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Anti-diabetic Activities of Zizyphus spina-christi Seeds Embryos Extract on General Characteristics of Diabetes, Carbohydrate Metabolism Enzymes and Lipids Profile in Rats

Mohammed S.A. Al-Awar[1]*

[1] Department of Biology, Faculty of Education and languages, Amran University.

ABSTRACT

Objectives: This study was aimed at evaluating the anti-diabetic activities of Zizyphus spina-christi seeds embryos extract (ZSC seeds embryos extract) on general characteristics of diabetes, carbohydrate metabolism enzymes and lipids profile in alloxan-induced diabetic rats.

Results: A single injection of alloxan to rats (150mg/kg b.w) caused pathological alterations in all studied parameters and histological structure of the pancreas. Treatment of diabetic rats with ZSC seeds embryos extract normalized this alterations. Diabetic rats were treated with ZSC seeds embryos extract (2doses; 200&400 mg/kg b.w) and glibenclamide (0.6 mg/kg b.w) for 6 weeks. Fasting blood glucose (FBG) levels were measured on zero time, 4 h, 8 h and 24 h. Also serum glucose level and body weight were measured every week for all rats. Results showed that oral administration of ZSC seeds embryos extract caused significant reduction in blood glucose level and plasma lactate together with significant elevation in serum insulin, serum pyruvate with normalization in body weight. Marked elevation in total antioxidant capacity (TAC) with lowering of percentage of glycated haemoglobin (HbA1C %) was reported. In line with amelioration of the diabetic state, ZSC seeds embryos extract restored hepatic and muscle glycogen content and hexokinase activity together with significant decrease of glucose-6-phosphatase and fructose 1, 6 biphosphatase enzymes activity. Moreover, the extract succeeded to reduce the elevated serum total cholesterol, triglyceride (TG) and low density lipoprotein (LDL) levels and to elevate the reduced high density lipoprotein (HDL) level of diabetic rats.

Conclusion: This study for the first time reveals that ZSC seeds embryos extract, showed marked amelioration in diabetic rats by stimulating of insulin release from the remnant β-cells, inhibiting glucagon secretion from alpha-cells and increase of antioxidant mechanisms, as well as attenuation of meal-derived glucose absorption. This may be attributed to the presence of saponin glycosides, polyphenols, flavonoids and terpenoids which phytochemical screening revealed its presences in ZSC seeds embryos extract in this study.

Keywords: Zizyphus spina-christi Seeds Embryos, Diabetes, Carbohydrate Metabolism Enzymes, Lipids Profile.

1. INTRODUCTION

Diabetes mellitus is a common metabolic disorder affecting more than 200 million people worldwide as recorded by WHO in 2008 and forecasts to increase to 592 million by 2035[1]. The disease is characterized by chronic hyperglycemia due to absolute or relative deficiency of circulating insulin level or insulin resistance. Hyperglycemia is accompanied by disturbance

* momed.sadeg@gmail.com or dr.msadeg@auye.ac

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of carbohydrate, fat, and protein metabolism and biochemical alterations of lipid metabolism[2]. Diabetes is associated with many complications, for instance, nephropathy, retinopathy, peripheral vascular disease and ischemic heart disease[3]. Many synthetic oral hypoglycemic agents currently are available but they all have several side effects. This necessitates the use of medicinal plants as a useful source for the development of new pharmaceuticals since they are effective, have fewer cost and less side effects[4].

Many medicinal plants have been used as an alternative source of treatment for various pathophysiological conditions including diabetes mellitus. Among these plants is *Zizyphus spina-christi* which is reported to possess hypoglycemic activity[5,6]. Michel et al.[7] showed that oral administration of *Zizyphus spina-christi* leaf extract, plain and formulated reduced blood glucose level with significant increase in serum insulin. The antihyperglycemic activity of fruit extract of *Zizyphus spina-christi* has also been reported[8] and was found to be comparable to the known hypoglycemic agent, glibenclamide. The root of *Zizyphus spina-christi* has also been studied for hypoglycemic activity and was found to possess a pronounced effect even on oxidative stress caused by diabetes[9].

Zizyphus spina-christi leaves extract contains various beneficial ingredients; saponin and polyphenols[7,10], polysaccharides[11], flavonoids, terpenoids, tannins[12,13] and alkaloids[14,15]. The *Zizyphus spina-christi* seeds extract contain the same components[16] of the leaves extract, which may be responsible for its biological activities as antihyperglycemic. Antihyperglycemic activity of *Zizyphus spina-christi* leaves is mediated by releasing insulin which block KAT P channels in pancreatic beta cell membranes[17]. *Zizyphus spina-christi* leaves extract improved glucose utilization in diabetic rats by increasing insulin secretion which may be due to both saponin and polyphenols content and controlling hyperglycemia through attenuation of meal-derived glucose absorption that might be attributed to the total polyphenols[7,10].Othman et al.[18] reported that the saponin glycoside which is the active constituent in *Zizyphus spina-christi* leaves stimulates insulin secretion.[19]

Zizyphus spina-christi (L.) Willd (*Rhamnaceae*) is a fruit tree widely grows in Yemen (known as sedr) with edible, fresh and dried fruits. Fruit (Drupe) of *Zizyphus spina-Christi* is formed from pericarp. The pericarp is typically made up of three distinct layers: the epicarp, which is the outermost layer; mesocarp, which is the middle layer; endocarp, which is the inner layer surrounding the seeds and inside the seed is the embryos[20]. The importance of the current work lies in the fact that study was premeditated with seeds embryos as the test material, which are usually thrown away as waste. Reviewing the current literature revealed that the *Zizyphus spina-christi* seeds or its embryos have not been studied for various antihyperglycemic activities. Therefore, the present study is the first study that was conducted to investigate the anti-diabetic activities of *Zizyphus spina-christi* seeds embryos extract on general characteristics of diabetes, carbohydrate metabolism enzymes and lipids profile in alloxan-induced diabetic rats.

