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The Safety and Efficacy of Rosa Damascena Extract in Patients with Type II Diabetes: preliminary Report of a Triple Blind Randomized Acarbose Controlled Clinical Trial

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Abstract

Background: Diabetes is a global health problem that its prevalence is increasing rapidly. *Rosa damascena* extract has shown to have an intensive non-competitive inhibitory effect on α-glucosidase in an animal study. The aim of this study was to assess the safety and efficacy of *Rosa damascena* (RD) Mill in diabetic patients and healthy subjects.

Methods: In a triple-blind, placebo and Acarbose-controlled randomized trial in Kerman in the south-east of Iran, we randomly allocated diabetic patients (n=32) and healthy volunteers (n=28) to 100mg Acarbose, 200 mg RD-methanolic extract, 400mg RD-methanolic extract and placebo groups. Over 15 days, the participants were followed up to monitor the changes in blood biochemical parameters and apparent symptoms. Analyses were carried out by intention to treat.

Results: RD extract decreased postprandial blood glucose levels comparable to the effects of Acarbose, demonstrating its α-glucosidase inhibitory activity. Besides, fasting plasma glucose levels significantly decreased in patients treated with 400 mg/day RD-methanolic extract compared to the 200 mg RD-methanolic extract (127.6±26.8 vs. 165.5±27.1, p=0.041), suggesting that *Rosa damascena* Mill is effective in a dose dependent manner. No major or minor hypoglycemic event was observed. NO adverse event was observed in the RD treatment groups in comparison with Acarbose or placebo groups. Serum levels of biochemical parameters did not fluctuate significantly in RD treatment groups compared to Acarbose and placebo controls.

Conclusion: *Rosa damascena* not only decreases blood glucose levels, but also is safe to be used for the purpose of controlling blood glucose levels in drug naïve patients with type II diabetes.

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Introduction

Diabetes mellitus (DM) is an emerging global disease and it is predicted that by 2025, its prevalence will increase by forty-eight percent in developing countries. Locally, it has been reported that twenty five percent of our population suffers from either diabetes or impaired fasting glucose (1). Additionally, metabolic syndrome, as a risk factor of diabetes is common in our region as well (2). Although there are several preventive modalities and management strategies, treatment of diabetes is not yet quite efficacious (1,3). Besides, Glycemic control targets for monotherapy continue to remain insufficient (4). Controlling postprandial plasma glucose plays a pivotal role in the management of DM as well as elimination of vascular events (5-7). The cost of treatment has also become a real concern.

A systematic review of clinical trials assessed the mechanism, efficacy and safety of consuming various herbs in patients with diabetes (8). A vast majority of such anti-hyperglycemic herbal drugs were not found to be effective in clinical trials. Although the systematic review supported the safety of these drugs, there was not sufficient evidence to ascertain their efficacy (8). As suggested previously, inhibition of α-glucosidase may lead to decrease in blood glucose levels in patients with type II diabetes. Correspondingly, plants are excellent sources of glucosidase inhibitors and Acarbose, one of the conventional anti-diabetic drugs, is obtained from natural sources (9).

In our previously published study, we showed potent glucosidase inhibitory effects of *Rosa damascenes* extract among 100 species of plants (10). In another study, we also showed that methanolic extract of *Rosa damascenes* has a dose dependent effect on lowering blood glucose levels in an animal model (11). The present study aimed to explore the safety and efficacy of methanol-Extract of the *Rosa damascena* flowers on fasting and postprandial plasma glucose levels in diabetic patients and healthy subjects, in comparison with the more conventional Acarbose treatment.

Materials and methods

The study was a 14-day, triple-blind and parallel placebo and Acarbose-controlled randomized trial carried out in Kerman, in the southeast of Iran (Clinical Trial Registration Number: IRCT138809221774N2). The study protocol was approved by Health Research Ethics Board of Kerman University of Medical Sciences (ethical code: K/87/187) and all participants signed an informed consent form before entering the study.

Sixty eligible participants (aged 17-85 years), including 32 diabetic patients (12 men and 20 women) and 28 healthy non-diabetic volunteers (8 men and 20 women) were selected. Cases were drug naive patients with type II diabetes who had been diagnosed at least six months prior to the study. The study was carried out at the endocrine clinic of a university hospital in Kerman. Two patients refused the study protocol (one in the Acarbose and one in the control group).

