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• Research Article

Effects of bee propolis supplementation on glycemic control, lipid profile and insulin resistance indices in patients with type 2 diabetes: a randomized, double–blind clinical trial

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ABSTRACT

BACKGROUND: Propolis, a natural resinous substance made by bees from material extracted from plants, flowers and bee's wax, has shown great therapeutic effects and been widely used in food and drug industries. Recently, some researchers have studied the effect of this substance in the treatment of diabetes.

OBJECTIVE: The purpose of this trial was to determine the effect of bee propolis on glycemic control, serum lipid profile and insulin resistance indices in patients with type 2 diabetes (T2D).

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: This randomized clinical trial involved 66 patients with T2D, which were randomly divided into two groups of intervention (IG) and placebo (PG). IG received 300 mg three times a day for a total of 900 mg/d of propolis pills, while PG received similar pills, lacking propolis, on the same schedule for 12 weeks.

MAIN OUTCOME MEASURES: Fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), serum insulin and insulin resistance indices were the main outcome measures.

RESULTS: The mean change in FBG between the IG ((17.76 ± 27.72) mg/dL decrease) and the PG ((6.48 ± 42.77) mg/dL increase) was significantly different (P = 0.01). Change in mean HbA1c had a similar pattern to FBG. The mean change in TC between the IG ((5.16 ± 43.80) mg/dL increase) and the PG ((28.9 ± 27.4) mg/dL increase) was also significantly different (P = 0.01), showing the protective role of propolis against the increase in TC. The change in mean LDL was similar to mean TC. There was no significant difference in other lipids or insulin resistance indices between the two groups.

CONCLUSION: Based on this study, the daily intake of 900 mg of bee propolis supplement for 12 weeks results in improvement of glycemic and some serum lipid levels in patients with T2D.

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1 Introduction

Diabetes mellitus (DM) is a disease characterized by high blood glucose and resulting in defects in insulin secretion, insulin action, or both. Insulin is a hormone produced by β-cells in the pancreas and is necessary for using or storing body fuels.[1] DM may be caused by low levels of insulin, dysfunction of pancreas cells, or tissue resistance, especially in skeletal muscle and adipose tissue.[1–3]

In 2013, it was reported that there were 382 million people with diabetes worldwide, accounting for 8.3% of the global population; 90% of these patients were diagnosed with type 2 diabetes (T2D).[4–6] The prevalence of this metabolic disorder is higher in men than women. The prevalence of DM varies by region around the world, especially in urban areas. The incidence of DM is increasing rapidly and it is estimated that the total number of people with DM will increase to 366 million by 2030.[7]

Propolis is a natural resinous substance made by bees from material extracted from plants and bee's wax, as well as saliva and enzymes secreted by the bee's salivary glands.[8–10] Propolis is a word of Greek origin; in this case, the "pro" means before and "polis" means a community or town. In this sense, the term is defined as a natural substance produced to protect the hive. Bee glue is another name of propolis.[11] From ancient times, propolis has been used widely by man in traditional medicine to treat diseases. Ancient Egyptians used it for embalming the dead. Incas used the substance as febrifuge. Greek and Roman physicians applied propolis to disinfect the mouth and also disinfect and heal wounds. The use of propolis has been approved in London pharmacies since the 17th century, and has been a popular remedy throughout the 17th–20th centuries due to its antibacterial properties. Propolis is a lipophilic, bitter material that is hard at room temperature; when heated, it becomes soft, flexible, and sticky. It has a spicy flavor and the color can range from yellow and green to red and dark brown depending on the materials used by the bees during its formation. Because of its waxy nature and physical characteristics, bees use this substance to build and repair the hive. It is also used as a defense barrier against animals and microbiological factors.[12]

