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Harnessing honey's nutraceutical potential for oral health

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ABSTRACT: Honey is one of the oldest natural compounds that come from ancient times to nowadays with health benefits. It has been used for the treatment of several diseases, but its role in oral health faces real skepticism due to the high concentration of carbohydrates in its composition. Many studies over the years have confirmed several pharmacological activities such as antioxidant, antibacterial, antihistaminic, etc. It is composed of different chemical compounds like carbohydrates, proteins, amino acids, vitamins, minerals, organic acids, phenolic compounds, and volatile substances. Honey contains many enzymes such as invertase, catalase, glucose oxidase, and acid phosphorylase, as well as traces of vitamins B_2, B_4, B_5, B_6, B_{11}, and vitamin C, minerals such as calcium, iron, zinc, potassium, magnesium. A promising challenge is the use of honey as a targeting product obtained from green synthesis, with high-efficiency thanks to nanotechnology. This study aims to investigate the potential benefits of honey in oral health, leveraging its diverse biological activity like antimicrobial, and antioxidant effects. Additionally, our scope was to provide scientific evidence supporting the use of honey in dentistry, emphasizing its broader health benefits and novel applications in oral health care.

KEYWORDS: Honey; biological activity; oral health; dental caries; periodontitis.

1. INTRODUCTION

Dental tissues are the strongest tissues in the human body and yet vulnerable to the cariogenic process. Dental caries is the most prevalent among oral diseases, which altogether affect about 3.5 billion people around the world, accounting for a global prevalence of 45%, higher than any other non-communicable disease [1-3]. Dental caries is a complex process involving oral microbiota, and other factors such as salivary, dietary, genetic, anatomic, and physiologic ones. This process initially causes demineralization of hard tissues, which under unchanged conditions leads to enamel and dentin destruction resulting in cavities [4-6]. The infectious nature of the carious disease is extensively documented in the literature. Oral microbiota is colonized by more than 700 species of microorganisms, and understanding their role in the initiation and propagation of dental caries is crucial [5, 7, 8]. In vitro and clinical studies have shown that species like *Streptococcus mutans*, *Streptococcus sobrinus,* and *lactobacilli* are consistently associated with dental decay, and levels of *Streptococcus mutans* from salivary samples are usually used as predictors or to monitor caries risk in patients [9]. *Lactobacillus* species were only detected in dentin caries, and a higher abundance of *Prevotella* was found deep in the dentin [10]. According to Richards et al. four species (*Streptococcus mutans*, *Scardovia wiggsiae*, *Parascardovia denticolens*, and *Lactobacillus salivarius*) exclusively exist in dentine caries [11]. It has been determined that *Streptococcus mutans* is the primary cariogenic bacteria responsible for the onset of caries, whereas *Streptococcus sobrinus* may be involved in the progression and development of carious lesions. However, there is increasing evidence that besides traditional caries-associated species (*Streptococcus mutans and lactobacillus* species), *Actinomyces*, *Bifidobacterium*, and other Gram-positive rod species play also important roles in dental caries, as well as fungi such as *Candida Albicans* [7, 12, 13]. Species such as *Lactobacillus* and *Bifidobacteria* were reported to be strongly related to caries progression, meanwhile, other species of these two

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genera were demonstrated to be effective probiotics in the context of caries prevention [11], proving that different species of the same genus may play opposite roles in the caries development process [12].

Although specific bacterial species are responsible for dental caries, they alone cannot cause tissue destruction. There has been strong evidence of the role of dietary substrates for microbial acid production as etiological factors in dental decay. Dental caries is considered a dietary-microbial disease, which cannot occur in the absence of pathogenic dental biofilm and frequent exposure to dietary carbohydrates, mostly in the form of free sugars [5, 14, 15]. Fermentable carbohydrates (monosaccharides and disaccharides) provided by the diet are metabolized to acids by plaque bacteria which leads to low pH and growth of acidogenic and aciduric bacteria. These species of resident flora gain a selective ecological advantage over other species which disrupts the homeostatic balance of the plaque biofilm [16, 17]. When pH levels drop under 5.5 within the dental plaque, calcium and phosphate ions are removed from the enamel surface starting the demineralization process and initiation of dental caries. However, this has been demonstrated to be a reversible process until a certain point, where saliva, fluoride therapy, diet control, and probiotic bacteria play an important role in remineralization arresting the evolution of the disease [18, 19]. Considering the multitude of factors involved in dental caries, from microbial to dietary, host, behavioral, and biological ones, efficient preventive therapies should take into consideration all of them. Traditional prevention interventions include mechanical removal of dental plaque aiming for the reduction of the cariogenic flora and the remineralization of dental surfaces through the application of fluoride. Later treatment options aim at rebalancing the dysbiotic caries microbiome with a particular focus on either *Streptococcus mutans* alone or the acidogenic/acid-tolerant bacteria to re-establish a symbiotic healthy microbiome [8, 20-23]. Diet control through limiting sugar intake is considered a priority among the strategies in caries prevention, because initial carious lesions may be arrested by dietary interventions. Apart from sugar restrictions, other dietary interventions to prevent caries include sugar substitutes and the recommendation of functional foods and probiotics [4]. There are an increasing number of studies in the last few years that are evaluating the potential antimicrobial, antifungal, and antiviral properties of natural foods involved in oral diseases, especially dental caries, periodontitis, and induced oral mucositis in patients with head and neck cancers [23-26].

Honey has been used for a long time in various oral procedures and is now supported by scientific evidence for its preventive and curative effects on common oral diseases such as dental caries and periodontitis, as well as their microbial etiologic factors including *Streptococcus mutans* and dental plaque. This study aims to investigate the potential benefits of honey in oral health, leveraging its diverse pharmacological properties such as antimicrobial, and antioxidant effects against oral pathogens, for oral health maintenance and disease prevention. Additionally, our scope was to provide scientific evidence supporting the use of honey in oral health, addressing skepticism related to its carbohydrate content by emphasizing its broader health benefits and novel applications in oral health care.

