WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 03, 1-19. Research Article ISSN 2277–7105

EFFECT OF *PEGANUM HARMALA* AQUEOUS EXTRACT ON EXPERIMENTALLY INDUCED DIABETES MELLITUS IN RABBITS

Tahani Y. Omar*

Zoology Department, Faculty of Science, Sirt University, Libya.

Article Received on
06 Dec. 2017,
Revised on 27 Dec. 2017,
Accepted on 18 Jan. 2018
DOI: 10.20959/wjpr20183-10748

***Corresponding Author**
Tahani Y. Omar
Zoology Department, Faculty of Science, Sirt University, Libya.

ABSTRACT

Objective: To investigate antidiabetic analysis of *Peganum harmala* seeds aqueous extract in streptozotocine induced diabetic rabbits by administering oral doses (5 mg/kg body weight). **Methods:** Experimental diabetes was induced by intraperitoneal injection of streptozotocin (STZ) at a dose of 45 mg/kg body weight per day for 3 days. Adult male rabbits were divided into four groups; normal control, diabetic control, diabetic+ *Peganum harmala* supplement (5mg /kg b.wt.), and normal+ *Peganum harmala* supplement (5mg /kg b.wt.) for 14 days. Serum glucose, insulin, triglycerids, cholesterol, urea, creatinine, activities of serum marker enzymes of liver function(AST and ALT) were measured. The oxidative stress was assessed by glutathione-S-transferase (GST) and catalase (CAT) in plasma. **Results:** The increase in serum glucose, triglycerides, cholesterol, AST and ALT, decreased insulin, plasma GST, CAT, were the salient features recorded in diabetic control rabbits. The *Peganum harmala* supplements significantly reverted the levels of the studied metabolites and enzymes activities to near normal control values. **Conclusions:** the current study suggest that aqueous extract of *Peganum harmala* seeds powder oral doses (5 mg/kg body weight) supplementation may be beneficial for preventing diabetic complications in this animal model.

KEYWORDS: *Peganum harmala*, Serum glucose, insulin, triglycerids, cholesterol, urea.

INTRODUCTION

According to the World Health Organization (WHO), there are approximately 160,000 diabetics worldwide, the number of diabetics has double in the last few years and is expected to double once again in the year 2025.[1] Diabetes mellitus is a group of metabolic disorders

characterized by hyperglycemia, with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[2] Natural remedies from medicinal plants are considered to be effective and safe alternative treatment for hyperglycemic and liver toxicity.[3] There is a growing interest in herbal remedies because of their effectiveness, minimal side effects in clinical experience, and relatively cost effective. Herbal drugs or their extracts are prescribed widely, even when their biological active compounds are unknown.[4] *Peganum harmala* (L.) is a member of the family Zygophyllaceae[5] commonly known as Harmal grows spontaneously in semi arid and predesertic regions of south-east Morocco and distributed in north Africa and the middle east[6] *P. harmala* has been traditionally used to treat diabetes in folk medicine of some parts of the world.[7,8] This effect of *P. harmala* has been pharmacologically confirmed in several studies one of which showed that the plant would lose its hypoglycemic activity at high doses instead of increasing it.[9]

The seeds of *P. harmala* L. contain about 2–6% pharmacologically active alkaloids[10], which are mostly b-carbolines such as harman, harmine, harmaline and harmalol.[11,12] Several reports indicate a wide spectrum of therapeutic activities for the crude extracts and these b-carbolines such as antinociceptive and analgesic effects[13,14] vasorelaxant[15,16] and hypothermic properties.[17] *P. harmala* and its alkaloid's activity against the protozoa and antibiotic resistant isolates of bacteria have been proved in earlier studies.[18] *P. harmala* derived protein (15KD) effectively alleviated the oxidative stress in erythrocytes, testes and brain of the experimental laboratory animals.[19] Similarly anti-diabetic and anti-oxidative properties of the plant seeds have been reported.[20]

Accordingly, in the present study was to clarify the antidiabetic role of *Peganum harmala* seeds water extract given orally in streptozotocin induced diabetic rabbits.

MATERIALS AND METHODS

Animals

Twenty local male rabbits were used in this experiment. Their body weight were from 1.31-1.52kg. The animals were grouped and housed in cages (100 *x* 85*x* 45 cm) at the laboratories of the zoology department, Omar AL- Mukhtar University. The animals were acclimatized to laboratory conditions for 10 days before commencement of the experiment. The photoperiod was regulated at 12 hours light / 12 hours dark cycle and temperature was adjusted at 25±1˚C. The rabbits were fed on commercial standard pellet and offered drink water *ad libitum.*

Plant Material and Preparation

The collected seeds of *Peganum harmala* L. were dried in air shade at room temperature. The dry seeds were then powdered and 100 g of powders were extracted in 500 ml of distilled water during 48 h at 65C˚. After filtration extracts were concentrated to 50 ml by rotary evaporation under vacuum at 35 C˚, then distributed in Petri dishes and leave for dried to powder at room temperature. The doses of 5mg/kg body weight. of *P. harmala* powder extract in 1ml distilled water[21] were used in this study.

Figure 1: *Peganum harmala* seeds.

Experimental design

The rabbits were divided randomly and equally in to 4 groups.

Group 1 (control group); the rabbits were treated by one ml of distilled water, once orally for 14 consecutive days.

Group 2 (diabetic group); diabetic mellitus was induced experimentally by treatment with streptozotocin (45 mg/kg), administered intraperitoneally.

Group 3 (diabetic+ *P.harmala* water extract). The rabbits in this group were suffering from diabetic mellitus, were treated for 14 consecutive days with a daily single oral dose of *P.harmala* water extract at dose 5mg/kg body weight. in 1ml distilled water by gavages' needle.

Group 4 these were normal rabbits, administered orally with the *P.harmala* water extract at dose 5mg/kg body weight. in 1ml distilled water by gavages' needle, for 14 consecutive days.

Induction diabetic mellitus

after the animals were fasted for 12 h they allowed access to the water before induction of diabetes. intraperitoneal injection of a freshly prepared solution of streptozotocin (STZ) **(Sigma Chemical Co., St. Louis, MO, USA)** in 0.05Mm citrate buffer (pH 4.5) at a dose of 45 mg/kg body weight per day for 3 days.[22] rabbits with blood glucose level of more than 300 mg/dl were considered diabetic and used for this study.

Biochemical Evaluations

At the end of the experimental period overnight fasting animals were sacrificed. Blood was collected in two cleaned vials, one with anticoagulant (EDTA) for separation of plasma for determination of catalase (CAT) and glutathione S – transferase (GST).The second vial was without anticoagulant and used for serum separation for determination of glucose, triglycerides, total cholesterol, activities of aspartate transaminase (AST) and alanine transaminase (ALT), urea, creatinine, and insulin. Both plasma and sera were obtained by centrifugation at 3000 rpm for 10 min.

