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Reducing the Inflammatory Interleukins with Anti-Inflammatory and Antioxidant Effects of Propolis in Patients with Type 2 Diabetes: Double-Blind, Randomized Controlled, Clinical Trial

ABSTRACT

Objective: This research was designed and conducted to evaluate propolis supplementation effects on insulin resistance and inflammation in patients with type 2 diabetes.

Materials and methods: In the double-blind, randomized controlled study, 60 patients with type 2 diabetes were enrolled. Patients were randomly assigned to receive Iranian propolis (1500 mg/day for 8 weeks) (n = 30) and the placebo (n = 30). The primary endpoint was to detect of changes in the fasting blood glucose (FBG), fasting insulin, the homeostasis model assessment insulin resistance (HOMA-IR) evaluation model, QUICKI, the homeostasis model assessment of β-cell function (HOMA-B), and inflammatory factors including Interleukin 6 and Interleukin 17 from baseline to the end of this study.

Results: Eight weeks after intervention, the mean of FBG, fasting insulin and HOMA-IR, were significantly decreased in patients treated with propolis compared with the placebo group. Furthermore, there was a considerable enhancement in the HOMA-B as a measure of β-cell function and QUICKI index after the administration of propolis in treated group. Serum IL-6 and IL-17 were diminished remarkably in the propolis group, while there was no significant change in the placebo group.

Conclusions: Based on this study, the daily intake of 1500 mg of bee propolis supplement for 8 weeks results in improvement of glycemic status, reduction in insulin resistance and inflammatory condition in patients with T2D. (Clin Diabetol 2023; 12, 6: 327–335)

Keywords: propolis, diabetes mellitus, insulin resistance, interleukin 6, interleukin 17

Introduction

Diabetes mellitus is one of the main endocrine problems with a multifactorial etiology. This severe metabolic condition is associated with high blood glucose, carbohydrate, lipid and protein metabolism defects, and absolute or relative insulin deficiency [1].

Several studies showed that patients with diabetes had a disturbance in the balance between cytokines.

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For example, it has been shown that monocyte cells in patients with type 2 diabetes tend to produce inflammatory cytokines [2]. Some investigations have also indicated a high serum level of inflammatory cytokines such as interleukin (IL)-18, interleukin-6, tumor necrosis factor α (TNF-α), and C-reactive protein in these patients [3].

On the other hand, diabetes is known as a chronic inflammatory procedure associated with insulin resistance, which is associated with systemic inflammation and a 2-3-fold increase in plasma concentrations of inflammatory cytokines such as TNF-α, interleukin-6, interleukin-1β and C-reactive protein [4].

Evidence suggests that T lymphocytes, especially TH-17 cells, play the main role in the production of inflammation in autoimmune diseases. The TH-17 cells stimulate the production of IL-1 and TNF-α in human macrophages, secretion of IL-6 and IL-8 from synovial fibroblast, and cartilage stimulation to produce metalloproteinases [5]. One of the most important intermediates in the action of TH-17 lymphocytes is interleukin 17 which is an important prophylactic cytokine and a strong inducer for the secretion of other inflammatory cytokines such as IL-6, IL-8, IL-1B, TNF-α and granulocyte colony-stimulating factor at various levels of epithelial, endothelial and fibroblast cells [6]. Interleukin 6 is produced not only by immune cells, but also at high levels by adipose tissue in non-inflammatory conditions [7].

Currently, researchers are looking for alternative therapies for diabetes, that could better control blood glucose levels while having fewer side effects. One of the compositions that have recently been considered is propolis. Propolis is a gummy and sticky substance that is collected by bees from various herbal sources. Propolis is mainly composed of flavonoids, terpenoids, phenolic compounds, hydrocarbons, salts, and minerals [8].

In the various models of acute and chronic inflammation, propolis and its subsidiary products exhibited anti-inflammatory effects [9]. Several specific effects of the propolis extract such as prevention of platelet aggregation, and expression of atherogenic growth factors [10], the inhibition of cyclooxygenase (COX) and consequent inhibition of prostaglandin biosynthesis in ulcerative colitis [11], reduction in atherosclerotic plaque development through modulation of inflammatory mediators [12] and suppressing inflammation-associated transcription factor NFκB in wound healing [13] have been detected. This study aimed to determine the effect of oral supplementation of Iranian propolis on reducing insulin resistance and inflammatory factors in patients with T2DM.

Materials and methods

Study design

Eligible patients with type 2 diabetes (62 patients) by using randomized block methods, were randomly divided into two groups of intervention (propolis) (n = 31) and placebo (n = 31). Patients in the intervention group received 1500 mg/day of propolis in 500 mg capsules three times daily. In the control group, patients received three capsules of the placebo containing wheat flour, which looked similar to the propolis capsules in terms of appearance. The shape, color, and size of the placebo were the same as the supplement capsules.

