

## The Combination Effect of Five Herbal Drugs "Peganum Harmala, Quercus Infectoria, Vaccinium Myrtillus, Citrullus Colocynthis, Securigera Securidaca" on Blood Glucose

Zahra Kashi<sup>1</sup>, Khadijeh Rabiei<sup>2</sup>, Seyyed Saeid Mosavidarka<sup>3</sup>, Adele Bahar<sup>4\*</sup>, Ozra Akha<sup>1</sup>,  
Mohammad Karami<sup>5</sup>

1- Endocrinologist, Associate Professor, Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, Iran and Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences,

2- Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences Sari, Iran

3- Mazandaran University of Medical Sciences Sari, Iran

4- Endocrinologist, associate professor, Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences, Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

5- Associate Professor of Basic Toxicology, School of Pharmacy-Department of Toxicology Pharmacology, Mazandaran University of Medical Sciences, Sari, Iran.

### \*Correspondence:

Adele Bahar, Traditional and Complementary Medicine Research Center Diabetes Research Center, Imam Khomeini Hospital, Razi Street, Sari, Iran.

Email: doctor\_bahar2000@yahoo.com

Tel: (98) 113 337 8789

Fax: (98) 113 337 8789

Received: 25 October 2014

Accepted: 21 December 2014

Published in February 2015

### Abstract

**Objective:** There are some studies about the good effects of herbal medicine on blood glucose. This study was designed to evaluate the synergism effect of Peganum Harmala (P.harmala), Quercus Infectoria (Q.i), Vaccinium Myrtillus (V.myrtillus), Citrullus Colocynthis (C.colocynthis), Securigera Securidaca (S.s) on blood glucose in type 2 diabetic patients.

**Materials and Methods:** Twenty four type 2 diabetic patients were enrolled in this cross over double- blinded clinical trial for receiving two months herbal medication and placebo. The subjects divided into two groups randomly. One group received herbal medication (the doses of 25mg/person of V.myrtillus, S.s and Mazoj and 62.5mg C.colocynthis, P.harmala) and the other group received placebo for 8 weeks. After washout period the herbal medication and placebo were replaced for the next 8 weeks. T-test and Chi-square were used for the comparison of variables between two groups.

**Results:** After two months, mean fasting blood glucose was  $135 \pm 27.1$  and  $139 \pm 36.8$  mg/dl, ( $P$ -value=0.64), and mean glycosylated hemoglobin was  $6.5 \pm 0.75$  and  $6.6 \pm 0.97$  percent, with herbal medication and placebo, respectively ( $P$ -value=0.51). About 15.4% of patients after herbal medication and 15.4 % after placebo consumption had 0.8% reduction in HbA1C ( $P$ -value=1/0). The mean HOMA IR index, after two months intervention with herbal medication or placebo, was  $2.9 \pm 1.95$  and  $3.9 \pm 1.97$ , respectively ( $P$ -value=0.05).

**Conclusion:** low dose combination of P.harmala, Q.i, V.myrtillus, C.colocynthis, S.s may improve the insulin sensitivity and we did not find significant effect on blood glucose with low dose of this combination.

**Keywords:** Diabetes mellitus, Herbal medication, Insulin sensitivity, Glycosylated hemoglobin

### Introduction

Diabetes mellitus is the most prevalent and costly chronic disease estimated up to 2025 which will get to 439 million diabetic patients (1-2). Diet, exercise

and chemical glucose lowering medicine are used for blood glucose control but despite the use of multiple oral medications many patients suffer from high blood glucose and most

patients do not accept to use insulin injection(2). Uncontrolled diabetes mellitus is associated to serious micro and macrovascular complications (3-4). The use of herbal medicine is more accepted by the patients and many people use the herbal medicine without enough information about the efficacy or side effects of herbal medicine.

