Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2017; 24(2): 132-140

The Effects of *Rosa canina* Fruit Hydro alcoholic Extract on Oxidative Stress, Total Antioxidant Capacity and Haematological Parameters in Diabetic Mice

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Received: 12 June, 2016 Accepted: 15 January, 2017

ARTICLE INFO

Article type:
Original article

Keywords:
Oxidative stress
Total antioxidant capacity
Hematological parameters
Diabetes
Rosa canina
Mice

Abstract

Background: Diabetes is a metabolic disorder with adverse effects on haematological parameters level, oxidative stress and antioxidant defence system. This study aimed to investigate the effects of Rosa canina (RC) fruit hydro alcoholic extract on oxidative stress, total antioxidant capacity (TAC) and haematological parameters in diabetic mice.

Method: In this study, 96 mice were randomly divided into the four groups (n=24). The control and diabetic groups received normal saline (p.o., 0.2 ml). Also, RC and treatment (diabetes+RC) groups received RC hydro alcoholic extract (p.o., 500 mg/kg). Diabetes was induced by a single dose of streptozotocin (i.p., 200 mg/kg).The study parameters were evaluated on day 10, 20, and 30 after the initiation of experiments.

Results: In the second and third sampling days, WBCs, lymphocytes, haemoglobin, RBC, MCV, MCHC, platelets, TAC and weight had a significant reduction ($p<0.01$) in the diabetic group in comparison to the control group. However, granulocytes, RDW, malondialdehyde (MDA) and glucose in the diabetic group significantly increased compared with the control group ($p<0.01$). Administration of the extract in the diabetic group significantly increased hemoglobin, MCV, MCHC, platelets, RBC, serum TAC and resulted in significant reduction in RDW and MDA levels in comparison to normal saline received diabetic animals ($p<0.01$).

Conclusion: Based on our results, RC fruit extract has a regulatory role in controlling oxidative stress, serum TAC and hematologic factors in mice model of diabetes.

Citation: Rahimi F, Sadigh-Eteghad S, Dehnad A.R, Mahmoudi J, Baradaran L. The Effects of Rosa canina Fruit Hydro alcoholic Extract on Oxidative Stress, Total Antioxidant Capacity and Haematological Parameters in Diabetic Mice. Journal of Kerman University of Medical Sciences, 2017; 24(2): 132-140.

Introduction

Diabetes mellitus (DM), as a metabolic disorder, is the fifth leading cause of death worldwide (1). Long-term exposure of body organs to high blood glucose level results in ocular, renal, neuronal and vascular disorders. Also, DM could affect haematological factors, so that a reduction in the MCV, PCV, MCHC and hemoglobin levels is observed during disease progress (2). Generally, low hemoglobin levels could be associated with reduced number of RBCs and/or a decline in PCV level. Low level of both hemoglobin and

hematocrit is considered as a cardinal sign of anemia, hence the majority of DM patients experience some degree of anemia (3). Enzymes such as aminolevulinic acid dehydrogenase and porphobilinogen deaminase are involved in heme biosynthesis. DM affects these enzymes and diminishes the heme biosynthesis which eventually leads to the development of anemic condition (4). Anemia as a predisposing factor increases the risk of myocardial infarction and hypoxic insults (5). It also accelerates renal and cardiovascular disorders and reduces life span (6). Significant increase in granulocytes and monocytes is also observed in DM. Small capillaries occlusion, cytotoxic factors release and cell injuries all happen by these leukocytes activation (7). Moreover, DM impairs the normal function of neutrophils and makes patients susceptible to infection (8). DM also affects the function and morphology of platelets (9) and leads to reduced platelets count (10).

Oxidative stress is defined as the result of excessive production of reactive oxygen species (ROS) and/or impaired ROS clearance (11). Hyperglycemic condition is associated with the occurrence of molecular events such as auto-oxidation of glucose, activation of polyol pathway and the formation of AGEs which leads to increase in oxidative burden in pancreatic structures (12).While pancreatic β-cells undergo oxidative damages, the ability of insulin gene promoter and its related mRNA levels is severely diminished (13). Elevated levels of malondialdehyde (MDA), as a lipid peroxidation marker, happen in DM. In this condition, the reduced ability of scavenging systems as well as over production of pro-oxidants lead to oxidation of membranous fatty acids (14).

