Effect of *Gundelia tournefortii* on some biochemical parameters in dexamethasone-induced hyperglycemic and hyperlipidemic mice

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Abstract

The aim of this study was conducted to evaluate the effect of *Gundelia tournefortii* on some biochemical parameters in hyperglycemic and hyperlipidemic mice. Male albino mice were induced hyperglycemic and hyperlipidemic by daily injection of dexamethasone 1 mg/kg of body weight intramuscularly (i.m.), the mice randomly divided into five groups (6-8 mice in each group). The group 1: served as negative control group; the group 2: injected with dexamethasone at dose 1 mg /kg.b.w.i.m and served as positive control group; the groups 3, 4, 5: treated with extract of *G. tournefortii* at doses: 75, 150, 300 mg/kg.b.w. orally respectively companied with injection of dexamethasone 1 mg/kg.b.w.i.m. All treatment were once daily for 22 days. Dexamethasone treatment lead to significant increase in levels of glucose, cholesterol, and triglyceride, and significant decrease of body weight, without any effect on level of total protein. *G. tournefortii* extract treatment at doses: 75 mg/kg.b.w. resulted significant decrease levels of glucose, and body weight. Beneficial effect were seen when mice treated with *G. tournefortii* at dose of 300 mg/kg.b.w. that lead to significant decrease in levels of glucose, triglyceride, and cholesterol. These results indicate the usefulness of *G. tournefortii* extract as hypoglycemia and hypolipidemia in dexamethasone treated mice.

Keywords: *Gundelia tournefortii*; Dexamethasone, Glucose; Lipid profile.
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تأثير المستخلص المائي لنبات الكعوب في بعض القيم الكيميائية الحياتية عند فرط الكلوكوز والدهون المستحدث بالدكساميثازون في الفئران

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الخلاصة

صممت تجارب هذه الدراسة لتقييم تأثير المستخلص المائي لنبات الكعوب *Gundelia tournefortii* في مستويات بعض القيم الكيميائية الحياتية في الفئران المرتفعة الكلوكوز والدهون. أُستخدمت ذكور فئران من نوع Albinoتجريبياً لرفع مستويات الكلوكوز وشحوم الدم بحقنها يومياً بمادة الدكساميثازون بالعضلة بجرعة ١ ملغم/كغم من وزن الجسم. قسمت الفئران عشوائياً إلى خمسة مجاميع (كل مجموعة ٦-٨ فئران):المجموعة الأولى: تركت دون معاملة كمجموعة سيطرة سليمة، المجموعة الثانية: حقنت بمادة الدكساميثازون بالعضلة بجرعة ١ ملغم/كغم من وزن الجسم وعُدت كمجموعة سيطرة مصابة، المجاميع ٣، ٤، ٥، تم إعطائها المستخلص المائي لنبات الكعوب *G. tournefortii* وبالجُرع: ٧٥، ١٥٠، ٣٠٠ ملغم/كغم من وزن الجسم على الترتيب وعن طريق الفم مع حقنها بمادة الدكساميثازون بنفس الجرعة أعلاه. كل المعاملات كانت لمرة واحدة باليوم ولمدة ٢٢ يوم. أدت المعاملة بالدكساميثازون إلى ارتفاع معنوي في مستويات الكلوكوز، الكولسترول، الكليسيريدات الثلاثية، مع خفض معنوي لوزن الجسم ولم يكن له تأثير على مستوى البروتينات الكلية. أظهرت نتائج المعاملة بالمستخلص المائي لنبات الكعوب *G. tournefortii* وبالجرعة ٧٥ ملغم/كغم من وزن الجسم إلى انخفاض معنوي في

مستويات الكلوكوز، ووزن الجسم. التأثير الأفضل لوحظ عند استخدام المستخلص المائي لنبات الكعوب *G. tournefortii* بالجرعة ٣٠٠ ملغم/ كغم من وزن الجسم حيث أدت الى خفض معنوي لمستويات الكلوكوز، الكليسيريدات الثلاثية، والكولسترول. تشير نتائج الدراسة الحالية إلى أن نبات الكعوب *G. tournefortii* يمتلك دوراً في خفض مستويات الكلوكوز، وشحوم الدم عند معاملة الفئران بالدكساميثازون .

