SOME PHYSIOLOGICAL EFFECTS OF MOMORDICA CHARANTIA AND TRIGONELLA FOENUM-GRAECUM EXTRACTS IN DIABETIC RAT AS COMPARED WITH CIDOPHAGE

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ABSTRACT

Ethanolic extract of Momordica charantia (BM) and Trigonella foenum-graecum(TG) were used to investigate their antidiabetic activity in streptozotocin (STZ) induced diabetic albino rats. BM and TG were given to the STZ induced diabetic rats at the concentration of 500mg/kg, 50mg/kg body weight respectively in different groups, orally once a day for 4 weeks. Cidophage is also given to another group to support the results at the concentration of 500mg/kg body weight orally once a day for 4 weeks. The results reveled that oral administration of plant extracts significantly reduced glucose levels in the following order: cidophage (1.08 fold), bitter melon (1.17 fold), and fenugreek (1.33 fold), as compared with healthy control rats. Insulin secretion was stimulated after 4 weeks of treatment with cidophage (0.87 fold), bitter melon (0.86 fold), and Fenugreek (0.79 fold) as compared with non-diabetic healthy control one. Levels of the liver enzymes AST and ALT were normalized with bitter melon and fenugreek treatment in a similar degree as with cidophage, suggesting an improvement in liver functions. Creatinine levels were normalized in all treated groups. Regarding to lipid profile, there were decreases in liver cholesterol, triglycerides, and LDL in diabetic rats after treatment with extracts. On the other hand, HDL levels were increased in the following order bitter melon, cidophage, and fenugreek respectively. Serum nitric oxide and malonaldehyde levels were reduced in all treated groups. Levels of the anti-oxidant GSH were increased in all treated groups. Evan's Blue extravasation test (as a measure of peripheral capillary permeability) significantly increased in the skin of diabetic animals. This effect was restored by ethanolic extracts of bitter melon, and fenugreek respectively. The diabetic group also showed delayed wound healing compared with the treated diabetic group as measured by histopathological observation. Applying the experimental extracts accelerated the rate of wound closure, indicating the beneficial role of the bitter melon and fenugreek extracts in the healing process of the diabetic wound. Histopathological examination of pancreas from diabetic rats showed shrunken islets and their shape were destroyed with infiltration of lymphocytes compared to control group. In the mean time, animals treated with the experimental extracts showed bigger and comparable islets to that of normal rats. The enlargement of islets in diabetic ani-

mals post treatment was higher in bitter melon-treated group followed by fenugreek-group.

It was concluded that the ethanolic extracts of bitter melon, and fenugreek exhibit promising and safe anti-diabetic activity especially on peripheral circulation as manifested by decreased peripheral capillary permeability and accelerated wound healing in an animal model of type-1 DM. Hence, it may be pursued for their clinical usefulness in the management of diabetes mellitus and other associated complications.

Key words: *Diabetic rats, Peripheral circulation, natural plants.*

INTRODUCTION

Diabetes mellitus (DM) is the syndrome of disturbed energy homeostasis, caused by an abnormal metabolism of carbohydrates, proteins and fats. It is the most common endocrine-metabolic disorder worldwide **(Powers, 2008)**. The most devastating complication of DM is vascular complications including poor wound healing as a result of peripheral vascular permeability dysfunction **(Nadas et al., 2009)**.

Until now, the research for new antidiabetic agents represents a challenge to medical professions. For many years, many herbs and plant products have been shown to have hypoglycemic action, among them are **fenugreek, and bitter melon**. Fenugreek seed **(Trigonella foenum-graecum L.)** has been shown to reduce glucose levels in type 2 diabetes and may help do so in type 1 (insulin dependent) diabetes **(Hannan et al., 2007)**. Momordica charantia, also is referred to as **bitter melon** or bitter gourd, is commonly known as vegetable insulin and has been used as a traditional anti-diabetic remedy for many years **(Virdi et al., 2003)**.

Most of the studies that handled these plants were focused on their action on hyperglycemia and/or insulin metabolism. However, their effects on peripheral circulation and vascular pathology are still unclear. Thus the present study was planned to investigate the effects of these plant extracts on vascular permeability in peripheral circulation in addition to their effects on nitric oxide and oxidative stress in rats with streptozotocin-induced diabetes.

MATERIAL AND METHODS

2-1: Experimental animals :

Adult male albino rats weighing 200 to 220 gm were housed in Physiology Department, Faculty of Veterinary medicine, Mansoura University. Animals were left for one week to acclimatize the place. Rats were kept in cages in a rate of six rats per cages and were provided with standard diet and water ad-libitum.

2-2: Streptozotocin-induced diabetic animal model :

Induction of diabetes was done using the diabtogenic compound streptozotocin (STZ) **(Elsner et al., 2000)**. In our study a single dose of 50 mg/kg of streptozotocin STZ (Sigma Chemical Company St. Louis, Missouri) in 0.1 M citrate buffer (0.1M Citric acid, 0.1M Trisodium citrate, pH is 4.5) was administrat-

ed intrapretoneally in a total volume of 1.0 ml. After 3 days of STZ injection, blood samples were taken from tip of the tail and hyperglyeemia was confirmed by measuring blood glucose levels directly using glucometer (One toueh technology, Roche group UK). Animals showing fasting blood glucose higher than 250 mg/dl were eonsidered diabetic and were included in the study. Treatments were given daily by stomach tube after 3 days of induction of diabetes and continued for 4 weeks. Animals were divided into the following groups (6 rats each):

Group (1): Includes healthy rats served as normal control.

