
Effect of fenugreek seeds and cinnamon bark aqueous extracts on liver and kidney functions in male diabetic rats

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Abstract:

Trigonella foenum-graecum (Fenugreek) seeds and *Cinnamomum zeylanicum* (Cinnamon) bark have long been utilized for culinary purposes prior to being recognized as a hypoglycemic agents. Here we tested the hypothesis that administration of fenugreek seeds and cinnamon bark modulates the adverse effects of diabetes on blood glucose, liver enzymes and kidney functions of diabetes induced by alloxan in male rats by using their aqueous extracts. Induction of diabetes significantly increased the blood glucose associated with a significant depression in the activity of liver enzymes and kidney functions. The animals is divided into 6 groups each contains 6 rats: normal group, diabetic group, two diabetic groups treated separately with low dose and high dose of aqueous fenugreek extract and two diabetic groups treated separately with low dose and high dose of aqueous cinnamon extract. Compared with untreated diabetic group, there were a significant decrease in F.B.G., ALT, AST, ALP, Urea and Creatinine levels in treated diabetic rats after administration with extracts and that effects were depend on doses, and also cinnamon had better effects than fenugreek.

Key Words: Fenugreek, Cinnamon, Extracts, Alloxan, Diabetes, Liver enzymes, Kidney functions.

Introduction:

Diabetes Mellitus (DM) is one of major metabolic disorders, it's characterized by high blood glucose levels⁽¹⁾. The number of people living with diabetes is expected to rise from 366 million in 2011 to 552 million by 2030. 80% of people with diabetes live in low and middle income countries⁽²⁾. It's generally considered that hyperglycemia is the major factor in the pathogenesis of diabetic complications⁽³⁾. Hyperglycemia and the effects of diabetogenic agent Alloxan in experimental diabetes increase the generation of free radicals that may lead to liver cells damage^{(4),(5)}, and that causes to impairment of liver function⁽⁶⁾. Impairment of kidney function is a

prominent feature of diabetes, Over time diabetic nephropathy will develop⁽³⁾.

Medicinal plants play an important role in the management of diabetes especially in developing countries where resources are meager^{(7),(8)}. Presently, there is an increased demand to use natural products with antidiabetic activity⁽⁹⁾ due to the secondary failure rates and side effects associated with the use of insulin and oral hypoglycemic agents^{(9),(6)}.

Trigonella foenum-graecum (Fenugreek) seeds and aromatic bark of *Cinnamomum zeylanicum* (Cinnamon) are used worldwide for culinary purposes, and

also are used as herbal medicine in many parts of the world. Various reports have demonstrated that fenugreek seeds and cinnamon bark can modulate hyperglycemia in experimental diabetic animals^{(10),(11)}.

Therefore, the aim of this study was to find if the administration of the aqueous extracts of *T. foenum-graecum* and *C. zeylanicum* could have beneficial effects on some physiological parameters of liver and kidney functions in alloxan-induced diabetic male rats after 6 weeks of administration of extracts.

Materials and methods:

Plant materials:

Trigonella foenum-graecum seeds and *Cinnamomum zeylanicum* bark were purchased from the local herbal market.

Aqueous Extracts Preparation:

Fenugreek Seeds Extract (FSE) preparation:

Fenugreek seeds were cleaned, washed, dried and finely powdered. Each 4g of seeds powder were macerated in 100 ml Normal Saline for 24 hours. Then, the extract was administered orally to rats at low dose (8 mL / 100 g BW) and high dose (1.8 mL / 100 g BW)⁽¹²⁾.

Cinnamon Bark Extract (CBE):

Cinnamon bark was powdered, each 50 g of powdered cinnamon bark was macerated in 100 ml Normal Saline for 48 h and shake each 6 h. Then the mixture was filtered. Filtration was evaporated under vacuum at (-70°C) by using vacuum evaporation and the extract was collected in dark bottle. Extract was mixed with normal saline to fresh orally administration

of rats at low dose (100 mg) and high dose (300 mg) of the extract / Kg BW dissolved in 5 mL of normal saline^{(13),(14),(15)}.

Chemicals:

Alloxan Monohydrate were purchased from S D Fine-Chem Limited Co, India. Glucose, ALT, AST, ALP, Urea and Creatinine kits were purchased from Biocon company - Germany, Biomaghreb company - Tunisia and Spinreact company - Spain.