Propolis capsules were filled with propolis powder collected from Alamut, Qazvin. Propolis was powdered and encapsulated by a traditional medicine researcher at the Azad University of Tabriz, Tabriz, Iran. All capsules had the same appearance and specific identification code to which both the researchers and patients were blind until the end of the supplementation. To ensure blindness, the allocation of the capsules was done by a trained researcher who was not involved in this study. Patients were closely followed up to control them in terms of using propolis capsules and prevent attrition, every 7 days by phone call to patients. In this study, the evaluation of patients' compliance with the use of propolis capsules by determining the number of the remaining capsules at the end of the eighth week of the study was performed and patients who had not consumed more than 10% of their supplementation were excluded from the review process.

Study participants

Patients with type 2 diabetes for less than 10 years were screened and enrolled if they were aged 35–55 years, had moderate physical activity levels, were taking oral medication for controlling blood glucose (metformin), and there was no change in the therapeutic and medicinal usage for at least 2 months before the study began.

Inclusion/exclusion criteria

Screened patients were excluded for any of the following criteria: unwillingness to continue participating in the study; insulin injection; pregnancy and breastfeeding; patients with severe renal and hepatic impairment; any illness that may affect the study (cardiovascular, pulmonary, kidney, cancer, etc.); changing the dose of blood glucose-lowering drugs; change in diet and physical activity; history of any type of allergy; smoking; alcohol consumption; travel; the occurrence of any side effects due to the intervention.

Ethical approval

The study was approved by the Ethical Committee of the Qazvin University of Medical Sciences and also registered by the identification code IRCT2017041019669N4 in the clinical trial registry of Iran. Before participating in the study, Informed consent was received from all patients. This study was a double-blind, placebo-controlled clinical trial, which lasted 60 days and involved patients who were selected from patients who attended the endocrine and metabolism clinics of Velayat Hospital affiliated with the Qazvin University of Medical Science.

Data collection

To determine the sample size of the study, considering a significance level (α) of 0.05 and test power of 90% to the TNF-α factor in the pilot study of Afsharpour et al. [14], the sample size was 16 in each group. When a probability drop of 35% was considered, the minimum group size for this study was determined to be 22. However, in this study, 60 patients with diabetes were examined.

The weight measurement was done without shoes and with light clothing, using the Seca scale with a precision of 0.1 kg, and measurements of height were performed using a 0.1 mm accuracy gauge. The diet and exercise at baseline were continued and were not changed during the study. To control the confounding factors of diet and physical activity, at the beginning of the study and the end of the eighth week, a three-day noncommunicative questionnaire (2 days normal and one day off) was collected through interviews.

At the beginning and the end of the study, 10 mL blood samples were taken from the venous blood of each patient. Blood samples were collected in tubes, containing EDTA and without it. For serum isolation, the blood sample without EDTA Centrifuged (Beckman Avanti J-25, USA) at a rate of 3,000 RPM for 10 minutes. Blood samples were kept at –70 ° C (Snijdes, Germany). Serum FBG was measured by the enzymatic method (Abbot Model Aclyon 300, USA auto analyzer with Pars-Azmone kit), and fasting insulin was analyzed by the ELISA kit. To measure insulin resistance, indicators such as the homeostasis model assessment insulin resistance (HOMA-IR), and the percentage of activity of pancreatic beta cells were used. The homeostasis model assessment of β-cell function (HOMA-B) is an index of insulin secretory functioning obtained from fasting plasma glucose and insulin concentrations. HOMA-IR index of software and pancreatic beta cells and indicators QUICKI (quantitative insulin sensitivity check index) was also calculated by the formula {HOMA-IR index and QUICKI (quantitative insulin sensitivity check index) were also calculated by the formula.

HOMA-IR = fasting insulin (mU/mL) * FPG (mmol/l) /22.5

QUICKI = 1/[log FBG (mmol/L) + log fasting plasma insulin (mU = mL)]

HOMA-B = 20 × fasting insulin (μIU/mL)/fasting glucose (mmol/mL) − 3.5

After serum separation, the biochemical parameters of inflammatory markers of interleukin 6 and interleukin 17 were detected with the ELIZA kit (KOMA BIOTECH INC., KOREA). Plates were read at 450 nm using a microliter plate reader (Bio-Rad, USA). Samples were stored at –80° C immediately. The HOMA of insulin resistance (HOMA-IR) index, the product of basal glucose and insulin levels divided by 22.5, is regarded as a simple, inexpensive, and reliable surrogate measure of insulin resistance, while the HOMA of β-cell function (HOMA-B) index, computed as the product of 20 and basal insulin levels divided by the value of basal glucose concentrations minus 3.5, has been proposed to be a good measure of β-cell function.

SPSS Version 20 software was used to analyze data. The normality of the distribution of data was assessed by a Kolmogorov-Smirnov test. The biochemical outcomes are presented as a mean ± standard deviation. The comparison of the mean changes in the levels of variation in the groups was done using paired-test methods. The independent t-test was used to compare the mean changes in the intervention group with the placebo. P-value < 0.05 is considered statistically significant.

