EFFECT OF ETHANOLIC EXTRACT OF *ROSA CANINA* ON SOME SERUM BIOCHEMICAL PARAMETERS OF DIABETIC MALE RATS

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ABSTRACT

The aim of the present study was to investigate the effect ethanolic extract of Rosa canina on some serum biochemical factors of diabetic male rats. Thirty two (32) male Wistar rats weighting 200 – 250 grams in 4 groups (control, diabetic control, diabetics + 250mg/kg/day extract, diabetics + 500 mg/kg/day extract) were used. Diabetes was induced by STZ (60mg/kg) intraperitoneal injection. The period of experiment was 4 weeks. At the end of experiments, the rats were sacrificed and their serums collected for glucose, creatinine, urea and albumin estimation. The results showed that glucose, creatinine and urea concentrations were significantly increased in the diabetic group (p<0.05), while the serum albumin concentrations was reduced. The levels of glucose, creatinine and urea in treated groups decreased significantly in comparison with the diabetic control group (p<0.05). But albumin concentrations showed no significant changes (p>0.05). The changes of glucose in treatment groups showed no significant differences (p>0.01).

Keywords: Streptozotocin, Diabetic male rat, *Rosa canina*, Serum glucose, Creatinine, Albumin, Urea

INTRODUCTION

Diabetes mellitus (DM) is one of very prevalent metabolic and endocrine disease caused by insulin deficiency and its major symptom is – hyperglycemia (Alebiosu and Ayodele, 2005; Sahib *et al.,* 2009). Diabetes mellitus is caused by the abnormality of carbohydrates, fat and protein metabolisms which are related with low blood insulin level or insensitivity of target organs to insulin (Maiti *et al.,* 2004). It is a major health problem with increasing prevalence over the entire world. It causes microvascular and macrovascular complications. The most common microvascular complications of diabetes mellitus are nephropathy, neuropathy, retinopathy and blindness that cause increased mortality rate (Raskin *et al.*, 2000; Atalay and Laaksonen, 2002; Memisogullari *et al.,* 2003). Because of the associated complications and eventual mortality, it is necessary to study treatment measures that will decreased or prevent procedures for proper diabetic management. Treatment of diabetes involves diet control, exercise and the use of conventional hypoglycemic or lipid-lowering drugs such as insulin, sulphonylureas (SUs), thiazolinediones (Stumvoll *et al.,* 2005), alpha glucosidase inhibitors (Dey *et al.,* 2002; Gilbert and Pratley, 2009), peroxisome proliferator gamma (PPAR-γ) agonists and biguanides has limitations. For instance, insulin therapy does not achieve gylcemic control in patients with insulin resistance, and oral hypoglycemic agents may lose their efficacy after prolonged use. Previous studies elsewhere suggested that

insulin was not only ineffective in preventing this condition, but can also lead to cardiovascular disease (Flodin, 1986; Perry *et al.,* 1996). Furthermore, conventional drugs are not easily accessible to the general population in developing countries due to socioeconomic conditions (Ducorps *et al.,* 1996). Hence there is an urgent need to find affordable treatments that are effective in slowing the progression of diabetic complications. Another problem faced is the cost of treatment, which is often prohibitively high in developing countries (Schoenfelder *et al.,* 2006). However, many oral medicines have a number of serious adverse effects, and the management of hyperglycemia and hyperlipidemia with low side effects is still a challenge for the medical sciences (Revilla-Monsalve *et al.,* 2007). The results of some studies that focused on alternative antidiabetic remedies with better risk-benefit ratios and greater patient acceptability indicated the importance of medicinal plants in diabetic management (Shane-McWhorter, 2005; Zareba *et al.,* 2005; Gilbert and Pratley, 2009). One of these medicinal plants that have anti-hyperglycemia properties and played an effective role on maintenance of normal physiologic and biochemical parameters in diabetes is *R. canina* (Jelodar *et al.,* 2007).