The use of medicinal plants has flourished as an alternative for the treatment of diabetes because modern medicines are tagged with several side effects and are also expensive. A multitude of herbs, medicinal plants and some compounds purified from them have been studied for the treatment of diabetes throughout the world .the herbal medicine might provide a basis of new synthetic antidiabetic analogues with potent activity. There are some studies about the acceptable effects of herbal medicine on blood glucose (5-6). This cross over double- blinded clinical trial was designed to evaluate the synergism effect of *Peganum harmala* (P.harmala), *Quercus infectoria* (Q.i), *Vaccinium myrtillus*(V.myrtillus), *Citrullus colocynthis*(C.colocynthis), *Securigerasecuridaca*(S.s) on blood glucose, this native herbal combination are used in our region for type two diabetic patients.

## Materials and Methods

After approval the research by the Ethics Board Committee of Mazandaran University of Medical Sciences, Sari, Iran (IRCT code 138811143180N1), this cross over double-blinded clinical trial was conducted on 20 type 2 diabetic patients who referred to Diabetes Healthcare Center in Sari, Iran from 2008 to 2011. The calculated sample size was 19 cases according to  $\alpha=0.05, \beta=0.9$  and minimal detectable difference in mean of HbA1C 0.8. The inclusion criteria were age range of 30 to 80 years old and  $HbA1C \leq 8\%$  and no medication for diabetes control. Immune deficiency, pregnancy and lactation, cardiovascular disease, current use of corticosteroids and thiazide, uncontrolled thyroid dysfunction, acute infection, history of

diabetic ketoacidosis,  $Cr > 1.5$  for male and  $> 1.4$  mg dl for female, acute hepatitis, cirrhosis, proliferative retinopathy and severe weight loss (at least 10% during the last 6 months) were considered as exclusions criteria .All patients were entered into the study after giving an informed consent. The 0.8 percent glycosylated hemoglobin reduction and difference was considered as good response to intervention.

## Plant Material

The plants were collected from Mazandaran (a Northern state in Iran) in November 2010 and dried in shadow followed by grinding. The selected plants were identified and confirmed by Department of Pharmacognosy. A voucher specimen has been deposited in Sari School of Pharmacy Herbarium. Fruits and seeds parts were dried at room temperature and powdered before encapsulation. Following the preliminary study, the doses of 25mg/person of V.myrtillus, S.s and Mazoj and 62.5mg C.colocynthis, P.harmala were chosen for the remaining of the study in order to evaluate the synergism effects of the plants on blood glucose. The placebo was lentil flour that was put in similar capsule. The maximum effects of V.myrtillus, S.s, Mazoj and C.colocynthis, P.harmala were observed at a dose of 250mg/person and 125 mg/person o.p respectively.

Sequential sampling was used and all the participants filled out the consent form. Information about age, sex, history of hyperlipidemia and hypertension were recorded in a checklist. Blood pressure, weight and height were measured and BMI was calculated. A nutritionist explained diabetic diet for all the patients and they were advised to be on diet during the study. The patients were divided into two groups according to sequential entering. One group received herbal medicine and other group placebo for 8 weeks. After one week washout period the herbal medicine and placebo were replaced for the next 8 weeks. Blood pressure, fasting blood sugar (FBS), creatinine, serum lipids, serum insulin and HbA1C were measured at baseline

of each period. the patients did not know type of treatment for every period. The numbers of remained drugs were counted and their adverse effects and the laboratory tests were recorded by a physician who was blind about type of treatment. The measurement of FBS and HbA1C (as primary outcomes) and serum insulin, creatinine, lipids, weight and blood pressure (as secondary outcomes) were repeated after 8 weeks in each period. We utilized chromatography with Bio-system kit (Italy, CV<5%) for HbA1C, enzymatic calorimetric method with glucose Parsazmoon Co kit (Iran) for blood glucose, Screening ELISA Test with Hitachi autoanalyzer using monobind kit(USA) for serum insulin levels. Insulin resistance was calculated through HOMA-IR methods (HOMA: Homeostasis model assessment method) (7).