RESULTS

Table 1 shows serum glucose, insulin concentrations. Serum glucose level was significantly elevated in STZ-diabetic rabbits and the percentage increase was 214.76%. *Peganum harmala* seeds aqueous extract supplementation significantly decreased STZ-induced hyperglycemia, the percentage reduction was - 64.60% in comparison with the diabetic control. Normal rabbits administered an aqueous extract of *Peganum harmala* seeds showed a significant decrease in their serum glucose concentrations as compared to the normal control (untreated), The percentage of decrease, as compared to the normal control rabbits (untreated) were found - 29.52% (Table 1 and figure 2). Accordingly, there was a significant decrease in serum insulin concentrations in diabetic rabbits, compared with normal control-56.07% and administration of *Peganum harmala* seeds water extract tended to increase the insulin levels and the percentage elevation was 112.77% as compared to the diabetic control (Table 1 and figure 3).

Table 1: Effect of treatment with seeds aqueous extract of *Peganum harmala* on serum glucose and insulin of diabetic and normal rabbits.

Groups / Parameters	(G1) Control	(G2) Diabetic	(G3) Diabetic+*P.harmala*	(G4) Normal+*P.harmala*
Glucose (mg/dl)	96.20±8.16	302.80±7.33[a] **214.76**	107.20±5.56[b] **11.43** **- 64.60**	67.80±2.33[a] **- 29.52**
% of Change from G1				
% of Change from G2				
Insulin (mU/ml)	2.14±0.00	0.94±0.03[a] **- 56.07**	2.00±0.00[ab] **- 6.54** **112.77**	2.13±0.01 **- 0.47**
% of Change from G1				
% of Change from G2				

Values are given as mean ± SE for 5 rabbits in each group.

[a] significant (P< 0.05) as compared with control group (G1).

b significant (P< 0.05) as compared with the (G2).

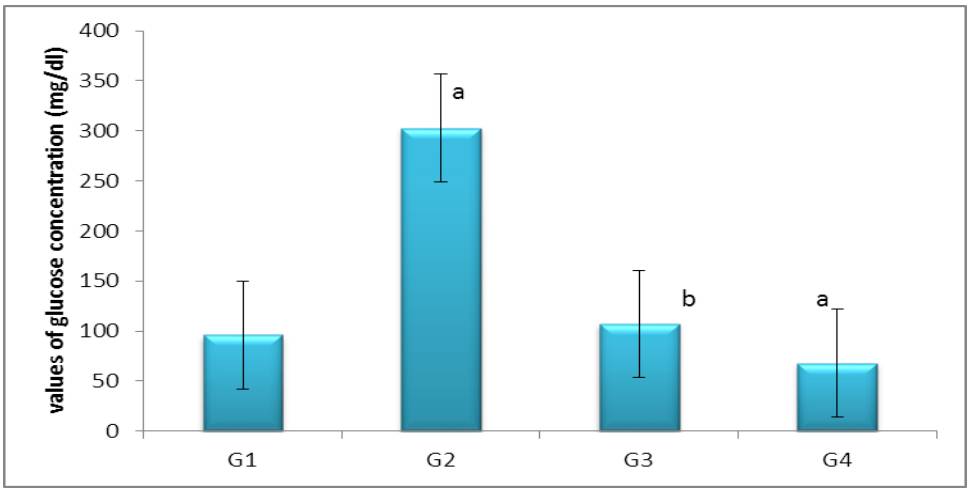

Figure 2: Values of glucose concentration (Means ± SE) for control and treated groups of rabbits.

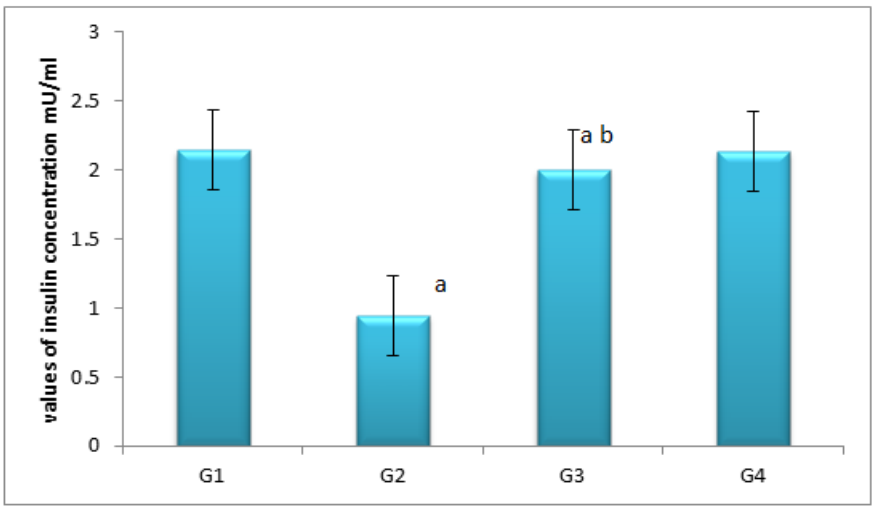

Figure 3: Values of insulin levels (Means ± SE) for control and treated groups of rabbits.

Serum triglycerides level was increased in STZ diabetic rabbits and the percentage of increase was 83.45%, when compared with the normal control rabbits. Daily administration of *Peganum harmala* seeds water extract for 14 days succeeded to reduce their concentrations significantly (Table 2 and figure 4), the percentage of reduction was -34.92%, when compared with corresponding diabetic control rabbits. However, administration of *Peganum harmala* seeds powder water extract caused a significant increase in serum triglycerides concentration of normal rabbits with percentage change of 53.43%, as compared to the corresponding normal control group. Meanwhile, a non-significant change was recorded in serum cholesterol level of rabbits after the treatment with an aqueous extract of *Peganum harmala* seeds powder in both the diabetic or non diabetic rabbits as compared to the corresponding control group (Table 2, figure 5).

Table 2: Effect of treatment with seeds aqueous extract of *Peganum harmala* on serum Triglycerides and Cholesterol of diabetic and normal rabbits.

Groups / Parameters	(G1) Control	(G2) Diabetic	(G3) Diabetic+*P.harmala*	(G4) Normal+*P.harmala*
Triglycerides (mg/dl)	84.60±0.98	155.20±1.36 [a]	101.00±7.12 [a b]	129.80±1.83 [a]
% of Change from G1		**83.45**	**19.39**	**53.43**
% of Change from G2			**- 34.92**	
Cholesterol (mg/dl)	65.40±21.69	55.00±0.63	42.60±3.34	34.80±2.13
% of Change from G1		**- 15.90**	**- 34.86**	**- 46.79**
% of Change from G2			**- 22.55**	

Values are given as mean ± SE for 5 rabbits in each group.

[a] significant (P< 0.05) as compared with control group (G1).

b significant (P< 0.05) as compared with the (G2).