2. MATERIALS AND METHODS

2.1 Plant collection and extract preparation

The fruits of *Zizyphus spina-christi* were collected from Sharris district, Hajjah, Yemen during the Sep to Oct 2016, and was identified and authenticated by Dr. Hassan M.H. Ibrahim, Assistant professor of Plant Taxonomy, Department of Biology, Faculty of Science, Sana'a University, Yemen. The pulp of *Zizyphus spina-christi* was peeled off, and broken to take the embryos inside, the seeds embryos were dried under shade at room temperature then they were finely powdered using an electric mill. The powdered sample (500gm) was extracted with ethanol 70% four times and then put on shaker at 35 °C. After continues shaking for 2 days, the mixture was filtered. The filtrate was completely dried under vacuum in the desiccator. The dry crude extract yield was 11.4% w/w (57gm extract/500gm raw material).

2.2 Oral acute toxicity study (LD_{50}):-

Acute toxicity test for the ZSC seeds embryos extract

was carried in male rats by OECD guidelines 423 for the determination of LD_{50}. The aim of determination of LD_{50} for the ZSC seeds embryos extract was to ensure safety *in-vivo* and for establishing therapeutic index of particular drug.

2.3 Phytochemical analysis

Preliminary phytochemical screening of ZSC seeds embryos extract was carried out according to the methods described by[21,22] for the detection of active components like carbohydrate, glycosides, alkaloids, flavonoids, sterols, triterpenes, saponins, proteins & amino acids, polyphenols, flavonoids, fixed oils & fats and tanins.

2.4 Animals

Male albino rats 3-4 months old, weighing 250 - 300 g were obtained from the zoo, Sana'a- Yemen. They were housed in stainless steel cages in a well-ventilated room at the Histological and Physiological laboratories-Faculty of Medical Sciences, Queen Arwa University. The animals were kept under controlled environmental conditions with free access to standard laboratory diet and water *ad libitum* during the entire period of the study. All animal experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institute of Health (NIH, 1978), and were approved by the Animal Experiments Local Ethics Committee at the Zoo, Sana'a, Yemen.

2.5 Chemicals

Alloxan monohydrate was obtained from Sigma Aldrich Chemicals Pvt, Ltd, Bangalore. Glibenclamide was purchased from Chennai, Tamil Nadu (India). Glucometer, was obtained from Roche (Germany), type (Accu chek-Active. Sensitive Rat Insulin RIA kit supplied from Linco Research Inc. (USA). Diagnostic kits for the blood glucose, blood lactate, blood pyruvate, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and triglycerides were obtained from Spinreact (Spain). Glycated hemoglobin kit was obtained from Stanbio, San Antonio (USA). All other chemicals and reagents were of highest purity commercially available.

2.6 Experimental induction of diabetes

All animals were allowed to adapt to cages for 7 days, after which they were fasted overnight. Diabetes was induced by i.p. injection of alloxan monohydrate (150 mg/kg b.w.) freshly prepared in normal saline. Alloxan is one of the most potent methods to induce experimental diabetes mellitus. It is a well- known diabetogenic agent that is used to induce Type I diabetes in experimental animals. Alloxan is a urea derivative which causes selective necrosis of the β- cells of pancreatic islets. In addition, it has been widely used to produce experimental diabetes in animals[38]. Rats were given 20% glucose solution for 24 h to prevent initial drug-induced hypoglycemic mortality and all animals were given free access to food and water. After two days of alloxan administration, blood samples were taken from the tail vein and glucose levels were measured. Hyperglycemia was considered by measuring the FBG level. Rats with a FBG level above 200mg/dL were considered as diabetic and included in the experiment. Treatment with ZSC seeds embryos started 72 h after alloxan injection.

2.7 Experimental design

The rats were assigned into five groups of eight rats in each group. Treatments were administered orally for 6 weeks.

Group I: control rats received vehicle solution (Distillated water) 5 ml/kg

Group II: Diabetic rats received vehicle solution (Distillated water) 5 ml/kg

Group III: Diabetic rats treated with ZSC seeds embryos extract at a dose 1/20 of LD_{50} (200 mg/kg b.w).

Group IV: Diabetic rats treated with ZSC seeds embryos extract at a dose 1/10 of LD_{50} (400 mg/kg b.w).

Group V: Diabetic rats treated with glibenclamide (0.6 mg/kg).

2.8 Testing of FBG level and Biochemical evaluation

FBG levels were measured on zero time, 4 h, 6 h, 8 h and 24 h. Also FBG of weeks 1, 2, 3, 4, 5 and 6 were measured. Blood samples were collected from the tail vein and FBG level was measured using single touch glucometer. Body weight (initial bw) of each rat was recorded before commencement of treatment, and was

recorded at weekly intervals throughout the experimental period i.e. 6 weeks and expressed as % change in body weight compared to initial body weight. At the end of the experiment, all animals were deprived from food for 12 h. Blood samples were taken from the eye and collected into sterile tubes without anticoagulants, and centrifuged at 3500 rpm for 20 min, and serum was separated for measurement of levels of blood glucose[23], serum insulin[24], TAC[25], total cholesterol[26], triglycerides[27], LDL and HDL[28]. A second portion of blood samples were collected in sampling tubes containing EDTA and used for the measuring of HbA1C%[29]. A third portion of blood samples were collected on 0.6M perchloric acid for immediate deproteinization and consequent estimation of serum lactate and serum pyruvate levels. Liver tissues and skeletal muscles were rapidly isolated and immediately digested in 30% potassium chloride solution for further analysis of glycogen. Meanwhile, the liver was homogenized in 0.1M citrate buffer pH (6.5). The supernatant was used to measure the activity of hexokinase[30], hepatic glucose-6-phosphatase[31] and fructose-1, 6-bisphosphatase[32]. Glycogen of hepatic and skeletal muscle tissues was determined according to the method of Van Handel[33].

