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HYPOGLYCAEMIC AND ANTIHPERGLYCAEMIC ACTIITIES OF AQUEOUS EXTRACT OF FICUS CARICA IN DIABETIC RATS

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Abstract

The Ficus carica (fig) is an important harvest worldwide for its dry and fresh consumption. Its common edible part is the fruit which is fleshy, hollow, and receptacle . The dried fruits of Ficus carica have been reported as an important source of vitamins, minerals, carbohydrates, sugars, organic acids, and phenolic compounds A short study was undertaken as a preliminary investigation to evaluate the antidiabetic effect of the aqueous leave extract by oral glucose tolerance test (OGTT) , normoglycemic and antihyperglycemic activity in streptozotocin (STZ)-nicotinamide in a dose of 120 mg kg induced non insulin-dependent diabetes mellitus Wister albino rats. Graded doses (250 and 500 mg/kg) of the aqueous leave extract suspended in gum acacia were administered to normal and experimental diabetic Wister albino rats. Effect on glucose tolerance test showed a significant reduction in the blood glucose level of extract treated animals after 1 hr, indicating its hypoglycemic activity. Continuous blood glucose lowering activity was observed till 4 hr of administration in normoglycemic and diabetic rats. The results were compared with standard drug glibenclamide. Also the extract showed a high LD50 value and could be used safetly.

Keywords: Ficus Carica (L) ; (Fig) ; Antidiabetic Activity; Streptozotocin; Nicotinamide; Rats.

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Introduction

Herbal drugs obtained from huge number of plants/herbs were extensively utilized in the prevention, diagnosis or treatment of various human diseases since ancient era [1] .Diabetes Mellitus is a group of metabolic disorders with impaired glucose metabolism that leads to an increase in blood glucose level, free radical production and increase in triglycerides and lipoproteins level with the risk of vascular and renal diseases. It has been classified as Type I, Type II and Gestational diabetes mellitus. According to World health organization (WHO) reports the number of patient is expected to be increasing progressively on daily basis. The Indian traditional system of medicine refers "science of life and longevity". The unbeaten heritage of this system is a real treasure house for both preventive and curative health care being easily available to mankind [2]. *Ficus carica* L. is an important member of the genus *Ficus*.It is ordinarily deciduous and commonly referred to as "fig". The common fig is a tree native to southwest Asia and the eastern Mediterranean, and it is one of the first plants that were cultivated by humans. The fig is an important harvest worldwide for its dry and fresh consumption. Its common edible part is the fruit which is fleshy, hollow, and receptacle [3]. The dried fruits of *F. carica* have been reported as an important source of vitamins, minerals, carbohydrates, sugars, organic acids, and phenolic compounds [4–7]. The fresh and dried figs also contain high amounts of fiber and polyphenols [8, 9]. Figs are an excellent source of phenolic compounds, such as proanthocyanidins, whereas red wine and tea, which are two good sources of phenolic compounds, contain phenols lower than those in fig [10]. Its fruit, root, and leaves are used in traditional medicine to treat various ailments such as gastrointestinal (colic, indigestion, loss of appetite, and diarrhea), respiratory (sore throats, coughs, and bronchial problems), and cardiovascular disorders and as anti-inflammatory and antispasmodic remedy [11, 12] . Phytochemical studies on *F. carica* revealed the presence of numerous bioactive compounds such as phenolic compounds, phytosterols, organic acids, anthocyanin composition, triterpenoids, coumarins, and volatile compounds such as hydrocarbons, aliphatic alcohols, and few other classes of secondary metabolites from different parts of *F. carica* . Most species of *F. carica* contain phenolic compounds, organic acids, and volatile compounds [13,14]. *F. carica* has been traditionally used for its medicinal benefits as metabolic, cardiovascular, respiratory, antispasmodic, and anti-inflammatory remedy [11, 12]. It is commonly referred to as "Fig". Leaves, fruits, and roots of *F. carica* are used in native medicinal system in different disorders such as gastrointestinal (colic, indigestion, loss of appetite, and diarrhea), respiratory (sore throats, cough, and bronchial problems), inflammatory, and cardiovascular disorders [15,16]. Fruits of *F. carica* can be eaten fresh or dried or used as jam. Figs are used as an excellent source of minerals, vitamins, carbohydrates, and dietary fibre because it is fat and cholesterol free and contain high number of amino acids [6, 7,17,18]. It is also reported that figs have been conventionally used for their therapeutic benefits as laxative, cardiovascular, respiratory, antispasmodic, and anti-inflammatory remedies [19].

