Series of Endocrinology, Diabetes and Metabolism

Open Access
Review Article
Vol 5 Iss 1

What We Know About Propolis, and Its Potential Role in Obesity and Diabetes

Sevim Y*, Uygunoz D, Alacam S, Yucel F, Turan GN and Ozdogan ON

[1]*Department of Nutrition and Dietetics, Faculty of Health Sciences, Bahcesehir University, Istanbul, Turkey*

***Correspondence:** Yonca Sevim, Department of Nutrition and Dietetics, Faculty of Health Sciences, Bahcesehir University, Istanbul, Turkey

Received on 02 February 2023; Accepted on 09 March 2023; Published on 20 March 2023

Abstract

Propolis, a resinous, dark-colored product produced by honeybees has been gaining attention in terms of its multiple proven health benefits. This natural product has different types and varieties but close to similar chemical compositions according to the environment and location where it is produced, as well as its plant source. It is mainly composed of resinous, balsamic, and gummy materials, waxes and essential oils, and pollen from the plants. Propolis contains plenty of polyphenols and it's a rich source of magnesium, calcium, iodine, potassium, sodium, copper, zinc, manganese, and iron as well as thiamin, riboflavin, vitamins B6, C, E, D, and provitamin A. It has been proven that propolis may help to reduce diet-induced obesity through its caffeic acid content. Studies proved the antibacterial, antiviral, anti-inflammatory, anticancer, antifungal, and antitumor effects of propolis and positive outcomes on diet-induced obesity, and diabetes. In this review, we aim to explain propolis extensively in terms of its types, chemical composition, bioactive compounds, digestion, health benefits on obesity and diabetes, as well as possible drug interactions, dosage, and safety.

Keywords: propolis, anti-obesity, anti-diabetic, polyphenols

Abbreviations: CAPE: caffeic acid phenethyl ester; ArtC: artepillin C

Introduction

The word propolis originally came from the Greek 'pro' which denotes 'the entrance of' and 'polis' stands for 'city'; a suitable word for implying that this product has the property of guarding the entrance of beehives [1]. Propolis, which is produced by honeybees using beeswax and saliva enzymes (β-glucosidase) to protect their hives, is a viscous, dark-colored product composed of resinous, balsamic, and gummy materials, waxes and essential oils, and pollen derived from specific plant types [1–4]. The composition of the propolis varies according to the sources, different

geographical locations, seasons, different hives, and the available parts of the plants that bees can access [2, 3]. It may be found in different colors such as brown, green, and red as well as different physical states according to the weather. Propolis can be considered a chemical defender against bacteria, viruses, and other pathogenic microorganisms that have the potential to spread over the hive. Mentioned protective properties of propolis against microorganisms can contribute remarkable benefits to human health [3].

Propolis has recently attracted attention with its protective and therapeutic effects on health. Studies recently indicate the antibacterial, antiviral, anti-inflammatory, anticancer, antifungal, and antitumor characteristics of propolis [5]. Therefore, propolis became a popular health supplement and is used as an ingredient in certain foods, drinks, and conventional medicine to ameliorate health and protect the body from inflammation and diseases like diabetes, cardiovascular diseases, and cancer. It can be found in different forms, such as tablets, capsules, toothpaste, mouthwash, facial creams, lotions, and solutions [5]. Today, numerous propolis products are available in the market, and their sales number keeps increasing, thus, most suppliers cannot meet the demands [3]. Especially propolis products on oral health and wound healing, as well as propolis products that aim to improve immunity, were the most preferred. Comprehensive investigations of the beneficial health effects and bioactivity of propolis have been done by many researchers *via* numerous scientific papers [3]. This current review aims to explain the chemical, physical, and biological properties, drug interactions, dosage, and safety of propolis, and its effects on human health focusing on the anti-obesity and anti-diabetes effects of propolis.

Types and Chemical Composition of Propolis

Propolis has a complex structure [5], and in general, it is composed of 50% resin and vegetable balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% various other substances, including organic debris [6]. It consists of various chemical compounds such as polyphenols (flavonoids, phenolic acids and their ester forms, phenolic aldehyde, and alcohols) which can be related to its anti-inflammatory and healing properties, terpenoids, steroids, and amino acids [3, 5]. Propolis also contains minerals like magnesium, calcium, iodine, potassium, sodium, copper, zinc, manganese, and iron; vitamins such as thiamin, riboflavin, vitamins B6, C, E, D, and provitamin A [4]. Starch and the mono and disaccharides, glucose, fructose, ribose, rhamnose, talose, gulose, and saccharose are common polysaccharides in propolis [4].