Given the high cost and wide ranges of adverse effects of chemical regimes, there has been an increasing interest in the use of medical herbs and traditional medicine approaches for the treatment of diseases (15, 16). The majority of medicinal herbs contain significant amounts of antioxidants (i.e. tocopherols, carotenoids, ascorbic acid, flavonoids and tannins), so they might have therapeutic potentials in DM (17, 18). Evidently, effectiveness of *Swietenia macrophylla*, *Heliotropium zeylanicum* and *Passiflora alata* has been established in experimental models of diabetes. It is believed that the mentioned plants affect both pro- and antioxidant systems in a way to regulate oxidative stress in DM (19, 20).

Rosa canina (commonly known as the wild rose or dog rose) is native to Europe, North Western parts of Africa and West Asia (21). It is rich in protective and antioxidant compounds such as, ascorbic acid, malic acid, proantocyanide, pectin, tannins, flavonoids, polyunsaturated fatty acids, phospholipids, minerals, carotenoids as well as galactolipids (22).

Rosa canina has different therapeutic properties, so that it shows diuretic, laxative, anti-inflammatory, anti-gout, antioxidant (23), analgesic, immune boosting and hypoglycemic activities (24).

Also, the ability of this plant for the treatment of conditions such as asthma (17), rheumatoid arthritis (25) and nephrolithiasis has been proved in different studies (24, 26).

Although it is established that *Rosa canina* attenuates oxidative stress burden and improves some of the haematologic factors as well as anti-oxidant capacity (24, 27), there is limited data about its probable anti-diabetic properties.

We conducted this study to evaluate if chronic administration of Rosa canina is able to attenuate hyperglycemic condition and alterations in oxidative and haematologic factors in STZ-induced mouse model of DM.

Materials and Methods

Animals

A total of 96 male albino mice weighing 25-30g (from Tabriz University of Medical Sciences) were used in this study. Animals were kept in standard polypropylene cages (4 per cage) under 23±2 °C temperature and 12h light/dark schedule with access to water and food *ad libitum*.

Plants collection and extraction

Samples of *Rosa canina* were collected from Ahar (In the East Azarbayjan) during the post-flowering period. The material was dried in the shade at room temperature before being processed for extraction.

Extraction of the plant material

Extraction of the dried plant was done as described by Sadigh-Eteghad et al. (24). Briefly, fruits were grounded to fine powder, and then about 60 gr of powdered fruit was mixed with 300 ml of methanol and water at a ratio of 1:1 in a Soxhlet apparatus for 10 h. Later, the extracted solvent was filtered and vaporized at 40°C to dryness. The dried extract was dissolved in 0.9% normal saline.

STZ-model of DM

To induce DM, mice in diabetic groups received a single dose of STZ (200 mg/kg) purchased from Sigma-Aldrich, USA (28). Hyperglycemia was confirmed using Star glucomometer based on blood from the tail vein. Animals with blood glucose level above 300 mg/dl were considered diabetic and included in the study (29).

Experimental groups

The experimental groups consisted of control, *Rosa canina*, diabetic and treatment groups (with 24 mice for each group). Animals in the control and diabetic groups received normal saline through oral route using intra-gastric gavage (p.o., 0.2 ml). *Rosa canina* hydro alcoholic extract (500 mg/kg, p.o.) was administrated to the treatment and *Rosa canina* groups. The parameters including alteration in body weight, blood glucose, total antioxidant capacity (TAC), lipid peroxidation levels as well as changes in hematologic factors were serially assessed in all groups on day 10, 20 and 30 after the initiation of experiments.

Blood sampling

Under ketamine and xylazine (80 and 8 mg/kg, respectively) deep anesthesia, the animals were decapitated and blood samples were collected into pre-labeled tubes containing 10% of K 2 EDTA anticoagulant (20 µL).

The measurement of MDA and TAC levels

Plasma MDA levels were assessed using thiobarbituric acid method (30).TAC status was measured using commercial Randox kit (Randox, United Kingdom) and according to the manufacturer recommendation.