2.9 Histopathological Procedure of pancreas

Tissue of pancreatic in all groups were subjected to histopathological studies. The whole pancreas from each rat was removed after sacrificing the rat and was collected in 10% neutral formalin and immediately processed by paraffin technique. Blocks were cut at 5 µm thickness using rotary microtome and stained with hematoxylin and eosin[34] for histological examination under light microscope.

2.10 Statistical Analysis

The mean±S.E.M value of each parameter was computed considering data on eight rats in each group. The mean value of each parameter of normal group and diabetic group were compared using one-way analysis of variance (ANOVA) followed by Duncan's new multiple range test fixing a minimum significance level of $P < 0.05$. Student's t-test was used to compare mean values wherever there were only two groups.

3. RESULTS

3.1 Acute toxicity study

Oral treatment of ZSC seeds embryos extract in male rats did not cause death and behavioral changes at 4000 mg/ kg b.w. No visible signs of toxicity were reported in the rats treated with the extract indicating its safety. Accordingly, the LD_{50} value was found to be higher than 4000 mg/ kg (Table 1).

Table (1)
LD_{50} of ZSC seeds embryos extract

Dose	No. of rats	No. of Death of rats
500 mg/dl	4	0
1000 mg/dl	4	0
2000 mg/dl	4	0
4000 mg/dl	4	0

LD_{50} be higher than 4000mg/ kg b.w.

3.2 Result of Phytochemical analysis of ZSC seeds embryos extract at 2, 4, 8 h and 24h in Alloxan-diabetic Rats

Preliminary phytochemical screening of ZSC seeds fixed oils and fats, as shown in table 2.

embryos extract tested positive for carbohydrate, glycosides, saponins, alkaloids, flavonoids, sterols, triterpenes, proteins, amino acids, polyphenols, tanins and flavonoids, In contrast the extract tested negative for

Table (2)
Result of Phytochemical analysis of ZSC seeds embryos extract

No.	Test	Positive or Negative
1	Carbohydrate	+
	Glycosides	+
2	Alkaloids	+
3	Phytosterols	+
4	Triterpenoids	+
5	Saponins	+
6	Proteins and amino acids	+
7	Fixed oils and fats	-
8	Tanins	+
9	Polyphenols	+
10	Flavonoids	+

3.3 Effect of ZSC seeds embryos extract on FBG level in Alloxan-diabetic rats at zero time, 2, 4, 8 and 24 h.

Rats treated with a single injection of alloxan showed gradual increase in blood glucose levels at time 2, 4, 8 and 24 h, in the mean percent 262.3±17.61, 293.4±19.82, 320.1±22.43 and 377.8±22.97 respectively, as compared to control. Administration of ZSC seeds embryos extract (200 & 400 mg/kg b.w) and glibenclamide (0.6 mg/kg b.w) significantly reduced ($p < 0.005$) blood glucose levels with time (2, 4 and 8 h). The onset of antihyperglycemic effect of glibenclamide was 2 h (191.5±14.65) and that of the extract at 200 mg/kg by 210.5±18.12 & 400 mg/kg by 197.5±14.82 were 4 h (Fig. 1). The peak of the effect was attained at 8 h but the effect diminished at 24 h was 225.7±18.65 and 221.8±17.90 of the extract at 200mg/kg and 400 mg/kg respectively, and that of glibenclamide was 219.4±18.92, as compared to control.

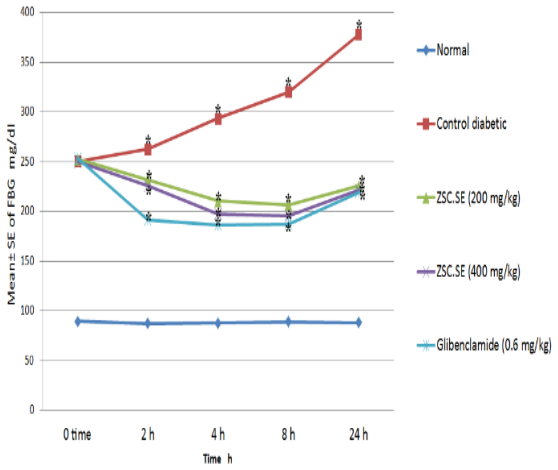

Figure (1): Effect of ZSC seeds embryos extract (doses 250 and 500 mg/kg) and glibenclamide (0.6 mg/kg) on FBG in alloxan-diabetes rats. FBG were assessed at regular interval of zero time, 2, 4, 8 and 24 h. The results are presented as Mean± SE (n = 8). *P < 0.05 compared to normal group.

3.4 Effect of ZSC seeds embryos extract on blood glucose levels in Alloxan-diabetic rats at 6 weeks.

The effect of repeated oral administration of ZSC seeds embryos extract on blood glucose levels in alloxan-diabetic rats is presented in fig- 1. The ZSC seeds embryos extract administered at doses of 200 & 400 mg/kg to alloxan-treated diabetic rats caused significant ($p < 0.05$) reduction of blood glucose levels which was related to dose and duration of treatment. Gradual increase in body weight was also observed. ZSC seeds embryos 400 mg/kg exhibited maximum glucose lowering effect in diabetic rats. glibenclamide group exhibited significant reduction in blood glucose levels and body weight when compared to diabetic control. ZSC seeds embryos 400 mg/kg exhibited maximum glucose lowering effect in diabetic rats (Fig. 2).