Group (2): Includes rats received STZ only and served as diabetic control.

Group (3): diabetic rats received daily dose of 500 mg/kg BW of **Cidophage®.**

Group (4): diabetic rats received daily dose of **fenugreek** ethanolic extract (50 mg/kg BW).

Group (5): diabetic rats received daily dose of **bitter melon** ethanolic extract (500 mg/kg BW).

2-3: Preparation of the ethanolic extracts :

Fruits of bitter melon were cultivated in the Faculty of Agriculture-Mansoura University. Fenugreek was purchased from local commercial sources of Mansoura city. A total of 250 g of either ground dry fenugreek seeds, or ground bitter melon were extracted with 1.0 L of 95% ethanol for 5 days. The extract was evaporated to dryness in a rotavapor (Air Blow Equipment, Chennai, India) at 40-50°C under reduced pressure. A semi-solid material was obtained (15-20 g). It was stored at 0-4°C until used. When needed, the residual extract was suspended in distilled water and used in the study in the previously stated concentrations **(Senanayake et al., 2004).**

2-4: Blood sampling

After 4 weeks post STZ injection, food was withdrawn for 12 hours. The fasting animals were sacrificed and blood samples were collected into clean centrifuge tube. The blood samples were allowed to coagulate and centrifuged at 3000 rpm for 20 minutes to separate blood serum. Separated serum was stored at -20°C for subsequent biochemical analyses.

2-5: Biochemical Analyses:

Serum Glucose was determined according to **(Trinder, 1969).** Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined according to method of **Reitman and Frankel, (1957).** Determination of serum creatinine was done according to **Larsen (1972).** Serum cholesterol, HDL-cholesterol levels were determined according to **Naito (1984).** Determination of serum triglyceride was done according to **Buccolo G and David H (1973).** Serum LDL-cholesterol was determined according to **Friedewald et al., (1972).** Determination of serum reduced glutathione (GSH) was done according to **Beutler et al., (1963).** Determination of nitric oxide (NO) was done according to method of **Giustarini et al., (2004).** Serum lipid peroxide (Malondialdehyde) was determined according to **Tatsuki et al., (1997).** Serum insulin was determined by automated insulin immunoassay using Elecsys autoanalyzer (Roche Diagnostics Mannheim, Germany), according to the manufacturer's instructions **(Sapin et al., 2001).**

2-6: Measurements of Microvascular Permeability (Evans Blue Assay):

Evans blue, (a tetrasodium diazo salt) extravasation test was used to measure vascular permeability **(Verel, 1958)**. Evans blue (20 mg/kg) was injected in the caudal vein, where it rapidly binds to plasma albumin. After 10 minutes, animals were killed and samples from dorsal skin were taken for determination of the extravasated Evans blue. Half of skin sample was dried at 60°C for 24 hours, and a dry/wet weight ratio was calculated to avoid underestimation of EB dye concentration due to local edema. The other half was placed in a formamide solution (4 mL/g wet tissue) for 24 h for dye extraction. The extracted amount of EB dye was determined by spectrophotometry at 620 nm using a 96-well microplate photometer. The concentration of EB was then calculated from a standard curve and expressed as µg of EB per g of dry tissues **(Chakir et al., 1998)**.

2-7: Wound creation:

Wounds were created after three days of induction of diabetes. Under anesthesia, the back of all the rats were shaved and skin wounds were prepared (2.5 cm diameter and a depth of about 0.1 mm) **(Whitby and Ferguson, 1991; Most et al., 1996)**. Animals were sacrificed at days 3 and 28 after wound creation. Skin samples were excised, fixed in 10% formalin. Slides were stained with hematoxylin and eosin (H&E) for light microscopy evaluation.

2-8: Histopathological analysis:

Pancreas and skin wound tissues from each rat were fixed overnight in 10% buffered formalin solution and embedded in paraffin. Sections (4 _m) were prepared and stained with H&E.

2-9: Statistical analysis:

Data were analyzed by analysis of variance using the general liner model procedure of SAS **(SAS Institute, 2004)**.

RESULTS

3-1: Serum Glucose Levels :

Serum glucose levels were significantly increased in diabetic group when compared with the control one. After four weeks of treatment, glucose levels were significantly decreased in all treated groups with eidophage, bitter melon, fenugreek respectively (Table 1).

3-2: Serum insulin levels :

Serum insulin levels were signifieantly decreased in diabetic group as compared to normal one. All treatments increases insulin levels significantly; however, this increase was higher in bitter melon than eidophage and Fenugreek respectively (Table 1).

3-3: Liver Enzymes :

After Four weeks of treatment, both AST and ALT levels were signifieantly normalized by the treatment with eidophage, bitter melon, and fenugreek respectively (Tables 1).

