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SHORT COMMUNICATION

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Potential Antidiabetic Activity of *Ficus Carica*: The Concept of Antioxidant Properties in a Rat Model

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Abstract

Background: The benefits associated with a healthy diet can be attributed to higher concentrations of antioxidants found in fruits and vegetables such as flavonoid-polyphenolic compounds, tocopherols, and carotenoids.

Objectives: The aim of the study was to investigate the antioxidant activity of *Ficus Carica* and the histopathological study in striptozotocin (STZ) induced T2DM in rats and compare the effect of the plant with sitagliptin.

Materials and Methods: Forty apparently healthy male Wister rats weighing between 180 and 250 grams were used in the current investigation, which began in December 2023. To create type 2 diabetes mellitus (T2 DM), rats were fed a high-fat diet (HDF) for two weeks before being injected intraperitoneal (STZ). Wistar rats were randomly divided into five groups, each group including eight rats. Group 1 animals received only normal saline. Group 2 animals received IP streptozotocin (STZ) 35 mg/kg and were left without any treatment. Group 3 animals received IP STZ 35 mg/kg and sitagliptin 10 mg/kg. Group 4 animals received IP STZ 35 mg/kg and *Ficus Carica* extract 200 mg/kg. Group 5 animals received IP STZ 35 mg/kg and sitagliptin 10 mg/kg and *Ficua Carica* extract 200 mg/kg. At the end of the study the animals were sacrificed, and collection of blood sample for the estimation of MDA and liver histopathological study.

Results: Treatment with *Ficus Carica* showed a highly significant ($p < 0.001$) increase in MDA levels in STZ group compared to the control group. For groups (3,4,5) MDA levels decreased significantly ($p < 0.001$) compared to the STZ group. Also, the histopathological study of rat livers in the control group showed normal tissue, no inflammatory cell aggregation, no congestion. Group 2 (striptozotocin) showed acute inflammation, congestion in the portal vein, and infiltration of leukocyte and macrophages in hepatocytes. However, the other groups (3, 4, and 5) showed mild changes in hepatocytes and portal veins. The following photomicrograph describes tissue changes in each group.

Conclusion: *Ficua Carica* possesses antioxidant properties by the effect on lipid peroxidation (MDA) in STZ induced T2DM at a dose 200 mg/kg and has liver protective activity. Additionally, sitagliptin exhibited antioxidant and anti-inflammatory activity at a dose 10 mg/kg in diabetic male rats.

Keywords: Dibetes mellitus, Ficus carica, Oxidative stress, Obesity, Histopathology, MDA, Redox

1. Introduction

Diabetes has emerged as one of the most serious and common chronic diseases of our times, causing life-threatening disabling,costly complications, and reducing life expectancy [1]. Type 2 diabetes is currently considered a worldwide epidemic. Diabetes is a substantial chronic disorder with severe consequences that contribute to high morbidity and mortality rates [2]. Several factors influence the progression of type 2 DM.

The ultimate manifestation of the hyperglycemic state in type 2 diabetes is a mix of reduced insulin secretion, insulin resistance, and increased hepatic glucose synthesis, and this depends on the individual genetic, pathologic, or environmental factors

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involved in a particular patient [3]. The evidence for oxidative stress biomarkers in both diabetic humans and rodents demonstrates the tight relationship between oxidative stress and diabetes. Hyperglycemia causes an increase in oxidative DNA damage indicators, lipid peroxidation products, and protein oxidation products, as well as impaired antioxidant enzyme activity [4]. DM and OS are connected. An imbalance in free radical production, or ROS, as well as disturbances in the antioxidant defense system, is a primary cause of DM problems. Pancreatic β-cells are extremely sensitive to OS due to poor production of antioxidant enzymes like catalase and SOD in pancreatic islets [5].

Fig peel includes beneficial chemicals such as anthocyanin at higher amounts than the edible fruit portion. Various phytoconstituents, including amino acids, phytosterols, organic acids, hydrocarbons, aliphatic alcohols, volatile components, fatty acids, and phenolic components, have previously been isolated from various sections of *Ficus carica* [6]. In DM the increase in thiobarbituric acid reactive substances (TBARS), oxidized glutathione, and a decrease in SOD and catalase concentrations indicate lipid peroxidation and abnormalities in the antioxidant system. Supplementing rats' diets with 0.5% anthocyanin extract reduced oxidative stress by decreasing TBARS and glutathione levels in the blood [7]. The World Health Organization (WHO) suggests indigenous plants as a potentially fantastic alternative for diabetes treatment because of their activity, nontoxicity, and minimal side effects [8].

