The Antioxidant and Anti-Inflammatory Effects of Propolis in Type 2 Diabetes Mellitus.

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Abstract. Propolis, a resinous polyphenolic compound produced by bees, has been used for its medicinal properties since ancient times. This study explores the potential effects of propolis on type 2 diabetes mellitus (T2DM), a chronic condition marked by high blood glucose levels and insulin resistance. A systematic literature review assessed existing research on propolis and its impact on T2DM, focusing particularly on Brazilian green propolis. The findings suggest that propolis may modulate inflammation and control oxidative stress in T2DM patients, potentially improving insulin resistance and antioxidant activity. These properties can help mitigate oxidative stress, a key factor in the progression of diabetes and its complications, as well as reduce inflammatory markers. While direct effects on blood glucose levels may be limited, propolis shows promise as a complementary therapy for managing T2DM and its associated complications, such as cardiovascular and renal issues. The natural properties and minimal side effects of propolis make it an attractive adjunct treatment alongside conventional therapies, with potential benefits in controlling diabetes-related symptoms and improving quality of life. Further research is essential to strengthen the evidence for propolis's efficacy in managing T2DM and its complications. Larger sample sizes and placebo-controlled studies could provide more definitive insights into propolis's role in diabetes management, including understanding its impact on lipid profiles, insulin resistance, and other relevant parameters. Comparative studies on different types of propolis and their specific effects on diabetes would also help optimize its therapeutic potential. In conclusion, propolis represents a promising approach for enhancing the quality of life for T2DM patients and reducing the risk of diabetes-related complications. However, its use should be approached with caution and under medical supervision. More research is needed to confirm propolis's efficacy and establish standardized protocols for its use in diabetes management

Keywords. Propolis, Diabetes mellitus, Type 2 diabetes, Antioxidant, Anti-inflammatory, Oxidative stress, Insulin resistance, Brazilian green propolis.

1. Introduction

Bees play a fundamental role in pollination and in our ecosystem, producing important foods such as royal jelly and honey itself. A third product that has been studied and used since ancient times is propolis. Propolis (pro in defense and polis city) is a resinous polyphenolic compound, the result of botanical exudates and bee saliva, used to protect the hive against pathogens and temperature changes (1).

The compound's medicinal properties have been known for a long time. Hippocrates used a mixture of honey-based mixtures to treat fever, pain and wounds. It is also known that the Egyptians used propolis as an anti-petrifying agent to embalm corpses.

The composition of propolis can vary greatly from region to region, plant species, season, etc. One study showed that Brazilian propolis produced in March and April has differences in color, phenolic composition and antioxidant properties compared to propolis produced in May and June, which indicates that its composition can vary from month to month (2). According to the literature, propolis can contain more than 300 compounds from the polyphenol class, terpenes, steroids, sugars, amino acids and others (2). The three compounds most present in all propolis species are flavonoids, phenolic acids and terpenes. There are 12 main flavonoids responsible for the product's anti-radical properties: pinocembrin, acacetin, chrysin, rutin, catechin, naringenin, galangin, luteolin, kaempferol, apigenin, myricetin and quercetin (3). The antioxidant

properties are derived from phenolic compounds, especially in Brazilian propolis, which contains 3,4,5-tricaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, and artepillin C (2). Finally, terpenes are responsible for the smell of each type and are considered an important criterion in differentiating each one (3). Other compounds present in propolis include volatile and aromatic oils, waxes, resins, pollen, minerals, vitamins and biometabolites (3). Some enzymes have also been detected in the composition of propolis, such as succinic dehydrogenase, glucose-6-phosphate, adenosine triphosphate and acid phosphate (3).
There is a wide variety of propolis spread all over the world. In temperate zones (Europe, North America, continental Australia and non-tropic regions of Asia) we have propolis derived from Populus spp. and P. nigra L, the main active compounds being flavones, flavonones, cinnamic acid and esters (2). Birch propolis is found in Russia and contains flavones and flavonols (different from poplar propolis), originating from Betula verrucosa Ehrh (2). Mediterranean propolis (Greece, Silicy, Malta, Cyprus, Croatia and Algeria), characterized by large quantities of diterpenes, comes from the Cupressus sempervirens plant (2). In Brazil, we have 13 different types of propolis, but the most commonly used are red, brown and green. Green, the most famous and studied, is rich in phenylpropanoids, such as artepilin C, and diterpenes, found in Baccharis dracunculifolia (2). Red, on the other hand, has various flavonoids and is found in D. ecastaphyllum (2).
In addition to regional differences, the composition can also vary depending on the extraction of the propolis and its solvents. As most of the compounds in the product are lipophilic, the most common solvent used is ethanol (concentration between 70-75%), which maintains the salutogenic properties better than water and other solvents (2). However, the types with the most hydrophilic compounds are best extracted in aqueous solvents.
Although the main action of propolis is antioxidant, it can also have other salutogenic properties depending on the type, such as antiseptic, antimicrobial, anti-inflammatory and antipyretic (4). In this article, the influence of propolis on Diabetes Mellitus was studied.
Diabetes Mellitus is one of today's major chronic diseases, characterized by high blood glucose levels and insufficiency in the production or action of the hormone insulin, produced by the pancreas (5). There are 4 types of Diabetes Mellitus: type 1, type 2, gestational and idiopathic, the main ones being type 1 and type 2 (6). Type 1, insulin-dependent diabetes, is known as insulin deficiency, i.e. the patient's immune system destroys the beta-cells in the pancreas that produce the hormone, leading to the disease. In this case, the patient is born with this disorder (6).
Type 2 diabetes, non-insulin dependent, is marked by a defect in insulin secretion or insulin resistance, in other words, the patient produces the hormone, but it is not used. In this situation, the person can acquire diabetes due to genetic defects, environmental factors and, above all, obesity (6). Both types of diabetes can lead to a series of complications, which can lead to death. People with this disease can have acute metabolic complications such as hypoglycemia, ketoacidosis and hyperosmolar non-ketonic coma (6). There are also long-term complications such as diabetic nephropathy, microangiopathy, diabetic neuro- and retinopathy, atherosclerosis and infections (6).
One of the main effects of diabetes is the increase in free radicals in the tissues, which cause a lot of damage to the body. The article aims to understand more about the effects of propolis with antioxidant action on free radicals in type 2 Diabetes Mellitus