1.1. Honey as a Nutraceutical

Food represents products consisting of different nutrients such as carbohydrates, proteins, and fats, necessary to sustain growth and development, energy, and vital processes, providing nutrition. Besides essential nutrients, some products, also known as functional foods, can contain other substances that have positive effects on health "beyond basic nutrition" called nutraceuticals. De Felice considers nutraceuticals 'a food or part of a food, such as a dietary supplement, that has a medical or health benefit, including the prevention and treatment of disease'. They are biologically active molecules coming from food with intermediate characteristics between food and drugs. They can be identified as nutrients, probiotics, prebiotics, phytochemicals, herbals, vitamins, dietary fiber, and enzymes [27-29].

A natural product of great interest is honey, very long and well-known for its nutritional and curative properties. Honey is the only insect-derived natural product with nutritional, cosmetic, therapeutic, and industrial values. Honey's medicinal properties come from flowers, whose nectar is digested by honeybees through their upper digestive tract, to produce this marvelous viscous and sweet substance. Its composition, properties, and pharmacological and pharmacokinetic effects will be reviewed in this study with emphasis on the beneficial effects on oral health and common oral diseases [30-32]. Later in the article, we will discuss honey as a novel drug target for use in dentistry, explore new clinical protocols for drug formulations based on honey, and address the challenges associated with these developments.

Honey is one of the oldest natural compounds since ancient times with available values, not only as a food but also as a medicine. In old medicine Ayurveda, there are many types of honey prescribed, from the

region with respective galenic formulations. The quality of honey as a bee product is related to the plants that bees use for production. Many studies over the years have confirmed a lot of pharmacological activities such as antioxidant, antibacterial, antihistaminic, dietary, etc. Honey contains a variety of more than 180 compounds, which include carbohydrates, proteins, amino acids, vitamins, minerals, organic acids, phenolic compounds, and volatile substances. Several enzymes can also be found such as invertase, catalase, glucose oxidase, and acid phosphorylase. Honey also contains eighteen free amino acids, most of which are proline. It contains many traces of vitamins like B_2, B_4, B_5, B_6, B_{11} and vitamin C, minerals such as calcium, iron, zinc, potassium, phosphorus, magnesium, selenium, chromium, and manganese (Table 1) which vary according to geographic region, soil type and local flora [33-37]. Carbohydrates represent 95% of its dry weight: approximately a total of 26 sugars (mono- and disaccharides) have been identified in honey with fructose (~ 40%) and glucose (~ 30%) as major sugars [38-41]. Honey contains proteins (roughly 0.5%), mainly enzymes and free amino acids listed in Table 2. Classical amino acids are: beta-alanine, alpha-alanine, gamma-aminobutyric acid (GABA), and ornithine (Orn) [42-46].

Table 1. Some key minerals and vitamins found in honey.

Minerals [47-51]	**Vitamins** [47-51]
Calcium (mg) 4.4 - 9.20	Ascorbic Acid (C) (mg) 2.2 - 2.4
Potassium (mg) 13.2 - 16.8	Thiamin (mg) < 0.006
Copper (mg) 0.003 - 0.10	Riboflavin (mg) < 0.06
Iron (mg) 0.06 - 1.5	Niacin (mg) < 0.36
Magnesium (mg) 1.2 - 3.50	Pantothenic acid (mg) < 0.11
Manganese (mg) 0.02 - 0.4	Pyridoxine (B6) (mg) < 0.32 mg
Phosphorus (mg) 1.9 - 6.30	
Zinc (mg) 0.03 - 0.4	
Se (mg) (trace element)	

Table 2. Enzymes present in honey.

Enzymes	**Properties**
Invertase	- splits sucrose releasing its simple constituents. - remains in honey and retains its activity for some time, completing its activity when honey is ripened. - represents an equilibrium between splitting and forming sucrose, when measuring the maturity and quality of honey [52-56].
Diastase or Amylase Alpha-Amylase Beta-Amylase Glucose Oxidase (GOX)	- digests starch to simpler compounds. Alpha-amylase breaks down starch chains, producing dextrin and beta-amylase which divides the reducing sugar maltose from the terminal starch chains. - is used as an important indicator of honey quality: the higher the content of this enzyme, the higher the quality of honey. - *Glucose oxidase* (GOX) is related to honey's antibacterial properties [52-56].
Catalase Acid phosphatase	- prevents honey from oxidation. - catalyzes the hydrolysis of phosphate esters in an acidic environment [52-56].

1.1.1. Honey: Insight into Polyphenolic Compounds

Honey is well known for its health benefits also in dentistry. The pharmacological effects of honey are related to the chemical compositions like phenolic compounds. These phenolic compounds have contributed by evaluating the absorption and metabolism, as a part of pharmacokinetics, pharmacodynamics,

and metabolism. There is not a clear process of absorption, metabolism, and excretion valid for all phenolic compounds [57], but there are studies that have been performed both in vitro and in vivo to try to understand the mechanisms behind the bioavailability of these compounds [58]. Schramm et al. showed that the total amount of polyphenols after honey ingestion in plasma was a minimal quantity compared to that present in honey, demonstrating a very low bioavailability and absorption [59]. The process of metabolism is related also to Phenol metabolism when the first phase of flavonoid metabolism concerns the hydrolysis reaction that can be performed both by bacterial enzymes present in the intestine and by two kinds of enzymes present in the small intestine. The β-hydrolysis of the sugar in the glycosylated flavonoids can be catalyzed by two β-endoglycosidases: the lactase phlorizin hydrolase (LPH) and the cytosolic β-glucosidase (CBG) [60]. Gee et al. in their study found that LPH in the brush border of the enterocytes catalyzes the hydrolytic reaction. Aglycon released can enter more easily to the epithelial cells, due to increased lipophilicity. When the hydrolysis reaction is catalyzed by CBG, the polar glucosides are transported inside the epithelial cells through a sodium-dependent glucose transporter 1 (SGLT1), where they are hydrolyzed [60]. The flavonoids enter the second phase of the metabolism, upon being absorbed by the intestinal epithelium and before arriving inside the bloodstream, which leads to the formation of different conjugated products: in particular, sulfotransferases (SULTs) generate sulfates, uridine-5′-diphosphate glucuronosyltransferases (UGTs) allows the formation of glucoronides, the catechol-*O*-methyltransferases (COMTs) produce methylated derivatives. These metabolic biotransformations that affect the absorption, bioavailability, and distribution of flavonoids at the cellular and tissue levels are also mediated by some proteins that are associated with multi-resistance (MRP1, MRP2), which are part of the third phase of the metabolism of flavonoids [61]. MRP2 is located in the apical membrane of the epithelial cells of the small intestine, and it transports flavonoids back into the intestinal lumen. MRP1 is located in the vascular pole of the enterocytes and promotes the transport of flavonoids inside the blood cells [62]. Also, MRP3 and the glucose transporter (GLUT2) aid in the transport of these compounds in the portal venous system; once they enter the latter, the metabolites quickly reach the hepatocytes, where the aglycones are transferred in the peroxisomes and in the Golgi apparatus, where they are subjected to further metabolic processes [63, 64]. The flavonoids of honey are presented in Figure 1.