Generally, raw propolis contains 50% resin, 30% wax, 10% essential oils, 5% pollen and 5% other organic compounds.[13,14] The main components of propolis responsible for its biological activities include flavonoids, phenols and aromatic compounds.[8,15] Propolis has shown great therapeutic effects, and is widely used in the food and drug industries. Its biological effects include anti-inflammatory,[16–19] antibacterial,[20] antifungal,[21,22] antioxidant,[23,24] anticancer,[25–29] and immune system regulation.[30,31] Some studies have also been performed to assess the effect of propolis on blood pressure.[32,33]

Flavonoids in propolis are powerful antioxidants that can eliminate free radicals and protect cell membranes from lipid peroxidation.[34] Propolis can reduce cellular levels of hydrogen perioxide and nitric oxide.[35] Another important component of propolis's antioxidant properties is caffeic acid phenyl ester (CAPE), which blocks the production of reactive oxygen species.[36] Propolis, *in vitro*, is a low-density lipoprotein (LDL) peroxidation inhibitor.[37] *In vivo*, it increases the antioxidant capacity of humans[38] and animals.[39] *In vivo* and *in vitro* studies have shown the mechanisms of action for propolis's cardiac protective effects, including regulation of glucose and lipoprotein metabolisms, regulation of gene expression, decreased activity of inflammatory cytokines, improved endothelial function and inhibition of platelet aggregation.[40] In addition, polyphenols commonly found in propolis reduce the risk of cardiovascular disease and prevent the formation of atherogenic plaques.[41–43]

The antimicrobial activity of propolis has been investigated on Gram-positive bacteria (*Staphylococcus* and *Streptococcus*) and Gram-negative bacteria (*Escherichia coli*).[44] It seems that its antimicrobial activity is due to the flavonoids pinocembrin, galangin, and pinobanksin.[44,45] Many studies have identified anti-inflammatory effects of propolis against both acute and chronic inflammation. Rossi et al.[46] and Lee et al.[47] showed that propolis inhibits cyclooxygenase-dependent activity. Among the compounds in propolis, CAPE and galangin have this effect, but CAPE is more effective and has shown regenerative properties for tissues and antineoplastic properties against most cancer cells. Propolis was also suggested as a feed additive with promising effect on animal productivity, immunity and health status.[48,49]

Recently, some researchers have studied the effect of this substance in the treatment of diabetes.[23,50–60] However, the effect of propolis on insulin resistance and lipid profiles in these studies has rarely been investigated. Accordingly, the present study aimed to investigate the effects of short-term use of bee propolis supplement on fasting blood glucose (FBG), lipid profile and indicators of insulin resistance in T2D.

2 Materials and methods

2.1 Study design

This was a double-blind, placebo-controlled clinical trial which lasted one year, from December 2014 to December 2015. Both the participants and researchers were unaware about the type of consumed supplements. The participants were randomly divided into intervention (IG) and placebo groups (PG) using a table of random numbers.

2.2 Inclusion and exclusion criteria

Included patients had five to ten years history of T2D and were using the conventional therapy of oral medications for blood glucose control. Screened patients were excluded for any of the following criteria: lack of desire to continue participating in the study; pregnancy or lactation; insulin injection; underlying diseases (autoimmune, gastrointestinal, liver, thyroid and unstable heart diseases, etc.); severe respiratory diseases (asthma, chronic bronchitis, etc.); taking any vitamin, minerals, or other nutritional supplements; and allergies to propolis, honey or any bee products.

2.3 Participants

To determine the sample size of the study, we presumed a significance level (α) of 0.05 and test power of 80% in order for our analysis to detect a difference of 2 units of the hemoglobin A1c (HbA1c); according to Murata et al.,[59] in two groups of previous studies, a sample of 30 individuals was determined to be necessary. When an attrition rate of 10% was considered, the minimum group size for this study was determined to be 33. Therefore, 66 patients with T2D were chosen from the Imam Ali and Yazd Diabetes Research Center, affiliated to the Shahid Sadoughi University of Medical Sciences in Yazd.