Results

At the beginning of this investigation, 70 patients were qualified. At the end of the study, 62 patients completed the study. Two patients withdrew from the study because of personal reasons. Their data were excluded from the final statistical analysis (Fig. 1).

Demographic characteristics and dietary intake

There were no significant differences in age, weight, body mass index (BMI), metformin dose, and duration of diabetes between two groups at baseline (Tab. 1). Also, the mean of energy and macronutrient intake were shown before and after the intervention in two groups in Table 2. There are no significant differences in the mean of energy, protein, fat, saturated fatty acids, unsaturated fatty acids and fiber ($p > 0.05$).

IL-6 and IL-17

Table 3 shows the biochemical parameters before and after 8 weeks of intervention. As it is seen, after the administration of propolis, serum IL-6 and IL-17

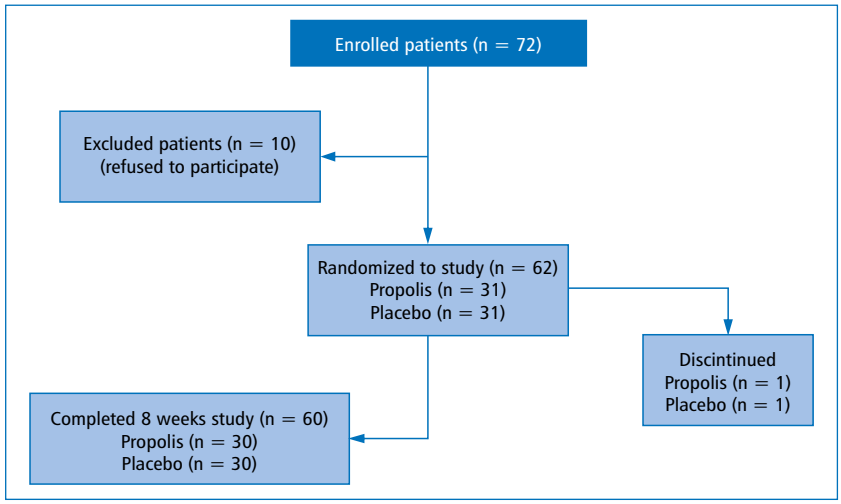

Figure 1. Enrollment and Outcomes of the Study

Table 1. General Characteristics of the Subjects at Baseline

Variables	Propolis [n = 30] Mean ± SD	Placebo [n = 30] Mean ± SD
Age [y]	51.81 ± 6.35	49.05 ± 8.2
Weight [kg]	68.2 ± 9.7	70.76 ± 11.7
BMI [kg/m^2]	26.7 ± 2.8	27.01 ± 3.7
Physical activity [Met-hour/week]	30.024 ± 7.69	30 ± 6.03
Metformin dose	1518.17 ± 329.2	1502.26 ± 410.91
Diabetes duration	5.47 ± 3.6	5.38 ± 3.1

Data are mean ± standard deviation (SD)
BMI — body mass index

were diminished remarkably in the propolis group, while there is no significant change in the placebo group. It was a considerable discrepancy in mean of IL-6 changes ($p = 0.017$) between the two groups, and IL-17 in Propolis-treated groups declined significantly ($p = 0.02$). Inside-group analysis, showed remarkable changes in IL-6 ($p < 0.031$) and IL-17 ($p < 0.015$) in the propolis group. There was no significant decrease in IL-6 and IL-17 in the placebo group

Insulin resistance indices

Findings of FBG, fasting insulin, HOMA-IR, QUICKI and HOMA-B in both groups before and after intervention are presented in Table 4. The mean FBG concentration in the two groups was not significantly different before the intervention. However, after 8 weeks, a significant decrease in FBG levels was observed in propolis group.

According to the Table 4, before the intervention, fasting insulin index was not significantly different in the two groups, but it significantly decreased after the

Table 2. The Average Intake of Calorie and Macronutrients at the Baseline and End of the Study

Outcome	Mean ± SD Propolis [n = 30]		Mean ± SD Placebo [n = 30]		Adjusted mean difference (95% CI)
	At baseline	After 8 weeks	At baseline	After 8 weeks	
Energy [kcal]	2060.10 ± 411.40	2089.85 ± 724.97	2115.03 ± 457.96	2070.28 ± 767.13	[–358.13, 397.27]
Protein [gr]	80.27 ± 19.04	81.05 ± 19.11	84.95 ± 23.67	83.54 ± 21.65	[–12.82, 7.84]
Carbohydrate [gr]	267.54 ± 45.18	268.05 ± 95.12	270.17 ± 52.16	271.32 ± 38.02	[–39.93, 33.39]
Fat [gr]	70.47 ± 16.22	68.55 ± 37.01	72.14 ± 20.48	71.31 ± 24.11	[–18.57, 13.05]
Saturated fatty acids [gr]	17.02 ± 5.18	18.45 ± 6.09	16.48 ± 5.56	16.72 ± 4.11	[–0.9, 4.36]
Monounsaturated fatty acid [gr]	24.08 ± 7.11	24.19 ± 9.15	22.02 ± 6.08	23.18 ± 7.14	[–3.14, 5.16]
Polyunsaturated fatty acid [gr]	18.11 ± 6.08	17.45 ± 5.111	17.15 ± 7.09	18.01 ± 5.11	[–3.15, 2.03]
Fiber [gr]	6.9 ± 1.72	6.13 ± 3.72	6.25 ± 1.9	6.93 ± 3.57	[–1.87, 1.81]

