Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

Scope of Probiotics in the Prevention and Management of Periodontal Health

Madhumitha G[1], Ramakrishna Saradha[2], Neha Singh [3], Selvalakshmi Saravanan[4], Rohan Vasanth Raj[5], TamilSelvan Kumar [6]

[1]CRRI, Vinayaka Mission's Sankarachariyar Dental College, Vinayaka Mission's Research foundation (Deemed to be University under section 3 of the UGC Act 1956), Sankari Main Rd, Salem, Tamil Nadu 636308

[2]Assistant Professor, Department of Periodontology Vinayaka Mission's Sankarachariyar Dental College, Vinayaka Mission's Research foundation (Deemed to be University under section 3 of the UGC Act 1956), Sankari Main Rd, Salem, Tamil Nadu 636308

[3]Assistant Professor, Department of Periodontology, G.Pulla Reddy dental college and Hospital, Kurnool, Andhra Pradesh 518007

[4]Assistant Professor, Department of Periodontology Vinayaka Mission's Sankarachariyar Dental College, Vinayaka Mission's Research foundation (Deemed to be University under section 3 of the UGC Act 1956), Sankari Main Rd, Salem, Tamil Nadu 636308

[5]Assistant Professor, Department of Periodontology Vinayaka Mission's Sankarachariyar Dental College, Vinayaka Mission's Research foundation (Deemed to be University under section 3 of the UGC Act 1956), Sankari Main Rd, Salem, Tamil Nadu 636308

[6]Associate Professor, Department of Periodontology Vinayaka Mission's Sankarachariyar Dental College, Vinayaka Mission's Research foundation (Deemed to be University under section 3 of the UGC Act 1956), Sankari Main Rd, Salem, Tamil Nadu 636308

Corresponding Author

Ramakrishna Saradha[2,] Assistant Professor, Department of Periodontology, Vinayaka Mission's Sankarachariyar Dental College, Sankari Main Rd, Salem, Tamil Nadu 636308

(Received: 16 September 2024 Revised: 11 October 2024 Accepted: 04 November 2024)

KEYWORDS
Periodontal health, Probiotics, dysbiosis, periodontal disease, periodontopathogen, microecological balance, immuno-regulation

ABSTRACT:
The human microbiome, including the oral cavity, is crucial for health. Probiotics, live microorganisms, can benefit periodontal health by inhibiting harmful bacteria, reducing inflammation, and improving clinical parameters. However, careful strain selection and consideration of individual health are essential. Probiotics work by preventing pathogens from adhering to tissues, modulating the immune system, enhancing intestinal barrier integrity, and inhibiting harmful bacteria. Studies suggest their effectiveness in reducing plaque formation, inhibiting periodontopathic bacteria, and improving clinical parameters like bleeding on probing and pocket depth. While probiotics offer potential benefits, careful strain selection and consideration of individual factors are crucial.

INTRODUCTION

The paradigm of periodontal disease treatment is evolving towards a more targeted approach, focusing on the eradication of specific bacteria and the subsequent restoration of a healthy oral microbiome.[1] The emergence of multi-resistant bacteria has necessitated a shift in therapeutic strategies, underscoring the importance of adjunctive therapies. Probiotic bacteria, capable of colonizing dental plaque and inhibiting the growth and metabolic activity of pathogens, offer a promising avenue for enhancing periodontal health. Oral administration of probiotics has demonstrated potential benefits in the management of periodontitis.[2]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

Probiotics, derived from naturally occurring bacteria, are commonly found in various foods, including yogurt, fermented and unfermented milk, soy drinks, and traditional meals. These microorganisms primarily belong to the Lactobacillus or Bifidobacterium genera.[3] As awareness of the significance of beneficial bacteria for overall health increases, the integration of probiotics into routine dental care is anticipated to become more prevalent.[4] However, the development of effective probiotic interventions for periodontal disease requires further research. The lack of a comprehensive understanding of the disease's pathophysiology and the factors that contribute to oral health has limited the design of rigorous studies on probiotic use.[5] Preliminary findings suggest that a probiotic mouthwash containing nisin may be beneficial in reducing plaque accumulation and gingivitis.[6] This article explores the current state of knowledge regarding probiotic applications in periodontal disease, including their scientific rationale and potential for prevention and treatment.

