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Changes in Lipid Profile, Liver Enzymes and Inflammatory Factors Following Oral Supplementation with Propolis in Patients with Type 2 Diabetes

ABSTRACT

Objective: Nutritional ingredients with anti-inflammatory and antioxidant properties such as flavonoids and phenolic acids have been reported in propolis. The present study investigated the effect of propolis supplements on lipid metabolism, liver enzymes, and inflammatory factors in patients with type 2 diabetes.

Materials and methods: This clinical trial was performed in a double-blind randomized manner with two parallel groups: intervention (n = 30) and placebo (n = 30) group. Each group received a capsule (propolis or placebo) of 500 mg 3 times a day for 8 weeks. The lipid profile, liver enzymes, and inflammatory factors were measured at the beginning and end of the study. Statistical analysis was performed by using SPSS software.

Results: The mean levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) decreased significantly at the end of the study in the intervention group ($p < 0.05$). Also, the serum high-density lipoprotein cholesterol (HDL) level increased significantly in this group ($p < 0.05$). Propolis supplementation significantly decreased C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) ($p < 0.05$). Also, propolis decreased the mean levels of aspartate transaminase (AST) and alanine transaminase (ALT), but it was not significant ($p > 0.05$).

Conclusions: Propolis supplementation can be helpful as a dietary supplement in patients with type 2 diabetes by improving blood lipid profile and inflammatory factors in patients with diabetes. (Clin Diabetol 2022, 11; 4: 224–231)

Keywords: propolis; lipid profile; inflammatory factor; liver enzyme; type 2 diabetes

Introduction

Similar to other types of diabetes, type 2 diabetes mellitus (DM) is an endocrine disease defined by the high blood glucose phenotype. The incidence of diabetes is increasing for a number of reasons, including lifestyle changes toward sedentary lifestyle, obesity, and fast food consumption [1]. The International Diabetes Federation predicts that by 2035 there will be 592 million people with diabetes worldwide. Type 2 diabetes affected approximately 9.9% of the population of Iran in 2013, which according to prediction will reach 10.1 % in 2035 [2].

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Impairment of the secretion of insulin and function of insulin receptors on cellular surfaces in people with diabetes leads to insulin resistance [3]. Abnormalities of lipid profile are the result of insulin resistance. Irregularity in the control of fat metabolism begins with the increase in triglyceride-rich very low density lipoprotein (VLDL). The death toll from cardiovascular disease is high in patients with diabetes. One of the reasons may be related to high levels of triglycerides, cholesterol, low density lipoprotein cholesterol (LDL-C), and low levels of high density lipoprotein (HDL) in serum of these patients [4]. Lipolysis occurs in this disease due to lack of glucose uptake by the tissues; therefore, the production of TG by the adipose tissue increases [5]. Despite previous views about adipose tissue, it is currently known that adipose tissue is responsible for secretion of adipokines, which plays an essential role in regulating the metabolism of the body. Also, some substances secreted from adipose tissues have inflammatory properties that can worsen insulin resistance. These biomarkers include C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) [6]. During fasting and feeding, the control of the major part of glucose metabolism is related to the liver. The presence of the disorders of macronutrient metabolism in type 2 diabetes causes some diseases such as non-alcoholic fatty liver (NAFLD) which is associated with the increase in liver enzymes. Chronic increase in transaminase levels in patients with diabetes has been reported. Also, when the liver is damaged and its function is disrupted, increased Alanine Transaminase (ALT) and Aspartate Transaminase (AST) levels are markers of the liver damage [7, 8].

