

REVIEW

Polyphenols and *Lactobacillus reuteri* in oral health

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Keywords

Mediterranean diet • Polyphenols • Oral health • *Lactobacillus reuteri*

Summary

Oral health is one of the necessary preludes to the overall quality of life. Several medical procedures and therapies are available to treat oral diseases in general and periodontal diseases in particular, yet caries, periodontitis, oral cancer, and oral infections remain a global concern. Natural molecules, with their anti-oxidant, anti-inflammatory, and anti-microbial properties, are one of the main sources of oral health and dental health care, and should be supplemented to exploit their beneficial effects. A possible way to improve the intake of these molecules is adhering to a diet that is rich in fruits, vegetables, and probiotics, which has many beneficial properties and can improve overall health and wellbeing. The Mediterranean diet, in particular, provides several beneficial natural molecules, mainly because of the precious nutrients con-

tained in its typical ingredients, mainly plant-based (olives, wine, citrus fruits, and many more). Its beneficial effects on several diseases and in increasing the overall wellbeing of the population are currently being studied by physicians. Among its nutrients, polyphenols (including, among other molecules, lignans, tannins, and flavonoids) seem to be of utmost importance: several studies showed their anticarcinogenic properties, as well as their effects in decreasing the incidence of non-communicable diseases. Therefore, plant-derived molecules – such as polyphenols – and probiotics – such as *Lactobacillus reuteri* – have shown a significant potential in treating and curing oral diseases, either alone or in combination, owing to their antioxidant and antimicrobial properties, respectively.

Introduction

Plant-based foods, such as the typical fruits and vegetables of Mediterranean diet, are rich in many important phytochemicals that confer several health benefits. Among these, an important role is played by Polyphenols, a group of chemicals having at least one phenol moiety, which are particularly beneficial for human health [1]. Dietary polyphenols are a diverse group of phytochemicals, having approximately 8000 types of phenolic structures that are naturally present in cereals, fruits, vegetables, and beverages; based on the number of phenolic rings they contain, they can be classified into five subclasses, which are: phenolic acids, lignans, tannins, stilbenes, and flavonoids (Fig. 1, Tab. I) [2]. Epidemiological studies have shown that polyphenols – more specifically flavonoids – have strong antioxidant, anti-inflammatory, anti-cancerous, and anticarcinogenic properties [3], which can reduce the severity and incidence of non-communicable diseases such as diabetes, cancer, and cardiovascular problems.

