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Outcome of Capparis Spinosa Fruit Extracts Treatment on Liver, Kidney, Pancreas and Stomach Tissues in Normal and Diabetic Rats

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Abstract

Aim and objectives: Herbal drugs such as, Capparis Spinosa (CS) has been used to treat several diseases from heart and cardiovascular disorders to diabetes in traditional Iranian medicine. The present study was aimed to determine beneficiary effects of CS fruit extract on a number of tissues in healthy and type 1 diabetic rat.

Materials and methods: In this experimental study, sixty male wistar rats were randomly divided into 6 groups (n=10) and subjected to gavage tube therapy for one months by following protocol: group I and IV: diabetic control and non-diabetic control rats which only received distilled water; groups II and III: non diabetic treatment rats which received 200 mg/kg and 800 mg/kg CS extract per day respectively; groups V and VI: diabetic treatment rats which received 200 mg/kg and 800 mg/kg CS extract per day respectively. Diabetes was induced by intra-peritoneal injection of 50 mg/kg of streptozotocin (STZ). After 4 weeks, their blood were collected and the serum levels of creatinine, bilirubin, urea, uric acid, AST, ALT and ALP were measured. The liver, kidney, pancreas and stomach tissues were immediately excised, and after slide preparation processes, the histological changes were studied.

Results: Our results illustrated that the gastric tissue in the diabetic group showed a small degree of changes and was not affected significantly by administration of the CS fruit extract. Liver, pancreas and kidney of diabetic rats exhibited considerable changes, like cellular necrosis. These changes in diabetic treatment groups were at lowest amounts. The decrease levels of creatinine, liver enzymes, and other factors were supporting these changes.

Conclusions: This study demonstrates that the CS fruit extract could be aid prevention of damage to the tissues due to the decreased levels of harmful oxidants in the body in diabetes. Moreover, according to our previous results altogether we showed beneficial impact of the plant on the treatment of diabetes.

Keywords: Capparis spinosa; Type 1 diabetes; Liver; Kidney; Pancreas and Stomach tissues

Introduction

Diabetes is one of the most frequent metabolic diseases with absolute or relative insulin deficiency and hyperglycemia-induced, associated with the long-term ocular, renal, cardiovascular, and nervous system complications [1-2]. Free radicals play fundamental roles in the pathogenesis of many diseases, including diabetes [3]. Increased free radicals associated cytotoxicity in STZ-induced diabetic rats as well as diabetic patients is well defined [4]. Spontaneous oxidation and non-enzymatic glycation of proteins by glucose and STZ in parallel with stimulation of in vitro H_2O_2 production in pancreatic beta cells leading to generation of free radicals [5]. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) are indicators of the safety liver and indicating its normal function. Increased AST and ALT activity induces the hepatic permeability and in turn facilitates liver cell necrosis [6]. Elevated serum urea/creatinine levels are critical markers for kidney damage. A balance between production and elimination of free radicals is observed in normal situations. Imbalance in this process lead to develop severe or prolonged oxidative stress which causes serious damage to the cells [7]. The antioxidant enzymes are responsible for function of detoxification of free radicals. Some of biochemical compounds, including quercetin are massively found in many plants. Quercetin has the ability to remove free radicals, xanthine oxide, superoxide and xanthine [8]. According to the fact that antioxidant synthetic drugs are associated with different unwanted side effects along with various clinical complications, thus replacement of useful drugs which lacked complications seems essential for attenuating these complexities. In recent decades, many studies have been conducted on the therapeutic properties of plants and herbs as natural resources suitable the treatment of various diseases [9-11]. More importantly due to the bio-availability and lower side effects, pharmaceutical plants have paramount importance in medicine for the treatment of human diseases, especially more frequent diseases, such as diabetes that have characteristic of the metabolic diseases [12]. The wild type CS is an aromatic plant growing in hot and dry or arid/waterless climate West and Central Asia and the Mediterranean. Some parts of Iran are of appropriate regions for growing CS [13]. This plant is used in traditional medicine as a diuretic, treatment of gout arthritis, rheumatoid, paralysis and neurological conditions as well as liver disorders [14]. Several bio-materials including alkaloids, lipids, polyphenols and flavonoids isolated from different parts of CS [15]. It is also known as the herb-rich source of flavonoids such as kaempferol,

