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The Comparative Effects of Aqueous Extract of Walnut (Juglans regia) Leaf and Glibenclamide on Serum Glucose Levels of Alloxan-Induced Diabetic Rats

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Abstract

***Background*:** The use of medicinal plants for lowering glucose level in diabetic patients is of clinical importance. The present study investigated the effect of a 30-day oral administration of aqueous extract of walnut leaf and glibenclamide on blood glucose level in normal and diabetic rats.

***Materials and Methods*:** In this experimental study, 120 male rats (Sprague-Dawley, 150-250 g) were divided into 12 equal groups as following: normal control group, normal group receiving glibenclamide (4 mg/kg), three normal groups receiving the extract doses of 50, 10, and 150 mg/kg, alloxan-diabetic control group (170 mg/kg), diabetic group receiving glibenclamide (4 mg/kg), and five diabetic groups receiving the extract in doses of 10, 50, 150, 300, and 500 mg/day by oral administration for 30 days. Glucose levels of the fasting rats were measured at 0, 7th, 14th, 21st, and 30th days using glucometer.

***Results*:** Administration of all doses and over 10 mg/kg significantly lowered the blood glucose level in normal rat and diabetic rats, compared with dose and duration-dependent control groups. This effect was higher for doses of 50 and 150 mg/kg in normal rats and for doses of 300 and 500 mg/kg in diabetic rats, similar to glibenclamide (4 mg/kg).

***Conclusion*:** Walnut leaf aqueous extract, depending on dose and duration, has dose and duration dependent declining effect on glucose level in normal rats and antihyperglycemic effect on diabetic rats, with a few side effects. This effect at some doses is greater or equal to that of glibenclamide.

Introduction

Diabetes mellitus includes a heterogeneous group of metabolic diseases characterized by increased blood glucose and metabolic disorder. This disease is developed due to the deficiencies in insulin secretion or function or both and is associated with specific changes in intracellular metabolism in a large number of tissues like liver [1]. Chronic hyperglycemia in fasting state or after meals accounts for the majority of acute and chronic symptoms of this disease and impacts the whole body systems and organs. It is the most prevalent cause of end-stage renal disease and contributes to new cases of blindness and non-traumatic lower-limb amputation [2]. In 2000, there were 177 million diabetic patients (type I and II) globally which swelled to 284.8 million in 2010 [1, 3]. In Iran, 8% of people aged 25-64 years are suffering from diabetes type II [1]. The common diabetic treatments include administration of insulin or insulin secretion stimulating drugs (herbal or synthetic), along with weight loss by exercise and diet, depending on the type of diabetes and hyperglycemia [2]. Of herbal remedies in traditional medicine are the use of fenugreek, cinnamon, valerian, blackberry leaves, coriander seed, garlic, onion, walnut, and walnut leaf [4, 5]. In traditional medicine, walnut leaves had been used for lowering blood sugar level [5]. Different studies have shown that the use of walnut leaves in form of aqueous-alcoholic extract, alcoholic, cyclohexane, and powder causes decreased blood glucose level in alloxan or streptozotocin-induced diabetic rats [4, 6-10]. Dietary intake of cyclohexane, ether, and ethanol extracts of walnut leaves for 21 days decreases the concentration of glucose, cholesterol, triglyceride, and serum urea nitrogen [4]. In this study, the effect of 30 days oral administration of walnut leaves aqueous extract on normal and diabetic rats is investigated and the result is compared with the effect of glibenclamide.

Materials and Methods

In this experimental research, 120 Sprague-Dawley rats (150-200 g) obtained from Animal House of Kashan University of Medical Sciences were divided into twelve equal groups and kept in special and standard cages, with washing equipments. Before the onset of the experiment, the rats were kept in a standard environment under 12:12h light-dark-cycle at 24±1ºC, with access to water and food for getting adapted to the environment. Then, the rats were divided into five groups of healthy male rats as normal group and seven groups of alloxan monohydrate-induced diabetic male rats as diabetic groups. Instruments and devices: animal weighing scale in gram (LTC Co., Japan), drug weighing scale (CP225D Sartorius,

Germany) with 0.1-0.00001 g weighing range, electric mixer (LTD delta, Model: HM), gavage tube, 5 cc syringe, animal cage, animal holding chamber for blood drawing, glucometer (Glucoplus, Canada), test strip (Glucoplus, Canada), and dissection instruments.