Experimental animals:

Thirty six adult male albino rats weighing 180-230 g obtained from The Animal House, Faculty of Science - Sebha University. All rats were housed in a temperature controlled animal room ($24 \pm 1^\circ\text{C}$) with a 12 h light / 12 h dark cycle and free access to water and food. All animals fed on basal diet and water *ad libitum*.

Induction of diabetes:

Male rats were fasted for 12 h and then diabetes was induced by a single intraperitoneal injection of alloxan at a dose of 150 mg/kg body weight at a concentration of 30 g dissolved in 1 L of a freshly prepared normal saline. After injection, all animals were fasted for 12 h^{(11),(5)}. After 3 days, the fasting blood glucose levels were measured from tail blood samples by using an electronic glucometer (Accu-Chek, Germany). Animals with blood glucose levels more than 270 mg/dL were considered diabetic and used for the experiment⁽¹⁶⁾.

Experimental design:

Male rats were divided into 6 groups of 6 each as follows:

- Group I: Normal control rats (Non-diabetic normal rats).
- Group II: Diabetic control rats (Untreated diabetic rats).
- Group III: Diabetic rats treated daily with low dose of FSE.
- Group IV: Diabetic rats treated daily with high dose of FSE.
- Group V: Diabetic rats treated daily with low dose of CBE.
- Group VI: Diabetic rats treated daily with high dose of CBE.

The experiment was continued for a period of 6 weeks⁽⁴⁾.

Blood sampling:

After 6 weeks, the rats were fasted for 12 h before blood sampling. Blood samples were collected from the heart after anesthetization and vivisection animals (heart puncture method) in tubes contain heparin⁽¹⁷⁾.

Measurement of parameters:

Collected samples were kept undisturbed in room temperature for 20 minutes. Plasma samples were separated by centrifugation by using centrifuge at 4000 rpm for 4 minutes and then collected for different biochemical analyses of Fast Blood Glucose (F.B.G.), liver enzymes: Alanine Amino Transferase (ALT), Asparatate Amino Transferase (AST) and Alkaline Phosphatase (ALP) and kidney functions parameters: Urea and Creatinine. Biochemical parameters were done by standard methods by using commercial kits

(supplied reagents) and Spectrophotometer^{(9),(4)}.

Statistical analysis:

The results were analyzed for statistical significance by one way ANOVA (Analysis of Variance) test by using computerized software SPSS to analyze differences among groups that were considered statistically significant at $P < 0.05$. Data are expressed as $M \pm SD$ (Mean \pm Standard Deviation)^{(17),(16)}.

Results and Discussion:

The mean values of F.B.G., ALT, AST, ALP, Urea and Creatinine in all experimental groups were analyzed and presented in Table (1). In this study there was a significant ($P < 0.05$) increasing in the levels of F.B.G., ALT, AST, ALP, Urea and Creatinine in diabetic rats as compared to normal rats.

Alloxan is a diabetogenic agent which induces "chemical diabetes" in a wide variety of animal species by rapid destruction of pancreatic β -cells and its administration to rats increases the blood glucose levels^{(4),(5)}. Hyperglycemia and alloxan increase generation of free radicals by glucose auto-oxidation that may leads to liver cells damage⁽⁵⁾ and impairment of kidney function is a prominent feature of diabetes due to insulin deficiency⁽³⁾ that decreases protein content in muscular tissue by proteolysis that leads to the formation of large amount of ammonia which is eventually converted to urea. The breakdown of amino acids during gluconeogenesis in the liver results in increased production of urea^{(18),(19)}.

Table-1: Effect of different doses of aqueous extracts of Fenugreek seeds and Cinnamon bark on F.B.G., ALT, AST, ALP, Urea and Creatinine levels of diabetic rats.

