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Propolis supplementation improves glycemic and antioxidant status in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study

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ABSTRACT

Objectives: The prevalence of type 2 diabetes has risen dramatically in recent years. There are many different safe therapies used for diabetes and also number of natural supplements that can be used to manage diabetes. We assessed the effect of oral propolis supplementation on blood glucose, insulin resistance and antioxidant status in type 2 diabetes.

Methods: We conducted a randomized, double-blinded, placebo-controlled trial for 8-week. Sixty two patients with type 2 diabetes (30–55 years of age) were randomly assigned in two group, propolis (n = 31) and placebo (n = 31). Patients were given doses of 500 mg, three times a day (1500 mg), of propolis or placebo three time a day. The fasting blood sugar (FBS), two-hour postprandial glucose (2-hp), insulin, insulin resistance (IR), hemoglobin A_1c (HbA_1c), total antioxidant capacity (TAC) and activity of glutathione peroxidase (GPx) and superoxide dismutase (SOD) were measured at the beginning and end of the study. Statistical analysis was performed using SPSS software.

Results: After two month, FBS, 2-hp, insulin, IR, HbA_1c was significantly decreased in patients treated with propolis compared with placebo group ($p < 0.05$). Additionally intake of propolis significantly increased the blood levels of TAC and activity of GPx and SOD ($p < 0.05$).

Conclusion: Propolis treatment can be helpful as a diet supplement in patients with type 2 diabetes through improvement in glycemic status, reduction in insulin resistance and amelioration in antioxidant status. This supplement without side effects can increase the effectiveness of prescribing drugs in diabetes.

1. Introduction

Diabetes is an endocrine disorder which, due to its high prevalence in the worldwide the patients are at risk of its complications.[1] Based on the mechanisms studied in the pathology of diabetes, complications can be categorized in macrovascular, microvascular and both micro- and macrovascular such as diabetic foot.[2] According to the World Health Organization, financial and economic losses of the disease, as well as the deaths caused by it, is high. The main cause of most mortality and morbidity from diabetes is due to macrovascular complications as compared to the microvascular complications in patients.[3,4]

Several of reactive molecules and free radicals acquired from molecular oxygen, explained as a Reactive Oxygen Species (ROS). Based on recent scientific research ROS have several important role in the cell signaling, of which apoptosis, gene expression; and the activation of cell signaling cascades can be mentioned.[5] In addition, ROS have a pivotal role in both intra- and intercellular messengers. However, they can disrupt the normal functions of the cell such as differentiation and migration. ROS can attack polyunsaturated fatty acids in the membrane of the cells, causing oxidation of fatty acids and, as a result, impaired

Abbreviations: 2-hp, two-hour postprandial glucose; BMI, body mass index; FBS, fasting blood sugar; GPx, glutathione peroxidase; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; ROS, reactive oxygen species; SOD, superoxide dismutase; TAC, total antioxidant capacity; TNF-α, tumor necrosis factor alpha; T2DM, type 2 diabetes mellitus

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cellular function.[6]

Results of scientific investigations clarified that in metabolic diseases such as type 2 diabetes mellitus (T2DM), impaired the balance of oxidants and antioxidants, then the body is exposed to oxidative stress condition, that resulting in the development of microvascular and microvascular complications.[7] Increased oxidative stress is a deleterious agent which leads to β-cell dysfunction, insulin resistance, impaired glucose tolerance, dyslipidemia and ultimately leading to T2DM. These conditions can be due to impaired function of the body's antioxidant system.[8,9] This system contains important antioxidant enzymes such as catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx). Variations and disruption of the system cause cell damage caused by oxidative stress that resulting in the development of diabetic complications. Therefore, the presence of compounds such as antioxidants is so important to reduce the effects of oxidative stress.[10] Many research have investigated to determine the role of antioxidant on prevention or treatment of diabetes complications.[11,12] Propolis is one of the antioxidant compounds that has been considered. Propolis have a long history of uses due to therapeutic characteristics. In experimental medicine, it was used to treat malignant tumors, ulcers, and local anesthetics.[13] Propolis compounds included flavonoids, terpenes, phenolic acids as well as protein, sugar, vitamins and abundant minerals. Flavonoids have an extent range of biological properties, including antioxidant, anti-inflammatory, anti-bacterial and anti-viral properties.[14] Recently, studies of the efficacy of propolis on glucose metabolism and lipids, insulin and antioxidant activity have been published.[15,16] Several studies reported that compounds found in propolis have insulin potentiating properties and also improve oxidative stress indices, so may be involved in the alleviation of the signs and symptoms of diabetes and its complications.[17,18] However the results of studies are contradictory. For example Li et al demonstrated that propolis supplementation significantly attenuated the blood glucose, insulin and also decreased insulin resistance type 2 diabetes mellitus rats.[19] Although, Fukuda et al indicated that there was no significant difference on insulin resistance between propolis group and placebo group after an 8-week intervention.[20] Therefore, confirm the above results of propolis are needed more studies. In this study, we investigated the effects of propolis on the glycemic status, insulin resistance and antioxidant status in type 2 diabetic patients.