Data are shown as the mean ± standard deviation (SD)

Table 3. Changes in the Parameters during 8 Weeks of Placebo or Propolis Administration

Outcome	Mean ± SD Propolis [n = 30]		Mean ± SD Placebo [n = 30]		Adjusted mean difference (95% CI)	P-value[a]
	At baseline	After 8 weeks	At baseline	After 8 weeks		
IL- 6 [pg/mL]	9.2 ± 2.04	8.01 ± 1.58	9.25 ± 2.52	9.32 ± 2.39	[–2.34, –0.28]	0.017
IL- 17 [pg/mL]	7.94 ± 2.65	5.19 ± 2.02	7.43 ± 2.88	7.25 ± 2.23	[–3.14, –0.98]	0.02

[a]Comparison of changes between placebo and Iranian propolis values after 8 weeks; p-values < 0.05 for baseline versus after 8 weeks within the group; data are mean ± standard deviation (SD); CI — confidence interval; IL-6 — interleukin-6; IL-17 — interleukin-17

Table 4. Effect of Propolis on the Fasting Blood Glucose and Insulin Resistance in Two Groups

Outcome	Mean ± SD Propolis [n = 30]		Mean ± SD Placebo [n = 30]		Adjusted mean difference (95% CI)	P-value[a]
	At baseline	After 8 weeks	At baseline	After 8 weeks		
Fasting blood glucose [mg/dL]	142.3 ± 29	122.5 ± 26.1	145.58 ± 23.4	146.28 ± 29.85	[–37.97, –9.59]	0.037
Fasting insulin [μU/mL]	11.86 ± 2.73	10.21 ± 2.52	12.13 ± 2.33	12.17 ± 2.78	[–3.27, –0.59]	0.001
HOMA-IR	4.16 ± 0.26	3.08 ± 0.22	4.36 ± 0.19	4.39 ± 0.27	[–1.43, –1.19]	0.02
QUICKI	0.510 ± 0.015	0.543 ± 0.018	0.505 ± 0.021	0.502 ± 0.015	[0.031, 0.051]	0.018
HOMA-B	54.40 ± 22.06	62.63 ± 24.2	53.43 ± 21.18	53.14 ± 18.6	[–1.43, 20.41]	0.024

[a]Comparison of changes between placebo and Iranian propolis values after 8 weeks; p < 0.05 for baseline versus after 8 weeks within the group; data are mean ± standard deviation (SD)
CI — confidence interval; HOMA-IR — homeostasis model assessment of insulin resistance; HOMA-B — homeostasis model assessment of β-cell function; QUICKI — the quantitative insulin-sensitivity check index

intervention in the propolis group compared to the placebo group (p=0.01), while the mean change in this index did not change in the placebo group after the intervention. The mean of the HOMA-IR index was not significantly different between the two groups before the intervention; however, after the intervention, there was a substantial difference between the two groups (p = 0.02). After 8 weeks intervention, HOMA-B as a measure of B-cell function in the treated group was significantly increased (p = 0.011). However, there was no change in the control group. Finally, there was a considerable enhancement in the QUICKI index in the intervention group, which indicates an increase in insulin sensitivity after supplementation with propolis. Also, this factor did not have any significant changes in the placebo group.

Discussion

Controlling hyperglycemia and insulin resistance, which increase the risk of morbidity and mortality from diabetes complications, can be very useful in improving the condition of patients with diabetes [15, 16]. Some in vitro and in vivo studies have shown that propolis has beneficial effects on insulin sensitivity, blood glucose, HbA1c, and insulin levels in animal models of T2D [17, 18].

The present study examined the efficacy of propolis supplementation on insulin resistance and inflammatory factors status compared to the placebo for 8 weeks in patients with type 2 diabetes. The results showed that a daily intake of 1500 mg propolis significantly decreased the FBG, fasting insulin, insulin resistance, and HOMA-IR index in patients with diabetes at the end of the study.

Many studies have shown similar results to our study. For example, in the study of Rivera-Yañez et al, the effects of ethanolic extract of Chihuahua propolis (EEPCh) (300 g/L) on streptozotocin-induced diabetes mellitus in a rat model were investigated. The results showed that propolis significantly prevented the increase in blood glucose and weight loss in diabetic rats and also increased plasma insulin levels in STZ diabetic rats, while there was no detectable insulin in untreated diabetic rats [19]. In contrast, in a study conducted by Fukuda et al, supplementation with Brazilian green propolis (226 mg/day over 8 weeks) did not affect insulin levels and homeostatic model assessment of insulin resistance (HOMA-IR) [20]. This different result is probably due to the different doses of propolis and the geographical location where the propolis is collected [21].

