Hypoglycemic Effect of the Aromatic Water of Leaves of Ficus Carica In Normal and Streptozotocin Induced Diabetic Rats

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Summary

Diabetes mellitus is the most important metabolic disorder worldwide. Use of medicinal plants for lowering blood glucose is clinically important in diabetic individuals. In this respect, the effect of oral administration of aromatic water of leaves of Ficus carica on blood glucose level in diabetic rats was investigated.
In this experimental study, male rats Sprague Dawley (n=80, 200-250 g), divided into two groups (40 normal and 40 diabetic surviving rats), each consisting of four subgroups (4 normal and 4 diabetic) including 10 animals each. Diabetic rats received streptozotocin (ip , 65 mg/kg). Subgroup one of each group was gavaged with vehicle (distilled water) and served as control, while subgroups 2, 3 and 4 of each group were gavaged with aromatic water of leaves of Ficus carica(extract) at doses of 0.05, 0.1, and 0.4 mg/dl, respectively. Blood glucose levels were measured 0, 3, 6, 12 and 24 hours after the administration of vehicle or the extract. Data were analyzed using repeated measure ANOVA and Dunnett t-test.

In normal rats at 12 and 24 hours after the administration of 0.05 and 0.1 mg/dl extract, blood glucose level decreased significantly. However, dose of 0.4 mg/dl of extract lowered blood glucose level significantly throughout the experiment. In diabetic rats at 3,6,12 hours after the administration, 0.1 and 0.4 mg/dl of extract decreased blood glucose levels meaningfully. At hour 24, only 0.4 mg/dl of extract lowered blood glucose levels significantly.

Our results show that the oral consumption of aromatic water leaves of Ficus carica decreased blood glucose level in normal and diabetic rats.

Keywords: Diabetes; Ficus carica; Hypoglycemia, rat.

Introduction

Diabetes mellitus (DM) is a syndrome characterized by disordered metabolism and abnormally high blood glucose (hyperglycaemia) and the commonest endocrine disorder that affects more than 100 million people worldwide [2 ,1]. The disease causes substantial morbidity, mortality, and long-term complications and remains an important risk factor for cardiovascular disease [2]. It is difficult for patients to follow a diet/exercise regime that would improve their symptoms, therefore the investigation of agents that may deal with its more serious aspects is an important medical field for research [3]. Plant derivatives with hypoglycemic properties have been used in folk medicine and traditional healing systems around the world [5 ,4]. Currently, with the active encouragement of the WHO, an attempt is being made to collect traditional medical lore concerning the treatment of diabetes for study in modern laboratories in order to scientifically evaluate its therapeutic efficacy and discard any possibility of undesirable effects. As part of this effort, a multitude of plants are being studied worldwide to check their possible hypoglycemic effect [6]. Herbal preparations of Ficus had been considered as effective, economical and safe ethnomedicines for various ailments in Iranian and Indian traditional system of medicine [7 ,5].The fig tree is believed to be a native of Persia and Asia Minor, but at present is raised in all mild latitudes [8 ,5]. The leaves are alternate, large, rough on the upper side, coarsely downy beneath, cordate, 3 or 5-lobed, or almost entire, coarsely serrated, and petioled [8 ,5]. Ficus carica is a popular plant used for patients with diabetes [4, 6, 7].. Several studies in animal models with diabetes have shown hypoglycemic effects, although human trials are lacking [7, 9-11]. The agent in Ficus carica leaves is responsible for these phenomena and its mechanism for glucose effect is unknown [4]. The present work was undertaken with the aim to study the effect of aromatic water leaves of ficus carica on the blood glucose level of normal and streptozotocin induced diabetic rats.

Materials and methods

Animals

Laboratory-bred Sprague Dawley rats of male sex weighing 200-250 g were employed for the study. All animals were procured from Iranian Pasture Institute. The rats were maintained under standard laboratory conditions at 25±2 °C, relative humidity 50±15% and normal photo period [12 h dark/12 h light] were used for the experiment. They were fed by Commercial pellet diet and water freely. The experimental protocol
has been approved by the Institutional Animal Ethics Committee. To induce Diabetes, Animals were allowed to fast 18 h and were injected with streptozotocin dissolved in sterile normal saline at a dose of 65 mg/kg body weight intraperitoneally.
After 4 days diabetic rats (glucose level≥ 250 mg/dl) were used for the experiment. In the experiment a total number of 80 rats (40 normal and 40 diabetic surviving rats) were used. The rats were divided into eight groups (4 normal and 4 diabetic), each group consisted of 10 animals. Group 1 normal rats were treated with vehicle (distilled water) and served as control, while Group 2, 3 and 4 normal rats were treated with aromatic

water of ficus carica leaf (extract) at a doses of 0.05, 0.1, and 0.4 mg/dl respectively; Group 1 diabetic rats were treated with vehicle and served as diabetic control, Group 2, 3 and 4 diabetic rats were treated with aromatic water of ficus carica leaf at a doses of 0.05, 0.1, and 0.4 mg/dl respectively.