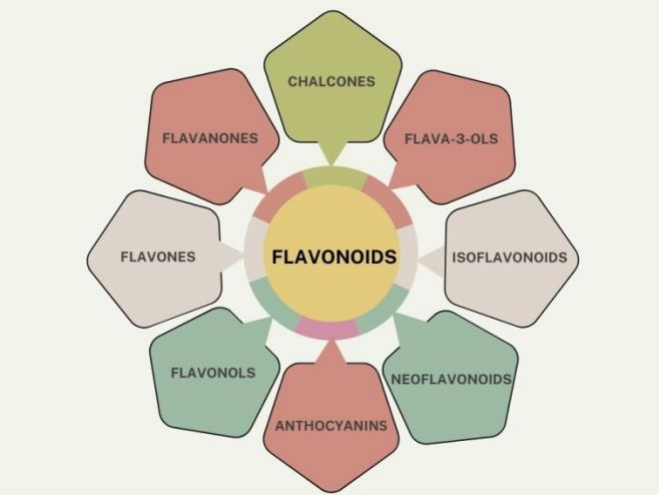

Figure 1. Flavonoids in honey

Phenolic compounds are phytochemicals of honey and are mainly present in honey but their qualities are dependent on honey origin [57-63], and therefore, expected to have different biological activities and huge biological potentialities in humans [64, 65]. The major class of phenolic compounds in honey is represented by flavonoids, a chemical group involving a structure with a molecule with three rings made up of a total of 15 carbon atoms. The carbons of the propane molecule (a three-carbon chain) connect two phenyl rings (a type of aromatic ring structure) to form a closed pyran ring. One of the benzene rings (a six-carbon aromatic ring) is part of this closed pyran ring, resulting in a structure with 15 carbon atoms arranged in three rings. These rings are labeled as A, B, and C (Table 3).

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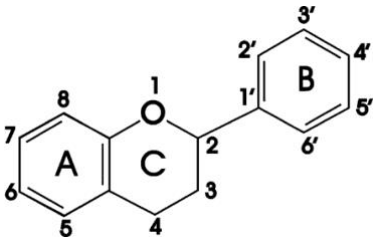
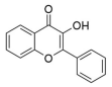
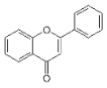
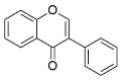
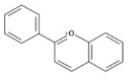
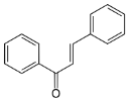
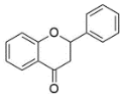
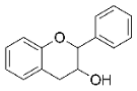
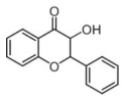
Table 3. Flavonoids in honey

	Flavonoids' type	Chemical stucture
Flavonoids 	***Flavonols:*** Morin , Quercetin Myricetin, Kaempferol Fisetin , Rutin	
	Flavones: Apigenin, Luteolin, Diosmetin, Chrysin Acacetin, Baicalein	
	Isoflavones Genisteine, Genistin,, Diadzein,, Glycitein, Diadzin , Biochanin A	
	Anthocyanidines: Malvidin, Peonidin,Cyanidin, Pelargoinidine	
	Chalcones*:* Cardamonim, Burtein, Isoliquiritigenine, Falvokawain B	
	Flavanones: Narigenin, Naringin, Eriodictyol, Hesperetin, Hesperidin, Butin	
	Flavan - 3 – ols: Catechin, Epicatechin, Epigallocatechin, Theaflavin, Thearubigin	
	Flavanonols: Taxifoline, Aromadedrin, Engeletin,Chlorospermin, Glysapinol, Puyanol	

These compounds generally have at least three phenolic OH groups and are generally combined with sugars to form glycosides, with glucose as the major sugar, but also galactose, rhamnose, and xylose can be found, as free aglycon.

The enzyme glucosidase in the bee salivary glands is responsible for the hydrolysis of the glycosylated flavonoids and releasing the aglycon form. The flavonoids in honey have been identified mostly as a form of aglycons and not in their glycosylated form. Phenolic aglycons are well absorbed through the gut barrier than their corresponding glycosides by passive diffusion [66] and therefore, flavonoids present in honey may be more readily bioavailable. Two -endoglycosidases capable of flavonoid glycoside hydrolysis have also been characterized in the human small intestine, namely lactase phlorizin hydrolase (LPH), acting in the brush border of the small intestine epithelial cells [48, 49] and a cytosolic -glucosidase (CBG) as an alternative hydrolytic step within the epithelial cells [66-69]. Some studies show that flavonoids can inhibit the non-Na+ -dependent facilitated diffusion of monosaccharides in intestinal epithelial cells.

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1.1.2. Honey: Acidity and pH value

The unique chemistry of honey originates from its buffering capacity, which allows it to maintain a stable pH through the addition of small amounts of acids and bases. This is due to the chemistry of honey related to the presence of carbonates, phosphates, and minerals. The buffer systems offer benefits, especially in dentistry when the oral pH can influence pharmacological effects [70-74].

