Review Article

The Role of Probiotics in Periodontal Disease: A Narrative Review

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ABSTRACT

Periodontal disorders (PD), also known as gum disease, involve inflammation and infection of the gum and bone tissue, which are preventable and treatable. Many worldwide suffer from such conditions, particularly in low- and middle-income countries. Risk factors related to periodontitis include poor oral cleanliness, regular alcohol consumption, betel quid chewing, and intake of tobacco. PD also raises the risk of fatal systemic diseases by provoking systemic inflammation. Oral homeostasis and prevention of periodontitis require healthy microbiota. PD results from alteration of the oral and gut microbiome environment. This host-microbe equilibrium interruption leads to inflammation, and tissue breakdown further acts to nourish the pathogens. There are several surgical and non-surgical means for managing PD.

However, the positive impact of probiotics, which include the genera *Lactobacillus* and *Bifidobacterium*, on PD has been noted. Probiotics kindle the immune system and synthesize anti-inflammatory cytokines that activate T regulatory cells. They also build antimicrobial molecules and inhibit oral pathogens. This narrative review was done to note the effects of probiotics on PD. The research used electronic search engines, including PubMed, Scopus, and Google Scholar. This study indicates that probiotics may be used as adjuvant therapy for gum disease. This may aid in faster healing, and since probiotics are found in accessible food sources like yogurt, the wider population may benefit. Thus, the global population may enjoy excellent oral health and an improved quality of life.

Keywords

Periodontal Attachment Loss, Gingival Recession, Alveolar Bone Loss, Periapical Diseases, Peri-Implantitis, Gingival Diseases, Lactobacillaceae, Lactic Acid Bacteria, Dietary Supplements, Mode of Action.

INTRODUCTION AND BACKGROUND

Periodontal disorders (PD) [1] are persistent multifactorial inflammatory diseases of periodontium. They are characterized by the devastating destruction of mineralized (tooth and bone) [2,3] and nonmineralized connective pulp (supporting) tissues of tooth [4] in the mouth cavity. The development and progression of periodontitis have equally local and systemic etiologic aspects [5]. Alteration of the oral and gut microbiome environment in the oral cavity often leads to oral disease, especially PD [6,7]. Healthy microbiota in the mouth cavity maintains

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oral homeostasis and prevents PD [8,9]. World Health Organization (WHO) reported that severe PDs are projected to affect about 19% of the adult population around the globe [10]. Globally, the number of severe PD patients has been estimated at over one billion cases, making it the 6th [11] or 11th [12] most prevalent disease worldwide [10-12]. The leading risk aspects for PD are poor cleanliness of the mouth cavity, regular consumption of alcohol, betel quid chewing, and intake of different forms of tobacco preparation [10,13-15]. The prevalence of severe periodontitis is higher in low and middle-income countries (LMICs) because of poor access to oral healthcare and high expenses that cause it to remain untreated and inappropriate intervention [16,17]. "The distribution of periodontitis communities' periodontal index of treatment needs (CPITN) code 3 + 4) in adults differed significantly in low- (28.7%), lower-middle- (10%), upper-middle- (42.5%), and high-income countries (HICs) (43.7%) (p=0.04)" [18]. The prevalence of severe periodontitis in Ethiopia [19], Ivory Coast [20], Rwanda [21], Uganda [22], Kenya [23], Vietnam [24], Thailand [25], China [26], and India [27] populations were 42.2%, 43.4%, 39.6%, 28.6%, 12-24%, 64.9%, 26%, 90% and 51%, respectively. The prevalence of severe periodontitis in selected countries around the globe (Figure 1).

Almost 50% of British adults have non-reversible periodontitis [28]. Chapple (2014 and 2022) mentioned in his studies that the British healthcare system must take stern preventive and curative initiatives regarding gum diseases and periodontitis [29,30]. It has been reported that among the US population, gum disease is widespread, and 40-42.2% of individuals aged 30 years or more are suffering from mild to severe periodontitis [31,32]. One more study revealed that among the US population 65 years or more had periodontitis no less than 68% or two-thirds [33]. Hakeem et al. (2024) conducted a systematic review and meta-analysis comprising 15 Saudia Arabian studies between 1992 and 2023 and reported that the overall prevalence of periodontitis was 48% [34]. Nearby, 20-50% of people around the globe suffer from periodontitis irrespective of LMICs and HICs [35].

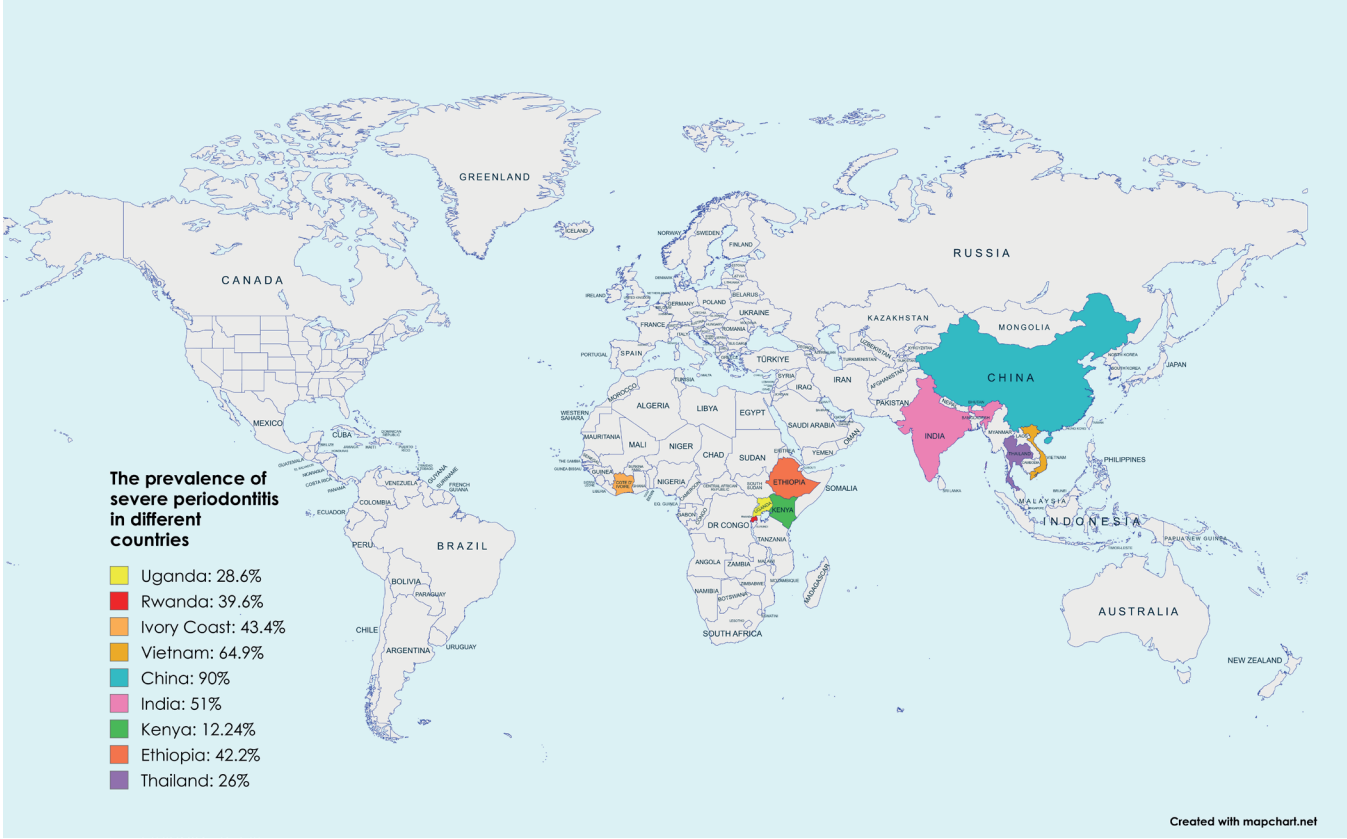

Figure 1: The prevalence of severe periodontitis in selected countries around the globe.
Illustration Credit: Susmita Sinha.

US Center for Disease Control and Prevention defines PD as disorders that encompass "inflammation and infection of the tissues (gum and bone) that surround and support the teeth, e.g., gingivitis and periodontitis, are largely preventable and treatable. The key is good oral hygiene, overall self-care, and regular care from a dental health care provider" [36]. PD is also known as gum disease [37]. PD is characteristically depicted by the continuing devastation of the soft and hard tissues of the periodontal latticework through persistent inflammatory disease [38,39]. PD results from interrupting host-microbe equilibrium among prone patients, evoking dysbiosis (a discrepancy in the dent types of commensals or microbiota living in your body) [40]. The commotion of host-microbe homeostasis led to devastating inflammation that not only triggers the osteoclast process and bone loss 40-42 but also provides nourishment through tissue breakdown products that facilitate the dysbiotic microbiota to propagate and sustain (Figure 2) [40,43].