The possible mechanisms of propolis in reducing blood glucose and insulin resistance are not fully under-

stood. It may be attributed to its bioactive components that can increase insulin production or enhance the cellular sensitivity to insulin. The improvement in the glycemic status by propolis is probably due to these reasons: Increase in glycolysis and use of glucose in liver cells, reduction in carbohydrate intake in the digestive system and intestinal cells, activation of insulin-sensitive glucose transporters (GLUT-4) and glucose reabsorption by peripheral cells, inhibition of glucose release from liver cells to blood circulation. These effects may occur in people taking propolis in doses ranging from 400 to 1,500 mg [22].

The present study revealed that after consumption of Iranian propolis for 8 weeks, IL-6 was diminished remarkably in the propolis group. According to clinical investigations, sub-clinical inflammation can affect the development of problems related to diabetes [23]. Moreover, excessive glucose induces an inflammatory effect through oxidative stress and reduces antioxidants [23]. The hyperglycemic condition leads to oxidative stress in diabetes mellitus patients by several mechanisms, such as glucose autoxidation, polyol pathway, and formation of glycosylated products [24].

Propolis has many pharmacological and biological properties. It contains more than 500 compounds, including flavonoids, polyphenols, phenolic compounds, terpenes, terpenoids, steroids, coumarins, amino acids, and aromatic acids [25]. Studies have shown that the major components of Iranian propolis are aromatic acids (mainly benzoic acid, ferulic acid, vanillic acid, p-coumaric acid, and caffeic acid) and their esters, alkaloids, flavonoids (pinocembrin, chrysin), fatty acids and their related esters (mainly oleic acid, palmitic acid, stearic acid, margaric acid, and eicosanoid acid [26].

Studies have shown that propolis in acute and chronic inflammation acts as a potent anti-inflammatory agent. In vitro and in vivo studies are being carried out using ethanol or aqueous extracts of propolis from different origins produced by various bee species to corroborate its anti-inflammatory activity [27]. The anti-inflammatory activity of propolis appears to be associated with the existence of flavonoids, phenolic acids phenolic acids such as caffeic acid phenethyl ester (CAPE), esters, terpenoids, steroids, and amino acids [28].

During the process of inflammation, the release of pro-inflammatory cytokines including Interleukin 1(IL-1), Interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) is activated by macrophages. These macrophages stimulate the translocation of nuclear factor-kappaB (NF-kB) which has a crucial role in the stimulation of cytokines and inflammatory mediators. The NF-κB is a key mediator in the expression of pro-inflammatory and inflammatory cytokines genes including TNF-α, IL-1, IL-2, IL-6, and IL-8 [29]. Other mediators are phospholipases such as lipoxygenase (LOX) and cyclooxygenase (COX) which play a main role in eicosanoid acid and arachidonic acid (AA) metabolism and ultimately produce major inflammatory factors such as leukotrienes and prostaglandins [30].

In Jurkat cells, caffeic acid phenethyl ester (CAPE) has been shown to prevent the release of AA from the cell membrane and inhibit gene expression of LOX and COX enzymes that are involved in the AA metabolism pathways [31]. Also, it suppresses the activation of NF-kB, COX-1, COX-2, and expression of the induced isoform cyclooxygenase-2 (COX-2). It inhibits the production of inflammatory cytokines and increases the production of anti-inflammatory cytokines, including IL-10 and IL-4, attenuating the levels of PGE2 [32, 33].

Zhao et al. surveyed administration of green propolis (900 mg/day) during 18 weeks in 65 patients with T2DM. At the end of the study, serum GSH and total polyphenols were significantly increased and serum levels of TNF-α were significantly decreased, but increased serum levels of IL-1β and IL-6 were found. As a result, propolis is effective in improving antioxidant function in diabetes patient. Zakerkish et al. evaluated the effect of propolis consumption (1000 mg/day) for 90 days in 94 patients with T2DM and revealed that propolis can significantly decrease the serum levels of HbA1c, insulin and 2-hour postprandial glucose, inflammatory cytokines and enhance the insulin sensitivity in T2DM patients [18].

In this study, we also observed a decrease in interleukin-17 in patients with diabetes after consuming propolis for 8 weeks. Recent studies have demonstrated an association between Th17 cells and T2D development [34]. IL-17 implicates in T2D pathogenesis by activation NF-κB pathway which up-regulates proinflammatory cytokine gene expression such as (IL-1β, IL-6, and TNF-α), which contributes to the induction of insulin resistance and finally leads to the development of T2D [35].