2. Materials and methods

The study was carried out on forty adult male Wister rats weighing 180–250 g and aged 10 to 12 weeks. The rats were housed at 25°C, with a room humidity of 60–65% and a 14-hour light-dark cycle. Animals were fed a regular laboratory meal mixed with peanut butter during the acclimation period, as well as two weeks before injection, and had unlimited access to tap water [9].

2.1. Hyperglycemia induction

To generate a rat model that resembles human T2DM with increased adiposity, a Martin-Carro *et al*. Protocol with simple modification each group of rats (except group 1 / healthy control group) was fed for 2 weeks before induction. A Fat Diet (30% fat (cholesterol powder and peanut butter) + 70% standard chow) was added to increase adiposity. Rats were fasted for 8–10 hr. and then injected intraperitoneally (IP) Streptozotocin at a dose of 35 mg/kg body weight (100 mg STZ dissolved in 10 ml normal saline). Streptozotocin must be stored in a dark and appropriate temperature immediately prior to use [10].

Fasting blood glucose (FBG) of the rats was measured using a glucometer (Roche, Switzerland),The development of hyperglycemia was confirmed after 72 h, Rats with fasting blood glucose levels higher than 126 mg/dl were considered to be diabetic and used as subjects in the study [11].

This study took place at the Animal House in Babylon University's College of Medicine from 25/12/2023 until 15/1/2024. The selected 40 rats were divided randomly into 5 groups with 8 rats in each group.

Group 1 (healthy control group): animals received only I.P. normal saline.

Group 2 (negative control group): animals received single IP striptozotocin (STZ) 35 mg/kg and were left without any treatment [12].

Group 3: animals received single IP STZ 35 mg/kg and sitagliptin 10 mg/kg for 21 days [13].

Group 4: animals received single IP STZ 35 mg/kg and *Ficus Carica* extract 200 mg/kg for 21 days [14].

Group 5: animals received single IP STZ 35 mg/kg and sitagliptin 10 mg/kg and *Ficua Carica* extract 200 mg/kg for 21 days. After ending the experiment, the surviving animals were sacrificed, and samples of blood and liver tissue were collected for investigation.

2.2. Ethical approval

This study was approved by the Committee on Publication Ethics at the College of Medicine, University of Babylon, Iraq according to document number 4/19, on 8/08/2023.

2.3. Statistical analysis

Data were expressed as the mean ± SEM. One-way (ANOVA) was used in statistical analyses, which were carried out using SPSS version 26. When the $p \leq 0.001$, differences were deemed highly significant, and when the $p \leq 0.05$,differences were deemed significant.

3. Results

3.1. Oxidative stress biomarker Malondialdehyde (MDA)

Malondialdehyde (MDA) is one of the final products of polyunsaturated fatty acids peroxidation in the cells. An increase in free radicals causes overproduction of MDA. Malondialdehyde level is commonly known as a marker of oxidative stress. Results are expressed as the mean (± SD). Fig. 1 shows a