Evaluation of Hematologic Factors

Alterations in the hematologic factors including RBCs, hemoglobin, MCV, MCH, MCHC, RDW, total and differentiated WBCs were assessed using automated hematological analyzer Exigo EOS Vet (Exigo, Sweden).

Statistical analysis

Statistical analysis of each data set was performed using IBM SPSS statistics version 22 for the Windows (IBM Corporation). Data were presented as mean ± SEM and were analyzed by one-way ANOVA. Statistical significance was confirmed at the level of $p<0.05$. In the case of significant variation ($p<0.05$), the values were compared by Tukey test.

Results

The finding of the present study revealed that induction of DM is associated with significant decline of hematologic parameters such as RBCs, hemoglobin, MCV, MCH and MCHC in all sampling days when compared with the control group ($p<0.01$). Also, when compared with diabetic mice, oral *Rosa canina* regimen increased the number of RBCs and hemoglobin level in the treatment group throughout the experiment. Also, the extract increased the MCV on days 10, 20 and 30 ($p<0.01$) and elevated the MCHC on day 10 ($p<0.01$), when compared with the diabetic group. This regimen was not able to alter the MCH levels in diabetic mice. Change in the RDW ($p<0.01$) was seen only in the two last sampling days ($p<0.05$, $p<0.01$). Extract administration significantly decreased RDW in the two last sampling days ($p<0.05$, $p<0.01$, Table1).

Also, the measurement of total WBCs in STZ-injected groups showed that, induction of DM significantly reduces the total number of these cells in all studied days, as compared with normal saline received mice ($p<0.01$).Total platelet counting on study days showed that DM significantly decreases the number of these cells when compared with mice in the normal saline group ($p<0.05$). However, following the administration of *Rosa canina* a marked increase in the number of platelets was observed on day 20 in comparison to diabetic mice ($p<0.01$). Also, the diabetic group showed a significant increase in monocytes level during the study ($p<0.01$). Change in the granulocyte count ($p<0.01$) and RDW was seen only in the two last sampling days ($p<0.05$, $p<0.01$). The extract, in used dose, did not affect levels of granulocytes and monocytes in diabetic animals (Table 1 and 2).

Table 1. Changes in RBC-related hematological parameters during the study period in different groups

Time	group	RDW (%)	MCHC (g/dl)	MCH (pg)	MCV (fl)	hemoglobin(g/dl)	Red blood cell (1012/l)
Day10	Control	14.33±1.03	29.17±1.18	22.04±0.43	71±1.41	15.54±0.56	6.91±0.23
	Rosa canina	14±0.89	27.16±0.75	21.92±0.21	69.13±2.32	15.62±0.5	7.55±0.44
	Diabetic	16.12±1.77	25.83±1.47**	19.34±1.04**	61.07±1.68**	13.2±0.47**	6.1±0.25**
	Treatment	14.5±1.05	29.33±0.82##	20.3±0.61	66.53±1.1##	14.76±0.76##	6.93±0.26##
Day20	Control	14.67±1.24	27.85±1.53	22.16±0.43	70.15±1.48	16.02±0.88	7.01±0.38
	Rosa canina	14.02±1.63	26.67±1.37	22.12±1.31	66.02±2.01	16.38±0.69	6.97±0.29
	Diabetic	17.52±0.73*	23.72±2.48**	19.24±0.41**	56.27±1.41**	14.3±0.29**	5.73±0.18**
	Treatment	14.18±1.24#	25±1.41	19.63±0.46	61.12±1.19##	14.85±0.5#	6.93±0.36##
Day30	Control	13.83±1.17	27.68±3.27	22.3±0.7	70.87±1.8	17.17±0.81	6.78±0.43
	Rosa canina	14.28±1.49	27±0.89	22.38±1.35	68.42±1.27	17.25±0.48	7.58±0.57
	Diabetic	17.67±1.21**	20.33±1.51**	19.08±0.85**	54.5±2.69**	13.19±0.74**	5.26±0.22**
	Treatment	13.11±0.75##	22.17±0.98	20±0.89	66.48±1.2##	14.43±0.64##	6.45±0.15##