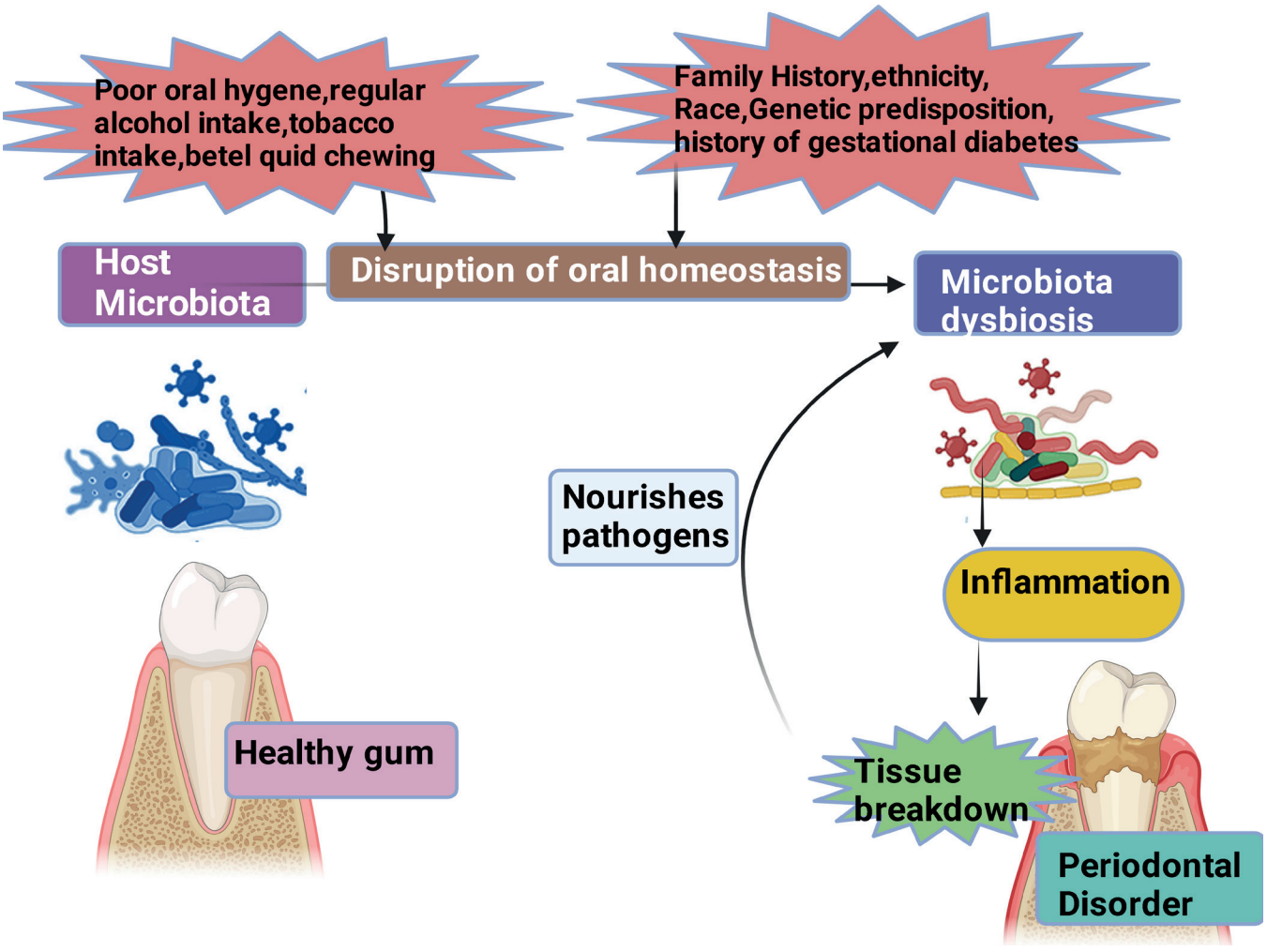

Figure 2: The development of periodontitis occurs due to disruption in the host microbiota of the oral cavity, resulting in inflammation tissue breakdown, which further fuels the pathogen microorganisms, causing the persistence of inflammation.

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The American Academy of Periodontology and the European Federation of Periodontology in 2017 organized a new catalog of periodontal and peri-implant diseases. The innovative and novel categorization of periodontitis can be partitioned into three types: (i) necrotizing PDs, (ii) periodontitis, and (iii) periodontitis as a manifestation of systemic diseases [45]. As PD is a chronic inflammatory disease of the tooth-supporting tissues, it often leads to a raised risk of morbidness and fatal outcomes by provoking various systemic diseases [46,47], e.g., diverse cardiovascular diseases [48-52] that include atherosclerosis, myocardial infarction, cerebrovascular accident (CVA), insulin resistance (IR), type 2 diabetes mellitus (T2DM) [51,52], gastrointestinal disorders [53,54], respiratory tract infection and pneumonia [55], oral and colorectal carcinoma [56,57], Alzheimer's disease [58], rheumatoid arthritis [59,60] and adverse outcome of pregnancy such as preterm birth associated to low-birth-weight (PBLW) [61,62]. A meta-analysis carried out on six cohort studies, which

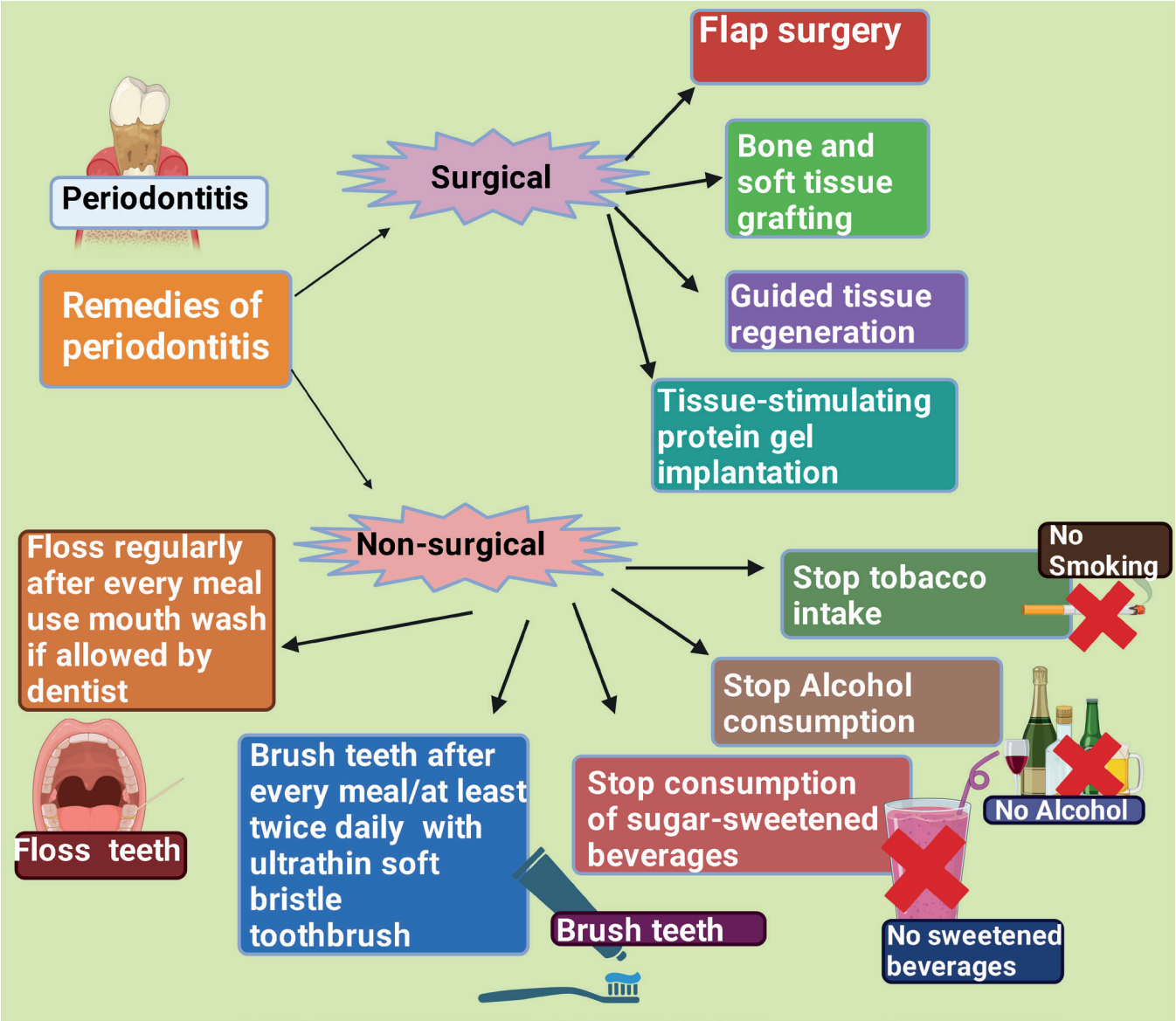

Figure 3: Remedies for periodontitis.
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included 7731 chronic kidney disease (CKD) patients, noted the all-cause mortality rate to be 44.8% in CKD patients with periodontitis compared to CKD patients without periodontitis (28%). A considerable association was also observed between cardiovascular mortality and periodontitis in CKD patients [63]. Another study analyzed the survival of patients with CKD with and without periodontitis using the Third National Health and Nutrition Examination Survey (NHANES III) and linked mortality data. It observed a rise in the 10-year all-cause mortality rate to 41% from 32% in CKD patients suffering from periodontitis [64].