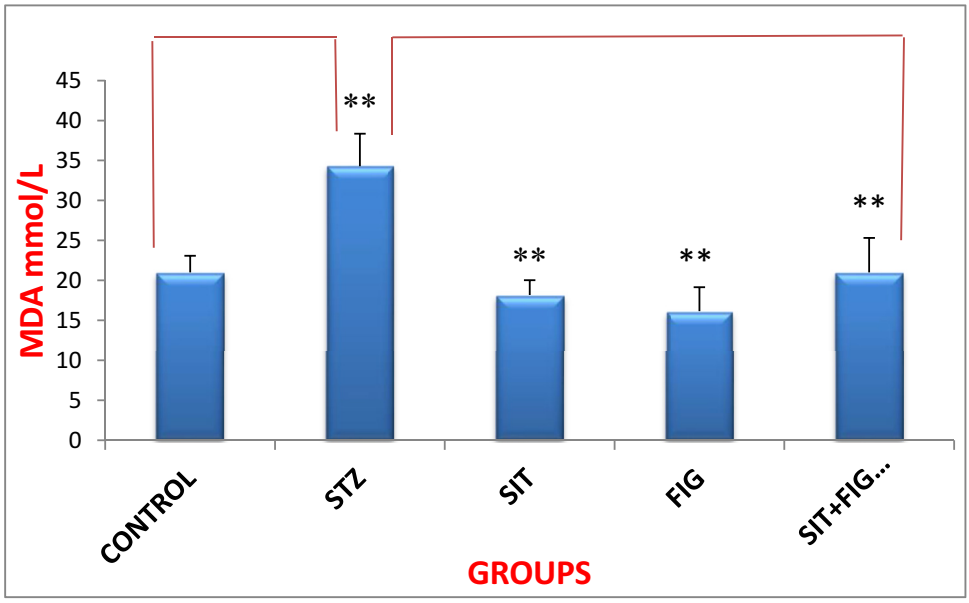
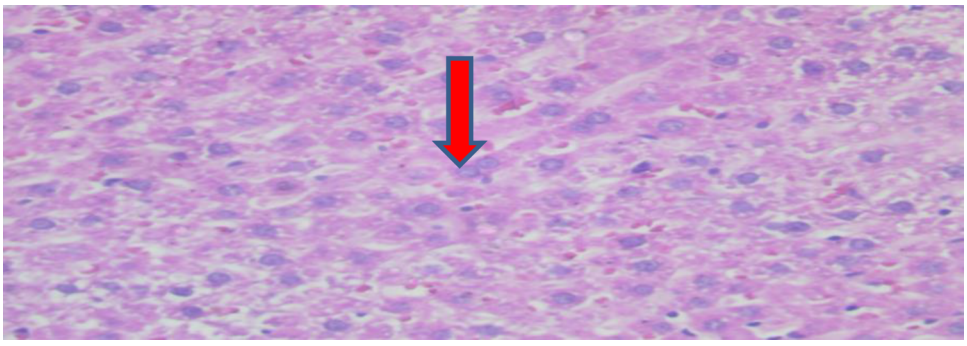


*Fig. 1. Effect of sitagliptin and Ficus Carica on MDA level (**p < 0.001).*



Pic. 1. Rat liver normal histology, no inflammation, no congestion and normal portal vein (H&E × 400) (control group 1).

highly significant the $p \leq 0.001$ increase in MDA level in the STZ group compared to the control group. Meanwhile, in groups (3,4,5), MDA level decreased highly significant the $p \leq 0.001$ compared to STZ group.

3.2. Histopathological results

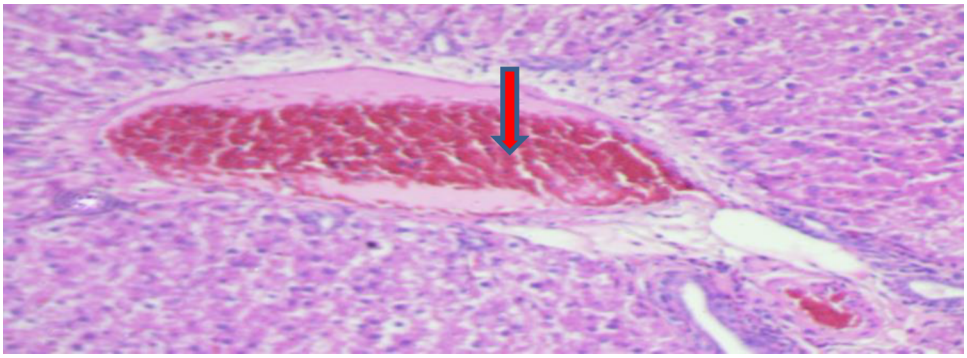
The histopathological examination of rat's liver in the control group showed normal tissue, no inflammatory cell aggregation, and xno congestion as presented in (Pic. 1), while (Pic. 2) shows the changes in group 2 (striptozotocin) acute inflammation, congestion in the portal vein, and infiltration of leukocytes and macrophages in hepatocytes. However, the other groups (3, 4, and 5) showed mild changes in hepatocytes and portal veins. The following photomicrograph describes tissue changes in each group (Pics. 3, 4, and 5),