2.4 Intervention

Patients in the IG received 300 mg propolis pills, three times a day, one hour after each meal with a glass of water. Patients in the PG received a daily dose of 3 placebo pills with the same shape, color and size, following the same protocol as the IG. It should be noted that placebo pills were produced by the same company (Soren Tech Toos, Mashhad, Iran) that manufactured the propolis pills, containing all the ingredients except the active ingredient of propolis. Both pills also had very similar packaging.

The study lasted 12 weeks. Patients were closely tracked to control and prevent attrition, and participants' commitment to the study protocol was verified once a week by phone and once every 3 weeks in person. Supplement tablets were distributed to patients every 3 weeks during office visits to reinforce the participants' adherence to the study protocol; a reminder calendar was given to each patient, which they were asked to mark after taking each pill. Patients were also asked to bring their checked calendar and empty cans in their next visit. Patients were advised to avoid changing their diet and physical activities during the intervention period.

2.5 Outcome measurements

In interviews, we collected participants' demographic characteristic, anthropometric measurement and 24-hour dietary intake data before and after the intervention. Laboratory analyses of blood characteristics were performed on fasting samples taken the day after these interviews marking the beginning and end of the study. To measure the blood variables, 5 mL venous blood was taken from each individual. The lipid profiles and FBG were performed on the day of blood sampling; samples for serum insulin (SI) levels were stored at –80 °C and analyzed at the end of the trial.

FBG was measured by enzymatic assay and HbA1c was measured following a turbidimetry protocol. Lipid profile data, including total cholesterol (TC) and triglycerides (TG), were measured using an enzymatic method. LDL was measured using the sedimentation method. Friedewald formula[61] was used to measure high-density lipoprotein (HDL). Fasting SI was measured with enzyme-linked immunosorbent assay kits (PadginTeb Co, Tehran, Iran). Other insulin resistance indices, including homeostasis model assessment (HOMA-IR), insulin sensitivity (%S) and β-cell function (%β) and quantitative insulin sensitivity check index (QUICKI) were calculated using HOMA calculator software (version 2.2.2 by Diabetes Trials Unit, University of Oxford, UK) and standard formulae.[62,63]

2.6 Data analysis

SPSS software (Version 19.0, IBM Corp., USA) was used for data analysis. The Kolmogrov-Smirnov test was used at the outset to examine the normality of data. Normally distributed data were tested with paired *t*-test and Student's *t*-test to compare means within and between groups, respectively. For data that were not normally distributed, the Wilcoxon test and Mann-Whitney test were applied to compare within and between group means, respectively. The Nutritionist IV (Bruno, CA, USA) was used to examine the 24-hour dietary recall data. *P*-value less than 0.05 was set as the threshold for significance.

2.7 Ethical considerations

The subject, objectives and methodology of this study were explained to all patients, and all participants

taking part in this study signed a consent form. Patients were assured that they were free to participate in the study and that their withdrawal would be permitted at any time, and not affect their treatment at the Imam Ali and Yazd Diabetes Research Center. Supplements had no side effects and were licensed by the Ministry of Health. Patients' information was coded, and protected from the public eye. The proposal was approved by the Ethics Commission of the Department of Research and Technology at Shahid Sadoughi University of Medical Sciences and Health Services of Yazd and archived on the website of Iranian Ministry of Health (www.irct.ir) with the proprietary code of IRCT2014080218659N1.

3 Results

3.1 Demographic characteristics and dietary intake

Of the 66 patients initially enrolled in the study, 9 withdrew from the study (3 from the IG and 6 from the PG) due to their lack of desire to continue the trial and initiation of insulin. At the end of the study, 30 patients remained in the IG and 27 patients in the PG. Data from these 57 patients were analyzed at the end of the twelfth week (Figure 1).

Demographic characteristics of both groups at the beginning of the study are shown in Table 1. As can be seen, qualitative and quantitative characteristics between the two groups had no significant differences. Average daily dietary intake and anthropometric indices before and after the intervention are shown in Table 2. As can be seen, means between two groups had no significant difference.