2. Material and methods

2.1. Ethics

This research was conducted at Velayat Hospital of Qazvin University of Medical Sciences, Qazvin, Iran from April 2017 to May 2018. The study was approved by the Ethical Committee of Qazvin University of Medical Sciences with grant number of IR.QUMS.REC.1395.294 and also registered by the identification code IRCT2017041019669N4 in clinical trials registry of Iran (https://en.irct.ir/trial/17534).

2.2. Inclusion and exclusion criteria

Subjects aged 33–55 years who type II diabetes diagnosis according to American Diabetes Association (ADA) criteria (HbA_1c level of 6.5% or higher; or FBS level of 126 mg/dL (7 mmol/L) or higher; or 2-hp glucose level of 200 mg/dL (11.1 mmol/L) or higher or random plasma glucose of 200 mg/dL or higher)[21] with moderate physical activity and no change in treatment and medications in the last two months were criteria for entering the study. Taking of insulin, diabetes for more than ten year, pregnancy and lactation, hospitalization during the study, kidney and hepatic failure, serious disease (such as coronary heart disease, lung disease, cancer), change in dosage of medications, diet and physical activity, taking any dietary supplement of 2 months ago to end of the study, history of any allergies, alcohol consumption, report any side effects of the intervention and unwillingness to participate or continue to cooperate were exclusion criteria.

2.3. Subjects

Male and female patients, aged 33 through 55, with a type II diabetes were eligible for inclusion in this study. Patients were studied for 8 weeks to evaluate the efficacy of 1500 mg/day of propolis on the glycemic and antioxidant status. At entry, 72 diabetic patients who were approved by an expert physician were invited. Of these, 10 persons didn't satisfied to cooperate, and in total, 62 person entered the study (31 in each group). Written informed consent was received from all subjects before participation.

2.4. Study design

This study was a randomized double - blind placebo controlled clinical trial. At first, patient's demographic characteristics, medical history, current medications, were registered. Anthropometric indices including: height and weight were measured then body mass index (BMI) was calculated in kilograms per meters squared. After matching subjects with demographic characteristics, patients were randomly assigned to a propolis (n = 30) or placebo (n = 30) group. Each subject was receive three propolis capsules (500 mg) or placebo capsules containing wheat flour three times a day with meals. The shape, color and size of placebo were similar to the supplement capsule. Propolis and placebo capsules were produced by the pharmacy faculty of Tabriz University of medical science, Tabriz, Iran. Both capsules had very similar packaging. In order to assess the diet of patients in terms of energy intake, macronutrients, types of fatty acids and fiber, 3 d food diary (2 weekdays and 1 weekend) completed through face-to-face interviews and telephone calls. Dietary intakes were analyzed using Nutritionist 4 software (First Databank, Inc., Hearst Corporation) using the database from tables of content and nutritional value of Iranian food products. Patients were followed by phone every week to monitoring their consumption of supplements. At the end of the study, each person should be return the bottle containing their supplement for count capsules. Patients who consumed less than 10% of capsules were removed from the study. Next, the fasting blood sample was taken from patients and the blood (serum) levels of FBS, 2-hp, Insulin, HOMA-IR, HbA1c, TAC, SOD and GPx were determined.

