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Effects of bee propolis on FBG, HbA1c and insulin resistance in healthy volunteers

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Abstract
Objectives: Bee propolis is a natural substance that is used in traditional medicine due to its versatile pharmacological actions. This work aims to evaluate whether short term use of bee propolis supplementation could have an impact on glycemic control in healthy individuals.
Materials and Methods: A single daily dose of 1000 mg of bee propolis was administered orally to thirty-four healthy individuals for 60 days. Body weight, body mass index (BMI), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c) and insulin resistance were measured in all participants prior to and after the use of bee propolis.
Results: Bee propolis was associated with a significant increase in body weight and BMI in healthy volunteers. Supplementation of bee propolis decreased FBG, HbA1c and did not affect the insulin resistance.
Conclusion: Based on these results, bee propolis supplement has a potential effect on glycemic control in healthy individuals and this should be addressed when using the supplement in some medical conditions.
Keywords: bee propolis, insulin resistance, healthy volunteers, fasting blood glucose, natural products

Introduction

Products based on nature are promising candidates for the development of new medications. Bee propolis is one such product. It is a resinous substance that is synthesised by bees from bee's wax and saliva combined with exudates from plants. Bee propolis main function for the bees is building and maintenance of beehives.[1] Anciently, bee propolis has been used in traditional medicine for healing purposes such as in care for wounds and ulcers.[2] The constituents of raw propolis are mainly resins (50%), waxes (30%), essential oils (10%), pollen (5%) and 5% of various other organic compounds. Chemically, bee propolis is composed of more than 300 natural ingredients including coumarins, phenolic compounds and esters, flavonoids, steroids, aldehydes, amino acids sesquiterpenes and stilbene terpenes.[3,4]

Bee propolis has become a healthy supplement, with support studies showing an association of bee propolis consumption to remarkable biological and pharmacological effects. Among those, bee propolis has shown antimicrobial,[5] anti-inflammatory,[6] antioxidant,[7] antiviral,[8] anticancer,[9] and immunoregulatory actions[10], and protective effects on the liver, pancreas, heart, and brain.[11,12] It has been documented that the main constituents of propolis responsible for its therapeutic effects include flavonoids, phenols and aromatic compounds.[13] Flavonoids and the phenolic compounds in bee propolis show a powerful antioxidant activity that acts against oxygen radicals and protects biological membranes from lipid peroxidation.[14] Oxidative stress is involved, among others, in β-cell dysfunction, insulin resistance, impaired glucose tolerance and a higher risk for the development of type 2 diabetes.[15,16] In this context, bee propolis can be considered for glycemic control because of its high antioxidant properties. More recently, studies have demonstrated that bee propolis results in a significant decrease in the blood glucose levels, serum levels of glycosylated hemoglobin and serum insulin with improvement of insulin resistance in patients with type 2 diabetes.[17,18]

The acclaimed beneficial effect of bee propolis in diabetes was the main motivation for conducting this study to test the safety of the dietary supplement in non-diabetic individuals. Bee propolis is used by many healthy, or at least not diabetic, people as a dietary supplement. Since it has shown some beneficial effects in diabetes, this study is aiming to investigate the effects of bee propolis, if any, on fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c) and insulin sensitivity in healthy subjects.

Materials and Methods

Study design and methodology

This study was conducted in compliance with the standards of research ethics of the institutional and national ethical committees. The study is also ethically compliant with the 1975 Helsinki declaration and its following revisions. The approval for conducting the study was obtained from the scientific and ethical committees at the College of Pharmacy, University of Mosul, and Nineveh Health Directorate respectively. The study was conducted on apparently healthy volunteers of both genders who were aged between 25 and 40 years and had a body mass index (BMI) that ranged from 18.5 $kg.m^{-2}$ to 25 $kg.m^{-2}$ (Table 1). Subjects with BMI that was below 18.5 kg/m^2 and above 25 kg/m^2 were excluded from the study as well as those with chronic diseases, FBG of more than 120 $mg.dL^{-1}$ or on dietary supplements. Subjects were selected randomly from different levels of employees at the College of Pharmacy, University of Mosul. Volunteers were recruited to the study from January to April 2019. A convenient sample of 40 subjects was initially taken, later on 6 people were excluded from the study due to the lack of compliance. All participants involved in this study were well informed of the approved study protocol; they were asked to sign an informed consent form before taking part in the study. The participants received 60 capsules of 1000 mg of bee propolis (Woods Supplements, United Kingdom) to be taken for two months as a single daily dose. Pre- and post-treatment 5-ml venous blood samples were collected from each individual following a minimum of 8-hour fasting period, between 9 am and 11 am. HbA1c test was performed using DCA Vantage Analyzer (Siemens®) and completed within 2 hours of blood collection.[19] For the other tests, blood samples were centrifuged for 10 minutes at room temperature, serums were collected and stored at -20 □ until the day of assay. Fasting serum blood glucose (FBG) was measured by hexokinase method with automated analyzer (Cobas c111, Roche) following manufacturer recommendation.[20,21] Serum insulin was measured by electro-chemiluminescence technology for immunoassay analysis (Cobas e 411 Roche).[22] FBG and serum insulin readings were used to calculate homeostasis model assessment-insulin resistance (HOMA-IR) by the following equation:

HOMA-IR = fasting glucose (mg/dl)*fasting insulin ($\mu U\ ml^{-1}$)/405.[23]

Data analysis

Data were normally distributed as all sample sets passed D'Agostino & Pearson normality test. All results were presented in the form of the mean ± standard deviation. Student's paired t-test for single data comparison was performed, using Graph Pad Prism 8.0 software to assess the statistical significance ($P < 0.05$) of any difference between mean values.

Results

Thirty-four healthy individuals aged 25-45 years were chosen according to the inclusion criteria for participation in the current study. The mean age of participants was 36.88 years. Females represented 32.4% of the participants and males were 67.6% (Table 1). The effect of bee propolis on body weight and BMI after 60 days are shown in Figure 1. By the end of the study, the means of weight and BMI increased significantly from 73.4 ± 7.2 to 74.8 ± 7.5, and from 24.2 ± 1.2 to 24.7 ± 1.5 ($P < 0.01$) respectively.

FBG, HbA1c and serum insulin were measured at the onset of the study and on day 60 after the administration of bee propolis as shown in Figure 2. There were significant reductions in the mean of FBG from 101.9 ± 9.1 to 92.69 ± 13 ($P < 0.01$) and in the mean of HbA1c from 5.1 ± 0.3 to 4.8 ± 0.4 ($P < 0.01$) after consuming bee propolis for 60 days. Insulin levels (from 7.3 ± 1.7 to 7.2 ± 2, $P = 0.1$) and HOMA-IR (from1.7 ± 06 to 1.66 ± 0.6, $P = 0.1$) were not significantly affected by the administration of bee propolis.

Discussion

People around the world take dietary supplements in a hope to boost their health. The past 20 years have seen a widespread use of dietary supplements as these products were suggested for several health benefits. Bee propolis is one of these natural dietary supplements that has several interesting effects protecting the health such that bee propolis has been attaining high popularity recently. However, more studies are required to substantiate the contribution of bee propolis on human health.

In this study, it was observed that the daily administration of 1000 mg of bee propolis for 60 days would result in an increase in body weight and BMI with a reduction in FBG and HbA1c in healthy volunteers. This study did not find a significant change in human insulin level, likewise, no significant effect of bee propolis on insulin resistance could be observed. This study has not confirmed previous research on weight and BMI. Zakerkish et al.[17] and Samadi et al.[18] did not report any significant change in body weight following administration of bee propolis for 3 months in their clinical studies.[17,18] Moreover, other studies demonstrated a weight loss in animals as a result of laxative effect and prevention of intestinal fat absorption from bee propolis.[24,25] The bee propolis used in this study for 2 months was associated with a significant increase in body weight and BMI of the enrolled people. One suggested mechanism is probably the propolis-stimulated hepatic glycolysis and glucose uptake by peripheral tissues through increasing insulin-sensitive glucose transporter, that also has a beneficial effect on glycemic control.[26–28] In this study, it was observed that appetite was enhanced among the volunteers and this could be another possible mechanism to explain the increase in body weight and BMI.