TNF-α is known to inhibit insulin signaling, resulting in insulin resistance by activating c-Jun amino-terminal kinase and an inhibitor of NF-κB kinase, leading to serine phosphorylation of insulin receptor substrate-1 [36]. Such findings indicate that IL-17 plays a crucial role in the inflammatory process and development of insulin resistance in T2D patients. Additionally, treatment with anti-IL-17 neutralizing antibodies elevated serum adiponectin concentration, reduced serum levels of TNF-α, and enhanced adipocyte-differentiation

markers [37]. As demonstrated in previous research, propolis components could have a suppressive activity on IL-17. For example, Tanaka et al. demonstrated the effect of propolis ethanolic extract on the pathogenesis of collagen-induced arthritis (CIA) in mice and they found that propolis directly inhibited the production of IL-17 and the differentiation of Th17 [38]. In contrast, the study of Fang et al. showed that propolis decreased the level of IL-6 while increasing IL-17 in a rodent model of dyslipidemia and atherosclerosis [39].

To the best of our knowledge, no previous studies have reported the effects of prolonged propolis supplementation on IL-17 in patients with type-two diabetes mellitus. To obtain a perfect picture of propolis treatment, it would be necessary to perform a randomized clinical trial with a greater number of participants.

In this study, we encountered at least two limitations. Firstly, the duration of the trial may have been too short to observe more effects of propolis, in the reduction of inflammatory factors and insulin resistance in patients with diabetes. Second, the dose of propolis may not have been adequate. Several studies have reported the effects of propolis on diabetes; however, most of them were animal experiments and administered doses of propolis were extremely high (such as 50–300 mg/kg of the body weight) [40]. Therefore, if a higher dose of propolis was administered to patients, the efficacy of propolis on inflammatory factors would be more effective.

The immune-modulatory effects of natural compounds have been considered as alternative adjuvant therapies in the treatment of various diseases. There is an essential need to find the best reliable and standardized compound, that has been approved for health-beneficial effects such as propolis in addition to classical treatment modalities.

Conclusions

In conclusion, after the administration of propolis, serum IL-6 and IL-17, FBG levels, HOMA-IR, and fasting insulin were diminished remarkably in the propolis group. After 8 weeks of intervention, HOMA-B as a measure of B-cell function and QUICKI index which indicates an increase in insulin sensitivity, was significantly increased in the propolis group. Eventually, the results of this study indicate that the application of Iranian propolis significantly decreases the inflammatory condition and insulin resistance in patients with diabetes. Thus, propolis can help to decrease complications of diabetes associated with metabolic disturbances and inflammatory conditions.

Article information

Data availability statement

It will be available to researchers after publication.

Ethics statement

The study was approved by the Ethical Committee of the Qazvin University of Medical Sciences and also registered by the identification code of IRCT2017041019669N4 in clinical trials registry of Iran. Prior to participating in the study, informed consent was received from all patients.

Author contributions

Conception and design of study: H. Khadem Haghighian

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Analysis and/or interpretation of data: H. Khadem Haghighian , Y. Koushan , M. Yousefi

Drafting the manuscript: M. Yousefi

Revising the manuscript critically for important intellectual content: M. Yousefi, H. Khadem Haghighian, M. R Shiri-Shahsavar

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Yedjou CG, Grigsby J, Mbemi A, et al. The Management of Diabetes Mellitus Using Medicinal Plants and Vitamins. Int J Mol Sci. 2023; 24(10), doi: 10.3390/ijms24109085, indexed in Pubmed: 37240430.
2. Randeria SN, Thomson GJA, Nell TA, et al. Inflammatory cytokines in type 2 diabetes mellitus as facilitators of hypercoagulation and abnormal clot formation. Cardiovasc Diabetol. 2019; 18(1): 72, doi: 10.1186/s12933-019-0870-9, indexed in Pubmed: 31164120.
3. Rohm TV, Meier DT, Olefsky JM, et al. Inflammation in obesity, diabetes, and related disorders. Immunity. 2022; 55(1): 31–55, doi: 10.1016/j.immuni.2021.12.013, indexed in Pubmed: 35021057.
4. Donate-Correa J, Martín-Núñez E, Muros-de-Fuentes M, et al. Inflammatory cytokines in diabetic nephropathy. J Diabetes Res. 2015; 2015: 948417, doi: 10.1155/2015/948417, indexed in Pubmed: 25785280.