Introduction

Diabetes mellitus is a metabolic disorder characterized by resistance to the action of insulin, insufficient secretion, or both (1). The major clinical manifestation of the diabetes state is hyperglycemia, however, insulin deficiency and/or insulin resistance also are associated with disturbance in lipid and protein metabolism (2). WHO indicates that diabetes mellitus is one of the major killers of humans in our time (3). Management of diabetes without any side effect is still a challenge to the medical system, this had led to an increasing demand for natural products with antidiabetic activity and fewer side effects (4).

Dexamethasone a synthetic glucocorticoids and a wide spread anti-inflammatory drug, and induce a decrease in insulin sensitivity (5), or insulin resistance and an elevation in the level of serum glucose and lipids (6). So this drug is used for the induction of hyperglycemia and hyperlipidemia in mice and rats as model for type -2 diabetes mellitus (7,8).

Throughout history, humans have derived many uses and benefits from the plants found in their own region (9). *Gundelia tournefortii* GT (kuub; Arabic and kanger; Kurdish names) from the Asteraceae (compositae) family. It is an nature born plant, native to Asian – temperate zones of western Asia, manly Cyprus, Egypt, Jordan, Turkey, Azerbaijan, Turkmenistan and Iraq, its leaves, seeds and stems are used as food sources (10). It is recorded that the water extracts of *G. tournefortii* roots were containing phenols, glycosides, tannins, flavonoids, carbohydrates, proteins, alkaloids and nitrate (11,12), and saponins (13). It is used to enhance gingivas and as an appetizer (14), also fresh seeds of it are used in pikles and also are effective diuretics (15), and inhibition of α-amylase activity (16). *G,tournefortii* also have an effect on platelet aggregation (17), and can decrease some cardiovascular risk factors, and decrease atherosclerosis (18). This study was conducted to evaluate the effects of *G,tournefortii* roots hot water extract in dexamethasone induced hyperglycemic and hyperlipidemic mice.

Materials and methods

Plant materials:

Naturally grown *G. tournefortii* plants were bought from vegetable market in Duhok city. The plant was classified at faculty of Agriculture and forestry / Duhok University, fresh roots were used in this study.

Plant extract

Boiled water extract was prepared by weighing and cutting up a certain weight of plant roots into small pieces, plant pieces were put in conical flask and submerged by 1cm of distilled water, the mixture heated in shaking water bath at 95C° for 30 minutes (19).The mixture was filtrated though a piece of cotton and several layers of gauze which put on the funnel mouth and left for 24 hr to complete the filtration process and the filtrate stored in dark bottles in the freezer. Dry matter was 0.56 gm per 50 ml of extract which is determined by using (Freeze dryer with shell freezer-LFD-55085-Daihan lab tech Co. LTD Korea).

Animals

Male albino mice weighing between 24.6 and 33.2 gm were procured from Veterinary college /Duhok University, they were housed under standard conditions of temperature (22 ±3C°) with a 14:10 dark light cycle. The animals were fed with standard diet and water ad libitum.

Induction of hyperglycemia

Dexamethasone sodium phosphate ampoules concentration 8 mg/2 ml (H-tech international enterprises Co.ltd) were used for inducing hyperglycemia at a dose (1 mg/kg of body weight intramuscularly diluted by normal saline and volume of injection was 5 ml/kg.b.w.) daily for 22 days (7).

Experimental design

Animals randomly were divided into five groups, each consisting of 6-8 mice. Group 1: Served as negative control group; Group 2: received dexamethasone 1.0 mg/kg of body weight and served as positive control group; Group 3: treated with dexamethasone 1.0 mg/kg of body weight. plus plant extract containing dry matter 75 mg/kg of body weight; Group 4: received dexamethasone 1.0 mg/kg of body weight plus plant extract containing dry matter 150 mg/kg of body weight; Group 5: treat with dexamethasone 1.0 mg/ kg of body weight plus plant extract containing dry matter 300 mg/kg of body weight.

Dexamethasone were given by intramuscular rout and volume of injection 5 ml/kg., While *G. tournefortii* extract were given orally at 5 ml/kg.b.w. by gavages needle. All treatment was once daily and lasted for 22 days.