Materials: alloxan, glibenclamide, glucose, acetate buffer (Sigma Co., Germany), ether, alcohol, distilled water.

Extraction method: after identifying the plant in Kashan Botanical Garden, its leaf was separated and dried in the shadow. Then, the grounded walnut leaf was extracted using Soxhlet extractor (aqueous). After evaporation and reduction of the solvent by rotary, it was dried with oven and refrigerated at 4ºC until its use time. All these processes were done in the Kashan Essence Research Center.

Preparation of the aqueous extraction: every day before using walnut leaves aqueous extract, the animals were weighted using weighing scale. The required amount of extraction was calculated daily based on the weight of the animal. After weighing the needed extraction, it was solved with required amount of distilled water in small beakers (mother solution). Then, it was given to normal rats in 10, 20, and 150 mg/kg doses. The diabetic rats were also received additional 300 and 500 mg/kg doses by gavage (10 ml/kg).

Preparation of glibenclamide solution: Every day before consumption of the drug, the animals were weighted. The required drug was calculated daily based on the weight of the animals. After weighing the required amount of glibenclamide, it was added to 0.5 ml of Tween 80 and mixed using a mixture. Next, 9.5 ml distilled water was added to it and a homogenous solution was prepared using electric mixer. The product (4 mg/kg) was given to the animal by gavage (10 ml/kg).

Investigation into the blood glucose level during one month medicinal treatment: For 30 days the normal rats received the medicine 30min before eating food as following. Three groups were given walnut leaf aqueous extract (10, 50, and 150 mg/kg), one group received glibenclamide (4 mg/kg), and one group was provided with substance containing walnut leaf aqueous extract (10 ml/kg). Diabetic rats were randomely allocated in seven groups among which five groups received walnut leaf aqueous extract, in turn, with 10, 50, 150, 300 and 500 mg/kg of doses. The sixth group was given glibenclamide (4 mg/kg). The seventh group, as negative-control group, received only 10 mg/kg extract carrier. The blood glucose level of all animals are measured 24h after receiving the previous dose and 15min before the next dose at 0th, 7th, 14th, and 30th days after blood sampling.

Introducing Blood sample via the tail vein: After placing the animal in the rat restrainer, blood sampling was performed by introducing the needle into the tail end. The obtained blood drop was tested using glucometer.

Inducing diabetes in the rats: in order to induce diabetes in the rats, their blood glucose level was, firstly, measured using glucometer (for selecting the normal rat and comparing glucose level change after alloxan injection). Then, 5% alloxan monohydrate solution (170 mg/kg body weight, acetate buffer at pH=4.5) was injected intraperitonealy. The rats were not allowed to eat 12h before and 12 after receiving alloxan. After six days, blood was drawn from their tails-end again, and in case which glucose level was higher than 250 mg/dl, they were confirmed as diabetics.

Data analysis: One-way ANOVA and post test Tukey were used for comparing the effect of one between-subjects factor between control and treatment groups. In addition, one within-subjects factor (repeated measure) ANOVA was employed for comparing the effect of a within-subjects factor between the groups. Moreover, the factorial ANOVA (with two mixed factors) was deployed for comparing the impact of two between-group factors (one within-subjects factor and one between-subjects factor). The values with $p<0.05$ were considered as significant.

Ethical considerations: In terms of blood collection and storing, all ethical regulations (Act 62, Section 6) of Ethics Committee of Kashan University of Medical Sciences (No. *p*.29.5.1.3507) were satisfied.

