Propolis

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The use of alternative medicine products has increased tremendously in recent decades and it is estimated that approximately 80% of patients globally depend on them for some part of their primary health care. Propolis is a beekeeping product widely used in alternative medicine. It is a natural resinous product that bees collect from various plants and mix with beeswax and salivary enzymes and comprises a complex mixture of compounds. Various biomedical properties of propolis have been studied and reported in infectious and non-infectious diseases. However, the pharmacological activity and chemical composition of propolis is highly variable depending on its geographical origin, so it is important to describe and study the biomedical properties of propolis from different geographic regions. A number of chronic diseases, such as diabetes, obesity, and cancer, are the leading causes of global mortality, generating significant economic losses in many countries.

Keywords: propolis ; diabetes ; obesity ; cancer ; chemical composition ; bioactive compounds

1. Introduction

Definition and History

The term propolis is derived from two Greek words, pro (which means for or in defense of) and polis (which means the city); thus, propolis means in defense of the city or beehive [1]. Propolis is a natural, complex resinous mixture produced by honeybees by mixing products collected in tree buds, plants, saps, resins, and other plant sources [2], with beeswax and salivary enzymes (?-glucosidase) [3]. Propolis is either a hard and breakable resin when it is cold, or soft, flexible, and very sticky when it is warm; it possesses different colorations, including brown, green, and red [3][4]. The bees use the propolis to cover surfaces, seal holes and close gaps, maintaining moisture and temperature stable in the hive throughout the year, and thus providing a sterile environment that protects them from microbes and spore-producing organisms, including fungi and molds [5]. In addition, bees use propolis as an embalming substance to mummify invaders, such as other insects, that have been killed and are too heavy to remove from the colony [5][6]. It is therefore considered to be a potent chemical defense against bacteria, viruses, and other pathogenic microorganisms that may invade the bee colony [7].

The ancient Greeks, Romans, and Egyptians were the first to use propolis, with applications in wound healing and as a disinfectant substance, and it is believed to have been in use since 300 BC [1][8][9]. Many other ancient civilizations, such as Chinese, Indian, and Arabian cultures, also used propolis to treat medical conditions such as skin lesions [10]. A large number of reports have been published showing numerous applications of propolis in treating various diseases due to its antibacterial, antifungal, antiparasitic, antiviral, antioxidant, anti-inflammatory, antitumor, and immunomodulatory properties, among others [11][12][13][14][15][16][17][18].

2. Chemical Composition of Propolis

To date, numerous studies have been published regarding the chemical composition and biological effects of propolis. Nevertheless, analysis of a large number of samples from different geographic regions has shown that its chemical composition is highly variable and difficult to establish because it depends on factors such as the vegetation and season at the collection site [6][19] and the bees species [20]. Propolis is generally composed of 50% resin, 30% wax, 10% essential oils, 5% pollen, and 5% other substances, which include minerals and organic compounds [6]. In addition, propolis samples from various regions of the world have been reported to contain over 300 different chemical compounds [21].

Using high throughput methods, such as mass spectroscopy, nuclear magnetic resonance, and gas chromatography coupled to mass spectrometry, it has been possible to identify several families of chemically active compounds. The main chemical groups present in propolis comprise phenolic acids or their esters, flavonoids, terpenes, aromatic aldehydes and alcohols, fatty acids, stilbenes, and ?-steroids [21][22]. Additionally, propolis contains minerals such as magnesium, calcium, iodine, potassium, sodium, copper, zinc, manganese, and iron; vitamins such as B1, B2, B6, C, E, and D, in addition to provitamin A; a few fatty acids; and enzymes derived from bee glandular secretion or possibly pollen, such as succinic dehydrogenase, adenosine triphosphatase, glucose-6-phosphatase, acid phosphatase, ?-amylase, ?-amylase, ?-lactamase, ?-lactamase, maltase, esterase, and transhydrogenase. Polysaccharides such as starch and the di- and monosacharaides glucose, fructose, ribose, rhamnose, talose, gulose, and saccharose are also commonly present in propolis [23][24].