### Statistical Analysis

The data was entered into SPSS software for analysis. Descriptive statistics (mean and standard deviation) was used for quantitative variables and paired T-test for the comparison of quantitative and Chi-square for comparison of qualitative variables between two groups. Statistical significance was recognized at  $P$ -value<0.05.

### Results

In this study, 24 diabetic patients (60% female) were enrolled. The mean age of the patients was  $47 \pm 6.9$  years old. The mean of BMI was  $28.5 \pm 2.68$  kg/m<sup>2</sup>. Thirty five percent of the patients were hypertensive and 84.2 percent were suffering from hyperlipidemia. Table 1 shows the patients'

data before intervention.

In the first period of study, four cases were excluded because of no compliance (two patients in herbal and 2 in the placebo group). Two months after treatment, mean fasting blood glucose was  $135 \pm 27.1$  and  $139 \pm 36.8$ , ( $P$ -value=0.64), and mean glycosylated hemoglobin was,  $6.5 \pm 0.75$  and  $6.6 \pm 0.97$  ( $P$ -value=0.51), in herbal medicine and placebo groups, respectively. Two patients (15.4 %) after herbal medicine usage and also two cases after placebo consumption had more than 0.8% reduction in HbA1C ( $P$ -value=1/0). The reduction of HbA1C levels in two patients with herbal medicine consumption were 2.6 and 1.6 % and in two cases with placebo were 1.5 and 0.9%. The mean HOMA IR index, after two months intervention with herbal medicine and placebo, was  $2.9 \pm 1.95$  and  $3.9 \pm 1.97$  respectively ( $P$ -value=0.05). HbA1C and HOMA IR differences were not significantly different in herbal medicine or placebo groups. (Table 2)

### Discussion

In the present study, the combination of low dose of five lowering blood glucose herbal medicine, P.harmala, Q.i, V.myrtillus, C.colocynthis, S.s did not have significant effect on blood glucose.

V.myrtillus (bilberry) is a member of Ericaceae family, its leave decoction had been used to lower blood glucose in diabetes even in the presence of concurrently injected glucose (8-9). This effect is attributed to the myrtillinantocyanoside, the most active hypoglycemic component. V.myrtillus

Table 1. Basic information of patients

Variable	Placebo mean±SD*	Herbal medicine mean± SD	P-value
Fasting blood glucose(mg/dl)	133±20.8	133±22.1	0.85
Postprandial blood glucose (mg/dl)	160±36.6	158±44.8	0.89
HbA1C	6.4±0.83	6.5±0.78	0.59
Body mass index(kg/m2)	30.1±6.51	30.5±6.37	0.25
Cholesterol(mg/dl)	192±30.6	193±29.1	0.92
Triglyceride(mg/dl)	164±80.9	157±90.7	0.63
HDL Cholesterol(mg/dl)	59±12.3	59±9.1	0.92
LDL Cholesterol(mg/dl)	106±16.1	92±17.8	0.05
Systolic blood pressure(mm/hg)	110±14.6	105±13.2	0.34
Diastolic blood pressure(mm/hg)	76±5.5	74±5.5	0.23

\*: Standard Deviation

enhances collagen integrity, stabilizes capillary Permeability and inhibits sorbitol accumulation, thus providing protection against vascular and neurological sequel of diabetes (10). Another significant property of myrtillin is the protective capacity against LDL particle during copper-mediated oxidation with only the trace amounts of *V.myrtillus* (15-20 mcq/ml) (11). It has also antinociceptive effect on diabetic rats (12). The hypoglycemic effect of bilberry may be because of  $\alpha$ -glucosidase activity (13), insulin secretion (14) and also glucose transport (15). The antilipidemic effect and lowering blood glucose of this plant was shown in several animal studies (16-18). Bilberry consumption is very safe and a dosage up to 400 mg/kg have been administered to rats without toxicity and also no toxic effects were seen with long-term oral consumption equivalent to 180 mg/kg anthocyanosides per day for six months in human (10). The dosage of this herbal drug in our study was 250 mg/d which was lower than the other studies.

