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Antioxidant, antilipidemic and antidiabetic effects of ficusin with their effects on GLUT4 translocation and PPARγ expression in type 2 diabetic rats

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ABSTRACT

In this study, the antioxidant, antilipidemic and antidiabetic effects of ficusin isolated from *Ficus carica* leaves and their effects on GLUT4 translocation and PPARγ expression were evaluated in HFD-STZ induced type 2 diabetic rats. Ficusin (20 and 40 mg/kg b. wt.) lowered the levels of fasting blood glucose, plasma insulin and body weight gain, in HFD-STZ induced diabetic rats. Ficusin also significantly lowered the serum antioxidant enzymes (SOD, CAT and GPx) and lipids (TC, TG and FFA) levels to near normal. Ficusin significantly enhanced the PPARγ expression and improved the translocation and activation of GLUT4 in the adipose tissue. Molecular docking analysis exhibited promising interactions of GLUT4 and PPARγ into their active sites. This study suggests that ficusin improved the insulin sensitivity on adipose tissue and it can be used for the treatment of obesity related type 2 diabetes mellitus.

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1. Introduction

Diabetes mellitus is a universal health problem and the prevalence of this disease is rapidly increasing. Type 2 diabetes accounts for more than 90–95% of world human diabetic population [1]. It is predicted that by the year of 2030, 366 million people will suffer from diabetes [2]. Hyperlipidemia is a disorder characterized by increase in blood lipoprotein or cholesterol levels causing obesity. It is one of the major causes of premature death globally and it is expected to be the most important cause of mortality in developed and developing countries [3]. Increase of serum TC and LDL is a primary risk factor for coronary heart disease. Importantly VLDL produced by the consumption of unhealthy diets stick's to the walls of the blood vessels and blocks the normal blood flow and cause coronary heart disease. TGs and FFA also plays an important role in the development of insulin resistance [4]. Currently used synthetic antidiabetic and antilipidaemic drugs cause some side effects. Therefore, there is a need to search for new herbal drugs as antidiabetic and antilipidaemic agents that retain therapeutic efficacy [5]. WHO also recommended the use of herbal drugs and preparations for the treatment of diabetes [6].

Abbreviations: HFD-STZ, high-fat diet fed – streptozotocin; OGTT, oral glucose tolerance test; ITT, insulin tolerance test; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; TC, total cholesterol; TG, triglycerides; FFA, free fatty acids; PPARγ, peroxisome proliferator-activated receptor γ; GLUT4, glucose transporter protein 4; LDL, low-density lipoprotein; VLDL, very low-density Lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease; WHO, world health organization; TLC, thin layer chromatography; UV, ultra violet; ^{1}H NMR, ^{1}H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; IR, infra red; ALT, serum glutamate pyruvate transaminases; AST, serum glutamate oxaloacetate transaminases; ALP, alkaline phosphatase; ANOVA, analysis of variance; SEM, standard error mean; RT-PCR, reverse transcriptase-polymerase chain reaction.

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Among many medications and other alternative medicines, traditional medicinal plants have been used throughout the world to treat diabetes mellitus. Natural compounds from plants are attracting more and more attention for their potential uses in the treatment and prevention of diabetes mellitus. Plants have always been excellent sources of drugs and many of the currently available drugs have been derived directly or indirectly from them. The isolated and identified compounds like phenolics, flavonoids, steroids, triterpenoids, alkaloids, other nitrogen compounds and aromatic compounds have been reported to possess hypoglycaemic activity [7].

Ficus carica Linn. (Moraceae) is commonly referred as Figs or Anjir found in tropical and subtropical regions of India and worldwide. Traditionally the plant has been used for the treatment of jaundice, diabetes, diarrhea, nutritional anemia and for inflammation in ayurveda, siddha and homoeopathy [8]. Hepatoprotective, hypoglycemic, antifungal, antispasmodic, antipyretic, anthelmintic, antioxidant and antimutagenic activities have been reported [9]. The antidiabetic property of *F. carica* has been reported in alloxan-induced insulin deficient diabetic rat model [10]. Dayanand et al. [11] and Joerin et al. [12] have evaluated the antihyperlipidemic effect of *F. carica* in high fat diet and Triton X -100 induced hyperlipidemic animal models. The present research was undertaken to evaluate the antioxidant, antilipidemic and mechanism of antidiabetic effect of ficusin in HFD-STZ induced type 2 diabetic rats.