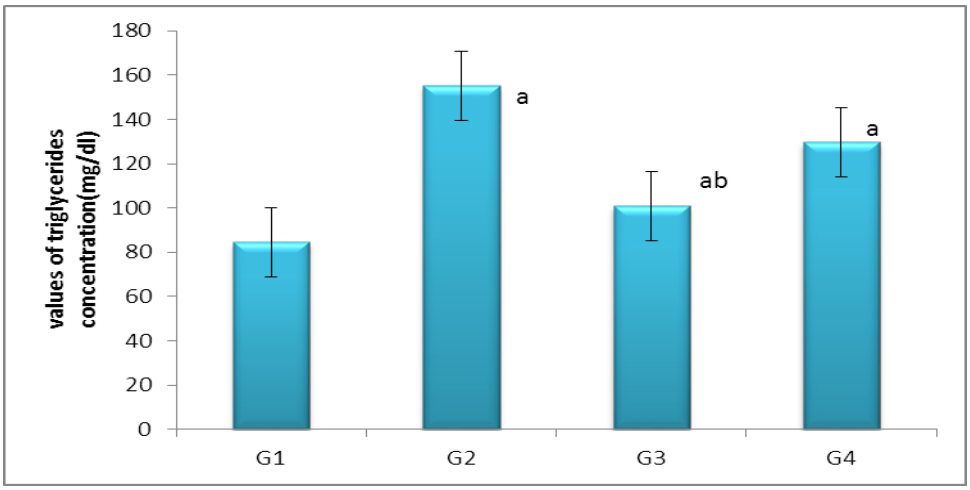

Figure 4: Values of triglycerides levels (Means ± SE) for control and treated groups of rabbits.

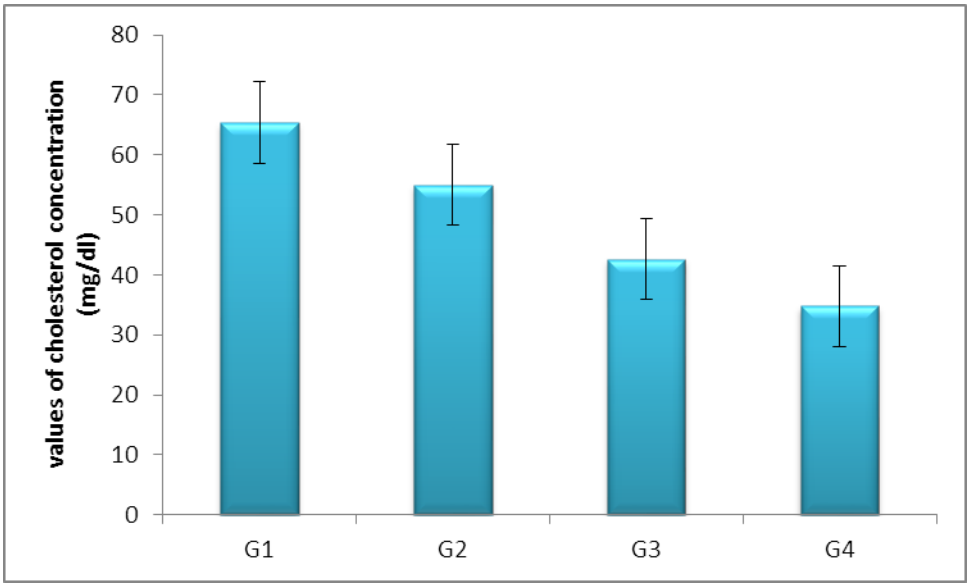

Figure 5: Values of cholesterol levels (Means ± SE) for control and treated groups of rabbits.

Intraperitoneal injection of streptozotocin (45 mg/kg b.wt.) significantly increased the concentration of serum creatinine as compared to the normal control group. On the other hand, serum creatinine concentration of diabetic rabbits orally administered the aqueous extract of *Peganum harmala* seeds powder decreased significantly as compared to the diabetic rabbits. The percentage of decrease was -72.67% (Table 3, figure 6). However, administration of *Peganum harmala* seeds powder water extract caused a non - significant change in serum creatinine concentration of normal rabbits, as compared to the corresponding normal control group. A significant increase was recorded in the serum urea concentration of diabetic rabbits. The percentage of increase was 28.71%, as compared to the normal control rabbits (Table 3, figure 7). Serum urea level of treated diabetic rabbits decreased significantly after 14 days of oral administration of seeds powder extract of *Peganum harmala*. The percentage of decrease was -65%, as compared to the corresponding values of diabetic rabbits. Oral administration of seeds powder aqueous extract of *Peganum harmala* for 14 days caused a non-significant change in the serum urea concentration of normal rabbits (Table 3).

Table 3: Effect of treatment with seeds aqueous extract of *Peganum harmala* on serum Creatinine and Urea of diabetic and normal rabbits.

Groups / Parameters	(G1) Control	(G2) Diabetic	(G3) Diabetic+*P.harmala*	(G4) Normal+*P.harmala*
Creatinine (mg/dl)	0.86±0.02	3.44±0.27 [a]	0.94±0.09 [b]	0.94±0.02
% of Change from G1		**300**	**9.30**	**9.30**
% of Change from G2			**- 72.67**	
Urea (mg/dl)	40.40±1.03	52.00±2.14 [a]	18.20±2.13 [a b]	32.80±5.63
% of Change from G1		**28.71**	**- 54.95**	**- 18.81**
% of Change from G2			**- 65**	

Values are given as mean ± SE for 5 rabbits in each group.

[a] significant (P< 0.05) as compared with control group (G1).

b significant (P< 0.05) as compared with the (G2).

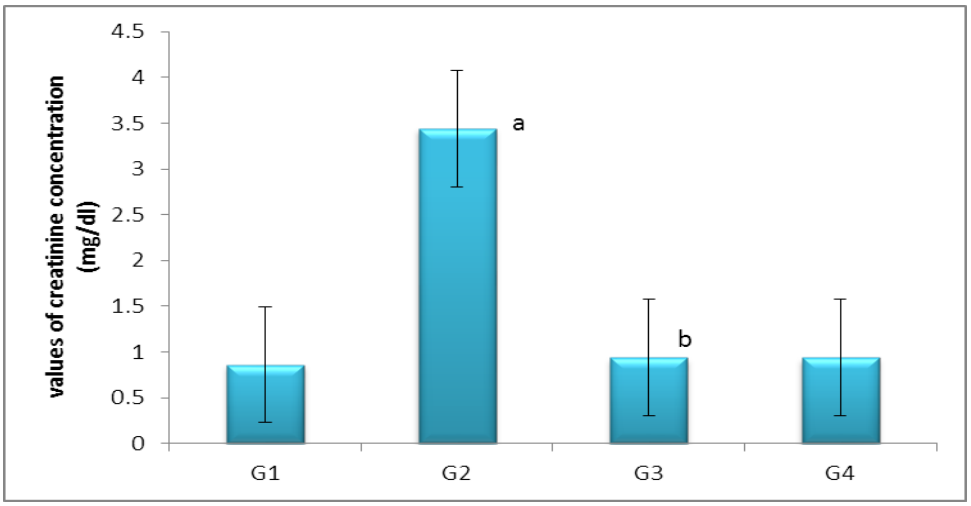

Figure 6: Values of creatinine levels (Means ± SE) for control and treated groups of rabbits.