4. Discussion

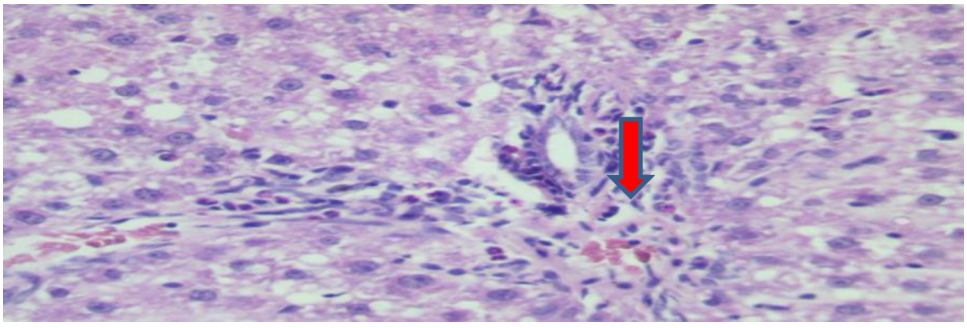
4.1. Evaluation of sitagliptin and Ficus Carica extract effects on oxidative stress

T2DM is significantly linked to oxidative stress, which is mostly indicated by increased production of reactive oxygen species (ROS). This causes damage to proteins, lipids, nucleic acids, and intracellular organelles, including mitochondria. ROS damage pancreatic β-cells and disrupt insulin action in target tissues, including skeletal muscle, liver, and adipose tissue [13].

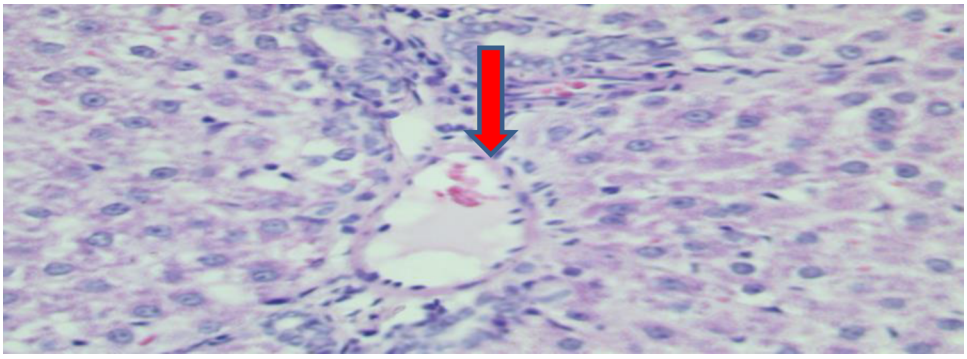
This study reveals a significant reduction in MDA in treated groups (3, 4, and 5) compared to diabetic group 2, that was left without any treatment, suggesting that sitagliptin drug and fig plant intervention can significantly reduce OS in diabetic rats. This was consistent with prior study findings [14]. The therapeutic benefits of DPP-4 inhibitors have been



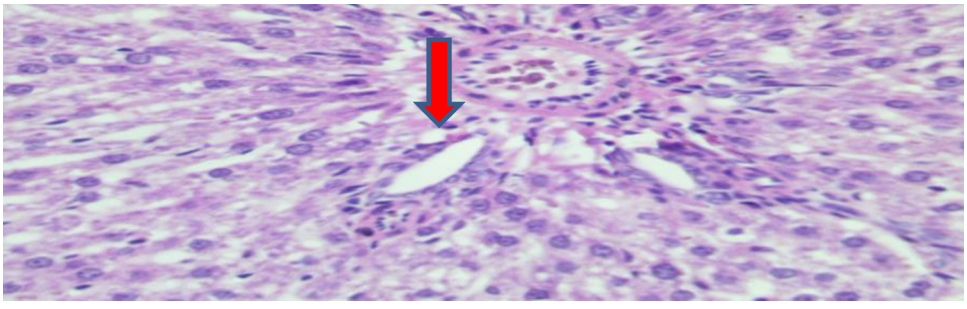
Pic. 2. Rat liver shows severe inflammation with frequent acute inflammatory cells infiltrate arrow (H&E × 400) (STZ group 2).