Conversely, mortality rates rise to 50-70% among one-year hospitalized instances [65]. The fatality frequently associated with PD is inflicted by aggravating hepatic failure, kidney disorders, and gastrointestinal bleeding [66-68]. The clinical picture becomes graver when patients have concurrently hepatic, renal, and cardiac disorders [68,69].

PD risk factors are conventionally categorized into amendable and non-amendable [70,71]. Several modifiable risk factors include triggering PDs, e.g., poor oral hygiene, lifestyle, regular different form tobacco intake, and alcohol consumption; stress often leads to various amendable risk factors that include physiologic, emotional responses, depression, low physical activity, obesity, T2DM, MetS, osteoporosis, and low dietary Ca^{2+} and vitamin D [72-76]. Non-modifiable PD risk factors include family history, genetics, epigenetics, history of gestational diabetes, racial or ethnic traits, and age over 45 [77-79].

Therapeutic intervention of chronic PDs include surgical [80,81], e.g., flap surgery (correspondingly known as pocket reduction surgery), bone and soft tissue grafting, guided tissue regeneration, tissue-stimulating proteins gel implantation [80,82,83]; non-surgical [80,81], e.g., antimicrobials, root planning, scaling [80,84]; and home remedies with lifestyle alteration [80], e.g., stopping of tobacco, alcohol consumption, and sugar- sweetened beverages (SSBs) in any form; brush your teeth after every meal or snack or at least teeth twice a day with fluoride containing toothpaste for two minutes for each time; delicate and ultra-thin toothbrush and change tooth brush as a minimum every three months or bristle start curving; power-driven toothbrush are more effectual in eradication of dental tartar and plaque, nevertheless, it is expensive; practice flossing daily or after every meal; regular use mouth washes if endorsed by your dental surgeon; and regular intervention by professional (graduate dental surgeon) care (Figure 3) [80,85-89].

PD is caused by a biofilm constituted by polymicrobial community dysbiosis, which involves a complicated interaction between pathogens and the host. The biofilm formed in the oral cavity, especially around it and its supporting tissues, eventually reconstituted or reconstructed after non-surgical intervention combined with antiseptics and antimicrobials. Hence, long-standing accomplishments in the management of PD remain unsubstantiated [43,90-93].

Probiotics have been utilized as a therapeutic intervention in many diseases, e.g., inflammatory bowel disease including irritable bowel disease (IBS), allergies, diarrhea, *Helicobacter pylori* infections, vaginal infections, respiratory tract infections, oral infection, dental caries, halitosis, colorectal cancer [94-98]. Multiple studies conducted by Hillman and the team revealed that *Streptococcus sanguis* can deter the progression of *Actinobacillus actinomycetemcomitans* in animal studies [99,100]. Later, Teughels and the team reported that *Lactobacillus spp*. and *Bifidobacterium spp*. (probiotics) posses' potential to inhibit PD- PD-triggering pathogens, e.g., *A. actinomycetemcomitans, Treponema denticola*, and *Porphyromonas gingivalis* [101,102]. Shirbhate et al. (2023) reported that Russian scientists and Nobel Prize laureate Elie Metchnikoff initiated probiotics in managing PD a century back [103]. The same study revealed that the principal invading periopathogens include *P. gingivalis, A. actinomycetemcomitans, Tannerella forsythia, and T. denticola* [103]. Subsequently, various studies demonstrated a positive impact of probiotics in treating chronic PD [104-108].

PROBLEM STATEMENT OF THIS NARRATIVE REVIEW

PD, a chronic inflammatory gum disease frequently associated with microbial infection, affects gum and tooth-supporting tissues. If left untreated, it can ultimately lead to tooth loss and other grave health issues [44]. Chronic PD was detected at 82%, 73%, and 59% among older adults and youngsters, respectively [18]. The aging process remains the primary triggering factor for PD, along with poor mouth hygiene practices, plaque control, xerostomia, lower socioeconomic status, and tobacco consumption [13-15]. One systematic review and meta-analysis reported that no less than 50% of the Indian population suffers from PD [27].

OBJECTIVES OF THE STUDY

This narrative review primarily concentrated on probiotics' role in managing *P. gingivalis*-induced PDs and their' destructive potential on alveolar bone.

MATERIALS AND METHODS

A comprehensive search was performed for relevant studies using Google Scholar, ResearchGate, and PubMed. The appropriate studies were gathered using the search keywords mode of action, dietary supplements, lactic acid bacteria (LAB), *Lactobacillaceae,* gingival diseases, peri-implantitis, periapical diseases, alveolar bone loss, gingival recession, periodontal attachment loss, oral and gut microbiome. Several substantial details were obtained from the shortlisted papers, including the year of study, place, sample categories, clinical manifestations, and references. Before inclusion in the research, each paper's relevancy was thoroughly reviewed. Again, a follow-up discussion was held to

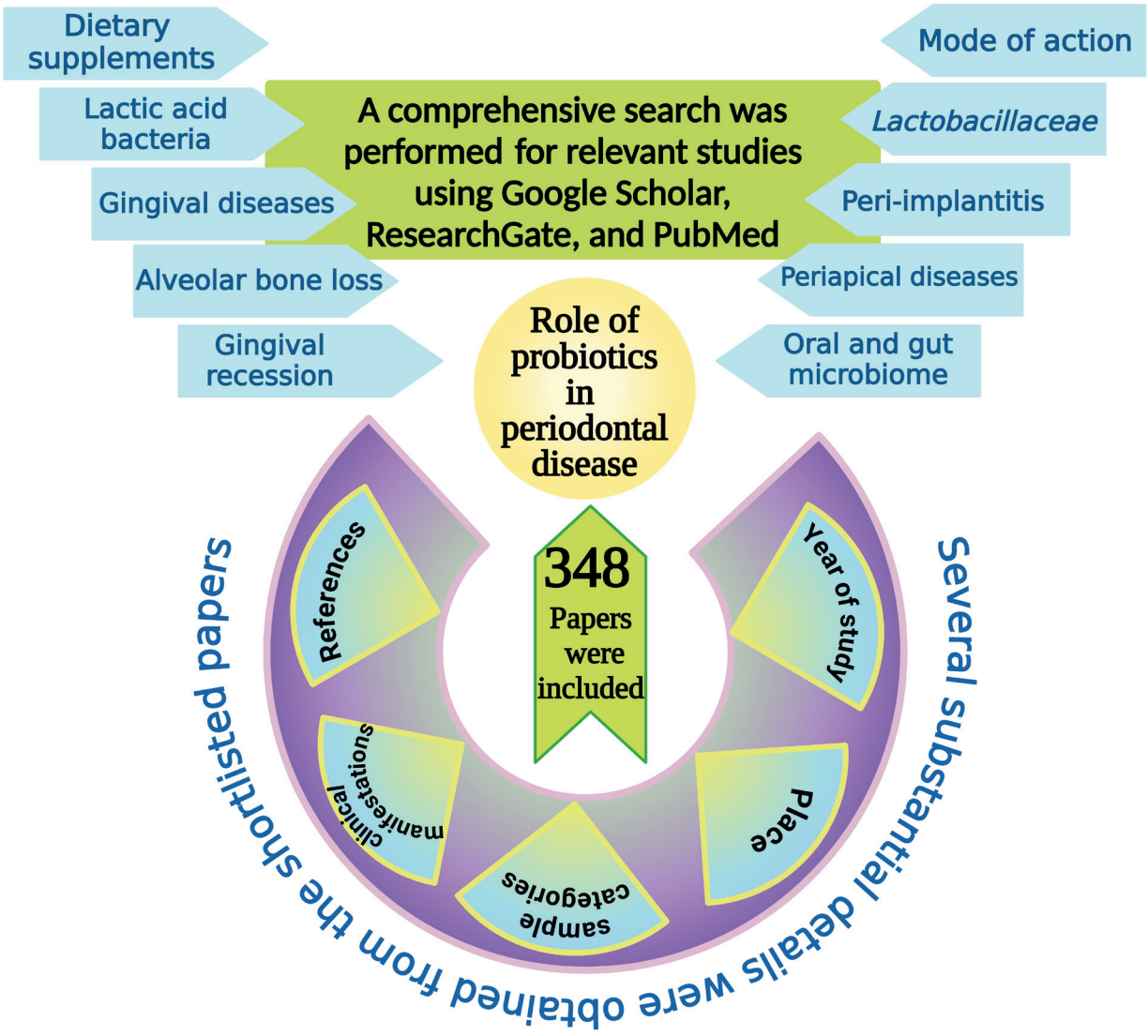

Figure 4: Flow Chart Showing The Methodology of The Study.

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address any inconsistencies in the findings, answer queries, and sort out errors following an independent evaluation of the chosen literature (Figure 4). This is a narrative review. No attempts were made to do a systematic review or meta-analysis.

