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EVALUATION OF THE THERAPEUTIC EFFICACY AND BIOACTIVE MECHANISMS OF FIG *(FICUS CARICA)* LEAVES IN MANAGEMENT OF HYPERGLYCEMIA

Asifa Bashir

Department of Human Nutrition and Dietetics, University of Agriculture, Faisalabad, Punjab. Pakistan. 38000.

asifabashir296@gmail.com

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Corresponding Author: *
Asifa Bashir

Abstract

Hyperglycemia is a major metabolic disorder associated with significant micro- and macrovascular complications, sustaining interest in medicinal plants as adjunct anti-hyperglycemic agents. This study evaluated the proximate composition, phenolic and flavonoid content, and glycemic effects of Ficus carica (fig) leaf tea. Total flavonoid content was 1.151% (water) and 1.252% (methanolic extract); total phenolic content was 5.857 mg (methanolic) and 4.30 mg (water), respectively. Fifteen male albino rats were divided into three groups (n=5/group), a healthy untreated control and two STZ-induced diabetic groups were given 2 g or 3 g fig leaf tea/cup daily for 28 days. Tea produced its largest glucose reduction 3 hours post-administration, with levels returning near baseline by 24 hours. Co-administration with insulin allowed an approximate 50% dose reduction without loss of glycemic control. These findings support a short-term hypoglycemic and insulin-sparing action of fig leaf tea, warranting further study of its long-term efficacy.

Introduction

Hyperglycemia a sustained elevation in blood glucose caused by insufficient insulin secretion, reduced tissue responsiveness to insulin, or both is among the most consequential chronic metabolic disorders worldwide (Duckworth, 2001; Gunasekaran et al., 2008). Over time it disturbs the metabolism of carbohydrates, proteins, and lipids, driving complications such as nephropathy, retinopathy, neuropathy, and cardiovascular disease (Lins et al., 2006; Raza & Movahed, 2003). Type 2 diabetes, the non-insulin-dependent form, makes up 90–95% of cases globally (Naik et al., 2013; Huang et al., 2015), and Pakistan alone carries the world's seventh-largest diabetes burden, with roughly 6.9 million people affected and a projected rise to 11.5 million by 2030 (Shaikh et al., 2010).

Insulin and oral agents such as biguanides and sulfonylureas remain the mainstay of treatment (Sulochana et al., 2003), but their cost, side effects, and the difficulty of sustaining long-term adherence (Eliza et al., 2009; Gunasekaran et al., 2008) continue to drive interest in plant-derived alternatives (Hopf et al., 2000; Yadav et al., 2002). Fig (Ficus carica L., family Moraceae) is one of the plants most extensively studied for anti-diabetic activity in the traditional-medicine literature (Stephen et al., 2017). The genus Ficus contains more than 750 species (Herre et al., 2008), and F. carica itself is cultivated widely across the Mediterranean and beyond (Ammar et al., 2015). Its leaves are reported to contain ficin, phenolic compounds, flavonoids, and micronutrients including vitamins B1 and B2, calcium, iron, phosphorus, manganese, sodium, and potassium (Bikshapthi et al., 2012), and various parts of the plant have long been used to treat gastrointestinal, inflammatory, and hepatic

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conditions (Stephen et al., 2017; Salem et al., 2013).

Many studies have reported that Ficus carica leaves may contribute to reduction of blood glucose and lipid levels showing their potential value in metabolic health. In rodent models, experimental studies have demonstrated significant hypoglycemic and hypolipidemic effects of following treatment with fig-leaf preparations hypolipidemic effects of fig-leaf preparations in rodent models (Stalin et al., 2012; Joerin et al., 2014). Furthermore, clinical evidence supports these findings; a trial evaluating fig-leaf decoctions in patients with type 1 diabetes reported reductions in postprandial blood glucose as well as decreased daily insulin requirements (Serraclara et al., 1998). Regarding the underlying mechanism, these metabolic improvements are attributed to an insulin-like action that enhances peripheral glucose uptake and increases the sensitivity of functional pancreatic β-cells (Campillo et al., 1994; Shane-McWhorter, 2001). Daily administration of fig-leaf tea alongside breakfast has also been shown to lower glucose levels by as much as 14%, an effect attributed to its phenolic content (Belguith-Hadriche et al., 2016).