3-4: Serum level of Creatinine :

There were signifieant increases in creatinine levels in diabetic group. Four weeks post treatment, creatinine levels were reduced in all treated groups (Table 1).

3-5: Serum Lipid Profile :

There were significant increases in levels of serum cholesterol, triglycerides, LDL, and sig-

nificant decreasc in HDL levels in diabetic group indicating a disrupting lipids metabolism. After four weeks of treatment, cholesterol, triglycerides, and LDL levels were reduced significantly in the following order bitter melon, eidophage, and fenugreek respectively (Table 2). HDL levels were significantly increased in the order bitter melon, eidophage, and fenugreek respectively (Table 2).

3-6: Free radicals and antioxidants :

There were significant increased in levels of serum nitric oxide (NO) and malonaldehyde (MDA), and significant decreased in reduced glutathione (GSH) levels in diabetic group. After four weeks of treatment, serum nitric oxide and malonaldehyde levels were significantly redueed in all treated groups (Table 3). Reduced glutathione levels were increased in all treated groups (Table 3).

3-7: Level of vascular permeability :

There was a significant increased in vaseular permeability in diabetic group as compared to normal one. After four weeks of treatment, Evans blue (EB) dye levels were significantly reduced in the following eidophage, bitter melon and fenugreek, respectively (Fig. 1).

3-8: Histopathology of the pancreas

Histological finding of normal pancreas (Fig. 2A) showed predominant exocrine pancreatic tissue composed of acini with draining ductules. Moreover, each islet was separated from the acini by reticular membrane and was arranged in anastomosing cellular plate or cords of cells, cells, D cells and F cells. Pancreatic islets of diabetic rats (Fig. 2B) revealed significant architectural disarray, which sometimes extended into the surrounding exocrine tissue. Islets were damaged, shrunken in size and infiltration of very few lymphocytes was observed.

In diabetic treated rats (Fig. 2C and 2D); the endocrine component of pancreas (islets of Langerhans) retained normal histology with a scattered nodules within the substanees of the exocrine pancreas and exhibited no pathological changes (No signs of panereatitis).

3-9. Histopathological results of skin wound :

a. Three days post wound creation :

In normal control group, the created wound was showed filling of the wound gap with blood clot (fibrin, neutrophils and blood platelcts). The inflammatory cells (mainly neutrophils) increased by time to peak at three days. Later on, macrophages started to replace the neutrophils (Fig. 3A). The inflammatory response covered with thick crust (necrotic inflammatory eells, tissue and bacterial colony). The re-epithellalization was seen starting from the wound edges. In diabetic control group, the created wound was showed less inflammatory cells as compared with non diabetic one (Fig. 3B). The wound of diabetic rat treated with Fenugreek showed increases in number of inflammatory cells as compared with diabetic group (Fig. 3C). The wound healing of diabetic rat treated with Bitter melon showed inflammatory phase with inflammatory cells more than which was observed in group 2 and 3 but still less than the control (Fig. 3D).

b. Twenty-eight days after wound creation

The created wound in the control group

showed mature epidermis with epidermal papillae besides mature fibrous tissues with few numbers of inflammatory cells (Fig. 4A). In the diabetic group, the created wound was showed complete re-epithelialization of the dermis with absence of epidermal papillae. Crust remnant was still observed. The dermis showed less mature granulation tissue infiltrated with numerous inflammatory cells (Fig. 4B). The wound of diabetic rat treated with Fenugreek was showed complete re-epithelialization with apparently normal epidermal thickness. Granulation tissue infiltrated with macrophages was seen in dermis (Fig 4C). The wound healing of diabetic rat treated with Bitter melon showed same picture of previous group except presence of epidermal papillae, more collagen fibers and less inflammatory cells (Fig. 4D).

DISCUSSION

Diabetes mellitus complications include cardiovascular disease, chronic renal failure, retinal damage, and poor wound healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, possibly requiring amputation **(Cobenas and Spizzirri, 2003)**. In diabetes, hyperglycemia often leads to various peripheral vascular complications **(Amini and Parvaresh, 2009)**. The present investigation showed that administration of ethanolic extract of bitter melon (BM) in a dose of (500 mg/kg BW) normalized fasting blood glucose levels to 1.17 fold changes of non-diabetic healthy control rats in comparison to 6.22 folds increases in STZ diabetic untreated rats. Fenugreek was reduced the blood glucose levels (1.33 fold) as compared with non-diabetic healthy control rats.

Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level when it elevated after meals. In the present investigation, serum insulin levels were significantly reduced with induction of diabetes. Treatment with clidophage and bitter melon were significantly enhanced insulin hormone secretion after 4 weeks of treatment. Whereas, Fenugreek was normalized the effects of STZ injection on insulin secretion to lesser extent. These data confirms with theoretical mechanism of bitter melon in normalizing blood glucose levels by enhancing insulin secretion **(Nerurkar et al., 2008; Shih et al., 2009)**.