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rutin, quercetin and derivatives of quercetin [16]. Xiong et al. reported that treatment of cells with flavonoids, lead to decreased beta-cell apoptosis and inversely increased antioxidant enzyme activities [17]. We have examined recently, the effect of CS extract on blood sugar and lipids in diabetic and normal rats [18]. According to the presence of antioxidant compounds in this fruit, the present study was aimed to determine the beneficiary effects of CS fruit extract on liver, kidney, pancreas and stomach in diabetic and normal rats.

Materials and Methods

Preparation of CS fruit extract

The CS fruits were collected from the local farms in south-eastern part of Iran (Ravar, Iran). Following authentication by botany department of Vali-Asr University, dried fruits of CS were powdered and extracted with 50% ethanol. The mixture was filtered, evaporated in vacuum evaporator (percolation method) and then lyophilized in order to obtain its dry form [19]. Using this procedure, the yield was 22% of the starting dry weight of the leaves. The obtained CS fruit extract was kept at -20°C for further use.

Animals

All of animal procedures were approved by the Rafsanjan University of Medical Sciences ethical committee board. Sixty male albino wistar rats weighting (250 ± 10g) and aging eight weeks were obtained from the experimental animal unit, faculty of medicine, Rafsanjan University of Medical Science, Rafsanjan- Iran. They were housed in clean polypropylene cages having six rats per cage and maintained in an air-conditioned room (22-25°C), 12 hours dark/light cycle which had free access to standard diet and tap water.

Induction of diabetes

As described previously [20] in brief, diabetes was induced by injection of a single intra-peritoneal dose of 50 mg/kg STZ (Sigma-USA) dissolved in 0.1M citrate buffer (Sigma-USA) (pH 4.5). Seven days after STZ injection, blood was collected from the animal's tail vein and the fasting level of blood glucose was measured by BT-3000 auto analyzer (Italy). Animals were considered as diabetic, if had a fasting blood glucose level over 200 mg/dL and then were recruited in further assessments.

Experimental design

Rats were divided into 6 groups (10 rats in each group) and subjected to gavage tube therapy for a period of one months by following protocol: group I: non- diabetic control rats (normal group) which only received distilled water; groups II and III: non diabetic rats which received 200 mg/kg and 800 mg/kg CS extract per day respectively (non-diabetic treatment groups). Group IV: diabetic control rats which received distilled water (diabetic non- treatment group); groups V and VI: diabetic rats which received 200 mg/kg and 800 mg/kg CS extract per day respectively (diabetic treatment groups). Diabetes was induced by intra-peritoneal injection of 50 mg/kg of streptozotocin (STZ). At the end of the 4th week all of rats were anesthetized and humanely killed. Blood specimens were collected and the serum levels of creatinine, bilirubin, urea, uric acid, AST, ALT and ALP were measured in all study groups by the activity assay kit (Sigma-Aldrich, USA) by BT-3000 auto-analyzer (England). The liver, kidney, pancreas and stomach were removed from the body. Following christen in 10% formalin for 48 h tissues were perched and then were fixed by tissue processor (SHANDON, Citadel-Madein-England). Tissues were incubated for 24 hours and then the slides were prepared and stained with Hematoxylin/Eosin (H&E) dye. After staining, slides were studied under Olympus BH2 microscope.

Statistical analysis

Data are reported as mean ± SEM. The difference between groups was evaluated using one-way analysis of variance (One Way ANOVA) and student t-test using SPSS version 18 statistical software. P values of less than 0.05 were considered significant.

Results

The H&E staining results obtained upon histological examinations are shown in Figures 1- 4. In non-treatment diabetic group, the spaces of the Bowman's capsule of the majority of nephrons were more than normal size as seen in the normal group and diabetic and non-diabetic treatment groups. Cellular infiltration under the renal capsule was observed in diabetic non- treatment group. These changes were not seen in normal group and diabetic treatment group VI (Figure 1).