The present study also demonstrated a favourable effect of bee propolis on FBG and HbA1c in healthy subjects, however, none of the subjects experienced hypoglycemic symptoms. This is consistent with some studies that showed a reduction in FBG and HbA1c in type 2 diabetic patients.[17,18,29,30] As a possible mechanism, research proposed a decrease in intestinal glucose absorption due to a reduction in carbohydrate digestion that is attributed to the inhibition of intestinal α-glucosidase and sucrase by aqueous ethanolic propolis extract.[26,31] Moreover, propolis extracts stimulate β-cells of islets of Langerhans, with an enhancement of insulin secretion.[32]

Insulin is a pancreas-secreted hormone that is responsible for glucose utilization by body cells, consequently resulting in a decrease in blood glucose levels.[33] In this research, bee propolis was found to lower blood glucose levels. Whether this outcome was associated with the production of insulin was assessed. Insulin levels and insulin resistance were determined, and the results indicated that propolis had no effect on these parameters in healthy subjects. However, some studies have found that prescribed propolis supplementation can significantly decrease the level of serum insulin and insulin resistance indices in type 2 diabetes mellitus.[17,34–36] Zakerkish et al.[17] demonstrated that insulin levels and insulin resistance in type 2 diabetic patients receiving propolis supplementations for 3 months were lower than controls.

Furthermore, the present study did not show any gender-related difference in results (data not shown) and this is in agreement with Jasprica and colleagues who found that the levels of glucose, iron binding proteins and uric acid in addition to lipid profile parameters were not different between men and women. However, in their study there was significant gender-based variation in the oxidative status and this was attributed to oestrogen which is known to have powerful antioxidant effect in women.[37]

The sample size and the short time of data collection might be the main limitations of this study, which suggest future studies with extended period of propolis administration (more than two months) and larger sample size. Based on our results, however, we recommend that for individuals who are already receiving bee propolis, BMI and waist circumference should

be monitored regularly. Bee propolis used in this study was supplied as a concentrate whole propolis product prepared in the form of capsules and not as an extract of a single or few active compounds. Our rationale for this formulation choice was that propolis effect may be obtained as a result of its numerous components rather than one active compound. Nevertheless, future studies are still needed to identify the exact quantitative composition of the active compounds, where knowing the concentrations of the active components might further help in explanation the obtained results.

Conclusion

In conclusion, this study revealed that the daily intake of 1000 mg of bee propolis supplements for 2 months was associated with an increase in body weight and BMI, as well as a decrease in FBG and HbA1c levels in healthy individuals. Moreover, the possible long-term effects of increased weight or BMI could provoke insulin resistance despite the fact that propolis enhanced glucose tolerance through increasing glucose uptake. Increased weight gain may be a result of this increased glucose uptake and therefore a vicious circle of events may be propagated especially with enhanced appetite.

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Table 1 General characteristics of healthy volunteers

Parameters	Values
Age, (mean) years	36.88
Male, n	23
Female, n	11
Weight, (mean) kg	73.4
BMI, (mean) kg/m^2	24.2
Smoker, n	7

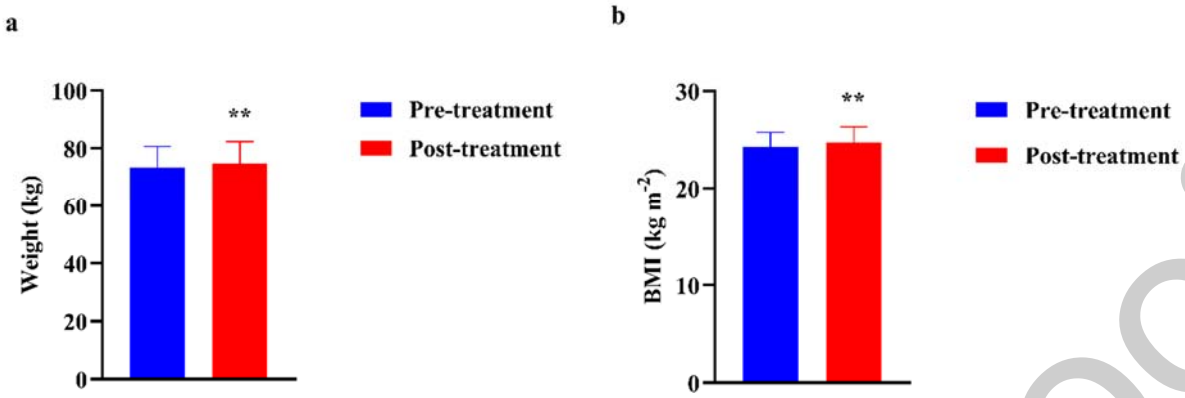

Figure 1 The effect of bee propolis treatment on body weight (a) and BMI (b). Bee propolis was given orally as 1 gram per day for 60 days. The measurements were done before (pre-treatment) and after bee propolis treatment (post-treatment). Data represented as the mean ± standard deviation. **P < 0.01 represents a difference with statistical significance (Student's paired t-test) between pre- and post-treatment.