DYSBIOSIS

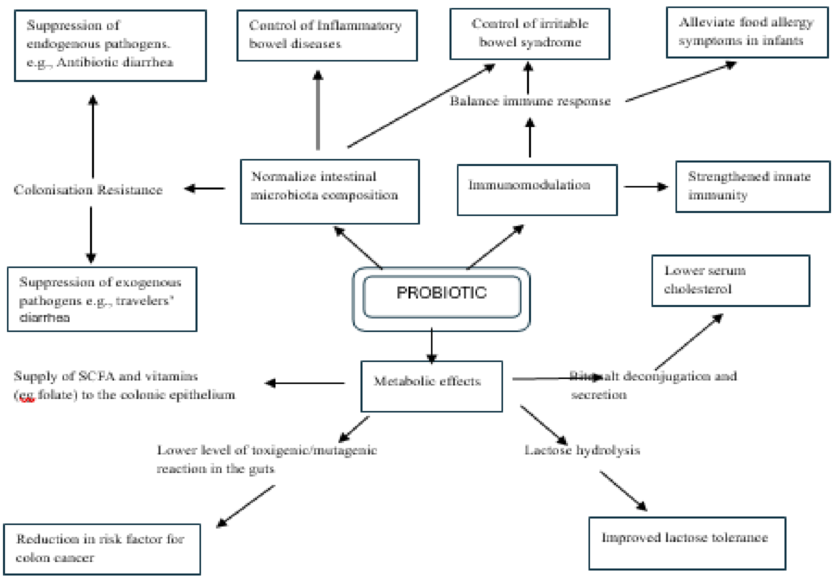
Dysbiosis, an imbalance in the gut microbiota, can be caused by various factors like antibiotics, reduced stomach acid, diet, and stress. It can affect not only the gut but also other body areas. The consequences of dysbiosis can be severe, impacting various body systems.[7] To address this issue, it is crucial to supplement the gut with beneficial bacteria, known as probiotics.[8]

PROBIOTICS: Definition and Mechanism of Action

The term "probiotic" is derived from the Greek words' "pro" and "bios," which translate to "for" and "life," respectively.

The term "probiotic" was initially coined in 1907 by Élie Metchnikoff, a distinguished biologist and Nobel laureate. Metchnikoff posted that the beneficial effects of yogurt were attributable to the presence of lactic acid-producing bacteria.

Hill et al. (2014) reiterated the **FAO/WHO** definition of probiotics, stating: "Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." This definition emphasizes the importance of both the viability of the microorganisms and their ability to provide beneficial effects to the host.



[Figure 1 : Proposed health benefits stemming from probiotic consumption]

Mechanism of Action

Several mechanisms have been proposed [9] [10-12][13], including:

- **Prevention of Pathogen Adhesion**: Probiotics prevent pathogens from adhering to host tissues.
- **Immune System Modulation**: They stimulate and modulate the mucosal immune system by reducing the production of pro-inflammatory cytokines through action on NFkB pathways, increasing the production of anti-inflammatory cytokines such as IL-10, enhancing IgA defences, and influencing dendritic cell maturation.
- **Enhancement of Intestinal Barrier Integrity**: Probiotics improve intestinal barrier integrity and upregulate mucin production.
- **Pathogen Inhibition:** They kill or inhibit the growth of pathogens through the production of bacteriocins or other antagonistic products such as acids or peroxides.

The primary organisms used as probiotics include certain species of lactobacilli and bifidobacteria. Additionally, Saccharomyces species, Streptococci, Enterococci, and commensal Escherichia coli have been reported to have beneficial effects in specific contexts. [14][15][13][16]

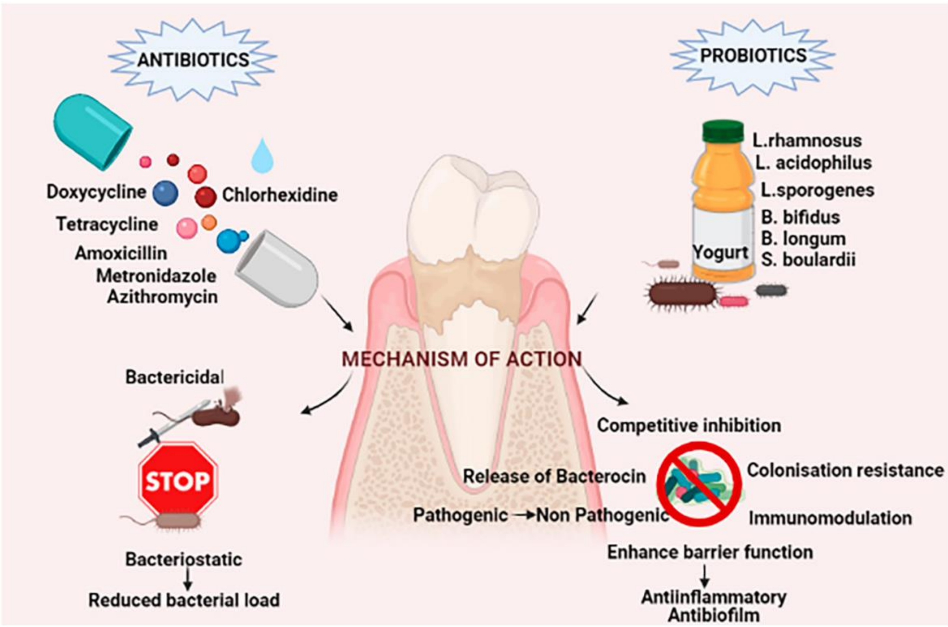


Figure 2: Schematic representation of the mechanism of action of probiotics versus antibiotics on periodontitis

