i>P</i> <0.001	3.844	5.201
GST (U/g T)	4180±396 ^a	2108±209 ^c	3532±202 ^b	4059±65.9 ^a	3627±182 ^b	<i>P</i> <0.001	280.8	379.9
GPx (U/g T)	181±23.1 ^a	61.7±16.6 ^c	170±7.56 ^a	91.0±13.9 ^b	92.6±12.9 ^b	<i>P</i> <0.001	18.60	25.17
GR (U/g T)	328±15.4 ^a	170±37.5 ^c	209±22.5 ^b	307±20.9 ^a	314±20.2 ^a	<i>P</i> <0.001	29.07	39.37
Cat (U/g T)	0.80±0.09 ^a	0.30±0.06 ^d	0.39±0.08 ^c	0.36±0.06 ^{cd}	0.60±0.07 ^b	<i>P</i> <0.001	0.075	0.101

Data are expressed as mean±SD *n*=6 animals per group, mean with the different letters in the row are significantly different, TBARS: Thiobarbituric acid reactive substance, GSH: Glutathione reduced, GST: Glutathione s-transferase, GPx: Glutathione peroxidase, GR: Glutathione reductase, SD: Standard deviation

Histopathological Results

Microscopically, liver of rat from negative control revealed no histopathology change [Figure 1a]. Meanwhile, section of liver of rat from positive control group (rats administrated with Dex) revealed fatty change was detected in diffuse manner all over the hepatocytes in association with inflammatory cells infiltration in the portal area [Figure 1b]; a section of liver of parsley extract treated rats showed there was no histopathological alteration [Figures 1c and d]: The liver of rats from group supplemented with aqueous basil extract showed normal liver with few individual hepatocytes [Figure 1e]. Moreover, the liver of rats from group supplemented aqueous chicory revealed no histopathological changes except mild congestion was observed in the central veins [Figure 1f].

DISCUSSION

The causes for diabetes after chronic Dex-treatment explained by reduced insulin sensitivity, impaired α and β -cell functions, increased hepatic gluconeogenesis, by stimulating amino acids releasing from skeletal muscle, fatty acids and glycerol from adipose tissue and enhance gluconeogenic enzymes expression as phosphoenolpyruvate carboxykinase [30].

Hyperlipidemia caused in Dex-induced diabetes is due to excess mobilization of fat from the adipose tissue, increase VLDL secretions by the liver and stimulate VLDL formation by the intestine, decreasing hepatic lipoprotein lipase activity that inhibit the removal of plasma VLDL and leading to an increase plasma VLDL level [31].

A decline in serum total protein level in diabetics due to decrease in protein synthesis, increase in catabolic processes, and reduction of protein absorption as inhibition of oxidative phosphorylation [32].

Corticosteroids therapy associated with several forms of liver injury leads to increase the liver function enzymes. ALT only significantly elevated in hepatobiliary disease and is liver specific enzyme AST level increased with damages of heart or skeletal muscle as well as of liver parenchyma. Changes in LDH may be attributed to severe damage to heart tissue as myocardial necrosis [33-35].

The Dex-induced oxidative stress and altered the antioxidant status in several tissues. The reduction of GSH contents corresponds to cellular oxidative damage and death as the cellular energy is impaired or due to the fast oxidation of GSH-induced by steroidal drug Dex. Depletion in the activity of antioxidant enzymes can be due to an enhanced radical production during Dex metabolism [36,37].

The current biochemical alterations were coincided with the present histological investigation for liver section, so the negative results associated with Dex may be attributed to the hepatic injury induced by superoxide anions and hydroxyl radicals which cause oxidative damage to cell membrane resulted in fatty change in diffuse manner all over the hepatocytes in association with inflammatory cells infiltration in the portal area. In agreement with our result [38] showed the treatment of rats with glucocorticoids led to the accumulation of lipids in the liver.

Parsley extract possess antihyperglycemic by facilitating glucose usage via extra-pancreatic ways as inhibition of gluconeogenesis and may be stimulate glycolysis process directly [6]. Aqueous extract of parsley possesses hypocholesterolemic and hypotriglyceridemic activities due to it has flavonoids that possess the bioactivity to beneficially affect the cardiovascular risk factors such as lipoprotein oxidation, dyslipidemia, endothelial dysfunction, and blood platelet aggregation and regulation of lipid levels in plasma or tissue leads to a decrease

in the risk of micro or macro vascular disease and related complications [39]. Flavonoids decreased blood cholesterol levels by decreasing the biosynthesis of cholesterol, enhancing the phosphorylation of 3-hydroxy-3-methylglutaryl coenzyme A reductase indirectly [40].