2.5. Biochemical measurements

Blood samples were collected into tubes with and without EDTA. Blood samples without EDTA Centrifuged (Beckman Avanti J-25, USA) at a rate of 3000 rpm for 10 min in order to separation of serum. Blood samples were kept at −70 °C (Snijdes, Germany) in Diabetes Research Center and then transferred to the laboratory of Velayat Hospital of Qazvin University of Medical Sciences and the measurements were carried out. FBS concentration was measured by the enzymatic method using an Abbot ModelAclyon 300, USA auto analyzer with Pars-Azmone kit (Tehran, Iran). HbA_1c (%) was determined by using an automated high performance liquid chromatography analyzer with commercially Bio-Rad D-10 Laboratories, Schiltigheim, France kit. Plasma insulin was measured by using a chemiluminescent immunoassay method (LIAISON analyzer (310360) Diasorin S.P.A., Verecelli, Italy). HOMA-IR was calculated according to the following formula: HOMA-IR = (fasting insulin (U/ml) × FBS (mg/dl))/405.[22] TAC was measured by a spectrophotometric method using Randox TAS (Laboratories, Crumlin, UK), by an autoanalyser (Abbott, Model Alcyon 300, and USA). Also activity of glutathione peroxidase enzyme was measured by spectrophotometric and superoxide dismutase enzyme activity was performed with Randox lab, UK.

2.6. Sample size

In the present study, the sample size was calculated according to Zhao et al.[23] before and after the intervention based on the TNF α variable, with α = 0.05 and the statistical power of 90%. The sample size was obtained 20.04 in each group. Considering 35% probable drop-out, the sample size was considered 30. In this research, 62 diabetic patients (male and female) were studied.

2.7. Statistical analyses

Statistical analyses were conducted using SPSS version 20. Results were presented as mean ± SD. Differences between groups at baseline were analyzed with One-sample Kolmogorov–Smirnov test. To comparison of mean biochemical variables before and after intervention in each group was used paired sample *t*-test statistical method and to compare the variables between two group was used independent sample *t*-test method. Differences were considered statistically significantly at $P < 0.05$.

3. Results

Of recruited patients, 60 person remained to the end of the study and two were excluded from the study due to change in dosage of medication.

The findings of this study are presented in three general sections as follows.

a) result for the general characteristics of the subjects
b) result for the dietary intake of the subjects
c) result for the biochemical indices of the subjects

3.1. Baseline characteristics of the subjects

In this study, a total of 62 patients with type 2 diabetes mellitus, 2 person, one from the propolis group and one from the placebo group were excluded from the study due to changes in the medication and 60 patients completed the study. Fig. 1 presents the flow of patients through the study. The patient's baseline characteristics are present in Table 1. As seen in Table 1, two groups no significant differences in mean of age, weight, BMI, dosages of medication and duration of diabetes.

3.2. Dietary intake of the subjects

The mean of energy and macronutrient intake were shown before intervention and eighth week study in two groups in Table 2. Two groups no significant differences in mean of energy, protein, fat, saturated fatty acids, unsaturated fatty acids and fiber ($P > 0.05$).

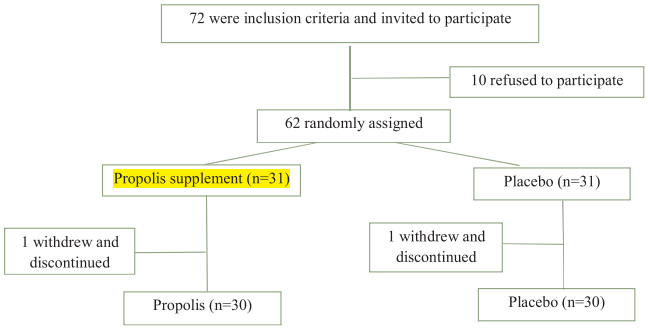

Fig. 1. Trial profile and design.

Table 1
Demographic characteristics of participants.

