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ORIGINAL ARTICLE

Effects of Bee Propolis on FBG, HbA1c, and Insulin Resistance in Healthy Volunteers

Sağlıklı Gönüllülerde Arı Propolisinin FBG, HbA1c ve İnsülin Direnci Üzerine Etkileri

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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 study evaluates 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 a total of 34 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 before and after the use of bee propolis.

Results: The results of this study showed that bee propolis was associated with a significant increase in body weight and BMI of healthy volunteers. Bee propolis supplementation decreased FBG and HbA1c, but did not affect insulin resistance.

Conclusion: Based on these results, bee propolis supplementation has a potential effect on glycemic control in healthy individuals and this should be considered when using this supplement in medical conditions.

Key words: Bee propolis, insulin resistance, healthy volunteers, fasting blood glucose, natural products

ÖZ

Amaç: Arı propolisi, çok yönlü farmakolojik etkileri nedeniyle geleneksel tıpta kullanılan doğal bir maddedir. Bu çalışma, kısa süreli arı propolis takviyesi kullanımının sağlıklı bireylerde glisemik kontrol üzerinde bir etkisi olup olmadığını değerlendirmektedir.

Gereç ve Yöntemler: Toplam 34 sağlıklı bireye 60 gün boyunca günde tek doz 1000 mg arı propolisi oral yoldan verilmiştir. Arı propolisinin kullanımı öncesi ve sonrasında tüm katılımcılarda vücut ağırlığı, vücut kitle indeksi (VKİ), açlık kan şekeri (AKŞ), glikozile hemoglobin (HbA1c) ve insülin direnci ölçülmüştür.

Bulgular: Bu çalışmanın sonuçları, arı propolisinin sağlıklı gönüllülerin vücut ağırlığında ve VKİ'sinde belirgin bir artış ile ilişkili olduğunu göstermiştir. Arı propolisi takviyesi AKŞ ve HbA1c'yi azaltmış, ancak insülin direncini etkilememiştir.

Sonuç: Bu sonuçlara dayanarak, arı propolis takviyesinin sağlıklı bireylerde glisemik kontrol üzerinde potansiyel bir etkisi olduğu söylenebilir ve bu takviye tıbbi durumlarda kullanılırken bu dikkate alınmalıdır.

Anahtar kelimeler: Arı propolisi, insülin direnci, sağlıklı gönüllüler, açlık kan şekeri, doğal ürünler

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INTRODUCTION

Natural products are promising candidates for the development of new medications. Bee propolis is one such product. It is a resinous substance that is synthesized by bees from bees' wax and saliva combined with exudates from plants. Bees make use of their synthesized propolis for the building and maintenance of their hives.[1] Anciently, bee propolis has been used in traditional medicine for healing purposes, such as wound and ulcer healing.[2] The constituents of raw propolis are resins (50%), waxes (30%), essential oils (10%), pollen (5%), and various other organic compounds (5%). 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 several studies demonstrating an association of bee propolis consumption with remarkable biological and pharmacological effects. Bee propolis has demonstrated antimicrobial,[5] antiinflammatory,[6] antioxidant,[7] antiviral,[8] anticancer,[9] 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 phenolic compounds in bee propolis exhibit a potent antioxidant activity against oxygen radicals and protect biological membranes from lipid peroxidation.[14] Oxidative stress is involved, among others, in β-cell dysfunction, insulin resistance, and impaired glucose tolerance, and it poses 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 glycosylated hemoglobin (HbA1c) levels, and serum insulin levels, 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 ascertain the safety of this dietary supplement in non-diabetic individuals. Bee propolis is used by many healthy, or at least, non-diabetic people as a dietary supplement. Since it has shown some beneficial effects in people with diabetes, this study aimed to investigate the effects of bee propolis, if any, on fasting blood glucose (FBG), HbA1c, and insulin sensitivity in healthy subjects.

MATERIALS AND METHODS

Study design and methodology

This study was conducted in compliance with the research ethics standards of the institutional and national ethical committees. This study is also ethically compliant with the 1975 Helsinki declaration and its following revisions. 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 Scientific and Ethical Research Committee within Nineveh Health Directorate approved the study, with its session numbered 180 on January 02, 2019.

