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Anti-hyperglycemic effect of aqueous extract of *Rosa canina* L. fruit in type 2 diabetic patients: a randomized double- blind placebo controlled clinical trial

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Abstract

Rosa canina L. (rose hip) have been traditionally used to treat diabetes in Iran. But yet, no scientific human study has determined its efficacy in diabetic patients. This study was conducted to evaluate the effect of aqueous extract of *R.canina* fruit on blood glucose in type 2 diabetic patients. Forty eight type2 diabetes patients aged 35-60 years with fasting blood glucose levels between 130 mg/dl and 250 mg/dl and HbA1c more than7% despite using conventional oral hypoglycemic drugs took the capsule of *R. canina* fruit (750 mg/BD) and toast powder capsule (placebo) randomly for 3 months. Fasting blood glucose (FBG) and postprandial blood glucose (PBG) were assessed as primary outcome measures. Glycosylated hemoglobin (HbA1c), lipid profile, hepatic and renal function were assessed as secondary outcome measures. They were compared with baseline in both groups with paired t-test in SPSS v: 17. Twenty five patients in *Rosa canina* group and 23 in control group with mean (±SD) of age 56.3(9.2) completed the study. The FBG level decreased significantly in *R. canina* group after 3 months compare to baseline (mean= 25.6, 95% CI= 11.5-39.5). Changes of PPG and HbA1c in *R. canina* group were not significantly more than placebo group. No serious side effects were reported in both groups during the study. This pilot study did not show the lowering effect of aqueous extract of *R. canina* in type 2 diabetic patients. Conducting other clinical studies with larger dose of this herb is suggested for precisely conclusion about the efficacy of this herb in diabetic patients.

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Introduction

Type 2 diabetes mellitus (T2DM) is a common disease worldwide. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (Shaw *et. al.*, 2010). The prevalence of diagnosed and undiagnosed diabetes mellitus in Iran is estimated as 7.7% in people aged 25-64 years] (Esteghamati *et. al.*, 2008).

The complications are the main causes of morbidities and mortalities due to T2DM and tight glycemic control is necessary for the management of type 2 diabetes (Shaw *et. al.*, 2010).

While insulin and oral anti-hyperglycemic drugs is the cornerstone of T2DM treatment, they have limited efficacies and important adverse effects. Thus, more efficacious and safer anti-hyperglycemic agents are needed (Philippe and Raccah, 2009; Gilbert and Pratley, 2009).

Currently, there is interest in complementary medicine (especially plant-based medicine) in the prevention and treatment of diseases and herbal medicine is the most frequent type of complementary/alternative medicine (Sadighi *et. al.*, 2005; Tehrani *et. al.*, 2008; WHO, 2003).

In Iran (especially in Azerbaijan province), the dried fruit of *Rosa canina L.* (rose hip, Rosaceae family); hereafter referred to as *R. canina*, is taken traditionally to treat diabetes mellitus. The medicinal parts are the petals, the rose hips with and without seeds, and the seeds. Unproven indications and usage of fruits are disorders of urinary tract and kidney, rheumatic conditions, colds, scurvy and fever (Fleming, 2009).

It was reported that the ***R. canina*** fruit, with its high ascorbic acid, phenolics and flavonoids contents, have antioxidant, antimutagenic, anticarcinogenic, anti-inflammatory and antinociceptive effects (Roman *et. al.*, 2013; Montazeri *et. al.*, 2011; Chrubasik *et. al.*, 2006; Cohen, 2012; Chrubasik *et. al.*, 2008).

In a study conducted in Turkey, the ethanol extract of *R. canina* fruits and its fractions were screened for their antioxidant, hypoglycaemic and antidiabetic activities. A remarkable hypoglycemic effect at 250 mg/kg dose of the ethanol extract was seen in streptozotocin induced diabetic rats (Orhan *et. al.*, 2009). Anderson (Anderson *et. al.*, 2011) also investigated the possible metabolic effects of rose hip powder by administering as dietary supplement to obese C57BL/6 J mice. Improved glucose tolerance, total plasma cholesterol and antidiabetic effects were observed.