Inclusion criteria for diabetic patients were as follows: a body-mass index between 25 and 40 kg/m^2, HbA_{1C} between 6.5% and 8% and fasting plasma glucose less than 200mg/dl. Exclusion criteria were pregnancy, breast feeding, renal or hepatic failure and uncontrolled or complicated diabetes.

A balance block randomization was done. Random allocation sequence was performed using a computer program. Numbered containers were used for the random allocation process. Three-part container labels were used to conceal the random codes and stored in a separate box until the end of data analysis. Formulation of allocation sequence, enrollment, and randomization was carried out by an independent statistics expert.

Eligibility for enrollment was determined at the screening visit by a physician two weeks prior to the baseline visit. Eligible patients were randomly allocated by a nurse, blinded to the treatment group during the study. In the baseline visit (day 1), subjects were randomized and received one of the following: A) 200 mg *Rosa damascena* (RD)-methanolic extract, B) 400 mg RD-methanolic extract, C) placebo, D) 100 mg Acarbose. The drugs were self-administered orally every morning. The air-dried flower of the plant (300g) was milled (mesh, 300 mm) and extracted by maceration method in 1000 ml methanol at room temperature for 24h. The RD extract was evaporated in vacuum to yield a waxy mass and was kept in dark vials at -20°C until the time of the study, as described previously (11). All participants, physicians and the statistician were blinded to the treatment groups. The subjects were followed up at the end of days 8 and 15 for clinical examinations by the attending physicians and the signs, symptoms and adverse events were examined and recorded carefully.

During the treatment period, recommendations for caloric intake and daily exercise remained unchanged.

All patients were asked not to take any other medication without the permission of the treating physicians. Fasting blood samples were drawn and transferred into the tubes containing ethylenediaminetetraacetic acid (EDTA). Whole blood was used for complete blood count (CBC) and HbA_1C determination. The remaining blood was centrifuged at 1500 g for 10 minutes for plasma separation in order to measure other biochemical parameters. Glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline-phosphatase (Alk. P), creatinin and HbA1c were measured using commercial kits (KIMIA Kits, Tehran / Iran) and an auto-analyzer (Roche, Hitachi 902) in a standard laboratory setting.

All parameters mentioned above, as well as urine analysis, were investigated during each visit (before the treatment and in the 8^{th} and 15^{th} post-treatment days). Blood pressure and weight were measured at the beginning of the study and at each study visit. Fructosamine levels were measured in plasma enzymatically with commercially available kit (Randox kit-RA1000) on the first and 15^{th} days in all four groups. Safety was assessed on day 8 and at the end of the study (day 15) using a prepared checklist. Basic features and demographic variables of all randomized subjects were summarized for the intention to treat the participants.

To compare the treatment groups, continuous and categorical variables were analyzed by Kruskal-Wallis test and Fisher's exact test, respectively. The p-value <0.05 was considered as significant difference.

Results

In this study, 32 diabetic patients and 28 non-diabetic healthy volunteers met the study eligibility criteria. The baseline features of the intention to treat subjects have

been summarized in Tables 1 & 2**.** Figure 1 shows the flowchart of subjects' allocation. Two diabetic patients in the 400mg RD-methanolic extract group left the study before completion. One patient in the Acarbose group and one in the placebo group dropped out from the study due to the individual noncompliance. All healthy volunteers completed the study. The mean age of participants was 51 ± 9 years and 68.3% were female. At baseline, in neither diabetic nor healthy subjects, no significant statistical difference was found between the treatment groups, except for sex (Tables 1& 2).

Table1. Baseline characteristics of diabetic subjects

Variables	Acarbose 100mg (n=8)	RD-methanolic extract		Placebo (n=8)	p. value
		200mg (n=8)	400mg (n=8)		
Gender					0.043*
Male	6 (75%)	2 (25%)	4 (50%)	0 (0%)	
Female	2 (25%)	6 (75%)	4 (50%)	8 (100%)	
Age (year) (mean ±SD)	52.4±5.5	52.3±8.3	51.7±12.8	47.8±8.1	0.77
Body Mass Index (kg/m^2) (mean ±SD)	29.8±5.1	31.6±7.4	28.3 ±2.4	26.8 ±4.3	0.374
Duration of diabetes(month) (mean ±SD)	34.3±40	36±25.1	28.5±20.9	24 ± 15.5	0.838