THE ORAL CAVITY AND INDIGENOUS PROBIOTICS

Recent studies have identified no fewer than 1,000 bacterial species residing or transiently present within the oral cavity. [17,18] These bacteria exist either in a planktonic state or as part of an oral biofilm on various oral surfaces or niches. Research has documented significant physiological differences between planktonic bacteria and those in biofilms. [19][20][21] Keigser et al. [18] reported the presence of over 1,000 species in the oral cavity in both planktonic and biofilm forms. Saliva contributes to microbial diversity through its composition and the continuous detachment of bacterial cells from biofilm surfaces. The presence of indigenous probiotics in the mouth remains unclear; however, given that Lactobacillus and Bifidobacterium constitute the majority of probiotics, it is plausible that some lactobacilli in the mouth may exhibit beneficial effects.[22]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

Although information on indigenous probiotics in the oral cavity is limited,[23] Koll-Klais et al. [24] reported that a healthy oral cavity is populated with Lactobacillus gasseri and Lactobacillus fermentum, whereas patients with periodontitis lack these species but are populated with Lactobacillus plantarum.

Numerous clinical studies have demonstrated the positive effects of regular probiotic yogurt consumption in reducing the numbers of cariogenic streptococci in the oral cavity, [25- 27] both in saliva and dental plaque. Further research on periodontal diseases, such as gingivitis and periodontitis, has shown that certain probiotic lactobacilli can antagonize pathogenic bacteria involved in periodontitis, such as Porphyromonasgingivalis and Aggregatibacter species.[24,29] The trend of positive reports on the role of probiotics in managing periodontal disease is significant, especially considering the complexity of periodontitis etiology, which is believed to be a biofilm-induced infection.[30] However, Bartold and Van Dyke[31] associated periodontal disease with imbalances in the host's local microbiome, characterized by increased numbers of pathogens and reduced proportions of health-associated bacteria.[32]Finally, since the goal of managing oral cavity infections is to reduce the pathogenic burden through antibiotics or other means, this effect is not permanent due to recolonization over time.[33] Additionally, the emergence of antibiotic-resistant bacteria poses challenges. Considering probiotics and beneficial bacteria with their potential disease-preventive capabilities offers a reasonable option for safer oral health.

PERIODONTAL DISEASES

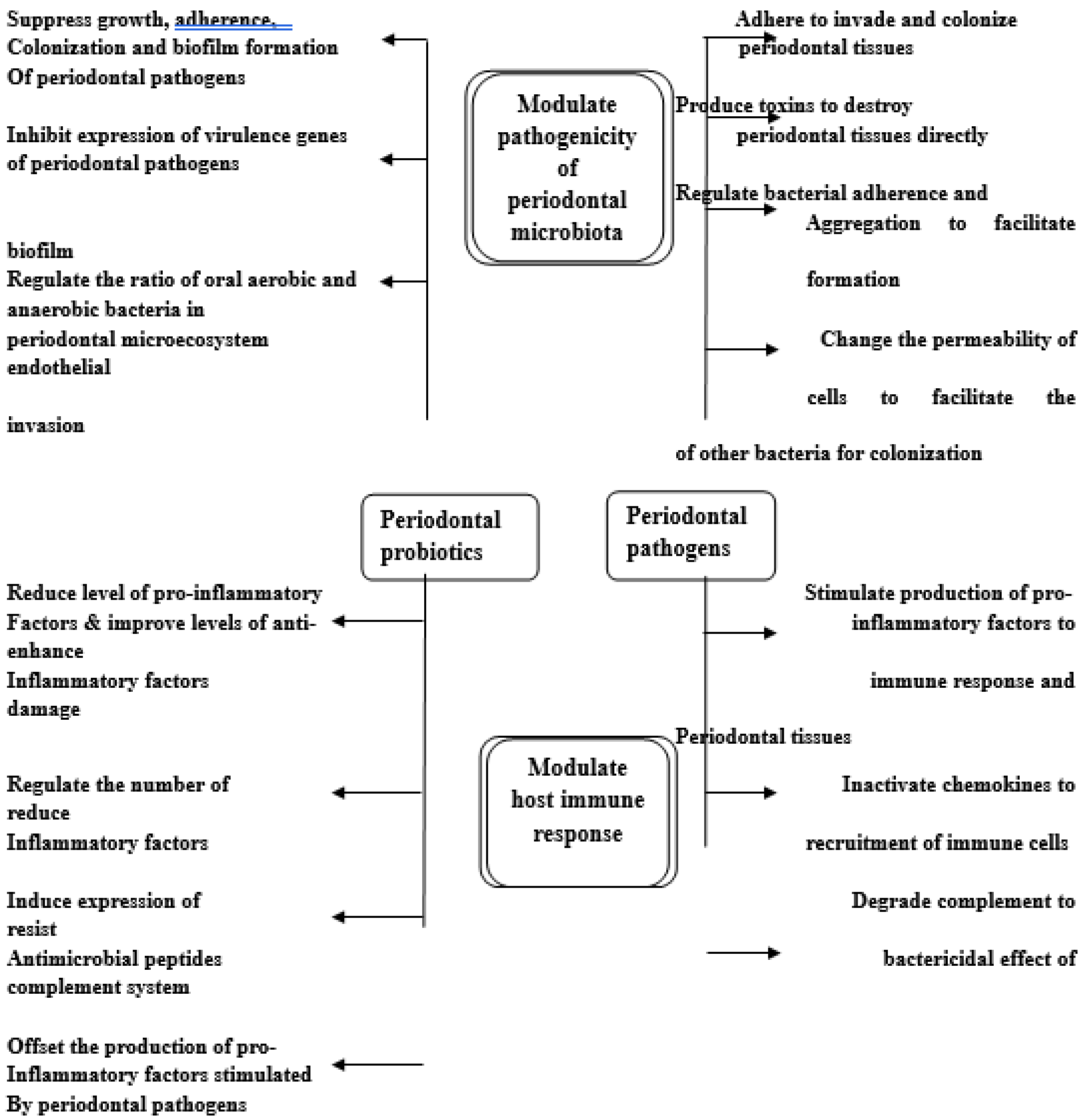
Periodontal diseases are chronic inflammatory conditions that compromise the bone and gingival tissues supporting the teeth, with gingivitis and periodontitis being the most prevalent forms.