G \ P	F.B.G. Mg/dL	ALT U/L	AST U/L	ALP U/L	Urea mg/dL	Creatinine mg/dL
Group I	91.3 ± 6.457	44.83 ± 1.472	78.5 ± 5.01	60.67 ± 2.58	22.0 ± 1.41	0.755 ± 0.044
Group II	482.1 ± 37.74*↑	69.83 ± 2.787*↑	116.83 ± 4.75*↑	98.67 ± 2.34*↑	44.83 ± 1.94*↑	1.47 ± 0.082*↑
Group III	471.12 ± 41.57	68.5 ± 2.345	106.33 ± 9.33*↓	97.0 ± 2.83	42.83 ± 1.72	1.44 ± 0.029
Group IV	337.48 ± 43.31*↓	66.67 ± 1.366*↓	114.5 ± 4.461	86.17 ± 1.72*↓	34.67 ± 2.07*↓	1.28 ± 0.034*↓
Group V	473.98 ± 45.55	64.0 ± 3.899*↓	93.33 ± 1.862*↓	92.83 ± 1.94*↓	41.67 ± 1.97*↓	1.36 ± 0.037*↓
Group VI	193.5 ± 21.53*↓	50.83 ± 2.137*↓	81.0 ± 2.098*↓	72.83 ± 3.55*↓	26.33 ± 1.03*↓	0.87 ± 0.051*↓

*Significant Differences (P<0.05). - Increase. - Decrease.

Administration of different doses of FSE and CBE decreased F.B.G., ALT, AST, ALP, Urea and Creatinine levels in diabetic rats as compared to untreated diabetic rats and that effects is dependent on doses. The effects were significant (P<0.05) in groups IV, V and VI to ALT, ALP, Urea and Creatinine levels but in groups IV and VI to F.B.G. levels and in groups III, V and VI to AST levels.

Comparative effects of different doses of extracts on liver and kidney functions showed that high dose of CBE has highest effects as compared to other doses of extracts and the levels in Group VI was nearly normal levels in group I.

The present study showed that FSE and CBE significantly (P<0.05) alleviated most signs of DM including hyperglycemia and impairment of liver and kidney functions indices resulting from experimentally induced diabetes.

The ability of fenugreek to modulate glucose levels in diabetic rats and to

alleviate the adverse effects of DM on kidney and liver functions is steady with the findings of other studies. Previous studies have shown that fenugreek exhibited anti-hyperglycemic effect and also helped to repair the kidney and liver damage in diabetic rats^{(4),(11),(20),(21)}.

The mechanism of action of anti-hyperglycemic effect of fenugreek isn't fully understood and has been attributed to seeds content of dietary fibers that help in reduce the rate of glucose absorption and may also delay gastric emptying, thereby prevent the rise in blood sugar levels following a meal, fenugreek seeds caused inhibition of glucose transport as the seeds contain of pectin that forms a colloid suspension when hydrated, which can decrease the rate of gastric emptying and slows carbohydrate absorption^{(13),(22),(23),(24)}. The hypoglycemic effect of fenugreek was also demonstrated by their effects on the metabolic enzymes of carbohydrate metabolism⁽²²⁾. And also may be due to the major existence of 4-hydroxyisoleucine

which stimulates insulin secretion from pancreas. It may be due to the regeneration of β -cells^{(25),(26)}.

In previous studies, the Cinnamon effectively reduced blood glucose levels in diabetic rats^{(9),(10)}. The mechanism of action may be has been attributed to cinnamon bark content of chromium that enhances insulin activity by increasing insulin receptor sensitivity and then facilitates binding between insulin and its receptors that follow by increasing in the cellular glucose intake^{(27),(28)}. The therapeutic role of aqueous cinnamon extract was also demonstrated by increase Phosphatidyl Inositol-3-kinase (PI-3-kinase) activity⁽²⁹⁾, that causes to activate GLUT-4 and then enhancing cellular glucose intake⁽³⁰⁾. Administration of cinnamic acid and its derivatives leads to activate glucose transport via increasing of GLUT-4 mRNA levels and then increasing numbers of GLUT-4 that enhances glucose transport⁽³¹⁾.

Numerous studies demonstrated that a variety of plant extracts effectively repair impairment of liver and kidney functions that is a prominent feature of diabetes^{(32),(33),(34)}.

Previous changes in serum ALT, AST, ALP, Urea and Creatinine concentrations strongly suggested impairment of liver and kidney functions in diabetic rats due to diabetic induction.