PHENOLIC ACIDS

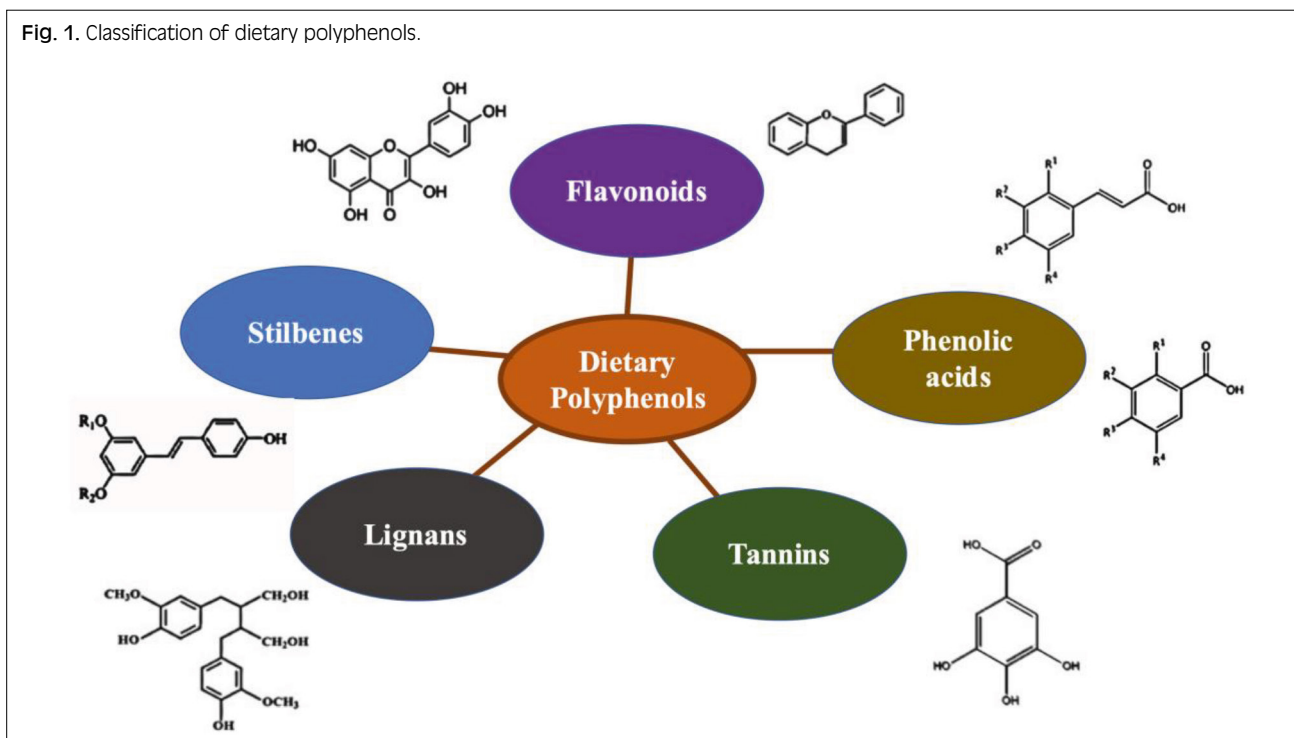
Abundantly present in fruits and vegetables, phenolic acids are derivatives of cinnamic and benzoic acids. Hydroxycinnamic acids (such as ferulic, p-coumaric, caffeic, rosmarinic, chlorogenic, and sinapic acids) are more common than hydroxybenzoic acids, which for example

are contained in high amounts in black radish, onions, and red fruits [4]; hydroxybenzoic acids include gallic, syringic, vanillic, protocatechuic, and salicylic acids. The major dietary sources of phenolic acids include cocoa, wholegrains, fruits, nuts, coffee, and beer [5]. Observational studies have shown an inverse relationship between phenolic acid consumption and non-communicable diseases, such as metabolic syndrome [6], type-2 diabetes [7], hypertension [8], and non-alcoholic fatty liver disease [9]. In addition, phenolic acid consumption had a profound effect in the management of depressive disorders and in sleep quality [10, 11]. However, studies related to cardiovascular effects of these phenolic acids are scarce.

FLAVONOIDS

Flavonoids are perhaps the most powerful antioxidants naturally present in plants. They can be structurally distinguished by the presence of a di-phenyl-propane moiety (C6-C3-C6) and can be further classified into isoflavones, flavones, flavanones, flavonols, anthocyanidins, and flavanols [12]. Flavonoids have strong antioxidant, antimutagenic, anti-proliferative (against tumor cells), cardioprotective, radio-protective, antiatherosclerosis, and antimicrobial properties. In addition, these molecules also help in maintaining hormonal balance in menopausal women [13-15]. Among them, quercetin and genistein manifest a highly beneficial property of

Fig. 1. Classification of dietary polyphenols.



Tab. I. Classes and properties of polyphenols.

Polyphenols	Subclasses and examples	Food sources	Health benefits	References
Phenolic acids	Benzoic acid and cinnamic acid derivatives (e.g. caffeic acid)	Cherries, black radish, onion, kiwi, berries, coffee	Antimicrobial, anticancer, anti-inflammatory, anti-mutagenic	[22]
Flavonoids	Flavonols (e.g. quercetin)	Leek, ginger, broccoli, onion, leafy greens, berries, tea	Antioxidant and radical-scavenging activities, inhibiting cell migration of hepatocyte growth factor-induced medulloblastoma	[23]
	Flavanols (e.g. catechins)	Grapes, chocolate, red wine, cocoa, apricots, black beans, green tea	Antioxidants, antimalarial, anticancer, antiviral, anti-inflammatory, anti-allergenic, UV protective	[24]
	Flavanones (e.g. hesperetin)	Citrus fruits (orange, grapefruit, lemon) and their juices	Antioxidative e anti-inflammatory. Ameliorate memory impairment and A β pathology	[25]
	Flavones (e.g. luteolin)	Oregano, celery, parsley, capsicum pepper	Neuroprotective, cardioprotective, antioxidant, anti-inflammatory, antiallergic	[26]
	Isoflavonones (e.g. genistein)	Milk, tofu, soy, tempeh miso	Anti-cancerous activity by inhibiting DNA topoisomerases and tyrosine kinases and inducing apoptosis, modulating PI3K/Akt and Wnt/ β -catenin signal conduction	[27]
	Anthocyanidins (e.g. delphinidin)	Aubergine, red cabbage, rhubarb, red wine, black grapes, berries, cherries	Antioxidative, antidiabetic, anti-inflammatory	[28]