This short term study thus aims to experimentally assess the antidiabetic effect of the *F. carica leave* extracts of *F. carica* as the preliminary investigation by oral glucose tolerance test (OGTT) and normoglycemic and antihyperglycemic activity in streptozotocin (STZ)-nicotinamide induced non insulin-dependent diabetes mellitus rats.

Materials And Methods

Plant material

Ficus carica leaves the fresh and soft leaves were collected from private gardens in Baghdad, and was authenticated by Iraqi National Herbarium in Baghdad.

Preparation of alcoholic root extract

The aqueous extract *F. carica leaves* was prepared by cold maceration of 250 g of the shade dried, coarse powder in 600 ml of water for 5 days. The extract was filtered, concentrated, dried *in vacuo* (yield 15 g) and the residue stored in a refrigerator at 2–8°C for use in subsequent experiments [20] .

Animals

Healthy adult male Wistar Albino rats between 2 to 3 months of age and weighing between 150–250 g were used for the study. Housed individually in polypropylene cages, maintained under standard conditions (12 h light and 12 h dark cycle, 25±30°C, 35–60% humidity), the animals were fed with standard rat pellet diet [21]

Acute toxicity

Nulliparous and non pregnant 2 month old female rats were used for the toxicity studies. The animals were marked to permit individual identification and kept in their cages for at least 5 days prior to dosing. The acute toxicity of the aqueous extract of *F. carica* t was evaluated by the methodology described in the OECD [22] , guidelines for the testing of chemicals. The animals were fasted for 4 hr prior to dosing. The fasted body weight of each animal was determined and the dose calculated according to its body weight starting from 0.1-4.5 g /kg body weight . The aqueous extract, prepared in drinking water was administered by gavage . The experimental procedure was performed in accordance with the Main Test of the OECD. Animals were observed individually during the first 30 min after dosing, every 4 h during the first 12 h and thereafter daily for 14 days.

Oral glucose tolerance test (OGTT)

The oral glucose tolerance test [23] was performed in overnight fasted (18 hr) normal animals. Rats divided into four groups (n=6) were administered 2% gum acacia solution, aqueous extract (250 mg/kg) , aqueous extract (500 mg/kg) and glibenclamide (0.25 mg/kg) respectively. Glucose (3 g/kg) was fed 30 min after the administration of extracts. Blood was withdrawn from the retro orbital sinus under ether inhalation to minimize the distress) at 0, 60, 90, 120 and 180 min of extract administration. The fasting blood glucose levels were estimated by glucose oxidase–peroxidase reactive strips (Accu-chek, Roche Di-agnostics, USA). The percentage decrease in the glucose concentrations were calculated with the formula

The percentage decrease in the glucose = [(Gh-Gf)/Gf] X 100

Where Gh = the highest blood glucose concentration during the study; Gf- fasting blood glucose concentration.

Normoglycemic study

For normoglycemic study, rats were divided into four groups (n=6) and were administered 2% gum acacia solution, aqueous extract (250 mg/kg), aqueous extract (500 mg/kg) and glibenclamide (0.25 mg/kg) respectively. Blood samples were withdrawn from the retro orbital sinus under ether inhalation at 0, 1, 2, 3 and 4 hr of extract administration [24]. The fasting blood glucose levels were estimated by glucose oxidase–peroxidase reactive strips.