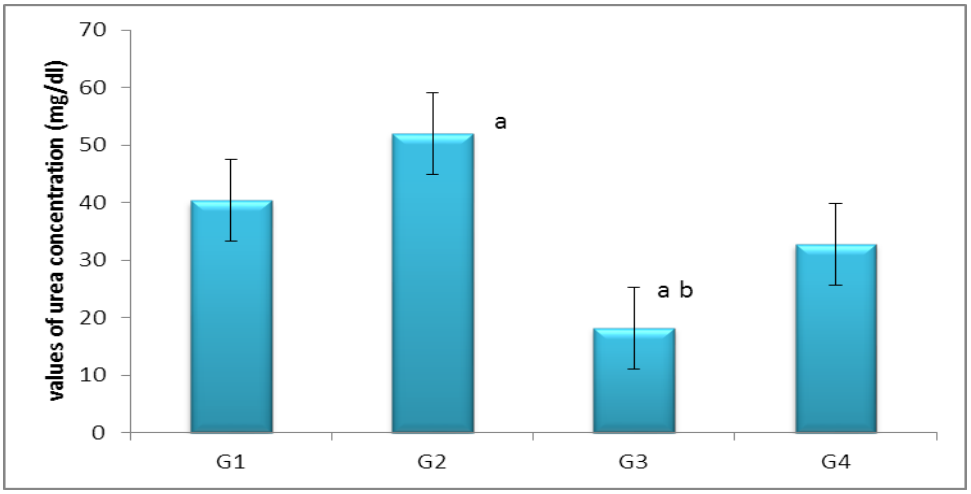

Figure 7: Values of urea levels (Means ± SE) for control and treated groups of rabbits.

As shown in Table 4 and figures(8,9), the activities of liver function markers (AST, ALT,) were significantly elevated in STZ-diabetic rabbits by 47.73%, 73.26%, respectively when compared with the normal controls rabbits. Rabbits administrated *Peganum harmala* seeds powder water extract for 14 days showed significant reduction in these marker enzyme activities. The percentage of decrease, when compared to diabetic control rabbits, was -29.33%, -10.25%, respectively. Oral administration of seeds powder aqueous extract of *Peganum harmala* for 14 days caused a non-significant change in the serum (AST, ALT,) activities of normal rabbits (Table 4, figure 8,9).

Table 4: Effect of treatment with seeds aqueous extract of *Peganum harmala* on serum AST and ALT activities of diabetic and normal rabbits.

Groups / Parameters	(G1) Control	(G2) Diabetic	(G3) Diabetic+P.harmala	(G4) Normal+P.harmala
AST (U/L)	42.53±1.07	62.83±0.74[a] **47.73**	44.40±1.50[b] **4.40** **- 29.33**	40.00±0.36 **- 5.95**
% of Change from G1				
% of Change from G2				
ALT (U/L)	37.17±0.71	64.40±2.62 [a] **73.26**	57.80±0.49 [a b] **55.50** **- 10.25**	34.19±0.48 **- 8.02**
% of Change from G1				
% of Change from G2				

Values are given as mean ± SE for 5 rabbits in each group.

[a] significant (P< 0.05) as compared with control group (G1).

b significant (P< 0.05) as compared with the (G2).

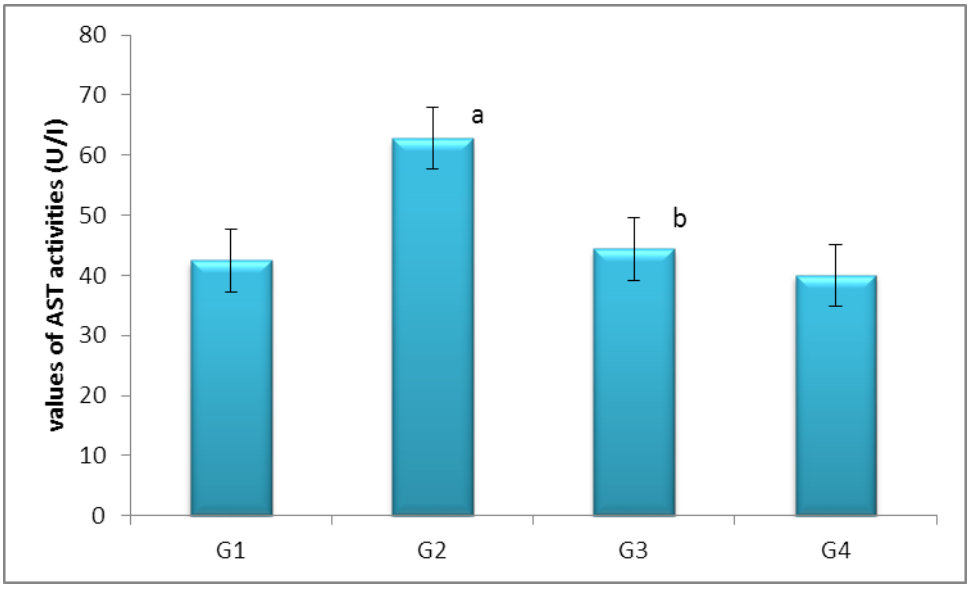

Figure 8: Values of AST activities (Means ± SE) for control and treated groups of rabbits.

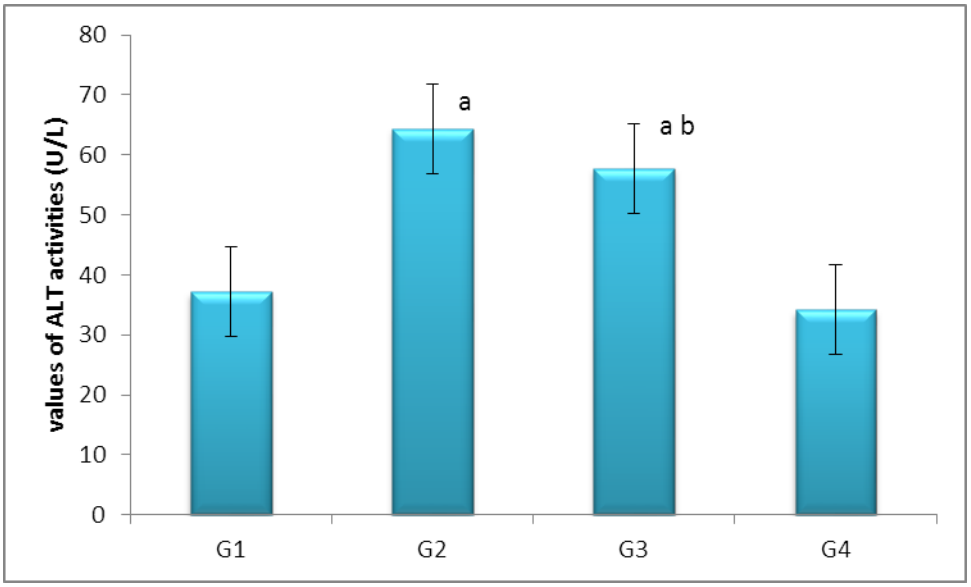

Figure 9: Values of ALT activities (Means ± SE) for control and treated groups of rabbits.