Table 2. Baseline Characteristics of healthy subjects

Variables	Acarbose 100mg (n=7)	RD-methanolic extract		Placebo (n=7)	p. value
		200mg (n=7)	400mg (n=7)		
Gender					0.036*
Male	3 (42.9%)	2 (28.6%)	2 (28.6%)	0 (0%)	
Female	4 (57.1%)	5 (71.4%)	5 (71.4%)	7 (100%)	
Age (year) (mean ±SD)	40.7±8.7	38.7±11.8	38.1±14.3	33.2±6.6	0.626
Body Mass Index (kg/m^2) (mean ±SD)	31.1±7.8	25.8±12.1	25.2 ±6.2	25.8 ±4.6	0.514

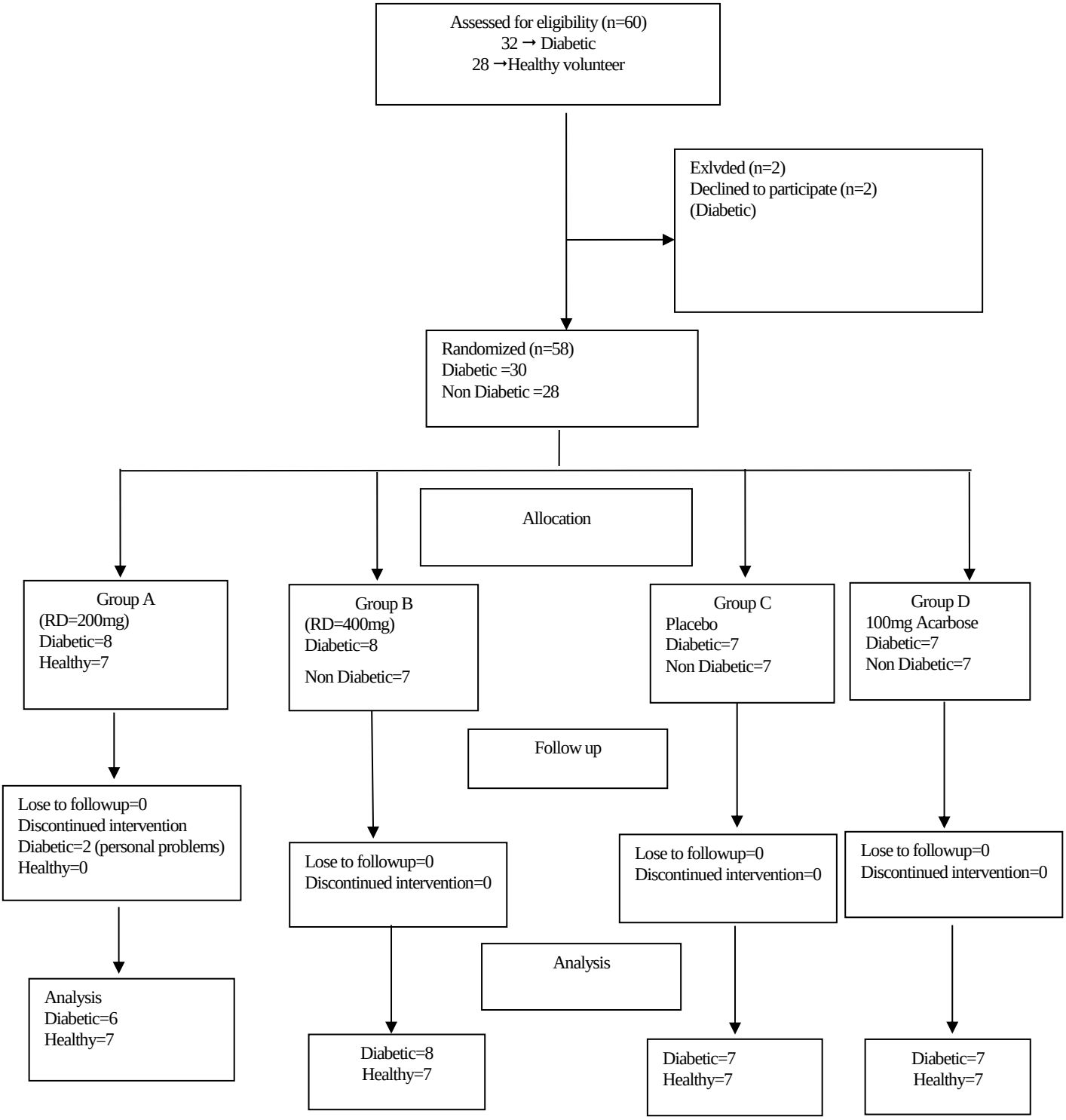

Figure 1. The consort flow Diagram

RD=Rosa Damascene
Analysis=Intention to treat

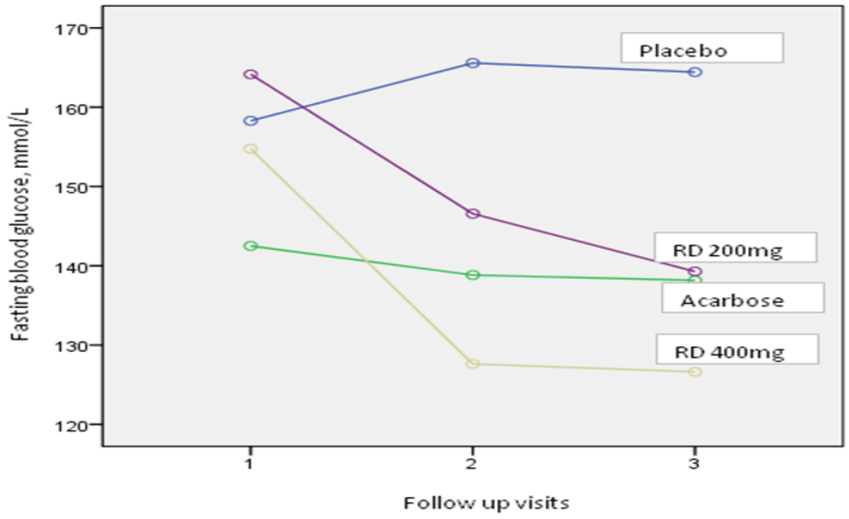

Figure 2. Fasting blood glucose changes in the four treatment groups of diabetic patients

Glycemic parameters

Tables 3 and 4 summarize the levels of HbA1C, fructosamine, fasting plasma glucose (FPG) and 2 hours postprandial plasma glucose (BS2HPG) in diabetic and healthy subjects. In diabetic patients, FPG level significantly decreased in the 400mg RD group and postprandial plasma glucose level reduced in Acarbose group; however, this reduction was not statistically significant in comparison to the three other groups (figures 3 &4).

