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Original Article

A Comparative Investigation of the Effects of the *Cynara scolymus L.* and Glibenclamide on Biochemical Parameters in Diabetic Rats

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Abstract

Background and Aim: The use of herbal medicines in the treatment of diabetes is increasing, because they have fewer side effects compared to chemical drugs. This research was carried out to compare the effects of artichoke and glibenclamide on serum glucose and lipid profiles in diabetic rats.

Materials and Methods: In this study, 24 male rats were divided into 4 groups. The control group (group I) received a standard diet. The second group, assigned as the diabetic control group, did not received any treatment. The third group (group II), the diabetic group, received a low-alcohol extract of artichoke of 300 mg/kg body weight via intraperitoneal injection for 14 days, and the fourth group (group IV), the diabetic group, received glibenclamide that was injected at a dose of 0.5 mg/kg body weight. Finally, blood samples were gathered through cardiac puncture, and serum FBG, TG, TC, LDL-c, VLDL-c, HDL-c and HbA1c were measured and compared by ANOVA and Tukey tests.

Results: Serum TG, TC, FBG and HbA1c significantly decreased, while HDL-c increased in the two groups of treated diabetic rats in comparison to diabetic control ($p<0.05$). Serum LDL-c, VLDL-c did not decrease significantly in the two groups of treated diabetic rats in comparison to diabetic control ($p>0.05$). With regard to TG, TC, LDL-c, VLDL-c and HbA1c, there was no significant distinction between the two treatment methods ($p>0.05$). However, HDL-c levels in group III were remarkably higher than the group IV ($p<0.05$), and FBG levels in the group IV were significantly higher than the group III ($p<0.024$).

Conclusion: The results indicated that artichoke alcoholic extract could improve hyperglycemia, hyperlipidemia and FBG in diabetic rats. Hence, it can be considered as an alternative remedy to control diabetes.

Keywords: Cynara scolymus, Diabetes mellitus, Hyperlipidemias, Glibenclamide, Lipids

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Introduction

Diabetes is a metabolic disease whose most important feature is hyperglycemia and a disorder of carbohydrate metabolism, fat and protein. This disease, which is induced by deficiencies in insulin secretion, insulin action, or both (1), has certain complications, such as nephropathy, retinopathy, and cardiovascular diseases in advanced stages (2). Today, insulin or other hypoglycemic agents, such as glibenclamide, are used to treat diabetes. Nevertheless, the administration of these drugs usually induces side effects, such as increasing fat stores and hypoglycemic shock (3). Hence, the use of alternative treatments, particularly herbal medicines, has been increasingly taken into consideration recently (4). Medicinal plants have been used for long years in the treatment of diabetes mellitus, for they contain significant amounts of natural antioxidants and at once bring about less toxic effects. Moreover, they are free from complications in comparison with synthetic drugs (5). Artichoke (Cynara scolymus L) is a Asteraceae family member, which is native to Southern Europe, the Mediterranean, and North Africa (6). The root and aerial parts of this plant are used to treat various diseases, such as diabetes, obesity, urticaria, asthma, kidney stones, atherosclerosis, rheumatoid arthritis, liver disease, nausea, flatulence and certain skin disorders, including eczema and inflammation (7). Furthermore, the hypoglycemic and hypolipidemic effects of the alcoholic extract of this plant in the form of intraperitoneal injection and short-term model (for seven days) were observed in the models of diabetic rats (8). Its antioxidant and radical elimination effects have been proven in vitro and in vivo (9). Moreover, its capability in the reduction of serum glucose and cholesterol in diabetic patients has been already indicated. The therapeutic effects of artichoke are found in its supportive effects on the liver, its antimicrobial properties, low blood cholesterol and lipid levels, stimulation of the expression of nitric oxide synthase gene and endothelial cells in atherosclerosis (10). The beneficial effects of artichoke on hyperlipoproteinemia have also been proven in clinical trials. Overall, since industrial chemicals, such as insulin and glibenclamide, involve costly and time-consuming processes and their endowing entails a painful and difficult method, investigation of medicinal herbs provides a natural key to address diabetes from a new point of view (11). Nowadays, these plants are considered for their ease of access and fewer side effects as suitable alternatives to chemical drugs. Hence, the purpose of this research was to examine the effect of the alcoholic extract of artichoke on biochemical parameters in comparison with glibenclamide in diabetic rats.