Gingivitis represents a mild form of periodontal disease; however, if left untreated, it can progress to the more severe periodontitis, characterized by the formation of deep periodontal pockets that may lead to tooth mobility or loss, significantly affecting patients' quality of life. As of 2019, it is estimated that 1.1 billion individuals globally suffer from severe periodontitis, with its prevalence increasing by 8.44% from 1990 to 2019 [34]. Dental plaque, a microbial biofilm that forms on the teeth and gingiva, is considered the primary etiological factor of periodontal diseases. The understanding of dental plaque biofilm pathogenicity has evolved, with historical hypotheses ranging from the "Specific Plaque Hypothesis" [35], the "Non-Specific Plaque Hypothesis" [36], to the "Ecological Plaque Hypothesis" [37]. Contemporary periodontology not only examines the pathogenicity of dental plaque biofilms but also emphasizes the interaction between oral microbes and the host.

In recent years, the "Keystone-Pathogen Hypothesis" (KPH) [38] and the polymicrobial synergy and dysbiosis (PSD) model [39] have garnered significant attention. The KPH posits that certain low-abundance periodontopathogens, such as Porphyromonas gingivalis, can undermine the host immune system's bactericidal effects and promote inflammatory responses, thereby disrupting the host-microbe homeostasis and leading to periodontal diseases. The PSD model highlights that the synergistic interactions between polymicrobial communities and the host's inflammatory response disorder drive periodontal diseases, with ecological imbalance and inflammatory responses reinforcing each other as the primary disease drivers.

Dysbiotic periodontal microbiota not only induce periodontal diseases but also contribute to systemic inflammation [40]. Research on oral microorganisms indicates that over 700 bacterial species colonize the oral cavity (Kumar et al., 2005). However, only a few bacteria, such as P. gingivalis, Aggregatibacteractinomycetemcomitans, Tannerella forsythia, Prevotella intermedia, and Fusobacteriumnucleatum, are proven to initiate and advance periodontal diseases [38]. Studies on the role of probiotics in managing periodontal diseases often focus on these key periodontopathogens, indicating that periodontal probiotics are typically associated with specific periodontal diseases driven by these pathogens. These pathogens, through various virulence factors, directly destroy periodontal tissues or stimulate host cells to activate a wide range of inflammatory responses, thereby disrupting host-microbe homeostasis and promoting the development of multiple periodontal diseases [41-47

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 623-632 | ISSN:2251-6727



[Figure 3 : How periodontal probiotics and pathogens play their roles in regulating periodontal health and disease. The diagram shows the primary mechanisms of periodontopathogens and probiotics in regulating periodontal microbiota and host immune responses, respectively]

APPLICATION OF PROBIOTICS IN MANAGING PERIODONTAL DISEASES

The long-term success of periodontal therapy necessitates meticulous oral hygiene practices to maintain plaque levels conducive to gingival health. [48] Periodontal treatment not only addresses supragingival plaque but also removes subgingival plaque, which often precedes periodontal disease.

Consequently, chemical plaque control has emerged as a valuable adjunct to mechanical plaque removal. Anti-plaque agents are increasingly recognized for their potential to inhibit or reduce plaque formation and subsequent gingival inflammation. [49] Chlorhexidine, a widely used antibacterial agent for over two decades, remains the most extensively tested and effective option. However, its use as a mouthwash can be associated with certain local adverse effects. Pre-surgical rinsing with 0.12% chlorhexidine gluconate

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

mouthwash for two minutes has been recommended. [50] Potential side effects include brown staining of teeth and tongue, mucosal membrane erosion, and altered taste.