Table 3. The results of glycemic control in diabetic patients. Data have been presented as mean ±SD

Variables	Acarbose 100mg (n=7)	RD-methanolic extract		Placebo (n=7)	p. value
		200mg (n=6)	400mg (n=8)		
HbA_{1c} (%)	8.9±0.8	8.2±0.8	7.7±0.8	8.5±0.8	0.073
Day 0	423.4±107.3	308.5±66.3	349.6±85.1	387.8±106.5	0.168
Day 15	374.7±68.3	297.3±68.6	320.1±78.5	350.1±62.5	0.228
Change	-48.7±57.0	-11.1±□45.7	-29.5±20.9	-37.7±73.7	0.590
FBS (mmol/L)					
Day 0	164.1±33.9	142.5±20	154.7±35.5	158.2±28.6	0.645
Day 8	146.5±23.7	138.8±15.1	127.6±26.8*	165.5±27.1	0.041*
Day 15	139.2±26.7	138.1±19.9	126.62±23	164.4±55.4	0.225
BS2HPG (mmol/L)					
Day 0	194.3±56.9	164.0±26	192.3±51.4	235.5±57.6	0.109
Day 8	190.5±49.4	146.5±33.5	160.7±43.2	214.5±57.7	0.061
Day 15	177.4±46.2	155.6±16.0	171.2±38.7	225.1±63.2	0.051

Table 4. Measures of glycemic control in healthy volunteers. Data are presented as mean ±SD