Materials and Methods

Animals, Chemicals and Reagents

In this experimental study, 24 male Wistar rats (200-250 g) were purchased from the Central Animal House, Tehran University of Medical Sciences. The rats were kept under 12 hours light/ 12 hours dark conditions, and the temperature was 25 ± 2 ºC. Appropriate humidity and standard laboratory conditions inside of special cages were maintained. The animals were provided with standard food (prepared from the Pars Animal Feed Company) and free access water. The alcoholic extract of artichoke was purchased from Barij Essence Co, based on the protocols and standards issued by the Ministry of Health. It has the competence certificate of National Center for Nuclear Validation of Iran the central laboratory, according to standard ISIRI-ISO / IEC 17025 requirements. Streptozotocin (STZ) was purchased from Sigma-Aldrich. The serum concentration of fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c) were calculated enzymatically by the use of commercial kits (Pars Azmoon, Tehran, Iran) and a spectrophotometer (JENWAY 6505, Europe Union). The serum low-density lipoprotein cholesterol (LDL-c) and very low-density lipoprotein cholesterol (VLDL) were measured by the Friedewald formula (12) as follows: LDL-c = Total cholesterol – [HDL-c + (TG/5)] VLDL-c =

TG/5. HbA1c was measured according to the manufacturer's instructions kit (Biosystem, Spain).

Induction and Selection of Diabetic Rats

The induction of type1 diabetes in male Wistar rats was conducted by a single-day intraperitoneal (IP) injection of 55 mg/kg b.w. STZ. After 3 days (while the rats were fasting for 12 hours), a single drop of blood was taken from every diabetic rat to be measured with glucometer, and rats with fasting blood glucose equal to or greater than 200 mg/dl were considered diabetic rats (13).

Experimental Design

The rats were randomly divided (simple randomization) into 4 groups (6 rats per group), and received the following regimens: the first group (group I) was the control group receiving normal water and food, the second group (group II) was the diabetic control group that did not receive any treatment, the third group (group II), the diabetic group, received a low alcoholic extract of artichoke of 300 mg/kg body weight via intraperitoneal injection for 14 days, and the fourth group (group IV), the diabetic group, received glibenclamide that was injected at a dose of 0.5 mg/kg body weight. The administration of the substance was intraperitoneally decussate for two weeks. Blood sample was collected by cardiac puncture, and serum was separated immediately (14)

Statistical Analysis

The data were analyzed by SPSS19 statistical software. All the data were expressed as means and standard deviation (SD) of two replicates for six rats per group. Shapiro Wilk test, One-way ANOVA and post hoc test (Tukey Test) were applied for testing the normality assumption, determining the differences between the studied groups, and comparing the data respectively. Significant level was defined as less than 5% (p <0.05).

Results and Discussion

Fasting Blood Glucose Level

Table 1 presents the effects of glibenclamide and the alcoholic extract of artichoke on the changes of FBG in normal and diabetic rats. The FBG of the group II was significantly higher than the group I (p< 0.0 01). The levels of FBG of the group III and group IV were significantly lower than the group II (p< 0.0 01). However, the mean FBG levels of the group IV were remarkably higher than the group III (p< 0.024). The mean FBG levels of the group IV were significantly higher than the group I (p< 0.001) and FBG levels in the group III was not significantly different from that of the group I (p< 0.03).

Serum Lipid Profile Levels

The effects of glibenclamide and the alcoholic extract of artichoke administration on lipid profile have been indicated in table 2. The TC, TG, VLDL-c and LDL-c concentrations in the serum were remarkably higher in group II than the group I (p<0.001). The administration of glibenclamide (group III) and the alcoholic extract of artichoke (group IV) significantly decreased the TC, TG (p<0.001), and had no significant effect on VLDL-c and LDL-c levels compared to the group II (p>0.05). Serum HDL-c was noticeably reduced by diabetes induction (p<0.001). Nevertheless, it was significantly increased in groups III and IV compared to group II (p<0.001). There was no remarkable distinction between the effects of glibenclamide and the alcoholic extract of artichoke administration in improving TC, TG and VLDL-c and LDL-c levels (p>0.05), but HDL-c levels in the group III were significantly higher than the group IV(p<0.05).