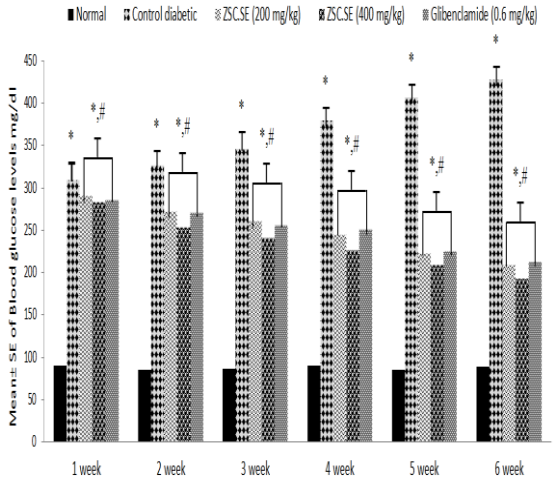

Figure (2): Vertical bars showing Mean± SE of Blood glucose levels administration of ZSC seeds embryos extract (doses 250 and 500 mg/kg) and glibenclamide (0.6 mg/kg) in Alloxan-diabetic rats at 6 weeks. (n = 8 in) *P < 0.05 compared to normal group. #P < 0.05 compared to control diabetic group

3.5 Effect of ZSC seeds embryos extract on body weight in Alloxan-diabetic rats at 6 weeks.

Controls showed consistent increase in body weight during treatment period and showed 14.3% increase at the end of the sixth week whereas that of rats in the alloxan-treated diabetic group showed 12.15% loss in its body weight during the same period. Diabetic rats that were treated with ZSC seeds embryos extract (2doses 200 and 400 mg/kg) and glibenclamide (0.6 mg/kg) showed 9.54%, 11.98% and 9.92% gradual rise in their body weight, respectively, during the same period, the maximum rise in body weight was found in dose 400 mg/kg (Fig. 3).

3.6 Effect of ZSC seeds embryos extract on general characteristics of diabetes in Alloxan-diabetic rats

Rats in the alloxan-treated diabetic group, as shown in table 3, exhibited significant elevation in blood glucose, HbA1C% and plasma lactate. The mean percent increase in blood glucose, HbA1C% and plasma lactate were 441.3±22.7, 14.1±2.1and 22.8±5.7 respectively, as compared to control. In contrast, the levels of serum insulin, serum pyruvate and total antioxidant capacity (TAC) were significantly decreased and were 4.6±0.7, 0.52±0.04 and 443.1±21.8 respectively, as compared to that of the control group. On the other hand, treatment with ZSC seeds embryos extract in dose of 200 mg/kg for 6 weeks, treatment with ZSC seeds embryos extract in dose 200mg/kg for 6 weeks, resulted in significant reduction in the level of blood glucose, HbA1C% and

plasma lactate, in the mean percent 210.3±15.5, 9.0±1.3 and 18.4±3.2 respectively, as compared to control, together with significant elevation in serum insulin, serum pyruvate and TAC was 210.3±15.5, 18.4±3.2 and 563.2±22.7 respectively, as compared to control. Similarly, that of rats treated with ZSC seeds embryos extract in dose 400mg/kg for 6 weeks showed significant reduction in the in the level of blood glucose, HbA1C% and plasma lactate, in the mean percent 198.5±15.1, 8.7±1.1 and 15.6±3.1respectively, as compared to control, together with significant elevation in serum insulin, serum pyruvate and TAC was 9.9±1.4, 0.92±0.06 and 600. 3±24.6 respectively, as compared to control. The mean percent decrease in the level of blood glucose, HbA1C% and plasma lactate of rats treated with Glibenclamide in dose 0.6 mg/kg, was 216.6±17.4, 8.7±1.8 and 17.0±3.3 respectively, as compared to control, while the mean percent increase in the level of serum insulin, serum pyruvate and TAC was 8.8±2.0, 0.80±0.05 and 557.1 respectively as compared to control

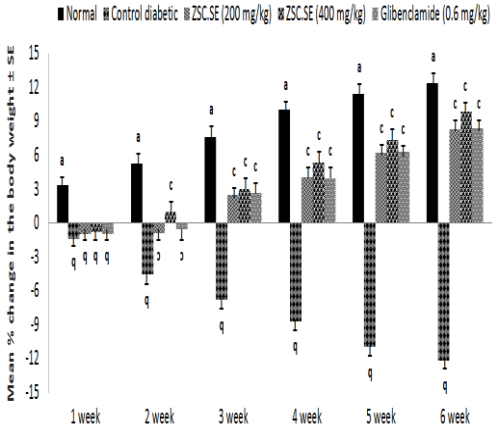

Figure (3): Vertical bars showing mean% change in body weight following administration of ZSC seeds embryos extract (doses 200 and 400 mg/kg) and glibenclamide (0.6 mg/kg) compared to initial body weight. Bars with same superscript letters are not significantly different, whereas those with different superscript letters are significantly (P < 0.05) different as judged by ANOVA followed by Duncan's multiple test.