The liver is an important insulin-dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during diabetes **(Doi et al., 2007; Inoue et al., 2008)**. In the present study, induction of diabetes by STZ in rats induced elevated liver enzymes ALT and AST. These results are in accordance with previously studies reported that the increase in ALT activities in diabetes were usually due to hepatocellular damage and was usually accompanied by an increase in AST activities **(Pepato et al., 1999)**. Moreover, the AST and ALT activity has been used as an indicator of liver functions **(Ezekwe and Martin, 1980)**. In the present study after four weeks of treatment, both AST and ALT levels were normalized in bitter melon and fenugreek in a similar degree as with clidophage. The decrease in AST and ALT in treated groups towards near normal levels is an evidence of the prevention of cellular and tissue damage under diabetic conditions. These results are in agreement with

previous study which reported that bitter melon significantly improves liver functions **(Badria et al., 2006)**.

Liver also participates in the uptake of oxidation and metabolic conversion of fatty acids, the synthesis of cholesterol and phospholipids and the secretion of specific classes of serum lipoproteins. In diabetes, fatty acids are increasingly taken up by the liver and, after esterification with glycerol phosphate, they are deposited as triglycerides. As a result, diabetic liver steatosis develops **(Martocchia et al., 2008)**. In the present investigation, there was an increase in serum cholesterol level of diabetic rats which in agreement with previous studies reporting that the imbalance in lipid profile observed in DM could be due to increased cholesterogenesis **(Kwong et al., 1991)**. The present study showed a decrease in liver cholesterol, triglycerides, and LDL in diabetic rats after treatment with bitter melon and fenugreek treatments in a similar degree as with cidophage treatment. This reduction may be attributed to increased clearance and decreased production of the major transporters of endogenously synthesized cholesterol and triglycerides. Whereas, HDL levels were increased in the order from bitter melon, cidophage, and fenugreek respectively. These data are in agreement with other studies reporting the ability of bitter melon **(Chaturvedi et al., 2004)** and Fenugreek **(Sharma et al., 1990)** in modulating lipid profile.

Diabetes mellitus affects the kidney and is the leading cause of diabetic nephropathy **(Iwasaki et al., 1998)**. Several studies have shown the presence of lipid deposits in the kidney of diabetic human may play an important role in the pathogenesis of diabetic kidney disease **(Guijarro et al., 1995)**. Levels of serum creatinine reflect the kidney functions **(Jafar et al., 2005)**. It has been reported that the rate of glomerular cell (podocyte) apoptosis is increased in rats with streptozotocin-induced diabetes mellitus **(Menini et al., 2007)**. In agreement with this study, in the present investigation, there was a significant increase in levels of serum creatinine after STZ injection. Four weeks post-treatment, creatinine levels were reduced in all treated groups. These results are in agreement with **Hamden et al., (2010)** who found fenugreek could reduce creatinine in alloxan-induced diabetes. Moreover, our results agree with other researchers who found bitter melon reduces serum creatinine and kidney weight and improves glomular filtration **(Shetty et al., 2005)**.

In diabetes, there is an increase the production of reactive oxygen species (ROS) **(Kakkar et al., 1995; Bhatia et al., 2003)**. ROS could be effectively eliminated by several intracellular and extracellular anti-oxidative systems **(Lapshina et al., 2006)**. When the generation of ROS exceeds anti-oxidant defense mechanisms, these unstable molecules interact with biologic macromolecules such as lipids, proteins and DNA and lead to structural changes as well as functional abnormalities. It has been reported that increased oxidative damage [measured as levels of malondialdehyde (MDA) or its product thiobarbituric reactive substances (TBARS)] and lowered antioxidant defenses (measured as activities of antioxidant enzymes, vitamin E or C) were the underlying mechanism of diabetes complications. An increase in TBARS level

promotes DNA and protein alterations including changes in the enzyme activities implicated in lipid metabolism and free radicals scavenging process **(Kakkar et al., 1995; Watanabe et al., 1999)**. Similarly, increased levels of nitric oxide end products have been reported in patients of DM **(Bhatia et al., 2003)**. Marked production of NO leads to pathological changes in various physiological systems **(Colasanti and Suzuki, 2000; Perreault and Marette, 2001)** leading to peripheral vascular diseases **(Maejima et al., 2001; Behrendt and Ganz, 2002)**. Glutathione, the primary endogenous antioxidant, has a multifaceted role in antioxidant defense and it is a direct scavenger of free radicals as well as a Co-substrate for peroxide detoxification by glutathione peroxidases **(Winterbourn, 1995)**. In agreement with these studies, we found that MDA and NO were increased in comparison to control group. Moreover, in diabetic group reduced glutathione was decreased indicating a disruption in the balance of the redox system. Four weeks post-treatment, serum nitric oxide and malonaldehyde levels were reduced in all treated groups bitter melon, cidophage, and fenugreek.