Despite these observations, little is known about the proximate composition, phytochemical profile, and physiological tolerability of locally grown fig leaves prepared as a practical tea. This study therefore set out to (i) determine the proximate composition of fig leaves, (ii) quantify the total phenolic and flavonoid content of their extracts, and (iii) evaluate the effects of two doses of fig leaf tea on feed and water intake, growth parameters, blood glucose, and serum insulin in an animal model of hyperglycemia.

Materials and Methods

Animal experiment

Fifteen healthy male albino rats (200–250 g body weight; 2–3 months old) were obtained from the Animal House, University of Agriculture, Faisalabad, Pakistan. The rats were maintained on a standard laboratory pellet diet with free access to water and in an air-conditioned room at 24 ± 2 °C under a 08:00-20:00 h light period. Diabetes was induced in fasted rats by a single intraperitoneal injection of streptozotocin (65 mg/kg body weight).

Plant material

The study was conducted at the National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan. Fresh, healthy, fully expanded leaves of Ficus carica L., Sp. Pl. 1059 (1753) were collected randomly in October from the nursery of the Department of Horticulture, University of Agriculture, Faisalabad, Pakistan. Fresh leaves were oven dried at 50 °C, then ground to a fine powder which was stored in sealed bags until use.

Preparation of Fig leaves extracts and animal treatment

For the treated animals, 10 g of dried fig-leaf powder was boiled in 100 ml water for 30 minutes, filtered while still warm (~50 °C). The animals were divided into three groups: G1 (normal control, non-diabetic/without STZ induction), G2 (Diabetic + 2 g / cup fig-leaf tea) and G3 (Diabetic + 3 g / cup fig-leaf tea).

(Table 1). Experimental groups

Group	Status	No. of subjects	Dose	Treatment
G1	Normal / control	5	–	No STZ; untreated
G2	Diabetic + T2	5	2 g/cup	Fig leaf tea
G3	Diabetic + T3	5	3 g/cup	Fig leaf tea

Blood sample collection and biochemical parameters

Following induction, animals were allocated to three groups (n = 5 per group) and given the assigned treatment for 4 weeks, during which feed consumption and body weight were recorded weekly. At the end of the experimental period, following a 4-hour fast, body weight was recorded, and 0.3 ml blood samples were collected by tail-vein puncture under anesthesia.

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Blood glucose was measured using a single-touch glucometer (glucose oxidase/peroxidase method), and serum insulin was measured following the method of Miller L. et al. (2011). Body length was measured with a measuring tape, and body mass index was calculated following Iyare et al. (2008).

Statistical analysis

Data were analysed using one-way analysis of variance (ANOVA), followed by a post-hoc test for mean comparison. Differences were considered statistically significant at $p < 0.05$

Results

Proximate composition of fig leaves

The proximate composition of fig leaves is presented in Table 2.

(Table 2). Proximate composition of fig leaves

Parameter	Value
Nitrogen-free extract (%)	54.51
Crude fiber (%)	14.70
Ash (%)	12.3
Moisture (%)	9.69
Crude protein (%)	9.08
Crude fat (%)	2.60

Total phenolic and flavonoid content

Total phenolic content (TPC) and total flavonoid content (TFC) for water and methanolic fig-leaf extracts are shown in Table 3. The methanolic extracts yielded higher flavonoid levels than the water extracts, whereas the water extracts showed a higher concentration of phenolics than the methanolic extracts.

(Table 3). Total flavonoid and total phenolic content of fig-leaf extracts

Extract	Total flavonoid content (%)	Total phenolic content (mg)
Methanolic extract	1.252	5.857
Water extract	1.151	4.30

Blood glucose

Acute administration of fig-leaf tea (Groups 2-3) produced a peak hypoglycemic response at 3 hours post-treatment, after which blood glucose levels gradually returned toward baseline within 24 hours. Long-term weekly monitoring demonstrated a significant, progressive reduction in both fasting and random blood glucose levels across the 4-week study period for tea-treated groups (G2 and G3) compared with control group (G1)

(Table 4a). Mean ± SE fasting blood glucose (mg/dL) by week and treatment

Week	G1	G2	G3
1	201.667±1	184.333±0.57	176.667±0.57
2	199±1.52	183.333±1.52	174.667±0.57
3	198.333±3.51	180.667±0.57	171.333±1.52
4	199.333±2.08	177.667±2.51	169±1

(Table 4b). Mean ± SE random blood glucose (mg/dL) by week and treatment

Week	G1	G2	G3
1	201.667±1.52	189±1.00	187.333±0.57
2	199±1.73	185.667±1.53	184±1.73

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3	198.333±0.57	179.333±0.57	181.667±1.52
4	199.333±2.08	178.333±1.52	177.333±1.52

Serum insulin

Serum insulin concentrations were significantly influenced by both the treatment type and study duration ($p < 0.0001$). Throughout this 4-week experimental period, the groups that administered fig-leaf tea (both G2 and G3) showed a slow and continuous reduction in serum insulin levels compared with the untreated control (G1).