Rosa canina (dog rose) is a shrub and member of Rosaceae family, genus *Rosa* with over 100 species that is widespread in Europe, Asia, the Middle East and North America (Lattanzio *et al.,* 2011). The pseudo-fruit of *R. canina* including of a u-shaped receptacle with numerous achene inside is rich in vitamin C (Hagebuttenschalen, 2011). Rosa canina is a major source of ascorbic acids, tocopherols, bioflavonoids, tannins, amino acids, proanthocyanidins, flavonoids, pectin, unsaturated and polyunsaturated fatty acids, phospholipids, gallactolipids, carotenoids and 14 minerals such as Ca, Mg, Fe, Al, Mn, Zn, Cu, Sr, Ba, Ni, Cr, Co, Pb, Cd (Chrubasik *et al.,* 2008; Lattanzio *et al.,* 2011; Ilbay *et al.,* 2013). The fruits (rose hip, with seeds) of *R. canina* are reported to possess prophylactic and therapeutic activities against a wide range of ailments, including the inflammatory disorders, arthritis, rheumatism, gout, sciatica, for diseases type 1 diabetes in patients at risk of developing with fever, for colds and infectious diseases including influenza, against gastrointestinal disorders, to aid digestion, prevention of inflammation of the gastric mucosa and gastric ulcer, for gallstones, biliary complaints, as a laxative, for disorders of kidney and the lower urinary tract, as a diuretic, for dropsy and as an astringent (Blumenthal *et al.,* 1998; Lattanzio *et al.,* 2011). The present study was carried out to study the effect of treatment with ethanolic extract of *R. canina* on serum biochemical parameters like blood glucose, albumin, creatinine and urea of diabetic male rats.

MATERIALS AND METHODS

Experimental Animals

The study was carried out using Wistar male rats ranging 180 – 220 grams that were obtained from University of Medical Sciences, Tabriz, Iran. Approval to use animal model for the experiment was obtained from the Institutional Animal Ethics Committee and the experiments were carried out as per the guidelines of Animal Ethics Committee. All protocols in the international law and care of laboratory animals were adhered to. The rats were acclimatized for a period of one week before the start of the experiments. Throughout the experimental period, the animals were fed pelleted commercial diet, had free access to water and were kept separately in metallic standard cages in a well-ventilated room maintained at 21 ± 22°C with a 12:12 hour light: dark cycle (Breyer *et al.,* 2005; Kumar and Padhy, 2011).

Plant Materials

Samples of *R. canina* growing wild in northwest of Iran were collected and authenticated at the herbarium of the Faculty of Pharmaceutical Sciences, University of Tabriz, Tabriz, Iran. It was dried under shade at ambient temperature before extraction. Dried fruits (1.5 kg) were submitted to extraction in absolute methanol (Merck) and distilled water mixture (1:1) in a Soxhlet apparatus for 10 hours. After extraction,

the solvent was filtered and then evaporated using a rotary evaporator set at 45ºC.
The extract yield was recorded and the resulting powdery extract stored in sealed glass vials at 4ºC pending use (Eidi *et al.,* 2005; Sadigh-Eteghad *et al.,* 2009). The powdery extract was re-suspended in normal saline before being administered orally to the rats (Kumar and Padhy, 2011).

Induction of Diabetes

Diabetes was induced by the intraperitoneal (i.p.) single injection of streptozotocin at a dose of 60 mg/kg body weight dissolved 1 ml/kg citrate buffer (1M, pH 4.5). Forty eight hours after STZ injection, blood samples were obtained from the tail vein and blood glucose concentrations were measured with a Surestep glucometer. The blood glucose levels higher than 220 mg/dl were considered to be diabetic. The animals showed diabetic behavior such as polyuria and polydipsia within one week (Sezik *et al.,* 2005).