In several experimental studies, the anti-diabetic effect of *C.colocynthis* was shown individually or in combination with *P.harmala* (19-26). The underlying mechanism of glucose lowering effect of *C. colocynthis* is not exactly clear. *C. colocynthis* contains a wide number of active constituents that may interact with several metabolic pathways of the human body which can directly or indirectly influence glucose or insulin metabolism. In type II diabetes mellitus, the elevation of plasma glucose and free fatty acid levels lead to the generation of reactive oxygen species and

oxidative stress markers (27). These metabolic abnormalities did not only induce diabetic complications but also lead to insulin resistance,  $\beta$ -cell dysfunction and impaired insulin secretion (28). *C. colocynthis* with its antioxidant properties inhibit lipoperoxidation (29-30) and is active against oxidative stress and may induce a positive effect on diabetic metabolic abnormalities. Nmilaand et al. showed the significant immediate stimulated insulin secretion with different kinds of *C.colocynthis* extract after 0.1 mg/ml perfusion for 2 minutes through the insulin tropic effect of *C. colocynthis* on isolated pancreatic islets too (22). *C. colocynthis* in another study inhibited the toxic effect of streptozotocin on pancreatic cells in rats (26, 31). The toxicity of large doses of *C. colocynthis* has been reported in experimental studies on both animals and human (32-34). However, in experimental studies, the aqueous extract of the *C. colocynthis* at lower doses can ameliorate some of the toxic effects of streptozotocin (26,29). Fallah Hoseini et al. have shown 300 mg/d of Citrulluscolocyn significantly decreases HbA1C and fasting blood glucose comparing to placebo without any notable gastrointestinal side effect and this dosage of drug was effective and safe after two months (20). In the present study, 125 mg/d of Citrulluscolocyn was used in combination to four other plants.

Some other plants such as *P.harmala* have antidiabetic activity. Nafisiand et al. in one study on streptozocine induced mouse showed the antidiabetic activity of *P.harmala* (270 mg/kg of oral form) (35). Singhand et al.

**Table 2. Comparison of variables after intervention in diabetic patients receiving herbal medicine and placebo**

Variable	Placebo mean $\pm$ SD	Herbal medicine mean $\pm$ SD	P-value
Cholesterol(mg/dl)	195 $\pm$ 41.9	1973 $\pm$ 9.0	0.77
Triglyceride(mg/dl)	154 $\pm$ 88.7	177 $\pm$ 84.4	0.15
HDL Cholesterol(mg/dl)	60 $\pm$ 16.3	53 $\pm$ 12.8	0.28
LDL Cholesterol(mg/dl)	92 $\pm$ 20.9	109 $\pm$ 21.9	0.02
Hemoglobin(mg/dl)	14.1 $\pm$ 1.39	15.1 $\pm$ 1.60	0.10
Creatinine (mg/dl)	0.8 $\pm$ 0.12	0.8 $\pm$ 0.19	0.38
Systolic blood pressure(mm Hg)	112 $\pm$ 18.6	112 $\pm$ 20.2	0.84
Diastolic blood pressure(mm Hg)	73 $\pm$ 15.3	77 $\pm$ 5.8	0.68
HbA1C (%) differences	0.05 $\pm$ 0.7	0.17 $\pm$ -0.9	0.52
HOMA IR differences	0.8 $\pm$ 1.6	-0.13 $\pm$ 3.2	0.39

showed that the ethanolic extract of *P.harmala* seed (150 and 250 mg/d) significantly lower blood glucose level in normal and diabetic rats, that was comparable with metformin effect (36). In another study on db/db mice, Singh also showed that the *P.harmala* (50 mg/kg hydroxyl pipelicolic acid isolated from feeds can cause the significant reduction in fasting blood glucose, plasma triglyceride, cholesterol, free fatty acid and low density lipoprotein cholesterol and significant increase in high density lipoprotein cholesterol level (37). Zakir Hussain et al reported in 2004 (38) that *P.harmala* has no insulin secretion activity and its hypoglycemic effect maybe according to glucose absorption. Some study must be conducted to find out the mechanism of action. In our study, we used 125 mg/d of *P.harmala* seeds powder.