Furthermore, it is proven that propolis contains more than 300 compounds, and this can be attributed to its different plant sources and diverse origin of geography as well as different bee species. Therefore, to be able to examine the chemical characteristics of the propolis, its geographic origin and plant source needs to be analyzed. According to its geographic origin, plant source, and chemical composition, propolis has four different types namely poplar, green, red, and *Macaranga* type propolis. Europe, North America, non-tropic regions of Asia, and Oceania are considered the main locations for poplar-type propolis. For green propolis, Southeast Brazil is regarded as the collection area whereas, Northeast Brazil is for red propolis. Additionally, the *Macaranga*-type propolis can be collected in Japan, Taiwan, Hawaii, and the Solomon Islands. As their different geographic places, each of these propolis types has its own plant source such as *Populus* spp., *Baccharis dracunculifolia*, *Dalbergia ecastaphyllum*, and *Macaranga tanarius* respectively. Furthermore, these different types of propolis contain various chemical compounds. Flavonoids, phenolic acid, and their esters in poplar, prenylated p-coumaric acids, diterpenes in green, isoflavonoids, polyprenylated benzophenones in red, and prenylated flavanones in *Macaranga* are the major chemical compounds [4, 5].

One of the main compounds found in poplar-type propolis is caffeic acid phenethyl ester (CAPE), which is a significant bioactive compound involved in many biological activities such as apoptosis of cells related to breast cancer, improvement in insulin resistance, and radioprotective properties. Other than CAPE, poplar-type propolis also contains chrysin, galangin, pinobanksin, and pinocembrin as a flavonoid. The latest studies indicate the cytotoxic and anti-inflammatory effects of chrysin [7] as well as the improvement of insulin resistance by the galangin and pinocembrin [8]. The main component of Brazilian green propolis is artepillin C (ArtC) which has anti-parasite (especially on *Leishmania* parasites) and gastroprotective actions [9, 10]. Different from poplar-type propolis and

green propolis, red propolis contains isoflavonoids [5]. Various pharmacological investigations have analyzed red propolis and indicated its role in specific human disorders such as dental caries, candidiasis, cancer, skin wounds, and complications associated with oxidative stress [11, 12], and have antimicrobial effects [13]. The main components of *Macaranga*-type propolis which were prenylated flavonoids have proven pharmacological effects such as antioxidant, antibacterial, antiangiogenic, and anticancer *via* in vitro studies [5].

Digestion of Propolis

In addition to investigating the antioxidant potential of food materials, it is critical to evaluate the composition and concentration of antioxidants available in the human gastrointestinal system [14]. Due to propolis' complex matrix with a large molecular weight, has poor bioavailability and absorption. The most important determinants of bioavailability are the form of polyphenol administered such as natural fruit, juice, or extract, and the presence of other polyphenolics that give synergistic effects [3]. Factors such as digestive instability, poor transcellular efflux in intestinal cells, and rapid metabolism and excretion affect the bioavailability of polyphenols [15]. Dietary polyphenols are in esters, polymers, or glycosylated forms, and so they must be hydrolyzed by the intestinal enzymes or by the colonic microflora before absorption [16]. Once these poorly absorbed polyphenols are in the intestinal system, they are converted to smaller phenolic acids with an increased bioavailability by the enzyme activity of the colonic microbiota [17]. Microbiota appears as an individual difference and is increasingly being taken into account. However, the recovered amounts detected in plasma were still high due to the high initial contents of propolis compared to other food materials such as fruits and vegetables [3].

There have been few studies on the bioavailability of phytochemicals in bee products, such as minerals in honey, polyphenols in propolis, and the disposition and metabolism of chrysin [18–20]. Professors stated that total phenolic and flavonoid content values ranged from 85–283 to 16–136 mg/g for ethanolic extracts of propolis samples collected from various geographical areas [21]. Even today, many researchers are focusing on propolis due to its broad spectrum of biological properties, and it is thus regarded as a functional food [22].

Health Effects of Propolis

Propolis phytochemicals contribute to a wide range of health-promoting properties such as antioxidant, anti-inflammatory, antibacterial, antifungal, antivirus, antimicrobial, antitumoral, immunomodulatory, anti-allergic, anti-diabetic properties, as well as neuroprotective, renoprotective, dermal protective, gastroprotective, and hepatoprotective activities [23–25]. Additionally, the possible effects of propolis against COVID-19 have been proposed [26]. In a recent review by Anvarifard et al., both human and animal studies evidence that propolis could potentially improve the glycemic status, oxidative stress, renal tissue damage, and renal function. But further studies are needed to determine the underlying mechanisms [27]. This review describes the beneficial effects of propolis on diabetes and obesity.