Table (3)
Effect of ZSC seeds embryos extract on general characteristics of diabetes in Alloxan-diabetic rats

Parameters	Groups				
	Normal	Control diabetic	Diabetic of ZSC.SE (200 mg/kg b.w)	Diabetic of ZSC.SE (400 mg/kg b.w)	Glibenclamide (0.6 mg/kgb.w)
Glucose (mg/dl)	90.4±8.5	441.3±22.7*	210.3±15.5$^{*,\#}$	198.5±15.1$^{*,\#}$	216.6±17.4$^{*,\#}$
Insulin (μU/ml)	14.8±2.3	4.6±0.7*	8.9±1.3$^{*,\#}$	9.9±1.4$^{*,\#}$	8.8±2.0$^{*,\#}$
Lactate (mg/dl)	12.4±2.0	22.8±5.7*	18.4±3.2$^{*,\#}$	15.6±3.1$^{\#}$	17.0±3.3$^{*,\#}$
Pyruvate (mg/dl)	0.99±0.07	0.52±0.04*	0.81±0.05$^{*,\#}$	0.92±0.06$^{\#}$	0.80±0.05$^{*,\#}$
Total antioxidant capacity(μmol/ml)	671.3±32.6	443.1±21.8*	563.2±22.7$^{*,\#}$	600.3±24.6$^{*,\#}$	557.1±19.5$^{*,\#}$
HbA1C%	5.8±0.94	14.1±2.1*	9.0±1.3$^{*,\#}$	8.7±1.1$^{\#}$	8.7±1.8$^{\#}$

Values are expressed means±S.E.M. (n = 8 in), *P < 0.05 compared to normal group. $^{\#}$P < 0.05 compared to control diabetic group.

3.7 Effect of the embryos of ZSC seeds embryos extract on carbohydrate metabolism enzymes in Alloxan-diabetic rats

Data presented in table 4 revealed that alloxan-induced diabetes in rats caused significant lowering in liver and muscle glycogen content when compared with the diabetic control group. The treatment with ZSC seeds embryos extract (200 and 400 mg/kg) and glibenclamide for 6 weeks, resulted in significant rise in hepatic and muscle glycogen content. As shown in the present study, alloxan-diabetic rats exhibited significant increase in the hepatic enzyme, glucose-6-phosphatase and fructose-1, 6 bisphosphatase activity together with significant decline in the activity of hexokinase enzyme. The decrease in serum hepatic glucose-6-phosphatase and fructose-1, 6 bisphosphatase activities with significant increase in hexokinase activity were brought about by the ZSC seeds embryos extract and glibenclamide.

Table (4)
Effect of ZSC seeds embryos extract on carbohydrate metabolism enzymes in Alloxan-diabetic rats

Parameters	Groups				
	Normal	**Control diabetic**	**Diabetic of ZSC.SE (200 mg/kg b.w)**	**Diabetic of ZSC.SE (400 mg/kg b.w)**	**Glibenclamide (0.6 mg/kgb.w)**
Hepatic glycogen (mg/g tissue)	34.6±5.5	17.9±4.8*	26.7±5.6$^{*,\#}$	29.5±5.1$^{\#}$	27.3±4.8$^{*,\#}$
Muscle glycogen (mg/g tissue)	2.7±0.33	1.3±0.87*	2.3±0.41$^{\#}$	2.3±0.61$^{\#}$	2.4±0.53$^{\#}$
Hexokinase (U/mg protein /min)	7.6±1.23	3.7±0.91*	6.2±1.76$^{*,\#}$	6.8±1.95$^{*,\#}$	6.1±1.47$^{*,\#}$
Liver glucose-6phosphatase (U/mg protein)	61.8±3.6	109.8±9.6*	81.5±8.3$^{*,\#}$	75.0±6.2$^{\#}$	79.2±6.9$^{*,\#}$
Fructose-1,6 bisphosphatase (U/mg protein)	73.5±7.8	115.6±11.5*	91.7±9.7$^{*,\#}$	83.8±5.8$^{*,\#}$	92.5±6.9$^{*,\#}$

Values are expressed means±S.E.M. (n = 8 in), *P < 0.05 compared to normal group. $^{\#}$P < 0.05 compared to control diabetic group.

3.8 Effect of the embryos of ZSC seeds embryos extract on lipid profile in Alloxan-diabetic rats

Serum T.Cholesterol, TG and LDL levels showed a significant rise ($p<0.005$) whereas level of HDL was significantly lowered in untreated diabetic rats. The treatment with ZSC seeds embryos extract (200 and 400 mg/kg) and glibenclamide for 6 weeks resulted in significant reduction in serum T.Cholesterol, TG and LDL levels together with significant rise in HDL level reverted to the near normal level (Table 5).

Table (5)
Effect of ZSC seeds embryos extract on Lipid profile levels in Alloxan-diabetic rats

Parameters	Groups				
	Normal	**Control diabetic**	**Diabetic of ZSC.SE (200 mg/kg b.w)**	**Diabetic of ZSC.SE (400 mg/kg b.w)**	**Glibenclamide (0.6 mg/kgb.w)**
T.Cholesterol (mg/dl)	51.6±7.9	81.7±13.4*	62.2±4.3*	54.1±5.4$^{\#}$	63.2±5.2$^{*,\#}$
TG (mg/dl)	78.2±4.8	126.3±15.7*	98.1±5.9*	84.4±6.2$^{*,\#}$	88.1±5.3$^{*,\#}$
LDL (mg/dl)	16.4±1.9	40.1±2.8*	21.1±2.0*	18.2±2.1$^{\#}$	19.9±1.7$^{*,\#}$
HDL (mg/dl)	48.7±1.6	21.6±2.1*	39.2±1.7*	45.1±1.5$^{*,\#}$	40.6±1.5$^{*,\#}$

Values are expressed means±S.E.M. (n = 8 in), *P < 0.05 compared to normal group. $^{\#}$P < 0.05 compared to control diabetic group.