Tab. I. *Continues.*

Polyphenols	Subclasses and examples	Food sources	Health benefits	References
Tannins	Dense tannins (e.g. pro-cyanidins)	Cocoa, chocolate, apples, grapes	Prevention, delay in the onset and treatment of cardiovascular diseases	[29]
	Hydrolyzable tannins (e.g., gallotannins)	Mango, pomegranate	Anti-inflammatory activity	[30]
Stilbenes	Resveratrol	Grapes, wine	Cardioprotective, antioxidant, antiplatelet, anti-inflammatory, anticancer activities, lowering blood glucose levels	[31]
Phenolic alcohols	Hydroxytyrosol	Olive	Antioxidant, anti-inflammatory, anticancer, protecting skin and eyes	[32, 33]

inhibiting ATP binding to tyrosine kinases, thus preventing proliferative diseases like cancer and psoriasis [15].

STILBENES

This class of flavonoids is present in low amounts in various food sources, but some of its members are widely studied because their intake brings a myriad of health benefits [16]. For instance, resveratrol, which is contained in high quantities in red grapes and grape juice (both fermented and non-fermented), manifests antioxidant, anti-inflammatory, antibacterial, and anticancer properties [17, 18]. Besides being a strong antioxidant, resveratrol also has antidiabetic and cardioprotective activity and, because of its several molecular targets, its usage is very promising in the development of novel remedial approaches against metabolic syndrome, atherosclerosis, ischemic heart disease, and heart failure [19].

TANNINS

Tannins are complex, water-soluble phenolic compounds derived from phenolic acids. They have a strong free radical-scavenging capability, which gives them antimutagenic and antibacterial activities. An example of powerful anticarcinogenic tannins are Ellagitannins derivatives, such as Ellagic acid, which can be found in many fruits and nuts like cranberries, strawberries, red grapes, raspberries, pomegranates, peaches, walnuts, and pecans [20].

LIGNANS

Lignans are diphenolic compounds, defined as phytoestrogens, which are derived from phenolic acids by the dimerization of two cinnamic acid residues. Lignans confer several health benefits, such as lowering the risk of cancer and cardiovascular diseases. In women, lignans help in alleviating the symptoms of menopause and osteoporosis. Wholegrain cereals and seeds – such as linseed, flaxseed and legumes – are rich sources of lignans [21].

Potential Effects of Polyphenols on Health

Polyphenols manifest a wide variety of health benefits, owing to their antioxidant, immunomodulator, anti-inflammatory, and radical-scavenging properties. For instance, resveratrol, curcumin, and epigallocatechin gallate (EGCG) have neuroprotective properties against neurodegenerative diseases (e.g. Alzheimer's-like diseases and dementia). Furthermore, these polyphenols inhibit the neurotoxic effects of the beta-amyloid protein that accumulated due to Alzheimer's disease [34, 35]. Moreover, the iron-chelating effects of EGCG, ginkgetin, curcumin, ginsenosides, and myricetin prevent neurotoxicity, thus protecting against Alzheimer's, Parkinson's, and Huntington's [35, 36].