In our knowledge, no clinical trial has been conducted for evaluating the efficacy of *Rosa canina*. We performed a randomized double-blind clinical study to analyze the effect of aqueous extract of *R. canina* fruit compared with placebo on the levels of blood glucose in patients with type 2 diabetes.

Material and methods

Preparation of the plant extract

The fruits of *Rosa canina* were purchased from a local herbal store in Maraghe (Azarbaiijan,Iran) and identified by Dr GA. Amin (faculty of pharmacy, Tehran University of medical sciences, Tehran, Iran). The voucher specimen "PMP-636" was deposited in the herbarium of faculty of pharmacy. The dried and ground rose fruits were extracted with distilled water by maceration and then filtered and the filtrate were concentrated to obtain dry powder. The percentage yield was 31%.

Measurement of total flavonoid content

The total flavonoid content (TFC) in aqueous extract of *R. canina* fruits was determined using $AlCl_3$ reagent.[19] Briefly, 2.5 ml of each sample (and/or quercetin as the standard), previously dissolved in 90% ethanol, was mixed with 2.5 ml of a 2% $AlCl_3$ solution in 90% ethanol. After 40 min, the absorbance of the yellow color produced was measured at 415 nm. The TFC [as µg quercetin equivalents/mg of sample] for the sample was calculated on the basis of a linear calibration curve obtained using quercetin (y=0.0169x+0.3526,

r^2=0.995)

Preparation of R. canina capsules and the placebo capsules

The extract powder as the phytomedicine and toast powder as the placebo were filled into oral gelatin capsules with identical appearance. The *R. canina* capsules contained 750 mg extract powder. Then the capsules were packed into indistinguishable labeled containers. The dosage of the extract (750 mg/BD) was based on the minimum dose of this plant in the folk medicine (15- 20 dried fruit which is about 5g, in a cup of hot water) and the yield of the extraction process used in this study.

Patients

Inclusion criteria included T2 diabetes mellitus outpatients aged 35-60 years with fasting blood levels of glucose between 130 mg/dl and 250 mg/dl and HbA1c more than7% despite using a combination of conventional oral hypoglycemic drugs (including metformine and glibenclamide). Patients receiving insulin or other hypoglycemic agents, patients with cardiac, renal or hepatic diseases, pregnant women, women planning pregnancy and breast-feeding women were excluded.

Protocol

This randomized double blind placebo controlled trial was conducted from March 2012 to June 2013 in Omid hospital of Zanjan province. The medical ethics committee of the Research Institute for Islamic and Complementary Medicine approved the protocol (approval number and date: 854/tm/p26 and September 2011). The trial was registered in the Iranian Registry of Clinical Trials with the number IRCT138803061957N2.

To estimate 20 mg/dl difference of FBG between the groups, considering type I error=0.05, 80% power and 20% attrition, the sample size was calculated as 30 patients in each group. This sample size was also adequate for estimating 30 mg/dl difference of PPG and 1% difference of HbA1c between the groups. The CONSORT flow diagram in Fig 1. describes the progress of the participants through the trial.

Written informed consent was obtained from the patients. Then they were allocated in two groups of interventions randomly using block randomization method. Blocks volume was 4, blocks selection was based on a computerized list of random numbers, number of patients and type of their interventions were written on a paper and put in an envelop. Patients and persons assigned them to interventions were blinded to the interventions. Each patient took 1 capsule orally every 12 hour for 3 months. They continued to take their conventional oral hypoglycemic agents as they were taking before without any dose changes. All the participants recorded the type and amount of daily consumed foods for 3 days every week. To monitor the patients' compliance with the medications, they were asked questions about taking the capsules on their monthly follow up (by telephone).

At the beginning and end of the study, the blood levels of fasting (for10 h) glucose (FBG), 2-hour postprandial glucose, blood urea nitrogen, creatinin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) were determined with standard enzymatic kits (Pars Azmoon company, Tehran, Iran) using an Auto analyzer (Hitachi 902, Japan). The serum samples were centrifuged for 10 minutes at a speed of 3000 rpm before the analyses. Glycosylated hemoglobin (HbA1C) was measured by high-performance liquid chromatography. The primary outcome measures were the FBG and PBG. The other parameters were the secondary outcome measures. All participants were requested to report any adverse effects. The SPSS software v17.0 (SPSS, Inc.) was used for statistical analyses with our data. Continuous data were described as mean ± standard deviation (SD) and analyzed using the two-sided paired t-test. Nominal variables were described using frequency counts and compared by treatment assignment using the two-sided chi-square test. P values < 0.05 were considered as significant.