Results

The effect of 30-day oral administration of glibenclamide (0.4 mg/kg) or walnut leaf aqueous extract with 150, 50, and 10 doses on blood glucose level of normal male rats: comparison of blood glucose level at different days of experiment with the 0th day in the same group showed that all groups receiving walnut leaf aqueous extract with 10, 50, and 150 mg/kg doses and glibenclamide (4 mg/kg) experienced a significant decline in blood glucose level at 30th day compared with 0th day. In addition, it was revealed that this effect increased by duration and dose, and was greater, compared with glibenclamide, when 150mg/kg dose was used (Table 1). *p*-values are expressed in comparison with the 0th day at the same group.

The effect of 30-day oral administration of glibenclamide (0.4 mg/kg) or 10, 50, 150, 300, and 500 mg/kg doses of walnut leaf on blood glucose level of diabetic male rats: in general, during 30-day experimental period, the blood glucose level was increased over the time in diabetic rats that received no treatment. 30-day treatment with 10 mg/kg dose of walnut leaf aqueous extract could not inhibit increasing level of glucose in diabetic rats.

However, higher doses of walnut leaf aqueous extract not only held back glucose level increase in diabetic rats, but also caused reduction of glucose level in these groups. This effect rose over the time and by dosage. In addition, 300 and 500 mg/kg doses of walnut leaf aqueous extract were as effective as glibenclamide (4 mg/kg) in reducing glucose level in diabetic rats (Table 2).

Table 1. Normal male rats blood glucose level at 0th, 7th, 14th, 21th, and 30th days of the treatment with drug carrier (10 ml/kg distilled water, control group), 4mg/kg glibenclamide, and 10, 50, and 150 mg/kg doses of walnut leaf aqueous extract

Groups	Dose (mg/kg)	Blood glucose level (mg/dl, Mean ±SEM)								
		0th	7th	*p*-Value	14th	*p*-Value	21th	*p*-Value	30th	*p*-Value
Normal Control	0	96.50±4.3	86.33±3.43	<0.01	89.83±3.66		95.16±3		93±5	
Glibenclamide	4	101.17±4.18	76.67±2.93	<0.001	98.5±9.61	>0,05	91.33±10.14		80.83±2.9	<0.01
Walnut leaf Aqueous extract	10	94.5±1.91	79.5±2.95	<0.001	81.5±6.47	>0,05	84.33±0.42	<0.01	81±0.77	<0.001
	50	97/83±2.51	79.5±2.95	<0.001	85.83±3.46	<0.05	77.16±3.98	<0.01	84.83±4.12	<0.01
	150	103.66±4.14	88±3.42	<0.05	97.33±8.67	>0,05	84.83±3.78	<0.05	74.83±0.47	<0.001

p-values are expressed in comparison with the 0th day at the same group

Table 2. The blood glucose level of diabetic male rats at 0th, 7th, 14th, 21th, and 30th days of the treatment with drug carrier (10ml/kg distilled water, control group), 4 mg/kg glibenclamide, and 10, 50, 150, 300, and 500 mg/kg doses of walnut leaf aqueous extract

Groups	Dose (mg/kg)	Blood glucose level (mg/dl, Mean ±SEM)								
		0th	7th	*p*-Value	14th	*p*-Value	21th	*p*-Value	30th	*p*-Value
Normal control	0	96.50±4.3	86.33±3.43	<0.01	89.83±3.66	>0,05	95.16±3		93±5	
Diabetic control		392±40.9	250.3±44.14	>0,05	459.5±39.9	>0,05	479.8±37.63	<0.05	501.8±26.8	<0.05
Glibenclamide	4	411.1±23.1	264.2±39.9	<0.01	244±39.2	<0.01	215.8±31.1	<0.001	219.2±34.5	<0.001
Walnut leaf aqueous Extract	10	304.6±17.2	257.9±26.7	>0,05	355.3±34	>0,05	432.4±41.1	< 0.01	393.2±45.7	<0.05
	50	357.5±19.53	262.9±42.8	<0.01	336.4±38.1	>0,05	293.5±31.5	< 0.05	304.6±25.5	<0.05
	150	366±20.3	294.8±25.5	<0.05	325.1±46.1	>0,05	286.2±35.4	< 0.05	258.8±32.8	<0.05
	300	370.6±32.6	225±51.4	<0.05	175±40.2	<0.01	226.8±37.5	< 0.05	199.6±36.3	<0.05
	500	443.5±66.4	250±50.7	<0.01	220.1±44.4	<0.01	214.6±46.3	<0.001	217.3±47.	<0.001