A significant decrease in CAT (-50.58%) and GST (-59.74%) plasma levels in rabbits with STZ- induced diabetes was recorded compared to that of normal control rabbits (Table 5, figures 10,11). Administration of *Peganum harmala* seeds powder water extract for 14 days, caused a significant elevation in the levels of CAT (74.99%) and GST (118.55%) when compared to diabetic control rabbits (Table 5, figures 10, 11). However, administration of *Peganum harmala* seeds powder water extract caused a significant increase in plasma (CAT, GST,) activities of normal rabbits with percentage change of 53.67% and 240.56%, respectively, as compared to the corresponding normal control group.

Table 5: Effect of treatment with seeds aqueous extract of *Peganum harmala* on plasma CAT and GST activities of diabetic and normal rabbits.

Groups / Parameters	(G1) Control	(G2) Diabetic	(G3) Diabetic+P.harmala	(G4) Normal+P.harmala
CAT (U/L)	155.58±19.84	76.89±7.55**a**	134.55±0.37**b**	239.08±23.12 **a**
% of Change from G1		**- 50.58**	**- 13.52**	**53.67**
% of Change from G2			**74.99**	
GST (U/L)	424.61±9.78	170.96±9.82 **a**	373.64±7.56 **b**	1446.07±125.84**a**
% of Change from G1		**- 59.74**	**- 12.00**	**240.56**
% of Change from G2			**118.55**	

Values are given as mean ± SE for 5 rabbits in each group.

[a] significant (P< 0.05) as compared with control group (G1).

b significant (P< 0.05) as compared with the (G2).

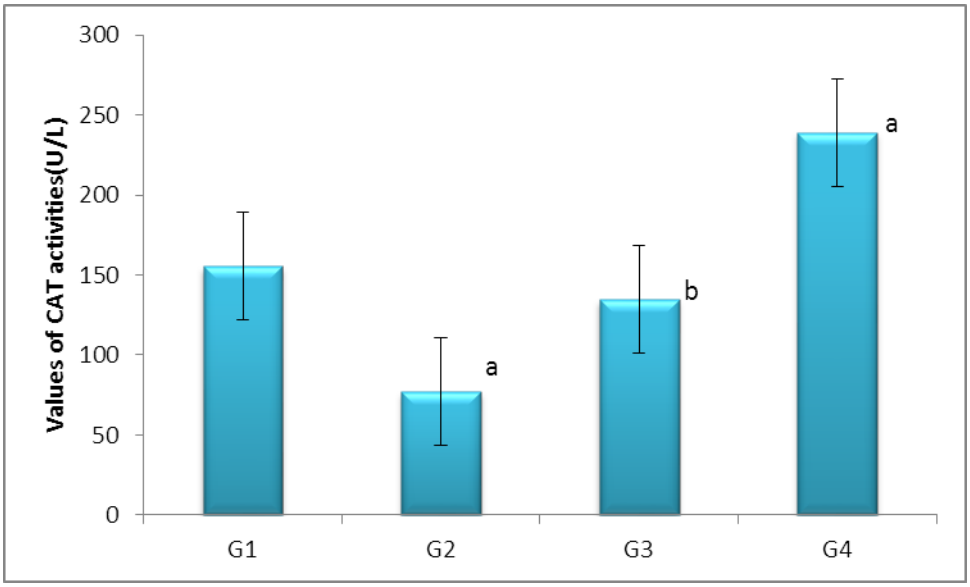

Figure 10: Values of CAT activities (Means ± SE) for control and treated groups of rabbits.

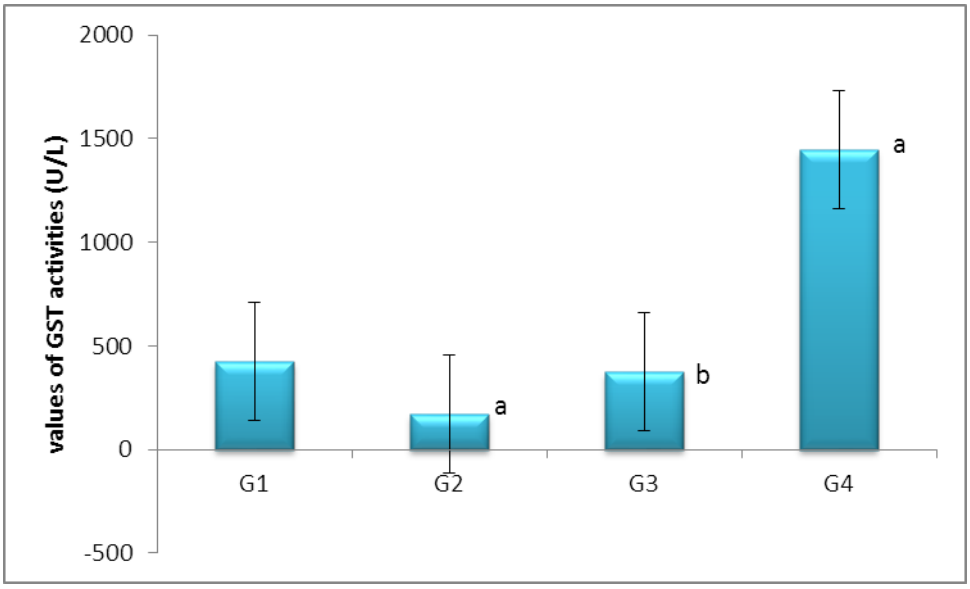

Figure 11: Values of GST activities (Means ± SE) for control and treated groups of rabbits.