Phytochemical screening of parsley has revealed the presence of flavonoids (apiin, luteolin, and apigenin-glycosides) and a considerable elevation in albumin concentration was recorded in apigenin-treated mammary adenocarcinoma group [41]. The parsley showed a significant decrease in the serum activity of AST, ALT, and LDH this result indicated that parsley had able to regenerate liver after liver cell damage and reduced incidence of heart disease in diabetes mellitus as it contains flavonoids, particularly the quercetin (as a flavonol) [42]. A variety of flavonoids, lignans, alkaloid, bisbenzyl, coumarins, and terpenes were tested for their antioxidant activity as showed they able to prevent the oxidative damage in epithelial cells kidney and liver [43]. Parsley extract has the ability to reduce the toxic effects may be recognized to the high nutritive value that determined too high percent of vitamins (A, C, riboflavin, and niacin) and minerals (Fe, Mg, P, K, Ca, Na, and Zn) [44].

O. basilicum decreased glucose levels in blood which act via inhibition renal glucose reabsorption and/or inhibition of hepatic glucose production, improving insulin action or stimulate peripheral tissues to utilize glucose [45]. The reduction of plasma total cholesterol and its LDL fraction by the *O. basilicum* extract was associated with an increase in plasma HDL-cholesterol, and the activity of *O. basilicum* extract to decrease cholesterol concentration by stimulating the elimination of cholesterol in the form of bile acids by promoting cholesterol mobilization from peripheral tissues to the liver [46]. There is a significant increase in the amount of protein and globulin levels as *O. basilicum* is immunostimulant herbals incorporated diets helped to increase the humoral elements in the serum [47]. Basil extract decreases the activities of serum AST and ALT due to it increase the level of antioxidant enzymes that may protect liver against the damaging effects and inhibit LPO [48]. Basil is a rich source of flavonoids, and the hepatoprotective effect of *O. basilicum* may be attributed to the antioxidant activity of its flavonoids [4], so the liver of rats from the group treated with aqueous basil extract showed normal liver.

Water-soluble extract of chicory reduced serum glucose may be due to the presence of inulin, oligofructose, and esculetin [49,50]. The decrease in blood cholesterol level might be due to chicory has the ability to stimulate lactic acid producing bacteria which secrete the hydrolase enzyme that in-turn converts bile salts into deconjugated bile acids and ultimately resulted in the reduced serum cholesterol level, and the insulin decrease the expressions of acetyl-coenzyme A carboxylase and fatty acid synthase messenger RNA [49,51]. Inulin and oligofructose decrease the synthesis of triglycerides and fatty acids in the liver and decreasing their level in serum by inhibiting hepatic lipogenesis and reducing the risk of atherosclerosis [34]. Significant improvement in albumin serum level of chicory protected rats compared to nitrosamine precursors-treated

rats [52]. The administration of chicory supplemented diet resulted in an improvement of protein pattern by preventing protein oxidation and improves liver and other organs functions which synthesized plasma protein [34,50]. The antihepatotoxic effect of chicory due to it contains isoflavones, polyphenols, and other antioxidants that can reduce the activity of serum ALT and AST, and it was noticed that chicory significantly lowers serum activity of AST and ALT enzymes in carbon tetrachloride (CCL₄) intoxicated rats. Liver function was improved due to protective activity of antioxidants components in chicory extract, and it was shown that chicory decreased levels of MDA and increased GSH, antioxidant enzymes in (CCL₄) intoxicated rats [52-55]. Chicory cause elevation of intracellular antioxidant enzyme activities and decreased oxidative stress in tissues due to chicory extract enhance endogenous antioxidant defense status [49,56]. This hepatoprotection of chicory prevent liver damage, and no histopathological changes occur.

CONCLUSION

The parsley, basil, and chicory extracts offered a hepatic protection against Dex-induced in rats. In a comparison of our result, we found that parsley has a potent hepatoprotective effect more than basil and chicory. All the aforementioned effects of extracts may explain their ameliorative impact on Dex changes in our study.

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