Diabetes and Propolis

Type 2 diabetes is a chronic disease of dysregulation of glucose metabolism, accompanied by micro and macro complications. The global diabetes population is projected to be 592 million by 2035 [28]. Identification of modifiable lifestyle factors including dietary factors that reduce the incidence of the disease is an important research area. There is an increasing interest in polyphenol-rich foods as a dietary factor. Dietary polyphenols have been suggested to lower the risk of type 2 diabetes [29]. Polyphenols from coffee, guava tea, whortleberry, olive oil, propolis, chocolate, red wine, grape seed, and cocoa have shown anti-diabetic effects in type 2 diabetes patients by promoting the uptake of glucose in tissues, glucose metabolism, and vascular function, reducing insulin resistance, HbA1c and inhibiting glucose absorption in the gut [30, 31].

Studies in animal and cellular models have indicated that propolis modulates oxidative stress, the accumulation of advanced glycation end products, and adipose tissue inflammation, all of which contribute to insulin resistance or

defects in insulin secretion. Consequently, propolis treatment may reduce diabetic complications such as nephropathy, retinopathy, foot ulcers, and non-alcoholic fatty liver disease [32].

It was observed that propolis treatment on mice consuming fructose significantly reduced plasma insulin levels. However, no decrease was observed in blood glucose and total cholesterol levels. These findings showed that propolis can prevent the development of insulin resistance [33]. Chinese propolis and Brazilian propolis can alleviate symptoms of diabetes mellitus in rats and these effects may partially be due to their antioxidant ability [34].

Studies with streptozotocin (STZ)-induced mouse models of diabetes show that propolis aqueous extracts can protect pancreatic beta-cells from the harmful effects of streptozotocin, which cause interleukin-1 (IL-1) to be inhibited and nitric oxide synthases to be produced [35]. Propolis was found to positively control blood sugar and blood fat levels, as well as to inhibit fat peroxidation and the emergence of free radicals, in a study conducted on diabetic rats [36].

The CAPE component of propolis can prevent the oxidative stress brought on by diabetes, and because of its antioxidant property, it reduces oxidative stress by preventing SOD and CAT pathways, according to recent studies on diabetes and propolis. Additionally, while diabetes has a negative impact on heart diseases, propolis can prevent the oxidative stress brought on by diabetes [37].

Studies with animal models of type 1 diabetes induced by streptozotocin or alloxan have shown that under propolis' anti-oxidative stress effects, it reduced blood glucose increase, complications of diabetes, and oxidative stress associated with elevated blood glucose [34, 38–40].

In animal models of type 2 diabetes, several administration methods of ethanolic extract of Brazilian propolis (100–300 mg/kg and 4–12 weeks) showed reduced obesity-associated inflammation in white adipose tissue, corrected insulin resistance, and attenuated increase in blood glucose and blood pressure [41–43]. A single-component chrysin administration for 16 weeks at 40 mg/kg, reduced diabetic nephropathy in diabetic rats [43].

There are several randomized, double-blind, placebo-controlled clinical trials with Iranian propolis on the anti-diabetes effects of propolis in patients with type 2 diabetes. Trials show a significant decrease in fasting blood glucose, blood hemoglobin A1c (HbA1c), and insulin concentration with different doses and duration plans such as 900 mg/day Iranian propolis for 12 weeks [44], 1 g/day Iranian propolis (total phenolic content: 28%) for 90 days [45], and 1.5 g/day Iranian propolis for 8 weeks [46], respectively. Moreover, a systematic review and meta-analysis of six studies published up to 2018 showed that propolis significantly reduced fasting blood glucose and HbA1c concentration in patients with type 2 diabetes [47]. In a trial by Zakerkish et al., the levels of high-density lipoprotein (HDL-C) significantly increased in diabetic patients following a propolis intake of 1000 mg/day for 90 days [45].

There are a few randomized, double-blind, placebo-controlled clinical trials with Brazilian green propolis on the anti-diabetes effects of propolis in patients with type 2 diabetes with different doses and duration times. Contrary to studies with Iranian propolis, trials could not show a significant decrease in fasting blood glucose, blood HbA1c (226.8 mg/day, 8 weeks) [48], (900 mg/day, 18 weeks) [49]. But it did inhibit hyperuricemia and impairment of glomerular filtration [47].

