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Diet-Oral Microbiome Crosstalk: From Microbial Modulation to Oral Health Promotion

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ABSTRACT: Periodontal diseases are prevalent, multifactorial inflammatory conditions that threaten oral health and are increasingly associated with systemic disorders, including cardiovascular disease, diabetes, and neurodegenerative diseases. Emerging evidence identifies diet as a pivotal modulator of the oral microbiome, influencing the onset and progression of periodontal diseases. This review synthesizes current findings on how specific dietary components—including high-sugar foods, dietary fibers, probiotics, and prebiotics—modulate oral microbial composition and function. High-sugar intake promotes cariogenic and periodontopathogenic biofilms through acidogenesis and biofilm maturation, while fiber-rich diets enhance oral microbial diversity and salivary protective factors. Probiotics demonstrate strain-specific effects in restoring microbial balance and modulating host immunity, whereas certain prebiotics, despite benefiting gut microbiota, may exacerbate oral dysbiosis. Notably, dysregulated oral microbiota can translocate beyond the oral cavity, contributing to inflammatory cascades implicated in respiratory, metabolic, and neurological diseases. This review highlights promising dietary intervention strategies and microbiome-targeted therapeutics, advocating for integrative and precision nutrition approaches to reduce the global burden of periodontal diseases and associated comorbidities.

Keywords: Periodontal diseases, oral microbiome, diet, immunity

1. Introduction

Periodontal diseases (PD) encompass a broad spectrum of pathological conditions affecting the oral cavity and supporting tissues. The World Health Organization (WHO) estimates that approximately 3.69 billion individuals worldwide are affected by oral health conditions (https://www.who.int/news-room/fact-sheets/detail/oral-health). The Global Burden of Disease Study 2021 reported an age-standardized prevalence of 12.50% for severe periodontitis, affecting about 1.07 billion people in 2021[1]. Despite public health advances, global prevalence rates and disability-adjusted life years (DALYs) related to PD have shown minimal improvement over three decades. Although marginal declines in

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untreated dental caries and edentulism have been observed, absolute case numbers continue rising due to global population growth and demographic aging. Additionally, lip and oral cavity cancer incidence continues increasing[2]. Importantly, PD contribute not only to local pathologies such as periodontitis and dental caries but also exacerbate systemic diseases—including cardiovascular disease, diabetes mellitus, and neurodegenerative diseases—through multifactorial mechanisms involving immune-inflammatory responses, metabolic dysregulation, and microbial translocation[3]. These findings underscore the urgent need for integrated strategies addressing oral-systemic health linkages to mitigate the global disease burden.

As the second-largest microbial community in the human body, the oral microbiota functions as a critical interface between external environments and internal physiological systems. Characterized by intricate structure and dynamic equilibrium, this microbial consortium plays a vital role in maintaining oral and systemic homeostasis[4]. Advanced sequencing technologies—including metagenomics, metatranscriptomics, and single-cell sequencing—have opened new avenues for precise PD diagnosis and treatment while enabling interdisciplinary research into systemic associations by elucidating diversity, pathogenicity, and host-microbiota interaction networks[5]. The expanded Human Oral Microbiome Database (eHOMD) documents nearly 800 identified bacterial species in the oral cavity, forming a complex biofilm ecosystem in continuous symbiosis with the host[6]. Subsequent oral microbiome investigations reveal that taxonomic composition and functional states closely correlate with host health, with dysbiosis frequently implicated in oral and systemic condition pathogenesis. These findings highlight the dual role of oral microbiota—as both a physiological balance gatekeeper and, under dysbiosis, a potential initiator of pathological cascades.

Emerging evidence demonstrates that dietary factors—from macronutrient profiles to long-term dietary patterns—profoundly influence oral microbial community structure, function, and metabolic activity, thereby shaping oral and systemic health outcomes[7]. While diet is widely recognized as a primary gut microbiota diversity modulator, food and beverage composition exerts similarly significant effects on oral microbiome stability and ecological balance. High intake of free sugars and refined carbohydrates may promote overgrowth of cariogenic bacteria such as *Streptococcus mutans* (*S. mutans*), whereas fermented foods and certain probiotics may enhance microbial diversity, fostering more resilient and health-promoting oral environments[8]. Notably, although many microbiota-beneficial dietary components provide parallel advantages across oral and gut ecosystems, certain substrates may elicit divergent effects. Fermentable carbohydrates like fructooligosaccharides (FOS) are well-established prebiotics that selectively stimulate beneficial gut bacteria such as *Bifidobacterium* and *Lactobacillus*, supporting gut health and metabolic function. However, these same compounds may also promote the growth of oral pathogens like *S. mutans*, potentially worsening oral inflammation, dental caries, and periodontal disease—though human clinical evidence for these effects remains limited and primarily derived from *in vitro* studies[9, 10]. This apparent dichotomy highlights the need for context-specific dietary frameworks that reconcile oral-gut microbial interactions while minimizing unintended ecological perturbations.

2. Periodontal disease prevalence and medical burden

PD represent a pressing global health concern, characterized by high prevalence, widespread impact, and strong associations with systemic health. More than half of the global adult population is affected, with over one billion individuals suffering from severe periodontitis. The burden increasingly concentrates in low- and middle-income countries, reflecting socioeconomic disparities in access to oral healthcare and preventive strategies.

In 2021, the global burden of severe periodontitis and complete tooth loss (edentulism) remained substantial. Epidemiological estimates indicate that severe periodontitis affected approximately 1.07 billion individuals (95% uncertainty interval [UI]: 896.55–1234.84 million), corresponding to an age-standardized global prevalence of 12.50% (95% UI: 10.53–14.49%)[1]. Notably, significant regional variation was observed, with South Asia exhibiting the highest prevalence at 17.57% (95% UI: 14.73–20.14%). Meanwhile, edentulism impacted an estimated 353 million people worldwide (95% UI: 300.60–416.20 million), with a global age-standardized prevalence of 4.11% (95% UI: 3.50–4.83%). The highest age-standardized prevalence was recorded in Latin America and the Caribbean, reaching 7.39% (95% UI: 6.44–8.39%).

Projection models indicate a sharp rise in the periodontal disease burden by 2050. The number of individuals with severe periodontitis is projected to exceed 1.5 billion—representing a 44.32% increase from 2021—while the edentulous population is expected to rise to over 660 million, reflecting an 84.40% increase. China alone is anticipated to account for 19.67% of global edentulism cases, equating to approximately 130.23 million individuals[11]. Furthermore, modeling forecasts that by 2050, among Level 4 causes of global years lived with disability (YLDs), severe periodontitis will advance by one rank, while edentulism will experience a more dramatic ascent of nine ranks, underscoring its emerging public health significance.

In 2019, the global economic burden of oral diseases was estimated at approximately USD 710 billion. Of this total, direct treatment costs accounted for USD 387 billion, representing an average of USD 50 per capita and approximately 5% of total global direct healthcare expenditures. Oral diseases rank among the highest in terms of direct health-related spending, constituting nearly 50% of the global expenditure associated with diabetes[12]. An analysis of European Union countries further revealed that oral healthcare costs rank third among chronic diseases, surpassed only by diabetes and cardiovascular disease.

In addition to direct costs, productivity losses linked to oral diseases are substantial, amounting to an estimated USD 323 billion globally. Notably, the magnitude of productivity losses is nearly equivalent to direct treatment costs. On a global scale, the average annual productivity loss per capita is approximately USD 42[13]. Strikingly, this burden is comparable to productivity losses from the world's top ten causes of death. The persistently high global prevalence of oral diseases clearly translates into a disproportionately high economic burden.

Importantly, the global economic impact of oral diseases reveals stark disparities across income levels. In low-income countries, average annual per capita dental expenditure is merely USD 0.52, compared to USD 260–500 in high-income countries—a difference exceeding 500-fold. Similarly, per capita productivity losses range from USD 1.49 in low-income settings to USD 185 in high-income contexts, representing more than a

100-fold disparity[14]. To address these challenges, WHO recommends prioritized strategies including tobacco control, improved oral hygiene practices, and integration of primary healthcare services (e.g., fluoride toothpaste use and regular dental screenings). Moving forward, it is essential to enhance regional epidemiological surveillance and promote the widespread adoption of innovative treatment modalities—such as minimally invasive site preservation surgery—to reduce disease burden and economic losses.