The role of alternative medicinal foods in prevention of diabetes has been confirmed in various laboratory and epidemiology findings [9]. So, nutritional supplements, such as spirulina, green tea, soybean, turmeric and vegetable or plant extracts rich in polyphenolic compounds play an important role in preventing or delaying the progression of type 2 diabetes [10]. One of the richest sources of polyphenols is propolis, a resinous material that is collected by bees from different plants and is used in medicine widely, due to its therapeutic benefits. Material decomposition studies indicate the presence of ingredients with nutritional-therapeutic properties such as flavonoids and a variety of micronutrients (amino acids, fatty acids, and vitamins) in propolis. However, the chemical composition and nature of propolis vary depending on the location, time of collection and production methods. The mechanism of propolis effect is related to its antioxidant and inflammatory activity [11]. So it can possess wide biological activities, such as anti-inflammatory, antioxidant, anti-diabetic, anti-atherogenic, and anticancer, that has been proven in various studies. According to studies in diabetic models, consumption of propolis reduces inflammatory markers by improving the level of antioxidant enzymes and, as a result, may be effective in improving liver enzymes and lipid profiles [12]. Fuliang's study demonstrated that propolis supplement significantly decreased serum total cholesterol, LDL cholesterol, and triglycerides, and increased HDL cholesterol in rats with diabetes mellitus [13]. Another study by Yajing et al. [14] showed that oral injection of propolis had no significant effect on total cholesterol, HDL-C, and LDL-C cholesterol levels in diabetic rats. Also, in the study of Zhao et al. [15] a significant reduction in serum TNF-α levels was observed within 18 weeks of treatment with Brazilian green propolis in patients with type 2 diabetes mellitus. However, the results of the Fukuda study showed that after 8 weeks of treatment with propolis in patients with type 2 diabetes, serum TNF-α levels were maintained at the same baseline level without significant enhancement [16]. Therefore, more studies are needed to prove these results. In this study, we investigated the effects of propolis on the lipid profile, liver enzymes, and inflammatory factors in patients with type 2 diabetes.

Materials and methods

Patients

The present study was approved by the ethics committee of the research deputy of Qazvin University of Medical Sciences (code: IR.QUMS.REC.1395.294) and was registered with the identification code of 2017041019669N4 in Iranian Registry of Clinical Trials. In this scientific study, all participants signed written consent, with full awareness about this clinical program. People participating in the study were in the age range of 33–55, and had fasting blood glucose level $\geq$ 126 mg/dL and two-hour postprandial glucose level $\geq$ 200 mg/dl (according to American Diabetes Association criteria (ADA)) [17]. Exclusion criteria included the use of insulin, pregnancy and lactation, major non-communicable diseases such as cardiovascular disease, kidney disease, cancer, allergies and alcohol consumption. At the beginning of the study, demographic characteristics were collected through interviews. Also, information about the history of drug use and the duration of diabetes were collected from the participants. The measurement of body weight was done by using the Seca scale with the accuracy of 0.1 kg, without shoes and with the least possible clothes. Also height measurements were done by using height gauge with the accuracy of 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by

the square of height in meters. Nutrition N4 software was used to analyze the diet.

Design

This was a randomized controlled study with parallel groups, designed to evaluate the effect of propolis on metabolic status in people with type 2 diabetes in Qazvin University of Medical Sciences. Patients were randomly assigned to two groups receiving propolis (n = 30) and placebo (n = 30). The intervention group received three daily doses of 500 mg of propolis (total 1500 mg) and the placebo group received similar capsules containing wheat flour for two months. Patients were told to take the capsules with the main meal. Questionnaires including personal information and medical history were filled out. To control the confounding factors including physical activity and diet, questionnaires related to the physical activity level and food recalls were completed through interviews. Patients were advised by researchers to avoid dietary changes and physical activity during the study to control confounding factors. Daily telephone follow-ups were performed to check the use of supplements. At the end of the intervention, patients were referred to the laboratory for blood sampling. The serum levels of TC, TG, HDL, LDL, AST, ALT, CRP and TNF-α were determined.

Biochemical measurements

Enzymatic colorimetric and enzymatic spectrophotometric methods were used to measure TG, HDL and total cholesterol, respectively. These factors were determined using an auto-analyzer (Abbott, model Alcyon 300, USA) with Pars-Azmoon Kit (Tehran, Iran). Since in this study the conditions for using the Friedewald formula were present, this formula was used to calculate LDL-C [18]. The automated biochemical analyzer (Hitachi-7180E, Tokyo, Japan) with a Pars Azmoon reagent kit (Iran) was used to measure liver enzymes including ALT and AST. CRP concentration was measured by using an immune turbidimetric assay (Pars Azmoon kit. Iran) and TNF-α levels were measured with an ELISA kit (bioscience).

Sample size

In the present study, the sample size was calculated according to Zhao et al. [15], before and after the intervention, based on the TNF-α variable, with $\alpha = 0.05$ and the statistical power of 90%. The obtained sample size was 20.04 in each group. Considering 35% probable drop-out, the sample size was set at 30. In this research, 62 patients with diabetes (male and female) were studied.