Obesity and Propolis

Obesity is a global public health problem that is becoming more prevalent among adults and children [50]. A high-fat or unbalanced diet over time contributes to obesity [51, 52], as evidenced by the rising global overweight ratio [53]. A recent study found that natural products, particularly those high in polyphenols, have a high therapeutic value in the prevention and treatment of obesity by inhibiting adipocyte lipid accumulation [54].

Propolis has long been recognized as a natural nutraceutical due to its anti-inflammatory, and antioxidant properties [55] and it has major anti-obesity effects. Increasing evidence on animal and cellular models suggests that propolis extracts have therapeutic effects on obesity by controlling adipogenesis, adipokine secretion, food intake, and energy

expenditure [32]. CAPE, a major component of propolis, has an anti-obesity effect on high-fat diet-induced adipogenesis at an early stage by regulating cyclin D1 [56]. Propolis treatment reduced body weight gain and increased thermogenesis in adipose tissue while reducing visceral adipose tissue accumulation [57, 58].

Repeated intraperitoneal injection of Brazilian propolis extracts (100 mg/kg, twice a week for 12 weeks) significantly decreased mesenteric adipose tissue mass, but epididymal and inguinal adipose tissue was not affected [41]. Intraperitoneal administration of ethanolic extract of 100 mg/kg Brazilian green propolis to obese mice for 2 weeks [41] and 12 weeks [59] significantly reduced visceral adipose tissue weight. 10 days of oral administration of 50 mg/kg Brazilian green propolis extract attenuated an increase in body weight and visceral adipose tissue weight in a mouse model of diet-induced obesity. And the same study also showed that 25 mg/kg propolis ethanol extract attenuated body-weight gain in pre-existing obese mice [58]. Similarly, 14 weeks of oral administration of 2% ethanolic extract of Brazilian propolis (ArtC content: 6.1%) with a high-fat diet attenuated weight gain and body fat accumulation [60]. It's been assumed that propolis decreases fat absorption due to the fat content of mice's feces. Ichi et al. report that propolis might regulate adipose tissue hypertrophy *via* repression of peroxisome proliferator-activated receptor gamma (PPAR-γ) in high-fat diet-induced obese rats [61].

Administration of 50 mg/kg ethanol extract of Croatian propolis for 30 days [62], and 20 mg/day ethanolic extract of poplar-type propolis for 12 weeks [63] significantly decreased body fat accumulation in a mouse model of diet-induced obesity. Studies on CAPE or chrysin as a sole component of propolis showed a significant reduction in body weight in mice fed with a high-fat diet containing CAPE (0.02−0.5%) [32], and chrysin (100 mg/kg) [64]. Other outcomes of these studies were decreased epididymal white adipose tissue weight, inhibition of pancreatic lipase, and, an increase in voluntary exercise. CAPE seems to be one of the compounds responsible for the anti-obesity effects of propolis. None of these studies have determined the individual factors or, the possible action mechanism of the anti-obesity effect.

It’s been reported that the effects of propolis were different between adipose tissues. In general, visceral adipose tissue is more sensitive to propolis than subcutaneous adipose tissue. Propolis has the potential to normalize dyslipidemia, so can be effective on obesity from that perspective also [56].

Dosage and Safety

Research on the recommended dosage of propolis is still ongoing. Clinical investigation in mice and humans reports that propolis and its constituents are generally well tolerated and non-toxic unless administered in very large quantities [3]. Burdock [6] suggested that as a safe dose, humans shouldn’t consume more than 1.4 mg/kg body weight/day or almost 70 mg/day. Doses of 300 mg/day have been used safely for up to ten months. Higher doses should be avoided [65]. Because of the scarcity of human clinical studies on propolis, it has been suggested that dosage be taken into account [66]. There have been insufficient studies on the acute and chronic toxicity of propolis. Studies in mice and humans have not shown any harmful or toxic effects of propolis. Propolis administration at doses of 200 and 5000 mg/kg body weight/day did not result in toxic deaths in experimental animals, and it was reported as safe [6, 66]. However, more than 26 allergenic substances have been identified in the composition of propolis. The most common allergic reaction is due to esters of caffeic acid and cinnamic acid obtained from poplar buds. They cause a contact allergic reaction in hypersensitive individuals. The presence of these esters in other materials may also cause cross-allergic reactions [67]. The LD50 (lethal dose 50) value in mice ranges from 2–7.3 g/kg. The no observed adverse effect level (NOAEL) in mice was over 1470 mg/kg/day at 60 days and over 2470 mg/kg/day in rats at 90 days. Toxic effects in humans occur at doses as high as 15 g/day [68]. High dosages may cause pro-oxidant effects, unlike antioxidants [69]. Its safety is unclear to use in pregnancy and lactating women; its use should be avoided [65]. Propolis can also give negative effects like dermatitis in the case of excess use [6]. Propolis has the potential to cause allergic reactions, particularly in people who are allergic to other bee products. Propolis lozenges can cause irritation and mouth ulcers [70].