1.1.3. Honey: Biological activity as an antioxidant

The antioxidant properties of honey result from the ability to reduce oxidative reactions. The antioxidant capacity (AOC) depends on the honey floral source, plant, and its secondary metabolites as polyphenolics and enzyme activities. Enzymes such as glucose oxidase and catalase, vitamins like ascorbic acid, organic acids, amino acids, phenolic acids, and especially flavonoids play a very important role in the antioxidant activity of honey [75-78].

Honey has a complex composition that seems difficult for standardization of AOC, but the lipid peroxidation model has been studied more by mimicking several mechanisms that may occur in vivo. It offers the possibility of identifying antioxidant compounds able to mitigate lipid oxidative damage. It is important to emphasize that the AOC of honey depends on polyphenol contents which are considered the main antioxidant components of honey. Polyphenols play an important role as metal chelators, free-radical scavengers that regulate cellular redox balance. The OH groups in the aromatic ring increase the capacity of dihydric and trihydric derivatives like gallic acid (3,4,5-trihydroxybenzoic acid), the most potent antioxidant within all the hydroxybenzoic acids. Benzoic acid also plays a role as a weak antioxidant. The antioxidant effect increases in cases of dihydric or trihydric derivatives due to the positions of OH groups in the aromatic ring. Several electron donor groups in the benzene ring structure (as hydroxyl or methoxy groups in structures) provide a greater number of resonant structures and increase the stability of the aryl radical in cinnamic acids, thereby favoring their antioxidant behavior [79-83]. Flavonoids are very effective as scavengers of reactive oxygen species (ROS) peroxyl, alkyl peroxide, hydroxyl, and superoxide radicals, as well as against reactive nitrogen species (RNS) like nitric oxide and peroxynitrite, protecting against the oxidative damage induced by these molecules [84, 85]. This activity is attributed to three chemical features in flavonoid structure, namely an ortho-dihydroxy structure in the B-ring [86-89], and the presence, in the C-ring, of a 2, 3 double bond and/or of a 4-oxo function [90, 91]. Hydroxyl groups on the B-ring donate hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, stabilizing them and giving rise to relatively stable flavonoid radicals. Oxidation of a flavonoid occurs on the B-ring when catechol is present [92-95], yielding a fairly stable ortho-semiquinone radical [96] through facilitating electron delocalization [97]. Examples are flavonols: the superiority of quercetin in inhibiting both metal and nonmetal-induced oxidative damage is partially ascribed to its free 3-OH substituent [98-101], which is thought to increase the stability of the flavonoid radical, while the substitution of 3-OH by a methyl or glycosyl group decreases the AOC of this flavonol [102]. In flavonoid classes the presence or absence of an unsaturated 2–3 bond in conjugation with a 4-oxo function. The conjugation phenomena between the A - and B rings permit a resonance effect of the aromatic nucleus leading stability of the flavonoid radical. This conjugation is critical in optimizing the phenoxyl radical-stabilizing effect of the 3`,4`-catechol [103]. Flavonols have a higher free radical scavenger capacity than flavones [104, 105] which leads to a greater number of hydroxyl groups and substituents 3-OH present in their structure.

1.1.4. Honey: Biological activity as antibacterial

Honey is well known for its antimicrobial effects which are dedicated to two mechanisms: (a) high osmolarity and acidity with non-peroxide antibacterial activity thanks to methylglyoxal, bee defensin-1, and flavonoid contents; (b) a peroxide antibacterial activity due to the specific hydrogen peroxide content [106-109]. Honey has demonstrated an inhibition of microorganisms with clinical significance reported in many studies. The antimicrobial activity of manuka and an artificial honey was tested in one solution using eighteen strains of methicillin-resistant *Staphylococcus aureus*, seven strains of vancomycin-sensitive enterococci, isolated from infected wounds, and 20 strains of vancomycin-resistant enterococci, isolated from hospital environmental surfaces the minimum inhibitory concentration of both kinds of honey was below 10%, while the concentrations of artificial honey necessary to achieve equivalent inhibition in vitro were at least three times higher, thus confirming that the inhibition of bacteria by honey is not exclusively due to its osmolarity but to its flavonoids compounds also [110].

2. Medicinal value of honey in dentistry

The role of honey in systemic health has been largely studied over the years confirming its antibacterial, anti-inflammatory, and wound healing properties as well as its contribution to physical and mental well-being. An increasing number of studies demonstrate its beneficial effects on several oral conditions like inhibition of *Streptococcus mutans* and dental caries consequently, periodontitis, oral mucositis induced by radiotherapy in cancer, xerostomia or promotion of wound healing [111- 114]. Honey's effects on oral health are presented in Figure 2.

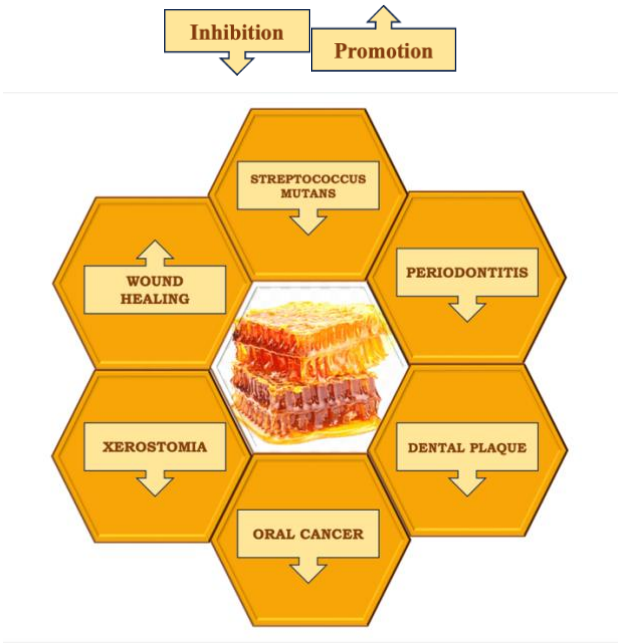

Figure 2. Effects of honey in oral health

2.1. Honey and dental caries prevention

As explained at the beginning of this review, dental caries happens when cariogenic bacteria within the biofilm metabolize sugars from the diet and produce acids. These acids cause pH to drop under the critical point of 5.5 encouraging the demineralization of dental enamel, which loses its minerals like Ca, Mg, and P, resulting in cavities.