Experimental Design

After a week of acclimatization, the animals were randomly divided into four experimental groups of 8 rats in each group. Group I non diabetic rats, received normal saline (10 ml/kg/day) (intact control). Group II diabetic rats received normal saline (10 ml/kg/day) (diabetic control). Group III diabetic rats received 250 mg/kg/day of *R. canina* extract (treated group I) and group IV diabetic rats received 500mg/kg/day of *R. canina* extract (treated group II). All treatment lasted for 28 days and extracts were administered orally every 24 hours. The experimental rats were monitored daily and no sign of toxicity was noticed on the behaviors and general health of the rats exposed to the plant extract. At the end of the experimental period, the rats were anesthetized by intraperitoneal injection of 100mg/kg body weight ketamine and 5 mg/kg body weight xylazine and sacrificed (Atalay and Laaksonen, 2004). The blood samples were obtained from the retro orbital sinus and were centrifuged at 3000 rpm for 10 minutes for serum separation.

The body weights of all rats were measured. The effect of an ethanolic extract of *R. canina* on serum glucose, albumin, creatinine and urea levels in diabetic rats were monitored daily using standard protocols. All data collected were analyzed using statistical package for social sciences (SPSS version 19 for windows) and comparisons were made using the one way ANOVA and regression statistics.

RESULTS

Effect of the Ethanolic Suspension of *Rosa canina* on Blood Glucose Levels in Diabetic Rats: Diabetes was induced in rats by a single injection of STZ where a significant increase in the level of blood glucose was obtained on day 2. The level of blood glucose in the diabetic control group was 242.72 ± 0.32mg/dl against 70.79 ± 0.56mg/dl in the normal control group ($p<0.01$) (Table 1). Treatment of diabetic rats with the ethanolic suspension of *R. canina* produced dose-dependent decrease in the levels of blood glucose. The anti-hyperglycemic effect of the ethanolic suspension of *R. canina* was observed throughout the study period of 28 days. Blood glucose levels in rats treated with the lower (250 mg/kg) and higher dose (500 mg/kg) of the ethanolic suspension of *R. canina* on day 28 were comparable to the level in the non diabetic rats ($p<0.01$) (Figure 1 A).

Effect of the Ethanolic Suspension of *Rosa canina* on Serum Albumin in Diabetic Rats: Diabetes excretes the blood proteins such as albumin in urine on course of disease. However, the amounts of proteins were decreased in diabetic patients. In this study observed that injection of STZ to induction of diabetes reduced the albumin amount in diabetic group which was 4.04 ± 0.01 mg/dl against control group that was 4.67 ± 0.10 mg/dl (Table 1). Administration of ethanolic extract of *Rosa canina* in treated groups can increase the albumin concentration of serum, but this increasing was not significant, and has not much different with diabetic group ($p<0.05$) (Figure 1 B).

Table 1: Effect of ethanolic extract of *Rosa canina* on serum glucose, albumin, creatinine and urea concentrations of diabetic male rats

Group	Glucose (mg/dl)	Albumin (mg/dl)	Creatinine (mg/dl)	Urea (mg/dl)
Control	70.79± 0.56a	4.67 ± 0.10a	0.51± 0.0a	47.06 ± 0.35a
Diabetic control	242.72 ± 0.32c	4.04 ± 0.01b	0.64 ± 0.003c	153.80 ± 028d
Diabetic + 250 mg/kg	205.26 ± 0.42b	4.12 ± 0.02b	0.55 ± 0.002b	121 ± 0.85c
Diabetic + 500 mg/kg	204.46 ± 0.74b	4.06 ± 0.004b	0.51 ± 0.01a	94.05 ± 0.92b

The data are given as mean ± standard error of the mean. Characteristics of the animals studied p<0.01 in glucose and p<0.05 in other parameters