Extraction procedure

leaves of Ficus carica collected during summer 2007 from Kashan area (Isfahan Province, Iran) at an altitude of ca. 2100 m. An authenticated specimen of the plant was deposited in the herbarium of the Kashan Research Botanical Garden, Research Institute of Forests and Rangelands, Kashan, Iran.100 gram of fresh *Ficus* carica leaves collected in summery and boiled in 1000 ml of distilled water. Aqueous extracts was obtained by conversion of steams into water. Aromatic water was stored in suitable contain prior to experimental.

Extract administration

The respective extracts were administered orally and in a single Dose/ days.

Blood collection and Determination of blood glucose level

The rats were fasted for 12 hours and blood samples were collected by puncture of tail immediately with needle (G 25) at 0 h (before treatment) and 3, 6, 12 and 24 h (after treatment). The plasma blood glucose levels were determined by using glucometer.

Statistical analysis

All values were expressed as mean ±SD. The differences were compared using repeated measure Analysis of variance (ANOVA) followed by Dunnet's test. P values <0.05 were considered as significant.

Results

The effect of different doses of aquaous extract of ficus carica leaf on fasting blood sugar level in normal rats was assessed at different time intervals. No significant difference was noticed between the support of this investigation blood glucose level of the experimental and the control groups on the time 0 (Table 1). At time12, 24 hours after the administration of 0.05 and 0.1 mg/dl decreased blood glucose levels significantly. 0.4 mg/dl decreased blood glucose levels throughout the experiment significantly (Table 1).
The antihyperglycemic effects of different doses of aqueous extract of ficus carica leaf on fasting blood glucose level in diabetic rats were assessed at different time intervals.
At time 3, 6, 12 hours after the administration of 0.1 and 0.4 mg/dl decreased blood glucose levels significantly. At time 24 only 0.4 mg/dl decreased blood glucose levels significantly (Table 2).

Table 1. Effect of Aqueous Extract of Ficus Carica Leaves on Fasting Blood Glucose Levels of Normal Rats

Group	Dose mg/dl	Blood glucose levels(mg/dl) at different hours the treatment				
		0 h	3 h	6 h	12 h	24 h
Control	-	63.6±2.8	62.4±2.6	61.9±2.0	61.9±2.4	61. ±2.
Extract	0.05	57.9±3.2	55.9±3.1	50.9±2.1	45.3±2.2 *	41.4±1.9 *
Extract	0.1	57.3±2.7	55.5±2.1	54.1±2.5	41.3±2.6 **	38. ±2 **
Extract	0.4	56.3±2.7	48.9±1.9 *	40.4±1.1**	37.1±1.2 **	36. ±1 **

All values are expressed as Mean ±SD. ** P< 0.001, * P< 0.05 statistically significant compared to 0 h of their respective group.

Table 2. Effect of Aquaous Extract of Ficus Carica Leaf on Fasting Blood Glucose Levels of Streptozotocin Induced Diabetic Rats

Group	Dose mg/dl	Blood glucose levels(mg/dl) at different hours the treatment				
		0 h	3 h	6 h	12 h	24 h
Control	-	367.0±15.5	343.7±17.9	335.3±13.2	352. ±18.9	359. ±13.
Extract	0.05	366.3±15.1	355.4±15.8	354.4±13.3	359.8±9.5	363. ±13.
Extract	0.1	386.0±8.8	263.8±7.2 **	250.9±7.2 **	176.4± 5.5 **	384. ±10
Extract	0.4	387.3±9.3	205.6±5.9 **	193.1±7.2 **	152.0±7.8 **	341. ±8.*

All values are expressed as Mean ±SD. ** P< 0.001, * P< 0.05 statistically significant compared to 0 h of their respective group.

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Discussion

The results show that aromatic water leaves of Ficus carica reduces normoglycemia in normal rats and hyperglycemia in diabetic ones in this dose dependent experiment.
Several studies have shown hypoglycemic effects of fig-leaf [1, 12, 13], fruits [14], stem & bark(11,12,15) and root [7].
Wadood N and et al showed that the extract of fig- fruits exerted a significant hypoglycemic effect in normal rabbits, which was however short lived. The hypoglycemic effect was not significant in alloxan treated rabbits [14].

Musabayane CT and et al showed that Ficus carica stem-bark extracts lowered blood glucose levels in normal and diabetic rats [11]
Singh RK, Mehta S and et al showed that aqueous extract of aerial roots of Ficus bengalensis exerted hypoglycemic effect in normoglycemic and antidiabetic effect in diabetic rats [7]
Canal JR, Torres MD, Romero A, Pérez C. A the administration of the organic phase rats with streptozotocin-induced diabetes led to a decline in the levels of total cholesterol and an decrease in the total cholesterol/HDL cholesterol ratio (with respect to the control group), together with a reduction of the hyperglycaemia [15].