Characteristics		Mean ± SD Propolis(n = 30)	Mean ± SD Placebo(n = 30)	Pv
Age (years)		51.81 ± 6.35	49.05 ± 8.2	0.24
Weight (kg)	baseline	68.2 ± 9.7	70.76 ± 11.7	0.63
	completion	68 ± 9.04	71.5 ± 11.84	0.42
BMI(kg/m2)	baseline	26.78 ± 3.01	26.74 ± 3.7	0.81
	End	26.7 ± 2.8	27.01 ± 3.7	0.62
Metformin dose		1518.17 ± 329.2	1502.26 ± 410.91	0.91
Diabetes duration		5.47 ± 3.6	5.38 ± 3.1	0.9

Data are expressed as means ± SD.
PV: The significance level of demographic characteristics of participants ($P < 0.05$).

3.3. Biochemical indices of the subjects

3.3.1. Glucose indicators

The mean of glucose indicators of the subjects are shown in two groups in Table 3. The results showed that the mean concentration of FBS and 2-hp were decreased in the propolis group and placebo group. But these differences were significant in intervention group. Also HbA_1c was reduced 1/19% in the propolis group ($p = 0.04$) while it increased in placebo group ($p = 0.06$). Additionally propolis supplementation decreased the mean of insulin and IR in propolis group significantly. However, there was a significant difference between two groups.

3.3.2. Antioxidant indices

The effect of propolis supplementation on plasma antioxidant indices in both groups before and after study is shown in Table 4. At the baseline, there were not any statistically significant differences in plasma level of TAC and activity of GPx and SOD between two groups. After intervention, in the propolis group, the mean of TAC level and activity of SOD and GPx were increased ($p < 0.05$) that were statistically significant, but there was no significant change in placebo group.

4. Discussion

Hyperglycemia is a common phenotype for all types of diabetes, that the main reason for this condition is reduced insulin secretion or incomplete insulin action which is due to the destruction of pancreatic beta cells.[24] The experimental studies established that propolis could practically control the hyperglycemia in the STZ-induced diabetic rat model.[25] Also hypoglycemic effects of propolis reported in clinical trials.[20] Our findings indicated that supplementation with 1500 mg/day of propolis for 8-weeks leads to significant differences in blood glucose level, insulin resistance and HbA1c in patients with type 2 diabetes. The results of Samadi et al. investigation that conducted in patients with type 2 diabetes, showed that daily intake of 900 mg of bee propolis supplement for 12 weeks results in improvement of glycemic in patients with T2D.[26]

In fact the major mechanism of regulating blood sugar level by propolis through network pharmacology is through antioxidant activity of flavonoids and suppression of free radicals. Flavonoids, in addition to increasing the performance of internal antioxidants, can also interact with free radicals in different ways, including the direct trapping of free radicals. Indeed, because of the high reactivity of the hydroxyl group of flavonoids, they can be oxidized by radicals and lead to a more stable and less reactive radical.[27,28]

Also the glycemic control achieved by propolis treatment could be due to the stimulation of glucose uptake by peripheral tissues, inhibition of its release in circulation, or reduced glucose absorption in the gut.[29] According to the scientific results propolis reduces fasting insulin levels and consequently decreases insulin resistance with its antioxidant properties.[30] In this line, in the study of Hung et al., supplementation

Table 2
Average intake of calorie and macronutrients at the baseline andthe end of the study.