Antihyperglycemic activity

Type II diabetes was induced [24] in overnight fasted animals by a single intraperitoneal injection of 60mg/kg STZ (Sigma Aldrich, Germany), 15 min after the i.p. administration of 120 mg/kg nicotinamide (Qualigens Fine Chemicals, division of Glaxo, Mumbai, India).

Hyperglycemia was confirmed by the elevated glucose level in the blood, determined at 72 hr and then on day 7 after injection. The animals exhibiting fasting blood glucose level of 200-350 mg/dl were used for the antidiabetic study. For antihyperglycemic study, the animals exhibiting fasting blood glucose levels between 200-350 mg/dl were used. The diabetic rats were divided into four groups (n=6) and were administered 2% gum acacia solution, aqueous extract (250 mg/kg), aqueous extract (500mg/kg) and glibenclamide (0.25 mg/kg) respectively. Blood samples were withdrawn from the retro orbital sinus under ether inhalation at 0, 1, 2, 3 and 4 hr of extract administration [15]. The fasting blood glucose levels were estimated by using glucose oxidase-peroxidase reactive strips.

Statistical analysis

Data was expressed as mean + S.E.M. The significance of the difference between the means of the test groups and control group was established by one way ANOVA followed by *post hoc* Levene's test for variance using SPSS, version 10. The values were considered significant when $p < 0.05$.

Results

Acute toxicity studies revealed the non-toxic nature of the alcoholic extract of *F. carica* up to a dose level of 2000 mg/kg body weight in rats. There was no lethality or toxic reaction found at any of the doses selected until the end of the study.

The difference between experimental and control rats were statistically significant ($p<0.05$). In OGTT, the aqueous extract of *F. carica* caused significant decrease in blood glucose level at both dose levels at 60 , 90 and 120 min as compared to the control (Table 1)

Table 1: Effect of aqueous extract of *F. carica* on the glucose tolerance test

Treatments	**Fasting blood glucose levels (mg/dl) (Mean+ S.E.M)**				
Group (n=6)	**0 min**	**60 mins**	**90 min**	**120 min**	**180 mins**
I -Control	**82.5 ±3.2**	**126.4 ± 5.1**	**110.4 ±4.7**	**102.6 ±2.2**	**89.8 ± 3.4**
II- Extract (250 mg/kg	**80.9 ±2.9**	**100.1 ± 3.4 b**	**108.7 ±2.6 b**	**93.3 ±2.5 b**	**85.6 ±2.3**
III- Extract (500 mg/kg)	**88.5 ±2.7**	**104.4 ± 2.1 a , b***	**92.3 ± 1.4 a , b***	**78.4 ±2.3 b**	**76.3 ± 2.3**
IV- Glibenclamide (0.25 mg/kg)	**78.8±1.6**	**99.4 ± 1.1 b**	**83.5 ± 1. 4 b**	**72.5 ±1.3 a**	**67.3 ± 1.6 a**

Values are mean+ S.E of 6 animals in each group; a = $p<0.01$ vs control ; b = $p<0.05$ vs control ; a*= $p<0.01$ vs Glibenclamide and b*= $p<0.05$ vs Glibenclamide.

In normoglycemic studies the mean blood glucose level decreased significantly after 2 hrs of the administration of the aqueous extract at the dose level of 250 and 500 mg/kg body wt (Table 2).