The cellular integrity of the hepatocytes, as examined in this study, revealed some cellular mass and the dilated sinusoids in diabetic non-treatment group (group IV). In comparison, the histology of liver showed distinct lobulation, central vein and well stained hepatocytes in normal and diabetic treatment group VI without any cellular mass and the dilated sinusoids. It appears that cellular mass is formed by the pressure of the surrounding sinusoids. Also necrotic cells were only seen sporadically in diabetic non- treatment group (Figure 2).

In some areas, cell infiltration was seen in the villi of stomach in all diabetic groups while this feature was not found in the normal group (Figure 3).

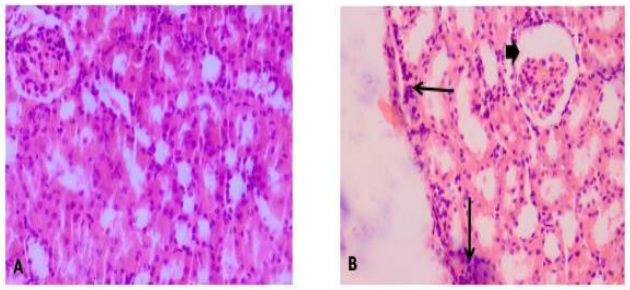

Figure 1: Shows sections of the kidney, stained by H&E
Left Panel (A): Renal tissue in diabetic group treated with 800 mg/kg per day of CS fruit extract. Cellular changes were not observed in this group.
Right Panel (B): Cell infiltration in some areas of the renal capsule (long arrow) and the dilated Bowman's capsule (short arrow) in the diabetic group which only received distilled water (control): Magnification 400x.

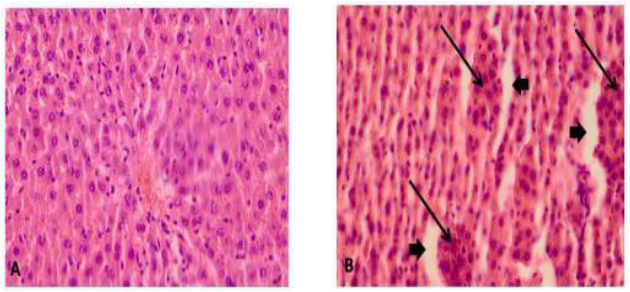

Figure 2: Shows sections of the liver- stained by H&E
Left Panel (A): Normal liver in diabetic group treated with 800 mg/kg per day of CS fruit extract.
Right Panel (B): The cellular mass, including hepatocytes (long arrow) and the dilated sinusoids (short arrows) in the diabetic group which only received distilled water (control): Magnification 400x.

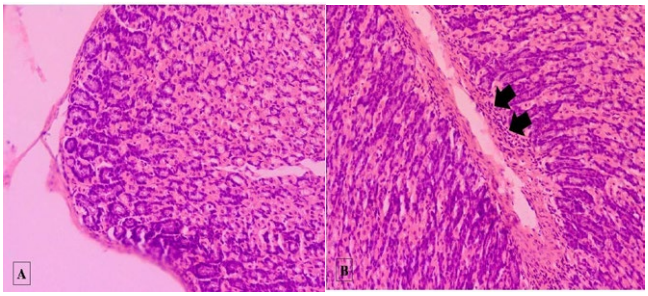

Figure 3: Shows sections of the stomach - stained by H&E
Left Panel (A): Normal stomach in non-diabetic groups.
Right Panel (B): In all of the diabetic groups, cell infiltration (arrow) were observed:

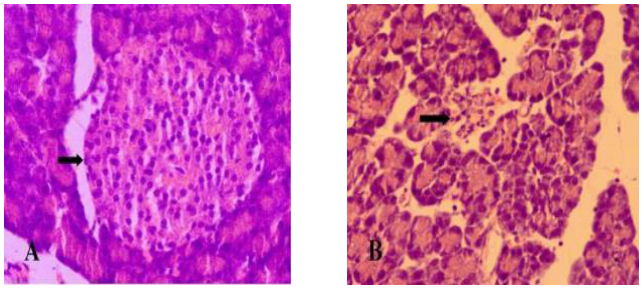

Figure 4: Shows sections of the pancreas: stained by H&E.
Left Panel (A): Pancreatic islets in diabetic group treated with 800mg/kg CS fruit extract. Cells of this tissue have less tissue damage compared to control and diameter of Langerhans islets has not reduced compared to control.
Right Panel (B): Pancreatic islets in diabetic group which only received distilled water (control). This cell necrosis and tissue destruction has been extensive. Islet size has also decreased: Magnification 400x.