*Q.i* is another glucose lowering plant that its alpha-glycosidase inhibitory activity has been shown in Hwang's study (39). In addition to hypoglycemic effect, *S.s* (L.) seeds have different activities such as antiepileptic, marked chronotropic, diuretic and hypokalemic effects (40-42). Phytochemical analysis has shown that the *S. securidaca* (L.) seed extracts are rich in flavonoids and so they have antioxidant properties (42). In Minaiyan and et al.'s study, different oral dosages (200,400,800 mg/kg) hydroalcoholic extract of *S.s* seeds were not effective to reduce blood glucose (43). Pouramirand et al.

showed the protective effect of *S.s* suspension against all oxan induced hyperglycemia and oxidative stress in rats (44). In Zahedi Asles'

study, oral form of chloroformic seeds extract of *S.s* (3 mg/kg) lowered blood glucose. It can be because of insulin release effect or insulin like activity of this plant but its hydroalcoholic extract did not have anti hyperglycemic effect (45). In our research, we used 250 mg /d of *S.s* seeds powder. The limitations of our study were finding of eligible patients that accept and sign the entrance to study and also beginning of antidiabetic agents by other physicians during the treatment.

### Conclusion

According to several studies about the effect of herbal drug on blood glucose, we prepared low dose combination of *P.harmala*, *Q.i*, *V.myrtillus*, *C.colocynthis*, *S.s* (125mg *V.myrtillus*, *S.s* and Mazoj and 62.5mg *C.colocynthis*, *P.harmala*), the combination witch is used in our region for lowering blood sugar. We did not find the significant effect on blood glucose, HbA1C and HOMA IR with combination of low dose this herbal drugs. The use of low dose of these plants may be the cause of this combination drug ineffectiveness. More research with higher dose of this combined extract and more sample size are recommended for defining blood sugar change.

### Acknowledgment

We gratefully thank the Traditional and Complementary Research center of Mazandaran University of Medical Sciences for supporting this study.

### References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract.* 2010;87(1):4-14.
2. Degli Esposti L, Saragoni S, Buda S, Sturani A, Degli Esposti E. Glycemic control and diabetes-related health care costs in type 2 diabetes; retrospective analysis based on clinical and administrative databases. *Clinicoecon Outcomes Res.* 2013;5:193-201.
3. Bash LD, Selvin E, Steffes M, Coresh J, Astor BC. Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absence of albuminuria and retinopathy: Atherosclerosis Risk in Communities (ARIC) Study. *Arch Intern Med.* 2008;168(22):2440-7.
4. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 2004;141(6):413-20.
5. Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. *Journal of ethnopharmacology.* 2002;81(1):81-100.