The introduction of sugars in the everyday diet has become a major community oral health problem due to their important role in the cariogenic process. Among all sugars, sucrose is considered the most cariogenic one, which along with its constituents' glucose and fructose, can be easily metabolized by cariogenic bacteria. So dental plaque is created, an environment rich in bacteria embedded in self-produced extracellular polysaccharides. This environment becomes home to acidogenic and aciduric microbial species responsible for the initiation and propagation of dental caries. It has been scientifically demonstrated that all foods and drinks rich in sugars or with an acidic pH are prone to induce hard tissue demineralization and caries. Honey is a very sweet substance with a pH varying between 3.2 and 4.5 (depending on the type of honey) theoretically having a high cariogenic potential [115]. So, Bowen and Lawrence [116] when comparing the cariogenicity of cola, honey, cow milk, human milk, and sucrose, found that cola, sucrose, and honey were very cariogenic. Moreover, cola and honey had erosive effects on dental enamel, discouraging the use of honey, among others, from nursing bottles.

In the same line are also the findings of Safii et al. [117] who found a relative resistance of cariogenic *Streptococcus mutans* to two types of honey (Manuka and clover honey). They observed that both types of honey promoted significant demineralization at lower concentrations, supporting the idea that the high concentrations of fermentable carbohydrates in honey and the direct demineralization of oral hard tissues caused by the low pH of honey could be damaging to calcified tissues.

However, Grobler and Basson [118], using scanning electron microscopy showed neither enamel erosion by natural honey for a period of over 30 minutes, nor any other deterioration of enamel structure. The

authors attributed this effect to the calcium, phosphorus, and fluoride levels in honey. The findings of Grobler and Basson were supported by later work from Ahmadi-Motamayel et al. [119], who demonstrated (in vitro) that honey possessed lower caries activity than fructose and glucose. Additionally, Habluetzel et al. [120] found that despite its low pH, honey did not cause erosion, and they concluded that treating the pellicle with honey, its components, or propolis did not provide any protection against erosion. Yet, Celik et al. [121] analyzing the remineralizing potential of honey (separately and mixed with other natural products like ginger and bitter chocolate), demonstrated a high remineralization potential of initial enamel caries lesions. A remineralization potential of honey has been also observed by Senthilkumar et al. especially when mixed with ginger powder [122].

Prevention of dental caries is founded on the eradication of at least one of the producing factors and eradication or at least inhibition of oral cariogenic microflora is of major importance in this sense [123]. The most studied species involved in the cariogenic process are *Streptococcus mutans* and *Lactobacillus salivarius* [11], but as has been demonstrated they are not the only responsible ones. Recent research using sequencing-based technology and bioinformatics analysis is helping in better understanding the complexity of oral microbiome and the interaction with dental caries showing important microbiome shifts in caries of different stages, with different activities, and in different locations [7]. However, it is widely accepted that *Streptococcus mutans* is the main virulent species in the pathogenesis of dental caries. It possesses three important properties that give it this status: the ability to use dietary sucrose to rapidly synthesize extracellular polysaccharides through the activity of glycosyltransferases and a fructosyltransferase, strong adherence to glucan-coated surfaces and acidogenecity and acidurance. Under this perspective, the potential prevention properties of natural foods have been analyzed in the following directions: the antimicrobial activity, especially the inhibition of growth and metabolism of acidogenic and aciduric organisms, inhibition of exopolysaccharide synthesis, and inhibition of bacterial adherence [124].

Several studies in the literature demonstrate the important inhibitory activity of honey against *Streptococcus mutans* both *in vitro* [125-129] and *in vivo* [130-132]. Manuka honey, produced by *Apis mellifera* from *Leptospermum scoparium,* originated from New Zealand, has been the most studied one, because of its demonstrated strong antimicrobial activity against a wide range of bacterial species [133, 134] and is considered probably as the "gold standard" of medical honey. Different types of honey have also been evaluated. So, Tualang Honey (Malaysian) [135-137], honey from New Zealand, Cuba, and Kenya [138], Greek honey [139], Polish honey [125], South African honey [140] have all shown different levels of antimicrobial activities. In these studies, honey originating from different plants and places has been evaluated in different concentrations, and on different species of microorganisms, which altogether are considered important factors that seem to play a role in its antibacterial power. It has been reported that honey shows an antimicrobial effect on concentrations starting from 2.5% [141] to 74% [142]. Ahmadi et al. showed significant antibacterial activity for honey on *Streptococcus mutans* in concentrations more than 20% and on Lactobacillus in 100% concentrations, recommending it for the prevention and reduction of dental caries [143]. Badawy et al. observed that higher honey concentrations perform better inhibitory activity, concluding that the higher the concentration the more effective it is as an antibacterial agent [144].

Preliminary data from Grabec-Lejko and Hyrchel in a recent study [125], show strong inhibitory activity on *Streptococcus mutans* and biofilm formation from the strongest honey samples, which also showed the highest antioxidant activity and polyphenols content. Their results suggest that honey can be a good natural product against *Streptococcus mutans*, identifying hydrogen peroxide as a crucial contributor to its antimicrobial action. Another study by Yadav et al. [131], concluded that honey has an antimicrobial effect on *Streptococcus mutans* after a definite time interval contributing this effect to the production of hydrogen peroxide, inhibition of glycosyltransferase activity, or presence of polyphenols in honey. When compared to artificial honey (AH), a mixture of ingredients, including 40.5% fructose, 33.5% glucose, 7.5% maltose, and 1.5% sucrose, added incrementally and stirred until dissolved in deionized water, Nasar et al. [126], concluded that natural honey (NH) demonstrated more inhibition of bacterial growth, viability, and biofilm formation than artificial honey (AH), highlighting the potential antibacterial properties of natural honey, attributed not solely to its high sugar content**.** Honey inhibitory potential on *Streptococcus mutans* was ascertained also by Abdelmegid et al. [130] who observed that a single time mouth rinsing with honey and green tea solutions for two minutes effectively reduced the number of *Streptococcus mutans* in the saliva of 7-10 years old Saudi boys, recommending this procedure as a potential measure for prevention of caries in children.