5. Raphael I, Nalawade S, Eagar TN, et al. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine. 2015; 74(1): 5–17, doi: 10.1016/j.cyto.2014.09.011, indexed in Pubmed: 25458968.
6. Parhi A, Das S, Mahapatra S, et al. The Level and Role of Interleukin-17 in Patients of Type 2 Diabetes Mellitus with and without Complications. Journal of Diabetes Mellitus. 2019; 09(04): 176–185, doi: 10.4236/jdm.2019.94017.
7. Qiao YC, Shen J, He L, et al. Changes of Regulatory T Cells and of Proinflammatory and Immunosuppressive Cytokines in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Diabetes Res. 2016; 2016: 3694957, doi: 10.1155/2016/3694957, indexed in Pubmed: 27777959.
8. Zabaiou N, Fouache A, Trousson A, et al. Biological properties of propolis extracts: Something new from an ancient product. Chem Phys Lipids. 2017; 207(Pt B): 214–222, doi: 10.1016/j.chemphyslip.2017.04.005, indexed in Pubmed: 28411017.
9. Junior PB, Farias L, Oliveira S, et al. The anti-inflammatory effect of propolis on human tissue: A systematic review. Brazilian Journal of Health and Biomedical Sciences. 2022; 21(2), doi: 10.12957/bjhbs.2022.71605.
10. Zhang YX, Yang TT, Xia L, et al. Inhibitory Effect of Propolis on Platelet Aggregation In Vitro. J Healthc Eng. 2017; 2017: 3050895, doi: 10.1155/2017/3050895, indexed in Pubmed: 29129989.
11. Bezerra GB, de Souza LdM, Dos Santos AS, et al. Hydroalcoholic extract of Brazilian red propolis exerts protective effects on acetic acid-induced ulcerative colitis in a rodent model. Biomed Pharmacother. 2017; 85: 687–696, doi: 10.1016/j.biopha.2016.11.080, indexed in Pubmed: 27955827.
12. Daleprane JB, Freitas Vd, Pacheco A, et al. Anti-atherogenic and anti-angiogenic activities of polyphenols from propolis. J Nutr Biochem. 2012; 23(6): 557–566, doi: 10.1016/j.jnutbio.2011.02.012, indexed in Pubmed: 21764281.
13. Corrêa FRS, Schanuel FS, Moura-Nunes N, et al. Brazilian red propolis improves cutaneous wound healing suppressing inflammation-associated transcription factor NFκB. Biomed Pharmacother. 2017; 86: 162–171, doi: 10.1016/j.biopha.2016.12.018, indexed in Pubmed: 27978495.
14. Afsharpour F, Hashemipour S, Khadem-Haghighian H, et al. Effects of Iranian propolis on glucose metabolic changes, inflammatory factors, liver enzymes levels in type 2 diabetic patients: a randomized, double-blind, placebo-controlled, clinical trial. J Nutr Sci & Diet. 2017; 3(2): 9–14, doi: 10.5812/jjnpp.102469.
15. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes. 2020; 13: 3611–3616, doi: 10.2147/DMSO.S275898, indexed in Pubmed: 33116712.
16. Macdonald IA. A review of recent evidence relating to sugars, insulin resistance and diabetes. Eur J Nutr. 2016; 55(Suppl 2): 17–23, doi: 10.1007/s00394-016-1340-8, indexed in Pubmed: 27882410.
17. Laaroussi H, Bakour M, Ousaaid D, et al. Effect of antioxidant-rich propolis and bee pollen extracts against D-glucose induced type 2 diabetes in rats. Food Res Int. 2020; 138(Pt B): 109802, doi: 10.1016/j.foodres.2020.109802, indexed in Pubmed: 33288184.
18. Zakerkish M, Jenabi M, Zaeemzadeh N, et al. The Effect of Iranian Propolis on Glucose Metabolism, Lipid Profile, Insulin Resistance, Renal Function and Inflammatory Biomarkers in Patients with Type 2 Diabetes Mellitus: A Randomized Double-Blind Clinical Trial. Sci Rep. 2019; 9(1): 7289, doi: 10.1038/s41598-019-43838-8, indexed in Pubmed: 31086222.
19. Rivera-Yañez N, Rodriguez-Canales M, Nieto-Yañez O, et al. Hypoglycaemic and Antioxidant Effects of Propolis of Chihuahua in a Model of Experimental Diabetes. Evid Based Complement Alternat Med. 2018; 2018: 4360356, doi: 10.1155/2018/4360356, indexed in Pubmed: 29713363.
20. Fukuda T, Fukui M, Tanaka M, et al. Effect of Brazilian green propolis in patients with type 2 diabetes: A double-blind randomized placebo-controlled study. Biomed Rep. 2015; 3(3): 355–360, doi: 10.3892/br.2015.436, indexed in Pubmed: 26137235.
21. Stojanović S, Najman S, Bogdanova-Popov B, et al. Propolis: chemical composition, biological and pharmacological activity – a review. Acta Medica Medianae. 2020; 59(2): 108–113, doi: 10.5633/amm.2020.0215.
22. El-Sharkawy HM, Anees MM, Van Dyke TE. Propolis Improves Periodontal Status and Glycemic Control in Patients With Type 2 Diabetes Mellitus and Chronic Periodontitis: A Randomized Clinical Trial. J Periodontol. 2016; 87(12): 1418–1426, doi: 10.1902/jop.2016.150694, indexed in Pubmed: 27468795.