Variables		Mean ± SD Propolis(n = 30)	Mean ± SD Placebo(n = 30)	P1
Energy(kcal)	Baseline	2060.10 ± 411.40	2115.03 ± 457.96	0.311
	End	2089.85 ± 724.97	2070.28 ± 767.13	0.701
	P2	0.604	0.422	
Protein(gr)	Baseline	80.27 ± 19.04	84.95 ± 23.67	0.201
	End	81.05 ± 19.11	83.54 ± 21.65	0.587
	P2	0.524	0.714	
Carbohydrate(gr)	Baseline	267.54 ± 45.18	270.17 ± 52.16	0.625
	End	268.05 ± 95.12	271.32 ± 38.02	0.68
	P2	0.502	0.411	
Fat (gr)	Baseline	70.47 ± 16.22	72.14 ± 20.48	0.101
	End	68.55 ± 37.01	71.31 ± 24.11	0.204
	P2	0.304	0.504	
Saturated fatty acids(gr)	Baseline	17.02 ± 5.18	16.48 ± 5.56	0.701
	End	18.45 ± 6.09	16.72 ± 4.11	0.402
	P2	0.511	0.608	
Monounsaturated Fatty acid (gr)	Baseline	24.08 ± 7.11	22.02 ± 6.08	0.231
	End	24.19 ± 9.15	23.18 ± 7.14	0.201
	P2	0.711	0.412	
Polyunsaturated Fatty acid (gr)	Baseline	18.11 ± 6.08	17.15 ± 7.09	0.65
	End	17.45 ± 5.111	18.01 ± 5.11	0.711
	P2	0.625	0.611	
Fiber(gr)	Baseline	6.9 ± 1.72	6.25 ± 1.9	0.711
	End	6.13 ± 3.72	6.93 ± 3.57	0.68
	P2	0.547	0.511	

Data are expressed as means ± SD.
P1: Comparison of the mean of food intake between the two groups of propolis and placebo (Independent samples *t*-test).
P2: Comparison of mean of food intake in each group at baseline and end of study (Paired samples *t*-test).

Table 3
Effect of propolis on the glycemic status in two groups.

Variables		Mean ± SD Propolis(n = 30)	Mean ± SD Placebo(n = 30)	P1
FBS (mg/dL)	Baseline	142.3 ± 29	145.58 ± 23.4	0.62
	End	122.5 ± 26.1	146.28 ± 29.85	0.037
	P2	0.04	0.711	
2-hp(mg/dL)	Baseline	192.69 ± 85.29	198.08 ± 86.08	0.41
	End	165.27 ± 76.75	197.13 ± 63.05	0.033
	P2	0.042	0.612	
Insulin (μU/ml)	Baseline	11.86 ± 2.73	12.13 ± 2.33	0.263
	End	10.21 ± 2.52	12.17 ± 2.78	0.001
	P2	0.01	0.44	
HOMA-IR	Baseline	4.16 ± 0.26	4.36 ± 0.19	0.51
	End	3.08 ± 0.22	4.39 ± 0.27	0.02
	P2	0.02	0.104	
HbA1c (%)	Baseline	7.65 ± 1.58	7.84 ± 1.35	0.3
	End	6.58 ± 1.46	7.87 ± 1.61	0.037
	P2	0.04	0.61	

Data are expressed as means ± SD.
P1: Comparison of the mean of the glycemic status between the two groups of propolis and placebo (Independent samples *t*-test).
P2: Comparison of mean of the glycemic status in each group at baseline and end of study (Paired samples *t*-test).

Table 4
Effect of propolis on the antioxidant status in two groups.

Variables		Mean ± SD Propolis(n = 30)	Mean ± SD Placebo(n = 30)	P1
TAC (mmol/L)	Baseline	0.97 ± 0.21	1.03 ± 0.71	0.1
	End	1.15 ± 0.31	0.98 ± 0.2	0.042
	P2	0.045	0.12	
SOD (U/mg Hb)	Baseline	1751.84 ± 258.46	1736.11 ± 117.79	0.172
	End	1811 ± 271.01	1745.08 ± 123.4	0.034
	P2	0.037	0.261	
GSH-Px (U/g Hb)	Baseline	39.1 ± 4.8	38.91 ± 10.03	0.419
	End	45.61 ± 6.03	37.01 ± 9.11	0.028
	P2	0.03	0.214	

Data are expressed as means ± SD.
P1: Comparison of the mean of the antioxidant status between the two groups of propolis and placebo (Independent samples *t*-test).
P2: Comparison of mean of the antioxidant status in each group at baseline and end of study (Paired samples *t*-test).