REVIEW OF LITERATURE

Probiotics are interpreted as live microorganisms as dietary components that converse a health improvement to the consumers when taken in the requisite portion. The most ingested probiotics reside in the genera *Lactobacillus* and *Bifidobacterium* and are exhibited to recover or reestablish the gut and other microbiota community [109,110]. The best recognizable significances of probiotics include intestinal diseases such as antibiotic-associated and infectious diarrhea, downgrade susceptibility to contagious diseases, e.g., respiratory and urinary infectious diseases, lactose intolerance, hypersensitivity, and up-and-coming evidence grows vis-à-vis their prospective function in diverse other diseases [93,108,110]. Kopacz and Phadtare (2022) highlighted the intestinal benefits achieved by probiotics through increasing and enhancing immunity, raising

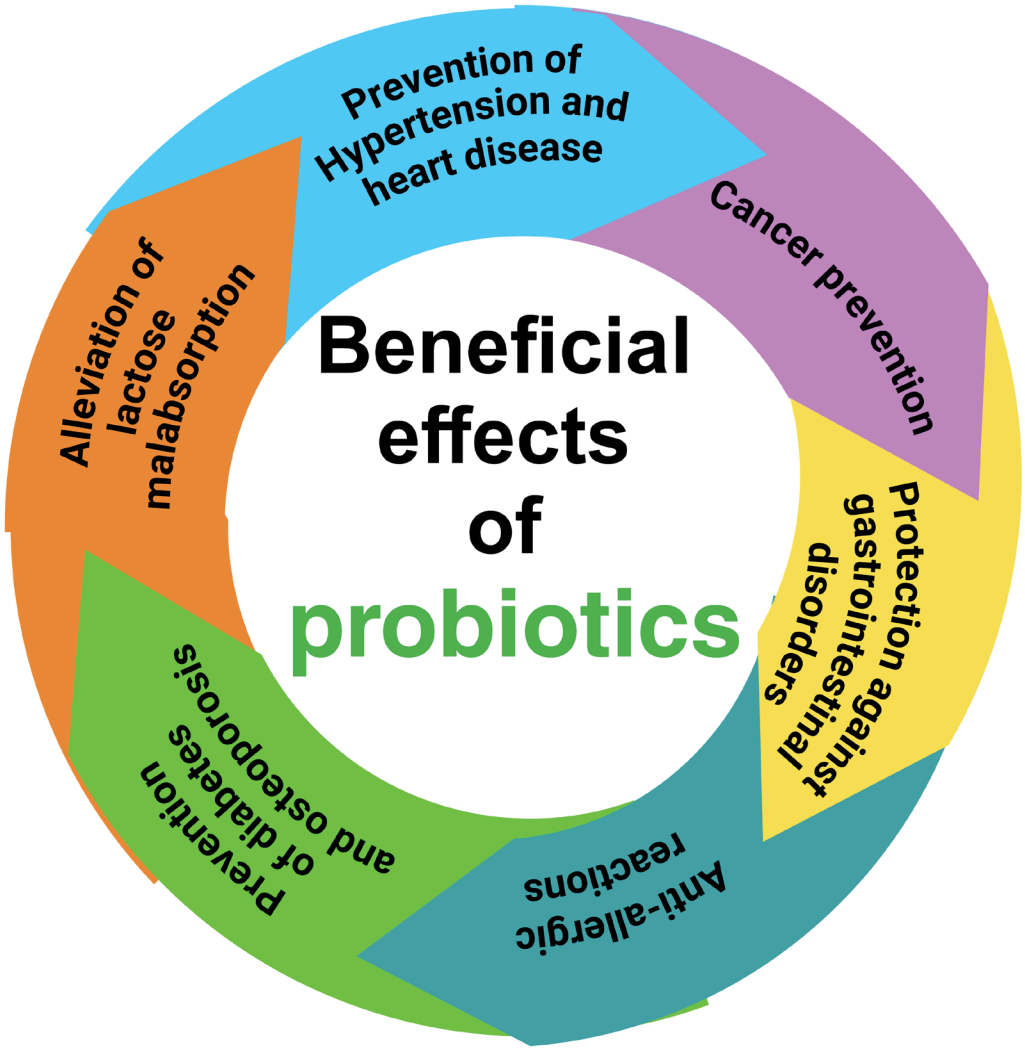

Figure 5: Schematic Diagram Showing the Beneficial Effects of Probiotics.

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the strength of gastrointestinal barricade functions, generating antimicrobial ingredients, reestablishment and improvement of the gut microbiome, improving water absorption physiological function, and subsiding opportunistic pathogenic microbes [111]. Another study revealed that probiotics have various health advantages (Figure 5), such as minimizing the development of colon carcinoma, curtailing lactose intolerance, diminishing susceptibility to infective diseases, especially respiratory, vaginal, and urogenital microbial diseases, alleviating allergic events, lowering serum cholesterol, hypertension, avert the gastrointestinal inflammatory disorders including diarrhea, and many more [112].

Probiotic Microorganisms that are Helpful to the Human Host

Binda et al. (2020) [113] interpreted four naïve and rational principles to qualify foods and dietary supplements of various strains of microbes (nonpathogenic living microorganisms) [114] as probiotics. Probiotic strains must possess the following criteria: (i) satisfactorily categorized; (ii) a safety profile must be ensured for the proposed use; (iii) a human clinical trial, as a minimum reported that these microorganisms (probiotics) possess positive health beneficial findings when consumed for anticipated utilization, and the clinical trial must follow broadly recognized scientific standards of national or international health research authorities requirements; and (iv) alive microorganism (probiotics) must remain effective across their shelf life [113]. Several categories of microorganisms that possess probiotic properties are unearthed [115,116]. The nine principal genera of microorganisms most frequently cast off in probiotic foodstuffs are *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia, Bacillus, Pediococcus, Leuconostoc* for health benefit [116]. Taxonomically, these microbes are divided into two phyla, *Actinobacteria* and *Firmicutes*. *Actinobacteria* phylum consists of only two microorganisms, *Atopobium* and *Bifidobacterium*, and *Firmicutes* comprises of multiple phylum, e.g, *Aerococcus, Alloiococcus, Carnobacterium, Enterococcus, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Symbiobacterium, Tetragenococcus, Vagococcus, Weissella* genera [117].

Human beings have been consuming fermented food for a few thousand years. Nevertheless, it has been very recently that a better understanding of its microbial health benefits has been developed, which are well-known [118]. Fermented foods are "foods or beverages produced through controlled microbial growth and the conversion of food components through enzymatic action" [119]. The purposeful characteristics of fermented foods are typically related to probiotic microbes and their synthesized bioactive molecules, such as peptides and targeted microbial generation of functional. Yogurt and fermented milk are the most conventional fermented, and probiotics contain an age-old diet of health benefits. Worldwide acquisition interest is in several fermented non-dairy products, especially cereal, millet, rice, maize, sorghum, and soy products, initially developed by indigenous communities of Asia and Africa [120-122]. Yogurt, kefir, some cheeses, pickles, sauerkraut, miso, tempeh, kombucha, kimchi, natto, and sourdough bread are top everyday consuming fermented foods that inherently comprise probiotics, or probiotics were added to these foods [122,123].

Fermented foods are prepared through two principal processes. Among the two approaches, one is known as "wild or spontaneous ferments," and the second is often called "culture-dependent ferments" [124]. The microbes are found instinctively in the raw food or processing environment, e.g., kimchi, sauerkraut, and certain fermented soy foods [123,125]. Second, the food fermentation process, known as starter cultures or "backslopping," includes products such as natto, kefir, and kombucha [123,126,127]. A small amount of a previously fermented batch is added to the raw food "backslopping" or "culture-dependent ferments," e.g., sourdough bread [124,128].

Health Benefits: Mechanism of Fermented Foods

It has been reported probiotics are heavily utilized in the conservation and therapeutic intervention treatment of PDs [103]. Fermentation - and beyond explicitly lactic acid fermentation - is one of the best old-time wholesome food conservation processes that subsists [129]. Thereby, fermented food contains many probiotic microbes, e.g., LAB, at minimum, 106 microbial cells per gram; nevertheless, the probiotic number varies with region, age, and time [130]. The LAB fermentation process synthesizes several bioactive

molecules, e.g., peptides and polyamines, that possess pharmacodynamics that improve immune, metabolic, and cardiovascular physiology [131]. LAB microbes have the potential to fight back against pathogenic organisms and benefit gastrointestinal physiology. Furthermore,

by inhibiting pathogens, LAB has consequences in generating immune and neurogenic supervisory molecules [132]. The LAB process often transforms fermented food comprising phenolic compounds into active molecules. These molecules possess antioxidant, anti-inflammatory, antispasmodic, antiulcer, antidepressant, and anti-carcinogenic properties [133-135]. LAB fermentation foods minimize toxins and anti-nutrients [136], e.g., soybeans decrease phytic acid concentrations [123], sourdough reduces fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and polyols, [123], that escalates the tolerance level among patient's irritable bowel disorders syndrome [123,137-139]. Additionally, LAB-fermented foods synthesize and comprise vitamins and prebiotics that enhance health benefits [119,140,141].

Immunomodulatory Mechanism of Probiotics

Scientific research regarding probiotics has a long history. Nevertheless, these studies did not detail the molecular pharmacology of probiotic microbes related to their immunomodulatory properties and how probiotics achieve host immune status [142]. The immunomodulation mode of action of consumed probiotics principally comprises activating the macrophage beckoning process, triggering neutrophils and IgA (Immunoglobulin A)-producing cells, initiating the synthesis of secondary immunoglobulin (Ig) formation, stimulating mucus-making activity, and restraining the liberation of pro-inflammatory cytokines [142-144].