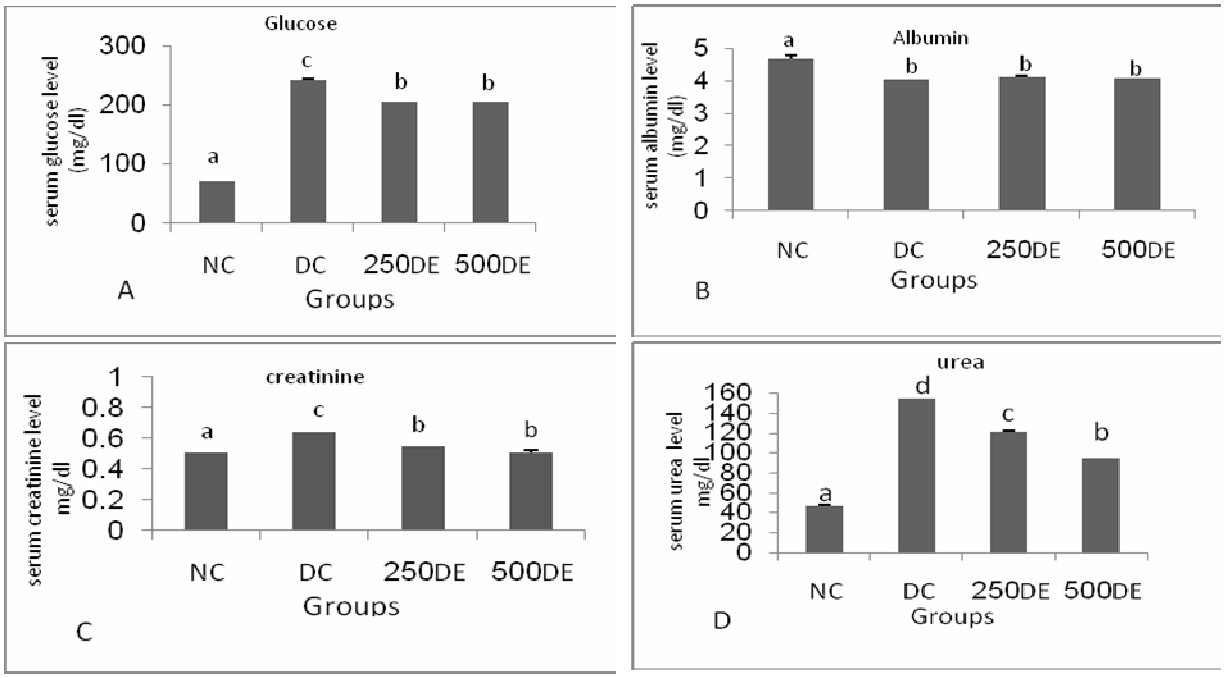

Figure 1: Effect of an ethanolic extract of *Rosa canina* on serum glucose, albumin, creatinine and urea levels in diabetic rats. Abbreviations: NC normal control; DC diabetic control; DE250 250 mg/kg extract of *R. canina*; DE500, 500 mg/kg extract of *R. canina*

Effect of the Ethanolic Suspension of *Rosa canina* on Serum Creatinine in Diabetic Rats: Creatinine is metabolic product of skeletal muscle creatinine. It is used to measure GFR. Excretion of creatinine in urine is equal to filtered of creatinine by glomerulus per minute time. Therefore creatinine clearance is a means to determine of GFR. In this study it was observed that diabetic groups had polyuria. Also analysis of serums showed that STZ causes increased the creatinine concentration in the diabetic groups. Administration of ethanolic extract of *R. canina* caused significant dose-dependent increase in creatinine concentration. Higher dosage of *R. canina* may lead to significant normalized serum creatinine concentration in the diabetic groups ($p<0.05$) (Figure 1 C).