2. Research Methology

A systematic literature review was conducted to select and analyze relevant articles on the topic. Searches were conducted in databases using keywords related to the study.
The selection of articles began with an analysis of titles and abstracts, followed by a review of the full text to verify their relevance to the study. The quality of the articles was evaluated based on criteria of relevance, credibility, and date of publication.
Relevant data were extracted and organized for qualitative analysis and, when applicable, quantitative analysis, identifying themes and trends in the literature.

3. Discussion

According to 2020 data, 9.3% of adults aged 20 to 79 worldwide live with diabetes, and there are 1.1 million children and adolescents under the age of 20 who have type 1 diabetes (7). While in rural areas the percentage is less than 7.2%, in urban environments it is estimated that the prevalence of type 2 diabetes is almost 11% (7). In addition to the numerous problems mentioned earlier, two of the most severe and concerning issues are the release of free radicals and chronic inflammation (6).

Free radicals have a high number of unpaired electrons, leading to the oxidation of important cellular components such as proteins and organelles (6). There are three types of reactive species: reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive chlorine species (RCS); all three are the main causes of oxidative stress in cells (6). Oxidative stress is defined as a disturbance in the balance of antioxidants and pro-oxidants inside and outside the cell and can be caused by various factors such as aging, toxicity, drug reactions, and inflammation (6).

The main source of oxidative stress in diabetes mellitus is the mitochondria (6). In the normal metabolism of the mitochondria, one component of the oxygen used is reduced to water, and the rest is converted into oxygen free radicals (ROS), which can be transformed into other reactive types (6). Insulin signaling is modulated by the production of ROS/RNS in two ways: it plays a positive role in the physiological functioning of the body and a negative role in regulating the signal, making the body develop insulin resistance (6). Hence, in individuals with diabetes, especially type 2, the production of free radicals is a major problem.

Another source believed to cause oxidative stress in patients with diabetes mellitus is the increase or decrease in the production of enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), which are responsible for destroying pro-oxidants (8). The tissue becomes susceptible to oxidative stress when the levels of these enzymes are altered. According to the literature, changes in the production of CAT cause the pancreatic beta cells, which have a large number of mitochondria, to become more susceptible to oxidative stress, worsening the individual's diabetes condition (6). Patients who have the disease, mainly type 2 diabetes, exhibit more lipids and fats than healthy individuals, and free radicals make the body more susceptible to lipid peroxidation, leading to a series of complications, such as the formation of highly reactive toxic lipid radicals (6).

There are various reasons why patients with diabetes develop chronic inflammations; some examples include the accumulation of adipose tissue, which is responsible for producing inflammatory mediators, and the accumulation of glucose in the vessels, which can lead to a series of complications such as high blood pressure, changes in blood viscosity, and atherosclerosis (9). Changes in blood viscosity prevent immune system cells from moving properly, reducing their activity, which further stimulates the release of inflammatory cytokines (9). Oxidative stress itself also leads to inflammation. Therefore, uncontrolled production of ROS/RNS and chronic inflammation worsens the situation of patients with this disease and should be combated or prevented through some form of therapy.