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 <18.5 kg/m^2 and >25 kg/m^2, those with FBG >120 $mg.dL^{-1}$, and those with chronic diseases or on dietary supplements were excluded from the study. Subjects were selected randomly from different levels of employees at the College of Pharmacy, University of Mosul. Volunteers were recruited for the study from January to April 2019. A convenient sample of 40 subjects was initially taken; however, 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 and 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), which they were instructed to take for 2 months as a single daily dose. Before and after treatment with bee propolis, 5 mL venous blood samples were collected from each individual following a minimum of 8 hours 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 other tests, blood samples were centrifuged for 10 minutes at room temperature and serums were collected and stored at -20°C until the day of assay. FBG was measured using the hexokinase method with an automated analyzer (Cobas c111, Roche) following the manufacturer's instructions.[20,21] Serum insulin was measured using 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) according to the following equation:

$$\text{HOMA-IR} = \text{Fasting glucose (mg/dL)} \times \text{fasting insulin } (\mu U\ mL^{-1})/405.$$[23]

Statistical analysis

Data obtained from this study were normally distributed as all sample sets passed the D'Agostino & Pearson normality test. All results were presented as mean ± standard deviation. Student's paired t-test for single data comparison was performed using

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

BMI: Body mass index

GraphPad Prism 8.0 software. Differences between means were considered significant at $p<0.05$.

RESULTS

Thirty-four healthy individuals aged 25-45 years were chosen according to the inclusion criteria of the current study. The mean age of participants was 36.88 years. Females represented 32.4% of the participants, whereas males represented 67.6% (Table 1). The effect of bee propolis on body weight and BMI after 60 days is shown in Figure 1. At the end of the study, the mean weight and mean BMI increased significantly from 73.4±7.2 to 74.8±7.5 kg and from 24.2±1.2 to 24.7±1.5 kg m^{-2} ($p<0.01$), respectively.

FBG, HbA1c, and serum insulin levels were measured at the onset of the study and on day 60 after the administration of bee propolis, as shown in Figure 2. There was significant reduction in the mean FBG level from 101.9±9.1 to 92.69±13 mg dL^{-1} ($p<0.01$) and in the mean HbA1c level from 5.1±0.3 to 4.8±0.4 ($p<0.01$) after consuming bee propolis for 60 days. Insulin levels (which reduced from 7.3±1.7 to 7.2±2, p=0.1) and HOMA-IR (which reduced from 1.7±06 to 1.66±0.6, p=0.1) were not significantly affected by the administration of bee propolis.

DISCUSSION

Globally, people consume dietary supplements to boost their health. The past 20 years have seen a widespread use of dietary supplements as these products provide several health benefits. Bee propolis is one of these natural dietary supplements that has several health-promoting effects, thereby making it gain high popularity recently. However, more studies are required to substantiate the contribution of bee propolis to human health.

In this study, it was observed that the daily administration of 1000 mg of bee propolis for 60 days resulted in an increase in body weight and BMI, with a reduction in FBG and HbA1c levels in healthy volunteers. This study did not find any significant change in human insulin level levels. Similarly, no significant effect of bee propolis on insulin resistance was observed.

This study has not validated the previous research on the effect of bee propolis on weight and BMI. Zakerkish et al.[17] and Samadi et al.[18] did not report any significant changes in body weight following the administration of bee propolis for 3 months in their clinical studies. Moreover, other studies demonstrated a weight loss in animals as a result of the laxative effect and prevention of intestinal fat absorption by bee propolis.[24,25] In the present study, the administration of bee propolis for 2 months was associated with a significant increase in body weight and BMI of the participants. One suggested mechanism is probably the propolis-stimulated hepatic glycolysis and glucose uptake by peripheral tissues via the increase of insulin-sensitive glucose transporter, which 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 for an increase in body weight and BMI.

The present study also demonstrated a favorable effect of bee propolis on FBG and HbA1c levels in healthy subjects; however, none of the subjects experienced hypoglycemic symptoms. This

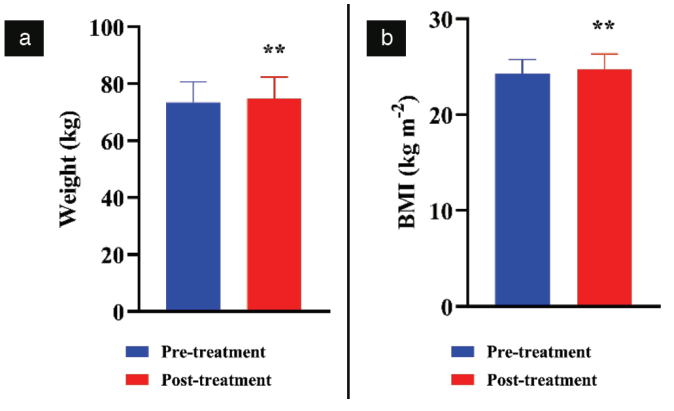

Figure 1. Effect of bee propolis treatment on body weight (a) and BMI (b). Bee propolis was administered orally as 1 gram per day for 60 days. The measurements were done before (pre-treatment) and after the bee propolis treatment (post-treatment). Data were presented as mean ± standard deviation