Table 2: Hypoglycemic effect of the aqueous extract of *F. carica* in normal rats Group

Treatments	Fasting blood glucose levels (mg/dl) (Mean+ S.E.M)				
Group (n=6)	0 hr	1 hr	2 hrs	3 hrs	4 hrs
I -Control	87.6 ±3.3	87.3 ± 3.3	86.4 ± 3.4	86.3 ±3.4	86.4 ±2.5
II- Extract (250 mg/kg	81.8 ±2.3	74.2 ± 2.3	68.3 ± 2.2 b	59.4 ± 2.3 a	47.6 ±2. 5 a3 b*
III- Extract (500 mg/kg)	88.7 ± 3.1	79.2 ± 3.4	72.1 ± 3.1 b	61.2 ±3.1 a	44.9 ± 3.4 a b*
IV- Glibenclamide (0.25 mg/kg)	82.9 ± 2.7	72.2 ± 1.6	68.5 ± 1.7 b	60.8 ± 2.1 a	54.4 ±2.4 a

Values are mean+ S.E of 6 animals in each group ; a = p<0.01 vs control ; b = p<0.05 vs control; a* = p<0.01 vs Glibenclamide and b* = p<0.05 vs Glibenclamide.

The fasting blood glucose level of diabetic rats significantly reduced after 2 hrs from the administration of the aqueous extract at the dose level of 250 and 500 mg/kg body wt respectively , which is comparable to that of the effect of glibenclamide (0.25 mg/kg) (Table 3).

Table 3: Antihyperglycemic effect of the aqueous extract of *F. carica* in diabetic rats

Treatments	Fasting blood glucose levels (mg/dl) (Mean+ S.E.M)				
Group (n=6)	0 hr	1 hr	2 hrs	3 hrs	4 hrs
I -Control	292.9 ±9. 5	291.8 ±8. 2	292.9 ±8.322	291.9 ± 8.9	290.1 ±8.7
II- Extract (250 mg/kg	299. 8±9.5	272.1 ±9.2	268.1 ± 9.44 b	253.3±9.1 a	250.8±24.8 a
III- Extract (500 mg/kg)	315.5±12.1	281.6±12.5	281.0±12.1 b	275.6±13.3 a,b*	270.5±12.4 a
IV- Glibenclamide (0.25 mg/kg)	291.1±7.89	277.0 ±8.1	263.1 ± 5.4 b	254.8±5.6 a	251.1±4.5 a

Values are mean+ S.E of 6 animals in each group ; a = p<0.01 vs control ; b = p<0.05 vs contro l ; a* = p<0.01 vs Glibenclamide and b* = p<0.05 vs Glibenclamide.

Discussion

The observation of the results of hypoglycemic effects of F. carica extract was encouraging , since the hypoglycemic effect started after 60 min from the treatment and continue for more than 4 hrs in both normoglycaemic and hyperglycemic rats , therefore, could have resulted from the combined activity of these compounds present in it. Also the calculated LD 50 indicate the the extract is safe and could be used safely. Regarding the mode action of the extract, the exact mechanism cannot be deduced from this experiment. It may be due to enhanced peripheral utilization of glucose However, the possibility of enhanced insulin release from surviving β-cells, pancreatic β-cells regeneration or the insulinomimetic of some of the components present in the F.carica extract or a combination of these effects cannot be ruled out. Furthermore, results of a previous study showed that aqueous extract of F.carica owers plasma glucose in normoglycemic mice, in a dose related pattern [25-27]. It was suggested that the mechanism of action may be due to increase in circulating insulin level (hyperinsulinemia) or by enhancing tissue utilization of glucose. In the oral glucose tolerance test on normoglycemic albino rats, F.caica extract showed significant reduction of serum glucose. It was observed that the hypoglycemic mechanism involved insulin-like effect, most probably through the peripheral glucose consumption [28-30] . The literature reports reveal that flavonoids and tannins present in the plant extract known to possess antidiabetic activity. In the present investigation, the observed antidiabetic potential of test extract may be due to presence of similar phytochemical which was evident by preliminary screening.

Conclusion

From this study, we can state that the aqueous extract of the leaves *of Ficus carica (Fig)* has beneficial effects on blood glucose levels .Further pharmacological and biochemical investigations will clearly elucidate the mechanism of action and will be helpful in projecting this plant as a therapeutic target in diabetes research.

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