Propolis consumption may increase the risk of bleeding in people with bleeding disorders, and during and after surgery. Hence, patients must stop consuming propolis 2 weeks before surgery [71].

Propolis and Drug Interactions

Propolis has interactions with some drugs which are duloxetine, warfarin, praziquantel, donepezil, levodopa, metformin, anticancer drugs, and finally antimicrobial drugs. Duloxetine and warfarin are affected negatively by the propolis but the other drugs are affected positively by the propolis or combining two of them together gave better consequences for the treatment [72–74]. Raw, water-soluble propolis combined with chemotherapeutic agents has been shown in studies to potentially reduce post-chemotherapeutic reactions, maximize enhanced immunity, and increase treatment efficacy without causing drug interactions [75]. Another study found that whether propolis interacts with chemotherapeutic drugs is still unknown, and its use during chemotherapy is contradictory [76].

Propolis intake during metformin therapy may give positively better consequences because propolis protects pancreatic β-cells from free radicals and inhibits oxidative or inflammatory damage resulting in functional production of insulin, increased insulin sensitivity, and thus low concentrations of glucose in the blood [74]. When propolis-involved products are taken at the same time as warfarin therapy, the activity and efficiency of warfarin would be inhibited or reduced related to chemical compounds that propolis involved [72]. When the propolis was taken into the body, the formation of the main metabolite of duloxetine called 4-hydroxy duloxetine decreased because of the inhibition activity of responsible enzymes. Propolis has an inhibitory effect on the action mechanism of CYP1A2 and CYP2D6 which metabolite duloxetine [77].

Conclusion

The utilization of various natural products for their health benefits is an early concept that dates back to ancient times. Propolis contains flavonoids and phenols, which add to its biological activity as a natural remedy for treating infected wounds, guarding against diabetes and cancer, and promoting cardiovascular health. Antioxidant and anti-inflammatory properties of propolis seem to be linked to its ability to promote health. The common suggestion is the need for further clinical and human trials to better understand the physiology and chemical composition of propolis so that there may be set guidelines for customized dosages for certain diseases.

References

1. Abdelrazeg S, Hussin H, Salih M, et al. Propolis composition and applications in medicine and health. Int Med J. 2020;25(3):1505-42.

2. Irigoiti Y, Navarro A, Yamul D, et al. The use of propolis as a functional food ingredient: A review. Trends in Food Science & Technology. 2021;115:297-306.

3. Braakhuis A. Evidence on the health benefits of supplemental propolis. Nutrients. 2019;11(11):2705.

4. Rivera-Yañez N, Rivera-Yañez CR, Pozo-Molina G, et al. Biomedical properties of propolis on diverse chronic diseases and ıts potential applications and health benefits. Nutrients. 2020;13(1):78.

5. Tsuda T, Kumazawa S. Propolis: Chemical Constituents, Plant Origin, and Possible Role in the Prevention and Treatment of Obesity and Diabetes. J Agric Food Chem. 2021;69(51):15484-494.

6. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol. 1998;36(4):347-63.

7. Naz S, Imran M, Rauf A, et al. Chrysin: Pharmacological and therapeutic properties. Life Sci. 2019;235:116797.

8. Liu Y, Liang X, Zhang G, et al. Galangin and Pinocembrin from Propolis Ameliorate Insulin Resistance in HepG2 Cells via Regulating Akt/mTOR Signaling. Evid Based Complement Alternat Med. 2018;2018:7971842.

9. Arruda C, Ribeiro VP, Mejía JAA, et al. Green propolis: Cytotoxic and leishmanicidal activities of artepillin C, p-coumaric acid, and their degradation products. Rev. Bras. Farmacogn. 2020;30:169−76.

10. Costa P, Somensi LB, da Silva RCMVAF, et al. Role of the antioxidant properties in the gastroprotective and gastric healing activity promoted by Brazilian green propolis and the healing efficacy of Artepillin C. Inflammopharmacology. 2020;28(4):1009-25.