Two of the main effects of propolis are its anti-inflammatory and antioxidant properties. The anti-inflammatory action is promoted by the flavonoids in propolis; they facilitate the inhibition of the activation of NF-kB, preventing the phosphorylation of p38 mitogen-activated protein kinases and c-junNH-terminal kinase (1). It was found that chrysin, a compound in propolis, mediates the inflammatory process, reducing the expression of TNF and also inactivating NK-kB pathways (1). Moreover, other compounds in propolis reduce the expression of inflammatory cytokines, inhibiting some extracellular signaling pathways, such as NF-kB. In Brazilian green propolis, the components baccharin, artepilin C, and kaempferide are primarily responsible for the anti-inflammatory action; they also stimulate the release of anti-inflammatory factors, such as luminal mucin, a mucosal protective agent, and cytokines (4).

The second action, the antioxidant effect, is even more significant and well-known. It has already been confirmed to decrease levels of malonaldehyde (MDA) and promote the release of antioxidant enzymes in animals' models (10). By inhibiting the release of MDA, the mitochondria can reestablish respiratory control, reducing the release of free radicals (10). It has been proven that compounds such as galangin and pinocembrin, phenolic compounds, have the ability to pair the electrons of free radicals again, donating hydrogen ions and also reducing lipid peroxidation (1).

Regarding the use of propolis as a preventive measure for some effects of diabetes, there are some theories and studies. Based on the literature, the plasma concentration of inflammatory mediators such as TNF-alpha and interleukin-6 is increased in patients with type 2 diabetes (10), so a decrease in the expression of TNF and oxidative species would lead to a decrease in blood glucose levels, which some compounds in propolis are capable of doing.

A study conducted in Japan (10) examined the effect of Brazilian green propolis on 80 patients aged 35-80 with type 2 diabetes, with half taking a placebo. Propolis was administered at 226.8 mg/day for 8 weeks to assess effects such as changes in blood tests, including the homeostasis model assessment of insulin resistance (HOMAR-IR), uric acid, and the estimated glomerular filtration rate (eGFR) from baseline. It was concluded that the HOMAR-IR value did not change from the placebo group to the group taking propolis; the levels of uric acid and eGFR in the blood worsened in patients taking the placebo, which did not occur in those taking propolis. Therefore, there was no significant change in insulin levels with the administered dose, but they proved that propolis can be used to prevent hyperuricemia and renal glomerular filtration dysfunction in patients with type 2 diabetes mellitus.

Another study conducted in China (8) involved 65 patients with type 2 diabetes, with half serving as the control group and the other half taking 900 mg/day of Brazilian green propolis for 18 weeks. They concluded that the administered dose did not significantly interfere with blood glucose levels, glycosylated hemoglobin, insulin, aldose reductase, and adiponectin. However, the amount of GSH and total polyphenols increased, and the activity of carbonyls and lactate dehydrogenase was reduced in the group taking propolis. The levels of TNF-alpha were also reduced. In other words, the administered dose promoted antioxidant activity in patients with type 2 diabetes; however, there were some limitations in the research, such as the lack of a placebo for the control group and the levels of ascorbic acid, tocopherol, and other antioxidants not being measured. The ascorbic acid levels were lower in the group taking propolis than in the control group, which may have affected the antioxidant and anti-inflammatory effects.

Finally, a study conducted in Iran (11) gathered 62 patients with type 2 diabetes, half taking a placebo and the other half taking 500 mg three times a day, or 1,500 mg/day for 8 weeks. At the end of the experiment, the levels of FBS, 2-hp, insulin, IR, and HbA1C were significantly reduced in patients treated with propolis compared to those taking the placebo. Propolis also increased blood levels of TAC and the activity of GPx and SOD. Therefore, the authors concluded that the administered dose can be useful for patients with type 2 diabetes to decrease insulin resistance, resulting in lower blood glucose levels and improvement in antioxidant status.

None of the studies cited reported adverse effects.

4. Conclusion

In conclusion, the literature points to significant potential for propolis, particularly Brazilian green propolis, in modulating inflammatory processes and controlling oxidative stress in patients with type 2 diabetes mellitus. Studies show that although the direct effects of propolis on blood glucose levels may be limited, there is evidence that propolis can improve insulin resistance and reduce the presence of inflammatory markers, as well as increase antioxidant activity.

Despite these promising results, there is still a need for more research to better understand the mechanisms by which propolis exerts its beneficial effects in diabetes patients. Studies with larger sample sizes and placebo control are essential to strengthen the evidence regarding the role of propolis in diabetes treatment. Furthermore, future research can evaluate the efficacy of different types of propolis and their respective concentrations in treatments, as well as interactions with other therapies.

Therefore, propolis represents a promising approach to complement conventional treatments for type 2 diabetes but should be used with caution and under medical supervision. Further exploration of its effects may provide valuable insights to improve the quality of life for diabetes patients and reduce complications associated with the disease.

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