p-values are expressed in comparison with the 0th day at the same group

Discussion

The results showed that the administration of walnut leaf aqueous extract with doses higher than 10 mg/kg in alloxan-induced diabetic rats inhibited increase in glucose level and reduced it. This effect swells over the time. Jelodar et al. in a study on biochemical parameters of serum blood of alloxan-induced diabetic rats showed that after inducing diabetes in rats, glucose concentration significantly increased [6]. Divband et al. in another study on the effect of weekly use of walnut leaf tincture extract on the level of serum glucose in streptozotocin-induced diabetic rats showed that the administration of walnut leaf tincture extract significantly decreased the serum glucose blood level [7].

Asgari et al. investigated the preventive effect of intraperitoneal injection of 200 mg/kg walnut leaf hydroalcoholic extract on alloxan-induced diabetic rats 4 weeks before and 4 weeks after diabetes induction, and concluded that the use of walnut leaf hydroalcoholic extract was effective in preventing diabetes [12]. In addition, they studied the effect of intraperitoneal injection of 200mg/kg walnut leaf ethanol extract on rat six weeks after receiving alloxan, and stated that the use of walnut lead alcoholic extract was effective in diabetes treatment [9]. Teimori et al. investigated the effect of daily oral administration of 250 mg/kg walnut leaf ethanol extract on alloxan-induced diabetic rats for 21 days and showed that the use of walnut leaf methanol extract caused decreased blood glucose level [13]. In addition, Fathi Azad and colleagues, reported blood glucose reduction over 24h after oral administration of dose-dependent walnut leaf aqueous-alcoholic extract in streptozotocin-induced diabetic rats [8].

In another study, blood sugar reduction after administration of walnut leaf cyclohexane extract in diabetic rats was reported [10]. Moreover, Jelodar et al. demonstrated anti-diabetic effects of walnut powder mixed with food on diabetic rats. They attributed anti-diabetic impacts of walnut leaf to its insulin-like substances. That is, serum glucose reduction after using walnut leaf is completely justifiable due to the existence of such substances [6]. Hajokhani and Solati showed that oral administration of walnut septum alcoholic extract for 14 days led to blood glucose level reduction in streptozotocin-induced diabetic rats [14]. Regarding the released reports, alloxan causes increased blood glucose level in the rats and the use of aqueous, aqueous-alcoholic, alcoholic, cyclohexane, and powder walnut leaf leads to glucose level reduction in alloxan or streptozotocin-induced diabetic rats. The above researchers did not investigate the effect of different doses at different days as extensively as our study and also have not compared this effect with the effect of glibenclamide. In contrast to other studies, our research investigated the aqueous extract and employed different diabetes inducing technique, drug administration and dose, and investigation duration.

The findings of this research conform to those of above studies, showing the existence of a common ingredient in

all above mentioned products with declining impact on glucose level. Therefore, the effect of common ingredient existing in above products should be explored and employed in the future studies. On the other hand, the present research showed that the administration of 50 and 150 mg/kg doses of walnut leaf aqueous in normal rats and 300 and 500 mg/kg doses of walnut leaf aqueous in diabetic rats are as effective as glibenclamide in lowering blood glucose level. This declining effect increases over time. In addition, in the present study, walnut leaf aqueous reduced glucose level in normal rats which was not in consistent with the results of other studies. In this study, the active ingredients and effective mechanism of aqueous extract were not investigated, but given such ingredients existing in walnut leaf extract as quercetin, kaempferol, eugenol, avicularin, nicotine, caffeic acid, hyperin, beta-eudesmol, juglone, p-Coumaric acid, ascorbic acid, ellagic acid, gallic acid, neochlorogenic acid, and cyaniding, it can be suggested that according to the below reports, the possible active ingredient can be quercetin and kaempferol [15-20].