Results

The total flavonoid content of the aqueous extract of *R. canina* fruits as µg quercetin equivalents/mg of sample was 14.54 ±0.67 µg /mg (mean ± SD, n=3).

Characteristics of the subject

From all 70 patients were screened and randomized, 48 (25 in *Rosa canina* and 23 in control group) patients completed the study and were analyzed. Demographic and baseline characteristics of study subjects are described in table 1.

Table 1. Demographic and characteristics of the patients in the *R. canina* fruits and placebo groups at baseline

Parameters	Group*	n
Sex	1	9 male,16 female
	2	12 male,11 female
		Mean (±SD)
age(year)	1	53.7(9.1)
	2	58.7(8.5)
duration of diabetes(year)	1	5.5(6)
	2	4.9(4.5)
body mass index(Kg/m2)	1	31.7(5.2)
	2	30.6(3.9)
dosage of oral hypoglycemic drugs (mg/day)	1	12.5(±6) glibenclamide, 1150(±435) metformin
	2	10(±9) glibenclamide, 1250(±425) metformin
FBG(mg/dl)	1	158.2(25.6)
	2	147.7(29.7)
PPG(mg/dl)	1	219.5(36.9)
	2	222.4(50.9)
HbA1c (%)	1	8(0.9)
	2	7.9(0.6)

*Group1=*Rosa canina L.*, group 2= Placebo.

The frequency of sex, age, duration of diabetes, BMI, type and dose of OHDs were similar between the groups.

Effects of R.canina extract on laboratory parameters

Laboratory parameters at baseline and post treatment are described by treatment assignment in Table 2.

As shown in this table, the FBG level was significantly decreased in the *R. canina* group (p= 0.002) after 3 months compared to base line. The PPG and HbA1c levels were not changed significantly in both groups. Also, cholesterol/HDL ratio was decreased significantly in the *R. canina* group (P= 0.02). There were no significant changes in the total cholesterol, triglyceride, LDL/HDL ratio, BUN, creatinin, SGOT and SGPT levels in both groups after 3 months. Differences of FBG, PPG, HbA1c and cholesterol/ HDL ratio before and after *R. canina* and their 95% confidence intervals are presented in table 3.

R. canina and placebo were well tolerated by the patients. There were no serious adverse effects in both groups and no attrition was seen due to side effects. The most common unpleasant reports in *R. canina* group were self limiting mild stomachache and nausea (n = 1), transient diarrhea (n = 1) and weakness (n=1) at the beginning of consumption. Two of the patients in the placebo group also reported transient diarrhea.

Discussion

The results of this study showed that 1.5 g/day of aqueous extract of *Rosa canina* L. fruit *R. canina* has not statistically significant advantages over placebo in type 2 diabetic patients because it could not significantly decrease HbA1c. To our knowledge, the

present study is the first assessment of effect of aqueous extract of *R. canina* fruit ingestion in the context of a randomized placebo-controlled trial in T2 DM. The mentioned dose of the extract in this study was taken from the folk medicine. Since the dosage of *R. canina* used in this study was based on lowest average doses used in the folk medicine and due to lack of any adverse effect reported in present study, testing the higher dosage of *R. canina* is suggested.

Table 2. Laboratory parameters of the *R. canina* fruits and placebo groups at baseline and post treatment.