23. Burgos-Morón E, Abad-Jiménez Z, Marañón AM, et al. Relationship Between Oxidative Stress, ER Stress, and Inflammation in Type 2 Diabetes: The Battle Continues. J Clin Med. 2019; 8(9), doi: 10.3390/jcm8091385, indexed in Pubmed: 31487953.
24. Lima JE, Moreira NCS, Sakamoto-Hojo ET. Mechanisms underlying the pathophysiology of type 2 diabetes: From risk factors to oxidative stress, metabolic dysfunction, and hyperglycemia. Mutat Res Genet Toxicol Environ Mutagen. 2022; 874-875: 503437, doi: 10.1016/j.mrgentox.2021.503437, indexed in Pubmed: 35151421.
25. Huang S, Zhang CP, Wang K, et al. Recent advances in the chemical composition of propolis. Molecules. 2014; 19(12): 19610–19632, doi: 10.3390/molecules191219610, indexed in Pubmed: 25432012.
26. Ahangari Z, Naseri M, Vatandoost F. Propolis: Chemical Composition and Its Applications in Endodontics. Iran Endod J. 2018; 13(3): 285–292, doi: 10.22037/iej.v13i3.20994, indexed in Pubmed: 30083195.
27. Chavda VP, Chaudhari AZ, Teli D, et al. Propolis and Their Active Constituents for Chronic Diseases. Biomedicines. 2023; 11(2), doi: 10.3390/biomedicines11020259, indexed in Pubmed: 36830794.
28. Devequi-Nunes D, Machado BA, Barreto Gd, et al. Chemical characterization and biological activity of six different extracts of propolis through conventional methods and supercritical extraction. PLoS One. 2018; 13(12): e0207676, doi: 10.1371/journal.pone.0207676, indexed in Pubmed: 30513100.
29. Kauppinen A, Suuronen T, Ojala J, et al. Antagonistic crosstalk between NF- B and SIRT1 in the regulation of inflammation and metabolic disorders. Cell Signal. 2013; 25(10): 1939–1948, doi: 10.1016/j.cellsig.2013.06.007, indexed in Pubmed: 23770291.
30. Cheng H, Wang H, Fan X, et al. Improvement of endothelial nitric oxide synthase activity retards the progression of diabetic nephropathy in db/db mice. Kidney Int. 2012; 82(11): 1176–1183, doi: 10.1038/ki.2012.248, indexed in Pubmed: 22785174.
31. Nie J, Chang Y, Li Y, et al. Caffeic Acid Phenethyl Ester (Propolis Extract) Ameliorates Insulin Resistance by Inhibiting JNK and NF- B Inflammatory Pathways in Diabetic Mice and HepG2 Cell Models. J Agric Food Chem. 2017; 65(41): 9041–9053, doi: 10.1021/acs.jafc.7b02880, indexed in Pubmed: 28799756.
32. Búfalo MC, Bordon-Graciani AP, Conti BJ, et al. The immunomodulatory effect of propolis on receptors expression, cytokine production and fungicidal activity of human monocytes. J Pharm Pharmacol. 2014; 66(10): 1497–1504, doi: 10.1111/jphp.12279, indexed in Pubmed: 24934761.
33. Pahlavani N, Malekahmadi M, Firouzi S, et al. Molecular and cellular mechanisms of the effects of Propolis in inflammation, oxidative stress and glycemic control in chronic diseases. Nutr Metab (Lond). 2020; 17: 65, doi: 10.1186/s12986-020-00485-5, indexed in Pubmed: 32817750.
34. Zhang C, Xiao C, Wang P, et al. The alteration of Th1/Th2/Th17/Treg paradigm in patients with type 2 diabetes mellitus: Relationship with diabetic nephropathy. Hum Immunol. 2014; 75(4): 289–296, doi: 10.1016/j.humimm.2014.02.007, indexed in Pubmed: 24530745.
35. Ohshima K, Mogi M, Jing F, et al. Roles of interleukin 17 in angiotensin II type 1 receptor-mediated insulin resistance. Hypertension. 2012; 59(2): 493–499, doi: 10.1161/HYPERTENSIONAHA.111.183178, indexed in Pubmed: 22184328.

36. Baker RG, Hayden MS, Ghosh S. NF- B, inflammation, and metabolic disease. Cell Metab. 2011; 13(1): 11–22, doi: 10.1016/j.cmet.2010.12.008, indexed in Pubmed: 21195345.
37. Abdel-Moneim A, Bakery HH, Allam G. The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus. Biomed Pharmacother. 2018; 101: 287–292, doi: 10.1016/j.biopha.2018.02.103, indexed in Pubmed: 29499402.
38. Tanaka M, Okamoto Y, Fukui T, et al. Suppression of interleukin 17 production by Brazilian propolis in mice with collagen-induced arthritis. Inflammopharmacology. 2012; 20(1): 19–26, doi: 10.1007/s10787-011-0088-2, indexed in Pubmed: 21861090.
39. Fang Y, Sang H, Yuan Na, et al. Ethanolic extract of propolis inhibits atherosclerosis in ApoE-knockout mice. Lipids Health Dis. 2013; 12: 123, doi: 10.1186/1476-511X-12-123, indexed in Pubmed: 23941539.
40. Usman UZ, Bakar ABA, Mohamed M. Phytochemical composition and activity against hyperglycaemia of Malaysian propolis in diabetic rats. Biomed Res. 2016; 27(1): 46–51.