Besides that, phenolic compounds manifest strong anti-inflammatory properties against systemic and localized inflammation by mitigating the cytokine pathway and reducing oxidative stress [37]. For instance, flavonoid-rich foods and resveratrol reduce inflammation, lower blood pressure, reduce platelet activity, block cholesterol oxidation, reduce LDL, and improve ventricular health, thereby preventing cardiovascular diseases [38]. The free radical-scavenging activity of Flavonoids such as catechins, flavanols, flavones, anthocyanins, flavanones, and isoflavones, prevents cellular growth in tumours, thereby decreasing the risk of oncogenesis [39]. Polyphenols have been observed to be beneficial in breast, endometrial, colon, prostate, and epithelial cancer [40].

Several polyphenols can inhibit lipid, starch, and protein digestion in the gastrointestinal tract by binding to the respective digestive enzymes, thus inhibiting it [41]. For instance, anthocyanins slow down the digestion of starch and can regulate and alter glucose transport, thus providing better glycaemic control in type 2 diabetes [42, 43]. Curcumin, catechins, and resveratrol exhibit anti-obesogenic effects by reducing inflammation, inhibiting lipogenesis, oxidating adipocyte and increasing energy expenditure, thus resulting in enhanced weight loss and improved weight maintenance [41].

In addition to that, polyphenols have been indicated in wound healing, but perhaps the most apparent effect of

polyphenols is maintaining oral health. Several researchers have reported health benefits of polyphenols in relieving periodontal diseases, maintaining oral health, and preventing oral cancer.

Polyphenols in the oral cavity

Oral mucosa is continuously under food- and environment-mediated oxidative stress. Polyphenols come in contact to the oral cavity directly and, due to their antioxidant and antimicrobial properties, prevent several diseases of the oral cavity, from infections to cancers [44]. In addition, polyphenols can be used as “processing cofactors” to enhance the mechanical and functional characteristics of the biomaterials that are used in dental tissue engineering [45]. For instance, grape seed extract, which is rich in proanthocyanidins (PAs), has been used in various dental applications, e.g. resin-dentin binding, because of its dual action of cross-linking with the collagen and of inhibiting the metalloprotein [46].

Polyphenols make stable complexes with proline-rich proteins and histatins in the oral cavity, which remain stable during their course from the oral cavity to the gastrointestinal tract and so on [47].

Polyphenols play multiple roles in dental diseases: for example, some polyphenol hydroxyls are very reactive, while others are very protective against microorganisms, yet another group acts as disinfectants by producing hydrogen peroxide and inhibiting bacterial proteins and enzymes [48]. This antimicrobial activity of polyphenols is concentration-dependent: for instance, at low concentration polyphenols interfere with specific sites, thus inhibiting the enzymes, whereas at high concentrations they cause enzyme denaturation [49]. In addition, polyphenols such as flavonoids affect the bacterial membrane permeability by interacting with membrane proteins, enzymes, and lipids, thus mediating loss of macromolecules, protons and ions [50].

Polyphenols in Oral cancer

Oral cancer is one of the most important medical issues and necessitates the development of effective strategies to reduce its incidence and mortality rates. Polyphenols are well known for their anti-cancerous activities against various types of cancers, based on their capability to inhibit enzymes and tumour development [51]. They are also known for their roles in preventing oxidative stress and DNA damage, modulating carcinogens metabolism and inhibiting DNA adduct formation [52-54]. For instance, catechins extracted from tea induce apoptosis, arrest cell growth, inhibit metalloproteinase synthesis, reduce metastasis risk by inhibiting the invasion and proliferation in both oral leukoplakia cell lines and in oral cancer [54, 55].

Two different case control studies, conducted in Uruguay and Italy, have reported an inverse relationship between flavonoids consumption and risk of oral cancer [56].

The Italian study demonstrated a significant inverse relationship of flavanones, flavonols, and total flavonoids, with risk of oral cancers, while this is not the case with isoflavones, anthocyanidins, flavan-3-ols, and flavones [57]. This indicates that different types of polyphenols have different effects on the risk and development of oral cancers. For instance, some polyphenols are particularly useful in human papillomavirus-mediated oral cancers because they considerably reduce the development of HPV-induced cancers by inhibiting DNA adduct formation and reducing cell proliferation, as well as preventing the invasion of affected cells into unaffected cells, exhibiting cytotoxic activity, apoptosis induction, and cell differentiation [58].