DISCUSSION

Fasting blood sugar in diabetic rabbits represents an important indicator of diabetic status. In the present study, observed significant decrease in serum glucose and elevated insulin level when STZ-diabetic rabbits were administered *Peganum harmala* seeds powder. *Peganum harmala* has been traditionally used to treat diabetes in folk medicine of some parts of the world.[23,24] This effect of *Peganum harmala* has been pharmacologically confirmed in several studies one of which showed that the plant would lose its hypoglycemic activity at

high doses instead of increasing it.[25] The hypoglycemic effect of bilberry may be because of α-glucosidaseactivity[26], insulin secretion[27] and also glucose transport.[28] Many authors have explained the antidiabetic effect of plants. They may stimulate insulin secretion from ß cells and induce regeneration, revitalization and/ or hyperplasia of the ß cells. Moreover, extracts of antidiabetic plants can act by imitating the action of insulin, an "insulin-like action". Antidiabetic plants can act by supplying ß cells with the necessary elements (Cu++, Mg++, Ca++). These plant extracts can also reduce the action of insulinase, an enzyme that destroys the insulin in the liver. On the other hand, extracts from antidiabetic plants may act on glucose homeostasis in a non-insulindependent diabetes model. They can decrease the level of glucagon, induce a decrease in the intestinal absorption of glucose and/or reduce the peripheral use of glucose. Moreover, they may act on liver enzymes causing stimulation of glucogenogenesis and/or inhibition of the glycogenolysis.[29] Harmine is the main alkaloid of *P. harmala* that is involved in its anti-diabetic effect.[30] One study shows that harmine regulates the expression of peroxisome proliferator-activated receptor gamma (PPARγ), the main regulator of adipogenesis and the molecular target of the thiazolidinedione antidiabetic drugs, through inhibition of the Wnt signaling pathway. Therefore, it mimics the effects of PPARg ligands on adipocyte gene expression and insulin sensitivity without showing the side-effects of thiazolidinedione drugs such as weight gain.[31]

Diabetes is a metabolism-associated disease, particularly closed related to lipid metabolism, affecting the plasma lipid and lipoprotein profile.[32] The current data demonstrated the occurrence of serum hypertriglyceridemia in STZ-diabetic rats. These findings agree with Veerapur *et al*[33], who indicated that the levels of serum lipids are usually elevated in diabetes mellitus and such elevation represents a risk factor for coronary heart disease. There is significant decrease in serum triglycerides in *Peganum harmala* seeds powder water extract treated diabetic rabbits. These results agree with the findings recorded by Vahidi-eyrisofla1., *et al*[34], who reported that total cholesterol, triglycerides and LDL cholesterol showed gradual significant decrease with the increasing dose level of *P. harmala* up to 250 mg/ml in drinking water.and lowering effect of *P.harmala* L 200,400 mg/kg dosage on triglyceride in treatment group compare by control group significant differences. The results show that with increasing extract dose, CYP7A1 gene expression is increased significant difference.

The significant increases in serum urea and creatinine observed in the STZ-induced diabetic rabbits could be attributed to the functional and/or morphological changes in the kidneys.[35]

The present results revealed that treatment of diabetic rabbits with *Peganum harmala* seeds powder water extract ameliorated the recorded increase in their serum urea and creatinine levels. These results are in agreement with Saddam Yahya Diwan**.**[36], who indicated this activity may be due to the presence of many active compounds in the extract of *P. harmala* like alkaloids and flavinoids. mahajan *et al*.,[37] reported that Alkaloids impaired the kidney and liver functioning. Wang *et al*.,[38] reported that alkaloids have been showed to exert protective effects on the renal function. Long *et al*.,[39] reported that flavonoids compounds prevents nephrotoxicity and improves kidney functions and promotes kidney primary epithelial tubular cell regeneration. Also, De *et al.,*[40] also reported that flavonoids mixture significantly lowered plasma creatinine and urea concentration, booth indicating a better postoperative kidney function.

The elevation of biomarker enzymes, such as serum AST, ALT was observed in diabetic control rabbits indicating the hepatic damage.[41] The present study illustrated a significant increase in serum AST, ALT activities in STZ-induced diabetic rabbits. These results agree with the findings recorded by Maritim *et al*[42] and Jung *et al*[43], who reported that the rise in activity of these enzymes is mainly due to their leakage from liver into blood stream. Administrating *P. harmala* seeds powder to STZ-diabetic rabbits reduction the activities of the AST and ALT. This could be due to the presence of flavonoids which are known for their excellent antioxidative capacity in various model systems.[44] In addition *P. harmala* have in their content active compounds such as vitamin A, B, C, E, and K, with high mineral content such as sodium iron, and calcium. These compounds have a strong antioxidant activity against reactive oxygen species (ROS), and the hepatoprotective activity.[45] Qi *et al.,*[46] reported that flavonoids compounds have a hepatoprotection function and has been used for clinical treatment of liver. Novikoff[47] reported that alkaloids compounds rapidly induce liver cells against toxicity. Also, Raj[48], reported that alkaloid compounds were able to normalize the biochemical levels which were altered due to intoxification. Khaled Hamden**,** *et al*.,[49] who reported that is probably related to the richness of this plant in substances of phenolic nature which may decrease the free-radical lipid peroxidation level leading to the stabilisation of membrane structures.

Earlier reports revealed that STZ-induced diabetic animals may exhibit most of the diabetic complications mediated through oxidative stress.[50] Oxidative stress in diabetes is coupled to

a decrease in the antioxidant status, which can increase the deleterious effects of free radicals.[51]

Besides the enzymatic antioxidants such as CAT and GST is also an important antioxidant.[52] The findings of this study shows a significant decrease in the activity of CAT and GST in STZ-induced diabetic rabbits. Administrating *P. harmala* to diabetic rabbits caused a significant increases in the activities of CAT and GST . Many pharmacological studies suggest an antioxidant and free radical scavenging effect of *P. harmala.* This effect has been attributed to the increasing effect of *P. harmala* extract on E2 (17β-estradiol) level as an important antioxidant and reactive oxygen species (ROS) scavenger[53,54,55] In another study, the effects of harmaline and harmalol were tested on Digoxin-induced cytochrome P450 1A1 (CYP1A1), a carcinogen-activating enzyme, in human hepatoma HepG2 cells. These alkaloids significantly inhibited the enzyme via both transcriptional and posttranslational mechanisms in a concentration-dependent manner.[56] In some cases, *P. harmala* showed a higher selectivity towards malignant cells than common anticancer drugs like doxorubicin.[57]

CONCLUSIONS

Peganum harmala seeds aqueous extract supplementation exhibited a hypoglycemic function and would be helpful in the prevention of diabetic complications through improving hyperlipidemia and enhancing the antioxidant defense system. However, the precise hypoglycemic mechanisms of these seeds were not investigated in this work and further investigations in purifying the active compounds from the seeds will be necessary to elucidate the precise mechanisms of their hypo- glycemic, correcting oxidative stress and hypolipidemic actions.

REFERENCES

1. Beretta A. (2001). Campanha de prevencao e diagnostic do diabetes realizada pela UNIARARAS e prefeitura municipal na cidade de Araras. Laes and Haes, 22(131): 188-200.
2. Nayak BS, Marshall JR, Isitor G, Adogwa A. (2011). Hypoglycemic and hepatoprotective activity of fermented fruit juice of Morinda citrifolia (Noni) in diabetic rats. *Evid Based Complement Alternat Med*, 875293.
3. Cho SY, Park JY, Park EM, Cho MS, Lee MK, Jeon SM, Kim MJ, Park YB.(2002). Alternation of hepatic antioxidant enzyme activities and lipid profile in streptozotocin-

induced diabetic rats by supplementation of dandelion water extract. *Clin Chim Acta,* 317: 109-117.