Probiotic mouthrinse incorporates Aspergillus niger and bacteriocins, short-chain polypeptides synthesized by Bacillus licheniformis. These peptides are extracted from the fermentation culture, excluding lactobacilli cells. Lactic acid bacteria produce antimicrobial substances such as amino acids, superoxide anion, diacetyl, and inhibitory enzymes. [51] Bacteriocins, ribosomally synthesized peptides or proteins, exhibit bactericidal activity against closely related organisms.

Antimicrobial resistance has become a global concern. [52] Nisin, an antibacterial compound, effectively targets Punnet bacteria in various settings. It has demonstrated susceptibility against a wide range of microorganisms, including Actinomyces, Bacillus, Candida, Mycobacterium, Enterobacterium, Gardnerella, Lactococcus, Listeria, Micrococcus, Mycobacterium, Propionibacterium, Streptococcus, and Staphylococcus. [53]

Previous studies have confirmed the bactericidal effects of nisin, the primary component of probiotic mouthrinse, against a broad spectrum of Punnet bacteria. The anti-plaque efficacy of the probiotic mouthrinse is likely attributed to its ability to limit the proliferation and survival of these microorganisms on tooth surfaces, modify plaque biochemistry to reduce cytotoxic product formation, and shift plaque ecology toward a less pathogenic flora. The aqueous delivery vehicle of nisin ensures its efficient release into the oral cavity for effective anti-plaque action.

THERAPEUTIC APPLICATION OF PROBIOTICS FOR THE MANAGEMENT OF HALITOSIS

Halitosis is primarily attributable to the production of volatile sulfur compounds (VSCs). These compounds are generated by bacteria such as Mycobacterium nucleatum, Porphyromonas gingivalis, Shigella, and Streptococcus pneumoniae. A specific probiotic strain, Weissella cibaria, has demonstrated the capacity to inhibit VSC development in both in vitro and in vivo environments. This strain holds significant promise as a novel probiotic for periodontal applications.

Mycobacterium nucleatum plays a pivotal role in the establishment of VSC within the oral cavity by facilitating the aggregation and colonization of other periodontopathogens. Hydrogen peroxide (H2O2) has been implicated in the maintenance of a healthy oral ecosystem and the prevention of disease. H2O2 has been shown to significantly reduce in situ concentrations of sulfur gases. Lactobacillus acidophilus and Lactobacillus casei both produce potent acids that inhibit the growth of anaerobic bacteria in culture. [54] The ecological pH of Weissella cibaria isolates was found to be higher than expected in the presence of Lactobacilli, suggesting its potential utility as a probiotic.

Streptococcus salivaris produces bacteriocins, antimicrobial substances that inhibit VSC-producing microorganisms. In a recent study, chewable tablets and gel containing Streptococcus salivaris were shown to reduce VSCs in individuals with halitosis.

THE EFFICACY OF PROBIOTICS IN PERI-IMPLANTITIS MANAGEMENT

Peri-implantitis, a pathological condition affecting dental implant supporting tissues, is characterized by progressive bone loss, increased probing depth, and bleeding on probing. [55,56] While numerous studies have explored the potential benefits of probiotics in peri-implantitis, most have focused on their combination with nonsurgical periodontal therapy. Despite the shared etiopathogenesis and treatment modalities between periodontal disease and peri-implantitis, limited research has investigated the efficacy of oral probiotics specifically for peri-implant diseases. [57]

Mulla Munaz et al. conducted in vitro studies demonstrating the susceptibility of various pathogenic bacteria implicated in peri-implantitis to Lactobacillus salivarius at a concentration of 50 mg/mL. These findings suggest that L. salivarius probiotics could be effective at this dosage in countering the primary pathogens involved in peri-implantitis, including P.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

gingivalis, P. intermedia, S. aureus, and S. salivaris. [58][59]

POTENTIAL RISKS RELATED TO PROBIOTIC USE

The application of probiotics in the management and prevention of oral disorders warrants cautious consideration. Lactobacilli and other bacteria constitute the predominant probiotic strains, with acid generation recognized as a key mechanism of their pathogen resistance. Conversely, Streptococcus species play a significant role in the development of dental caries and acid production by acidogenic plaque populations.

A probiotic strain, Lactobacillus salivarius, was found to exhibit cariogenic properties in a rat model. [60] Consequently, a primary challenge lies in the potential for probiotic activities and microorganisms that protect against oral disease to simultaneously increase the risk of dental caries.[61] Therefore, employing a prebiotic approach to enhance endogenous beneficial commensals may be a more promising strategy.