Variables	Acarbose 100mg (n=7)	RD-methanolic extract		Placebo (n=7)	p. value
		200mg(n=7)	400mg(n=7)		
HbA_{1c}, %	5.8±0.2	5.5±0.4	5.7±0.5	5.4±0.4	0.326
Day 0	220.5±29.8	227.5±33.9	211.5±24.8	199.2±23.4	0.297
Day 15	184.2±30.6	220±34	194.5±53.2	201.7±23.4	0.347
FBS, mmol/L					
Day 0	88.5±8.8	86.8±10.6	86.8±8.7	84.4±6.8	0.855
Day 8	85.8±11.4	80.1±5.0	81.8±13.3	83.2±9.2	0.762
Day 15	78.0±9.2	76.2±9.5	83.4±12.1	88.5±8.9	0.225
BS2HPG, mmol/L					
Day 0	93.0±14.7	103.8±22.7	94.2±17.3	95.4±15.8	0.670
Day 8	86.0±16.7	81.5±9.3	90.8±15.4	94.2±12.5	0.354
Day 15	90.1±20.4	80.2±12.1	88.4±22.0	92.5±17.3	0.628

summarizes the results of HbA1C, fructosamine, fasting plasma glucose (FPS) and 2hours post prandial blood glucose (BS2HPG) in diabetic and healthy subjects

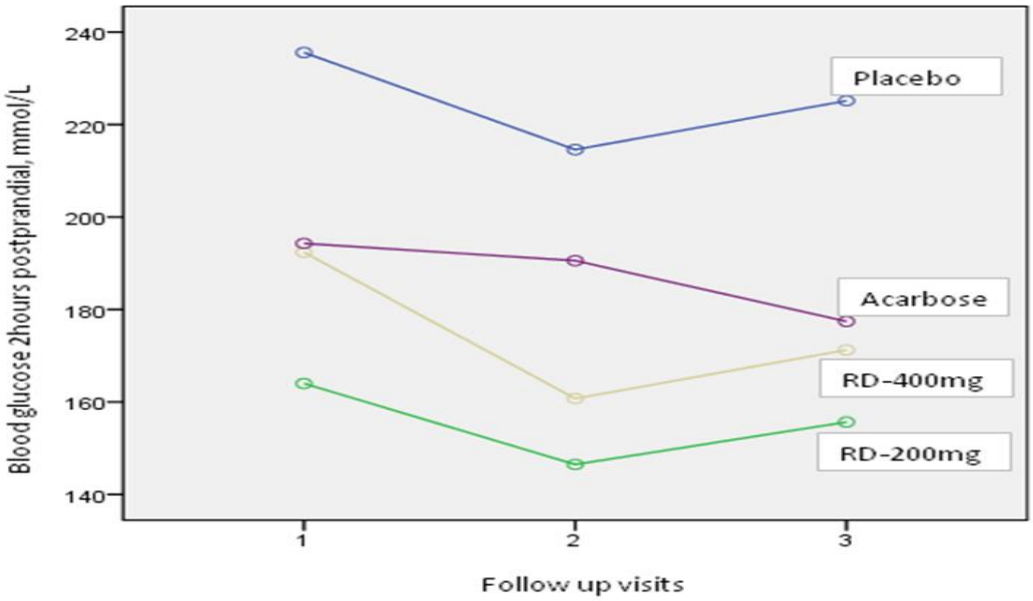

Figure 3. 2hours post prandial Blood Glucose changes in the four treatment groups of diabetic patients