3. Oral microbiota and its impact on overall health

The oral microbiota constitutes a complex and dynamic microbial ecosystem colonizing various niches within the oral cavity, including bacteria, fungi, viruses, and archaea. Figure 1 illustrates the oral microbiota and its significant implications for systemic health, including PD, respiratory disorders, Alzheimer's disease, and intestinal conditions. The distribution of microorganisms differs markedly across distinct oral anatomical sites. Dental plaque on the tooth surfaces represents a highly structured biofilm primarily composed of *S. mutans*, *Selenomonas sputigena*, *Fusobacterium nucleatum* (*F. nucleatum*), *Actinomyces*, and *Lactobacillus*. The gingival sulcus harbors pathogenic taxa such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Aggregatibacter actinomycetemcomitans*. Additionally, the oral mucosa is colonized by a range of species including *F. nucleatum*, *Streptococcus salivarius*, *Lactobacillus*, *Prevotella*, *Neisseria*, and fungal species such as *Candida*[15]. The tongue surface predominantly supports microbial communities composed of *Streptococcus salivarius*, *Prevotella*, *Veillonella*, and *Neisseria*.

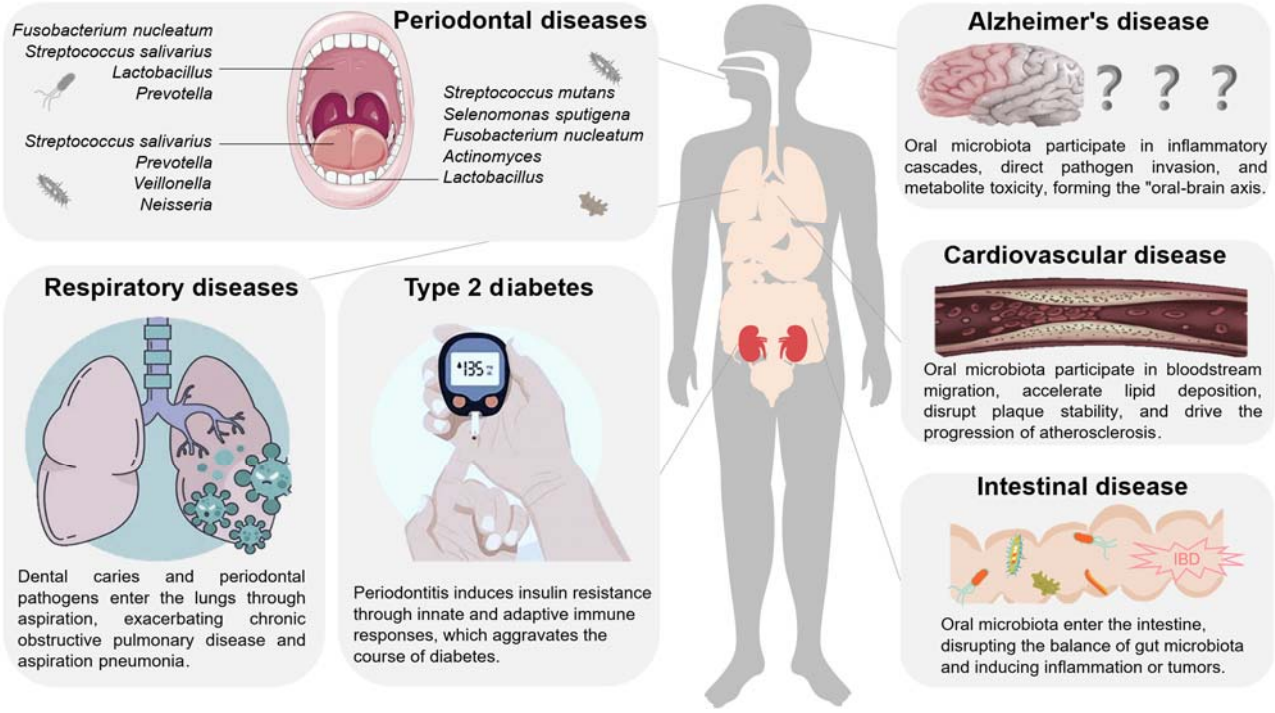

Figure 1. Oral microbiome dysbiosis and its systemic implications in chronic diseases: host-microbial interactions driving inflammation and tissue-specific pathology.

The oral microbiota plays a critical role in maintaining and disrupting systemic metabolic homeostasis through dynamic interactions within the "oral-intestinal metabolic axis," emerging as a novel focus in metabolic disease research. Halitosis, the most immediate external symptom of periodontal disease, originates

from the oral cavity in approximately 80% to 90% of cases. Dysbiosis of the oral microbiota underlies both periodontal disease and halitosis, characterized by the enrichment of pathogens such as *P. gingivalis*, *F. nucleatum*, and *Prevotella intermedia*[16].

Among these pathogens, *P. gingivalis* is a principal periodontal pathogen that degrades host tissue proteins—including collagen and fibrinogen—via secretion of gingipains (e.g., Rgp and Kgp). This proteolytic activity releases peptides utilized by other bacteria and leads to the production of volatile sulfur compounds (VSCs), such as hydrogen sulfide (H_2S). *Prevotella intermedia* markedly increases during the active phase of periodontitis, where it degrades hemoglobin to release hydrogen sulfide and methyl mercaptan (CH_3SH), and produces short-chain fatty acids (SCFAs) by breaking down salivary glycoproteins, thereby compromising the gingival epithelial barrier[17]. Additionally, *Solobacterium moorei*, a Gram-positive anaerobic bacterium predominantly colonizing the tongue coating, generates substantial quantities of VSCs by metabolizing sulfur-containing amino acids like cysteine and methionine, representing a significant contributor to halitosis. Furthermore, periodontal abscesses and periodontal pocket exudates are frequently associated with *Staphylococcus aureus* co-infection alongside periodontal pathogens, which can also produce malodorous compounds[18].

Periodontal pathogens can invade the lungs via inhalation or hematogenous routes, synergistically accelerating the progression of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and pneumonia via systemic inflammatory responses. Agarwal et al. investigated differences in nasal and oral microbiota between healthy individuals and COPD patients in a rural Indian cohort, revealing significant disparities in key taxa. For example, nasal samples from COPD patients showed markedly increased abundances of *Actinomyces*, *Actinobacillus*, *Megasphaera*, and *Selenomonas* compared to healthy controls[19]. Oral secretions—including saliva and periodontal exudate—are frequently aspirated into the lower respiratory tract during sleep, coughing, or impaired swallowing, representing the primary route for oral microbes to access the lungs. Individuals with periodontitis exhibit oral bacterial loads 10 to 100 times higher than healthy counterparts, substantially elevating aspiration risk. Periodontitis-induced bacteremia can facilitate bacterial dissemination to the lungs via the bloodstream, particularly during periodontal therapy or mastication when gingival ulcerations provide entry points for microbial invasion. *Streptococcus pneumoniae* colonizing the oral cavity is a well-recognized etiologic agent of bacterial pneumonia, especially in elderly or immunocompromised populations at heightened risk. Moreover, oral fungal infections such as candidiasis may disseminate to the lungs through inhalation of *Candida albicans*, leading to fungal pneumonia, which is more prevalent among patients undergoing prolonged antibiotic or immunosuppressive treatments[20].

Recent studies have demonstrated a close association between oral microbiota dysbiosis and the onset and progression of Alzheimer's disease (AD), with periodontal pathogens playing a particularly critical role by potentially inducing or exacerbating neurodegenerative processes through multiple mechanisms. Periodontal bacteria such as *P. gingivalis* can enter the systemic circulation via bacteremia, where their lipopolysaccharides (LPS) trigger endothelial inflammation, increase blood–brain barrier (BBB)

permeability, and facilitate the invasion of bacteria and toxins—including outer membrane vesicles (OMVs)—into brain tissues[21]. These bacteria may also invade AD-relevant brain regions, such as the brainstem and hippocampus, via cranial nerves including the trigeminal and olfactory nerves. For instance, *P. gingivalis* secretes gingipains that degrade the extracellular matrix of neural cells, accelerating neuronal injury. Moreover, certain oral bacteria, including *Escherichia coli* and *P. gingivalis*, can interfere with host amyloid precursor protein metabolism, promote amyloid-β (Aβ) aggregation, form protective biofilms, and induce neurotoxicity. Additionally, periodontal pathogens such as *Prevotella* may displace beneficial nitrate-reducing bacteria like *Neisseria* in the oral cavity, thereby inhibiting nitric oxide (NO) synthesis—a molecule essential for synaptic plasticity and long-term potentiation (LTP)[22]. Notably, these links are supported mainly by heterogeneous human observational studies together with mechanistic evidence from *in vitro* and animal models; definitive human causal relationships remain to be established.