**$p<0.01$when compared with control group,##$p<0.01$and #$p<0.05$ in comparison to diabetic mice.

Table 2. Changes in WBC-related hematological parameters during the study period in different groups

Time	group	PLT (10^9/l)	GRAN (%)	MID (%)	LYM (%)	White blood cells(10^9/l)
Day10	Control	450.33±8.14	48.05±0.69	4.62±0.5	47.33 ±1.03	6.95±1.25
	Rosa canina	433.67±18.64	46.48±1.66	3±0.86	50.52±1.68	6.88±1.49
	Diabetic	406.94±16.89*	47.94±1.52	8.41±0.78**	43.55±1.19**	7.05±0.86
	Treatment	446.17±15.51	48.53±0.76	8.03±1.58	42.43±1.46	7.12±1.03
Day20	Control	458.19±13.54	47.6±1.24	4.2±1.28	48.2±1.37	7±1.02
	Rosa canina	447.33±22.66	47.17±1.3	4.73±2.02	48.12±1.51	6.96±0.89
	Diabetic	352.83±12.93**	51.33±0.77**	8.39±0.37**	40.28±0.5**	5.73±0.56**
	Treatment	380.5±22.54##	51.73±0.92	8.53±1.83	39.73±1.63	5.95±0.58
Day30	Control	454.24±14.49	47.67±1.85	4.65±1.05	47.68±1.89	7.35±0.53
	Rosa canina	449.83±13.43	46.87±1.58	4.23±1.08	48.9±1.95	7.42±1.03
	Diabetic	333.5±14.90**	52.72±2.32**	8.67±0.88**	38.6±2.72**	5.58±0.6**
	Treatment	347.67±26.26	55.07±1.27	8.3±0.96	36.43±0.90	5.73±0.61

**$p<0.01$ and ##$p<0.01$ when compared with control and diabetic groups, respectively.

Assessment of TAC in diabetic mice showed that DM lowers TAC levels in studied days as compared with the control group ($p<0.01$). Also, an increase in the TAC value was observed only on days 20 and 30, following initiation of *Rosa canina* regimen in the treatment group, in comparison to diabetic mice ($p<0.01$).When compared with control group, STZ-treated mice showed a significant increase in MDA levels throughout the study ($p<0.01$). However, oral *Rosa canina* decreased the MDA levels on day 30 in the treatment group, when compared to diabetic mice ($p<0.01$). Monitoring of blood glucose following STZ injection in mice showed that STZ significantly increases glucose level in the treated animals as compared with normal mice and this increase was persistent throughout the study ($p<0.01$). *Rosa canina*, at the administrated dose, could not alter the level of blood glucose on study days. A significant decrease in body weight was observed in the diabetic group on days 20 and 30 after induction of DM, as compared with the normal group ($p<0.01$) and the extract prevented the weight loss on the mentioned days, compared with diabetic mice ($p<0.05$). The results have been presented in Table 3.

Table 3. Alterations in the body weight, glucose levels and oxidative stress markers during the study period in different groups

Time	group	Weight (gr)	Glucose(mg/d)	TAC (mM/l)	MDA (nM/mg protein)
Day 10	Control	28±2.9	136.66±18.21	0.39±0.05	0.3±0.04
	Rosa canina	28.6±2.5	124.5±21.87	0.4±0.05	0.36±0.02
	Diabetic	25.3±1.5	552.83±31.72**	0.21±0.04**	0.69±0.05**
	Treatment	27.6±1.8	534.16±24.71	0.3±0.08	0.66±0.03
Day 20	Control	30.3±1.3	128.16±20.31	0.31±0.03	0.31±0.02
	Rosa canina	30±2.09	111.6±17.21	0.42±0.04	0.38±0.03
	Diabetic	22.5±1.6**	567.83±28.94**	0.20±0.04**	0.69±0.04**
	Treatment	26.1±1.3#	542.83±27.04	0.31±0.05##	0.61±0.03
Day 30	Control	34±2.6	132.3±21.07	0.32±0.03	0.3±0.03
	Rosa canina	33.6±1.2	124.5±19.67	0.46±0.06	0.38±0.02
	Diabetic	20.8±1.7**	534.6±23.33**	0.19±0.02**	0.7±0.04**
	Treatment	24.8±1.9#	521.5±27.76	0.35±0.03##	0.6±0.04##