Plaza-Diaz et al. (2019) [145] reported that probiotics probably apply beneficial pharmacodynamics through four principal processes. Those eliminated pathogenic microbes through competition, enhanced gastrointestinal wall defensive physiological performances by increasing the product of ion mucin protein [146], substantially improved host immune properties, and augmented the building of neurotransmitters synthesis procedure. The same study additionally revealed that probiotics contest with pathogenic microbes for micronutrients (trace elements and vitamins) and receptor-binding spots; hence, the persistence of pathogens in the gastrointestinal tract becomes arduous and ensures their eradication [145]. Ahire et al. (2021) reported that probiotics, especially fermented food isolate *Lactobacillus plantarum,* often synthesize hydrogen peroxide, organic acids, bile salt hydrolase and phytase, short chain fatty acids (SCFA), and antioxidative action. These substances possess antimicrobial pharmacodynamic properties [147]. Fantinato et al. (2019) [148], in their study, revealed probiotics (LAB-fermented food) generate bacteriocins (ribosomally synthesized antimicrobial peptides) [148-150]. These molecules serve as an alternative to aging antimicrobials [151]. Therefore, it reduces the pathogenic microbial load in the gastrointestinal system [152].

Furthermore, multiple studies determined that probiotic supplementation encourages considerably increased synthesis of interepithelial tight junction proteins with the relocation of these proteins, which restores the gastrointestinal hemostasis, wall function, and immune function of the gastrointestinal system [153-156]. Periodontitis causes oral and gut dysbiosis. Thereby, the number of beneficial microbial communities reduces, and the number of pathogens increases, such as *Proteobacteria* and *Fusobacteria*. An enormous number of *P.* gingivalis, *Fusobacterium*, *Tannerella*, and *Treponema*, detected in stool specimens among these cases, evidenced the translocation of oral pathogens into the gastrointestinal tract [157].

Probiotics reverse these pathological issues of periodontitis [158]. Additionally, it has been reported that probiotics commendably suppress or prohibit oral pathogens triggering PDs and inflammatory biological indicators, e.g., "tissue inhibitor of metalloproteinase (TIMP)-1, matrix metalloproteinase (MMP)-8, and interleukin (IL)-1β." Henceforth, the focus will be on repairing and bettering indicators of orthodontic well-being, such as "probing pocket depth (PPD), bleeding on probing (BOP), gingival crevicular fluid (GCF) volume, and clinical attachment loss (CAL)" [103].

Periodontal Diseases and Predominant Pathogens

These species comprise but are not limited to *Treponema, Bacteroides, Porphyromonas, Prevotella, Capnocytophaga, Peptostreptococcus, Fusobacterium, Actinobacillus*, and *Eikenella* in causing PDs [46,159]. Pathogens responsible for PDs are categorized according to color coding, such as red (*P. gingivalis*, *T. denticola*, and *T. forsythia*) [160], orange (*Fusobacterium*, *Prevotella*, and *Campylobacter* species) [161,162], purple (*Aggregatibacter actinomycetemcomitans*) [163], yellow (*Streptococcus* species) [161,164], and green [161,164] (*Capnocytophaga* species) [160-165]. The colors signify diverse pathogenic microbial clusters responsible for various stages of periodontitis [166]. The orange, red, green, and purple [167] include PD pathogens accountable for instigating, extremely inflammatory capability, local perseverance and devastation proficiency, cell

death, and activate or equivocate inflammation [167], respectively. Another study reported that the paramount and subservient colonist pathogens identified with color coding of yellow (*Streptococcus* species), purple, and green (*Actinomyces naeslundii*, *Capnocytophaga ochracea*, *Eikenella corrodens*, and *Veillonella atypica*) [168]. *P. gingivalis* remains the most common gram-negative anaerobic pathogen, causing chronic destructive periodontitis [169-171].

Effects of Probiotics on *P. gingivalis*

Multiple studies reported that when *P. gingivalis* confronted the tooth and its binding tissues, probiotics decreased the synthesis of CXCL8 proteins. CXCL8 is the mightiest human neutrophil-pulling chemokine and participates in essential functions in the reaction to infection and tissue injury. Probiotics inhibit the negative impact (ceases) of *P. gingivalis*-induced CXCL8 protein synthesis, thereby improving the re-epithelization process among periodontitis cases [172-175].

P. gingivalis, the principal periodontal pathogenic microbe, also synthesizes one molecule named gingipains (trypsin (arginine or lysine)-like cysteine proteinases), which remains the primary triggering factor for the deteriorating pathogenesis of adult PDs [176-178]. Gingipains, also recognized as RgpA, RgpB, and Kgp proteinases, are the prime notorious factors of *P. gingivalis* W50 [179]. Gingipains cleave (reduce expression) macrophage CD14 [180,181]. The cell surface

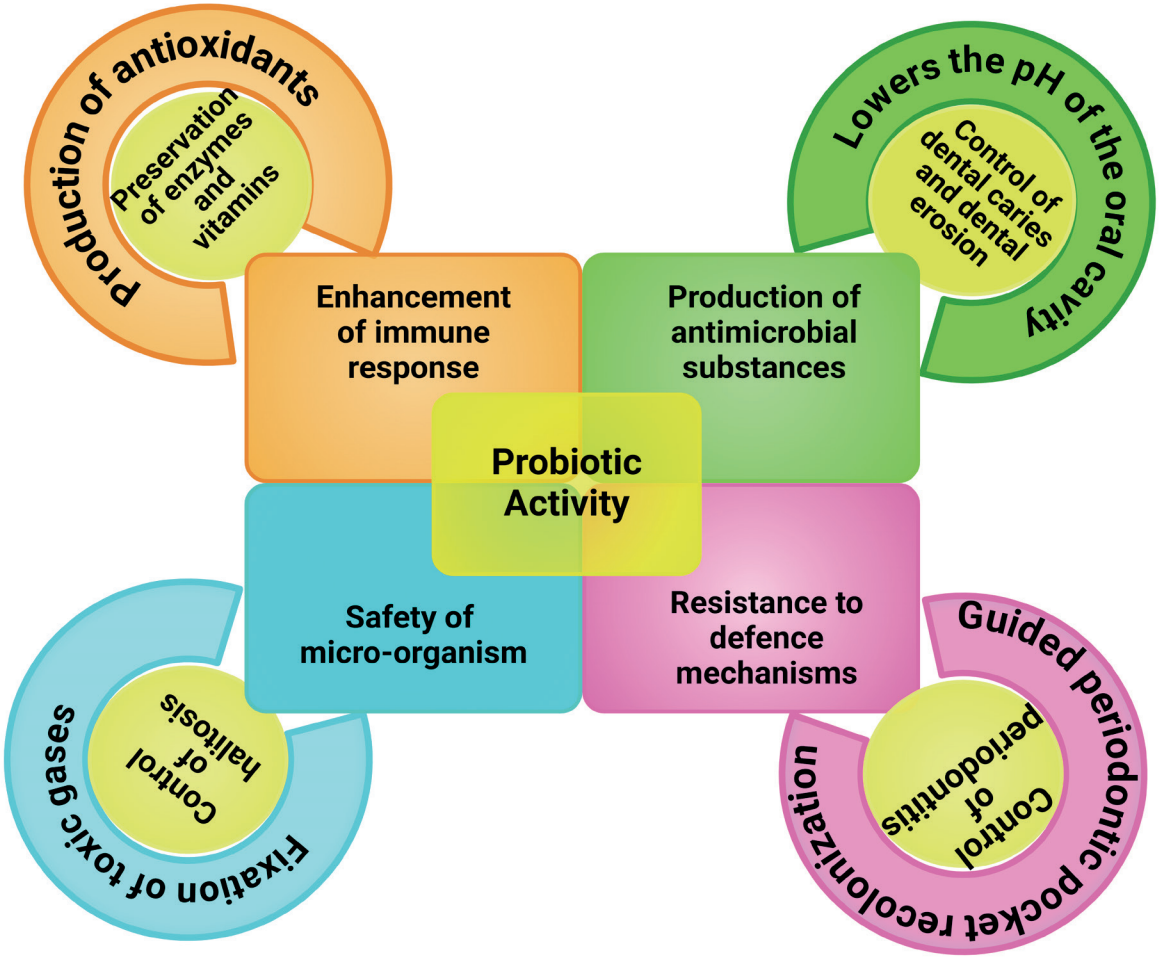

Figure 6: Chart showing the effects of probiotics on periodontal health.