Epidemiological studies have demonstrated that patients with periodontitis exhibit a 1.5- to 2-fold increased risk of inflammatory bowel disease (IBD), with IBD patients also presenting more severe gingival inflammation. Adults typically swallow between 1.0 and 1.5 liters of saliva daily, and oral bacteria such as *P. gingivalis* and *F. nucleatum* can survive gastric acidity to colonize the intestine. The relative abundance of oral pathogens—including *F. nucleatum* and *Campylobacter*—is significantly elevated in both saliva and intestinal samples of Crohn's disease (CD) patients[23]. Sequencing analyses of the oral microbiota in IBD patients revealed substantial differences in salivary microbial communities compared to healthy controls[19]. Notably, there was a pronounced increase in the relative abundance of *Bacteroidetes* alongside a concomitant decrease in *Proteobacteria*. These compositional shifts were associated with altered microbial metabolites, including butyrate, thereby contributing to oral microbiota dysbiosis and further exacerbating gut microbial perturbations in IBD.

4. Regulatory mechanisms of dietary components on the oral microbiota

The influence of dietary patterns on periodontal health is garnering increased scrutiny, particularly the contrasting roles of high-sugar and high-fiber diets. High-sugar diets promote the proliferation of cariogenic and periodontal pathogens, exacerbating plaque accumulation and inflammatory responses. Conversely, high-fiber diets may confer protective effects on periodontal tissues by modulating microbial composition, enhancing salivary secretion, and exerting anti-inflammatory actions. Figure 2 illustrates the regulatory mechanisms of dietary components on the oral microbiota and periodontal health.

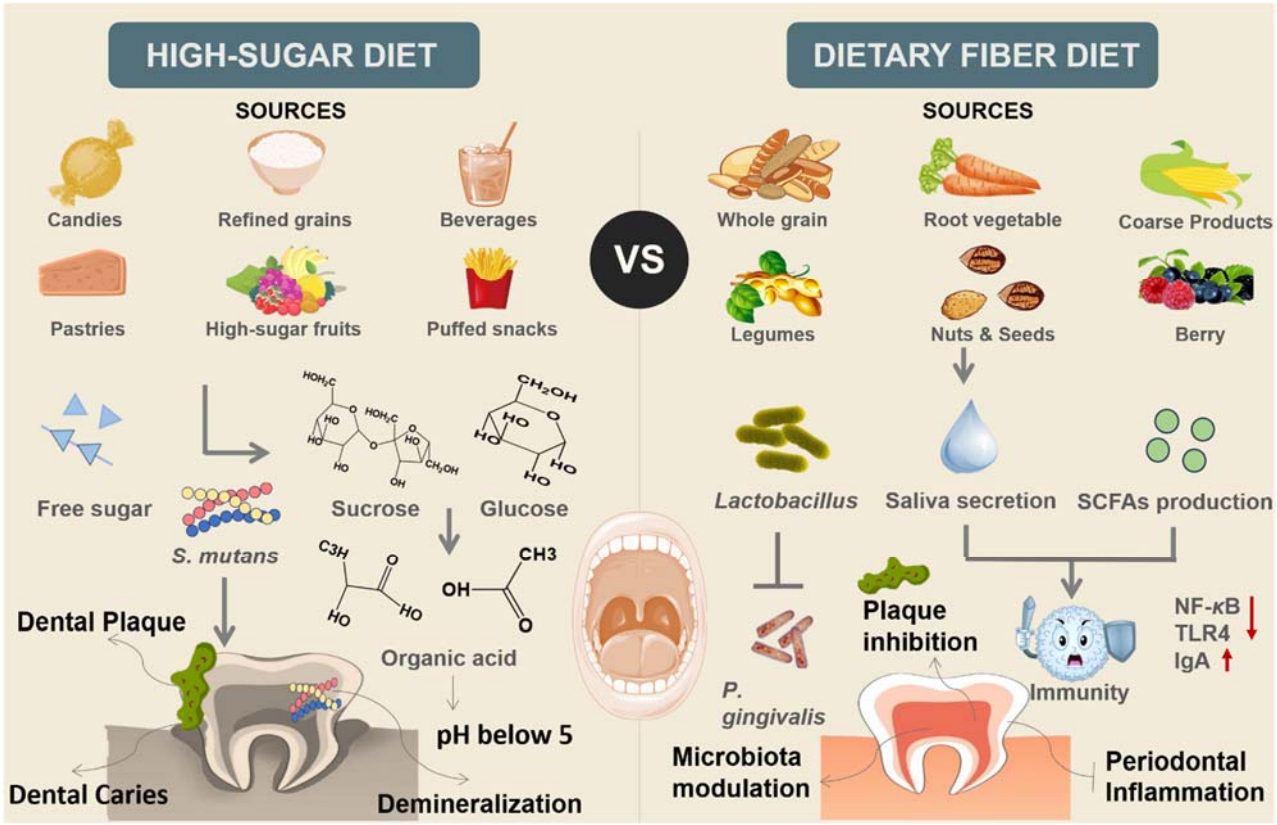

Figure 2. Comparative analysis of high-sugar and dietary fiber diets: sources and mechanistic impacts on oral health. A high-sugar diet induces dental plaque, demineralization, and caries via free sugar metabolism, Streptococcus mutans proliferation, and organic acid production. Conversely, a dietary fiber-rich diet protects against periodontal inflammation by promoting Lactobacillus, salivary secretion, and short-chain fatty acid production, while inhibiting plaque, modulating oral microbiota, and enhancing immune responses.

4.1 High-sugar diet

High-sugar foods, characterized by elevated sugar content, are predominantly sourced from processed products that constitute a major component of modern dietary patterns. The WHO recommends limiting daily free sugar intake to less than 10% of total energy consumption (approximately 50 g), with an optimal target of under 5% (approximately 25 g), while the American Heart Association (AHA) advises restricting added sugar intake—defined as sugars incorporated during food processing and preparation—to less than 36 g/day for men and 25 g/day for women[24]. Chronic consumption exceeding these thresholds is classified as a high-sugar diet and has been associated with increased risk of metabolic, cardiovascular, and oral health complications. Dietary sugars, primarily in the form of added or free sugars, are commonly present in six major food categories: (1) candies (e.g., hard candies, milk-based sweets, and candied fruits), with sugar content typically ranging from 50% to 70%; (2) refined grains (e.g., white rice, white bread, and glutinous rice products), with 15–30% sugar content; (3) sugar-sweetened beverages (e.g., cola, milk tea, and concentrated fruit juices), containing approximately 10 g of sugar per 100 mL; (4) pastries and desserts (e.g., cakes, ice cream, cookies, and donuts), with 20–30% sugar content; (5) high-sugar fruits (e.g., custard apple, lychee, fresh jujube, and banana), containing 10–25% sugar; and (6) puffed snacks (e.g., potato chips, popcorn, and shrimp crackers), with sugar content ranging from 10% to 30%. These products cumulatively contribute to excessive sugar

intake and underscore the urgent need for dietary guidelines and public health interventions aimed at curbing sugar overconsumption[25-27].

Accumulating clinical evidence has identified dietary sugar intake as a significant and modifiable risk factor in the etiology of periodontal disease. A recent machine learning analysis of dietary records from 11,704 participants in the National Health and Nutrition Examination Survey (NHANES) revealed that higher sugar consumption was significantly associated with increased risk of chronic periodontitis (adjusted odds ratio [OR] = 2.12; 95% confidence interval [CI]: 1.06–4.26; p = 0.036), exceeding conventional risk thresholds in periodontal epidemiology[28]. Complementary findings from a meta-analysis involving 209 participants demonstrated that restricting free sugar intake, compared to no restriction, significantly improved gingival health scores (standardized mean difference [SMD] = −0.92; 95% CI: −1.43 to −0.42; P < 0.004; heterogeneity I-squared [I^2] = 46.8%), with a non-significant trend toward reduced dental plaque accumulation (SMD = −0.61; 95% CI: −1.28 to 0.05; P < 0.07; I^2 = 41.3%)[29]. Additionally, a cross-sectional study of 2,515 adolescents aged 18–19 years reported a significant association between high sugar intake and periodontal disease affecting four or more teeth (prevalence ratio [PR] = 1.42; 95% CI: 1.03–1.94; p = 0.030)[27, 30]. Collectively, these findings underscore the detrimental impact of excess dietary sugar on periodontal health and support dietary sugar reduction as a viable public health intervention for periodontal disease prevention.