Perez C. and et al showed that aqueous (basic) and organic (chloroform) extracts of Ficus carica leaves have similar effects in reducing hyperglycemia in diabetic rats [13]

Serraclara A and etal showed Hypoglycemic action of an oral fig-leaf decoction in type-I diabetic patients [6].
Our results showed that the consumption of aromatic water leaves of Ficus carica orally decreased blood glucose level in normal and diabetic rats which agrees with another results mentioned previously.
In the other hand there are some studies investigating the mechanism of action of *F. carica.. For example*
Campillo J.E and et al showed that in earlier in vivo and in vitro studies on rats, an action at the peripheral (skeletal muscle) level was suggested as facilitating glucose uptake [9]. There is no action at the pancreatic level (no rise in peptide C). Accepting this hypothesis, it is believe that the action of the *F. carica* decoction might well be more marked in type-II diabetic patients [9].

Another study suggests the facilitation of glucose uptake peripherally. The one available clinical trial is a small crossover study of fig leaf tea for 4 weeks in patients with type 1 diabetes (n _ 10); investigators showed a decrease in postprandial glucose and insulin requirements, but no change in fasting glucose when compared with the control commercial tea [6]. No effect was seen in C-peptide levels, thereby supporting a non–insulin-mediated effect. No adverse effects were reported. Clearly, more information is needed before the efficacy of Ficus carica can be properly assessed [6].
Some studies suggest that antioxidant status is affected in the diabetes syndrome. They conclude that the administration of the basic and chloroform extracts of *Ficus carica* affects the oxidative stress in diabetes, and that *Ficus carica* extracts tend to normalize it [13] or conclude that *Ficus carica is* effective drugs for diseases in which free radical damage play a pathogenical role [5].

It may be concluded that there is a common agent in aromatic water of leaves or other extract of *F. carica* leaves, fruits and bark that is responsible for these phenomena which remains unknown.
Oliveira AP, Valentão P and etal performed metabolite profiling on the leaves Ficus carica. Phenolics and organic acids profiles were determined by HPLC/DAD and HPLC/UV, respectively. All samples presented a similar phenolic profile composed by 3-O- and 5-O-caffeoylquinic acids, ferulic acid, quercetin-3-O-glucoside, quercetin-3-O-

rutinoside, psoralen and bergapten. 3-O-Caffeoylquinic acid and quercetin-3-O-glucoside are described for the first time in this species. Leaves' organic acids profile presented oxalic, citric, malic, quinic, shikimic and fumaric acids, while in pulps and peels quinic acid was absent [16]. Vaya J, Mahmood S. found that the major flavonoids in Ficus are quercetin and luteolin [17].

phenolic compounds including quercetin and luteolin [17 ,16] are effective in diabetic treatment The studies done by other researchers reveal that

Oliveira AP, Valentão P, Pereira JA, Silva BM, Tavares F, Andrade PB showed that Leaves were always the most effective part, presented capacity to scavenge superoxide radical, which seems to be related with phenolics compounds [16].

In the other hand Singh AB etal [18]. Musabayane CT etal [19] reveals the antihyperglycaemic activity of the alpha-amyrin acetate (alpha-AA) isolated from the aerial roots [18] , bark or stem [19] of the Ficus bengalensis in normal and diabetic rats and model of type-2 diabetes, i.e. db/db mice.
Kannappan S, Anuradha CV.(2009) [20] showed that Plant polyphenols have been known to exert anti-diabetic action and promote insulin action. their findings indicated that quercetin improved insulin signaling and sensitivity and thereby promoted the cellular actions of insulin in an acquired model of insulin resistance(in a rat model) [20].

Kobori M, Masumoto S, Akimoto Y, Takahashi Y [21] showed that Quercetin is a food component that may ameliorate the diabetic symptoms. they fed normal and STZ-induced diabetic mice with diets containing quercetin for 2 wk. Diets containing 0.1 or 0.5% quercetin lowered the STZ-induced increase in blood glucose levels and improved plasma insulin levels [21].

Fang XK, Gao J, Zhu DN.,(2008) [22] showed that Kaempferol and quercetin could significantly improve insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes [22]

Coskun O, Kanter M, Korkmaz A, Oter S.,(2005) [23] suggest that Quercetin treatment has protective effect in diabetes by decreasing oxidative stress and preservation of pancreatic beta-cell integrity [23].

Ding L, Jin D, Chen X.,2009 [24] suggest that, luteolin influences insulin action
Zarzuelo A, Jim‡©nez I, G‹‡mez MJ, Utrilla P, Fernadez I, Torres MI, Osuna I.,(31)(1996) suggest that luteolin effect was evidenced by a significant decrease in glycemia levels (> 50%), a 2.5-fold increase in insulin blood levels and an increase in body and pancreas weight, compared to the diabetic control group [25].

It is therefore believed that not only should the present study be continued, but a rigorous investigation undertaken of the numerous plants traditionally used in diabetes for their potential usefulness as an adjunct to conventional therapy.

Conclusion

It is concluded that the oral consumption of aromatic water leaves of Ficus carica decreased blood glucose level in normal and diabetic rats. Probably there are common factors in F. carica leaves, fruits and bark that are responsible for these phenomena, for example: quercetin and luteolin. Possible mechanism of this phenomena is via increasing effect of insulin on absorption by cells or antioxidant and protective effect of these compounds on B cells . these suggestions should be examined and approved by other experiments .

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