In diabetes, several mechanisms participates in the pathologic changes observed in endothelial cells, including hyperinsulinemia, increased oxidative stress, and inactivation of NO **(Joshua et al., 2005; de Jager et al., 2006; Picchi et al., 2006)**. Early in the course of diabetes, intracellular hyperglycemia causes abnormalities in blood flow and increased peripheral vascular permeability **(Brausewetter et al., 2001; Gordon, 2004)**. The increase in capillary permeability is a sign for the microvascular dysfunction at the arteriolar and capillary level resulting in both structural as well as functional changes especially in peripheral organs, accounting for a group of disorders called peripheral vascular disease (PVD) in which obstruction of large arteries in the arms and legs may occur **(Abaci et al., 1999)**. In the present investigation, vascular permeability to albumin was assessed at the end of the experiment using Evans' Blue dye **(Hulthen et al., 1995)**. We found a significant increase of Evans blue (EB) leakage primarily in skin of STZ-diabetic animals, this finding is in agreement with previous studies **(Viberti, 1983; Lawson et al., 2005)**. Four weeks post-treatment, dye extravasation levels were reduced in the following order cidophage, bittermelon, and fenugreek respectively. However, cidophage and bittermelon appears to exert higher but similar effects in reducing capillary permeability than fenugreek. Other studies also reported the ability of some other plant products in normalizing capillary permeability **(Nakajima et al., 2001)**.

PVD is a common and severe complication of diabetes that is characterized by damage to or blockage in the blood vessels distant from heart.. In the diabetic foot, the thickened basement membrane is believed to impair migration of leukocytes as well as blood flow through the capillaries. These changes, and an impaired neurogenic vasodilatory response, results in an inability to achieve a normal hyperemic response needed after foot injury and increase the risk of infection **(Bild et al., 1989)**. These findings account for the 15-fold increase in risk for lower extremity amputation seen in diabetic patients **(Pinzur et al., 2005)**. It has been reported previously

that cutaneous wounding results in a decrease in antioxidant status as a result of the production of ROS. One research study reported that any diabetic ulcer that lasts for more than 4 weeks is usually an indication of worse outcome and may lead to amputation **(Jeffcoate et al., 2004)**. In the present study, the diabetic group showed delayed wound healing compared with the treated diabetic group as measured by histological observation. These findings are in agreement with earlier studies **(Kawanabe et al., 2007; Qiu et al., 2006)**. The administration of Bitter melon and Fenugreek extract was found to accelerate wound closure. Moreover, we found that the treated group with fenugreek and Bitter melon showed increased granulation tissue as compared with the non-treated group that may be due to stimulation epithelial cell proliferation and migration to wound area. This was evident in the histologieal studies indicating the beneficial role of the bitter melon and fenugreek extracts on accelerating wound healing. These observations are in agreement with other studies reporting that if the histopathology of the wound shows rapid epithelial development, it may be considered as a positive sign **(Seraralan et al., 2007)**.

We further investigated the effects of the different extracts on the pancreas histology. Diabetes in the present study was indueed by injection of STZ that targets pancreatic β-cells via the glucose transporter (GLUT2) and causes alkylation of DNA, thereby damaging the pancreatic β-cells **(Elsner et al., 2000; Szkudelski, 2001)**. In agreement with these studies, the histopathological examination of pancreatic sections from diabetic group showed shrunken islets and their shape were destroyed with infiltration of lymphocytes. In contrast, treated animals showed more islets and they become comparable to normal rat islets, although there were individual differences. Enlargement of islets in diabetic animals post treatment was higher in bitter melon-treated group than fenugreek-treated group. These data are in agreement with previous studied showed ability of bitter melon **(Teoh et al., 2009)** and fenugreek **(Chevallier, 2000)** in accelerating wound healing.

CONCLUSIONS

It was concluded that the ethanolic extracts of bitter melon, and fenugreek exhibit promising and safe anti-diabetic activity especially on peripheral circulation as manifested by decreased vascular capillary permeability and accelerated wound healing in an animal model of type-1 DM. Hence, it may be pursued for their clinical usefulness in the management of diabetes mellitus and other associated complications.

Table (1): Effect of different treatments on studied biochemical parameters.

Group	Glucose mg/dl	Insulin uU/mL	AST IU/L	ALT IU/L	Creatinine mg/dL
Normal control	98.33 ± 4.84^{d}	5.29 ± 0.005^{a}	30.66 ± 1.20^{d}	8.33 ± 1.86^{a}	0.54 ± 0.08^{c}
Diabetic control	611.33 ± 7.26^{a}	2.11 ± 0.06^{e}	81 ± 2.08^{a}	38.33 ± 2.60^{a}	1.56 ± 0.09^{a}
Cidophage	106.33 ± 4.80^{d}	4.61 ± 0.16^{b}	31 ± 2.08^{d}	12 ± 0.58^{de}	0.61 ± 0.01^{c}
Fenugreek	130.33 ± 6.48^{c}	4.18 ± 0.04^{c}	35.33 ± 0.33^{cd}	13.66 ± 0.67^{cd}	0.6 ± 0.06^{c}
Bitter melon	115 ± 7.09^{cd}	4.50 ± 0.17^{b}	32 ± 3.61^{d}	13 ± 1.15^{cd}	0.57 ± 0.03^{c}
LSD	19.82	0.36	7.015	4.289	0.1666

Values are mean ±S.E, Values with different letters in each column are significantly different at (P< 0.05).