Overall, according to the literature, honey's antimicrobial efficacy originates from several factors: the production of hydrogen peroxide with antiseptic properties, the high sugar content causing an osmotic effect,

the low pH level, and the presence of organic acids, especially gluconic acid. Although some types of honey have no hydrogen peroxide activity, called non-peroxide honey (manuka honey) they have important antimicrobial activity which may be due to the low pH, high sugar content, and presence of methylglyoxal (MGO) compound which are enough to prevent microbial growth. There are also several enzymatic constituents regularly found in honey that may inhibit the cariogenic process such as bee-derived enzyme Glucose Oxidase (GOX), a regular but quantitatively variable glycoprotein of honey, lactoperoxidase, and iodide [34, 115, 145, 146, 147]. Kwakman et al. fully characterized the antimicrobial activity of honey and they found that honey contains an antimicrobial peptide, bee defensin-1 with a substantial contribution to its bactericidal activity [148]. Polyphenols, which are found at high levels in honey, are a diverse group of chemicals that include flavonoids and phenolic acids and may contribute to its antibacterial activity. They are biological compounds transmitted from plants' nectar to honey and represent important components of honey's health-promoting properties [149, 150].

An important observation regarding natural honey is that it has a wide antibacterial activity which extends to more than 80 species, and none is observed to develop resistance against honey, as it happens with many antibiotics available [151]. This fact is attributed to the variations in honey composition which depends on nectar source, climate, time of preservation, and also preservation conditions [150] and is very encouraging for deeper investigation.

2.2. Honey against dental plaque formation and in periodontitis

Periodontal disease is one of the most common four oral conditions that affect people worldwide, along with dental caries, tooth loss, and oral cancer. Severe gum disease - a major cause of tooth loss - is estimated to affect 1 billion people worldwide, according to WHO [152, 153].

Periodontal disease is defined as the inflammatory response of the gingiva and the surrounding connective tissue to the bacterial or plaque accumulations on the teeth surface, which produce real specific infections. These bacteria through their various compounds such as H_2S, NH_3, endotoxins, enzymes, and antigens initiate a plaque-induced inflammatory response. Initially, this inflammation causes swallowing and bleeding of the soft tooth surrounding tissues, called gingivitis, which if not treated advances to collagen destruction, detachment of tooth from bone structure, bone loss (periodontitis), and ultimately tooth loss [4]. However, periodontitis is a multifactorial disease in which environmental and genetic factors play an important role in its onset, where besides oral bacterial flora, smoking and diabetes are other important risk factors, strongly related to the disease [154].

Plaque control can be achieved through good oral hygiene, which has been demonstrated to change subgingival flora to a more compatible with periodontal health. Usually, rigorous plaque control is achieved by regular and adequate toothbrushing, but in many cases, this is difficult to realize leading to the need for other chemical products such as mouthwash to complete dental plaque removal. Moreover, advances in plaque theory highlight the importance of using chemical antimicrobials with the necessary properties to suppress and/or eradicate the pathogenic players, due to the observations that pathogens like *A. actinomycetemcomitans* and *P. gingivalis* invade the epithelium and cannot be as responsive to mechanical debridement and need additional antibiotic therapy or even surgery [155].

Periodontitis standard treatment is based on non-surgical periodontal therapy that consists of mechanical root debridement, to eliminate or reduce dental plaque, by removing as much as possible of the subgingival plaque colonized by a great number of pathogens. Although this therapy is very effective, bacteria can recolonize the space, and residual pockets can still remain [156].

Several agents with antiplaque and antigingivitic properties, such as triclosan (dentifrice), stannous fluoride (dentifrice), a combination of essential oils (mouth rinse), chlorhexidine (mouth rinse), etc., have been used throughout the years, to decrease gingival inflammation so that destructive periodontal disease will not develop [157]. There is strong evidence of the antiplaque and antigingivitis effects of these agents [158-160] but also concerns regarding their safety [161], or adverse effects like discoloration [162], so attention to natural compounds have been drawn.

Among other uses, honey has also been evaluated as an antiplaque agent and for use in periodontal disease. Different types of studies, from in vitro to clinical evaluations, have been conducted to test the antibacterial properties of honey against dental plaque, in gingivitis or periodontitis.

Schmidlin et al, [129] tested in vitro, the antibacterial efficacy of Manuka honey against *S. mutans*, *P. gingivalis*, and *A. actinomycetemcomitans*. They found that Manuka honey has a significantly higher antibacterial effect at

an NPA (Non-Peroxide Activity) value above 15, being more effective against *P. gingivalis* and *A. actinomycetemcomitans*, rather than *S. mutans*. Their study showed an NPA dose-dependent antibacterial efficacy of Manuka honey.

Similar results were obtained by Safii et al. [117] when testing in vitro, antimicrobial, and demineralizing effects in the periodontal application of Manuka honey and clover honey. They found both honeys active against plaque-associated bacteria, and that Medical-grade manuka honey (of NPA > 20) is especially antimicrobial towards the gram-negative anaerobes associated with gingivitis and periodontal diseases. Gram-negative anaerobes were more sensitive than the gram-positive species like streptococci.
Voidarou et al. [139] analyzing in vitro different types of Greek honey as potential natural antimicrobials against oral pathogens, found that in most cases the Greek honey, particularly the citrus honey and the oregano and sage honey, outperformed the antibacterial activity of manuka honey showing high antibacterial activity against all tested oral bacteria. Their study indicated that in a clinical environment, Greek honey can be used as an anti-cariogenic, anti-erosive, and/or oral wound healing factor in patients with hyposalivation, suggesting the necessity of investigating the botanological profiles of different types of honey for their classification and derivation of more specific suggestions.