(Table 5). Serum Insulin Levels (µU/mL) During 4-Week Study

Week	G1	G2	G3	ANOVA Summary
1	14±0.707	12.5±0.707	12.83±1.060	Treatment (V002)
2	13.33±0.353	13±1.060	12.33±0.707	DF = 2

Discussion

The proximate composition of fig leaves found in present study is consistent with previously reported findings, although some variations in individual components were noted (El-Shobaki et al., 2010; Joseph and Raj, 2011; Ghazi et al., 2012). The relatively higher ash and crude fiber contents, along with lower nitrogen-free extract (NFE) may be related with differences in cultivar, growing conditions, leaf maturity and drying methods. Water extraction also produced higher total phenolic content than methanolic extractions, suggesting that aqueous solvents can effectively extract polar phenolic compounds from *Ficus* species (Ghazi et al., 2012; Jahangiri et al., 2011). The phenolic and flavonoid compounds present in *Ficus carica* leaves may also contribute to their antioxidant activity (El-Shobaki et al., 2010; Manian et al., 2008; Krishna et al., 2007).

No adverse behavioural changes were noticed in animals after administration of fig-leaf tea. Water intake remained stable, whereas feed intake showed only minor changes suggesting that the treatment was well tolerated (Pérez, C. et al., 2000). A lower increase in body weight was also reported (El-Shobaki et al. (2010), which may be related with changes in and likely in lipid and carbohydrate metabolism rather than toxicity. Blood glucose increased to its highest point three hours after treatment and gradually moved towards baseline within 24 hours. These results showed blood glucose-lowering effect of aqueous fig-leaf extract in diabetic rats may be short-term and does not persist for an extended period. Past studies also reported antidiabetic effects in fruits, stems and roots of *Ficus* species, indicating that different parts of fig plant may also have potential antidiabetic properties (Pérez, C. et al., 2000; Nisar et al., 2003; Musabayane et al., 2007). When fig-leaf tea (2 g/ cup) was given with insulin, the insulin dose could be reduced from 10 units to 5 units while maintaining glycemic control. A similar effect also reported in a clinical study of Serraclara et al. (1998), reported a 15.5% reduction in daily insulin requirements in type 1 diabetes patients without a significant change in C-peptide levels.This reduction of insulin may indicates an insulin-sparing effect, related to glucose uptake by muscles, increase insulin receptor activity, or increase glucose transport across cell membranes rather than increasing endogenous insulin secretion (Campillo et al., 1994; Karam, 1998; Shane-McWhorter, 2001). Flavonoids such as quercetin and luteolin may be involved in these effects because of their potential role in the metabolism of glucose. The gradual decrease in serum insulin levels during the 4-week treatment period may also indicate improved insulin sensitivity (Vaya & Mahmood, 2006).

Limitations

In real-world scenarios, which limits the precision of the glycemic and insulin estimates and the generalizability of the findings. This study was conducted with small group sizes (n=5/ group) over a single 4-week trial and a single extraction protocol. The mechanistic interpretations offered above are consistent with the observed data but were not tested directly (e.g., via receptors-binding or glucose-uptake

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assays) and should be confirmed in future work. Longer-term studies with larger chorots, additional dose levels, and direct mechanistic assays are needed before fig-leaf tea can be recommended as an adjunct anti-hyperglycemic therapy.

Conclusion

The tea made from locally cultivated *Ficus carica* leaves exhibited a beneficial, nutritional and phenolic-flavonoid composition and produced a measurable short-term reduction in blood glucose levels in STZ-induced diabetic rats, it also showed reducing the requirement of insulin when administered alongside insulin. These findings suggest fig-leaf may be low-cost supplementary option alongside the standard treatment of diabetes and further studies and research is needed to confirm its potential benefits.

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