Histology of pancreas in all groups was evaluated after 30 days of treatment. Although, in the diabetic treatment groups V and VI and normal group, there were normal Langerhans islets and pancreatic cells and architecture, but, Langerhans islets with very small size, cell necrosis and tissue destruction were observed in diabetic group receiving distilled water (diabetic non-treatment group) (Figure 4).

The effects of CS extract on blood factors are listed in Table 1. After 30 days CS 800 mg/kg extract treatment, AST, and ALP were measured 251.5 ± 135.2 and 1238.7 ± 162.9 in diabetic treatment group VI, respectively. At the beginning of the study these values were 267.3 ± 64.9 and 1694.7 ± 124.9 in group VI, respectively. So the values of AST and ALP markers decreased after one month treatment compare to non-treatment diabetic group. Similar differences were seen in diabetic and non-diabetic groups treated with 200 mg/kg CS extract (group V and II). In the non-diabetic treatment groups (groups II and III), urea decreased after 30 days treatment significantly (Table 1). The direct and total bilirubin levels in diabetic and non-diabetic groups was not changed significantly compare to control. Creatinine levels did not change in non-diabetic group, but was changed in the diabetic group of rats treated with CS. The changes in these groups were not statistically significant.

Discussion

Our histological analysis revealed that renal tissues in diabetic non-treatment group were slightly changed in comparison with diabetic treatment groups (Figure 1). Histological characteristics changed in a dose dependent manner from 200 to 800 mg/kg CS fruit extract, so that, in the treated group with high dose of extract, the damage tissues was decreased. In fact, CS fruit extracts prevented renal cell/tissue destruction in STZ-induced DM. These findings were confirmed by biochemical examinations (Table 1). Although, the parameters such as uric acid, blood urea and creatinine were decreased in diabetic rats treated with CS fruit extract compared to the control group, but from these three parameters only creatinine is specific enough to be addressed for DM associated renal complications. Slight reduced levels

groups	Biochemical parameter	Control		200 mg/kg		800 mg/kg	
		Before	After	Before	After	Before	After
Diabetic	urea	53.62±4.77	55.24±-10.84	52.25±2.8	45.25±7.2	53.57±3.7	45.35±7.57
	Before – After	-1.62±15.61		7±-4.4		8.22±-3.87	
Normal	urea	37±2.78	37.6±5.68	40.75±4.06	33.87±5.96	40.4±15.8	32.3±7.19
	Before – After	-0.6±-2.9		6.88±-1.9*		8.1±8.61*	
Diabetic	Uric acid	2.11±0.08	2.05±0.5	1.82±0.05	2.02±0.17	1.88±0.27	2.2±0.59
	Before – After	0.06 ± -0.42		-0.2 ± -0.12		-0.32 ± 0.09	
Normal	Uric acid	1.7±0.09	1.5±0.15	2.07±0.1	1.73±0.26	1.65±0.1	1.3±0.3
	Before – After	0.2 ± -0.06		0.34 ± -0.16		0.35 ± -0.2	
Diabetic	AST	266.6±94.5	517.8±345.9	269.6±66.5	259.6±134.7	267.3±64.9	251.5±135.2
	Before – After	-251.2 ± -251.4		10 ± -68.2*		15.8 ± -70.3*	
Normal	AST	187.6±5.2	188.9±24.88	180.25±52.9	181.15±93.7	185.1±29.25	185.8±21.35
	Before – After	-1.3 ± -19.68		-0.9 ± -40.8		-0.7 ± 7.9	
Diabetic	ALT	99.87±94.5	171.99±178.1	101.25±62.01	148.96±64.51	103.71±6.64	116.71±-39.36
	Before – After	-72.12 ± -83.6		-47.71 ± -2.5		-13 ± 46	
Normal	ALT	51.5±7.5	52±7.49	53.75±6.31	49.45±6.81	52.7±5.6	47.6±8.1
	Before – After	-0.5 ± 0.01		4.3 ± -0.5		5.1 ± -2.5	
Diabetic	ALP	1197.25±37.41	2042.75±297.41	1201±590	1758±175	1694.7±124.9	1238.7±162.9
	Before – After	-845.5 ± -260		-557 ± 415		-456 ± 38*	
Normal	ALP	602.66±118.15	601.66±125.03	606.75±53.27	577.38±68.49	605.8±128.31	534.3±122.31
	Before – After	1 ± -6.88		29.37 ± -15.22*		71.5 ± 6*	