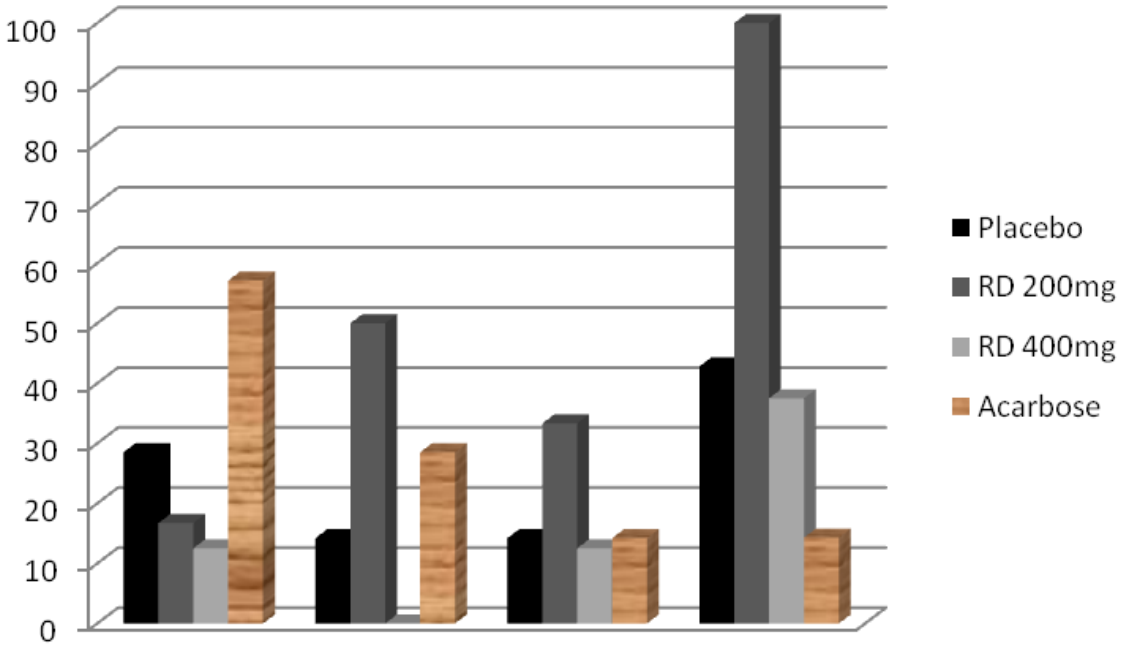

Figure 4. Common Side effects in the four treatment groups of diabetic patients

Safety assessments

To investigate the drug's safety, multiple biochemical and hematological parameters were evaluated. No systemic effect on any safety parameter was detected in subjects assigned to the RD extract treatment, when compared with placebo and Acarbose groups.

Among healthy subjects, plasma prothrombin time and other safety parameters (AST, ALT, Alk.P and blood cell count) did not change over the study period in the four treatment groups **(**Table 5).

The systolic and diastolic blood pressure did not alter throughout the study period too.

Systolic and diastolic blood pressure did not differ in any treatment groups at follow up. Laboratory testing including RBC, WBC, platelet count, ESR, AST, ALT, Alkaline Phosphatase, bilirubin (total and direct), PT, PTT, hemoglobin, urea, creatinine and urine parameters did not change significantly in either group.

Liver function tests in all groups were within the normal range throughout the study (Table 6). No hypoglycemic event was reported in diabetic or healthy groups.

Table 5. Laboratory investigations of healthy subjects

Variables	Acarbose 100mg (n=7)	RD-methanolic extract		Placebo (n=7)	p. value
		200mg(n=7)	400mg(n=7)		
AST(mmol/L) (mean±SD)					
Day 0	20.4±8.5	19.7±8.6	18.4±3.8	15.0±3.5	0.440
Day 8	18.4±5.9	19.4±4.9	17.1±4.2	19.2±7.5	0.875
Day 15	17.5±4.5	18.8±6.2	18.0±5.9	13.1±1.9	0.163
ALT(mmol/L) (mean±SD)					
Day 0	25.0±17.1	21.8±9.8	21.1±10.5	17.8±7.6	0.733
Day 8	24.3±13.1	19.7±11.1	17.5±6.6	18.0±7.0	0.574
Day 15	23.0±15.9	18.8±12.6	18.8±8.1	16.1±6.6	0.734
Alk.p (mmol/L) (mean±SD)					
Day 0	122.4±53.4	106.8±45.1	137.7±50.0	113.2±34.5	0.631
Day 8	144.5±75.4	101.5±32.3	142.1±46.8	114.8±33.7	0.321
Day 15	142.0±67.8	110.0±27.8	140.4±45.5	112.1±33.7	0.414
Hb(gr/dL) (mean±SD)					
Day 0	14.4±2.5	15.1±2	13.5±2.7	14.2±1	0.594
Day 8	14.1±2.2	14.6±1.4	13.6±2.9	13.9±0.8	0.821
Day 15	14.2±1.9	14.6±1.8	13.4±2.3	13.8±0.8	0.590
PT(sec) (mean±SD)					
Day 0	11.8±0.3	12.2±0.4	12.6 ±0.4	12.1±0.4	0.265
Day 8	11.9±0.7	11.5±0.5	11.6 ±0.8	11.4±0.5	0.523

Among healthy subjects, neither serum prothrombin time, nor the safety parameters (AST, ALT, Alk.P and blood cell count) were altered throughout the study period in the four treatment groups.