FUTURE ASPECTS OF PROBIOTICS

Probiotics in dentistry have a bright future ahead of them for improving oral health. Important elements consist of:

- Cavity Prevention: Preventing cavities by inhibiting certain strains of bacteria, such as Streptococcus mutans.
- Periodontal Health: By lowering inflammation and encouraging good bacteria, probiotics can be used to treat gum disease.
- Biofilm Management: Creating probiotics to change dental biofilms and reduce the buildup of plaque.
- Treatment for Halitosis: Providing natural remedies for foul breath by combating microorganisms that cause odour. Customizing probiotic treatments according to each patient's unique microbiome profile is known as personalized oral care.
- Consumer Products: Mouthwashes and toothpastes with probiotics are becoming more widely available. Improving the results of current dental therapies by integration with traditional treatments. Probiotics may revolutionize dentistry's therapeutic and preventive approaches as research advances, improving oral health in general.

CONCLUSION

The integration of probiotics into oral care is a burgeoning field. In our contemporary technological landscape, it is an opportune moment to re-evaluate traditional bacterial treatment paradigms. Contemporary research suggests the potential oral health advantages of established probiotic strains. However, additional investigations are required to fully optimize and quantify these benefits. Rigorous systematic studies and randomized controlled trials are indispensable for identifying the most efficacious probiotic and prebiotic strains, as well as their optimal modes of administration for diverse oral health conditions. Ultimately, a comprehensive understanding of the broader ecological transformations within the oral cavity and the long-term implications of probiotics and prebiotics on oral health and disease is paramount.

REFERENCES

1. Parvez S, Malik KA, Ah Khang S, Kim Probiotics and their fermented food products are beneficial for health.JApplMicrobiol 2006 Jun;100(6):1171-85.
2. Meurman JH, Stamatova I. Probiotics: Contributions to oral health. Oral Dis 2007;13:443-51.
3. Reid G, Jass J, Sebulsky MT, McCormick JK. Potential uses of probiotics in clinical practice. ClinMicrobiol Rev. 2003;16:658- 66.
4. Pandit N, Pandit IK, Bali D, Oberoi S. Probiotics and periodontal diseases: The link. IJOS 2013 Sep-Dec;4(3):114-119.
5. Krasse P, Carlsson B, Dahl C, Paulsson A, Nilsson A, Sinkiewicz G. Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri. Swed Dent J. 2006;30:55_60.
6. Johnson IH, Hayday H, Coleman G. The effects of nisin on the microbial flora of the dental plaque of monkeys (Macacafascicularis). Journal of Applied Bacteriology. 1978;45: 99-109.

JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

7. Floch MH, Moussa K. Probiotics and dietary fiber: the clinical coming of age of intestinal microecology. J ClinGastroenterol 1998;27:99-100.
8. Gibson GR, McCartney AL. Modification of the gut flora by dietary means. BiochemSoc Trans 1998;26:222-8.
9. Geier MS, Butler RM, Howarth GS. Inflammatory bowel disease: Current insights into pathogenesis and new therapeutic options; probiotics, prebiotics and symbiotics. Int J Food Microbiol 2007;115:1-11.
10. Marco ML, Pavan S, Kleerebezem M. Towards understanding molecular modes of probiotic action. CurrOpiBiotechnol 2006;17:204-10.