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of monocytes, polymorphonuclear leukocytes, and macrophages possesses a protein known as CD14. CD14 is a glycosylphosphatidylinositol-anchored glycoprotein that accomplishes as a receptor for endotoxins [182]. Endotoxins are lipopolysaccharides (LPS) identified in the cell surface of gram-negative pathogens, which can stimulate immune retort, e.g., fever, inflammation, anaphylactic shock, and fatal clinical outcomes among patients [183]. Consequently, impeding initiation of the white blood cells (WBCs) function through the LPS receptor, thereby expediating unremitting settlement of *P. gingivalis* on the tooth surface [178,184,185]. Multiple studies revealed that LPS is well-known as an exceedingly morbific endotoxin accountable for organ enfeeblement in septicemia [186-188]. Therefore, gingipains perform domestic duties for *P. gingivalis* and other infective disorders, including periodontitis [189,190]. Gingipains facilitate pathogenic periodontal microbes to uptake amino acids from affected patients' proteins and fimbriae growth [191]. The obtainable research revealed that probiotics comprise efficacious pharmacodynamics that can eradicate periodontopathogens and diverse clinical indicators associated with periodontal health modified towards healthy periodontal issues (gum). Those markers include "plaque index (PI), gingival index (GI), BOP, PPD, CAL, and GCF volume, as well as inflammation-associated biochemical markers, such as IL-1β, MMP-8, and TIMP-1" [192]. Therefore, eradication of P. gingivalis and, subsequently, the synthesis of gingipains are expected to be impeded [193-195]. It can be proposed that gingipain molecules possibly have future potential in research areas to combat PD.

P. gingivalis is among the most identified pathogenic microbes in PDs and root canal infectious diseases. *P. gingivalis* capability and pathogenic potential are immensely boosted in dental plaque (a gluey film of microbes that accomplishes continuously on our teeth) biofilms [196,197]. Oral periodontopathogens gram-negative anaerobic pathogens, *P. gingivalis*, is characteristically a late colonist in forming biofilms beneath the gums and exclusively between the gums and the basal part of the crowns of the teeth [169,194,196-200] and has been strongly associated with various destructive PDs, including peri-implantitis and periodontitis [201-203]. Cell-free pH-neutralized supernatants (CFS) of probiotics, especially *Lactobacilli* FT 12 and FT6, cut down *P. gingivalis* ATCC 33277-induced single-strain biofilms. Planktonic probiotics and multispecies biofilms bring down *P. gingivalis* plethora. *L. acidophilus* LA5 probiotics minimize *P. gingivalis* biofilm formation and transcription virulence-associated factors (PgVAFs) and gingival epithelial cells (GECs) [171,192,204-206].

Probiotics build antimicrobial molecules, e.g., acetic acid, bacteriocins, hydrogen peroxide, diacetyl, reuterin, and lactic acid [207,208]. These antimicrobial molecules hinder the progression of periodontal pathogenic microbes in the oral cavity (Figure 6) [158,207-209]. Furthermore, probiotics straightforwardly inhibit dental plaque construction through the interference of pathogens add-on or clumping between them, reducing the mouth's pH and synthesizing antioxidant that antagonizes free electrons, which is required for the plaque mineralization process. After that, it impedes microorganisms' affinity and sticking properties with teeth and prevents attachment by creating a bay and biofilm formation (Table 1) [207,209- 211].

Table 1: Prospective Mode of Action of Probiotics on Oral Health and Periodontal Disorders.

Number of Action	Mode of Action	References
1.	Probiotics directly act on pathogenic microbes and avert pathogen settlement within the mouth cavity, especially gum tissues	212,213
2.	Probiotics are hostile toward periodontal microbes, biofilm formation, extracellular matrix, and cytotoxic end products synthesized by these microorganisms.	94,212,213
3.	Probiotics synthesize antimicrobial peptides, such as bacteriocins.	212,214
4.	Probiotics alter the bonding, accumulation, settlement process, and propagation of pathogenic microbes within the mouth cavity through their mode of elimination and antagonism.	212,215,216
5.	Probiotics create the protective wall in the mouth cavity, including the tooth, inhibiting pathogens from acting on tooth and gum tissues.	212,217
6.	Probiotics preserve oral ecology equilibrium by generating cytoprotective proteins and regulatory and antioxidant molecules to protect oral cells.	212,218,219
7.	Probiotics compete with periodontal pathogens in capturing micronutrients.	105,212,220-222

Systemic Mechanism of Action of Probiotics

Liang et al. (2022) reported that probiotics' clear-cut mechanism of action remains incomprehensible [223].

Table 2: Illustrated Findings of Randomized Clinical Trial Regarding Probiotic's Systemic Mechanism of Action.

Article Details With References	Methods	Results	Conclusions
Dixit et al. (2024) [234]	A single-blinded randomized clinical trial was conducted on 12-17-year-olds who underwentendodontic therapy. The effectiveness of calcium hydroxide (CH) paste, probiotics (PBs), and triple antibiotic paste (TAP) was evaluated.	Each type of medication showed antimicrobial activities, but PBs were more effective than theCH group and demonstrated analogous potency as TAP therapy.	During the treatment ofroot canals in young patients with permanentteeth, probiotics can be used as an effective antimicrobial therapy.
Togawa et al. (2024) [235]	A placebo-controlled, double-anonymized clinical trial where the case group received *Heyndrickxia coagulans* SANK70258.	Considerable progress was observed in the test group regarding reducing fecal phenol level, liver function tests, stool frequency, skinscaliness, and attenuated skin lightness.	*H. coagulans* SANK70258 may contribute to both skin health and systemictissue improvement.
Dierikx etal. (2024) [236]	A secondary analysis was done from a placebo-controlled, quadruple-blind, randomized clinical trial. Children who received broad-spectrum antibiotics were included in this study, and the test group received a multispecies probiotic formulation.	Both alpha and beta diversity did not differ significantly between placebo and test groups.	The multispecies probiotic formulation didnot considerably influence the intestinal microbiome; further studies are needed.
Aida et al. (2024) [237]	A randomized, placebo-controlled, double-masked parallel-group study where the efficacy of *H. coagulans* strain SANK70258(HC) was observed.	Several symptoms of upper respiratory tract infection (URTI) and the duration of infection showed significant improvement in the study group. The activation of natural killer (NK) cellsand secretory immunoglobulin A (sIgA) levels were also enhanced.	This probiotic may raise resistance against viral diseases and URTI via anti-inflammatory impact.
Savytska et al. (2024) [238]	A secondary analysis was done from a previously published randomized controlled trial where the efficacy of multispecies probiotics was observed on pancreatic betacell function in diabetic patients.	Parameters including fasting glucose, HOMA02, HbA1c, and insulin sensitivity considerably improved in the probiotic group.	Probiotics can act as anadjunct therapy in T2 DM, although further research is needed to draw a definite conclusion.

Nevertheless, probiotics considerably improve gastrointestinal mucosal barricade or wall physiological functions [155,224,225]. Probiotics kindle the immune system and synthesize anti-inflammatory cytokines (e.g., IL-4, IL-10, IL-11, and IL-13) that activate T regulatory (Treg) cells, which conserve immune homeostasis in the gastrointestinal mucosa [142,226]. Probiotics, e.g., *Lactobacillus spp.* and *Bifidobacterium,* also inhibit inflammatory cytokines such as IL-1, IL-6, and TNF-α [226]. Moreover, it augments anti-inflammatory cytokines such as IL-10 [227], escalates the making of secretory IgA (eliminate antigens from intestinal mucosa) [228], diminishes escape of antigens across the mucosal sheath, and mortifies dietetic antigen (Figure 7) [229,230].

Multiple studies reported that various taxonomic categories of probiotic LAB restrain the pathogens by contesting for the finite number of substrates necessary for fermentation, food sources, or receptors. Probiotics dodge the adherence of the pathogenic microbes to the patients' cells by reinforcing the fencing function of the gastrointestinal mucosa [231-233].

We searched PubMed using the keywords "systemic mechanism of action" And "probiotics." Again, we filtered randomized control trials published within one year and free full text. It was accessed on October 26, 2024. Initially, we found 852 papers without a filter, after "free full text" reduced to 414, and when the filter "randomized clinical trial," the number of literature was 34; finally, we applied "within 1 year," the number reduced to five. Table 2 depicts the findings of these papers.

This narrative review mainly concentrated on probiotics'