3.2 FBG, HbA1c and lipid profiles

Means of the FBG, HbA1c and lipid profile characteristics are reported in Table 3. There were no significant differences in these variables between groups at the beginning of the study. At the end of the intervention, the means of FBG and HbA1c had significantly decreased in the IG, and there was a significant difference in mean FBG changes ($P = 0.010$) between the two groups: the mean decrease in FBG of the IG was 17.76 mg/dL, while the PG had a mean increase of 6.48 mg/dL. Change in HbA1c was similar to that of FBG.

The mean TC before and after the intervention showed no significant difference in the IG, but there was a significant increase in the PG ($P < 0.001$); thus, the amount of change in TC was significantly different between the two groups ($P = 0.010$). The pattern of change in LDL levels was similar to that found in TC. The mean of HDL in the IG did not change significantly during the intervention, but it significantly increased post-treatment in the PG ($P = 0.020$). This change did not result in significant difference between the two groups. There were not significant differences in serum TG or very low-density lipoprotein (VLDL) either between groups or over the course of the study.

3.3 Insulin resistance indices

Kolmogrov-Smirnov test results showed that the insulin indices data did not follow a normal distribution. Therefore, the medians and percentiles of these variables are reported in Table 4. As it can be seen, the median of SI significantly increased in both groups ($P < 0.001$,

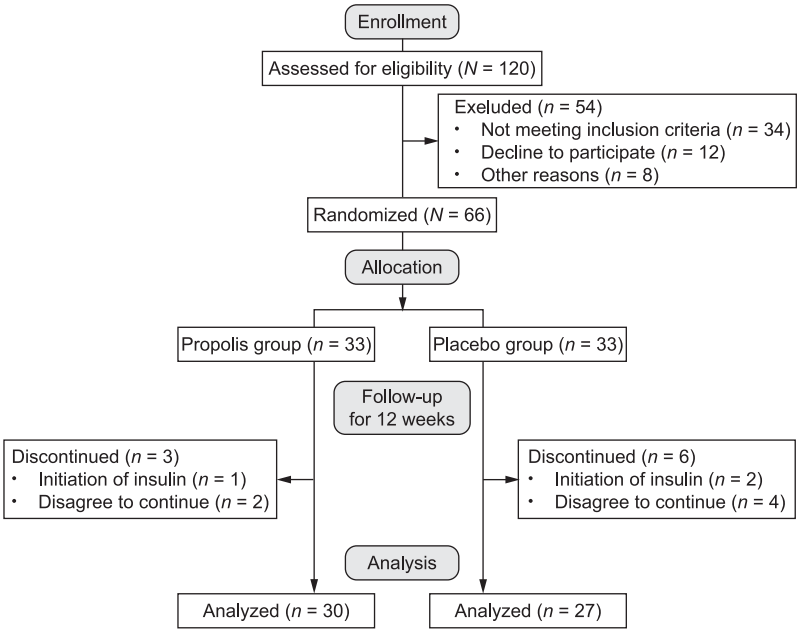

Figure 1 Participant flowchart

P = 0.003), but there was no significant difference between groups or their changes in SI over the course of the study. Insulin resistance data were quite similar to SI. The median of both %S and %β decreased significantly in both over the course of the study; however, there were no significant differences in those variables between groups or their changes. QUICKI mean is reported in Table 5, with between and within group comparison statistics. The changes of this variable are similar to insulin sensitivity and β-cells performance.

4 Discussion

Based on the results of this study, the addition of 3 propolis pills to the daily medication regimen of T2D patients for 12 weeks can lead to better glycemic control, reduction of FBG and HbA1c, and also limit TC and LDL cholesterol increases; however, there was no significant effect on insulin resistance indices.