**p<0.01when compared with control group,##p<0.01and #p<0.05 in comparison to diabetic mice.

Discussion

Diabetes is divided into the two main categories of type 1and type 2. In type 1 diabetes, loss of pancreatic β-cells results in the reduction of insulin levels, while type 2 diabetes is characterized by insulin resistance and/or impaired insulin secretion (2). Hematologic factors have been considered to be a reliable predictor for disease, which undergo wide changes in diabetes. In this study, RBC and platelets loss and reduction in hemoglobin, MCV and MCHC levels in diabetic mice, were prevented by chronic oral *Rosa canina* extract, indicating the ability of this compound to improve hematologic factors in DM.

Saliu et al. used a diet of *Occimum gratissimum*, *Pterocarpus soyauxii* and *Corchorus olitorius* plants in the diabetic mice and concluded that these plants can increase RBCs, hemoglobin and platelets levels in the blood of diabetic mice and this might be due to being rich source of antioxidants such as ascorbic acid, tocopherol and phenolic acids (31). Rosa canina, too, contains the same ingredients that might be the cause of the effects observed in this study. In another study by Edet et al. *Nauclea lafiloia* extract was used in diabetic

mice; they found that the mentioned herbal extract contain high amounts of flavonoids and its consumption increases MCH, MCV and platelets levels of diabetic mice (32). Since *Rosa canina* extract has the same flavonoids, its increasing effects on hematologic factors, in the present study, might follow the same mechanism.

Another study by Muhammad et al. showed that administration of *Jatropha curcas* root extract in diabetic mice, can increase RBCs count and hemoglobin in the blood of diabetic mice (33). Lange et al. explored the effect of Cinnamon extract in diabetic mice and concluded that it could increase RBCs count and hemoglobin, which could be due to the large amounts vitamin C and E in the extract (34). *Rosa canina* extract used in this study has also a large amount of vitamin C. The previous studies also proved that the use of *Rosa canina* extract could increase total leukocytes count and phagocytic activity in mice (26).

In this study, we showed that administration of *Rosa canina* fruit hydro alcoholic extract increases TAC in the serum of diabetic group. On the other hand, extract administration reduces oxidative stress and MDA production in the treatment group compared with the diabetic group. Orhan et al. investigated the effect of sub-acute administration of *Rosa canina* fruit hydro alcoholic extract and did not find decrease in the blood glucose levels in diabetic animals which is in line with our findings. However, the fractions extracted from total extracts have shown some levels of suppressing effects on the blood glucose levels on the seventh day after the induction of diabetes in mice (27).

In a study by Kanter et al., it was found that administration of *Nigella sative* extract in diabetic mice could reduce MDA levels probably via antioxidant modulation (35). Dutta et al. investigated the effect of *Swietenia macrophylla* extract and showed flavonoids and other antioxidant compounds in herb extract that through restoring the equilibrium between the production of free radicals and antioxidant defense system, prevented oxidative stress and reduced MDA levels in diabetic mice (19). Ugochukwu et al. showed that administration of the hydro alcoholic extract of *Gongranema latifolium* leaves in diabetic mice, due to its high content of vitamin C, could strengthen the antioxidant defense system and reduced oxidative stress and MDA levels (36). Fallahi et al. used *Allium ascalonicum* in diabetic mice and concluded flavonoid content of this regime prevents lipid peroxidation and could reduce MDA levels (37).The hydro alcoholic extract of Rosa canina fruit, contains a wide range of antioxidant compounds and could reduce oxidative stress as well as MDA levels and increase TAC. Our results also showed that extract administration causes a significant increase in the average weight of the mice in the treatment group compared with diabetic mice. There is evidence that use of other plants such as *Commiphora mulculor* black tea and kombucha tea in diabetic mice reduces the weight loss and this may relate to its flavonoid and phenolic acids content (38, 39).

In conclusion, the results of this study showed that *Rosa canina* fruit hydro alcoholic extract administration could reduce oxidative stress, improve TAC and hematologic factors without affecting glucose levels in diabetic mice and could be a supplementary strategy in the treatment of diabetes complications.

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