11. Franchin M, Freires IA, Lazarini JG, et al. The use of Brazilian propolis for discovery and development of novel anti-inflammatory drugs. Eur J Med Chem. 2018;153:49-55.

12. Freires IA, de Alencar SM, Rosalen PL. A pharmacological perspective on the use of Brazilian Red Propolis and its isolated compounds against human diseases. Eur J Med Chem. 2016;110:267-79.

13. Bueno-Silva B, Alencar SM, Koo H, et al. Anti-inflammatory and antimicrobial evaluation of neovestitol and vestitol isolated from Brazilian red propolis. J Agric Food Chem. 2013;61(19):4546-50.

14. Yesiltas B, Capanoglu E, Firatligil-Durmus E, et al. Investigating the in-vitro bioaccessibility of propolis and pollen using a simulated gastrointestinal digestion System. J Apic Res. 2014;53(1):101-08.

15. Weaver CM, Barnes S, Wyss JM, et al. Botanicals for age-related diseases: from field to practice. Am J Clin Nutr. 2008;87(2):493S-7S.

16. Pandareesh MD, Mythri RB, Srinivas Bharath MM. Bioavailability of dietary polyphenols: Factors contributing to their clinical application in CNS diseases. Neurochem Int. 2015;89:198-208.

17. Alkhaldy A, Edwards CA, Combet E. The urinary phenolic acid profile varies between younger and older adults after a polyphenol-rich meal despite limited differences in in vitro colonic catabolism. Eur J Nutr. 2019;58(3):1095-1111.

18. Pohl P, Stecka H, Greda K, et al. Bioaccessibility of Ca, Cu, Fe, Mg, Mn and Zn from commercial bee honeys. Food Chemistry. 2012;134(1):392-96.

19. Gardana C, Simonetti P, Berti C, et al. Evaluation of propolis polyphenols absorption in humans by liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom. 2007;21(23):3849-54.

20. Walle T, Otake Y, Brubaker JA, et al. Disposition and metabolism of the flavonoid chrysin in normal volunteers. Br J Clin Pharmacol. 2001;51(2):143-46.

21. Ahn M, Kumazawa S, Usui Y, et al. Antioxidant activity and constituents of propolis collected in various areas of China. Food Chemistry. 2007;101(4):1383-92.

22. Yen CH, Chiu HF, Wu CH, et al. Beneficial efficacy of various propolis extracts and their digestive products by in vitro simulated gastrointestinal digestion. LWT. 2017;84:281-89.

23. Nakajima M, Arimatsu K, Minagawa T, et al. Brazilian propolis mitigates impaired glucose and lipid metabolism in experimental periodontitis in mice. BMC Complement Altern Med. 2016;16(1):329.

24. Sampietro DA, Vattuone MMS, Vattuone MA. Immunomodulatory activity of Apis mellifera propolis from the North of Argentina. LWT Food Sci. Technol. 2016;70:9-15.

25. Sforcin JM. Propolis and the immune system: a review. J Ethnopharmacol. 2007;113(1):1-14.

26. Berretta AA, Silveira MAD, Cóndor Capcha JM, et al. Propolis and its potential against SARS-CoV-2 infection mechanisms and COVID-19 disease: Running title: Propolis against SARS-CoV-2 infection and COVID-19. Biomed Pharmacother. 2020;131:110622.

27. Anvarifard P, Anbari M, Ostadrahimi A, et al. A comprehensive insight into the molecular and cellular mechanisms of the effects of Propolis on preserving renal function: a systematic review. Nutr Metab (Lond). 2022;19(1):6.

28. Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014;103(2):137-49.

29. Kim Y, Keogh JB, Clifton PM. Polyphenols and glycemic control. Nutrients. 2016;8(1):17.

30. Cao H, Ou J, Chen L, et al. Dietary polyphenols and type 2 diabetes: Human Study and Clinical Trial. Crit Rev Food Sci Nutr. 2019;59(20):3371-79.

31. Guasch-Ferré M, Merino J, Sun Q, et al. Dietary polyphenols, mediterranean diet, prediabetes, and type 2 diabetes: a narrative review of the evidence. Oxid Med Cell Longev. 2017;2017:6723931.

32. Kitamura H. Effects of propolis extract and propolis-derived compounds on obesity and diabetes: knowledge from cellular and animal models. Molecules. 2019;24(23):4394.