Several studies have been conducted to evaluate the effect of propolis on FBG, and they mostly pointed the effectiveness of this substance, findings which were consistent with the current study. For example, several researchers have reported that supplementation for different periods of time as well as with different doses of propolis had the same decreasing effect on rats' FBG.[23,50,54–56,58] Furthermore, a human study conducted on this subject also reported that supplementation with a mixture of propolis and mulberry leaf extract reduced FBG significantly.[59]

One mechanism that has been proposed in the literature suggests that this substance might reduce the expression and activity of the glucose-6 phosphatase enzyme.[52] On the other hand, with the increased activity of glucose transporter 4 in skeletal muscle, glucose uptake is increased.[53] The 8-week study conducted by Zhu et al.[55] on diabetic rats showed a 4.8% decrease in

Table 1 Baseline demographic characteristics of the two groups

Variables	Propolis group (n = 30)	Placebo group (n = 27)	P-value
Quantitative variables			
Height (mean ± standard deviation, cm)	164.01 ± 9.42	166.19 ± 7.35	0.32*
Weight (mean ± standard deviation, kg)	76.00 ± 12.39	75.98 ± 12.37	0.99*
Body mass index (mean ± standard deviation, kg/m^2)	28.18 ± 3.64	27.53 ± 4.28	0.53*
Waist circumference (mean ± standard deviation, cm)	99.11 ± 11.31	99.89 ± 11.11	0.79*
Age (mean ± standard deviation, years)	51.30 ± 6.57	56.07 ± 9.02	0.02*
History of disease (mean ± standard deviation, years)	6.06 ± 1.81	6.70 ± 2.58	0.28*
Qualitative variables (n (%))			
Gender			
Female	17 (56.7)	11 (40.7)	0.230**
Male	13 (43.3)	16 (59.3)	
Marital status			
Single	0 (0.0)	1 (3.8)	0.288**
Married	30 (100.0)	26 (96.2)	
Education			
Elementary	3 (10.0)	5 (18.5)	0.516**
Under high school diploma	12 (40.0)	11 (40.7)	
High school diploma	4 (13.3)	3 (11.1)	
Academic	8 (26.7)	5 (18.5)	
Occupation			
Homemaker	15 (5.0)	11 (40.7)	0.685**
Self-employed	9 (30.0)	7 (25.9)	
Employee	2 (6.7)	4 (14.8)	
Retired	4 (13.5)	5 (18.5)	

*: compare propolis group to placebo group's quantitative variables (P-value, Student's t-test); **: compare propolis group to placebo group's qualitative variables (P-value, Chi-squared test).

Table 2 Comparison of daily intake mean at the beginning and end of the study in the two groups

Variables	Propolis group (n = 30)	Placebo group (n = 27)	P-value**
Energy (kcal)			
Before	1 671.40 ± 437.02	1 555.40 ± 322.69	0.26
After	1 686.30 ± 414.89	1 584.18 ± 295.01	0.29
P-value*	0.53	0.17	
Carbohydrate (g)			
Before	248.83 ± 67.84	220.00 ± 61.43	0.10
After	239.18 ± 66.68	227.84 ± 51.74	0.48
P-value*	0.13	0.24	
Protein (g)			
Before	73.54 ± 26.04	76.72 ± 19.71	0.60
After	76.48 ± 27.60	79.67 ± 22.19	0.63
P-value*	0.59	0.45	
Fat (g)			
Before	45.83 ± 19.26	45.06 ± 12.05	0.85
After	47.63 ± 16.77	43.02 ± 12.32	0.24
P-value*	0.55	0.44	
Weight (kg)			
Before	76.00 ± 12.39	75.98 ± 12.37	0.99
After	75.27 ± 12.19	75.98 ± 12.37	0.83
P-value*	0.009	0.87	
Body mass index (kg/m^2)			
Before	28.18 ± 3.64	27.53 ± 4.28	0.54
After	27.91 ± 3.51	27.52 ± 4.39	0.71
P-value*	0.01	0.96	
Waist circumference (cm)			
Before	99.11 ± 11.31	99.89 ± 11.11	0.79
After	98.47 ± 11.04	99.80 ± 11.19	0.65
P-value*	0.15	0.78	

Data are expressed as mean ± standard deviation. *: P-value in the same group comparing before to after intervention (paired t-test); **: P-value between propolis group and placebo group at the beginning or end of the study, respectively (Student's t-test).