Table 6. Laboratory investigations of the diabetic subjects

Variables	Acarbose 100mg (n=7)	RD-methanolic extract		Placebo (n=7)	p. value
		200mg(n=6)	400mg(n=8)		
AST, mean±SD, mmol/L					
Day 0	16.0±6.6	13.8±3.0	19.6±3.8	20.29±6.5	0.113
Day 8	20.7±9.8	16.8±3.1	18.8±6.5	19.7±6.7	0.793
Day 15	16.5±5.4	17.3±5.2	19.6±4.2	15.5±3.9	0.405
ALT(mmol/L)					
(mean±SD)					
Day 0	17.8±9.9	22.8±14.0	27.7±16.4	26.5±14.2	0.542
Day 8	21.7±16.1	21.8±10.5	25.6±16.3	23.5±14.4	0.951
Day 15	21.3±12.6	26.3±11.0	25.2±14.7	20.0±10.6	0.752
Alk.p(mmol/L)					
(mean±SD)					
Day 0	175.1±61.4	127.0±19.1	152.0±54.8	165.4±56.1	0.394
Day 8	179.0±60.4	131.0±24.4	147.5±48.6	167.14±65.1	0.383
Day 15	172.4±64.8	134.5±26.1	146.3±41.1	162.1±51.4	0.510
Hb(gr/dL)					
(mean±SD)					
Day 0	13.1±2.3	13.9±1.1	13.7±1.5	11.68±1.1	0.074
Day 8	13.2±2.3	13.6±1.1	13.4±1.3	11.6±1.1	0.089
Day 15	13.0±2.5.	14.2±1.6	13.5±1.4	11.9±1.4	0.164
PT(sec)					
(mean±SD)					
Day 0	12.1±0.5	11.7±0.6	12.1±0.5	12.3±0.2	0.192
Day 8	12.2±0.2	12.1±0.8	12.1±0.8	12.1±0.7	0.974
Day 15	12.1±0.9	11.4±0.6	12.1±0.6	12.2±0.5	0.203
PTT, mean±SD, sec					
Day 0	30.4 ±0.8	30.5±0.5	30.1±0.3	30.1±0.4	0.463
Day 8	30.4±0.8	31.0±0.9	30.3±0.7	30.4±0.5	0.410
Day 15	30.2±0.5	30.3±0.5	30.8±1.4	30.4±1.1	0.672
Urea(mg/dL)					
(mean±SD)					
Day 0	27.7±13.7	25.8±5.8	28.8±6.9	27.4±13.7	0.940
Day 8	29.7±6.4	24.3±4.7	30.1±8.6	22.8±6.5	0.133
Day 15	29.5±7.3	24.6±6.5	28.7±7.5	23.8±8.2	0.401
Creatinin(mg/dL)					
(mean±SD)					
Day 0	1.1 ±0.2	1.1±0.3	0.9±0.2	0.9±0.2	0.434
Day 8	1.0± 0.2	1.0 ±0.3	1.0±0.2	0.8±0.2	0.472
Day 15	1.1 ±60.2	1.1 ±0.3	0.9±0.1	0.9±0.2	0.207

No subject in any dose group had an increase in any measure of liver function that exceeded the upper limit of the normal central laboratory's reference range.

Likewise, the laboratory parameters of urine analysis including pH and SG were within the normal range in all 4 four treatment groups in both healthy and diabetic groups at follow up.

Among the diabetic subjects, one or more adverse event occurred in five out of seven 5/7 (71.4%) participants in the placebo group, 100% and 62.5% in the RD-methanolic extract 200 and 400mg groups, respectively and in 7/7 (100%) of Acarbose group. None of the patients experienced any serious adverse event during the study period. The common side effects of RD-methanolic extract were gastrointestinal disorders. Gastrointestinal side effects such as anorexia, constipation, diarrhea, nausea and vomiting were not dose dependent, while abdominal pain occurred in a dose-dependent manner in the RD-methanolic groups (16.7% and 50% in the 200mg and 400mg groups, respectively). RD extract was generally well tolerated by the healthy individuals. None of the healthy or diabetic subjects developed hepato-splenomegally, lymphadenopathy or pallor. Four common side-effects reported by the diabetic participants in the four treatment groups have been shown in Figure 4.

Discussion

In the present study, FPG significantly decreased at 400 mg dosage of RD-Methanolic extract in diabetic patients and the effect on fasting blood glucose had a dose-dependent pattern. Glucose control and especially BS2HPG was improved by using RD. On the other hand, none of the reported adverse events were more common in RD treatment groups compared to Acarbose and placebo groups. Therefore, the RD-Methanolic extract is not only effective, but also safe to use for drug naïve diabetic patients.