11. Nomoto K. Prevention of infections by probiotics. J BiosciBioeng 2005;100:583-92.
12. Tagg JR, Dierksen KP. Bacterial replacement therapy: adapting ‘germ warfare’ to infection prevention. Trends Biotechnol 2003;21:217-23.
13. Picard C, Floramonti J, Francois A, Robinson T, Neant F, Matuchansky C. Review article: bifidobacteria as probiotic agents – physiological effects and clinical benefits. Aliment Pharmacol Ther 2005;22:495-512.
14. Caglar E, Kargul B, Tanboga I. Bacteriotherapy and probiotics role on oral health. Oral Dis 2005;11:131-7.
15. Reid G, Jass J, Sebulsky MT, McCormick JK. Potential uses of probiotics in clinical practice. ClinMicrobiol Rev 2003;16:658-66.
16. Morelo MR, Sarantinopoulos P, Tsakalibou E, De Vuyst L. The role and application of enterococci in food and health. Int J Food Microbiol 2006;106:1-24.
17.Mark-Welsh, J.L.; Rosseti, B.J.; Rieken, C.W.; Dewhirst, F.W.; Boristy, G.G. Biogeography of a human oralmicrobiome at the micro scale. Proc. Natl. Acad. Sci. USA 2016, 113, E791–E800.
18. Keijser, B.J.; Zaura, E.; Huse, S.M.; Van der Vossen, J.M.; Schuren, F.H.; Montigen, R.C.; Ten Cate, J.M.; Crielaad, V.V. Pyrosequencing analysis of the oral microflora of healthy adults. J. Dent. Res. 2008, 87, 1016–1020.
19. Marsh, P.D.; Zura, E. Dental biofilms: Ecological interactions inhealth disease. J. Clin. Periodontol. 2017, 44, S12–S22.
20. Rudney, J.D. Saliva and dental plaque. Adv. Dent. Res. 2000, 14, 29–39.
21. Burne, R.A.; Quivey, R.G.; Marquis, R.E. Physiologic homeostasis and stress responses in oral biofilms. Meth. Enzymol. 1999, 310, 441–460.
22. Bernaedeau, M.; Venoux, J.P.; Henri-Dubernet, S.; Gueguen, M. Safety assessment of dairy microorganisms: The Lactobacillus genus. Int. J. Food Microbiol. 2008, 85, 88–94.
23. Yli-Knuuttila, H.; Snall, J.; Kari, K.; Meurman, J.H. Colonization of Lactobacillus rhamnosus GC in the oral cavity. Oral Microbiol. Immunol. 2006, 21, 129–131.
24. Koll-Klais, P.; Mandar, R.; Leibur, E.; Marcotte, H.; Hammarstrom, L.; Mikelsaar, M. Oral lactobacilliin chronic periodontitis and periodontal health: Species composition and antimicrobial activity.Oral Microbiol. Immunol. 2005, 20, 354–361.
25. Bizzini, B.; Pizzo, G.; Scapagnini, G. Probiotics and oral health. Curr. Pharm. Des. 2012, 18, 5522–5531.
26. Scully, C.; Greenman, J. Halitosis (breath odour). Periodontology 2012, 48, 66–75.
27. Islam, B.; Khan, S.; Khan, A. Dental caries: From infection to prevention. Med. Sci. Monit. 2007, 13, 196–205.
28. Ruiz-Martinez, R.C.; Bedani, R.; Saad, S.M. Scientific evidence for probiotics and prebiotics: An update forcurrent prospectives and future challenges. Br. J. Nutr. 2015, 114, 1993–2015.
29. Sookkhee, S.; Chulasiri, M.; Pradyabreud, W. Lactic acid bacteria from healthy oral cavity of Thai volunteers,inhibition of oral pathogens. J. Appl. Microbiol. 2001, 90, 172–179.
30. Hajishengallis, G. The inflammophilic character of the periodontitis-associated microbiota.Mol. Oral Microbiol. 2014, 29, 248–257.
31. Bartold, P.M.; Van Dyke, T.E. Periodontitis: A host mediated disruption of microbial homeostasis. Unlearninglearned concept. Periodontology 2013, 62, 203–217.
32. Wade, W. Has the use of molecular methods for the characterization of the human oral microbiome changedour understanding of the role of bacteria in