Flavonoids have been reported to be the main compounds of propolis, including flavones (luteolin), flavonols (quercetins and derivatives), flavanones (pinocembrin and naringenin), flavanonols (garbanzol and alnustinol), chalcones and dihydrochalcones, isoflavones (calycosin), isodihydroflavones (daidzein), flavans, isoflavans (vestitol and derivatives), and neoflavonoids (homopterocarpin and medicarpin) [25]. Terpenoids, which represent only 10% of the content, are responsible for the odor of propolis because they are volatile components of plants, and also contribute to its biological properties. Terpenoids include monoterpenes (terpineol, camphor), diterpenes (the main groups, such as ferruginol, junicedric acid and derivatives, pimaric acid, and totarolone), triterpenes (such as lupeol and derivatives, lanosterol, and amyrone and derivatives), and sesquiterpenes (such γ-elemene, valencene, ?-ylangene, and ?-bisabolol). Phenolic compounds include various acids such as cinnamic, *p*-coumaric, chicoric, caffeic, and fulric acids [25].

The general composition of propolis described above is known to depend on the collection area. It has been reported that propolis samples from Europe, North America, and other temperate zones are mainly composed of flavonoids (pinocembrin, pinobanksin, quercetin, chrysin, and galangin), and phenolic acids and their esters [26].

3. Biomedical Properties of Propolis on Diabetes, Obesity, and Cancer

3.1. Effect of Propolis on Diabetes

Diabetes mellitus is a heterogeneous and chronic disease, characterized by hyperglycemia caused by an absolute or relative deficiency in insulin secretion or action, resulting in impaired function in carbohydrate, lipid, and protein metabolism [27][28]. Dyslipidemia is also a common feature of diabetes, and is characterized by elevated triglyceride and low-density lipoprotein cholesterol (LDL-C) levels [29]. Hyperglycemia and dyslipidemia easily induce extensive oxidative stress, which causes serious cellular dysfunction [30][31]. In addition, persistent hyperglycemia increases the production of reactive oxygen species (ROS) in several tissues [32] and also diminishes biological antioxidative mechanisms by glycation of the scavenging enzymes [33]. Thus, effective control of hyperglycemia in diabetic patients is critical for reducing the risk of micro- and macrovascular complications [34]. In this context, the prevalence of diagnosed diabetes is dramatically increasing and has become a major concern globally [35]. According to Saeedi et al. the International Diabetes Federation reported that the prevalence of diabetes was estimated to be 463 million in 2019, and is projected to reach 463 million by 2030 and 700 million by 2045 [36]. Thus, alternative therapies based on natural sources with antihyperglycemic properties, such as propolis, could play an important role in the management of diabetes, delaying the development of diabetic complications, and correcting metabolic abnormalities.

Numerous studies have shown that treatment with propolis decreases the glucose levels in the blood. Alloxan-induced hyperglycemia in Wistar rats treated with Nigerian propolis (300 mg/kg) orally for 28 days decreased fasting blood glucose level in a manner similar to that in a group treated with metformin. Furthermore, the serum malondialdehyde (MDA) level was reduced and superoxide dismutase (SOD) levels were elevated in the propolis group. Histologically, improvement was evident in the pancreas and liver of the group treated with propolis. These findings suggest that Nigerian propolis confers protection against hyperglycemia-induced oxidative stress in both the liver and pancreas of Wistar rats [37]. Similarly, other investigations have reported that oral administration of Nigerian propolis (200 mg of propolis/mL of Tween 80) for 42 days in diabetic rats induced by alloxan, decreases the fasting blood glucose level at two weeks, and partially decreases glycated hemoglobin A1c (HbA1c) at six weeks of treatment. Moreover, Nigerian propolis treatment increased serum high-density lipoprotein (HDL), and reduced serum very low-density lipoprotein (VLDL) and cholesterol levels. The study concluded that Nigerian propolis contains compounds exhibiting hypoglycemic, antihyperlipidemic, and HbA1c-reducing activities [38]. Although studies on diabetes animals models induced with alloxan are not the most reliable in terms of the similarity of the damage process of this disease, they provide initial insights into whether propolis shows any activity on diabetes; however, it is necessary corroborate the results with a model that better resembles the course of diabetes, such as streptozotocin-induced animal models. We agree Jain et al. (2011) and Misra et al. (2012), who reported that alloxan shows doubtful potential as a drug regarding the induction of experimental diabetes. This, however, is contradictory to many studies where alloxan has been successfully used [39][40]. Another limitation of these works is the absence of the chemical composition; as we have already mentioned, this is essential for the correct pharmaceutical and medical application of propolis [41].