Table 2: Effect of different treatments on lipid profile parameters.

Group	Cholesterol mg/dl	Triglycerides mg/dL	LDL mg/dL	HDL mg/dL
Normal control	114.33 ± 4.37^{b}	119 ± 2.08^{b}	48.53 ± 4.65^{b}	42 ± 0.90^{a}
Diabetic control	204.67 ± 5.49^{a}	245.67 ± 6.39^{d}	141.51 ± 6.23^{a}	14.03 ± 2.04^{d}
Cidophage	97.33 ± 4.91^{cd}	111 ± 5.29^{bc}	34.61 ± 4.46^{c}	$40.53\ 0.63^{ab}$
Fenugreek	106 ± 4.04^{bcd}	118 ± 4.16^{b}	45.10 ± 4.68^{cbd}	37.3 ± 1.48^{bc}
Bitter melon	93.67 ± 2.85^{d}	105 ± 2.65^{c}	31.18 ± 3.28^{d}	41.48 ± 1.02^{a}
LSD	13.183	12.535	14.35	3.835

Values are mean ±S.E, Values with different letters in each column are significantly different at (P< 0.05).

Table (3): Effect of different treatments on oxidants and anti-oxidant parameters.

Group	NO umol/L	MDA ng/mL	GSH mmol/L
Normal control	1.26 ± 0.10^{c}	1.21 ± 0.13^{b}	34.59 ± 1.23^{a}
Diabetic control	25.43 ± 2.39^{a}	2.7 ± 0.09^{a}	17.03 ± 0.65^{c}
Cidophage	4.64 ± 0.18^{b}	1.36 ± 0.03^{b}	34.24 ± 0.56^{a}
Fenugreek	3.06 ± 0.09^{bc}	1.35 ± 0.02^{b}	33.36 ± 0.02^{ab}
Bitter melon	3.94 ± 0.20^{bc}	1.36 ± 0.06^{b}	33.65 ± 1.10^{ab}
LSD	2.776	0.205	3.486

Values are mean ±S.E, Values with different letters in each column are significantly different at ($P < 0.05$).

Table 4: Fold change of the studied biochemical parameters after the different treatments as compared to normal control values .

	STZ	Cidophage	Bitter melon	Fenugreek
Glucose	6.22	1.08	1.17	1.33
Insulin	0.40	0.87	0.86	0.79
AST	2.64	1 01	1.04	1.15
ALT	4.60	1.44	1.56	1.64
Creatinine	2.91	1.13	1.06	1.11
Cholesterol	1.79	0.85	0.82	0.93
Triglycerides	2.06	0.93	0.88	0.99
HDL	0.33	0.97	0.99	0.89
LDL	2.92	0.71	0.64	0.93
GSH	0.49	0.99	0.97	0.96
NO	20.18	2.10	2.33	2.43
Permeability	9.60	1.75	1.94	2.66

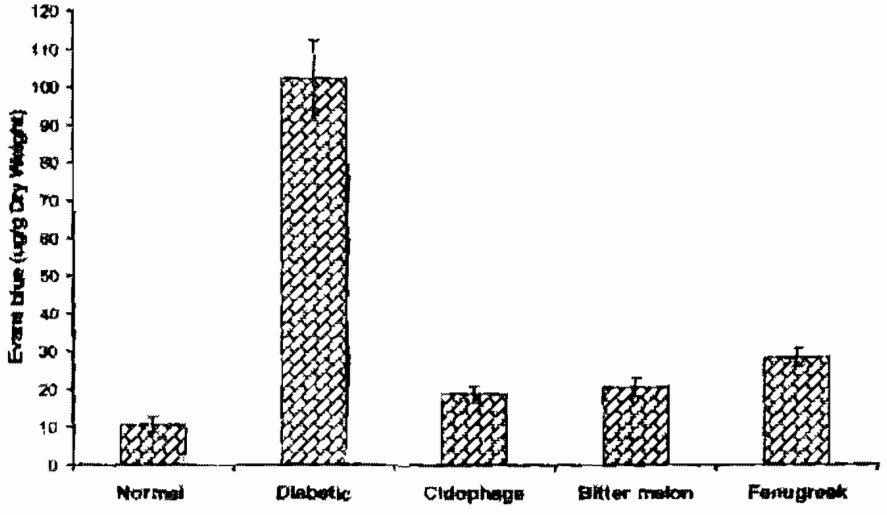

Figure 1: Vascular permeability as indicated with Evans Blue assay in skin.