HbA1C Levels

As shown in Table-3, changes in the percentage of HbA1C during the study indicated that the percentage of HbA1C in the group II was significantly higher than the group I (p<0.001). The percentage of HbA1C in the group III was significantly lower than the group II (p<0.001). The percentage of HbA1C in the group IV was significantly lower than the group II (p<0.001), and there was no significant difference in its level compared to the group I (p>0.05). Moreover, the percentage of HbA1C in the group III was significantly higher than the group I (p<0.001). However, the values of this index were not significant between the group III and group IV(p>0.05).

The result of this study indicated that the glibenclamide and alcoholic extracts of artichoke significantly decreased serum TG, TC, FBG, and HbA1c HDL-c increased and had no significant effects on LDL -C, VLDL-C in the two groups of treated diabetic rats in comparison to the diabetic control. The

Table 1: The Effects of the Intraperitoneal Injection of Glibenclamide and the Alcoholic Extract of Artichoke on FBG Levels in the Studied Rats [a,b].

Group	FBG (mg/dl)
I	97.9 ± 1.2
II	80.7 ±286.5
III	118.7±52 [c]
IV	205.6 ± 21.6 [c,d]

[a]Each value is mean ± SD of 6 rats in each group
[b] Abbreviations: FBG: fasting blood glucose; Group I: Non-diabetic rats; Group II: diabetic control rats or untreated diabetic rats; Group III: diabetic rats that received glibenclamide; Group IV: diabetic rats that received the alcoholic extract of artichoke.
[c] $P < 0.05$ in comparison with Group II.
[d] $P < 0.05$ in comparison with Group III.

antidiabetic effect of artichoke, related to chlorogenic acid, is rooted in the most active antioxidant present in the extract of the artichoke, and its hypoglycemic effect has been proven in the studies conducted by Wiedenfeld and Andrade-Cetto (15). One of the reasons for the decrease in blood glucose level induced by the consumption of artichoke in this study is likely to be the existence of chlorogenic acid whose use has been shown to decrease blood glucose and HbA1c levels. The results of this study revealed that the alcoholic extract of artichoke in the treated rats had a significant effect on cholesterol and triglyceride levels in diabetic rats compared to the rats without treatment. The findings of a research carried out by Bundy *et al.* confirm the results of the present study. They demonstrated the significant role of artichoke leaf extract in lowering the levels of blood cholesterol and triglyceride (11). The effect of chlorogenic acid in reducing lipids and lipoproteins has been demonstrated. These compounds could decrease cholesterol synthesis by indirectly interfering with the synthesis of cholesterol and also by inhibiting the hydroxymethylglutaryl co-orectase (liver) enzyme (16). These studies indicate that the mechanism of action of artichoke in the reduction of lipids and lipoproteins involves interfering with the biosynthesis of cholesterol as well as the production and secretion of bile in the liver (17). The results of this study are in agreement with the findings of a research, conducted by Pittler *et al*., on the effect of the aqueous extract of artichoke on serum cholesterol levels. Pittler *et al*. evaluated the clinical effects of artichoke extract on hypercholesterolemic patients (18). In another study, with a low dose of extract of artichoke, a 20% reduction in cholesterol and a 60% decline in high dose cholesterol in hepatocytes were reported (16). A research conducted on type 2 diabetic individuals with high cholesterol and high triglycerides revealed that artichoke extract could have a protective effect on these patients (19). The reduction of triglyceride levels can be attributed to the decrease of blood glucose levels by artichoke extract, which results in the use of glucose instead of fat for the production of energy from the pyruvate. Rather than entering the synthesis steps of triglyceride, Acetyl coenzyme A enters the Krebs cycle and causes the final metabolism of glucose (19). On the other hand, according to the

Table 2: The Effects of the Intraperitoneal Injection of Glibenclamide and the Alcoholic Extract of Artichoke on Serum lipids in the studied Rats [a,b].