Values are given as means ± SD of 10 rats.
* $p < 0.05$, compared with control group

Table 1: Effects of administration with CS fruit extracts of blood factors in diabetic rat.

of these parameters were, also observed in non-diabetic rats treated with CS fruit extract when compared with the control group. We also observed that negative effects of diabetes such as cellular/tissue damage and necrosis decreased in liver, pancreas, stomach and kidney tissues of diabetic groups treated with CS fruit compare to control group (Figures 2-4). Examination of liver enzymes showed decrease in diabetic and non-diabetic groups treated with CS fruit extract compare to distilled water group (Table 1)

There are numerous reports showing that hyperglycemia in parallel with increased oxidative stresses and free radicals play a significant role in DM (Diabetes Mellitus) complications [21]. Oxidative stress is triggered by mass of free radicals which are produced from hyperglycemia and hyperlipidemia [22]. Moreover, it has been demonstrated that lipid peroxidation is enhanced during diabetes which can cause tissue damage by production of free radicals and oxidative stress from one side and decreased activity of oxidative stress such as malondialdehyde and nitrite in the other side [23]. The AST (Aspartate aminotransferase) and ALT (Alanine aminotransferase) are two appropriate markers to assess the level of liver damage [24]. Dysfunction of liver associate to increase levels of AST and ALT and these changes were observed in our STZ-induced DM model, one week after STZ injection which got worsened at about 4 weeks later [25]. Note that the ALT is a specific index for healthy liver cells, while AST presents in other tissues rather than liver, so has less specificity [26]. Liver is an organ effective in maintaining normal blood glucose levels and increases blood sugar levels leading to imbalance oxidation reduction reactions in the hepatocytes. Thus, hyperglycemia [via increased production of AGEs (advanced glycation end products)] facilitates the production of free radicals throughout impaired production of endogenous scraper (ROS: reactive oxygen species) such as superoxide dismutase (SOD) and catalase [27].

With regard to previous statements, moreover the control hyperglycemia; there are several factors which causing liver damage and diabetes complications [28]. In other words, controlling of the blood glucose alone is not sufficient for prevention of the complications of diabetes. In diabetes, liver cells damages caused by free radicals. Several mechanisms and antioxidant enzymes such as superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase have a central role in to reduce the damage of liver cells. The reduction of free radicals is one way to treat DM damages [29]. Exorbitance compounds (such as quercetin) are flavonoid antioxidant which existing in the CS fruit. Probably, these compounds as antioxidants organic (non-synthetic) may reduce the negative effects of oxidants and control cell/tissue damages. Aghel et al. show that Capparis spinosa root bark has a hepatoprotective activity and administration of CS root bark repaired liver tissue damage caused by CCL4 [30]. Heidari and Mirshamsi indicated that the methanol extract of the CS fruit has not harmful impacts on the liver, but, a slight level of toxicity was reported on the kidney [31]. To the best of our knowledge a similar work on CS was not found for comparison. Present results also showed that CS fruit extract has no negative effects on kidney in contrast to Heidari and Mirshamsi study, which first used methanolic extract; and second their study period was different (28 days). According to our results, the extract had also no adverse impact on kidney, liver and stomach and prevents cell damage in diabetes.

Conclusions

Our results show that Spinosa as a herbal drug possibly due to the enrichment in some natural compounds such as comarin and flavonoids (with anti-oxidant effects) has medicinal properties and could prevent diabetes complications. However, further investigation on the effects of this plant appears to be essential in the other human body parts.

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