2. Materials and methods

2.1. Plant material collection and extraction

Fresh leaves of *F. carica* were collected from Western Ghats, Tamil Nadu, India, during the month of January, 2013 and authenticated by the taxonomist at Entomology Research Institute, Loyola College, Chennai (Voucher no. ERI/ETHPH/FC/234). 3 kg of powdered leaves were soaked in 9 L of hexane, ethyl acetate and methanol sequentially for 3 days. The extracts were filtered and concentrated using rotary evaporator at 40–55 °C. The yield of hexane, ethyl acetate and methanol extracts were 42, 36 and 19 g, respectively.

2.2. Isolation and identification of compound

Ethyl acetate extract of *F. carica* (38 g) was subjected to column chromatography over silica gel column (Acme's silica gel, 100–200 mesh, 750 gm, 60 cm × 3.5 cm). The column was eluted with solvents of increasing polarity hexane, ethyl acetate, methanol and their mixtures (0, 5, 10, 20, 30, 50, 70 and 100%). A total number of 108 fractions (each 100 ml) were collected. Similar fractions were combined on the basis of their TLC profiles. Among 7 fractions, fraction 5 eluted with hexane: ethyl acetate (4:1) gave a colourless amorphous powder, melting point (m.p.) 162–164 °C (yield 6.8 g). It gave a single spot (Rf = 0.64) on TLC over silica gel with hexane: ethyl acetate (4:1) as the developing system. The spot turned yellow on dipping the plate in 1% aqueous NaOH, showing it to be a coumarin derivative. It did not answer for phenol ($FeCl_3$ test) or flavonoids (Shinoda test). It answered (EHRILISCH test) for furan. Physical and spectroscopic data like melting point, UV, Mass, ^1H and ^{13}C NMR and IR spectrums were analysed and compared with the literature data's explained by Renmin et al. [13] and Behrooz et al. [14]. The compound was identified as ficusin, it showed 97% of purity by GCMS analysis and the quality of the compound was confirmed using authenticate sample. Chemical structure of ficusin is shown in Fig. 1.

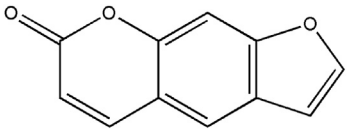

Fig. 1. Structure of ficusin.

2.3. Experimental animals

Male Wistar rats (180–200 g) rose from the central animal house of Entomology Research Institute were used for the studies. They were provided with environmentally controlled conditions like temperature (22 ± 2 °C), relative humidity (45 ± 5%) and 12/12 h day/night cycle for 7 days. The animals were fed with standard pellet diet and water ad libitum throughout the experimental period. The usage of animals and experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC- ERI-LC-05/13).

2.4. Acute toxicity study

The acute toxicity study was performed as per OECD - 425 guidelines [15]. The criteria for the selection of species, doses and number of animals were according to the OECD guidelines. Overnight fasted rats were divided into five groups of six rats each and one group was considered as control group. They were administered orally with ficusin (100, 200, 400 and 800 mg/kg b. wt.) dissolved in 0.2% Tween-80. According to Irwin test, the rats were observed for any gross behavioral changes and physical signs of toxicity for 1 h, then next for 6 h and then again at 24 h [16]. The behavioral, neurological and autonomic profiles of rats were monitored for 14 days and on 15th day rats were sacrificed and organs were collected for histopathology analysis. No behavioral alterations observed between 1/10th–1/20th dose was considered as safe dose and used for further assays [17]. Hence, doses of 10, 20 and 40 mg/kg b. wt. were chosen for antidiabetic study.

2.5. Antidiabetic study of ficusin

2.5.1. Induction of diabetes

Male Wistar rats were used for the study. They were fed with high fat diet (Table 1) for 15 days except normal control rats. Diabetes was induced in overnight fasted rats by a single intraperitoneal injection (i.p.) of freshly prepared solution of streptozotocin (40 mg/kg b. wt.) in 0.1 M citrate buffer (pH 4.5) [18]. The blood glucose levels were estimated after seven days and the animals having plasma glucose levels (≥200 mg/dl) were used for the

Table 1
Composition of high-fat diet (%, W/W).

Ingredients	High-fat diet (g/kg)
Lard	310
Dalda (saturated fat)	110
Casein	250
Cholesterol	10
Cornstarch	120
Sucrose	85
Cellulose	50
Vitamin mixture	30
Mineral mixture	30
DL-Methionine	03
L-Cystine	01
Sodium chloride	01
Total metabolizable energy (kcal/kg)	5941

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