The impact of dietary sugar on the oral microbiota represents a multifaceted biological process involving dynamic microbial transitions, metabolite interplay, and alterations in the host microenvironment. Dietary sugars are generally categorized into free sugars and intrinsic sugars. Free sugars—including sucrose and fructose—are rapidly fermented by oral bacteria and possess strong cariogenic potential, commonly found in processed foods and beverages[31]. Conversely, intrinsic sugars, naturally present in fruits and lactose, exert lower cariogenicity due to slower metabolic rates and structural encapsulation within plant cell walls. Excessive intake of fermentable carbohydrates promotes the overgrowth of cariogenic microorganisms within dental plaque, with free sugars serving as key metabolic substrates. Upon entering the oral cavity, dietary starches undergo hydrolysis by salivary α-amylase into oligosaccharides, including maltose, maltotriose, and dextrins. Cariogenic species such as *S. mutans* and *Lactobacillus* further convert these intermediates into monosaccharides like glucose and fructose via enzymes such as glucosidase and sucrase[32]. These monosaccharides undergo rapid metabolism through glycolysis, producing organic acids (e.g., lactic and acetic acid) that lower the local pH below 5.0. This acidified niche not only drives enamel demineralization but also selects for aciduric species such as *S. mutans* and *Leptotrichia*, thereby exacerbating caries progression. Simultaneously, bacterial glucosyltransferases (GTFs) convert sugars into extracellular polysaccharides (e.g., insoluble glucans), enhancing bacterial adhesion and promoting the development of dense, acid-retentive biofilms (dental plaque)[33]. These biofilms shield microbial communities from mechanical disruption and sustain localized acid exposure, accelerating enamel erosion and contributing to the chronicity of dental caries.

4.2 Dietary fiber diet

Dietary fiber, composed of indigestible carbohydrate polymers primarily derived from plant sources, resists hydrolysis by human oral and gastrointestinal enzymes. Current nutritional guidelines recommend a daily intake of 25–38 g for adults, achievable through consumption of whole grains (e.g., oats, brown rice), legumes, leafy vegetables, and low-sugar fruits (e.g., guava, blueberries)[34]. However, epidemiological data indicate that most adult populations fail to meet these targets. Increasing evidence suggests that dietary fiber exerts beneficial effects on oral microbial ecology by enhancing microbial diversity and selectively promoting the proliferation of health-associated taxa such as *Lactobacillus* spp., particularly via substrates derived from grains, vegetables, and fruits[35]. These commensal bacteria competitively inhibit the colonization and persistence of key periodontal pathogens, including *P. gingivalis* and *F. nucleatum*, thereby contributing to the maintenance of ecological homeostasis within the oral cavity[36]. High-fiber diets also mitigate acidogenic oral environments by reducing the availability of fermentable substrates necessary for periodontopathogen metabolism, thus limiting their growth and virulence. Moreover, the mastication of fiber-rich foods (e.g., apples, carrots) stimulates salivary secretion, facilitating mechanical biofilm clearance and enhancing innate defense via salivary components such as lysozyme and secretory immunoglobulins. Additionally, the physical properties of dietary fiber aid in the removal of food debris and enhance the self-cleaning capacity of the oral cavity, collectively contributing to the prevention of plaque accumulation and the promotion of oral health[37, 38].

Supplementation with dietary fiber resulted in statistically significant improvements across various parameters of periodontal health. A recent meta-analysis investigating the effect of dietary fiber on periodontitis management demonstrated that 4–8 weeks of fiber-enriched dietary intervention significantly reduced key periodontal metrics, including clinical attachment loss (mean reduction of 0.48 mm per tooth; 95% CI: −0.63 to −0.33; $P < 0.001$), bleeding on probing (27.57% site reduction; 95% CI: −50.40 to −4.74; $p = 0.02$), and periodontal inflamed surface area (decreased by 173.88 mm²; 95% CI: −288.06 to −59.69; $p = 0.003$). These improvements were accompanied by modest decreases in plaque index (0.02 units; 95% CI: −0.04 to 0.00; $p = 0.04$) and gingival index (0.41 units; 95% CI: −0.67 to −0.16; $p = 0.002$). Conversely, probing depth showed no statistically significant change (mean change of −0.17 mm per tooth; 95% CI: −0.37 to 0.02; $p = 0.09$)[39].

In a randomized controlled pilot study, a carbohydrate-restricted diet supplemented with omega-3 fatty acids, vitamins C and D, and dietary fiber elicited significant reductions in caries- and periodontitis-associated pathogens, accompanied by beneficial shifts in oral microbiota composition[40]. Salivary analyses demonstrated significant decreases in *Actinomyces* spp. and *Capnocytophaga* spp. within the intervention group. Furthermore, supragingival plaque analysis revealed reductions in *Streptococcus mitis* group, *Granulicatella adiacens*, *Actinomyces* spp., and *Fusobacterium* spp. following implementation of the nutrient-dense, low-carbohydrate diet. While earlier studies posited that dietary fiber fermentation occurs exclusively in the intestine, recent research has confirmed that oral microbiota can initiate fiber degradation.

Studies have demonstrated that oral microbiota directly contribute to dietary fiber degradation, notably by converting fiber into SCFAs precursors via carbohydrate-active enzymes (CAZymes), such as glycoside hydrolases. SCFAs (e.g., butyrate) generated through oral microbiota metabolism of dietary fiber exhibit localized immunoregulatory effects and may inhibit periodontal pathogens, including *P. gingivalis*, with evidence primarily derived from *in vitro* studies and genome-based functional annotations of cultivated oral bacteria[41].

5. Probiotics and prebiotics

Probiotics and prebiotics represent promising therapeutic approaches for periodontal disease management. Specific probiotic strains demonstrate three key beneficial effects: direct antagonism against periodontal pathogens, inhibition of microbial adhesion, and modulation of host immune responses toward an anti-inflammatory state. Complementary to this, prebiotics selectively stimulate the growth of beneficial commensal bacteria, thereby promoting microbial homeostasis and enhancing ecological stability. Figure 3 systematically illustrates these interconnected mechanisms, encompassing microbial modulation, immune regulation, and mucosal barrier reinforcement.

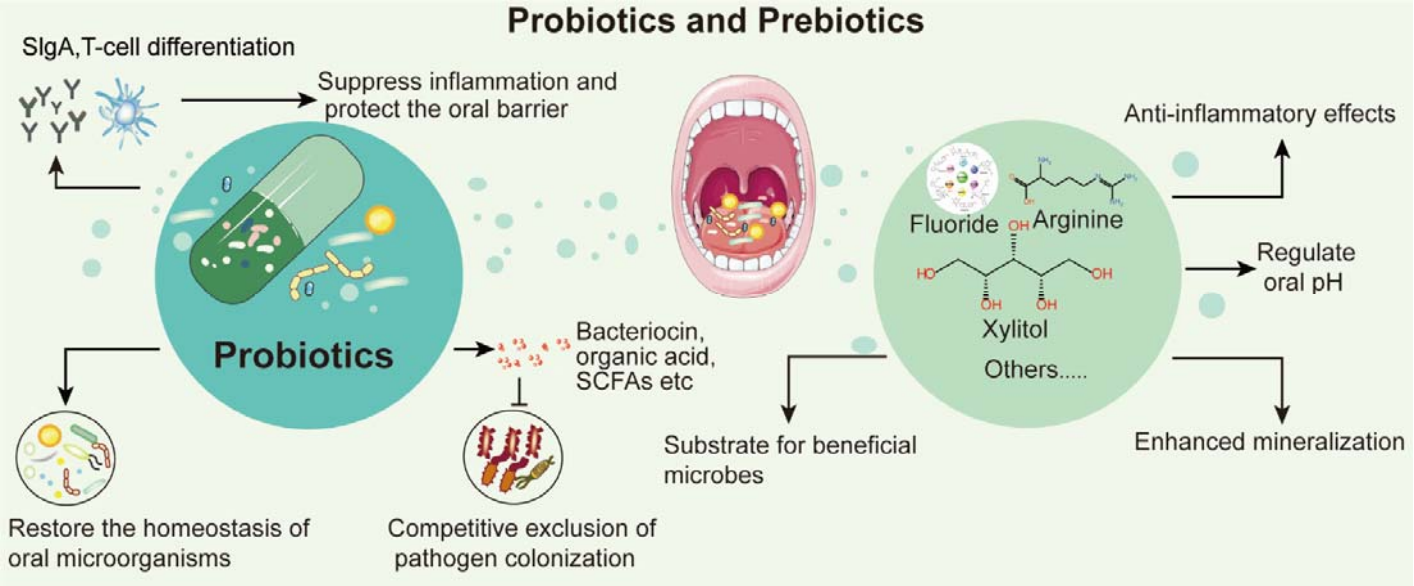

Figure 3. Mechanisms of probiotics and prebiotics in oral health modulation. Probiotics restore oral microbial homeostasis, competitively exclude pathogen colonization, and suppress inflammation through bacteriocin, organic acid, and short-chain fatty acid production. Prebiotics further support beneficial microbes by regulating oral pH, enhancing mineralization, and exerting anti-inflammatory effects.