Clinical evaluation of honey antimicrobial efficacy in different form products can be found in the literature. Honey mouthwash rinsing is the most tested due to easy performance and clear results. Recent studies have shown antimicrobial honey properties when used as a rinsing agent. So, in a study by Yasmin et al, [163], 52 children 9–12 years old, with the same mean plaque scores, were divided into two groups. The control group rinsed with distilled water and the test group rinsed with a forest honey (10%) solution. The children rinsed three times daily for 30 s with 10 ml of mouthwash for 4 days, in all 10 times. After the 4-day period, the plaque scores were reassessed and it was observed that rinsing with the forest honey solution (10%) had reduced the plaque score. The mean plaque score after rinsing with forest honey solution (10%) was significantly lower than the mean plaque score after rinsing with distilled water showing that rinsing with a forest honey solution of 10% has a positive effect on the reduction of dental plaque in children 9 - 12 years.

A randomized controlled trial study was conducted by Sruthi et al. [14] among 12–15 years old children with DMFt index (decayed, missing, filled teeth) scores of 1-4 and plaque and gingival scores of 1-2, to analyze the efficacy of Manuka honey and chlorhexidine on gingivitis and *Streptococcus mutans*. Students were instructed to rinse with 5 ml of Manuka honey and 10 ml of Chlorhexidine twice daily for 14 days. Plaque and gingival indices were assessed at baseline, 7th day, and 14th day as well as *Streptococcus mutans* count obtained from unstimulated saliva, showing comparable effectiveness of Manuka honey with Chlorhexidine mouthwash in reducing gingivitis and *Streptococcus mutans* count. Authors recommend Manuka honey as a promising antimicrobial agent effective in improving gingival health and reducing caries risk.

In another recent study, Al-Kubaisi & Al-Ghurabi [164] randomly selected 45 individuals between 20-40 years old to clinically evaluate the effect of Manuka honey on dental plaque and microbial load. They were separated into three groups, each receiving Manuka honey mouthwash, chlorhexidine, and a placebo mouthwash. Dental plaque index (PLI) and bleeding on probing (POB) scores as well as *Streptococcus mutans* were estimated before and after 21 days of using the mouthwash for each participant. The findings of this study have proven the antibacterial and anti-biofilm properties of Manuka honey by a significant reduction in PLI and POB scores and *Streptococcus mutans* in both the Manuka honey and chlorhexidine groups. Authors suggest manuka honey as appropriate for antibacterial defense against *Streptococcus mutans* and to enhance oral health.

Several other studies have demonstrated honey antibacterial efficacy in plaque control or gingivitis by direct oral application of different concentrations of honey, massaging gingiva with honey, chewing honey products, or honey gum. So, the effect of Manuka honey was compared to chlorhexidine and xylitol chewing gum in a clinical study by Nayak et al. conducted on 60 individuals aged 21 - 25 years old, on dental plaque levels. Undiluted honey was applied directly into the gingival sulcus of all teeth twice within an interval of 5 minutes, twice a day after meals, in a 72-hour experiment. Chlorhexidine was used by rinsing twice a day for 60 s with 10 ml solution, and sugarless xylitol gum was chewed for 5 min three times a day after meals. The results showed comparable effects of manuka honey and chlorhexidine, performing significantly better than xylitol in reducing plaque formation [165].

In another randomized controlled study by Atwa et al. [166], the effect of honey was tested in preventing gingivitis and dental caries, compared to treatment with 10% sucrose and 10% sorbitol solutions. The levels of *Streptococcus mutans*, *Lactobacilli*, and *Porphyromonas gingivalis* in dental plaques were measured

in 20 orthodontic patients, of 12-18 years old, after chewing undiluted honey or rinsing with sucrose and sorbitol solutions. The results showed a statistically significant reduction in bacterial counts in the honey group, with a significant inhibition of all studied bacterial strains, which was comparable to the inhibition observed with antibiotics. Authors agreed that honey can be used as an alternative to conventional treatments in preventing dental caries and gingivitis in orthodontic patients.

Gum massage therapy with honey and olive oil has been found to have a significantly effective reduction potential of gingival scores and colony counts of oral microorganisms' formation [167]. Olive oil and honey can reduce gingivitis and can be used as preventive and therapeutic agents.

A very recent study by Ahmadi-Motamayel et al. [168] tested the effect of chewing gum containing G glabra, honey, and vitamin E, on gingival index, plaque index, and bleeding on probing, and salivary bacterial counts, on 155 dental students. They observed a decrease in all periodontal parameters and bacterial counts, with the highest reduction in gingival inflammation, concluding that chewing gum with G glabra, honey, and vitamin E, improved oral health.

In their study, Opšivač et al. evaluated the effects of a Manuka honey-containing product on periodontal indicators as an adjunct to nonsurgical periodontal treatment in patients with stage 3 periodontitis [156]. They found statistically significant improvements in periodontal probing depth (PPD) reduction and clinical attachment level (CAL) gain after 3, 6, and 12 months of follow-up, compared to the outcomes of the non-surgical periodontal treatment only. Their results were comparable to studies of other adjunctive products such as antibiotics or else, indicating the potential use of Manuka honey as a simple and affordable adjunct to non-surgical periodontal therapy.

3. Honey as a novel targeting product from green synthesis

In recent years, nanotechnology has shown significant potential in biomedical use, especially in antibacterial applications [169, 170]. Partially because of their unique nanoscale physicochemical properties, nanomaterials can penetrate biofilm barriers and various antibiotic-resistant bacteria [171], thus strengthening traditional antibiotic effects and reducing their harm to human health [172]. Moreover, such drug delivery systems can be multifunctional, including functions such as remineralization promotion [173] and drug release control [174]. These characteristics support their significant potential for use in dental caries therapy and dental plaque control. Honey can be utilized as a natural source of bioactive compounds that can be incorporated into targeted drug delivery systems or as a component in environmentally friendly synthesis methods. Its unique composition and therapeutic properties make honey a valuable resource for developing sustainable and effective targeting products through green synthesis approaches.