Sample collection

Blood samples were collected at zero,11 and 22 days after overnight fasting from the orbital plexus of vein into

clean dry centrifuge tubes allowed to clot, serum was separated after centrifugation at 1500 rpm for 15 minutes (20), Glucose, total cholesterol, triglyceride and total protein were estimated calorimetrically using (Biolabo standard kits, France).

Statistical analysis

All data analyzed by one way analysis of variance, the specific group differences were determined using duncan multiple range test; the accepted level of significance was $P<0.05$ (21).

Results

As shown from table 1 the results reflect the effect of dexamethasone treating alone or in combination with different doses of *G. tournefortii* extract on the body weight in mice, the results show that dexamethasone causes a significant decrease in body weight after 22 days when compared with zero time in the same group, also dexamethasone combination with *G. tournefortii* extract causes significant decrease in body weight in dose 75 mg/kg.b.w. when compare with dexamethasone treated group, and the doses 150 and 300 mg /kg.b.w lead to significant decrease in body weight when compared with zero time in same groups.

Table (1): Effect of *Gundelia tournefortii* extract on body weight (g) in dexamethasone treated mice.

Groups	Time		
	Zero	11 days	22 days
Normal	BC 29.68 ±1.521	B 29.81 ±1.43	BCD 28.58 ±1.028
Dexamethasone 1 mg/kg.b.w.i.m	BC 29.64 ±0.564	BCD 27.72 ±0.627	D 27.06 ±0.537
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 75 mg/kg.b.w.orally	CD 27.2 ±0.73	D 26.77 ±0.963	E 24.51 ±0.723
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 150 mg/ kg.b.w. orally	A 32.2 ±0.428	BCD 29.23 ±0.276	BCD 27.33 ±0.724
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 300 mg/ kg.b.w. orally	A 32.05 ±0.461	B 29.75 ±0.588	BCD 28.26 ±0.31

No. of mice (6-8) in each group, Data is the mean ± SEM. Different letters indicate significant differences between groups horizontally and vertically at $P < 0.05$.

Table 2 is indicating that dexamethasone treatment causes a significant increase in serum glucose level in mice when compared with the normal group,also the table show that treatment with *G. tournefortii* extract at doses 75,150, 300 mg/kg b.w. causes a significant decrease in glucose level when compared with dexamethasone treated group,the more significant effect was in the group of mice which received 75, 300 mg/kg.b.w. after 22 days and it was close to the normal level.

Table (2): Effect of *Gundelia tournefortii* extract on serum glucose level (mg/dl) in dexamethasone treated mice.

Groups	Time		
	Zero	11 days	22 days
Normal	DE 182.45 ±5.026	DE 185.91 ±3.084	DE 179.91 ±6.033
Dexamethasone 1 mg/kg.b.w.i.m	DE 188.01 ±4.505	C 210.29 ±3.934	A 261.76 ±8.123
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 75 mg/kg.b.w.orally	DE 189.28 ±4.824	CD 193.01 ±8.188	E 170.24 ±8.399
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 150 mg/ kg.b.w. orally	DE 190.42 ±4.706	DE 186.56 ±6.697	B 229.29 ±7.955
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 300 mg/ kg.b.w. orally	DE 187.95 ±3.485	DE 182.72 ±4.742	DE 184.87 ±6.502

No. of mice (6-8) in each group, Data is the mean ± SEM. Different letters indicate significant differences between groups horizontally and vertically at $P < 0.05$.

The results in table 3 show that dexamethasone treating in mice cause a significant elevation in the serum triglyceride level when compared with the normal group,but in the groups that received *G. tournefortii* extract doses 150,300 mg/kg.b.w. there was a significant reduction in serum triglyceride level after 22 days of treatment when compared with dexamethasone treated group.

The level of total serum cholesterol as shown in table 4 were increased in the group of mice which received dexamethasone when compared with the normal, also this table indicates that treatment with *G. tournefortii* extract cause a reduction in serum cholesterol levels after 11 days in the group that received 75 mg/kg B.W. and at 11,22 days of treatment in the other groups when compared with dexamethasone treated group, the more significant result was in the group of mice which received 300 mg/kg b.w. of the extract.