It seems that quercetin, like an antioxidant, and a scavenger of free radicals has protective impact, and so has a role in beta cells regeneration and protects pancreatic islets against streptozotocin or alloxan [21]. Vesal et al. reported that 10 and 15 mg/kg doses of quercetin had no impact on plasma glucose level in normal animals, but significantly decreased the level of plasma glucose in streptozotocin-induced rats after 8-10 days, in that after this period, blood glucose returned to its normal level [22]. Quercetin increases hepatic glucokinase activity and flavonoid quercetin inhibits intestinal absorption of glucose. In addition, treatment with quercetin significantly increases antioxidant activity, decreases oxidative stress, and lowers blood glucose level [23-26].

Lukacinova et al. showed that oral administration of 50 and 100 mg/kg doses of quercetin three days before and seven days after alloxan injection can prevent the increment in serum glucose level. On the other hand, glucosuria was increased in all alloxan-received groups [27]. However, oral quercetin is absorbed by gastrointestinal system and penetrates into the organs, negligibly [28]. The walnut leaf aqueous extract dose consumed in the present study is as many times as quercetin dose consumed in the experiments. On the other hand, the study shows that in addition to quercetin, walnut leaf aqueous extract has other ingredients that may affect absorption of quercetin, and eventually brings plasma quercetin to effective level, and/or there are other ingredients, in addition to quercetin, that cause blood glucose level reduction. Sousa et al. stated that the use of oral kaempferol (200 mg/kg) caused blood glucose reduction in the normal and alloxan-induce diabetic rats [29].

Madani et al. in a study on the effect of dill hydroalcoholic extract (*Anethum Graveolons* L.) showed that, due to containing flavonoid quercetin and kaempferol, hydroalcoholic extract of this plant had significant impact on the reduction of serum parameters level such as glucose [30]. Lu et al. showed that dosage and duration dependent total flavonoid fraction from folium eriobotryae, containing quercetin and kaempferol, significantly decreases plasma glucose concentration in normal and streptozotocin-diabetic rats, indicating declining impact as equal as or higher than 50 mg/kg gliclazide [31]. Sokeng et al. attributed hypoglycemic effect of methanol extract and fractions from anacardium occidentale in streptozotocin-diabetic rats to the effects of such compounds as kaempferol and corestrol in this plant on direct stimulation of insulin secretion from remaining β-cells and/or insulin-like external pancreatic mechanisms such as stimulation of glucose consumption and hepatic gluconeogenesis [32].

Zanatta et al. stated that kaempferol 3-neohesperidoside (100 nm) increased glucose uptake and glycogen content in the rat soleus muscle [33]. El Naggar et al., showed that after oral administration of 100 and 200 mg/kg doses of methanol extract from Cleom Droserifolia, containing quercetin, kaempferol, and phenolic acids such as coumaric acid, for three weeks, blood glucose level and urinary glucose level significantly decreased, indicating greater impact compared with glibenclamide [34].

In general, given the above mentioned studies, it can be said that anti-hyperglycemic and hypo-glycemic effects of walnut leaf aqueous extract is probably due to flavonoides, such as quercetin and kaempferol. Their possible mechanisms can be associated with anti-diabetic effect [25, 34, 35], anti-oxidant effect [21, 26, 34, 35], impact on hepatic glucokinase [23], and inhibition of gastrointestinal absorption of glucose, glucosuric effect [27], and/or insulin-like external pancreatic mechanisms [32, 33]. The degree of this effect is equal and in some cases higher than glibenclamide.