5.1 Probiotics

Probiotics have emerged as a promising therapeutic approach for managing oral diseases through three primary mechanisms: restoration of oral microbial homeostasis, competitive exclusion of pathogenic colonization, and modulation of host immune responses. Recent mechanistic studies have elucidated that successful initial mucosal colonization is a critical prerequisite for probiotic efficacy in managing periodontitis (Table 1). Probiotics exert direct antimicrobial effects through biosynthesis of effector molecules—including bacteriocins, organic acids, SCFAs, and antimicrobial peptides—that disrupt essential

metabolic pathways in periodontal pathogens[42]. Competitive exclusion occurs through two mechanisms: spatial occupation of mucosal adhesion receptors, preventing pathogen binding, and nutrient sequestration, limiting substrates essential for pathogen proliferation. Concurrently, probiotics modulate mucosal immunity by coordinating T-cell differentiation, enhancing secretory immunoglobulin A (sIgA) production, and inducing anti-inflammatory cytokine cascades[43]. Furthermore, probiotics strengthen oral mucosal barrier integrity by suppressing epithelial apoptosis and upregulating tight junction protein expression, such as claudin-1 and occludin[44].

Table 1. Bioactive substances and their documented modulatory effects on periodontal pathophysiological parameters.

Bioactive Category	Compound/Formulation	Documented Effects on Periodontal Parameters	Reference
Probiotics	*Lactobacillus acidophilus*, *L. rhamnosus*, *Bifidobacterium longum*, *Saccharomyces boulardii* in probiotic mouth rinse	Elevated salivary IgA and pH levels; significant improvements in gingival index (GI), probing depth (PD), and clinical attachment level (CAL)	[45]
	L. reuteri suspension (administered via blunt syringe)	Reduction in *Porphyromonas gingivalis* load; decreased plaque index and bleeding on probing (BOP)	[46]
	L. salivarius WB21 tablets	Decrease in oral malodor at 2 weeks; significant reductions in organoleptic test scores and BOP at 4 weeks	[48]
	L. casei Shirota in probiotic milk	BOP and gingival crevicular fluid (GCF) volume significantly decreased despite higher baseline PI, GI, and GCF	[47]
Prebiotics / Fluoride-based Therapies	Fluoride toothpaste (1450 ppm NaF)	1450 ppmF group showed 16% lower dmft vs. control ($P < 0.05$); no significant effect in 440 ppm F group	[86]
	Sodium fluoride dentifrice (2200–2800 ppm)	Reduction in DMFS index by 18.6% and 20.4%, respectively; statistically significant ($P < 0.05$)	[87]
Arginine-based Therapies	Dentifrice with 1.5% arginine + 1450 ppm fluoride	Reduced lesion scores (0.7%) vs. control (18.2%); ECM readings improved	[88]
	8.0% arginine + calcium carbonate toothpaste	Significant reduction in dentin hypersensitivity ($P < 0.001$); faster desensitization response ($P < 0.05$)	[89]
Xylitol-based Therapies	Pediatric xylitol oral syrup	Significantly fewer decayed teeth (0.6±1.1 vs. 1.9±2.4); Relative Risk = 0.30; $p = 0.003$	[90]
	Xylitol lozenges	40% reduction in root caries incidence (IRR = 0.60; 95% CI: 0.44–0.81; $P < 0.001$); no effect on other caries types	[91]
	Xylitol Chewing gum	Xylitol gum significantly reduced caries (RR: 0.27; 95% CI: 0.20–0.36; $P < 0.0001$); sorbitol gum moderately effective (RR: 0.74; $p = 0.0074$); sucrose slightly increased caries risk (RR: 1.20; $p = 0.11$)	[92]
Others	Intra-pocket application of Grape Seed Extract	Significant reduction in probing depth ($p = 0.002$) and relative attachment level ($p = 0.01$); no significant effect on plaque or gingival index	[63]
	Oral supplementation of Resveratrol	Significant improvement in plaque index ($p = 0.0001$); no significant change in PD, CAL, BI, IL-8, or IL-1β levels	[64]
	Oral supplementation of Aged Garlic Extract	Significant reduction in pocket depth at 18 months compared to placebo ($P < 0.001$), showing improvement in periodontitis.	[65]
	Mouthwash containing Glycyrrhiza uralensis extract	Significant reduction in O'Leary index, plaque index, GI, and periodontal pathogens compared to control ($P < 0.05$)	[66]

Current research on probiotics for periodontal disease treatment presents conflicting findings, reporting both significant and negligible effects. A randomized controlled trial assessed a probiotic mouth rinse containing *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Saccharomyces boulardii* as an adjunct to mechanical debridement in stage II periodontitis[45]. The probiotic group exhibited significant improvements in clinical parameters—including gingival index, probing depth, and clinical attachment gain—and salivary biomarkers such as IgA and pH, compared to placebo at both 1- and 3-month follow-ups, supporting its adjunctive therapeutic potential. Chronic periodontitis patients undergoing scaling and root planing (SRP) combined with subgingival administration of 1 mL probiotic *L. reuteri* suspension demonstrated statistically significant reductions in mean plaque index and bleeding on probing (BOP) scores at 3–6 months compared to baseline ($P < 0.05$). Additionally, *P. gingivalis* levels were significantly decreased at 3–6 months ($P < 0.05$)[46], highlighting the antimicrobial efficacy of *L. reuteri* as a promising adjunctive treatment for periodontal improvement. A pilot study investigated the effects of daily consumption of a probiotic milk drink over 28 days on clinical inflammatory parameters of the oral gingiva during different stages of plaque-induced gingivitis. The study found that such consumption mitigated plaque-induced gingival inflammation despite higher plaque scores, which were attributed to the high carbohydrate content of the probiotic beverage[47]. Mayanagi et al. examined the impact of orally administered *Lactobacillus salivarius* WB21 on halitosis severity and related clinical parameters[48]. Their findings indicated that this probiotic strain primarily alleviated physiologic halitosis and reduced bleeding on probing of periodontal pockets. However, several studies have reported that probiotic intake does not significantly alter the oral microbiota in certain clinical contexts. Recent systematic reviews consistently show that probiotic supplementation fails to induce clinically meaningful changes in peri-implant microbial communities or improve therapeutic outcomes when used alongside conventional treatments for peri-implant mucositis and peri-implantitis[49]. Given the lack of demonstrated clinical efficacy, incorporation of probiotics into non-surgical treatment protocols for these inflammatory conditions remains unsupported by current evidence.

5.2 Prebiotics

The International Scientific Association for Probiotics and Prebiotics defines prebiotics as “a substrate selectively utilized by host microorganisms and capable of providing health benefits”[50]. Xylitol, arginine, nitrate, urea, and other compounds are considered potential prebiotics capable of improving the ecological balance of the oral microenvironment. Some of these compounds are utilized as prebiotic preparations for the prevention and treatment of oral diseases (Table 1).

5.2.1 Arginine

Arginine, a semi-essential amino acid and a natural component of saliva, exerts multi-targeted mechanisms in the prevention and treatment of oral diseases, particularly in caries prevention, periodontal disease management, and dentin hypersensitivity treatment. Research has demonstrated that arginine not only promotes hydroxyapatite deposition and occludes dentinal tubules, but its remineralizing and desensitizing

effects have also been scientifically validated[51]. Kleinberg revealed that arginine can buffer and regulate salivary pH through bacterial metabolism that produces ammonia. Due to its high solubility, arginine readily adsorbs onto tooth surfaces and within dentinal tubules. The positively charged arginine molecules bind to negatively charged dentin surfaces, thereby increasing the local pH and facilitating the adsorption of calcium and phosphate ions from saliva, promoting their deposition onto the dentin surfaces and within the tubules[52]. Based on recent findings, continuous use of an 8% arginine-containing dentifrice over eight weeks enhances the arginolytic capacity of saliva, reduces sucrose metabolism, and shifts the microbial profile toward an ecologically balanced and health-associated microbiota[53].