blood glucose among rats receiving bee propolis for 3 months. In addition to this, using a combination of bee propolis with mulberry leaf extract for 30 d considerably reduced this index; this reduction was comparable to the effect of acarbose.[59]

In fact, it can be concluded that in the current study, the use of propolis has prevented a significant increase in TC. Other studies have found that propolis supplementation can actually reduce TC.[23,48,54,55,58] In the case of LDL, no significant increase was observed in IG, while PG showed significant increase in this variable. The mean difference between the two groups was significant. Hence, it can be said that taking supplements of this substance can prevent an increase in LDL. Fuliang et al.[23] showed that the use of bee propolis can significantly reduce LDL and increase HDL. But in study of Li et al.,[50] the administration of propolis to rats for 10 weeks had no significant effect on HDL. The propolis used in this study also had no effect on triglycerides. In the studies of Fuliang et al.[23] and Tang et al.,[58] both of which were performed on rats, propolis significantly decreased triglycerides, while the results of Li et al.[50] pointed to a significant increase in this substance.

In the present study, prescribed propolis had no effect on insulin resistance indices. However, Tang et al.[58] found that propolis supplementation significantly decreased the level of serum insulin. Al-Hariri et al.[56] showed that insulin levels in diabetic rats receiving propolis and insulin combination therapy, were higher than those of rats that just received insulin. Based on the results

Table 3 Within and between groups comparison of FBG, HbA1c and lipid profile

Variables	Propolis group (n = 30)	Placebo group (n = 27)	P-value**
FBG (mg/dL)			
Before	152.20 ± 35.79	159.62 ± 48.20	0.510
After	134.43 ± 33.96	166.11 ± 65.77	0.240
Changes	–17.76 ± 27.72	6.48 ± 42.77	0.010
P-value*	0.001	0.430	
HbA1c (%)			
Before	8.20 ± 1.89	7.95 ± 1.42	0.560
After	7.43 ± 1.29	8.14 ± 1.46	0.050
Changes	–0.77 ± 1.34	0.19 ± 1.0	0.004
P-value*	0.004	0.320	
Total cholesterol (mg/dL)			
Before	164.83 ± 37.40	161.50 ± 35.06	0.730
After	170.00 ± 34.85	190.46 ± 36.38	0.350
Changes	5.16 ± 43.80	28.96 ± 27.41	0.010
P-value*	0.520	< 0.001	
LDL (mg/dL)			
Before	89.46 ± 30.84	88.71 ± 31.98	0.920
After	97.00 ± 31.41	113.43 ± 35.46	0.070
Changes	7.54 ± 36.87	24.71 ± 25.07	0.040
P-value*	0.270	< 0.001	
HDL (mg/dL)			
Before	44.26 ± 8.20	41.05 ± 6.54	0.100
After	45.18 ± 10.17	43.38 ± 5.84	0.420
Changes	0.91 ± 5.71	2.33 ± 3.56	0.270
P-value*	0.380	0.020	
Triglycerides (mg/dL)			
Before	155.38 ± 66.66	158.64 ± 68.85	0.850
After	144.21 ± 44.75	168.20 ± 93.97	0.230
Changes	–11.166 ± 65.49	9.55 ± 48.58	0.170
P-value*	0.350	0.310	
VLDL (mg/dL)			
Before	31.07 ± 13.33	31.72 ± 12.77	0.800
After	28.84 ± 8.95	33.64 ± 18.79	0.210
Changes	–2.2 ± 1.30	1.90 ± 9.71	0.180
P-value*	0.350	0.310	

Data are expressed as mean ± standard deviation. *: P-value in the same group comparing before to after intervention (paired t-test); **: P-value between propolis group and placebo group at the beginning or end of the study, respectively (Student's t-test).
FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin A1c; LDL: low-density lipoprotein; HDL: high-density lipoprotein; VLDL: very low-density lipoprotein.