Pic. 3. Rat liver shows mild inflammation with acute inflammatory cells infiltrate arrow (H&E × 400) (STZ+SIT group 3).



Pic. 4. Rat liver shows mild inflammation with acute inflammatory cells infiltrate arrow (H&E × 400) (STZ+FIG group 4).



Pic. 5. Rat liver, mild inflammation shows astrocytes with acute inflammatory cells infiltrate arrow (H&E × 400) (STZ+FIG+SIT group 5).

proposed to play a crucial role in potentiating intestinal GLP-1 production, in addition to blocking GLP-1 metabolism [15].

The mechanism by which Ficus carica reduces MDA (malondialdehyde) involves several pathways:

1. Antioxidant Activity: Ficus carica contains high levels of polyphenolic compounds, which are strong antioxidants. These compounds inhibit lipid peroxidation, thereby reducing MDA levels.
2. Inhibition of Lipid Peroxidation: The polyphenols in Ficus carica extracts inhibit lipid peroxidation by scavenging free radicals and reducing the formation of MDA.
3. Modulation of Oxidative Stress: Ficus carica extracts have been shown to modulate oxidative stress by increasing the activities of antioxidant enzymes such as SOD, GSH, and CAT, which helps to reduce MDA levels.
4. Inhibition of Inflammatory Cytokines: Ficus carica extracts have been found to inhibit the production of pro-inflammatory cytokines like TNF-α, which can contribute to oxidative stress and MDA formation [16].

These mechanisms collectively contribute to the ability of Ficus carica to reduce MDA levels, thereby providing hepatoprotective and antioxidant effects.

MDA is one of the critical markers related to ROS and oxidative damage, and when free radicals increase, MDA production will be increased [17]. Our data indicated that giving SIT reduced MDA levels. SIT has been linked to antioxidant advantages.SIT can attenuate STZ-induced oxidative stress by decreasing DPP-4 protein levels while boosting GLP-1 [13].

Hyperglycemia can also produce free radicals, which contribute to increased lipid peroxidation and a decrease in cellular antioxidants [18]. These results were in consistant with previous work carried out on the model of diabetes-induced using HFD/STZ results agreed with those obtained from the current study [19].

Ficus Carica extract could significantly reduce blood glucose levels in diabetic rats and have a role in reducing oxidative stress, which is consistent with prior study conducted by [20]. Our results revealed that fig extract had a powerful antioxidant and many protective effects in diabetic rats in group 4 that was treated with 200 mg/kg fig extract orally [21]. The extract of *Ficus carica* used in this study possesses a hypoglycemic effect on streptozotocin-induced diabetic rats and highly significant reduction in oxidative stress as a result of a previous study [22].

4.2. Evaluation of sitagliptin and Ficus Carica extract effect on Liver Tissue

The histopathological analysis of H&E-stained liver slices from non-diabetic rats revealed normal liver tissue with normal hepatic lobule and portal tract architecture (Pic. 1).

Liver slices from diabetic rats showed various regions of hepatic degeneration, including the loss of a group of hepatocytes, inflammatory cellular infiltrations, and hepatocyte cytoplasmic degeneration (Pic. 2).

On the other hand, slices from the liver of diabetic rats receiving SIT showed a considerable decrease in inflammatory cellular infiltrations; most of the hepatocytes appeared to have normal cytoplasm and nuclei [23]. The microscopic appearance of liver tissue from healthy rats (group 1) is normal physiological, with well-structured and demarcated centrilobular veins, bile ducts, and portal spaces. Several research that focused on the histological study of rat liver tissue showed the same characteristic [24].

Treatment with sitagliptin for 21 days significantly reduced hepatocellular damage and resulted in a reduction in inflammation [25]. The liver structure of rats treated with *F. carica* extract resembled that of healthy subjects. This suggests that therapy with this extract may increase the ability of liver cells to regenerate after damage [26].

Given all of the foregoing, the current investigation sought to confirm the use of figs in traditional medicine as well as their contemporary use as nutraceuticals by proving their high antioxidant content, which, when consumed, contributes to the prevention of multiple oxidative stress-related disorders. The future goal is to develop novel therapies based on natural medicinal plant ingredients that have fewer adverse effects than synthetic ones. Figs are an exciting fruit for the future of natural medicine and functional meals [27].

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