33. Lee KW, Chun KS, Lee JS, et al. Inhibition of cyclooxygenase-2 expression and restoration of gap junction intercellular communication in H-ras-transformed rat liver epithelial cells by caffeic acid phenethyl ester. Ann N Y Acad Sci. 2004;1030(1):501-07.

34. Zhu W, Chen M, Shou Q, et al. Biological activities of chinese propolis and brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats. Evid Based Complement Alternat Med. 2011;2011:468529.

35. Matsui T, Ebuchi S, Fujise T, et al. Strong antihyperglycemic effects of watersoluble fraction of Brazilian propolis and its bioactive constituent, 3,4,5-triocaffeoylquinic acid. Biol Pharm Bull. 2004;27(11):1797-1803.

36. Kang LJ, Lee HB, Bae HJ, et al. Antidiabetic effect of propolis: reduction of expression of glucose-6-phosphatase through inhibition of Y279 and Y216 autophosphorylation of GSK-3α/β in HepG2 cells. Phytother Res. 2010;24(1):1554-61.

37. Okutan H, Ozcelik N, Yilmaz HR, et al. Effects of caffeic acid phenethyl ester on lipid peroxidation and antioxidant enzymes in diabetic rat heart. Clin Biochem. 2005;38(2):191-96.

38. Nna VU, Bakar ABA, Mohamed M. Malaysian propolis, metformin and their combination, exert hepatoprotective effect in streptozotocin-induced diabetic rats. Life Sci. 2018 ;211:40-50.

39. Nna VU, Bakar ABA, Md Lazin MRML, et al. Antioxidant, anti-inflammatory and synergistic anti-hyperglycemic effects of Malaysian propolis and metformin in streptozotocin-induced diabetic rats. Food Chem Toxicol. 2018;120:305-20.

40. Oršolić N, Sirovina D, Končić MZ, et al. Effect of Croatian propolis on diabetic nephropathy and liver toxicity in mice. BMC Complement Altern Med. 2012;12:117.

41. Kitamura H, Naoe Y, Kimura S, et al. Beneficial effects of Brazilian propolis on type 2 diabetes in ob/ob mice: Possible involvement of immune cells in mesenteric adipose tissue. Adipocyte. 2013;2(4):227-36.

42. Zamami Y, Fujiwara H, Hosoda M, et al. [Ameliorative effect of propolis on insulin resistance in Otsuka Long-Evans Tokushima Fatty (OLETF) rats]. Yakugaku Zasshi. 2010;130(6):833-80.

43. Aoi W, Hosogi S, Niisato N, et al. Improvement of insulin resistance, blood pressure and interstitial pH in early developmental stage of insulin resistance in OLETF rats by intake of propolis extracts. Biochem Biophys Res Commun. 2013;432(4):650-53.

44. Samadi N, Mozaffari-Khosravi H, Rahmanian M, et al. Effects of bee propolis supplementation on glycemic control, lipid profile and insulin resistance indices in patients with type 2 diabetes: a randomized, double-blind clinical trial. J Integr Med. 2017;15(2):124-34.

45. 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.

46. Afsharpour F, Javadi M, Hashemipour S, et al. Propolis supplementation improves glycemic and antioxidant status in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study. Complement Ther Med. 2019;43:283-88.

47. Karimian J, Hadi A, Pourmasoumi M, et al. The efficacy of propolis on markers of glycemic control in adults with type 2 diabetes mellitus: A systematic review and meta-analysis. Phytother Res. 2019;33(6):1616-26.

48. 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):355-60.

49. Zhao L, Pu L, Wei J, et al. Brazilian green propolis ımproves antioxidant function in patients with type 2 diabetes mellitus. Int J Environ Res Public Health. 2016;13(5):498.

50. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27.

51. Buettner R, Schölmerich J, Bollheimer LC. High-fat diets: Modeling the metabolic disorders of human obesity in rodents. Obesity. 2007;15(4):798-808.

52. Ikemoto S, Takahashi M, Tsunoda N, et al. High-fat diet-induced hyperglycemia and obesity in mice: Differential effects of dietary oils. Metabolism. 1996;45(12):1539-46.

53. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition. 2007;23(11-12):887-94.

54. Chang E, Kim CY. Natural Products and Obesity: A Focus on the Regulation of Mitotic Clonal Expansion during Adipogenesis. Molecules. 2019;24(6):1157.

55. Sforcin JM, Bankova V. Propolis: Is there a potential for the development of new drugs? J Ethnopharmacol. 2011;133(2):253-60.