There is no significant changes in serum total protein level in dexamethasone treated group when compared with the normal group,also in the groups of mice which treated with all doses of *G. tournefortii* (Table-5).

Table (3): Effect of *Gundelia tournefortii* extract on serum triglyceride level (mg/dl) in dexamethasone treated mice.

Groups	Time		
	Zero	11 days	22 days
Normal	CDE 140.84 ±5.295	DE 136.35 ±4.725	CDE 139.95 ±3.848
Dexamethasone 1 mg/kg.b.w.i.m	CDE 143.64 ±4.973	BC 156.17 ±4.126	A 188.03 ±2.971
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 75 mg/kg.b.w.orally	CDE 141.32 ±6.324	BCD 151.28 ±1.629	B 166.09 ±9.184
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 150 mg/ kg.b.w. orally	CDE 145.14 ±5.744	CDE 142.14 ±4.174	CDE 144.25 ±5.164
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 300 mg/ kg.b.w. orally	CDE 143.4 ±5.638	CDE 143.26 ±0.309	E 133.2 ±6.186

No. of mice (6-8) in each group, Data is the mean ± SEM. Different letters indicate significant differences between groups horizontally and vertically at $P < 0.05$.

Table (4): Effect of *Gundelia tournifortii* extract on serum total cholesterol level (mg/dl) in dexamethasone treated mice.

Groups	Time		
	Zero	11 days	22 days
Normal	BC 235.42 ±16.481	BC 230.93 ±3.124	C 228.99 ±7.512
Dexamethasone 1 mg/kg.b.w.i.m	BC 240.45 ±14.826	A 305.85 ±14.703	A 334.11 ±14.04
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 75 mg/kg.b.w.orally	BC 231.39 ±9.433	BC 233.04 ±8.803	A 333.15 ±14.843
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 150 mg/ kg.b.w. orally	BC 237.03 ±11.837	C 212.77 ±9.334	B 269 ±14.375
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 300 mg/ kg.b.w. orally	BC 238.57 ±11.704	C 212.71 ±10.104	C 226.02 ±9.449

Data is the mean ± SEM, Different letters indicate significant differences between groups horizontally and vertically at $P < 0.05$.

Discussion

The present study demonstrated that dexamethasone treatment produced a significant decrease in body weight when compare with zero time, this result agree with other studies in normal rats (22,23). This may be due to that dexamethasone stimulate production of myostatin leading to muscle atrophy and decrease of body weight (22), (23) reported that dexamethasone have an ability to decrease body weight by prevent enter of glucose to the cells leading to loss of calories.

Dexamethasone produced significant increases in serum glucose, and this result agree with (5,7,24,25) in mice, and (8) in rats, but disagree with (26) in rats. The increase of serum glucose level may be due to decrease insulin-stimulated glucose uptake in muscle (27), or dexamethasone disrupts insulin-mediated recruitment of glucose transporters at the cell surface (28,29). Also dexamethasone stimulate gluconeogenesis in liver cells by stimulate glucose-6-phosphatase (30,31).

Dexamethasone lead to significant increase in serum cholesterol, similar result reported by (32) in normal and diabetic rats, and disagree with (33) in human. The increase of serum cholesterol level may be due to that dexamethasone inhibit nitric oxide synthesis which have a role in regulation of lipid levels in blood (26).

Table (5): Effect of *Gundelia tournifortii* extract on serum total protein (g/dl) in dexamethasone treated mice.

Groups	Time		
	Zero	11 days	22 days
Normal	ABC 5.66 ±0.164	BC 5.51 ±0.048	ABC 5.73 ±0.112
Dexamethasone 1 mg/kg.b.w.i.m	ABC 5.65 ±0.176	ABC 5.73 ±0.239	C 5.45 ±0.186
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 75 mg/kg.b.w.orally	BC 5.55 ±0.165	AB 6.07 ±0.308	C 5.29 ±0.176
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 150 mg/ kg.b.w. orally	BC 5.57 ±0.139	ABC 5.84 ±0.147	BC 5.5 ±0.276
Dexamethasone 1 mg/kg.b.w.i.m + *GT* 300 mg/ kg.b.w. orally	ABC 5.61 ±0.16	A 6.17 ±0.139	C 5.29 ±0.063