In a tri-species biofilm model consisting of *S. mutans*, *Actinomyces naeslundii*, and *Streptococcus gordonii*, arginine significantly suppressed total biofilm formation while selectively promoting the growth of *A. naeslundii* and *S. gordonii*. Concurrently, it reduced the synthesis of insoluble extracellular polysaccharides, suppressed bacteriocin production in *S. mutans*, and enhanced hydrogen peroxide (H_2O_2) generation by *S. gordonii*[54]. Furthermore, fluoride contributes to caries prevention by disrupting dental plaque ecology and modulating the physicochemical balance between demineralization and remineralization. Notably, arginine and fluoride exhibit synergistic interactions: their combined application enriches alkali-producing *Streptococcus sanguinis* while suppressing acidogenic *S. mutans*, thereby optimizing the enamel's de-/remineralization balance[55]. This dual-action approach demonstrates superior clinical efficacy compared to fluoride-only dentifrices in promoting remineralization.

Building upon the foundational concept of arginine-induced remineralization and desensitization, Colgate-Palmolive developed and optimized its proprietary Pro-Argin® Technology. This patented system employs a dual-active formulation containing 8% arginine and calcium carbonate, which synergistically occlude dentinal tubules through targeted mineral deposition[56]. Dentifrices utilizing this technology have demonstrated significant clinical efficacy in managing dentin hypersensitivity, with multiple randomized controlled trials confirming superior outcomes in patient-reported sensitivity reduction.

5.2.2 Xylitol

Xylitol functions as a non-cariogenic, cariostatic polyol that resists bacterial fermentation, thereby preventing acidogenesis and subsequent caries development[57]. One primary mechanism involves the passive substitution of cariogenic free sugars—such as sucrose—with xylitol. Sugar alcohols have been consistently demonstrated in *in vitro*, animal, and human cariogenicity studies to be non-acidogenic or hypo-acidogenic, and thus minimally or non-cariogenic. Replacing fermentable sugars with non-cariogenic sugar alcohols has been shown to significantly reduce dental caries incidence[58].

Xylitol also exhibits antimicrobial activity via intracellular phosphorylation through bacterial glycolytic pathways, resulting in the formation of unmetabolizable xylitol-5-phosphate. This cytotoxic intermediate depletes intracellular ATP reserves, induces cytoplasmic efflux, and ultimately leads to energy collapse and bacterial cell death. Additionally, xylitol stimulates salivary flow, increases plaque pH, and stabilizes calcium and phosphate ion concentrations, thereby promoting enamel remineralization and buffering dietary acids.

Saliva contributes to caries prevention through four distinct mechanisms: (1) mechanical cleansing and flushing action; (2) provision of calcium, phosphate, and fluoride ions necessary for enamel remineralization; (3) buffering of plaque acids via carbonate, phosphate, and protein systems; and (4) defense through intrinsic antibacterial components[59].

Experimental evidence demonstrates that xylitol begins to exert inhibitory effects on *P. gingivalis* at a concentration of 5%, with efficacy increasing in a dose-dependent manner and achieving complete growth inhibition at 20%. In addition to its antimicrobial properties, xylitol significantly attenuates the production of pro-inflammatory cytokines—tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β)—which are prominently expressed in inflamed periodontal tissues and play critical roles in bone remodeling. By reducing insoluble extracellular polysaccharides and suppressing *S. mutans* proliferation, xylitol enhances the efficacy of fluoride dentifrices through synergistic mechanical biofilm disruption.

Beyond dental applications, xylitol exhibits selective antimicrobial activity in wound care contexts. Concentrations ranging from 2% to 20% (optimal at 20%) have been shown to inhibit *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis* within chronic wound biofilms. Moreover, a combination of 5% xylitol and 2% lactoferrin effectively suppresses methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms[60]. Additional oral health benefits include inhibition of both *S. mutans* and *Lactobacillus* spp. growth, as well as modulation of sucrose-induced salivary pH without contributing to increased plaque acidity[61].

A long-term randomized trial assessed the caries-preventive efficacy of low-dose xylitol chewing gum (2.5 g/day) over a one-year period in adults at high risk of dental caries. Compared to polyol-based control gum, the xylitol group exhibited a significantly lower total caries increment (1.25 ± 1.26 vs. 1.80 ± 2.33; p = 0.01). This corresponded to a 23% reduction in per-tooth caries risk, with a number needed to treat (NNT) of 55 teeth. Furthermore, xylitol significantly reduced the area under the curve (AUC) at pH 5.7—indicating diminished acid exposure—and markedly decreased salivary *mutans streptococci* concentrations during follow-up ($P < 0.01$)[62].

5.2.3 Others

Recent studies have highlighted the potential of various natural bioactive compounds in preventing and managing periodontal diseases through antimicrobial, anti-inflammatory, and ecological modulation of the oral microbiome. Intra-pocket application of grape seed extract has been associated with significant reductions in probing depth and relative attachment loss (p = 0.002 and p = 0.01, respectively), although without notable effects on plaque or gingival indices[63]. Similarly, resveratrol oral supplementation resulted in marked improvement in plaque index (p = 0.0001), albeit without significant changes in other clinical or inflammatory parameters such as probing depth, clinical attachment level, bleeding index, or key cytokines[64].

In a long-term randomized controlled trial, aged garlic extract (AGE) supplementation over 18 months significantly reduced periodontal pocket depth compared to placebo ($P < 0.001$), suggesting durable anti-inflammatory and tissue-protective effects[65]. Moreover, the use of a mouthwash containing *Glycyrrhiza*

uralensis extract demonstrated clinically meaningful reductions in O'Leary index, plaque index, gingival index, and periodontal pathogens over a 5-day intervention ($P < 0.05$), indicating both antibacterial and anti-inflammatory benefits[66].

Inulin, a well-characterized prebiotic, demonstrates promising potential in modulating oral microbiota and mitigating periodontitis. Emerging evidence indicates that inulin supplementation significantly enhances the relative abundance of beneficial probiotic genera, particularly *Lactobacillus* and *Bifidobacterium*, while simultaneously exerting dose-dependent suppressive effects on periodontitis-associated pathogens including *Streptococcus*, *Veillonella*, *Fusobacterium*, *Porphyromonas*, and *Prevotella*. Furthermore, inulin reduces biofilm alpha diversity, indicating a potential mechanism of pathogenic inhibition through microbial community structure simplification. These findings, though primarily derived from *in vitro* experimental models, collectively suggest that inulin can modulate biofilm composition in a manner conducive to oral health. This prebiotic-mediated ecological shift may attenuate dysbiosis-driven inflammation and provide theoretical foundation for utilizing inulin as an adjunctive strategy in periodontitis prevention and management[67]. Nevertheless, further studies are warranted to elucidate precise molecular mechanisms and validate clinical efficacy through well-designed human trials.

Polydextrose functions as a prebiotic that plays a critical role in immunomodulation and oral health maintenance by enhancing SCFAs production and absorption, particularly acetate and butyrate. Experimental evidence demonstrates that polydextrose supplementation facilitates increased SCFAs synthesis and rapid uptake, which indirectly stimulates salivary sIgA secretion through autonomic nervous system activation. As a key mucosal immunity component, sIgA binds microbial antigens, preventing pathogen adhesion to oral surfaces and thereby contributing to microbial homeostasis and periodontopathogenic bacterial overgrowth suppression[68]. Among SCFAs, butyrate is well-recognized for its potent anti-inflammatory properties, downregulating pro-inflammatory cytokine release and modulating host immune signaling pathways to mitigate tissue inflammation. Although precise mechanistic involvement of polydextrose-derived SCFAs in periodontitis pathogenesis and progression remains to be fully elucidated, current findings suggest that polydextrose may exert beneficial effects through oral immune barrier enhancement and microbial ecology regulation[69]. These attributes position polydextrose as a promising candidate for adjunctive periodontal disease management intervention.

Polyphenolic compounds present in fermented lingonberry juice (FLJ), including anthocyanins, proanthocyanidins, and quercetin, possess potent anti-inflammatory and antimicrobial activities, highlighting their potential as prebiotic agents in periodontitis management. FLJ contributes to oral microbial homeostasis by suppressing major periodontal pathogens, including *P. gingivalis* and *F. nucleatum*, while concurrently enhancing beneficial *Lactobacillus* spp. growth. Moreover, FLJ significantly reduces active matrix metalloproteinase-8 (aMMP-8) levels, thereby attenuating periodontal tissue degradation and dampening local inflammatory responses[70]. These effects are mediated through polyphenol-induced inhibition of pro-inflammatory cytokine secretion and protease activity via antioxidant and anti-inflammatory pathways.