Statistical analyses

Statistical analyses were conducted using SPSS version 20. All data were presented as mean ± SD and were checked for normality by the Kolmogorov–Smirnov test. Due to the normal distribution of variables, the paired sample t-test and the independent sample t-test were applied to analyze differences in variables within and between groups, respectively. The $p < 0.05$ was considered statistically significant. Statistical analyses were performed by a significant level of $p \leq 0.05$.

Results

Of the 62 volunteer patients who entered the study, two (one from each group) did not participate in the final analysis due to non-compliance with the condition of maintaining the drug dose during the research project (Fig. 1). Therefore, considering this drop-out, 30 patients in each group completed the study and the rate of patient compliance in this study was 96.77%.

The patients' demographic and baseline characteristics are presented in Table 1. There were no significant differences between two groups (propolis and placebo) in age, weight, body mass index (BMI), duration of diabetes and dosages of medication and this means that two groups were well matched in terms of the baseline characteristics ($p > 0.05$) (Tab. 1). The patients' dietary intake is summarized in Table 2. Two groups were similar in terms of energy, protein, fat, saturated fatty acids, unsaturated fatty acids and fiber and there were no significant differences in terms of received energy and macronutrients at the beginning and end of the study ($p > 0.05$).

The mean of total cholesterol level in the propolis group at the beginning of the study was 237.6 ± 45.2 mg/dL, which significantly decreased to 198.1 ± 40.2 after 8 weeks of intervention with propolis ($p < 0.05$). The mean of triglyceride level in the propolis group significantly decreased from 255.72 ± 81.6 mg/dL to 213.21 ± 72.5 mg/dL. Also, the LDL level significantly decreased and the HDL level significantly increased with propolis. These changes were not notable in the placebo group (Tab. 3).

The mean of CRP and TNF-α in both groups are shown in Table 3. Based on the results, there was no significant difference in CRP and TNF-α concentrations between the two groups at the beginning of the study ($p > 0.05$). At the end of the eighth week, the mean of CRP and TNF-α was significantly decreased in the propolis group and the difference between the two groups was significant ($p < 0.05$). Also, the concentration of ALT and AST decreased by 1.44 and 1.85 U/L,