No. of mice (6-8) in each group, Data is the mean ± SEM. Different letters indicate significant differences between groups horizontally and vertically at $P < 0.05$

Triglyceride levels also increased significantly when we use dexamethasone to induce hyperglycemia and hyperlipidemia, (8,34) reported similar results in rats, and (35) in human. This may be due to that dexamethasone stimulate production and secretion of lipoproteins mainly very low density lipoprotein from liver that rich in triglyceride (36), or may dexamethasone cause insulin

resistance which decrease effect of insulin on liver and adipose tissue leading to secret triglyceride from liver and prevent ability of tissue to remove lipoproteins from blood (37).

In our study, treatment mice with *G. tournefortii* leads to significant decrease in serum glucose levels in all three doses when compare with dexamethasone group. The possible mechanism is due to presence of flavonoide in it (11) which stimulate secretion of insulin from pancreas leading to increase its level in blood (38), or flavonoide may increase the insulin sensitivity (39), also flavonoide activated peroxisoe-proliferator-activated-receptor (PPAR) that regulate the transcription of gene involved in lipid and glucose homeostasis and metabolism within the cell (40), this effect of flavonoide may be like flavonoide of soybean (38). Also may flavonoide of *G. tournefortii* decrease glucose absorption from intestine through decrease processes of glucose transports depended on calcium (41), flavonoide can acts as antioxidant by increasing antioxidant enzymes (42), similar observation reported by (43) when flavonoide of *trifolium alexandrium* acts as antioxidant in streptozotasin induced diabetic rats.

Also decreases of serum glucose level may be due to inhibition of α-amylase by *G. tournefortii* (16) that found in saliva and pancreatic secretions which degrade starch first to oligosaccharide and then to maltose and glucose, (44) that *phaseolus acutifolius A. Gray, pistacia atlantica, and paranychia argentea* have hypoglycemic activity through α-amylase inhibition. as wall as may the hypoglycemic activity of *G. tournefortii* is due to presence of sterol in it (17) and in study of (45) shown that extract of *Anacandina occidentale* that contain sterols cause significant decrease in blood glucose level in normal dogs, and (46) referred that sterol presence in extraction of *centaure serdis L.varmentime lge* leaves cause significant decrease of blood glucose level in rats. Sterol acts by increase blood insulin levels through stimulation its secretion from β-cells in pancreas (47).

A significant decrease in blood serum cholesterol levels was observed in *G.tournefortii* treatment in 150,300 mg/kg.b.w. and this results agree with (18) in rabbit. Possible explanation of lowering cholesterol is may due to presence of flavonoids that have antioxidant and hypolipidemic activity which act by inhibition of lipoprotein oxidation and increasing low density lipoprotein receptor activity (48), similar result showed by (49) in mice when treated by soybean seeds that contain flavonoide. Also may be the lowering of cholesterol levels due to presence of saponin in *G. tournefortii* (13) report that treatment by seeds of *fenugreek* that contain saponin lowers cholesterol levels in human with type 2 diabetes. The effect of saponin may be due to hydrolysis of saponin to sapogenin in gastrointestinal tract which stimulate secretion of bile acids by liver, also saponin decrease absorption of cholesterol in intestine (50), or effect of saponin may due to stimulate liver to convert cholesterol to bile acids (51). The other mechanisms of lowering cholesterol is that sterol of *G. tournefortii* (17) acts to decrease estrification of cholesterol in gastric cells and reveres the unestrified cholesterol again to intestine (52).

Significant decrease of blood triglyceride levels were observed in mice treated with *G.tournefortii*, our result agree with (18) in rabbit, the decrease of blood triglyceride levels may due to flavonoide of *G. tournefortii* have antioxidant effect that increase insulin's activity as hypolipidemic (53), or flavonoide may affect in cellular lipid homeostasis by the down regulation of sterol-regulatory-element-binding-protein (SREBP) and its target genes in the liver which are involved in the synthesis of triglyceride (54).