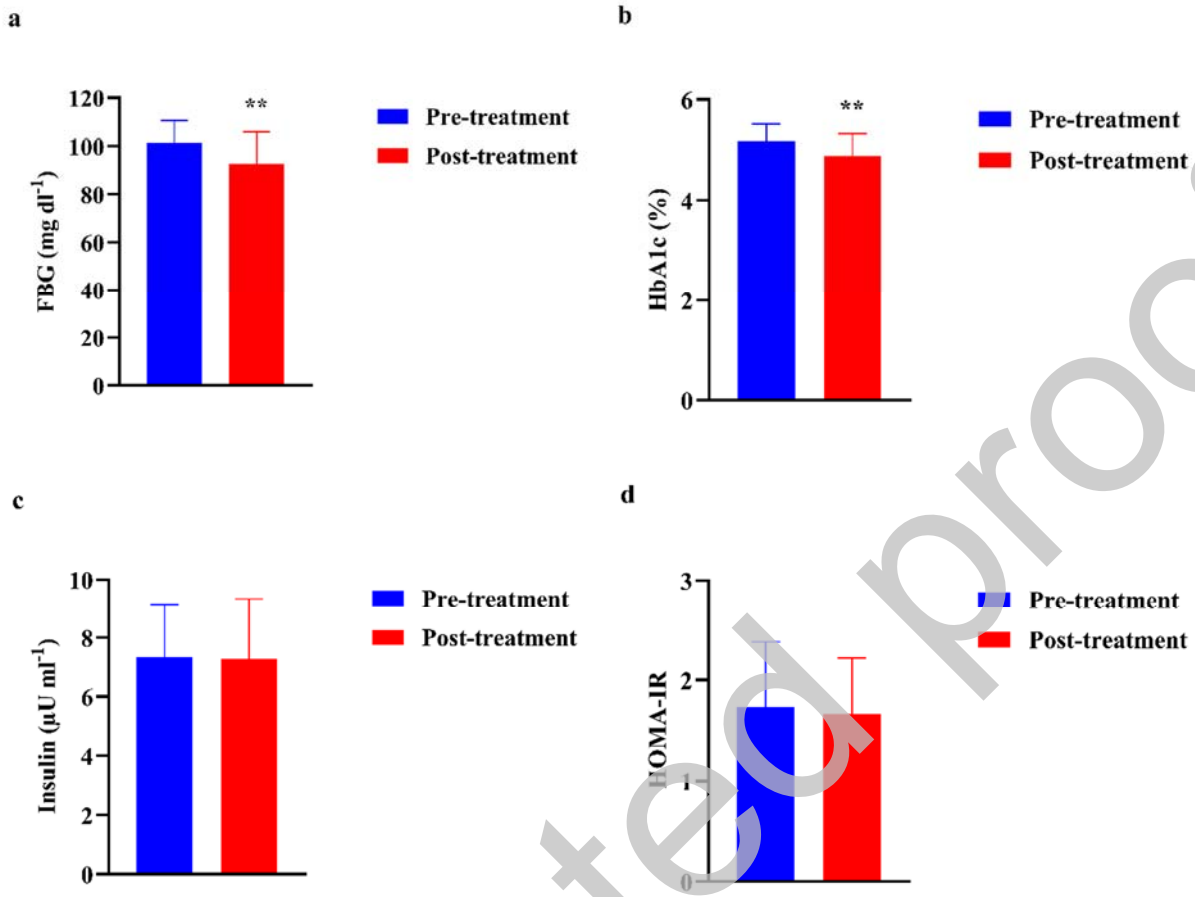

Figure 2 The effect of bee propolis treatment on FBG (a), HBA1c (b), serum insulin (c) and HOMA-IR (d). Bee propolis was given orally as 1 gram per day for 60 days. The measurements were done before (pre-treatment) and after bee propolis treatment (post-treatment). Data represented as the mean ± standard deviation. **P < 0.01 represents a difference with statistical significance (Student's paired t-test) between pre- and post-treatment.