Effect of the Ethanolic Suspension of *Rosa canina* on Serum Urea in Diabetic Rats: The ethanolic extract of *R. canina* significant decreased urea levels in the diabetic groups treated with the extract. Serum concentration of urea in diabetic control increased to 153.80 ± 0.28 mg/dl contrary to the control group 47.06 ± 0.35 mg/dl (Table 1). Administration of extract of *R. canina* caused significant dose

dependent reduction in serum urea concentration ($p<0.05$) (Figure 1 D).

DISCUSSION

A number of clinical and experimental studies have shown the efficacy of various herbs in decreasing blood glucose in diabetes. These herbal products showed their beneficial effects by different mechanisms which may or may not affect insulin release (Hui *et al.,* 2009). In view of the traditional use of *R. canina* in treating diabetes and lowering blood glucose levels in experimental conditions, the present study was carried out to evaluate the efficacy of ethanolic suspension of *R. canina* on some serum biochemical parameters of diabetic male rats. Diabetes was induced in rats by single intraperitoneal injection of STZ; an agent that brings about reactive oxygen species mediated β-cell toxicity and produces hyperglycemia (Srinivasan and Ramarao, 2007; Lenzen, 2008). In the present study STZ produced hyperglycemia in two days and its effect was maintained throughout the study period of 28 days when a marked increase in the level of urinary glucose and protein was observed. The phytochemical composition of *R. canina* fruits and seeds has been reported by several researchers to include phenolic acids, anthocyanides, tannins, flavonoids, carotenoids, fatty acids and organic acids (Hvattum, 2002; Deliorman *et al.,* 2007; Chrubasik *et al.,* 2008; Lattanzio *et al.,* 2011; Ilbay *et al.,* 2013). Study of the effect of the aqueous and ethanol extracts of *R. canina* fruits on blood glucose level in normoglycemic rabbits indicated no hypoglycemic activity. In another study, oral administration of a single dose of transtiliroside isolated from *Viscum album* has shown hypoglycemic effect at a dose of 10 mg/kg in normoglycemic mice (Deliorman *et al.,* 2005). Moreover, it is well known that the rose hip is rich in polyphenols (e.g., flavonoids and phenolic acids) that display and antioxidant properties as well (Bravo, 1998; Hvattum 2002; Guo *et al.,* 2009). It is now widely accepted that the antioxidant nutrients, vitamins C and E, carotenoids and other phenolic compounds may help to protect the human body against damage by reactive oxygen and nitrogen species (Gao *et al.,* 2000). Polyphenols in green tea with its inhibition of lipid peroxidation and superoxide radicals can decrease the blood glucose level in diabetic rats (Sadighzadeh *et al.,* 1987). Furthermore, the levels of antioxidants found would make them suitable sources of compounds to be used commercially to retard rancidity in fatty materials in food manufacturing, to reduce the effects of ageing and to help to prevent oxidative-stress related diseases such as cancer and diabetes mellitus. The pharmacological actions of phenolic antioxidants stem mainly from their free radical scavenging and metal chelating properties as well as their effects on cell signaling pathways and on gene expression (Sobratee *et al.,* 2005). In a study on the effect of *R. canina* on body weight, Anderson *et al.* (2012) demonstrated that daily intake of the rose hip drink was found had no effect on body weight and body mass index of humans, this result was contrary to our result in diabetic rats. The study on effect of *R. canina* on urinary concentration of creatinine, no significant effects was observed with regards to the volume of liquid consumed on the creatinine concentration in normal female rats (Grases *et al.,* 1992). Coles (1986) demonstrated increased urea concentrations in diabetic patients. In another study reported by Coles (1986), both the serum urea and creatinine levels increased in diabetic dogs. Also in this study, urea increased in diabetic control was noticed p and the ethanolic extract of *R. canina* caused significantly reduction in the amount of urea.

Conclusion: The ethanolic extract of *R. canina* caused a dose-dependent reduction in serum glucose, creatinine and urea levels in the diabetic rats that received 250 and 500 mg/kg, respectively, when compared to the diabetic control and the normoglycemic rats.

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