All treatment doses of *G.tournefortii* with dexamethasone lead to significant decrease of body weight when compare with zero time in same group, our result may be due to the non significant lowering of serum total protein level. The decrease in body weight observed might be the result of protein wasting due to unavailability of carbohydrate for utilization as an energy source (55).

Our study indicate the usefulness of *G. tournefortii* extract as hypoglycemia and hypolipidemia in dexamethasone treated mice.

References

1. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2002;23:S5-S20.
2. Vats V, Grover JK, Rathi SS. Evaluation of anti-hyperglycaemic and hypoglycaemic effect of Trigonella foenum-graecum Linn., Ocimum sanctum Linn and Pterocarpus marsupium Linn in normal and alloxanised diabetic rats. J Ethnopharmacol. 2002;79:95-00.
3. Ashok KT, Madhusudana RJ. Diabetes mellitus and multiple therapeutic approaches of phytochemicals:present status and future prospects Current Science. 2002;83(1):30-38.
4. Galletto R, Siqueira VL, Ferreira EB, Oliveira AJ, Bazotti RB. Absence of Antidiabetic and hypolipidemic effect of Gymnema sylvestre in non diabetic and alloxan diabetic rats. Braz Arch of Bio and Tech. 2004;47:545-551.
5. Steven MW, Adele K, Penny W, Elizabeth G, Nikki LR, Timonthy WG. Troglitazone antagonizes metabolic effects of glucocoprticoids in humans. Diabetes. 2002;51:2895-2902.
6. Mahendran P, Devi CS. Effect of Garcinia cambogia extract on lipids and lipoprotein composition in dexamethasone administered rats. Indian J Phsiol Pharmacol. 2001;45:345-50.
7. Jatwa R, Kar A. Antihyperglycaemic and antiperoxidative roles of acarbose in type 2 diabetes mellitus are possibly mediated through changes in thyroid function**.** Clinical Experimental Pharmacol Physiol 2006;33(11):1104 -1106.
8. Prashantha Kumer BR, Praveen TK, Nanjan MJ, Karvekar MD, Suresh B. Serum glucose and troglyceride lowering activity of some novel glitazones against dexamethasone-induced hyperlipidemia and insulin resistance. Indian J Pharmacol. 2007;39(6):299-302.
9. Akan H, Korkut MM, Balos MM. An ethnobotanical study around Arat Mountain and its surroundings (Birecik, Sanlıurfa). Fırat University J Sci Eng. 2008;20:67-81.