In addition, during this study, weight loss or mortality was not observed in diabetic or normal rats, receiving plant extraction. That is, oral administration of desired doses of walnut aqueous extract during the experiment not only had no adverse effects on the growth but also decreased diabetes caused mortality. Walnut leaf aqueous extract had, in turn, hypoglycemic and antihyperglycemic effects on the normal and diabetic rats. These effects, which are probably due to the existence of quercetin and kaempferol active ingradians, are magnified by increase in walnut leaf aqueous dose and experiment duration. The blood glucose lowering effects of 50 and 150 mg/kg doses of walnut leaf aqueous extract on the normal rats and 300 and 500 mg/kg doses of it on the diabetic rats are, in turn, higher and equal to those of glibenclamide.

In addition, weight loss and mortality were not observed in the normal and diabetic rats, receiving walnut leaf aqueous extract. Investigation into the chronic impacts of effective dose of walnut leaf aqueous extract on Langerhans islets, serum level of ALT, AST, ALP enzymes, creatinine, and c-peptide, and also the side effects and lethal dose is recommended.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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References

1. Delavari A, Alikhani S, Nili S, et al. Quality of care of diabetes mellitus type II patients in Iran. Arch Iran Med 2009; 12(5): 492-5.
2. Fauci AS, Braunwald E, Kasper DL, et al. Endocrine, metabolism and nutrition diseases. In; Longo DL, Fauci AS, Kasper DL, editors. Harrison's principles of internal medicine. 17th ed. Brazil: McGraw-Hill Press; 2008: 1509-14.
3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87(1):4-14.
4. Jelodar GA, Nazifi-Habibabadi S. Effect of walnut leaf extracts on serum biochemical parameters of diabetic rats. J Shaheed Beheshti Univ Med Sci 1998; 22(2): 25-18.
5. Mirheidar H. Plants information and plants apply in disease protection and treatment. Tehran Nashr-e-Farhang e-Eslami Press; 2001.
6. Jelodar GA, Nazifi-Habibabadi S. Effect of coriander, pomegranate and walnut leaf on serum biochemical parameters of diabetic rats. J Shahid Sadoughi Univ Med Sci 1999; 7(1): 77-82.
7. Divband K, Komeili GR, Saeidi-Neek F. Effects of Walnut leaves aqueous extract on blood sugar and serum lipids in diabetic rats. J Birjand Univ Med Sci 2010; 17(1): 11-18.
8. Fathiazad F, Garjani A, Motavallian-Naini A. Study of hypoglycemic activity of the hydroalcholic extract of Juglans regia in normal and diabetic rats. Pharm Sci 2006; 2(2): 13-7.
9. Asgary S, Parkhideh S, Solhpour A, et al. Effect of ethanolic extract of Juglans regia L. on blood sugar in diabetes-induced rats. J Med Food 2008; 11(3): 533-8.
10. Jelodar G, Nazifi S. Effect of walnut leaf extracts on serum biochemical parameters of diabetic rats. J Faculty Vet Univ Tehran 2001; 56(2): 37-40.
11. Asgary S, Rahimi P, Madani H, et al. Effects of hydroalcoholic extract of Carthamus tinctorius on activity of hepatic transaminases in alloxan - induced diabetic rats. J Shahr-e-Kord Univ Med Sci 2010;12(1):46-52.
12. Asgary S, Rahimi P, Madani H, et al. Preventive effect of Juglans regia on Diabetic I in adult male Rats. Iran J Diabetes Lipid Disord 2008; 7(4): 363-70.
13. Teimoori M, Montaser-Kouhsari S, Ghafarzadegan R and Hajiaghaee R. Antidiabetic effects of Juglans regia leave's methanolic extract on alloxan-induced male wisrar rats. J Med Plants 2010; 9(34): 142-9.
14. Hajikhani R, Solati J. Effects of walnut alcoholic extract (Juglans Regia L.) Septum on serum glucose, insulin and activities of aminotransferase enzymes. J Appl Chem Res 2010; 12: 17-23.