Additionally, FLJ enhances salivary flow, contributing to mucosal protection and reducing both plaque accumulation and gingival bleeding.

6. Dietary intervention strategies for periodontal disease prevention via oral microbiota modulation

Functional food development offers a promising strategy for oral microbiota modulation. The primary objective involves enhancing oral microbial homeostasis by introducing targeted bioactive components, thereby supporting both oral and systemic health. Current research efforts have increasingly focused on key areas of investigation, as illustrated in Figure 4.

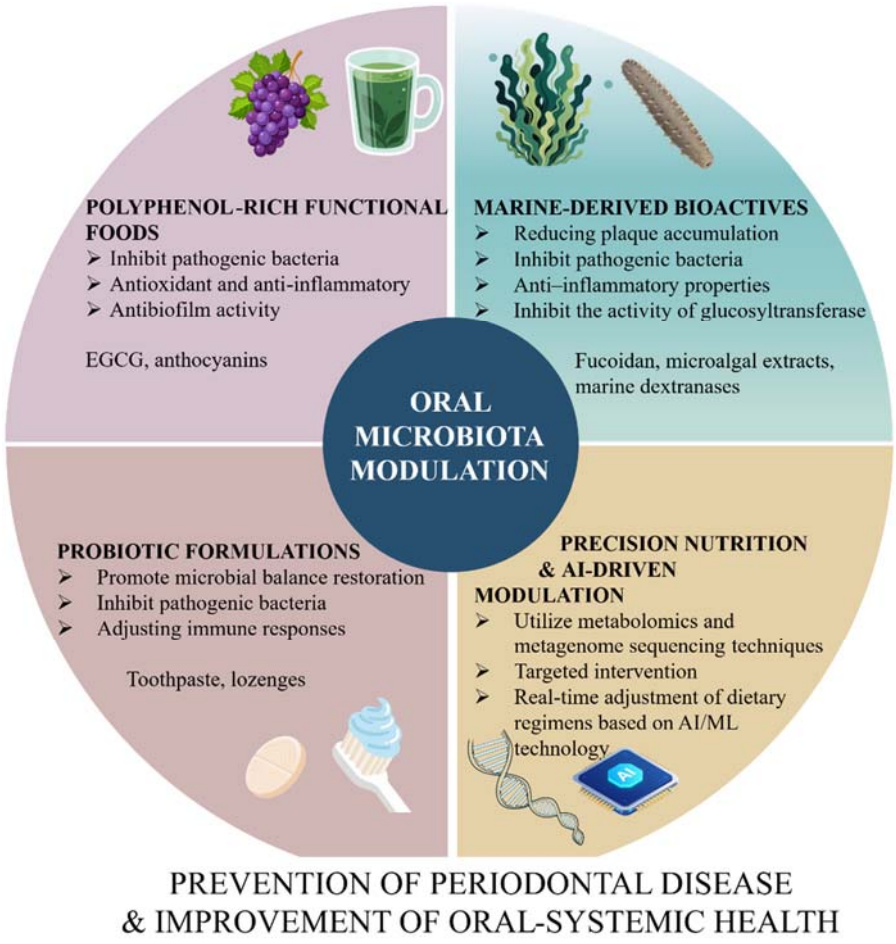

Figure 4. Oral microbiota modulation strategies for periodontal disease prevention and oral-systemic health improvement. Polyphenol-rich functional foods, marine-derived bioactives, probiotic formulations, and precision nutrition with AI-driven modulation represent four core strategies to prevent periodontal disease and enhance oral-systemic health through mechanisms including pathogenic bacterial inhibition, microbial community balancing, and immune enhancement.

6.1 Polyphenol-rich foods

Polyphenolic compounds—including tea catechins, grape seed proanthocyanidins, and blueberry anthocyanins—have garnered substantial attention due to their potent antioxidant and anti-inflammatory properties. For instance, epigallocatechin gallate (EGCG), the principal green tea catechin, effectively inhibits major periodontal pathogens such as *P. gingivalis* and mitigates chronic periodontal inflammation. These effects are mediated through EGCG-induced bacterial biofilm disruption, protease activity inhibition, and virulence gene expression suppression. Primary mechanisms involve reactive oxygen species (ROS) scavenging and macrophage polarization modulation[71]. Unmodified anthocyanin monomers significantly

reduce the adhesive capacity and competitive fitness of cariogenic bacteria such as *S. mutans*. These compounds interfere with biofilm formation, reduce acidogenicity, and inhibit extracellular polysaccharide biosynthesis—especially insoluble glucans. Furthermore, anthocyanins decrease *S. mutans* prevalence within polymicrobial biofilms while increasing the relative abundance of commensal species, including *Streptococcus sanguinis* and *Streptococcus gordonii*, thus promoting oral microbial homeostasis. These bioactivities may be mediated through ROS scavenging and inhibition of virulence determinants, such as glucosyltransferase enzymes (GtfB and GtfC), ultimately mitigating inflammation and preserving host tissue integrity[72].

6.2 Marine-derived foods

Recent research has successfully integrated marine-derived bioactive compounds into functional food delivery systems, resulting in improved oral health outcomes. For instance, toothpaste formulated with *Stichopus horrens* (sea cucumber) extract exhibited marked anti-inflammatory effects, significantly reducing gingival inflammation and facilitating tissue regeneration. Similarly, mouthwash containing *Enteromorpha linza* (green algae) extract effectively suppressed *Prevotella intermedia* and *P. gingivalis* growth, thereby reducing plaque accumulation and gingival bleeding while enhancing overall periodontal health. Moreover, mouthwash formulated with seawater-derived components demonstrated antibacterial efficacy comparable to chlorhexidine while mitigating side effects such as tooth discoloration associated with prolonged use[73]. These findings suggest that marine bioactive integration with functional carriers not only enhances bioavailability and efficacy but also provides promising avenues for oral health management innovation.

Although numerous *in vitro* studies have confirmed the potential of marine-derived compounds in promoting oral health, their practical incorporation into delivery systems such as toothpastes, mouthwashes, and chewing gums remains limited. For instance, fucoidan has demonstrated potent anti-*Streptococcus mutans* activity by inhibiting biofilm development. Extracts from microalgae such as *Dunaliella salina* and *Chlorella vulgaris* have been shown to reduce glucosyltransferase (GTF) activity, thereby inhibiting *S. mutans* synthesis of water-insoluble glucans and ultimately decreasing plaque formation. Concurrently, dextranases derived from marine bacteria—*Catenovulum* spp. and *C. agarivorans* MNH15—have demonstrated significant inhibition of *S. mutans* biofilm formation through targeted cleavage of α-1,6-glycosidic linkages. Notably, these enzymes retained bioactivity when co-formulated with conventional oral health agents such as fluoride and xylitol. Collectively, these findings highlight the broad potential of marine-derived compounds for application in oral health-oriented functional foods. However, translating these *in vitro* findings into clinically validated, carrier-integrated products requires substantial further research.

6.3 Probiotic toothpaste, lozenges, chewing gum

Heat-inactivated *Lacticaseibacillus paracasei* GMNL-143 exhibits strong efficacy in inhibiting biofilm formation by oral pathogens and modulating the oral microbial ecosystem. Studies have demonstrated that GMNL-143 engages with pathogens such as *S. mutans* and *P. gingivalis* through its surface layer proteins (SLPs), leading to co-aggregation that reduces pathogen adhesion and impedes initial biofilm formation.

Moreover, lipoteichoic acid (LTA) and peptidoglycan (PGN) components derived from GMNL-143 have been reported to further impair *S. mutans* biofilm maturation and contribute to the reestablishment of microbial homeostasis[74]. Clinical evidence further supports the therapeutic potential of GMNL-143 in gingivitis management. In a randomized, double-blind, crossover, placebo-controlled trial, individuals with mild-to-moderate gingivitis used either GMNL-143-formulated or placebo toothpaste for a four-week period. Notably, use of the GMNL-143-containing toothpaste significantly decreased the gingival index ($p = 0.0184$) and was associated with a significant reduction in *S. mutans* levels in the gingival crevicular fluid and a concomitant increase in health-associated genera (e.g., *Campylobacter*), although some shifts were not statistically significant. These trends indicate that GMNL-143 may help alleviate oral dysbiosis by reshaping the microbial community structure. Collectively, these findings suggest that GMNL-143 inhibits pathogenic biofilm formation, promotes microbial homeostasis, and mitigates inflammatory responses, thereby offering strong support for the development of functional oral care products—such as toothpastes and lozenges—for the prevention and management of gingivitis[74].