Table 4 Comparison of the median of serum insulin, insulin resistance, insulin sensitivity and β-cell function before and after intervention in the two groups

Variables	Propolis group (n = 30)	Placebo group (n = 27)	P-value*
Fasting insulin (mU/L)			
Before	2.95 (2.90, 4.35)	3.70 (3.00, 4.70)	0.09
After	6.43 (3.56, 10.00)	7.61 (3.10, 10.90)	0.93
P-value**	< 0.001	0.003	
Changes	1.73 (0.30, 6.66)	1.68 (0.00, 6.20)	0.47
Insulin resistance (%)			
Before	0.45 (0.43, 0.62)	0.59 (0.45, 0.66)	0.12
After	0.89 (0.52, 1.45)	1.05 (0.59, 1.47)	0.80
P-value**	< 0.001	0.002	
Changes	0.22 (0.02, 0.93)	0.18 (0.00, 0.76)	0.68
Insulin sensitivity (%)			
Before	220.10 (160.00, 234.70)	170.20 (151.00, 220.40)	0.08
After	112.20 (68.70, 190.50)	95.30 (61.60, 168.40)	0.66
P-value**	< 0.001	0.001	
Changes	–69.55 (–155.22, –12.20)	–58.20 (–103.90, 0.40)	0.43
β-cell function (%)			
Before	20.80 (14.60, 28.30)	22.10 (13.80, 37.10)	0.82
After	6.43 (3.50, 10.00)	7.61 (3.10, 10.90)	0.32
P-value**	< 0.001	< 0.005	
Changes	19.00 (5.52, 30.90)	13.00 (–0.10, 24.20)	0.16

Data are expressed as mean (Q_{25}, Q_{75}). *: P-values between propolis group and placebo group before and after intervention, respectively (Mann-Whitney test); **: P-value in the same group comparing before to after the intervention (Wilcoxon test).

Table 5 Within and between groups comparison of QUICKI

Group	QUICKI			
	Before	After	P-value*	Changes
Propolis group (n = 30)	0.37 ± 0.03	0.34 ± 0.03	< 0.001	–0.03 ± 0.03
Placebo group (n = 27)	0.36 ± 0.03	0.03 ± 0.33	0.003	–0.02 ± 0.03
P-value**	0.10	0.48		0.29

QUICKI: quantitative insulin sensitivity check index. *: P-value in the same group comparing before to after intervention (paired t-test); **: P-value between propolis group and placebo group at the beginning and end of the study, respectively (Student's t-test).

of Zamani et al.,[57] treating diabetic rats with propolis decreased their serum insulin significantly. As it can be seen, results of these studies have been contradictory and non-conclusive. In the study carried out by Tang et al.,[58] insulin resistance was significantly reduced which is in line with the results observed by Kitamura et al.[54] Also, in the study of Zamani et al.,[57] the intervention improved insulin function.[58] In the 8-week study of Fukada et al.,[60] which included 80 diabetic patients, supplementation with propolis reduced insulin resistance. The contradictory results of this study and the study carried out by Fukada et al.[60] could be due to small sample sizes.

Similar to many pilot projects, our study also had some limitations. For instance, a larger sample size could demonstrate stronger relationships among response variables. Similarly, the short intervention period is another limitation, as 12 weeks may be enough for measuring changes in HbA1c. One of the main limitations may have been the small propolis dose. The doses of propolis were prescribed based on safe dose of propolis; however, the chosen dose may have been inadequate to inspire changes in some variables, such as insulin resistance indices. Finally, more powerful study designs, such as crossover design, could be implemented in future

RCTs to connect propolis consumption with changes in response variables. So, studies with larger sample size, long-term intervention, larger dose of propolis, and more powerful designs, such as crossover, are proposed for further studies in this field.

5 Conclusions

This trial showed that, compared with placebo, the daily intake of 900 mg of bee propolis supplement for 12 weeks can result in the control of blood glucose and some lipid levels in T2D; however, no significant effects were observed on parameters related to insulin resistance. Thus, propolis supplements can be useful for treatment of T2D and its complications.

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8 Competing interests

None declared.

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