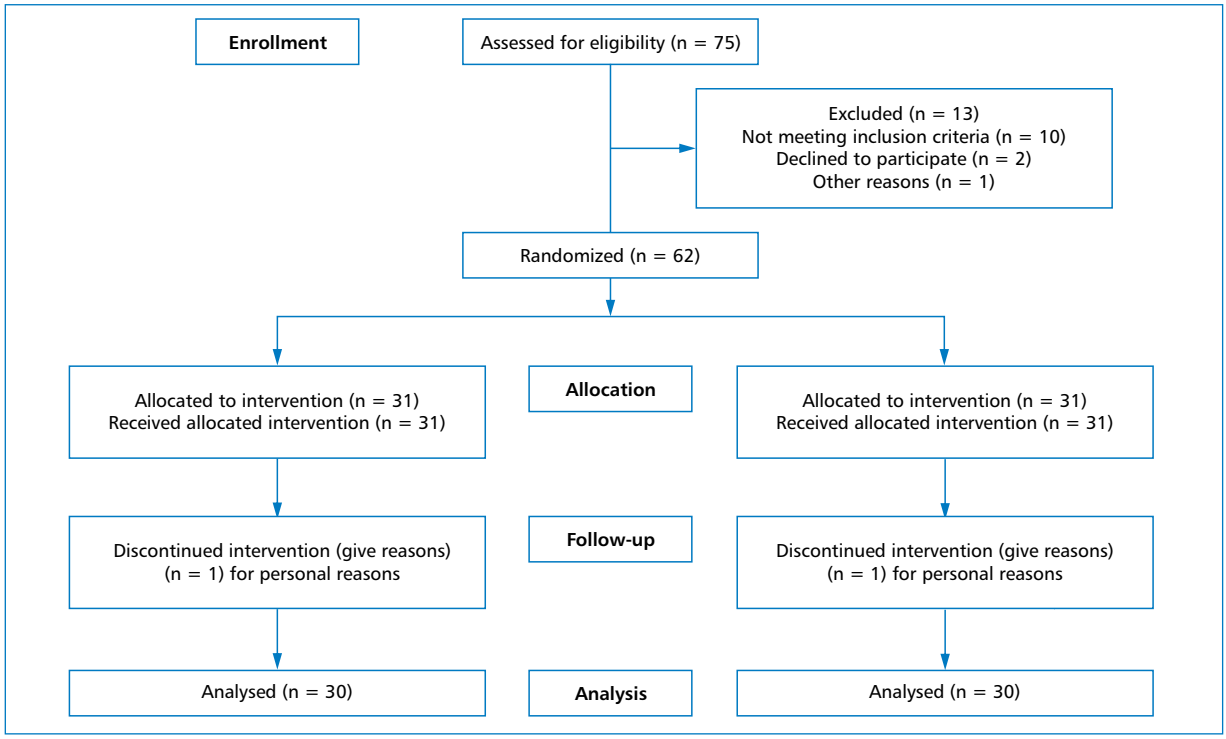

Figure 1. Trial Design and Follow-up

Table 1. Demographic Characteristics of Participants at Baseline

Characteristics	Propolis (n = 30) Mean ± SD	Placebo (n = 30) Mean ± SD	P
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
End	68 ± 9.04	71.5 ± 11.84	0.42
BMI [kg/m^2]			
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. Comparison of mean characteristics by independent samples t-test
BMI — body mass index; SD — standard deviation

respectively, in the propolis group, but these changes were not statistically significant. Also, these changes were not significant in the placebo group.

Discussion

The results of this study showed that oral supplementation of propolis at a dose of 1500 mg per day for 2 month was effective in improving metabolism of lipids and inflammatory factors, but wasn't effective for liver enzymes in patients with type 2 diabetes. Patients with type 2 diabetes often have increased concentration of triglycerides and cholesterol due to impaired glucose and lipids metabolism, which ultimately leads to high blood pressure, atherosclerosis and cardiovascular disease [19]. On the other hand, in these patients, insulin resistance affects lipid metabolism. In this disease, a decrease in lipoprotein lipase enzyme activity is associated with reduction in the clearance of triglycerides and low plasma HDL cholesterol level and increasing lipase enzyme activity results in production of small dense LDL. Furthermore, in type 2 diabetes, enhancement in lipolysis enzyme causes an increase in serum

Table 2. Diet Analysis of Participants at Baseline and End of the Study

Variables	Propolis (n = 30) Mean ± SD	Placebo (n = 30) Mean ± SD	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 [g]			
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 [g]			
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 [g]			
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 [g]			
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 [g]			
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 [g]			
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 [g]			
Baseline	6.9 ± 1.72	6.25 ± 1.9	0.711
End	6.13 ± 3.72	6.9 3± 3.57	0.68
P2	0.547	0.511	

Data are means ± standard deviation; * P1: Comparison of the means between two groups (independent samples t-test); P2: Comparing the means in each group at the baseline and end of the study (paired samples t-test)
SD — standard deviation

free fatty acids, which leads to hypertriglyceridemia and decreases insulin sensitivity [20]. Several studies have shown that propolis can reduce blood lipids, cholesterol, and high blood viscosity, which causes reduction in atherosclerosis and improves blood circulation [21]. Therefore, considering that most patients with diabetes have high levels of lipids and cholesterol, treatment with propolis may be helpful by reducing the level of lipids in the blood vessels. Our results in terms of reducing serum total cholesterol, triglyceride and LDL cholesterol levels, as well as increasing HDL cholesterol level are consistent with the study performed by Fuliang et al. [13]. In the Fuliang's study, treatment with ethanolic extract of propolis for 8 weeks in diabetic rats significantly decreased total cholesterol, triglycerides and LDL cholesterol. Also, in their study, HDL cholesterol levels increased at the end of the study compared with the baseline. Another study by Yajing et al. [14] showed that oral intake of propolis had no significant effect on total cholesterol, HDL-C, and LDL-C cholesterol levels in diabetic rats. In this study, supplementation with propolis only influenced blood triglyceride and significantly reduced it; this positive effect was attributed to improvement in insulin sensitivity and lipoprotein