15. Madani H, Rahimi P, Mahzoni P. Effect of hydroalcoholic extract of Juglans regia leave on activity of AST and ALT enzymes in alloxan-induced diabetic rats. Pharmaceutical Sci 2009; 15(2): 213-8.
16. Duke JA. Handbook of phytochemical constituents of GRAS herbs and other economic plants: Herbal reference library. Philadelphia: Taylor & Francis; 2000.
17. Mokhtari M, Shariati M, Sadeghi N. Effect of alcohol extract from leave Juglans regia on antinociceptive induced by morfine in formalin test. Med Sci J Islamic Azad Univ 2008; 18(2): 85-90.
18. Pereira JA, Oliveira I, Sousa A, et al. Walnut (Juglans regia L.) leaves: Phenolic compounds, antibacterial activity and antioxidant potential of different cultivars. Food Chem Toxicol 2007; 45(11): 2287-95.
19. Nadkarni KM. Indian materia medica. Indian: Popular Prakashan Press; 2005.
20. Blumenthal M, Goldberg A, Brinckmann J. Herbal Medicine. expanded commission e monographs. Integrative Med Communications 2000; 5(3): 232.
21. Akiyama T, Takasawa S, Nata K, et al. Activation of Reg gene, a gene for insulin-producing β-cell regeneration: Poly (ADP-ribose) polymerase binds Reg promoter and regulates the transcription by autopoly (ADP-ribosyl) ation. PNAS 2001; 98(1): 48-53.
22. Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem Physiol C Toxicol Pharmacol 2003; 135C(3): 357-64.
23. Hii CS, Howell SL. Effects of flavonoids on insulin secretion and 45Ca2+ handling in rat islets of Langerhans. J Endocrinol 1985; 107(1): 1-8.
24. Song J, Kwon O, Chen S, et al. Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and glucose. J Biol Chem 2002; 277(18): 15252-60.
25. Abdelmoaty MA, Ibrahim MA, Ahmed NS and Abdelaziz MA. Confirmatory studies on the antioxidant and antidiabetic effect of quercetin in rats. Indian J Clin Biochem 2010; 25(2): 188-92.
26. Mahesh T, Menon VP. Quercetin allievates oxidative stress in streptozotocin-induced diabetic rats. Phytother Res 2004; 18(2): 123-7.
27. Lukacinova A, Mojzis J, Benacka R, et al. Preventive Effects of flavonoids on alloxan-induced diabetes mellitus in rats. Acta Vet Brno 2008; 77: 175-82.
28. Middleton Jr E. Effect of plant flavonoids on immune and inflammatory cell function. Adv Exp Med Biol 1998; 439: 175.
29. de Sousa E, Zanatta L, Seifriz I, et al. Hypoglycemic Effect and antioxidant potential of kaempferol-3, 7-O-((α))-dirhamnoside from bauhinia f. orficata leaves. J Nat Prod 2004; 67(5): 829-32.
30. Madani H, Ahmadi-Mahmoudabadi N, Vahdati A. Effect of hydroalcoholic extract of Anethum graveolens L. in reduce glucose and lipids in alloxan-induced diabetic rats. J Diabetes Lipid Iran 2005; 5: 109-16.
31. Lu H, Chen J, Li WL, et al. Hypoglycemic effect of the total flavonoid fraction from Folium eriobotryae. Phytomed 2009; 16(10): 967-71.
32. Sokeng SD, Lontsi D, Moundipa PF, et al. Hypoglycemic effect of anacardium occidentale L. methanol extract and fractions on streptozotocin-induced diabetic rats. Global J Pharmacol 2007; 1(1): 01-05.

33. Zanatta L, Rosso A, Folador P, et al. Insulinomimetic effect of kaempferol 3-neohesperidoside on the rat soleus muscle. J Nat Prod 2008; 71(4): 532-5.
34. EL Naggar EM, Bartosikova L, Zemlicka M, et al. Antidiabetic effect of Cleome droserifola aerial Parts: lipid peroxidation–induced oxidative stress in diabetic rats. Acta Vet Brno 2005; 74: 347-52.
35. Wolff SP. Diabetes mellitus and free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. Br Med Bull 1993; 49(3): 642-52.

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