56. Shin SH, Seo SG, Min S, et al. Caffeic acid phenethyl ester, a major component of propolis, suppresses high fat diet-induced obesity through inhibiting adipogenesis at the mitotic clonal expansion stage. J Agric Food Chem. 2014;62(19):4306-12.

57. Nishikawa S, Hyodo T, Aoyama H, et al. Artepillin C, a key component of Brazilian propolis, induces thermogenesis in inguinal white adipose tissue of mice through a creatine-metabolism-related thermogenic pathway. J Agric Food Chem. 2019;68(4):1007-14.

58. Koya-Miyata S, Arai N, Mizote A, et al. Propolis prevents diet-induced hyperlipidemia and mitigates weight gain in diet-induced obesity in mice. Biol Pharm Bull. 2009;32(12):2022-28.

59. Washio K, Shimamoto Y, Kitamura H. Brazilian propolis extract increases leptin expression in mouse adipocytes. Biomed Res. 2015;36(5):343-46.

60. Sakai T, Ohhata M, Fujii M, et al. Brazilian Green Propolis Promotes Weight Loss and Reduces Fat Accumulation in C57BL/6 Mice Fed A High-Fat Diet. Biol Pharm Bull. 2017;40(4):391-95.

61. Ichi I, Hori H, Takashima Y, et al. The beneficial effect of propolis on fat accumulation and lipid metabolism in rats fed a high-fat diet. J Food Sci. 2009;74(5):H127-H131.

62. Oršolić N, Landeka Jurčević I, Đikić D, et al. Effect of propolis on diet-ınduced hyperlipidemia and atherogenic ındices in mice. Antioxidants (Basel). 2019;8(6):156.

63. Cardinault N, Tourniaire F, Astier J, et al. Poplar propolis ethanolic extract reduces body weight gain and glucose metabolism disruption in high-fat diet-fed mice. Mol Nutr Food Res. 2020;64(18):e2000275.

64. Pai SA, Martis EA, Munshi RP, et al. Chrysin mitigated obesity by regulating energy intake and expenditure in rats. J Tradit Complement Med. 2019;10(6):577-85.

65. Gebaraa EC, Pustiglioni AN, de Lima LA, et al. Propolis extract as an adjuvant to periodontal treatment. Oral Health Prev Dent. 2003;1(1):29-35.

66. Alkis HE, Kuzhan A, Dirier A, et albur. Neuroprotective effects of propolis and caffeic acid phenethyl ester (CAPE) on the radiation-injured brain tissue (Neuroprotective effects of propolis and CAPE). Int J Radiat Res. 2015;13(4):297-303.

67. Kaya E, Izol E, Gurcay M, et al. Potential effects of propolis against coronaviruses. Turkish Journal of Nature and Science. 2021;10(2):303-11.

68. Cornara L, Biagi M, Xiao J, et al. Therapeutic properties of bioactive compounds from different honeybee products. Front Pharmacol. 2017;8:412.

69. Xuan H, Li Z, Yan H, et al. Antitumor activity of Chinese propolis in human breast cancer MCF-7 and MDA-MB-231 cells. Evid Based Complement Alternat Med. 2014;2014:280120.

70. Black RJ. Vulval eczema associated with propolis sensitization from topical therapies treated successfully with pimecrolimus cream. Clin Exp Dermatol. 2005;30(1):91-92.

71. Grange JM, Davey RW. Antibacterial properties of propolis (bee glue). J R Soc Med. 1990;83(3):159-60.

72. Di Minno A, Frigerio B, Spadarella G, et al. Old and new oral anticoagulants: Food, herbal medicines and drug ınteractions. Blood Rev. 2017;31(4):193-203.

73. Ngo TL, Lee CH, Han N, et al. Application of an ınter-species extrapolation method for the prediction of drug ınteractions between propolis and duloxetine in humans. Int J Mol Sci 2020;21(5):1862.

74. Hossain S, Yousaf M, Liu Y, et al. An overview of the evidence and mechanism of drug–herb ınteractions between propolis and pharmaceutical drugs. Front Pharmacol. 2022;13: 876183.

75. Patel S. Emerging adjuvant therapy for cancer: propolis and its constituents. J Diet Suppl. 2016;13(3):245-68.

76. Münstedt K, Männle H. Using bee products for the prevention and treatment of oral mucositis induced by cancer treatment. Molecules. 2019;24(17):3023.

77. Ryu CS, Oh SJ, Oh JM, et al. Inhibition of cytochrome P450 by propolis in human liver microsomes. Toxicol Res 2016;32(3):207-13.