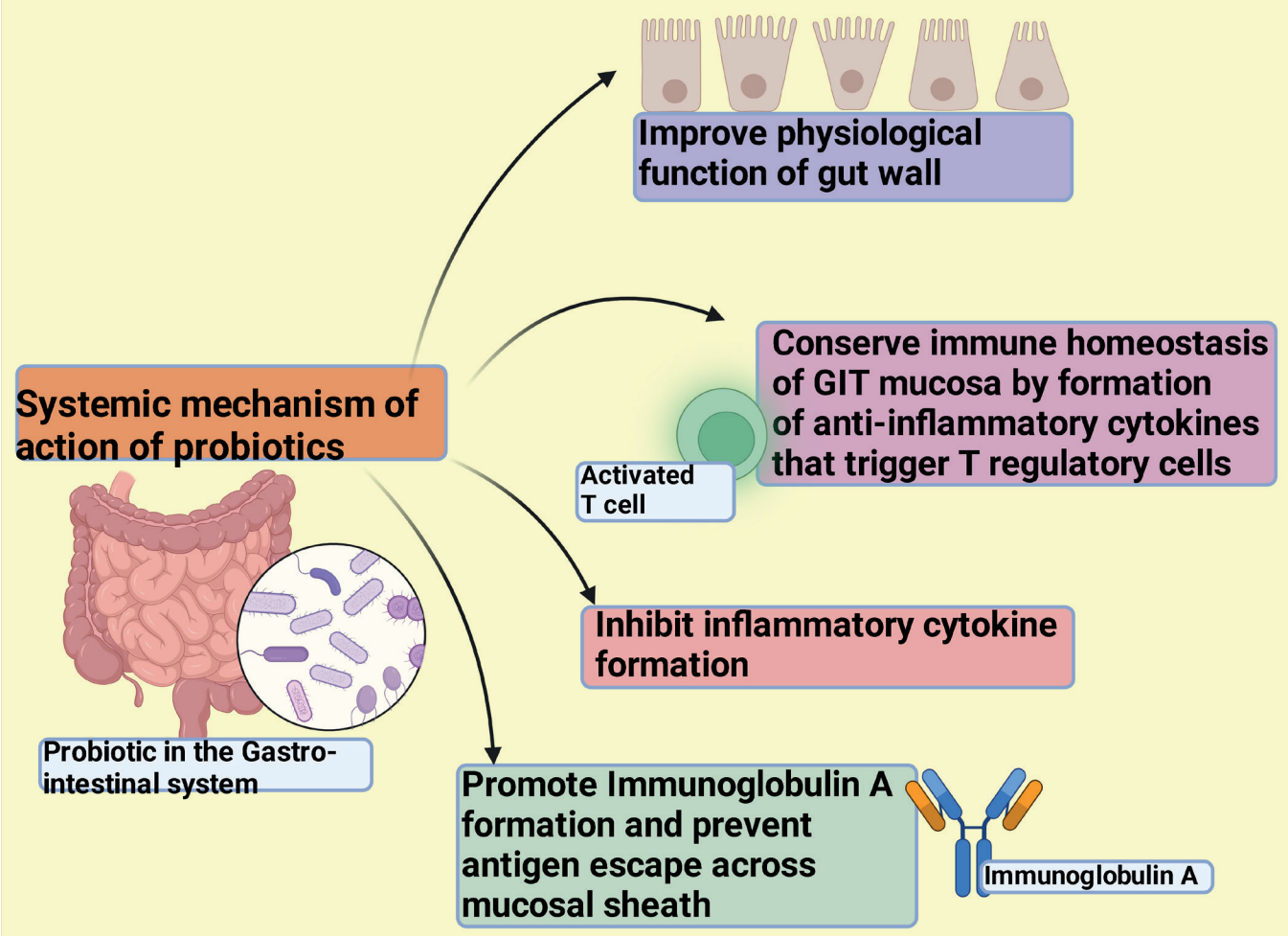

Figure 7 : This Figure displaying the systemic mechanism of action of probiotics. GIT: Gastrointestinal tract.
Notes: The premium version of BioRender (https://biorender.com/) was used to draw this figure and was accessed on 17 December 2024 with license number IV27OEU708 44.
Illustration Credit: Rahnuma Ahmad.

effects on PDs. After that, we also conduct on searched PubMed using the keywords "probiotics," AND "mechanism of action," AND "mouthwash," AND "periodontal diseases." Again, we filtered randomized control trials published within one year and free full text accessed on October 26, 2024. Initially, we found 133 papers without a filter, after "free full text" reduced to 50, and when the filter "randomized clinical trial," the number of literature was six; finally, we applied "within 5 years," the number reduced to three. Table 3 depicts the findings of these papers.

Probiotics Effect on Gingivitis

Akram et al. (2020) reported that consumption of probiotics, especially *Lactobacillus reuteri*, in plummeting inflammatory periodontal variables in gingivitis and plaque formation weighted mean difference (WMD)=- 0.48, 95% confidence intervals (CI)=-1.69 to 0.72, p=0.42 and WMD=0.18, 95% CI=-0.23 to 0.61, p=0.37, respectively [242]. Multiple studies reported that probiotics act as adjuvant therapy controlling gingivitis, especially *L. plantarum* and *L. reuteri* [213,243] and plaque formation (in addition to mechanical intervention) [244,245] through stabilizing normal microbial flora (microbiome) of the mouth [246]. Yousuf et al. (2017) revealed that "freeze-dried powdered probiotics" with mouthwash considerably improve oral health by minimizing plaque and gingivitis indices [247]. Castro et al. (2024) indicated that *Lactobacillus* and *Bifidobacterium* positively reduced several oral diseases, e.g., microbial plaque caused S.

mutans [248] and biofilm formation [249], for interim and extended times in diverse populaces. These probiotics reduce the number of (quantity) oral *S. mutans* [250]. Oral probiotics, e.g., *Lactobacillus* and *Bifidobacterium*, improve the oral ecosystem by influencing oral microbiota, thereby mitigating PDs, candidal fungal infections, oral mucositis, dental caries, and halitosis [210,212].

Scaling and root planning (SRP) (non-surgical periodontal therapy) combined with probiotics, remarkably, *L. reuteri* decreases gingival inflammation [251,252]. Pregnant women [253-255], fishermen, and mariners [256-258], both navy and merchant ships, often had poor oral hygiene practices and health, expressly gingivitis. In these vulnerable groups, when consuming probiotics purposely, *L. reuteri* showed considerable improvement in oral health status, including gingiva [258-261].

Probiotics' Effect on Alveolar Bone

Jia et al. (2022) reported that probiotics can efficiently diminish alveolar osseous tissue injury [261]. Postulated mechanism of action of probiotics, such as *L. paracasei LMT18-32*, *L. acidophilus LA-5*, and *L. rhamnosus GG,* includes improving gut microbiome status, gastrointestinal fencing physiology, halting leakage of inflammatory cytokinin, promoting bone regeneration, and additionally controlling osteoimmune effect. Accordingly, probiotics epitomize an auspicious supportive agent in treating mandibular bone loss even if a patient suffers from estrogen deficit [262-265]. It has been reported that complex probiotics performance shows a much better effect in controlling alveolar osseous tissue loss than individual strains of *L. rhamnosus* and *B. longum* [262,266]. The therapeutic application of probiotics such as *L. reuteri* MG5346 and *L. salivarius* MG4265 noticeably cut down the rate of tartrate-resistant acid phosphatase (TRAP or TRACP or TRAPase) + cells 267,268. It increased osteocalcin (OCN) + cells [262,269] in the alveolar bone, thereby equipoising the augmented commotion of bone resorption. TRAP is a cluster of enzymes containing glycoproteins synthesized by mature osteoclasts. TRAP is copiously squeezed from tissues, e.g., the bone, spleen, liver, lungs, and skin. It is responsible for bone resorption. They are a well-known biomarker for bony destruction and cancer metastasis (TRACP 5b) [270-274]. OCN, typically produced by osteoblasts, controls bone development and throughput. Therefore, OCN often denotes a serum marker of bone growth and thruput to detect the gravity or magnitude of the disease. OCN detected in GCF [275]. Low salivary OCN levels denote chronic smoking instigating PDs triggering CAL [276,277].

Effect of Probiotics on Halitosis

Huang et al. (2022), in their metanalysis [278], reported that probiotics, e.g., *Weissella cibaria, L. reuteri, L. salivarius,* and *S. salivarius*, possess the potential to prevent foul mouth odor for a brief period (less than or equal to four weeks) by decreasing volatile sulfur compound (VSC), quality saliva improved, and boosting overall oral health [278,279]. In their randomized control trial, Jamali et al. (2016) detected chlorohexidine oral infection control followed by probiotics, e.g., *S. salivarius* Strain K12, a therapeutic intervention that minimizes oral foul smell for a more prolonged time [280]. Karbalaei et al. (2021) reported that *Streptococcus*, *Weissella*, and *Lactobacillus* genera [281] are the most beneficial probiotics for the management and deterrence of foul-smelling disorders [282]; additionally, they have a positive impact on PDs, oral epithelial lining ulcer, and tooth caries of the mouth cavity [283] by reducing pathogenic microbial settlement [284]. Multiple studies reported that possible beneficial mechanisms of action of probiotics regarding oral foul smelly odor were predominantly associated with controlling and improving oral ecosystem and through impediment of bonding of oral periopathogens, restoring of the gastrointestinal mucosal barricade task, immunomodulation of stomach and intestines, and neurotransmitter fabrication, and reticence of magnification and ballooning of pathogenic microbes by way of generating of bacteriocins [152,284-288].

Role of Probiotics in Oral Lichen Planus (OLP)

OLP is a typically T-cell arbitrated long-lasting inflammatory illness [289]. Probiotic microbes can regulate the immunological system by treating dysbiosis [145,290]. They can alleviate oral pathogenic infection [142] and repress T-cell instigation, insinuation, and propagation [142,291]. Probiotics possess pharmacodynamics that restores the equilibrium of the microbiome and immune function of affected individuals. Hence, probiotics protect periodontal cases from pathogenic microbial damage.

Additionally, probiotics minimize the nuclear factor-kappa B (NF-kB) signaling system, an unrestrained effector T cell response, and elementary keratinocytes' abnormal programmed cell death. Thereby altering

the mucosal reaction and promoting the synthesis of anti-inflammatory cytokines. Consequently, it controls damaging potential PD [292]. Additionally, probiotics restrain the synthesis of inflammatory cytokines interferon-gamma (IFN- γ) and interferon-alpha (IFN-α), MMP-9 utterance, and microRNAs ((miRNAs) are a category of non-programing RNAs that execute essential functions in controlling gene expressions) [97,226,293,294].