3.9 Histopathological observation of pancreas

The histological structure of the pancreas in diabetic control rats showed normal architecture of normal acini (exocrine cells) and normal cellular population in the islets of Langerhans (endocrine cells) (Fig. 4a). In contrast, the light microscopic study of diabetic rats revealed pathological changes of endocrine part of the pancreas represented by degeneration of pancreatic islets (β-cells) (Fig. 4b). Treatment of ZSC seeds embryos extract (200 and 400 mg/kg) and glibenclamide for 6 weeks showed no recovery on pancreatic damage (Fig. 4-c, d,e &f).

4. DISCUSSION

It is not constantly simple to determine if the consumed plant extracts are safe. In fact, there are large number of plant extracts with a wide range of adverse effects[35]. In our study, oral administration of ZSC seeds embryos extract to male rats did not produce any signs of toxicity and none of the rats died at doses up to 4g/kg during 48 h of observation. Accordingly, the LD_{50} value was found to be higher than 4000 mg/kg b.w. Therefore, ZSC seeds embryos extract can be categorized as quietly safe since substances possessing LD_{50} higher than 50 mg/kg are non-toxic[36].

The data showed that phytochemical screening of ZSC seeds embryos extract revealed the presence of carbohydrate, glycosides, alkaloids, flavonoids, sterols, triterpenes, proteins & amino acids, phenolic compounds, tanins and flavonoids. Most of these compounds have variously been reported to have antihyperglycemic activity and could be the reason of the activities recorded against diabetes. There is no available data showing phytochemical analysis of ZSC seeds embryos extract. Therefore, the present study is the first study that was conducted to reveal some chemical compounds, but studies that was conducted on leaves[7,12,15,37] and seeds[16] found the same components.

The present results showed that a single injection of alloxan (dose 150mg/kg b.w) to rats caused a significant increase in serum glucose levels and percentage of HbA1C% with significant decrease in serum insulin levels as compared to the normal group. Alloxan-induced diabetes is one of the widely used model to induce Type I diabetes mellitus in the experimental animals[38]. Alloxan has been found to be selectively toxic to pancreatic beta cells as it preferentially accumulates in the beta cells as glucose analogues as shown in fig. 4. In addition, the cytotoxic action of alloxan is mediated mainly by the generation of reactive oxygen species (ROS) [39]. Alloxan and the product of its reduction, dialuric acid, has been noted to establish a redox cycle with the formation of superoxide radicals, which undergo dismutation to hydrogen peroxide (H_2O_2) and more highly reactive hydroxyl radicals are formed by the Fenton reaction. Further, the massive increase in cytosolic calcium

concentration ultimately causes rapid destruction of beta cells of pancreatic islets[38]. The hyperglycemia were accompanied by marked reduction in total antioxidant capacity (TAC), blood pyruvate and significant increase in plasma lactate.

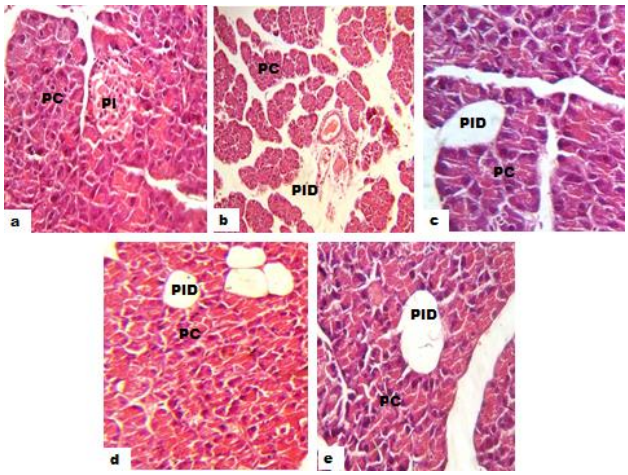

Figure (4): Photomicrographs of sections of the pancreases. (a): Normal control group showing a normal architecture without pathological alterations. Pancreatic cells (Exocrine glands; PC), Pancreatic islet (Endocrine glands; PI). (b): Control diabetic; showing of Pancreatic islet degeneration. (c): EZSCS 250mg; (d): EZSCS 250mg; (e): Diabetic glibenclamide; showed no recovery on pancreatic damage (HE) stain.

A significant reduction in blood glucose together with significant elevation in serum insulin and serum pyruvate with the concomitant elevation of plasma lactate was observed in diabetic rats treated with ZSC seeds embryos extract (200 and 400 mg/kg) for 6 weeks. This could be due to the active principles present such as saponin and polyphenols glycosides, flavonoids and terpenoids which may stimulate insulin release from the remnant beta cells and attenuate meal-derived glucose absorption. The current results are in harmony with those obtained by Glombitza et al.[5] who revealed that the alcoholic extract of *Z. spina-christi* leaves improved glucose utilization in diabetic rats after 4 weeks of treatment because of the presence of major saponin glycoside (christinin-A). Abdel-Zaher et al.[17] reported that the saponin glycoside which is the active constituent in *Z.spina-christi* leaves stimulate insulin secretion. Michel et al.[7] reported that the determination of the flavonoids in *Z. spina-christi* leaves, contributed to the anti-diabetic activity and succeeded to reduce the blood lactate levels and to elevate the reduced blood pyruvate contents. Increased lactate production may result from increased glucose conversion to lactate in adipocytes as shown by Newby et al [40]. The increase in serum lactate concentration is also in accordance with the study of Mondon et al[41]. Othman et al.[18] stated that the hypoglycemic effect of Z. *spina christi* leaves in diabetic rats may be due to the presence of saponin glycosides by stimulate insulin release. Hii and Howell[42,43] reported that the exposure of isolated rat islets of pancreas to certain flavonoids such as epicatechin or quercetin enhances insulin release. They argue that such flavonoids may act on islet function, at least in part, via alteration in Ca++ fluxes and in cyclic nucleotide metabolism. Al-Mayahi[19] stated that the hypoglycemic effect may be attributed to the triterpenes and alkaloids content of *Nigella sativa* which stimulate insulin release from the remnant β-cells, or through inhibiting glucagon secretion from α-cells of the pancreas in Alloxan-induced diabetic rabbits. Quercetin are reported as potential hypoglycemic agents with regeneration of the pancreatic islets, as shown by