		R. canina (n=25)	P-value	Placebo (n=23)	P-value
FBG(mg/dl)	pre	157.9 (23.1)	0.002*	144.8(41.9)	0.8
	post	132.25(29.2)		142.5(58.3)	
PPG(mg/dl)	pre	222.1(29.2)	0.053	198.2(54.7)	0.6
	post	188.6(55)		191.2(60.5)	
HbA1c (%)	pre	8.1 (1)	0.19	7.9(0.7)	0.3
	post	7.7(1.1)		7.7(0.9)	
Triglyceride(mg/dl)	pre	198(93.3)	0.4	199.6(112)	0.5
	post	185.8(113.2)		184.1(64.5)	
Total Cholesterol(mg/dl)	pre	191.2(43)	0.1	176.1(33.3)	0.08
	post	171(32.2)		167.3(30.8)	
HDL cholesterol(mg/dl)	pre	42.6(4.8)	0.1	43.4(3.6)	0.4
	post	44.9(5.9)		44.5(5.1)	
LDL cholesterol(mg/dl)	pre	110.3(44)	0.4	99.4(36.2)	0.07
	post	99.5(39.1)		86.2(29.3)	
Cholesterol/HDL	pre	4.6(1)	0.02*	4(0.8)	0.2
	post	3.8(0.8)		3.8(1)	
LDL/HDL	pre	2.5(1)	0.4	2.3(0.9)	0.2
	post	2.2(1.1)		2(0.8)	
BUN(mg/dl)	pre	27.9(9.2)	0.1	29.2(11.5)	0.2
	post	26.4(9.5)		31.3(12.3)	
Creatinin(mg/dl)	pre	.9(0.2)	0.5	0.9(0.1)	0.8
	post	0.9(0.1)		0.9(0.2)	
SGOT (u/l)	pre	22(8.9)	0.5	21.5(6.8)	0.2
	post	23.5(11.6)		23.5(10.4)	
SGPT (u/l)	pre	24(13.1)	0.5	27.2(12)	0.06
	post	25.4(12.3)		23.6(7.6)	

All parameters are described as mean (±Sd). FBG: fasting blood glucose, PPG: postprandial blood glucose, BUN: blood urea nitrogen, *SGOT: serum glutamic oxaloacetic transaminase, SGPT:* serum glutamic pyruvic transaminase, pre: baseline, post: post treatment. * Statistically significant.

There are a few animal studies suggest the hypoglycemic and anti diabetic effects of *R. canina*. Orhan *et. al.* (2009) and Anderson *et. al.* (2011) presented the antidiabetic effects of *R. canina* in laboratory animals.

In the present study, the aqueous extract of *R. canina* fruit was used. So conducting clinical studies with other types of extract (alcoholic, hydroalcoholic) are recommended.

Bioactive profile of rose hip extract has been studied using several techniques. Salminen *et al.* have isolated 15 individual proanthocyanidin aglycones and 19 glycosides and detected a complex mixture of non-separated tetrameric to octameric proanthocyanidin glycosides from R. canina hips (Salminen *et. al.*, 2005). Along with these phenolics, a 50 % aqueous ethanol extract of rose hip was found to contain high levels of vitamin C. The bioactive compounds isolated from rose hips are quercetin, ursolic acid, betulinic acid, oleanolic acid, licopene, Linoleic acid, α- linoleic acid, lutein, proanthocyanidin (Andersson *et. al.*, 2012).

Table 3. Paired differences of FBG, PPG, HbA1c and cholesterol/ HDL in *R. canina* group.

	Paired difference before and after *R. canina*			
	Mean	Standard deviation	Standard error	95% Confidence interval
FBG[mg/dl]	25.6	25.5	6.5	11.55–39.8
PPG[mg]dl]	33.5	61.3	15.8	-0.43– 67.46
HbA1c[%]	0.3	1.1	0.2	-0.18– 0.86
Cholesterol/HDL	0.8	1.3	0.3	0.13– 1.42

Results of the present study showed a significant percentage of flavonoids in the aqueous extract of *R. canina* fruit. Flavonoids are one of the most popular compounds in the plant kingdom and have effectiveness in reducing blood lipids, as an anti-oxidative, in assimilating cholesterol, inhibiting thrombosis, dilating the coronary artery, etc. Anti-oxidants inhibit peroxidation by scavenging free radicals and increasing intracellular concentration of glutathione, and thereby decrease oxidized LDL and improve insulin receptor activity (Patel, 2013; Kamalakkannan and Prince, 2006; Rao *et. al.*, 2006).