Table 3. Mean Changes in Outcomes after 8 Weeks of Treatment

Variables	Propolis (n = 30) Mean ± SD	Placebo (n = 30) Mean ± SD	P1
TC [mg/dL]			
Baseline	237.6 ± 45.24	235.9 ± 44	0.375
End	198.1 ± 40.2	237.1 ± 3.84	0.021
P2	0.01	0.311	
TG [mg/dL]			
Baseline	255.72 ± 81.6	253.89 ± 76.65	0.7
End	213.21 ± 72.5	255.18 ± 79.35	0.034
P2	0.031	0.69	
HDL-c [mg/dL]			
Baseline	40.1 ± 3.7	41.71 ± 3.9	0.32
End	47.3 ± 4.4	42.11 ± 5.1	0.045
P2	0.04	0.27	
LDL-c [mg/dL]			
Baseline	146.36 ± 25.22	143.42 ± 23.27	0.61
End	108.16 ± 21.3	143.96 ± 23.03	0.039
P2	0.035	0.78	
TNF-α [pg/mL]			
Baseline	17.87 ± 3.34	17.98 ± 4.11	0.62
End	15.2 ± 3.7	18.1 ± 3.91	0.03
P2	0.036	0.41	
CRP [ng/mL]			
Baseline	9.71 ± 3.11	9.84 ± 3.4	0.54
End	7.21 ± 2.6	9.17 ± 3	0.046
P2	0.029	0.201	
AST [U/dL]			
Baseline	25.95 ± 11.8	26.54 ± 11.15	0.54
End	24.33 ± 11.72	26.67 ± 9.5	0.1
P2	0.12	0.81	
ALT [U/dL]			
Baseline	25.31 ± 8.13	25.89 ± 6.5	0.6
End	24.7 ± 7.3	26.01 ± 8.3	0.09
P2	0.19	0.23	

Data are means standard deviation; * P1: Comparison of the means between two groups (independent samples t-test); P2: Comparing the means in each group at the baseline and end of the study (paired samples t-test)
ALT — alanine transaminase; AST — aspartate transaminase; CRP — C-reactive protein; HDL-c — high-density lipoprotein cholesterol; LDL-c — low-density lipoprotein cholesterol; TC — total cholesterol; TG — triglyceride; TNF-α — tumor necrosis factor-alpha

lipase activity. Various research have shown that diabetes causes liver damage through increasing oxidative stress by active oxygen radicals [22]. The flavonoids of propolis with antioxidant properties can suppress the free radicals [23]; thus, it may result in improvement of hepatic tissue damage. The study by Kismet et al. [24] supports this hypothesis. This study showed positive effects of propolis on the levels of ALT, ALP and TNF-α in rats with non-alcoholic fatty liver. In the present study, the level of AST and ALT liver enzymes decreased by 1.7 and 1.44 U/L, respectively, but these changes were not significant. Perhaps the main reason for that is a short period or insufficient dose of propolis. It is worth mentioning that the liver enzymes of participants in this study were in a normal range and, therefore, no significant changes were observed in them.

Type 2 diabetes is an inflammatory disease that increases serum CRP and TNF-α concentrations [25]. Also Wang and Hoy observed in their prospective study that high concentrations of CRP could independently increase the risk of diabetes [26]. In inflammatory conditions, neutrophils and macrophages are activated

and produce free radicals such as hydrogen peroxide and superoxide, which contributes to progression of oxidative stress [27]. Cellular studies have shown that in cells exposed to high concentrations of TNF-α insulin resistance increases through phosphorylation of serine sequences in insulin receptors and their stimulation, thus worsening the patient's diabetes status [28]. In the present study, propolis supplementation caused a significant decrease in serum CRP and TNF-α concentrations compared to the control group. At the end of the study, no significant change in the mean levels of inflammatory factors was observed in the placebo group. The results of the present study were in line with the results of the Faried et al. investigation [29]. In their study, intervention with propolis significantly decreased serum CRP level and other inflammatory cytokines compared with untreated diabetic rats. Also in the Zhao et al.'s [15] study, significant decrease in serum TNF-α level was seen after 18 weeks of treatment with Green Brazilian propolis. Additionally, the results of the Fukuda study showed that 8 weeks of propolis supplementation in patients with type 2 diabetes maintained serum TNF-α at the same baseline level without significant increase, while patients who were receiving placebo had increased serum TNF-α level [16].

The present study, like other clinical trials, had limitations, such as not assessing different doses of propolis, budget deficit, and measuring multiple factors. To ensure the effectiveness of propolis, it is necessary to execute randomized clinical trial with a greater number of participants and different doses of propolis. Also, if possible, study on active compounds in propolis could help in determination their effects on the diseases.

Conclusions

In conclusion, the results showed that propolis supplementation (500 mg, three times daily) had a beneficial effect on reducing total cholesterol, triglycerides, LDL cholesterol, CRP, and TNF-α and it also increased HDL cholesterol in patients with type 2. In addition, propolis decreased the mean levels of AST and ALT, but it was not significant. Therefore, propolis can be used as supplementary therapy in these patients.

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Conflict of interests

None declared.

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