increased number of islet cells, and increasing insulin release in STZ-induced diabetic rats [44]. ZSC seeds embryos extract contains good amount of flavonoids which can be potentially beneficial for the treatment of diabetes[45] Compounds that facilitate glucose transporter-4 (GLUT-4) translocation can be potentially beneficial for the treatment of diabetes. Flavonoids-rich fraction from *Cephalotaxus sinensis* leaves extract, showed a potent antihyperglycemic effect on induced diabetic rats by demonstrating that GLUT-4 is translocated to the cell membrane of mice adipocytes after incubation with flavonoids-rich fraction[45].

HbA1c levels are monitored as a reliable index of glycemic control in diabetes[46]. During diabetes, the glucose or other reducing sugars react with the amino residues of proteins to form Amadori products, for instance, glycated hemoglobin[47]. The rate of HbA1c is directly proportional to that of serum glucose level. Our results showed that, the high level of HbA1c in diabetic rats was improved by the administration of ZSC seeds embryos extract (200 and 400mg/kg), this marked improving in percentage of HbA1c% could be related to the improvement in insulin release from the existing β-cells of the pancreas that resulted in improvement the glycemic state due to the presence of active compounds such as flavonoids which have strong antioxidant properties, as they are scavengers of reactive oxygen species and diminishe their toxic properties[48]. Dembinska-Kiec et al.[49]; Michel et al[7] reported that *Zizyphus* spp have antioxidant effect for STZ diabetic rats. This may be attributed to the presence of flavonoids which have an antioxidant activity. However, many researches showed that *Z. spina christi* is a strong antioxidant agent because of the presence of saponins glucosides and flavonoids[50], tannins[51] and carotenes[52]. Antioxidants can inhibit oxidative glycation (glycoxidation) of tissue proteins with reducing sugars as reported by Yamaguchi et al.[53] . These findings could explain the observed enhancement of the total antioxidant capacity with the concomitant lowering of HbA1C% in rats treated with ZSC seeds embryos.

In the present study the data showed significant lowering of liver and muscle glycogen content when compared with the diabetic control group because alloxan causes selective necrosis of the β- cells of pancreatic islets resulting in marked decrease in insulin levels. It could be predicted that glycogen levels in tissues (muscle and liver) decrease as the influx of glucose is inhibited in the absence of insulin[54]. As shown in the present study, alloxan-diabetic rats exhibited significant increase in the hepatic glucose-6-phosphatase and fructose-1,6 bisphosphatase activities together with significant decline in the activity of Hexokinase enzyme. This could be referred to increased blood glucagon/insulin ratio reflecting under-utilization of glucose in the liver[7]. The activities of key glycolytic enzymes, hexokinase, glucose- 6-phosphatase and fructose-1, 6-bisphosphatase were significantly altered during diabetic illness[55]. Murray et al.[56] reported that the decrease of insulin lead to inhibiting glycogenolysis through inhibiting activities of enzymes; pyrovate carboxylase, glucose -6-phosphatase and fructose 1,6 biphosphatase. The decreases in serum hepatic glucose-6-phosphatase and fructose-1,6 bisphosphatase activities with the increases in hepatic and muscle glycogen contents and hexokinase activity brought about by the ZSC seeds embryos were consistent with the increased insulin secretion in diabetic rats, this is probably due to enhanced insulin action. Insulin plays a role in regulating glycogen metabolism through activation or inhibition of several mediatory enzymes and proteins[57]. Glombitza et al.[5] showed that administration of the saponin glycoside in the butanol extract of *Z. spina christi* leaves significantly raised the liver glycogen content and serum insulin in diabetic rats. Michel et al.[7] who revealed that the administration of *Z. spina christi* extract either plain or formulated succeeded to correct significantly the defective glycogen storage of diabetic muscle and liver and caused significant decrease of hepatic glucose-6-phosphatase and increase in glucose-6-phosphate dehydrogenase activities because of the presence of flavonoids (christinin-A).

In the present study the data showed significant body weight lowering when compared to the normal group. This may be due to protein sparing action i.e.

gluconeogenesis from muscle protein (ketogenic amino acid) and this would result in decrease in total protein[58]. Goldstein et al.[59] also referred that the metabolism of glucose, proteins and lipids is abnormal in diabetes due to insulin secretion defect, leading to various metabolic disorders and hence decrease body weight. Treatment of diabetic rats with ZSC seeds embryos resulted in body weight gain as compared to the diabetic group. This marked improving in body weight may be attributed to the improvement in blood glucose, serum insulin level and carbohydrate metabolism enzymes. There is no available data showing the effect of ZSC seeds embryos extract on body weight in diabetic rats. However Othman et al.[18] showed that *Zizyphus spina christi* leaves altered body weight as compared to the diabetic group.