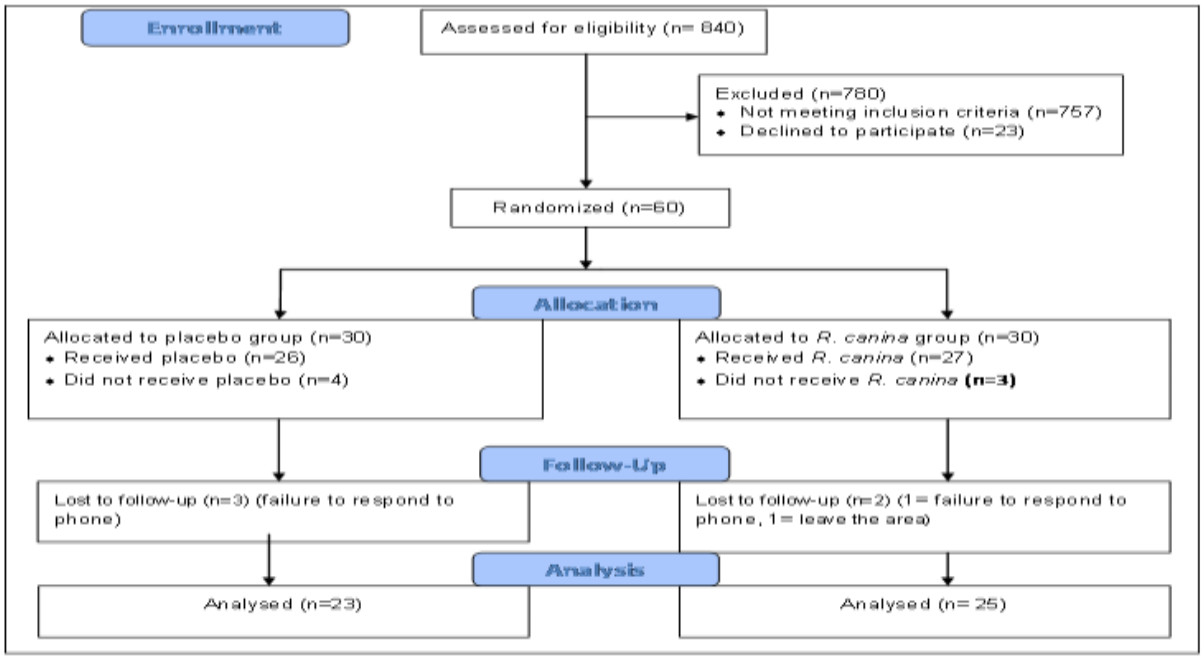

Fig. 1. The CONSORT flow diagram of participants.

Although these antioxidant and anti inflammatory effects of *R. canina* can support the anti-diabetic effects of this herb (because diabetes is one of the advanced glycation end product-mediated inflammatory diseases), anti diabetic effect and the mechanisms of action of *R. canina* has to be investigated more precisely in human and animal studies (Yasunari *et. al.*,1999; Triggiani *et. al.*, 2006).

The effect of *R. canina* fruit extract on cholesterol/HDL ratio is another result of the present study. Anderson *et al* investigated the possible beneficial metabolic effect of daily intake of 40 g rose hip powder over 6 weeks in a randomized, double-blind, cross-over study. A total of 31 obese individuals were enrolled for the trial. In comparison with the control drink, consumption of the rose hip potion resulted in a significant reduction in systolic blood pressure, total plasma cholesterol, low-density lipoprotein cholesterol and LDL/HDL ratio. It was concluded that the daily consumption of rose hip powder can significantly reduce cardiovascular risk in obese people mediated by lowered systolic blood pressure and plasma cholesterol levels (Rahimi *et. al.*, 2005).

Effects of *R. canina* on the lipid profile can also be evaluated in patients with or without diabetes in some well designed studies.

The main week point of the present study that the taste of capsules (if were opened and tasted) were not similar and it is a week point in blinding of many studies on herbal medicines.

Conclusion

Aqueous extract of *R. canina* fruit (1.5 g/ day) along with other oral hypoglycemic drugs, can not decrease the glycemic indexes in T2 diabetic patients more than placebo. It is recommended to evaluate the effects of this herb with various dosages of different types of extracts for controlling T2DM.

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