4. Gupta RK, Kesari AN, Murthy PS, Chandra R, Tandon V, Watal G. (2005).Hypoglycemic and antidiabetic effect of ethanolic extract of leaves of Annono squamosal L in experimental animals. *J Ethnopharmacol*, 99: 75-81.
5. Hilal HS, Young Ken HW. (1983). Certain poisonous plants of Egypt. In: Dokki, Editor, Pharmaceutical Society of Egypt, The National Information and Documentation Centre, NIDOC, Cairo, Egypt, 88-90.
6. EL-Bahri L, Chemli R.(1991). *Peganum harmala* L.: a poisonous plant of North Africa. *Vet Hum Toxicol*, 33: 276-277.
7. Bnouham M, Mekhfi H, Legssyer A, Ziyyat A. (2002). Medicinal plants used in the treatment of diabetes in Morocco. *Int J Diabetes Metab*, 10: 33–50.
8. Bellakhdar J.(1997). Medecine arabe ancienne et savoirs populaires. Paris: Ibis Press. *La pharmacopee marocaine traditionnelle*, 529–30.
9. Nafisi S, Asghari MH, Nezhadi MA, Ekhtiari MS.(2011). Possible antidiabetic effect of Peganum harmala on streptozocine-induced mouse. *World Appl Sci J*, 14: 822–4.
10. Hilal, H.S, Young ken, H.W, (1983). Certain poisonous plants of Egypt. In: Dokki (Ed.), Pharmaceutical Society of Egypt. The National Information and Documentation Centre, NIDOC, Cairo, Egypt, 88–90.
11. El-Saad El-Rifaie, M, (1980). Peganum harmala. Its use in certain dermatoses. *Int. J. Dermatol*, 19: 221–222.
12. Kartal, M, Altun, ML, Kurucu, S, (2003). HPLC method for the analysis of harmol, harmalol, harmine and harmaline in the seeds of *Peganum harmala L. J. Pharm. Biomed. Anal*, 31: 263–269.
13. Monsef HR, Ghobadi, A, Iranshahi, M, Abdollahi, M, (2004). Antinociceptive effects of Peganum harmala L. alkaloid extract on mouse formalin test. *J. Pharm. Pharm. Sci*, 7: 65–69.
14. Farouk L, Laroubi A, Aboufatima R., Benharref A, Chait A, (2008). Evaluation of the analgesic effect of alkaloid extract of Peganum harmala L.: possible mechanismsinvolved. *J. Ethnopharmacol*, 115: 449–454.
15. Shi CC., Liao JF, Chen CF, (2001). Comparative study on the vasorelaxant effects of three Harmala alkaloids in vitro. *Jpn. J. Pharmacol*, 85: 299–305

16. Berrougui H, Martín-Cordero C, Khalil A, Hmamouchi M, Ettaib A, Marhuenda E, Herrera MD, (2006). Vasorelaxant effects of harmine and harmaline extracted from Peganum harmala L. seeds in isolated rat aorta. *Pharmacol. Res,* 54: 150–157.
17. Kuhn MA, Winston D, (2000). Herbal Therapy and Supplements, a Scientific and Traditional Approach. Lippincott, *New York,* 347–350.
18. Arshad N, Zitterl-Eglseer K, Hasnain S, Hess M, (2008). Effect of Peganum harmala or its betacarboline alkaloids on certain antibiotic resistant strains of bacteria and protozoa from poultry. *Phytother Res*, 22: 1533-1538.
19. Soliman AM, Fahmy SR.. (2011). Protective and curative effects of the 15 KD isolated protein from the Peganum harmala L. seeds against carbon tetrachloride induced oxidative stress in brain, tests and erythrocytes of rats. *Eur. Rev. Med. Pharmacol. Sci*, 15: 888-899.
20. Singh AB, Khaliq T, Chaturvedi JP, Narender T, Srivastava AK. (2012). Anti-diabetic and anti-oxidative effects of 4- hydroxypipecolic acid in C57BL/KsJ-db/db mice. *Hum. exp. Toxicol,* 31: 57-65.
21. Ahmad M, Ashraf M, Khan M S, Javeed A, Durrani A Z, Khan MR, Altaf,I, Ijaz M, Malik NA. (2013). Toxic Effects of Chloroform and Aqueous Extracts of *Peganum harmala* on Hematological and Growth Parameters in Rabbits. *Pakistan J. Zool*, 45(4): 989-995.
22. Kamalakkanan N, Rajadurai M, Prince PSM. (2003). Effect of *Aegle marmelos* fruits on normal and streptozotocin-diabetic wistar rats. *J. Med. Food,* 3: 93-98.
23. Bnouham M, Mekhfi H, Legssyer A, Ziyyat A. (2002). Medicinal plants used in the treatment of diabetes in Morocco. *Int J Diabetes Metab, 10: 33–50.*
24. Bellakhdar J. (1997). Medecine arabe ancienne et savoirs populaires. Paris: Ibis Press; *La pharmacopee marocaine traditionnelle,* 529–30.
25. Nafisi S, Asghari MH, Nezhadi MA, Ekhtiari MS. (2011) .Possible antidiabetic effect of *Peganum harmala* on streptozocine-induced mouse. *World Appl Sci J,* 14: 822–4.
26. McDougall GJ, Kulkarni NN, Stewart D. (2008). Current developments on the inhibitory effects of berry polyphenols on digestive enzymes. *Biofactors,* 34(1): 73-80.
27. Jayaprakasam B, Vareed SK, Olson LK, Nair MG.(2005). Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. *J Agric Food Chem,* 53(1): 28-31.
28. Martineau LC, Couture A, Spoor D, Benhaddou- Andaloussi A, Harris C, Meddah B, *et al*. Antidiabetic properties of the Canadian lowbush blueberry Vaccinium angustifolium Ait. *Phytomedicine,* 2006; 13(9-10): 612-23.