3.2. Effect of Propolis on Obesity

Obesity is a significant public health threat because it is associated with increased incidences of cancer, type 2 diabetes, dyslipidemia, cardiovascular diseases, among other pathologies [42][43]. The global prevalence of obesity has reached epidemic proportions, with an estimated 671 million people suffering from obesity in 2016 [44]. Furthermore, obesity is the fifth leading cause of death globally [42]. A long-term high-fat or unbalanced diet contributes to obesity [45][46]. To increase adipose tissue mass, adipocytes undergo hypertrophy (an increase in size) and hyperplasia (an increase in number). Large lipid-laden adipocytes in hypertrophic tissue secrete several mediators that trigger metabolic dysfunction [47]. In parallel with adipocyte hypertrophy, the infiltration of immune cells, such as macrophages, into adipose tissue is frequent, causing mild inflammation in the adipose tissue [48][49] and increasing circulating levels of adipokines, fatty acid mediators (lipokines), and miRNA-containing exosomes, which affect energy metabolism in the liver and skeletal muscle [50][51][52]. In addition, chronically obese individuals acquire leptin resistance and show deterioration of energy metabolism [53]. Thus, the search for natural alternatives, such as propolis, that can help in the treatment of obesity for the management of weight gain, lipid metabolism regulation, and consequent pathological complications induced by obesity, is now of utmost importance.

Although little research exists relating to the effect of propolis on obesity, Brazilian red propolis treatment (0–100 µg/mL) for three days has been found to induce adiponectin mRNA in 3T3-L1 preadipocytes, probably through activation of the adiponectin promoter by peroxisome proliferator-activated receptor γ (PPAR-γ). In addition, in the same study, propolis treatment for eight days restored adiponectin expression in TNF-α-treated, differentiated 3T3-L1 cells, suggesting the value of Brazilian red propolis as a diet supplement for prevention and treatment of obesity and obesity-associated disorders [54]. Similarly, an in vitro assay using differentiated 3T3-L1 adipocytes showed that Brazilian green propolis (100 µg/mL) directly elevated leptin expression [55]. Although in vitro studies have helped provide an overview of the activity of propolis on obesity, most only evaluate only a chemical or molecular aspect, so its effect is still partial. The studies did not consider that this disease is multifactorial; therefore, in vivo studies are essential to reach clinical trials [56][57].

3.3. Effect of Propolis on Cancer

Cancer is characterized by aberrant cell cycle activity. This occurs either as a result of mutations in upstream signaling pathways or by genetic lesions within genes encoding cell cycle proteins [58]. Cancer is an important cause of morbidity and mortality globally, with variation across countries and states. Among males, lung cancer is the leading cause of cancer death, followed by liver and stomach cancer. Among females, breast cancer is the leading cause of cancer death, followed by lung, colorectal, and cervical cancer [59]. In addition to current cancer treatments, such as surgery and chemotherapy, combination therapies exist. However, in several cases, these therapies have led to a significant increase in adverse effects and may thus not be tolerated by many patients [58]. Thus, the innumerable applications of natural products offer considerable opportunities for the improvement of human well-being and health. As such, propolis and some of its active compounds could have potential in the development of drugs that can act as complementary therapeutic agents in cancer treatments.

Antitumoral effects of propolis on cancer cells have been described in a number of studies. Diverse research has reported that propolis from distinct countries (Brazil 50 µg/mL; Mexico 15–500 µg/mL; and Thailand 0–1 mg/mL) presents antitumor activity in different tumor cell lines (human ovarian cancer cells, OVCAR-8; human colon cancer cells, HCT-116; human promyelocytic leukemia cells, HL-60; human glioblastoma cells, SF-295; human cervical cancer cells, HeLa, SiHa, and CaSki; human adenocarcinomic alveolar basal epithelial cells, A549) [60][61][62]. Notably, that these studies report the evaluation of various biomedical activities of different extracts of propolis, so the reported evidence is limited to a cytotoxic approach; therefore, we consider is necessary to include controls with non-malignant cells to determine if the effect is selective for cancer cells. However, only one of the reports described the chemical composition, providing a basis for discussion. The description of the chemical composition is relevant for some authors since they mention that the systematic classification of propolis will be impossible without it [6].

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