Gold nanoparticles synthesized using honey as a reducing and stabilizing agent highlight a significant advancement in nanotechnology, particularly in biomedical applications. Philip et al. [172] have successfully demonstrated that $HAuCl_4$ can be reduced with diluted honey, with the rate of reduction increasing proportionally to the volume of honey used. At room temperature, honey functions not only reduce $HAuCl_4$ but also stabilize the resulting gold nanoparticles. Transmission Electron Microscopy (TEM) studies have elucidated that the presence of H_2O_2 and gluconic acid, formed when honey is diluted with distilled water, plays a pivotal role in this reduction process. Fructose, an intrinsic component of honey, acts as a potential reducing agent, while the proteins within honey contribute to the stabilization of these nanoparticles.

Moreover, the antibacterial properties of nano-honey have been investigated, revealing moderate activity against both gram-positive and gram-negative bacterial strains. These findings underscore the potential of nano-honey in dental applications, particularly in combating oral pathogens effectively. The integration of honey into nanotechnology not only enhances the functional properties of nanoparticles but also opens new paths for innovative approaches in dental materials and treatments, as explored by Philip et al. [172]. Silver nanoparticles synthesized using honey as both a reducing and stabilizing agent represent a significant advancement in nanotechnology, particularly in biomedical applications, as studied by Ghramh et al. [173]. The process involves conducting synthesis at room temperature, where honey demonstrates dual functionality. Ghramh et al. [173] observed a notable correlation: as the concentration of honey increases, the size of the silver nanoparticles decreases, a phenomenon confirmed by Scanning Electron Microscopy (SEM). This size modulation is crucial for optimizing the properties of silver nanoparticles for dental applications. Proteins present in honey play a pivotal role as capping agents, effectively stabilizing the nanoparticles during synthesis. Meanwhile, fructose, a component of honey, acts as the primary reducing agent in this green synthesis approach. These mechanisms highlight nano-honey's capability to produce silver nanoparticles with

tailored properties that enhance their antibacterial efficacy, particularly beneficial for combating oral pathogens relevant to oral health.

The integration of honey into nanotechnology not only enhances the functional properties of nanoparticles but also underscores its potential in developing advanced dental materials and treatments. Ghramh et al.'s [173] research contributes significantly to expanding the understanding of nano-honey's applications, offering promising avenues for future innovations in dental care.

Palladium nanoparticles synthesized with the assistance of honey, acting as both a reducing agent and stabilizer, represent a significant advancement in nanotechnology, as explored by Mitt et al. [174]. This synthesis method highlights the versatility of nano-honey in facilitating advanced catalytic processes, particularly in biomedical and dental applications. Mitt et al. [174] have demonstrated that honey effectively reduces palladium ions, facilitating the synthesis of nanoparticles suitable for catalyzing Suzuki cross-coupling reactions and hydrogenation of conjugated olefins. Their research underscores the potential of nano-honey to revolutionize dental care by providing efficient and environmentally friendly solutions, thereby expanding the possibilities for innovative applications in oral health.

Yang et al. [175] have explored the utilization of nano-honey in synthesizing carbon nanoparticles, emphasizing its dual role as a reducing and stabilizing agent. This innovative green synthesis method enables the real-time production of carbon nanoparticles on surfaces coated with polysorbate and polyethylene glycol. Such nanoparticles possess considerable potential for diverse dental applications, owing to their unique properties facilitated by nano-honey. By leveraging nano-honey's capabilities, this approach not only enhances the efficiency of nanoparticle synthesis but also contributes to the development of functional materials that could significantly advance dental treatments and dental materials science. Yang et al.'s [175] findings underscore the promising role of nano-honey in expanding the horizon of dental research and innovation, offering sustainable solutions for improving oral health outcomes.

Green synthesis of nanoparticles is eco-friendly which embodies the efficacy and safety of nanomaterial using biological resources like honey. This green approach has opened a new era of safe nanotechnology. Special chemical properties of honey are used in the green synthesis of nanoparticles. These characteristics are crucial in the development of sustainable dental materials and treatments. Consequently, honey-mediated synthesis offers several advantages over microorganism-mediated methods [176, 177].

Nanomaterials combined with honey can potentially influence the speed and efficacy of wound repair and infection prevention in several ways: a) Enhanced Antibacterial Properties: Honey itself has natural antibacterial properties due to its low pH, high sugar content, and production of hydrogen peroxide. When combined with nanomaterials like nanoparticles of metals (e.g., silver, zinc oxide) or metal oxides (e.g., titanium dioxide), the antibacterial effectiveness can be enhanced [178]. Nanomaterials provide a large surface area and unique chemical properties that can disrupt bacterial cell membranes or inhibit bacterial growth more effectively than honey alone; b) Improved Healing: Nanomaterials can help create a scaffold or matrix that supports tissue regeneration and wound healing [179]. They can promote cell adhesion, migration, and proliferation, speeding up the formation of new tissue and thereby accelerating the overall healing process [180, 181]; c) Controlled Release of Bioactive Compounds: Nanomaterials can be engineered to encapsulate bioactive compounds present in honey, such as phenolic acids, flavonoids, and enzymes. These compounds have antioxidant and anti-inflammatory properties, which can further aid in wound healing by reducing inflammation and oxidative stress [182].

4. CONCLUSION

Honey shows promise in oral health applications due to its antibacterial, anti-inflammatory, and wound-healing properties. It is now seen as a reliable alternative thanks to technological interventions through nanotechnology, where combined with metal nanoparticles improves the efficiency and safety of several dental treatments and oral health care. Enhanced antibacterial properties when combined with nanomaterials of metals, provide a large surface area and unique chemical properties that can disrupt bacterial cell membranes or inhibit bacterial growth more effectively than honey alone. Honey nanomaterials can help create a scaffold or matrix that supports tissue regeneration and wound healing. They can promote cell adhesion, migration, and proliferation, speeding up the formation of new tissue and thereby accelerating the overall healing process. However, further clinical studies are essential to validate its efficacy, safety, and specific uses in dental practice. Integrating honey-based products or treatments into oral care routines could offer novel approaches to maintaining oral health and managing oral diseases.

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