Known traditionally for its use as a flavoring agent, Rosa damascene works as a laxative and tranquilizer. Many biological and medical advantages of this plant have recently been established, namely hypnotic (12, 13), anti-solar (14), anti-HIV (15), antioxidant and antibacterial (16), anti-depressant (17), antitussive (18) and anti-aging (19) effects.

Although a strong history is available for the clinical use of herbal drugs, the reproducibility of the safety and efficacy of anti-diabetic herbal drugs has remained uncertain. To our best knowledge, this is the first clinical trial on the efficacy and safety of RD-Methanolic extract in patients with diabetes.

Dose-dependent effect of this extract on lowering postprandial glucose levels has previously been shown in an animal model study (11). The observed difference between the results of this study and the mentioned animal study (11) may be due to the lower RD dose applied in the present study. Given the minimal dose in rats (100mg/kg) and the rat/human metabolic ratio, the desired dose was considered to be 800 mg (20) which was found intolerable in the pilot study. Hence, lower doses were used in our human study. Clinical data support the anti-diabetic effects of many herbs and multiple herb mixtures in Traditional Chinese, Native American, and Tibetan Medicine. Animal and in vitro studies also suggest several glucose lowering mechanisms for these herbs. These mechanisms include delayed glucose absorption in the gut byAloe. vera and prickly pear cactus, raised glucose absorption/removal by fig leaf and

ivy gourd, glucose stimulated insulin secretion by garlic, holy basil and gurmar), the first two mechanisms by fenugreek, the last two mechanisms by bitter melon or all three mechanisms byginseng (8, 21, 22). The flower buds of Tussilagofarfara has shown to have α-glucosidase inhibitory effect in diabetic rats (23). The methanol extract of the flowers of *Rosa damascena* has also demonstrated to be a potent inhibitor of α-glucosidase inhibitors, resulting in decreased carbohydrate absorption from the intestine and reduced postprandial glucose level in diabetic rats (24). Glucosidase inhibitory effects of RD, however, could not explain our results regarding the significant reduction of fasting plasma glucose with 400mg RD dose in diabetic patients. A recent study showed that *rosa damascena* significantly increases the mRNA level of PPAR.γ in the liver along with PPAR.γ protein production. On the other hand, *rosa damascena* was shown to decrease blood glucose, insulin levels and HOMA-IR in insulin-resistant rats (25).

Increased insulin action and insulin sensitivity without increased insulin secretion not only explains FPG reduction, but also provides an explanation for the lack of hypoglycemia in healthy individuals.

We did not observe any toxic effects of RD-Methanolic extract in this study, except for gastrointestinal side effects that may be due to the shift of undigested carbohydrate complex into the large intestine. However, compared to Acarbose, fewer gastrointestinal side effects were associated with the RD-Methanolic extract treatment, while its efficacy is comparable in the dose of 200mg. Another study reported that the use of RD along with a high-fat diet may increase the risk of hypertension in rabbits (26). None of our participants had any change in blood pressure.

One of the limitations of this study was the single dose administration of RD and Acarbose. Alternatively, three times administration of the extract per day may be more effective. Although it has been reported that Acarbose leads to weight loss over time (27), the duration of our study was too short to find any changes in participants' weight. The inclusion of Acarbose as a known positive control for type II diabetes allows us to demonstrate the apparent differences in tolerability, in addition to the effects on blood glucose level.

According to the results of this study, 200mg dose of RD-methanolic extract suppresses postprandial hyperglycemia in diabetic patients. These effects are comparable to the Acarbose treatment which demonstrates α-glucosidase inhibitory activity.

Our results illustrate that intervention with *Rosa damascena* Mill is dose- dependently effective. Therefore, treatment of type II diabetes mellitus with higher doses is recommended. The restricting inclusion criteria in the present study caused a smaller sample size. Hence, a larger sample size and longer follow up duration (at least 3 months, according to the previous studies on Acarbose) with Hb A_{1C} are suggested for future studies, especially given our study's results supporting the safety of RD-methanolic extract in diabetic patients and healthy subjects. Nevertheless, identification of RD-Methanolic extract active components should be considered for future studies. In the absence of such standardizations, health practitioners and consumers should remain cautious with its application.

Conclusion

Rosa damascena is not only effective in treatment, but also safe to consume for the purpose of controlling blood glucose levels in drug naïve type II diabetic patients.

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