29. Mohamed Bnouham, Hassane Mekhfi, Abdelkhaleq Legssyer, Abderrahim Ziyyat (2002)*: Ethnopharmacology Forum* Medicinal plants used in the treatment of diabetes in Morocco. *Int J Diabetes & Metabolism,* 10: 33-50.
30. Fortunato JJ, Réus GZ, Kirsch TR, Stringari RB, Stertz L, Kapczinski F, *et al*. Acute harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry,* 2009; 33: 1425–30.
31. Waki H, Park KW, Mitro N, Pei L, Damoiseaux R, Wilpitz DC, *et al*. (2007). The small molecule harmine is an antidiabetic cell-type-specific regulator of PPAR sssssgamma expression. *Cell Metab,* May; 5(5): 357-70.
32. Pushparaj PN, Low HK, Manikandan J, Tan BKH, Tan CH. (2007). Anti-diabetic effects of Cichorium intybas in streptozotocin-induced diabetic rats. *J Ethnopharmacol,* 111: 430-434.
33. Veerapur VP, Prabhakar KR, Parihar VK, Bansal P, Srintvasan KK, Priyadarsini KI, Unnikrishnan MK. (2010). An- tidiabetic, hypolipidemic and antioxidant activity of Dodonaea viscosa aerial parts in streptozotocin- induced diabetic rats. *Int J Phytomed,* 2: 59-70.
34. Nazila Vahidi-eyrisofla, Sepide Jafarzade Rastin, Fateme Taghvaei, Mehdi Ahmadifar, Ali Mohammad Eini. (2015). Effect of *Peganum Harmala* L. on lipid Metabolism and Changes Cyp7a1 gene Expression in male Wistar Rat. *Bhu.J.RNR,* 3.1: 213-220.
35. Alderson NL., Chachich ME, Frizzell N, Canning P, Metz TO, Januszewski AS. (2004). Effect of antioxidants and ACE inhibition on chemical modification of proteins and progression of nephropathy in streptozotocin diabetic rat. *Diabetologia,* 47: 1385-1395.
36. Diwan SY. (2013). Effect of Peganum Harmala Methanol Extract on Liver and Kidney of Mice Administered MTX Drug. *Journal of Al-Nahrain University*, December, 16(4): 161-166.
37. Mahajan M, Kumar V, Yadav S, K.(2011) "Alkaloids: Properties', Application and Pharmacological Effects". ***ISBN:*** *978-1-61761-130-8*
38. Wang Y, Fu X., Wang X, Jia X, Gu X, Zhang J, Su J, Hao G, Jiang Y, Fan W, Wu W, Li S.(2011). "Protective effects of anisodamine on renal function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention"; *Tohoku J. Exp. Med,* 2: 7-91.
39. Long M, Qiu D, Li F, Johnson F, Luft B. (2005). "Flavonoid of Drynaria fortune protects against acute renal failure"; Phytotherapy Res, 19: 422–427.

40. De V H, Rj N, Pg B, Hofman Z, Pa V L, Van NK.(2006). "Effects of preoperative flavonoid supplementation on different organ functions in rats". *J Parenter Enteral Nutr,* Jul-Aug. 30: 8-302.
41. Selvan VT, Manikandan L, Senthil Kumar GP, Suresh R, Kakoti BB, Gomathi P, Kumar DA, Saha P, Gupta M, Mazumder UK. (2008). Antidiabetic and antioxidant effect of methanol extract of Atanema sesamoides in streptozotocin-induced diabetic rats. *Int Appl Res Nat Prod,* 1: 25-33.
42. Maritim AC, Sanders RA, Watkins JB. (2003). Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Toxicol,* 17: 24-38.
43. Jung CH, Zhou S, Ding GX, Kim JH, Hong MH, Shin YC, Kim GJ, Ko SG. (2006). Antihyperglycemic activity of herb extracts on streptozotocin-induced diabetic rats. *Biotechnol Biochem,* 70: 2556-2559.
44. Jahaniani F, Ebrahimi S A, Rahbar Roshandel N, Mahmoudian M.(2005). "Xanthomicrol is the main cytotoxic component of Dracocephalum kotschyii and a potential anti-cancer agent", *Phytochemistry,* 66(13): 1581–1592.
45. Zaker F, Ody A, Arjmand A.(2007). "A study on the antitumoral and differentiation effects of Peganum harmala derivatives in combination with atra on leukaemic cells", *Arch Pharm Res,* 30: 844–849.
46. Qi L, Chun-Yu Liu; Wen-Qian Wu; Zhen-Lun Gu; Ci-Yi Guo. (2010). "Protective effect of flavonoids from Astragalus complanatus on radiation induced damages in mice", 82: 383-392.
47. Novikoff P M, Touster O, Novikoff A B, Tulsiani D P.(1985). "Effects of Swainsonine on Rat Liver and Kidney: Biochemical and Morphological Studies" *J. Cell Biol,* 101: 339-349.
48. Raj V P, Chandrasekhar R H, Vijayan P, Dhanaraj S A, Rao M. C, Rao V J, Nitesh K. (2008). "In vitro and in vivo hepatoprotective effects of the total alkaloid fraction of Hygrophila auriculata leaves". *Indian J. Pharmacol,* 42: 99-104.
49. Hamden K, Masmoudi H, Ellouz F, ElFeki1 A Carreau S.(2008). (Protective effects of *Peganum harmala* extracts on thiourea-induced diseases in adult male rat. Journal of Environmental Biology, January 2008; 29(1): 73-77.
50. Sathishsekar D, Subramanian S.(2005). Antioxidant properties of Momordica charantia (bitter gourd)seeds on streptozotocin-induced diabetic rats. *Asia Pac J Clin Nutr,* 14: 153-158.

51. Picton SF, Flatt PR.(2001) Differential acute and long term actions of succinic acid monomethyl ester. *Int J Exp Diabetes Res*, 2: 19-27.
52. Zhang W, Zhao J, Wang J, Pang X, Zhuang X, Zhu X, Qu W.(2010). Hypoglycemic effect of aqueous extract of seabuckthorn (Hippophaer hamnoides L.) seed residues in streptozotocin-induced diabetic rats. *Phytother Res*, 24: 228-232.
53. Berrougui H, Martín-Cordero C, Khalil A, Hmamouchi M, Ettaib A, Marhuenda E, *et al*.(2006). Vasorelaxant effects of harmine and harmaline extracted from *Peganum harmala* L. seeds in isolated rat aorta. *Pharmacol Res*, 54: 150–7.
54. Hamden K, Silandre D, Delalande C, Elfeki A, Carreau S.(2008). Protective effects of estrogens and caloric restriction during aging on various rat testis parameters. *Asian J Androl*, 10: 837–45.
55. Hamden K, Carreau S, Ayadi F, Masmoudi H, El Feki A.(2009). Inhibitory effect of estrogens, phytoestrogens, and caloric restriction on oxidative stress and hepato-toxicity in aged rats. *Biomed Environ Sci*, 22: 381–7.
56. El Gendy MA, El-Kadi AO.(2009). *Peganum harmala* L. Differentially modulates cytochrome P450 gene expression in human hepatoma HepG2 cells. *Drug Metab Lett*, 3: 212–6.
57. Jahaniani F, Ebrahimi SA, Rahbar-Roshandel N, Mahmoudian M.(2005). Xanthomicrol is the main cytotoxic component of *Dracocephalum kotschyii* and a potential anti-cancer agent. Phytochemistry, 66: 1581–92.