The augmentation in ALT, AST and ALP enzymes levels may be due to the hepatotoxic effect of alloxan or maybe a result following hepatic necrosis that leads to liver cells damage^{(4),(5)}. Therefore, increase in liver enzymes in blood may be mainly due to the leakage of these enzymes from the liver cytosol into the blood

stream⁽³⁵⁾. Hyperglycemia also increases the generation of free radicals by glucose auto-oxidation that maybe lead to liver cells damage. The increase in oxygen free radicals in diabetes could be primarily due to the increase in blood glucose levels and secondarily due to the effects of diabetogenic agent alloxan and streptozotocin^{(5),(36)}. Alloxan causes various pathological changes were dilatation and severe congestion of central veins and sinusoids necrotic areas of hepatocytes⁽⁴⁾. Significant increase in urea and creatinine levels was observed in diabetic rats, which attributed to increased protein catabolism⁽³⁴⁾ and to glomerular or tubular destructive changes. The pathology of kidney appeared due to increment of free radicals as dilatation and severe congestion of blood vessels, Majority of convoluted tubules cloudy swelling, contained hyaline cast in their lumen. Diffuse extravagations of red blood cells between renal tubules. The glomerular tuft were congested, atrophied and some of them were swollen^{(3),(4)}.

In fenugreek treated diabetes significant decrease was noticed in ALT, AST, ALP, urea and creatinine levels. Fenugreek has an extremely beneficial role in overcoming the occurred adverse effects of diabetes, which is probably through its antioxidant properties and highly nutritional values^{(37),(38)}, such as alkaloids that suppress the oxidative stress together with converting liver and kidney pathology caused by diabetes to normal pattern⁽³⁹⁾. An improvement in kidney structure and appearance occurred in fenugreek treated rats. The involvement of free radicals in alloxan nephrotoxicity may be normalize by fenugreek due to fenugreek antioxidant property^{(4),(40)} which repairs liver and kidney damage and improves organ

functions^{(4),(41)}. So phenolic components of fenugreek makes it a radical scavenger for alternations induced by alloxan⁽⁴⁾.

Treatment of diabetic rats with *C. zeylanicum* extract caused reduction in ALT, AST, ALP, urea and creatinine levels compared to diabetic group. The possible mechanism of this action could be related to antioxidant components that aid to recover from impaired metabolism of glucose and have proven free radical scavenging repairs kidney damage and improves organ functions⁽³⁶⁾. So cinnamon has extremely protective effects against oxidative stress in diabetic rats^{(42),(43)}.

Conclusion:

The results of this study indicate that aqueous extracts of Fenugreek (*T. foenum-graecum* L.) seeds and Cinnamon (*C. zeylanicum*) bark possess hypoglycemic effects and also modulate the negative effects of diabetes on liver enzymes and kidney functions parameters in Alloxan-induced diabetic male rats and suggest that these plants may be an excellent adjuvant support in the therapy of diabetes and its complications.

تأثير المستخلص المائي لبذور الحلبة (*T. foenum-graecum*) ولحاء القرفة (*C. zeylanicum*) على وظائف الكبد الكلى لذكور الجرذان المصابة بالسكري

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الملخص

استخدمت بذور الحلبة (*T. foenum-graecum*) Fenugreek ولحاء القرفة (*C. zeylanicum*) Cinnamon كمواد اختبارية في هذه الدراسة لاختبار فرضية أن المعاملة ببذور الحلبة ولحاء القرفة تعدل التأثيرات السلبية للإصابة بالسكري على سكر الدم ووظائف الكبد والكلى في الجرذان المصابة بالسكري المستحدث بالآلوكسان باستخدام المستخلصات المائية لهذه النباتات. أحداث السكري سبب زيادة معنوية لسكر الدم مصحوبة بانخفاض معنوي لنشاطات ووظائف الكبد والكلى. قسمت الحيوانات المختبرة لستة مجموعات بكل مجموعة ستة حيوانات: المجموعة الطبيعية، المجموعة المصابة بالسكري، مجموعتين مصابتين بالسكري معاملتين بجرعتين منخفضة وعالية لمستخلص الحلبة ومجموعتين مصابتين بالسكري معاملتين بجرعتين منخفضة وعالية لمستخلص القرفة. بعد المعاملة بالمستخلصات سجلت انخفاضات معنوية في مستويات ALT, AST, ALP, Urea و Creatinine مقارنة بالحيوانات المصابة بالسكري. واعتمدت الانخفاضات على مقدار الجرعة المستخدمة. كما أن القرفة أظهرت تأثيرات أفضل من الحلبة.

كلمات مفتاحية: الحلبة، القرفة، الآلوكسان، مستخلصات، السكري، وظائف الكبد والكلى.

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