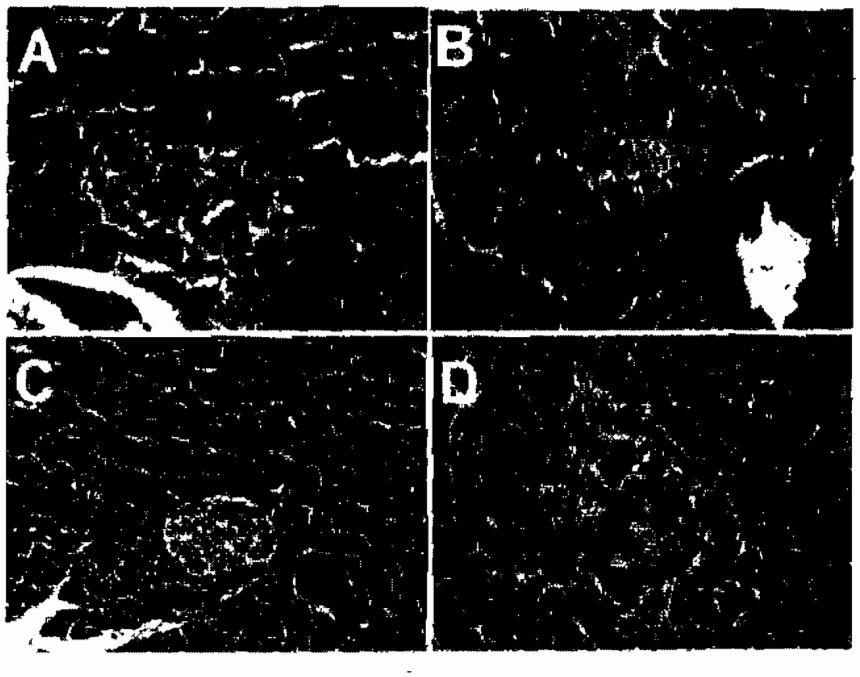

Figure 2: Photomicrographs of pancreas show: A. normal panereas with normal acini (Ac) and islets (IL) containing β-cells. B: pancreas of diabetic control rats with shrunken islets. C: pancreas of diabetic rats treated with 50 mg/kg b.wt of Fenugreek. D: pancreas of diabetic rats treated with 500 mg/kg b.wt of Bitter melon (H & E x 10).

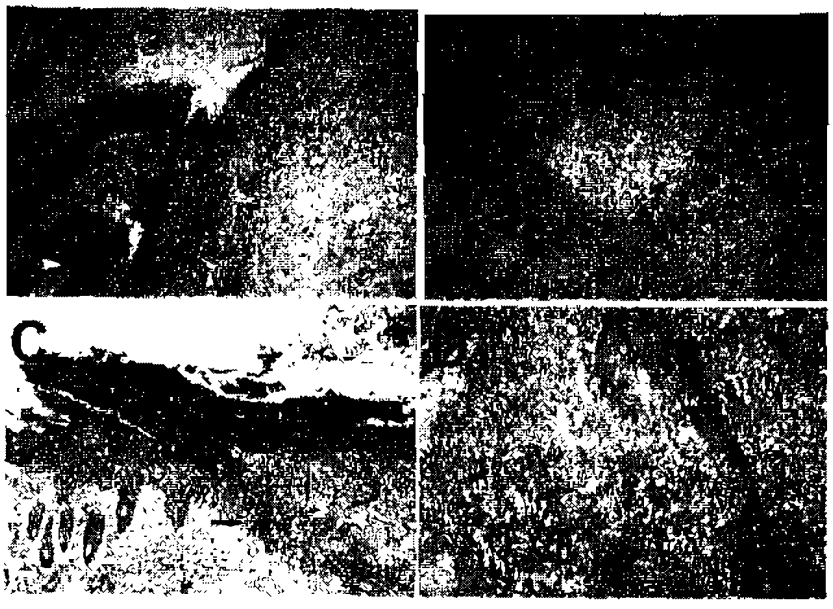

Figure 3: Photomicrograph of skin sections 3 days post wound creation show A: skin of normal control rat showing crust (arrow head) covering blood clot represented by fibrin (arrow) and neutrophils (yellow arrow head) and blood platelets besides re-epithelialization (corrugated arrow). B: Skin of diabetic rat showing less inflammatory cells in inflammatory phase. C: Skin of diabetic rat treated with Bitter melon thick crust (arrow head) granulation tissue (thin arrow) and re-epithelialization (thick arrow). D: Skin of diabetic rat treated with Fenugreek showing increase number of neutrophils (corrugated arrow), fibrin (thin arrow) besides re-epithelialization (thick arrow) H&E, x 10.