Polyphenols in Dental Caries and Periodontal Diseases

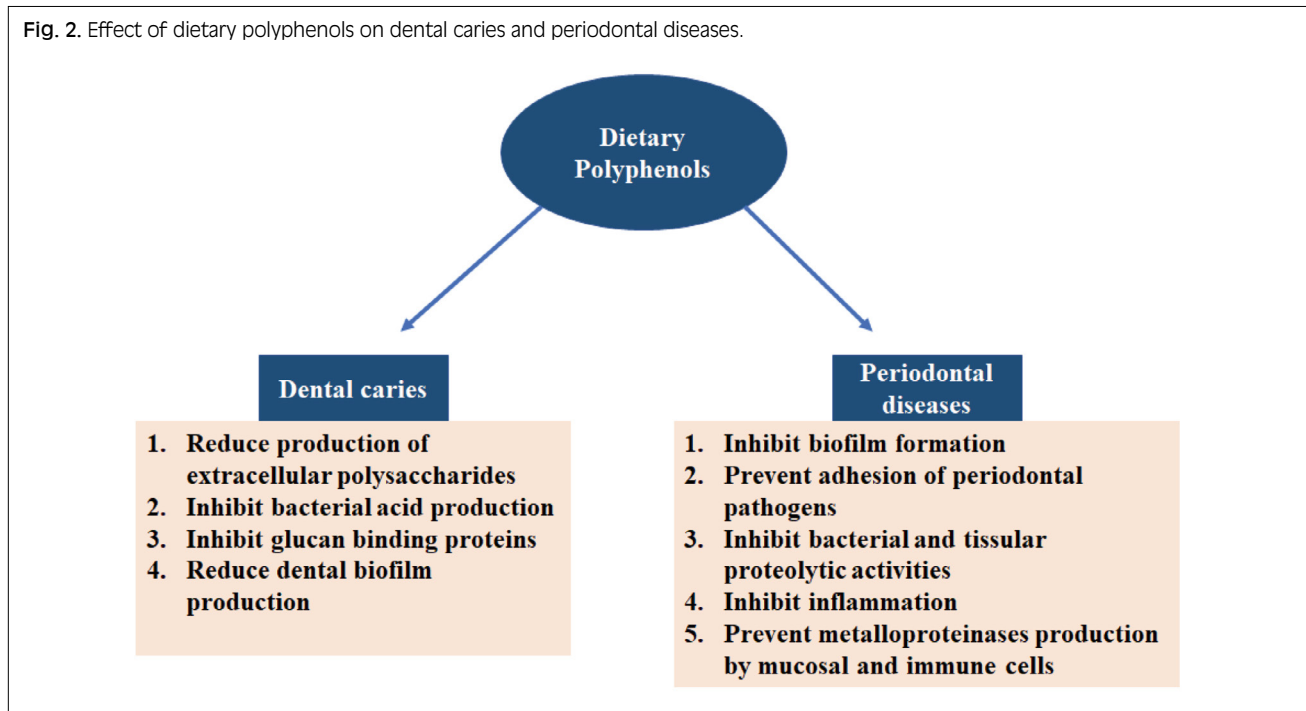
Containing over 700 bacterial species, the oral cavity is one of the most complex microbial ecosystems of the human body [59]. Integrated in an extracellular matrix of polysaccharides, the dental biofilm formed on hard and soft tissues of the oral cavity (containing food debris, epithelial cells, proteins, enzymes, and microbial cells) is the source of dental caries and periodontal diseases – the two main problems of oral cavity of bacterial origin [60]. For instance, the cariogenic *Streptococcus mutans* and *Streptococcus sobrinus* ferment sugars contained in food particles stuck to the teeth or other parts of the oral cavity, resulting in the production of organic acids that reduce the pH to 5.5, demineralising tooth enamel and thus causing dental caries. Dental caries is the most common infectious, multifactorial disease that results in the dissolution of tooth enamel [61]. Therefore, fruits and vegetables (and their extracts) that are rich in polyphenols not only reduce the number of harmful pathogens in the oral cavity, but also maintain oral hygiene (Tab. II).