10. Oweis DS, Shibli RA, Eriefej KI. *In vitro* propagation of *Gundelia tournefortii* L. Adv Hort Sci. 2004;18(3):127-131.
11. Al-Younis NK, Argushy ZM. Antibacterial evaluation of some medicinal plants from kurdistan region. J Duhok Univ. 2009;12(1): 256-261.
12. Cakilcioglu U, Khatun S. Nitrate, moisture and ash contents of edible wild plants. J Cell and Plant Sci. 2011;2(1):1-5.
13. Hildebert W, Hubertus N, Aynehchi Y. Molluscicidal saponins from *Gundelia tournefortii*. Phytochemistry 1984;23(11):2505-2508
14. Yapici IU,Hosgoren H, Saya O. Ethnobotanical features of kurtalan (siirt) district. J of Ziya Gokalp Faculty of education. 2009;12:191-196.
15. Coruh N, Sagdıcoglu Celep AG, Ozgokce F, Iscan M. Antioxidant capacities of Gundelia tournefortii L. extracts and inhibition on glutathione-S-transferase activity. Food Chemistry. 2007;100:1249–1253.
16. Namam SH, Hamid GH, Nawzad NA. Inhibitory effect of Gundelia extract on urinary. α-amylsae activity of type-1 diabetes mellitus. The First International Conference of Food Industries and Biotechnology and Associateted Fair Al-Baath University. 2008.
17. Halabi S, Battah AA, Aburjai T, Hudaib M. Phytochemical and Antiplatelet Investigation of *Gundelia tournifortii*. Pharmaceutical Biology. 2005;43(6):496-500.
18. Asgary S, Movahedian AA, Badiei A, Naderi GA, Amini F, Hamidzadeh Z. Effect of *Gundelia tournefortii* L on some cardiovascular risk factors in animal model. J of Medical Plants. 2008; (28):112-119.
19. Kasuga S, Uda kyo E, Ushijima N, Itakara Y. Pharmacologic activiteisof aged garlic extract in comparison with other garlic preperations. J Nutri. 2001;131:1080s-1084s.
20. Fox JG, Cohen BJ, Loew FM. Laboratory Animal Medicine. Academic press London, U.K. 1984:19-120.
21. Bruning JL, Kintz BL. Computational Handbook of Statistics. 2ed ed. Scott Foresman and Co.Glenveiw. Illionois, USA. 1977. pp.75-80,102-138.
22. Kun M, Con M, Shalender B, Vahid M, Jorge A, Gonzalez C, Jose A, Behrouz S. Glucocorticoid - induced skeletal muscle atrophy is associated with upregulation of myostatin gene expression. Am J Physiol Endocrinol Meta. 2003;285:363-371.
23. Margarita FC, Ivan V, Manuel P, Radu R. The effects of sympathoectomy and dexamethasone in rats ingesting sucarose. Int J Biol Sci. 2006;2:17-22.
24. Bernal-Mizrachi C, Weng SFC, Finck BN, Knutsen RH, Leone TC, Coleman T, Mecham RP, Kelly DP, Semenkovich CF. Dexamethasone induction of hypertension and diabetes in PPAR-alpha dependent in LDL receptor-null mice. Nat Med. 2003;9(8): 1069-75.
25. Gholap S, Kar A. Gymnemic Acids from *Gymnema sylvestre*. Potentially Regulates Dexamethasone-Induced Hyperglycemia in Mice. Pharmaceutical Biology. 2005;43(2):192-195.
26. Severino C, Brizzi P, Solinas A, Secchi G, Maioli M, Tonolo G. Low dose dexamethasone in the rat: a model to study insulin resistance. Am J Physiol Endocrinol Metab. 2002;283:367-373.
27. Dimitriadus G, Leighton B, Parry-Billings M, Sasson S, Young M, Krause U, Bevan S, Piva T, Wegener G, Newsholme EA, Effects of glucocorticoid excess on the sensitivity og glucose transport and metabolism to insulin in rat skeletal muscle. Biochem J. 1997;321: 707-712.
28. Weinstein SP, Wilson CM, Pritsker A, Cushman SW. Dexamethasone inhibits insulin-stimulated recruiment of GLUT 4 to the cell surface in rat skeletal muscle. Metabolism. 1998;47:3-6.
29. Haber RS, Weinstein SP. Role of glucose tramsporters in glucocortiocoid-induced insulin resistance: GLUT 4 isoform in rat skeletal muscle is not decreased by dexamethasone. Diabetes. 1992; 41:728-735.
30. Chatterjea MN, Shinde R. Textbook of Medical Biochemistry.6th ed. Jaypee Brothers. India. 2005:511-513.
31. 31-Van-Schaftinger E, Gerin I.The glucose-6-phosphatase system. Biochem J. 2002;32:513-532.
32. Bruder ED, Lee PC, Raff H, Metabolic consequences of hypoxia from birth and dexamethasone treatment in the neonatal rats: comprehensive hepatic lipid and fatty acid profiling. Endocrinology. 2004;145:5364-5372.