Another study demonstrated that *Lacticaseibacillus paracasei* L9 markedly inhibited *S. mutans* biofilm formation and modulated microbial homeostasis in both *in vitro* and *in vivo* models. *In vitro*, L9 suppressed the initial adhesion and polysaccharide synthesis of *S. mutans*, thereby impairing its biofilm formation capacity. This inhibitory effect was associated with downregulation of key cariogenic genes, including *spaP*, *luxS*, and *gtfB*. Furthermore, L9 disrupted sugar metabolism and cariogenic potential through secreted metabolites. *In vivo*, administration of L9 in a murine model significantly reduced early caries scores in *S. mutans*-infected mice and disrupted biofilm architecture on tooth surfaces. Moreover, L9 optimized oral microbiota composition by decreasing the abundance of pathogens such as *Pseudomonas aeruginosa* and *Veillonella*, while promoting beneficial taxa including *Lactobacillaceae* and *Streptococcus salivarius*. Collectively, these findings demonstrate that *Lacticaseibacillus paracasei* L9 effectively inhibits dental caries initiation and progression via multiple mechanisms, offering critical insights for the development of L9-based functional products such as probiotic toothpastes or lozenges[75].

6.4 Fluoride: remineralization and antimicrobial interventions

Fluoride, recognized as an essential trace element, confers significant physiological benefits when ingested at optimal concentrations and is extensively employed in dental clinical practice. Its anti-cariogenic properties are mediated through two primary mechanisms. First, salivary fluoride adsorbs onto apatite crystal surfaces during acidic challenges, thereby impeding demineralization. Conversely, under rising pH conditions, the formation of fluorohydroxyapatite is favored due to high supersaturation, thereby enhancing remineralization[76]. Second, fluoride disrupts microbial metabolism by inhibiting critical enzymes—such as enolase and urease—and compromising bacterial membrane integrity, ultimately suppressing bacterial proliferation.

For instance, enolase—a pivotal enzyme in microbial glycolysis essential for energy production and growth—catalyzes the conversion of 2-phosphoglycerate into phosphoenolpyruvate (PEP). Intracellular

accumulation of fluoride ions directly inhibits enolase activity, thereby diminishing ATP synthesis. This energy deficit impairs the pyruvate kinase-mediated conversion of PEP to pyruvate, consequently stalling intracellular glycolysis and significantly reducing glucose uptake via the phosphotransferase system (PTS)[77]. Furthermore, fluoride-mediated inhibition of H^+-ATPase disrupts proton efflux, resulting in intracellular hydrogen ion accumulation. This cytoplasmic acidification impairs metabolic functions and reduces bacterial tolerance to acidic environments. Supporting this, a clinical study involving ten children with caries who received weekly topical fluoride applications for one month identified predictive shifts in bacterial composition associated with high treatment sensitivity, specifically a decline in *Lautropia mirabilis* abundance accompanied by increases in *Gemella haemolysans* and *Schwartzia succinivorans*[78]. Meta-analytical evidence confirms the superiority of fluoride-containing toothpastes over non-fluoride alternatives (overall effect size = −0.29; 95% CI: −0.34 to −0.24). However, the addition of antimicrobial agents (overall effect size = −0.03; 95% CI: −0.07 to 0.02) and variations in abrasive systems (overall effect size = −0.02; 95% CI: −0.09 to 0.04) did not yield statistically significant improvements[79].

However, with the widespread excessive use of fluoride, recent research has increasingly focused on its adverse effects on periodontal and systemic health. Chronic fluoride poisoning initially manifests in the oral cavity as dental fluorosis (DF), a condition resulting from excessive fluoride intake during the critical period of tooth development. The pathological changes predominantly affect enamel but also involve dentin and alveolar bone. Affected teeth display patches varying in color from chalky white to brown, depending on severity. In severe cases, substantial enamel defects develop, significantly compromising tooth morphology, structural integrity, and function. These changes adversely affect mastication, digestion, and aesthetics, and may also impact patients' psychological well-being.

A significant drawback associated with widespread fluoride use is microbial adaptation, whereby prolonged fluoride exposure can induce genomic mutations that confer fluoride tolerance. Nassar et al. investigated the effects of fluoride concentrations typical of oral care products on biofilm development and metabolic activity in *S. mutans*. Notably, isolates from caries-susceptible subjects (strains A32-2 and NG8) exhibited significantly enhanced biofilm formation under fluoride exposure[80]. Furthermore, Liu et al. identified *Enterobacter cloacae* FRM, a strain exhibiting exceptional fluoride resistance capable of proliferating at fluoride concentrations as high as 4,000 mg/L[81]. This fluoride-resistant phenotype is attributed to the synergistic action of six genes clustered on genomic island GI3 (*ppaC*, *uspA*, *eno*, *gpmA*, *crcB*, and *orf5249*). Concerns regarding excessive fluoride use arise from these detrimental outcomes, including dental fluorosis caused by overexposure and the potential reduction in fluoride's caries-preventive efficacy due to the emergence of resistant microbial populations. Furthermore, recent evidence indicates that fluoride exerts selective pressure, thereby reshaping the composition of the oral microbiome. Consequently, elucidating the molecular mechanisms underlying fluoride tolerance within oral microbial communities is imperative for developing targeted anti-caries therapeutics, guiding optimal clinical and preventive oral health strategies, and devising novel approaches to maintain microbial homeostasis and prevent oral diseases.

6.5 Precision nutrition strategies targeting the oral microbiome

Advances in next-generation sequencing technologies, including metatranscriptomics, metaproteomics, and single-cell sequencing, have enabled high-resolution profiling of oral microbial communities, thereby facilitating the development of personalized interventions to restore microbial homeostasis. For example, in individuals exhibiting *Fusobacterium nucleatum*-dominant periodontal dysbiosis, increased consumption of fiber- and polyphenol-rich foods may suppress pathogenic overgrowth and attenuate inflammatory responses[82]. In parallel, micronutrients such as vitamin D, zinc, and magnesium have gained recognition for their immunomodulatory roles in oral health. Targeted supplementation—particularly with vitamin D—has demonstrated promise in enhancing immune defense and alleviating periodontal inflammation in deficient individuals[83]. Moreover, synbiotic administration—the combined use of prebiotics and probiotics—confers synergistic benefits. Prebiotics (e.g., fructooligosaccharides) facilitate the colonization of beneficial strains such as *Lactobacillus reuteri*, thereby reducing periodontal pathogen load via bacteriocin production and immune modulation. Emerging artificial intelligence (AI) technologies further refine the precision of nutritional interventions by integrating dietary patterns, microbiome data, and metabolomic profiles to predict dynamic host–microbe–diet interactions[84, 85]. Machine learning algorithms allow real-time optimization of dietary regimens in response to microbiota fluctuations, paving the way for adaptive, microbiome-informed strategies to enhance both oral and systemic health outcomes.

7. Conclusion

PD represent a major public health challenge due to their widespread prevalence and strong associations with systemic health outcomes. At the center of this interaction lies the oral microbiome, which functions as both a protective barrier and a potential reservoir of systemic inflammation. Diet plays a dual and context-dependent role in shaping the oral microbial ecosystem. While excessive sugar intake exacerbates oral dysbiosis and promotes cariogenic biofilms, fiber-rich diets and selective prebiotics can foster microbial diversity and suppress pathogenic colonization. Probiotics offer additional promise by reestablishing microbial equilibrium and enhancing mucosal immunity, although clinical efficacy varies by strain and condition. Importantly, dietary interventions must account for the interconnectedness of the oral and gut microbiota, as some substrates beneficial to gut health may paradoxically promote oral pathogenicity.

Future strategies should focus on individualized dietary modulation informed by microbiome profiling, and the development of functional foods enriched with antimicrobial phytochemicals and precision probiotics. Aligning dietary recommendations with public health policies, such as global sugar-reduction campaigns and responsible fluoridation practices, is essential. Ultimately, a systems-level approach integrating nutrition science, microbiome research, and clinical practice holds transformative potential for managing periodontal and systemic diseases through oral microbial modulation.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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