Group	TC, (mg/dl)	TG,(mg/dl)	LDL-c ,(mg/dl)	HDL-c ,(mg/dl)	VLDL-c ,(mg/dl)
I	6.75±7.5	4.3±59.6	7±37.8	2.5±48.1	0.16±2
II	10.4±98.5	33.9±177.8	7.5±46.6	4.6±28.6	0.28±3.8
III	9±۷۷/۶	43.4±127	3.5±42.4	4±44.5	0.2±2.38
IV	4.5±78	55.6±136	2.7±44.9	5.5±38.9	0.2±2.3

[a]Each value is mean ± SD of 6 rats in each group
[b]Abbreviations: TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol and VLDL-c, very-low-density lipoprotein cholesterol. Group I: Non diabetic rats; Group II: diabetic control rats or untreated diabetic rats; Group III: diabetic rats that received glibenclamide; Group IV: diabetic rats that received the alcoholic extract of artichoke.

Table 3: The Effects of the Intraperitoneal Injection of Glibenclamide and the Alcoholic Extract of Artichoke on the Percentage of HbA1C in the Studied Rats [a,b].

Group	HbA1C %
I	4.9
II	8.3
III	6[c]
IV	5[d]

[a]Each value is mean ± SD of 6 rats in each group
[b] Abbreviations: Group I: Non-diabetic rats; Group II: diabetic control rats or untreated diabetic rats; Group III: diabetic rats that received glibenclamide; Group IV: diabetic rats that received the alcoholic extract of artichoke.
[c] $P < 0.05$ in comparison with Group II.
[d] $P > 0.05$ in comparison with Group III.

findings of Ignacimuthu and Amalaj, the reduction of triglyceride by artichoke extract significantly decreased VLDL-c level (20). In this regard, the increase in intracellular triglycerides could lead to an increase in the synthesis of VLDL. Since the artichoke extract significantly reduced triglyceride levels, it is likely to decrease the synthesis of VLDL-c (20). The results of our study indicated that LDL was increased, whereas and HDL-c decreased in the diabetic rats. These results are consistent with the findings of other researchers (21, 22). On the other hand, the aqueous extract of artichoke reduced the level of LDL-c, and increased HDL. Since VLDL-c indirectly interferes with the formation of LDL-c particles, increasing the level of VLDL-c in plasma leads to an increase in plasma LDL-c. Moreover, since the extract caused a significant decrease in VLDL-c, the LDL-c level decreased (23). In contrast with our findings, Fallah *et al.* indicated that HgA1c in type 2 diabetic patients that received fiber-free artichoke leaf extract was not significantly reduced. It has already been indicated that glibenclamide could significantly improve the blood glucose and lipid profiles and HbA1c in diabetic models (24), which is in agreement with our results. With regard to FBG, there was no significant difference between two treatment methods concerning triglycerides, total cholesterol, LDL-c and VLDL-c and HbA1c in the present study. Nevertheless, HDL-c levels in the group III were significantly higher than the group IV. As an oral hypoglycemic drug, Glibenclamide (GBC) stimulates the pancreatic beta cells in order to secrete insulin. This drug is often utilized as a treatment of diabetes (25). The most important complications of this drug include hypoglycemia, haemolysis and cholestatic jaundice (26). Since the effects of the alcoholic extract of artichoke and glibenclamide are similar, the use of complementary medicines is recommended to prevent the complications of chemical drugs. This study does not address the mechanism of the effect of artichoke extract on laboratory parameters. Hence, further and longer studies are required to accurately identify the possible compounds in the extract, and purify them, and to investigate the effect of this purified extract on animal and human models.

Conclusion

This study indicated that Artichoke, at the administrated dose and for the period of administration, like glibenclamide, could improve diabetes parameters. Moreover, due to the complications of glibenclamide, and fewer side effects of artichoke, the use of this plant for diabetic patients is recommended. Nonetheless, further studies are required to shed light on other aspects of Artichoke.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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