with propolis in rats leads to decrease insulin levels and insulin resistance.[31] Also this results was observed in the Zamami et al study.[32] Suggested mechanisms of the experimental and clinical studies indicate that probably the effects of supplementation with propolis, extracts of propolis and phenolic compounds of propolis such as caffeic acid phenethyl ester on regulation of blood glucose level caused by decreasing insulin resistance, coping with oxidative stress, reducing the production inflammatory factors, increasing the adiponectin levels, increasing transfer of glucose to tissues, inhibition of carbohydrate digestive enzymes especially alpha-amylase and alpha-glycosidase.[33] Elissa et al [34]study can be support some of the proposed mechanisms. Based on their results, insulin resistance decreased significantly by decreasing in TNFα level that ultimately led to decrease in fasting blood glucose level. Also it was shown that propolis lead to increases glucose transfer through glucose transporter 4 by reducing insulin resistance. On the other hand, increasing the concentration of propolis lead to inhibition of alpha-amylase, which can cause delay in the hydrolysis of polysaccharides and reduce glucose absorption.[35] Also reduction in HbA_{1c} level in the propolis group in our study was consistent with the results of the study by Zhu et al.[16] In this study HbA_{1C} level decreased by 8.4% in diabetic rats treated with Chinese propolis compared to control group. In our study, supplementation with propolis reduced HbA_{1C} by 1.19% in compared to basal level. Despite the positive results there is evidence that propolis may not affect in patients with diabetes. For example, in a placebo-controlled clinical trial supplementation with 230 mg / day of Brazilian propolis for 60 days did not have effect on blood glucose and antioxidant status in diabetic patients and only prevented the increase of blood uric acid levels and decrease glomerular filtration rate.[20] Also in Samadi et al study, there was no significant difference in serum insulin level and insulin resistance between two groups' propolis and placebo after 12 weeks.[26] Perhaps the low

dose of propolis is one of the reasons that these researchers should not be considered.

One of the most important reasons for impairing balance between the oxidative and antioxidant in diabetic patients is hyperglycemia, which leads to the stress oxidative condition. In fact, elevation and oxidation of glucose are one of the sources of reactive oxygen species production.[36] Following the increase in ROS, oxidation of fats occurs especially in the membrane of cells which worsens insulin resistance and oxidative stress.[37] Several intra- and extracellular antioxidant defense mechanisms counteract the destructive effects of free radicals by attenuating or omitting their activities. However, in DM the oxidative stress exceeds the body's antioxidant defense mechanisms.[38] Propolis is a substance with various therapeutic effects due to its active compounds, including flavonoids and antioxidants.[31] In patients with type 2 diabetes, insulin resistance or insufficient secretion of insulin lead to hyperglycemia and disturbance in metabolism of glucose, lipids and proteins which ultimately leads to the generation of reactive oxygen species and oxidative stress and disorder in antioxidant defense.[5] Studies have shown that in patients with uncontrolled diabetes, the level of SOD, GPx enzymes and antioxidants such as vitamin E and Alpha-Lipoic Acid as well as total antioxidant capacity decrease. Specially, the SOD enzyme activity is disrupted before other enzymes due to it is one of the first line of defense system against oxidative stress.[33] Therefore, in these patients, anti-oxidant compounds such as flavonoids, which are exist a lot of in propolis, can have a positive effect on reducing the complications of the disease and suppressing the free oxygen radicals.[16] In the present study, the total antioxidant capacity, SOD and GPx increased significantly after supplementation with propolis. The results of the study are similar with the results of Zhao et al.[23]

Like the many first studies, some limitations were in our research. Including non-evaluation of other indicators of oxidative stress and inflammatory factors, lack of investigate the different doses of propolis and time limitation were our study limitations. Therefore, further studies are needed due to the contradiction in the results of various studies and confirm the above results. It is worth mentioning this research was the first study on investigate Alamut area propolis that is the strength of our study. Also, in this study, we could evaluate the new effective dose in a short time, which is another one of the strengths of this research. In addition, the present study is a double-blind randomized clinical trial that has a high reliability. It is hoped more research be done with different doses of this substance and on various diseases in the future. Also no side effect were reported during the study in either group.

In Conclusion, overall, the results of this study showed the potential benefit of propolis in the improvement the blood glucose and antioxidant indicator in type 2 diabetes. Daily supplementation with 1500 mg of propolis for 8 weeks can help to better control of glycemic status and can be used as auxiliary therapy in these patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

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