33. Perry CG, Spiers A, Cleland SJ, Lowe GD, Petrie JR, Connel JM. Glucocorticoids and insulin sensitivity, dissociation of insulin's metabolism and vascular actions. J clinical Endocrinology and metabolism. 2003;88(12):6008-14.
34. Erik BD, Oing CL, Hershel R. Dexamethasone treatment in the newborn rat: fatty acid profiling of lung, brain and serum lipids. J Ap Physiol. 2004;98:981-990.
35. Amin SB, Sinkin RA, Mcdermott MP, Kendig JW. Lipid intplerance in neonats receiving dexamethasone for bronchopulmonary dysplasia. Arch Pedolesc Med. 1999;153:795-800.
36. Plonne D, Schulze HP, Kahlert U, Seidolt H, Bennett AJ, Cartright IJ, Higgins JA, Till U, Dargel R. Postnatal development of hepatocellular apolipoprotein B assembly and secretion in the rat. J Lipid Res. 2001; 42:1865-78.
37. Nathalie N, Vittorio, Christine B, Luc T. Metabolic adaptation to dexamethasone-induced insulin resistance in healthy volunteers. Obesity Research. 2003;11:625-631.
38. Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. MJCN. 2002;76(6):1191-1201.
39. Wagner JD, Cefalu WT, Anthony MS, Litwak KN, Zhang L, Clarleson TB. Dietary soy protein and estrogen replacement therapy improve cardiovascular risk factors and decrease aortic cholesterol. Metabolism. 1997;46(6):698-705.
40. Mezei O, Banz WJ, Stager RW, Peluso MR, Winters TA, Shay N. Soy isoflavones exerts antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264. 7 cells. J Nutr. 2003;1334(5):1238-1243.
41. Vedavanam K, Srijayanta S, O' Reilly J, Raman A. and Wiseman H. Antioxidant action and potential antidiabetic properties of an isoflavonoid containing soybean phytochemicalse extract (SPE). Phytother Res. 1999;13(7):601-608.
42. Fitzpatrick L. Soy isoflavones: hope or hype? European Menopause J. 2003;44:21-29.
43. Amer M, El-Habibi E S, El-Gendy A. Effect of Trifolium alexandrinum extracts on streptozotocin-induced diabetes in male rats. Ann. Nutr. Metab. 2001;48(5):343-347.
44. Tsuyshi Y, Ryuichi M. Plant science. 2005;169(3):502- 511.
45. Alexander – Lindo RL, Morrison EY, Nair MG. Hypoglycemic effect of stigmast 4-en- 2-one and its corresponding alcohol from the brake of Anacardium occidentale (casheow). Phytother Res. 2004;18(5): 403-407.
46. Ivorra MD, D'Ocon MP, Paya M, Villar A. Antihyperglycemic and insulin-releasing effect of beta sitosterol 3-beta D-glycoside and its aglycone, beta-sitosterol. Arch Int Pharmacodyn. 1988;296:224-231.
47. Anonymous. Plant sterol and sterolins. Alt Med Rev. 2001;6(2):203.
48. Arliss RM, Biermann CA. Do soy isoflavones lower cholesterol, inhibit atherosclerosis and play a role in cancer prevention. Holist Nurs Pract. 2002;16(5):40-48.
49. Kirk EA, Sutherland P, Wang SA, Chait A, Boen C. Dietary isoflavones reduce plasma cholesterol and atherosclerosis in (57BL/6) mice but not LDL receptor deficient mice. J Nutr. 1998;128(6):954-959.
50. Petit P,Sauvaire Y, Hillaire-buys D, Leconte OM, Baissac Y, Ponsin G, Ribes G. Steroid saponin from fenugreek seeds: extraction, pruification, and pharmacological investigation on feeding behavior and plasma cholesterol. Steroid. 1995;60:674-680.
51. Sauvaire Y, Bassiac Y, Leconte O, Petit P, Rebes G. Steroid saponins from fenugreek and some of their biological properties Adv Exp Med Biol. 1996;405:37-46.
52. Matvienko OA, Douglas SL, Swanson M, Arudt B, Raiuwater DL, Stewart J, Alekel OL. Asingle daily doses of soybean phytosterol in

ground but decrease serum total cholesterolemic men. AJCN. 2002;76 (1):57-64.

53. Nikander E, Tlitinen A, Laitinen K, Tikkanen M, Ylikorkala O. Effect of isolated isoflavonoides on lipids, lipoproteins, insulin sensitivity and ghre postmenopausal women. J clin Endocrinol Metab. 2004;889 (7):3567-3572.
54. Shukla A, Brandsch C, Bettzieche A, Hirche F, Stangl GI, Eder K.Isoflavone-poor soy protein alters the lipid metabolism of rats by SREBP-mediated down-regulation of hepatic genes. J Nutr Biochem. 2007;18(5):313-21.
55. Alireza N, Mohammad B, Mohsen S, Ali, Azim. Attenuation of oxidative stress in streptozotocin-induced diabetic rats by eucalyptus globulus. Indian Journal of Clinical Biochemistry. 2009;24(4):419-425.