Probiotics stimulate the synthesis of forkhead box P3 (Foxp3) Treg cells by impeding the mammalian target of rapamycin (mTOR) heralding process and deter mast cell degranulation activity [295], and betterment of mental difficulties [296]. These issues are precepting factors instigating the harmful process of OLP [297]. Therefore, researchers assume that probiotics possess effective pharmacodynamics in treating OLP; moreover, probiotics are low-priced, cost-effective, highly safe, and contemporaneous therapeutic interventions [298].

Probiotics Effect on Aggressive Periodontitis

"Aggressive periodontitis is a destructive disease characterized by the following: the involvement of multiple teeth with a distinctive pattern of periodontal tissue loss; a high rate of disease progression; an early age of onset; and the absence of systemic diseases"[299]. Treatment of chronic destructive periodontitis is increasingly difficult because of development resistance against almost all available antimicrobials [300,301]. Inappropriate or indiscriminate use promotes the development of resistance among pathogens [302]. Additionally, imprudent use of antimicrobials causes dysbiosis in typical microbiota communities in the oral and gastrointestinal tract [303-305]. A rich microbiome promotes periodontal health and disease by preventing periodontal pathogens and periodontitis [6,7,306]. Pacheco-Yanes et al. (2023) revealed that "modulation of the oral-gut dysbiosis is an essential factor for preventing periodontitis" [307]. Probiotics possess potential pharmacodynamics to revert oral and gastrointestinal dysbiosis [308-310]. Consequently, probiotics could be potential therapeutic agents for treating and preventing aggressive periodontal diseases.

Probiotics' Effect on Peri-Implant Health

Renvert et al. (2028) revealed that the diagnostic definition of peri-implant health is based on the following criteria: (1) the absence of peri-implant signs of soft tissue inflammation (redness, swelling, profuse BOP), and (2) the absence of further additional bone loss following initial healing [311]. Peri-implantitis is an increasingly growing new health issue [312]. It is defined by succeeding gages: (1) presence of peri-implant signs of inflammation, (2) radiographic evidence of bone loss following initial healing, and (3) increasing pocket probing depth (PPD) as compared to probing depth values collected after placement of the prosthetic reconstruction [311]. Peri-implantitis often instigates detrimental effects on the soft and hard tissue across dental implants, directing toward bone loss, periodontal pocketing, and loss of osseointegration across the implant - the process initiated through oral pathogens biofilm and tartar-related clinical situation. This initiates an adverse impact on dental implants [313-315]. Probiotic therapeutic intervention represses periodontopathogens and halts alveolar bone loss [158,192,316]. Probiotics comprising *L. reuteri*, *L. brevis*, and *L. plantarum* demonstrate a considerable decrease in PPD, PI, and B0P scores [106,317-321]. Therefore, multiple studies reported that probiotics minimize peri-implantitis [322-324].

Role of Probiotics on Bone Regeneration and Bone Homeostasis

A healthy gastrointestinal microbiome is essential for bone health and progression during developmental [325]. Schepper et al. (2017) reported that probiotics improve intestinal health [325] by regulating gut dysbiosis, minimizing intestinal porousness and inflammatory mediators' responsible destruction of osseous tissues [325], thereby preventing bone loss or improving bony structure [325,326]. Probiotics, e.g., *L. plantarum*, brought insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP3), bringing back original category (wild type) levels. Therefore, it proposes that *L. plantarum* can reiterate the advantageous properties of the microbiota on the IGF-1-R [327]. IGF-1, accompanied by growth hormone (GH), supports and stimulates typical bone and tissue progression and elaboration 328,329. It has been reported that osteoblast genesis, bone matrix, and mineralization activity were instigated by probiotics, e.g., the *Bacillus subtilis* process is enhanced by supplementation of probiotics, which is considered cost-effective and has low adverse drug reactions (ADRs) [330,331].

Effect of Probiotics on Osteoporosis of Postmenopausal Women

Osteoporosis is a persistent metabolic disorder with depressed osseous tissue concretion and infinitesimal

architectonic or constructive worsening of the skeletal part with an amplified risk of fracture of the bone. It is often classified into two methods: primary or secondary, depending on whether it strikes to a certain extent of the biological senescence course (insufficient serum estrogen level) or comprises non-communicable diseases pathological process [332,333]. Globally, postmenopausal osteoporosis is a substantial public issue for women because of receding bone quality and orthopedic complications [334].

Osteoporosis also happens in men but is a little more aging than in women [335]. One of the foremost reasons for this is the rising average age and geriatric community worldwide [336]. Probiotic supplementation increases bone density and health among healthy individuals, and there are already cases of diagnosed osteoporosis because of estrogen insufficiency [332]. Chen et al. (2023) reported that innovative stratagems must be developed at the earliest possible time in the pharmacological management of osteoporosis, which possess effective pharmacodynamics with low ADRs and low-cost (cost-effective) [337]. Multiple randomized clinical trials reported that probiotics, e.g., *L. reuteri* NCIMB 30242 and *L. reuteri* ATCCPTA 6475, controls bone metabolism by improving serum 25-hydroxyvitamin D levels, Ca^{2+} absorption in the small intestine, quickens bone mineralization process, and mitigates osteoporosis [338-341]. Jansson et al. (2019) reported that *L. paracasei* DSM 13434, *L. plantarum* DSM 15312, and *L. plantarum* DSM 15313 strains safeguard against compensation lumbar spine bone loss in healthy aged women with estrogen with insufficiency [342]. Similarly, Bose and Sharan (2024) reported that probiotics comprise potential pharmacodynamics that improves bony health and minimize insufficient estrogen-triggered osteoporosis among women [334]. Therefore, probiotic oral supplementation is considered worthwhile in preventing osteoporosis, evaluating its safety and cost [332].

Safety Concerns About Probiotics

Probiotics possess an outstanding safety profile and usually deliberate a health advantage for humans [343,344]. The unremitting, extensive, and mounting intake of probiotics, seldom ADRs, has been reported [345]. Principally consumed probiotic strains remain as constituents of regular healthful gastrointestinal microbiota. These are *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria,* and *Verrucomicrobia*. Among these six phyla, *Bacteroidetes* and *Firmicutes* are the principal types [345-347].

Widely used probiotics remain a component of our system; subsequently, they are not expected to harm consumed patients or individuals. Instead, probiotics are frequently reported to have beneficial health effects [96,110,348,349].

Recommendations for Future Research

Treatment with probiotics seems to boost clinical parameters in PD. Due to the multifactorial nature of the disease and the application of multispecies probiotics, long-term, large-scale, well-designed RCTs are needed to enact the specific role and determine distinct probiotic strain that demonstrates efficacy for different periodontal diseases. Before commencing the use of probiotics as a treatment modality, its long-term impact on health and interactions with other drugs, compliance of drugs, and approval by various age and ethnic groups also demand future research. Finally, a better perception of immunomodulatory properties and the mechanism of establishing the host immune status of probiotics have future potential in research areas.

Limitations of the Narrative Review

Narrative reviews do not propose or answer targeted questions based on documentary evidence, and the search strategy does not follow any decisive regulation. Furthermore, the narrative review suggests further analysis and evaluation [350]. Conventional narrative reviews endure to have an imperative role in medical sciences. However, narrative reviews have integral deficiencies, e.g., the literature search does not possess any predetermined planning, thereby increasing the possibility of prospective preference in selecting papers and construal findings. Therefore, these reviews principally work as springs of speedy, up-to-date reference for precise interest areas for readers [351]. Narrative reviews permit authors to portray what is already identified on a particular issue while steering a subjective analysis and appraisal of a total body of paper. It is advantageous for research inquiries transversely to diverse issues [350,352]. These review papers often support other content professionals, such as scholars, scientists, and legislators, to recognize breaches in their understanding and knowledge [353]. The principal findings of this narrative review are illustrated in Figure 8.

Figure 8: The Principal Findings of this Narrative Review.

Notes: IL: Interleukin; TNF: Tumor Necrosis Factor; TIMP: Tissue inhibitor of metalloproteinase; MMP: Matrix metalloproteinase. This figure was drawn using the premium version of BioRender (https://biorender.com/) GN27NQHS53, accessed on October 30th, 2024, with license number [44].

Illustration credit: Rahnuma Ahmad.

CONCLUSIONS

PD is evoked through host-microbe dysbiosis, aggravating inflammation within the oral cavity and other body systems. This study noted research works that found the benefits of probiotics on PD. Probiotics modulate the immune system and produce antimicrobial molecules to combat oral pathogens. Probiotics have several health benefits and have not yet had adverse effects upon consumption. Further research needs to be carried out to understand the mechanisms underlying the impact of probiotics on health, including the oral cavity. The oral microbiota homeostasis is essential to prevent PD. Therefore, the general population should be encouraged to consume easily accessible probiotics, promoting oral health and overall health.

Consent for Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

DISCLOSURE

The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to

the subject matter or materials presented in this review paper. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

Data Availability

Information for this review paper is taken from freely available sources.

Authorship Contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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