Diabetic rats showed disturbance in lipid profile levels as they had high levels of T.cholesterol, T.G and LDL and low levels of HDL. These results are similar to those obtained by Zargar et al.[60]. Hye et al.[61] stated that the levels of serum lipids are usually elevated in diabetes mellitus, and this represents the risk of coronary heart disease. Treatment of diabetic rats with 200 mg/kg and 400 mg/kg b.w ZSC seeds embryos significantly altered the lipid profiles by decreasing T.cholesterol, T.G and LDL levels and increasing HDL levels. This may be due to functional ingredients, saponins in *Zizyphus* spp which have hypolipidimic effects by decreasing total cholesterol, triglycerides and LDL-C in hyper lipidemic rats[62,63]. Parsaeyan and Rezvani[64] revealed that *Z. spina christi* leaves extract has beneficial effects on lipid profile and lipid peroxidation in diabetic rats. Othman et al.[18] reported that the treatment of diabetic rats with *Z. spina christi* leaves, normalized measured lipid profile (cholesterol, T.G, LDL-c and HDL-c) as compared to the diabetic group. This was due to the presence of saponin glycosides. As well as El-Beshbishy et al.[65] stated the same effect of *Morus alba* on lipid profile levels. This was due to the presence of flavonoids. On the other hand Weggemans and Trautwein[66] revealed that flavonoids intake decreased LDL-C and increased HDL-C.

5. CONCLUSION

The study first time reveals that ZSC seeds embryos extract, showed marked amelioration in diabetic disorders induced by alloxan in rats. ZSC seeds embryos extract contains principle ingredients such as saponin glycosides, polyphenols, flavonoids and terpenoids that possibly exert multiple actions involving different mechanisms in exerting hypoglycemic and antihyperglycemic effects. These proposed mechanisms include; stimulating insulin release from the remnant β-cells, inhibiting glucagon secretion from α-cells, increase antioxidant mechanisms, as well as attenuation of meal-derived glucose absorption. In line with amelioration of the diabetic state, ZSC seeds embryos extract positively altered the deranged carbohydrate metabolism in the diabetic rats. Moreover, they succeeded to normalize the lipids profile levels of diabetic rats.

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النشاطات المضادة للسكري لمستخلص أجنة بذور نبات السدر Zizyphus spina-christi على الخصائص العامة للسكري وإنزيمات أيض الكربوهيدرات ومستويات الدهون في الفئران

محمد صادق عبدالله الاعور [١،٢]

[١] قسم علوم الحياة– كلية التربية والألسن عمران–جامعة عمران

[٢] قسم المختبرات– كلية العلوم الطبية–جامعة الملكة أروى.

ملخص

الأهداف: هدفت هذه الدراسة إلى تقييم النشاطات المضادة للسكري لمستخلص أجنة بذور نبات السدر على الخصائص العامة للسكري وإنزيمات أيض الكربوهيدرات ومستويات الدهون في الجرذان المستحثة لمرض السكري.

النتائج: أدى حقن الفئران بجرعة واحدة من الالوكسان (١٥٠ ملغم/كغم من وزن الجسم) إلى حدوث تغيرات مرضية في جميع المؤشرات المدروسة وفي التركيب النسيجي للبنكرياس، وأدى علاج الجرذان المستحثة لمرض السكري بمستخلص أجنة بذور نبات السدر إلى تطبيع هذه التغيرات. تم علاج الفئران المصابة بمرض السكري بمستخلص أجنة بذور نبات السدر بجرعتين (٢٠٠ و ٤٠٠ ملغم/كغم من وزن الجسم) والغليبنكلاميد (٠,٦ ملغم/كغم من وزن الجسم) لمدة ٦ أسابيع. تم قياس مستوى الجلوكوز في الدم بعد ٠، ٤، ٨، ٢٤ ساعات. كما تم قياس مستوى الجلوكوز في الدم ووزن الجسم كل أسبوع لجميع الجرذان. أوضحت النتائج أن المعالجة بمستخلص أجنة بذور نبات السدر والغليبنكلاميد تسببت في انخفاض ملحوظ في مستوى السكر واللاكتات مع ارتفاع معنوي في مستوى الأنسولين والبيروفات في المصل بالإضافة إلى تطبيع وزن الجسم. كما تسببت في ارتفاع ملحوظ في القدرة الكلية المضادة للأكسدة مع انخفاض نسبة السكر التراكمي. وترافقاً مع تحسن حالة مرض السكري نجحت خلاصة أجنة بذور نبات السدر في استعادة محتوى جليكوجين الكبد والعضلات ونشاطات إنزيم الهيكسوكيناز إلى جانب انخفاض معنوي في نشاطات إنزيمات جلوكوز–٦– فوسفاتاز وفركتوز ١،٦ ثنائي الفوسفاتاز، علاوة على ذلك نجحوا في خفض مستويات الكوليسترول الكلي والدهون الثلاثية والبروتينات الدهنية منخفضة الكثافة ورفع مستوى البروتينات الدهنية عالية الكثافة في الفئران المستحثة لمرض السكري.

الخلاصة: تكشف هذه الدراسة للمرة الأولى أن مستخلص أجنة بذور نبات السدر أظهرت تحسنا ملحوظا في الفئران المصابة بمرض السكري عن طريق تحفيز إفراز الأنسولين من خلايا بيتا المتبقية، ومنع إفراز الجلوكاجون من خلايا ألفا، وزيادة آليات مضادات الأكسدة، فضلا عن تقليل امتصاص الجلوكوز من الأمعاء الدقيقة، ويمكن أن يعزى ذلك إلى وجود الصابونين جليكوسيدات، الفينولات الكلية، الفلافونيدات والتربينات والقلويدات التي كشف التحليل الكيميائي في هذه الدراسة وجودها في مستخلص أجنة بذور نبات السدر.

الكلمات الدالة: أجنة بذور نبات السدر، السكري، إنزيمات أيض الكربوهيدات، مستويات الدهون.

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