Periodontal diseases are the diseases of the tissue that supports and surrounds the teeth; they can manifest episodically. Periodontal diseases can be further classified into gingivitis and periodontitis, which result in the inflammation of the free gingiva and the progressive destruction of all of the tooth-supporting tissue, including periodontal ligament and alveolar bone, respectively. These diseases follow a pattern of active destruction, latency and healing periods, and are dependent on accumulation of gram-negative anaerobes in the subgingival region and immune-destructive response of the host.

Dietary polyphenols play an important role in preventing the disequilibrium between oxidative stress and antioxidant activities in the oral cavity, thereby preventing periodontal tissue destruction. This implicates the effectiveness of these dietary phytochemicals in fighting periodontal diseases, especially when the oral cavity is exposed to oxidative stress from environment and food sources. For instance, tea polyphenols enhance the antioxidant capacity of saliva if the (green or black) tea is held in the mouth for 2-3 minutes. Localised application

Tab. II. Beneficial effects of polyphenols in oral cavity pathogens.

Polyphenols/food sources	Beneficial effects	References
Tea Polyphenols	Inhibition of glucosyltransferase (GTF), acid production, adherence to hard surfaces	[62]
Polymeric polyphenols	Inhibition of <i>Streptococcus mutans</i> polysaccharide synthesis	[63]
Extracts of unfermented cocoa, epicatechin, red grape seed, and green tea	Bacteriostatic against <i>S. mutans</i> , inhibit acid production, and reduce adherence of the bacterium against glass	[64]
Tannins from grapes	Salivary alpha-amylase inhibition in humans	[65]
Cocoa flavonols	Enhance interleukin 5 secretion by peripheral blood mononuclear cells and trigger IgA production against <i>S. mutans</i>	[66]
Oolong tea extract and its polyphenols	Significant reductions in caries and plaque development in rats infected with <i>S. mutans</i>	[67]
Barley coffee, coffee, wine, and tea	High consumption accompanies lower <i>Lactobacillus sp.</i> and <i>S. mutans</i> in plaque and saliva, thus lowering dental plaque scores	[68]
Oolong tea extract	Cariostatic activity against <i>S. sorbinus</i> in the oral cavity	[69]
Hydroxytyrosol from olives and olive tree	Reduces the viral load of the oral and nasal cavity mucosa during SARS-CoV-2 infections	[70-73]

Fig. 2. Effect of dietary polyphenols on dental caries and periodontal diseases.

of fruit extracts prevents biofilm formation and reduces pocket depth. Furthermore, increased phagocytic activity of polymorphonuclear leucocytes in the gingival crevicular fluid was observed upon daily intake of two fresh grapefruits for 2 weeks. The effects of dietary polyphenols on oral cavity diseases are presented in Figure 2. Perhaps the most widely studied polyphenols in connection to periodontal conditions are those from various kinds of tea: they not only enhance the proliferation of human periodontal ligament fibroblasts, but also inhibit virulence manifestation of the periodontic anaerobic pathogen *Porphyromonas gingivalis*. Therefore, regular consumption of polyphenol-rich diets presents an effective method of fighting periodontal diseases.

***Lactobacillus reuteri* in oral health**

Lactobacillus reuteri (*L. reuteri*) is one of the most widely studied bacteria, having a huge repertoire of beneficial effects on human health. It colonizes a variety of niches in human body such as the oral cavity, the gastrointestinal tract, the skin and the urinary tract [74]. Owing to its antimicrobial activities (production of antimicrobial organic acids, ethanol, and reuterin), *L. reuteri* can inhibit the colonization of pathogenic microbes in its vicinity and even reshape the microbial communities in the host [75]. Second, *L. reuteri* can have beneficial impact on the immune system of the host. For instance, it has strong immunomodulatory and anti-inflammatory properties, as manifested by the synthesis of pro-inflam-