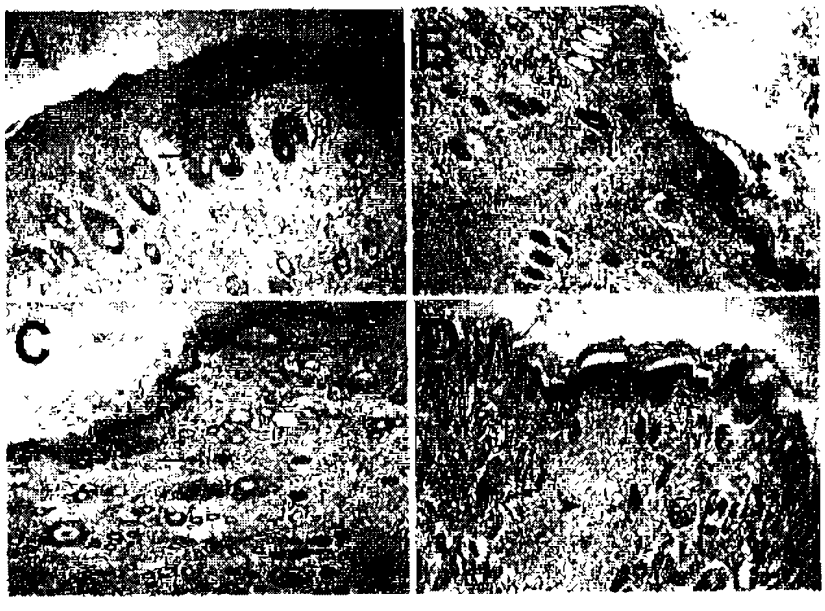

Figure 4: Photomicrograph of skin sections 3 days post wound creation show A: skin of normal control rat showing crust (arrow head) covering blood clot represented by fibrin (arrow) and neutrophils (yellow arrow head) and blood platelets besides re-epithelialization (corrugated arrow). B: Skin of diabetic rat showing less inflammatory cells in inflammatory phase. C: Skin of diabetic rat treated with Bitter melon thick crust (arrow head) granulation tissue (thin arrow) and re-epithelialization (thick arrow). D: Skin of diabetic rat treated with Fenugreek showing increase number of neutrophils (corrugated arrow), fibrin (thin arrow) besides re-epithelialization (thick arrow) H&E, x 10.

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الملخص العربى

بعض التأثيرات الفسيولوچية لكل من الشمام المر والحلبة فى الجرذان المصابة بمرض البول السكرى مقارنة بالعلاج بعقار السيدوفاج

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تم فى هذه الدراسة إعطاء المستخلصات الكحولية لكل من نبات الشمام المر والحلبة فى الجرذان المصابة بمرض البول السكرى التجريبى، تم إحداث مرض السكر باستخدام مادة الستربتوزوتوسين وتم إعطاء مستخلصات نبات الشمام المر والحلبة عن طريق الفم فى الجرعات الأتية على الترتيب 500 و50 ملليجرام لكل كيلوجرام من وزن الجسم لمدة 4 أسابيع ومقارنة ذلك بالمجموعة الضابطة، وقد وجد أن إستخدام المستخلصات النباتية لهذه النباتات أدى لخفض مستويات السكر إنخفاضاً كبيراً على الترتيب التالى : سيدوفاج () ، الشمام المر () ، وحلبة () أضعاف الجرذان الغير مصابة بالبول السكرى، وقد لوحظ زيادة فى إفراز الأنسولين بعد أسابيع من العلاج بالسيدوفاج () الشمام المر () ، والحلبة () أضعاف الجرذان بالمجموعة الضابطة، كما وجد هناك تحسن ملحوظ فى مستويات إنزيمات الكبد فى كل العلاجات المستخدمة حسب الترتيب التالى السيدوفاج، الشمام المر، والحلبة ، ولوحظ أيضاً إنخفاض فى معدلات الكولسترول، الجليسريدات الثلاثية، والبروتينات الدهنية منخفضة الكثافة فى الجرذان المصابة بداء السكرى بعد العلاجات التجريبية تقارن مثيلاتها بعد العلاج بالسيدوفاج، من ناحية أخرى، كانت هناك زيادة فى مستويات البروتينات الدهنية عالية الكثافة بعد العلاج حسب الترتيب التالى الشمام المر، سيدوفاج، والحلبة، وانخفضت مستويات الكرياتينين فى كل العلاجات المستخدمة، كما لوحظ انخفاض مستويات أكسيد النيتريك والمالون داى الدهيد، وكانت مستويات الجلوتاثيون المختزل (كمقياس لنشاط مضادات الأكسدة) زائدة بعد العلاجات وكانت مستويات نفاذية الشعيرات الدموية الطرفية فى زيادة بالجرذان المصابة بالسكرى، ولكن لوحظ انخفاض فى نفاذية الأرعية الدموية بالعلاج بالسيدوفاج، الشمام المر، والحلبة على التوالى، وأظهرت المجموعة المصابة بالبول السكرى تأخر إلتئام الجروح مقارنة مع المجموعة الضابطة، ولكن إستخدام هذه العلاجات التجريبية قد زاد من معدل إلتئام الجروح مما يؤكد على الدور الفعال لكل من الشمام المر والحلبة فى عملية إلتئام الجرح السكرى.

كما أظهرت الدراسات النسيجية على البنكرياس فى الجرذان المصابة بداء السكرى تقلص وتدمير جزر لانجر هانز مقارنة مع المجموعة الضابطة وفى المقابل، أظهرت نتائج الحيوانات المعالجة بمستخلصات النباتات زيادة فى حجم جرز لانجرهانز.

لذا نستنتج من هذه النتائج أن إستخدام المستخلص الإيثانولى من الشمام المر، والحلبة مفيد فى علاج السكرى، خاصة فى تنشيط الدورة الدموية الطرفية وزيادة معدل إلتئام الجروح.

ونوصى هذه الدراسة باستخدام هذه الخلاصات الطبيعية للوقاية أو للعلاج لمرضى البول السكرى.