6. Ivorra MD, Paya M, Villar A. A review of natural products and plants as potential antidiabetic drugs. *Journal of ethnopharmacology*. 1989;27(3):243-75.
7. Suvarna J, Ingle H, Deshmukh CT. Insulin resistance and beta cell function in chronically transfused patients of thalassemia major. *Indian Pediatr*. 2006;43(5):393-400.
8. Bever B ZG. Plants with oral hypoglycemic action. *Quart J Crude Drug Res* 1979;17:139-96.
9. ;89:1577-1581. AF. Blueberry leaf extract. Physiologic and clinical properties in relation to carbohydrate metabolism. *JAMA*. 1972;89:1577-81.
10. Monograph. *Vaccinium myrtillus* (bilberry). *Altern Med Rev*. 2001;6(5):500-4.
11. Laplaud PM, Lelubre A, Chapman MJ. Antioxidant action of *Vaccinium myrtillus* extract on human low density lipoproteins in vitro: initial observations. *Fundam Clin Pharmacol*. 1997;11(1):35-40.
12. Roghani M BT. Antinociceptive Effect of *Vaccinium Myrtillus* in Diabetic Rats. *Journal of Babol University of Medical Sciences*. 2011;13(3):22-8.
13. McDougall GJ, Kulkarni NN, Stewart D. Current developments on the inhibitory effects of berry polyphenols on digestive enzymes. *Biofactors*. 2008;34(1):73-80.
14. Jayaprakasam B, Vareed SK, Olson LK, Nair MG. Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. *J Agric Food Chem*. 2005;53(1):28-31.
15. 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.
16. Roghani M BT, Taheri S The effect of feeding with aerial part of *Vaccinium myrtillus* on blood glucose and lipids of diabetic rats. *Iran J Diabetes Lipid Disord* 2007;7(2):151-8.
17. Torronen R, Kolehmainen M, Sarkkinen E, Poutanen K, Mykkanen H, Niskanen L. Berries reduce postprandial insulin responses to wheat and rye breads in healthy women. *J Nutr*. 2013;143(4):430-6.
18. Takikawa M, Inoue S, Horio F, Tsuda T. Dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. *J Nutr*. 2010;140(3):527-33.
19. Bnouham M MH, Legssyer A, Ziyat A. *Ethnopharmacology Forum Medicinal plants used in the treatment of diabetes in Morocco*. *Int J Diabetes & Metabolism* 2002;10:33-50.
20. Huseini HF, Darvishzadeh F, Heshmat R, Jafariazar Z, Raza M, Larijani B. The clinical investigation of *Citrullus colocynthis* (L.) schrad fruit in treatment of Type II diabetic patients: a randomized, double blind, placebo-controlled clinical trial. *Phytother Res*. 2009;23:1186-9.
21. Hasani-Ranjbar Sh LB, Abdollah M. A systematic review of Iranian medicinal plants useful in diabetes mellitus. *Arch Med Sci* 2008;3:285-92.
22. Nmila R, Gross R, Rchid H, Roye M, Manteghetti M, Petit P, et al. Insulinotropic effect of *Citrullus colocynthis* fruit extracts. *Planta Med*. 2000;66(5):418-23.
23. Ziyat A, Legssyer A, Mekhfi H, Dassouli A, Serhrouchni M, Benjelloun W. Phytotherapy of hypertension and diabetes in oriental Morocco. *Journal of ethnopharmacology*. 1997;58(1):45-54.
24. Bellakhdar J, Claisse R, Fleurentin J, Younos C. Repertory of standard herbal drugs in the Moroccan pharmacopoea. *Journal of ethnopharmacology*. 1991;35(2):123-43.
25. Abdel-Hassan IA, Abdel-Barry JA, Tariq Mohammeda S. The hypoglycaemic and antihyperglycaemic effect of *Citrullus colocynthis* fruit aqueous extract in normal and alloxan diabetic rabbits. *Journal of ethnopharmacology*. 2000;71(1-2):325-30.
26. Al-Ghaithi F, El-Ridi MR, Adeghate E, Amiri MH. Biochemical effects of *Citrullus colocynthis* in normal and diabetic rats. *Mol Cell Biochem*. 2004;261(1-2):143-9.
27. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes*. 2002;51(1):7-18.
28. Rosen P, Nawroth PP, King G, Moller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes/metabolism research and reviews*. 2001;17(3):189-212.
29. Zaree A, Fallahhossini H, Sharifabady R, zadeh A, Emani H, Ghoshooni H. The Effect of *Citrullus Colocynthis* Extract on Preventing/ Reducing Streptozotocin- Induced Diabetes in Rat. *Trauma Mon*. 2007;0(0):13-20.
30. Gebhardt R. Antioxidative, antiproliferative and biochemical effects in HepG2 cells of a homeopathic remedy and its constituent plant tinctures tested separately or in combination. *Arzneimittel-Forschung*. 2003;53(12):823-30.
31. Ramachandran B, Ravi K, Narayanan V, Kandaswamy M, Subramanian S. Protective effect of macrocyclic binuclear oxovanadium complex on oxidative stress in pancreas of streptozotocin induced diabetic rats. *Chem Biol Interact*. 2004;149(1):9-21.
32. Goldfain D, Lavergne A, Galian A, Chauveinc L, Prudhomme F. Peculiar acute toxic colitis after