**P<0.01 indicates a difference with statistical significance (Student's paired t-test) between pre- and post-treatments, BMI: Body mass index

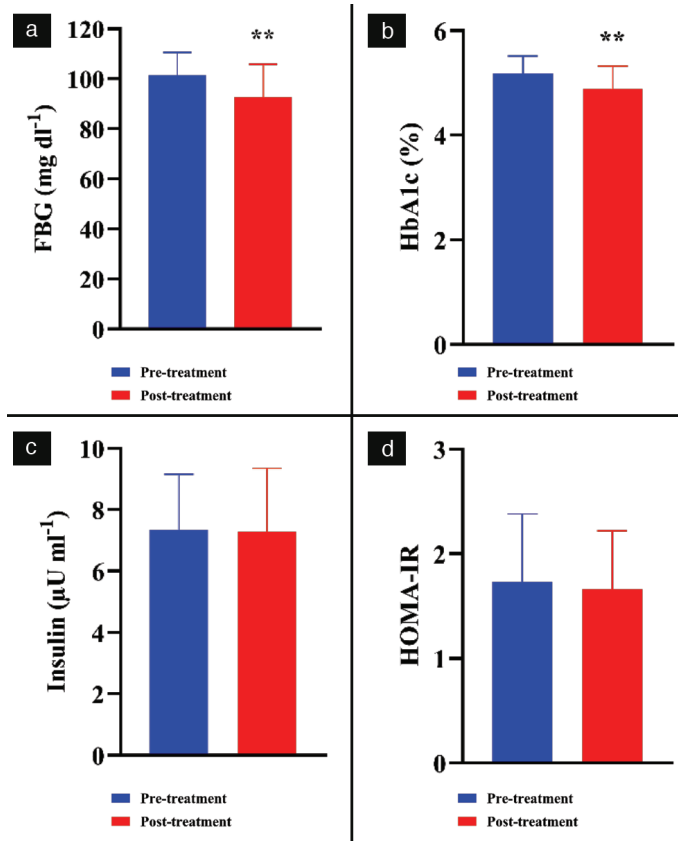

Figure 2. Effect of bee propolis treatment on FBG (a), HBA1c (b), serum insulin (c), and HOMA-IR (d). Bee propolis was administered orally as 1 gram per day for 60 days. Measurements were done before (pre-treatment) and after the bee propolis treatment (post-treatment). Data were presented as mean ± standard deviation

**P<0.01 indicates a difference with statistical significance (Student's paired t-test) between pre- and post-treatments, FBG: Fasting blood glucose, HBA1c: Glycosylated hemoglobin, HOMA-IR: Homeostasis model assessment-insulin resistance

is consistent with some studies that showed a reduction in FBG and HbA1c levels in type 2 diabetic patients.[17,18,29,30] As a possible mechanism, a decrease in intestinal glucose absorption due to reduction in carbohydrate digestion, which is attributed to the inhibition of intestinal α-glucosidase and sucrase by aqueous ethanolic propolis extract, was proposed.[26,31] Moreover, propolis extracts stimulate the β-cells of the islets of Langerhans, causing 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. To ascertain whether this outcome was associated with the production of insulin, 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 demonstrated that prescribed propolis supplementation can significantly decrease the level of serum insulin and insulin resistance indices in patients with type 2 diabetes mellitus.[17,34-36] Zakerkish et al.[17] demonstrated that insulin levels and insulin resistance in patients with type 2 diabetes receiving propolis supplementations for 3 months were lower than those in healthy controls.

Furthermore, the present study did not show any gender-related difference in the results (data not shown) and this is in agreement with Jasprica et al.[37] 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 a significant gender-based variation in the oxidative status and this was attributed to estrogen, which is known to exhibit a potent antioxidant effect in women.[37]

Study limitations

The sample size and the short time of data collection are the main limitations of this study, which suggest the need for future studies with extended period of propolis administration (more than 2 months) and larger sample size. However, based on our results, we recommend that the BMI and waist circumference of individuals receiving bee propolis should be monitored regularly. The bee propolis used in this study was supplied as a concentrate of 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 choice of formulation was that propolis effect may be obtained as a result of the synergistic action 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, and knowledge of the concentrations of the active components might further help to explain the obtained results.

CONCLUSION

This study revealed that a daily intake of 1000 mg of bee propolis supplements for 2 months is 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 by 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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