matory cytokines and promotion of regulatory T cell growth and function and strengthening of the intestinal barrier, which prevents transfers of gut microbiota from the lumen to tissues [76]. As periodontal diseases are caused by bacteria inhabiting these niches, one of the basic methods of prevention and cure is to decrease the pathogen load by scaling and root planning (SRP), involving the probiotic bacteria. Alternatively, deploying probiotic bacterial strains as a method of biological control of pathogenic ones holds promise in treating the periodontal diseases. Many studies have shown the efficacy of the probiotic bacterium *Lactobacillus reuteri* *Prodentis* (LrP) as a useful therapeutic supplement, as part of periodontal maintenance regime post-intervention. This not only replenishes the oral cavity with useful bacteria, but also decreases the harmful ones. For instance, daily oral administration of *L. reuteri* strains – DSM 17938 and PTA 5289 – in human subjects for 12 weeks resulted in changes in oral microbiota in a randomized controlled trial, while keeping the bacterial species richness unaltered throughout the duration of the trial [77]. In addition, oral *L. reuteri* treatment suppressed the growth of periodontal pathogens in the subgingival microbiota [78]. Studies have also shown that *Lactobacillus reuteri* *Prodentis* can sustainably increase the population of beneficial bacteria in the oral cavity, thus restoring the natural oral flora lost during infection [79].

Several in vitro studies showed *L. reuteri*'s inhibitory effects on periodontopathogens, which are likely due to its by-products: an example is reuterin, a non-protein broad-spectrum antibiotic that can inhibit the growth of a variety of gram-positive/negative bacteria, yeast, and fungi [80]. Many periodontopathogens, such as *P. gingivalis* ATCC 33277, *P. intermedia* ATCC 25611, and *F. nucleatum* ATCC 25586, are effectively inhibited by *L. reuteri* ATCC PTA 5289, except for *A. actinomycetemcomitans* ATCC 33384 [81].

Both live *L. reuteri* PTA 5289 and DSM 17938 and their CFS show inhibition on *P. gingivalis* ATCC 33277 and *F. nucleatum* ATCC 25586; however, only the live form of the two *L. reuteri* inhibited the growth of *A. actinomycetemcomitans* ATCC 29522 in vitro [82, 83]. Another subspecies, *L. reuteri* ATCC 55730, inhibited the growth of *F. nucleatum* ATCC 10953, *P. gingivalis* ATCC 33277, and *A. actinomycetemcomitans* ATCC 33384, also preventing the mortality of HOK cells infected with periodontal pathogens [84].

Exopolysaccharide (EPS) is a substance that *L. reuteri* DSM 17938 produces to enhance in adherence to epithelial cells and to compete with pathogenic bacteria for adhesion sites [85]. The release of IL-6 triggered by *F. nucleatum* in KB cells was shown to be suppressed by *L. reuteri* KCTC 3594. *L. reuteri* was used in clinical trials to inhibit *P. gingivalis*, supragingival plaque, subgingival plaque, and *P. intermedia* in saliva [86, 87]. In patients with peri-implant mucositis, *L. reuteri* DSM 17938 and PTA 5289 for peri-implant diseases could only reduce the load of *P. gingivalis* [88]. In animal investigations, it was discovered that live *L. reuteri* DSM 17938 and PTA 5289 improved immune reactions and increased

hemocyte density in *Galleria mellonella* infected with *P. gingivalis* ATCC 33277 [81, 82]. The immunomodulatory properties of *L. reuteri* may help to manage the imbalance between MMP and TIMP or to inhibit the effectiveness of pro-inflammatory cytokines, which may minimize the inflammation and degeneration of periodontal tissues [89]. This implicates that *L. reuteri* has a repertoire of beneficial traits that can be deployed to successfully manage periodontal pathogens and subgingival microbiota.

Conclusion

The benefits of polyphenols and probiotics in management and cure implicate that these molecules should be given due consideration in terms of clinical evaluation. Although there are numerous in vitro and in vivo studies demonstrating the potential benefits of polyphenols in oral health, strong evidence from well-designed clinical trials is still lacking. On the other hand, *L. reuteri* is already well known for its probiotic effects and bio-antagonism against oral pathogens. It would be interesting to see how these two can act synergistically in combating oral diseases and maintaining oral health.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; ZN, MCM, Kristjana D, Kevin D, STC, FB, PG: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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