- ingestion of colocynth: a clinicopathological study of three cases. *Gut*. 1989;30(10):1412-8.
33. Bakhiet AO, Adam SE. An estimation of *Citrullus colocynthis* toxicity for chicks. *Vet Hum Toxicol*. 1995;37(4):356-8.
  34. Elawad AA, Abdel Bari EM, Mahmoud OM, Adam SE. The effect of *Citrullus colocynthis* on sheep. *Vet Hum Toxicol*. 1984;26(6):481-5.
  35. Nafisi S AM, Mohammad Nezhady M , Ekhtiari m. possible Antidiabetic Effect of *Peganum Harmala* on Streptozocine- Induced Mouse. *World Applied Sciences Journal*. 2011;14:822-4.
  36. Singh AB, Chaturvedi JP, Narender T, Srivastava AK. Preliminary studies on the hypoglycemic effect of *Peganum harmala* L. Seeds ethanol extract on normal and streptozotocin induced diabetic rats. *Indian journal of clinical biochemistry: IJCB*. 2008;23(4):391-3.
  37. Singh AB, Khaliq T, Chaturvedi JP, Narender T, Srivastava AK. Anti-diabetic and anti-oxidative effects of 4-hydroxypipericolic acid in C57BL/KsJ-db/db mice. *Hum Exp Toxicol*. 2012;31(1):57-65.
  38. Hussain Z, Waheed A, Qureshi RA, Burdi DK, Verspohl EJ, Khan N, et al. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. *Phytotherapy Research*. 2004;18(1):73-7.
  39. Hwang JK, Kong TW, Baek NI, Pyun YR. alpha-Glycosidase inhibitory activity of hexagalloylglucose from the galls of *Quercus infectoria*. *Planta Med*. 2000;66(3):273-4.
  40. al-Hachim GM, Maki B. Effect of *Securigera Securidaca* on electroshock seizure threshold in mice. *Psychol Rep*. 1969;24(2):551-3.
  41. Ali AA, Mohamed MH, Kamel MS, Fouad MA, Spring O. Studies on *Securigera securidacea* (L.) Deg. et Dorfl. (Fabaceae) seeds, an antidiabetic Egyptian folk medicine. *Pharmazie*. 1998;53(10):710-5.
  42. Hosseinzadeh H, Ramezani M, Danaei AR. Antihyperglycaemic effect and acute toxicity of *Securigera Securidaca* L. seed extracts in mice. *Phytother Res*. 2002;16(8):745-7.
  43. Minaiyan M MF, Vali A. Effect of *Securigera securidaca* Seeds on Blood Glucose Level of Normal and Diabetic Rats. *Iranian Journal of Pharmaceutical Sciences*. 2006;2(3):151-6.
  44. Pouramir M ESM, Moghadamnia AA ,Parastouei K. To study the effects of *Securigera securidaca* (L.) seed against alloxan-induced hyperglycemia. *Journal of Medicinal Plants Research*. 2011;5(14):3188-91.
  45. Zahedi Asl S MH, Zare B Study on the effects of Chloroformic extract of *Securigera Securidaca* on serum Glucose level and liver Glycogen content of mice. *Journal of Kerman University of Medical Sciences*. 2005;12:32-8.