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 623-632 | ISSN:2251-6727

the pathogenesis of periodontal disease? J. Clin. Periodontol.2011, 38, 7–16.
33. Gatej, S.; Gully, N.; Gibson, R.; Bartold, P.M. Probiotics and periodontitis—A literature review. J. Int. Acad. Periodontol. 2012, 19, 42–50.
34. Chen, M. X., Zhong, Y. J., Dong, Q. Q., Wong, H. M., and Wen, Y. F. (2021).Global, Regional, and National Burden of Severe Periodontitis 1990-2019: AnAnalysis of the Global Burden of Disease Study 2019. J. Clin. Periodontol. 48(9), 1165–1188. doi: 10.1111/jcpe.13506
35. Loesche, W. J. (1976). Chemotherapy of Dental Plaque Infections. Oral. Sci. Rev. 9, 65–107.
36. Theilade, E. (1986). The non-Specific Theory in Microbial Etiology ofInflammatory Periodontal Diseases. J. Clin. Periodontol. 13, 905–911. doi: 10.1111/j.1600-051X.1986.tb01425.x
37. Marsh, P. D. (1994). Microbial Ecology of Dental Plaque and its Significance in Health and Disease.Adv. Dent. Res. 8, 263–271. doi: 10.1177/08959374940080022001
38. Hajishengallis, G., Darveau, R. P., and Curtis, M. A. (2012). The KeystonePathogen Hypothesis. Nat. Rev. Microbiol. 10, 717–725. doi: 10.1038/nrmicro2873
39. Hajishengallis, G., and Lamont, R. J. (2012). Beyond the Red Complex and Into More Complexity: The Polymicrobial Synergy and Dysbiosis (PSD) Model of Periodontal Disease Etiology. Mol. Oral. Microbiol. 27, 409–419. doi: 10.1111/ j.2041-1014.2012.00663.x
40. Hajishengallis, G. (2015). Periodontitis: From Microbial Immune Subversion to Systemic Inflammation. Nat. Rev. Immunol. 15, 30–44. doi: 10.1038/nri3785
41. Zhao, J.-J., Feng, X.-P., Zhang, X.-L., and Le, K.-Y. (2012). Effect ofPorphyromonasGingivalis and Lactobacillus Acidophilus on Secretion ofIL1B, IL6, and IL8 by Gingival Epithelial Cells. Inflammation 35, 1330–1337.doi: 10.1007/s10753-012-9446-5
42. Jaffar, N., Ishikawa, Y., Mizuno, K., Okinaga, T., and Maeda, T. (2016). MatureBiofilm Degradation by Potential Probiotics: AggregatibacterActinomycetemcomitansversuslactobacillusspp. PloS One 11, e0159466. doi:10.1371/journal.pone.0159466
43. Zhao, J. J., Jiang, L., Zhu, Y. Q., and Feng, X. P. (2019). Effect of Lactobacillus Acidophilus and PorphyromonasGingivalis on Proliferation and Apoptosis of Gingival Epithelial Cells. Adv. Med. Sci. 64, 54–57. doi: 10.1016/ j.advms.2018.04.008
44. Ishikawa, K. H., Mita, D., Kawamoto, D., Nicoli, J. R., Albuquerque-Souza, E.,Lorenzetti Simionato, M. R., et al. (2020). Probiotics Alter Biofilm Formationand the Transcription of PorphyromonasGingivalis Virulence-AssociatedGenes. J. Oral. Microbiol. 12, 1805553. doi: 10.1080/20002297.2020.1805553
45. Moman, R., O'neill, C. A., Ledder, R. G., Cheesapcharoen, T., and Mcbain, A. J.(2020). Mitigation of the Toxic Effects of Periodontal Pathogens by CandidateProbiotics in Oral Keratinocytes, and in an Invertebrate Model. Front.Microbiol. 11, 999. doi: 10.3389/fmicb.2020.00999
46. Ding, Q., Sun, X., Cao, S., Zhao, C., Wang, Y., and Wang, X. (2021). Heat-KilledLactobacillus Acidophilus Mediates FusobacteriumNucleatum Induced ProInflammatory Responses in Epithelial Cells. FEMS Microbiol. Lett. 368 (5),fnaa160. doi: 10.1093/femsle/fnaa160
47. Jansen, P. M., Abdelbary, M. M. H., and Conrads, G. (2021). A ConcertedProbiotic Activity to Inhibit Periodontitis-Associated Bacteria. PloS One 16,e0248308. doi: 10.1371/journal.pone.0248308
48. Axelsson P, Lindhe J. The significance of maintenance care in the treatment of periodontal disease. J Clin Periodontol. 1981;8:281-94.
49. Addy M. Chlorhexidine compared withlocally delivered antimicrobials. A shortreview. J Cin Periodontol. 1986;13:957-60.
50. Durge KJ, Baliga VS, Sridhar SB, Dhadse PV, Ragit GC. Extraction socket grafting using recombinant human bone morphogenetic protein-2-clinical implications and histological observations. BMC Reasearch Notes. 2021;14. DOI: https://doi.org/10.1186/s13104-021- 05476-0
51. Lindgren Se, Dobrogosz WJ. Antagonistic activities of lactic acid bacteria in food and feed Fermentations. FEMS Microbial. Rev. 1990;87:149-64.
52. Toshniwal V, Mudey G, Khandekar A, Kubde V, Mudey A. Gram positive bacteria carriage among

health care workers: an under-reported source of infections? Journal of Pure And Applied Microbiology. 2020;14:2677–2682. DOI:https://doi.org/10.22207/JPAM.14.4.45

53. Mota-Meira M, Lapointe G, Lacroix C, Lavoie MC. MIC of mutacin B-Ny266, nisin A, vancomycin and oxacillin against bacterial pathogens. Antimcrob. Agents Chemother. 2000;44:24-9.
54. Shimazaki Y, Shirota T, Uchida K, Yonemoto K, Kiyohara Y, Iida M,. Intake of dairy product and periodontal diseases: The hisayama study. J Periodontol. 2008;79:131-7.
55. Di Spirito, F.; Schiavo, L.; Pilone, V.; Lanza, A.; Sbordone, L.; D'Ambrosio, F. Periodontal and Periimplant Diseases and Systemically Administered Statins: A Systematic Review. Dent. J. 2021, 9, 100.
56. Schwarz, F.; Giannobile, W.V.; Jung, R.E. Groups of the 2nd Osteology Foundation Consensus Meeting. Evidence-based knowledge on the aesthetics and maintenance of peri-implant soft tissues: Osteology Foundation Consensus Report Part 2-Effects of hard tissue augmentation procedures on the maintenance of peri-implant tissues. Clin. Oral Implants Res. 2018, 29 (Suppl. 15), 11–13.
57. Matsubara, V.H.; Bandara, H.M.; Ishikawa, K.H.; Mayer, M.P.; Samaranayake, L.P. The role of probiotic bacteria in managing periodontal disease: A systematic review. Expert Rev. Anti-Infect. Ther. 2016, 14, 643–655.
58. Mulla, M.; Hegde, S.; Koshy, A.; Mulla, M. Effect of Probiotic Lactobacillus salivarius on Peri-Implantitis Pathogenic Bacteria: An In Vitro Study. Cureus 2021, 13, e20808.
59. Amato M, Di Spirito F, D'Ambrosio F, Boccia G, Moccia G, De Caro F. Probiotics in periodontal and peri-implant health management: biofilm control, dysbiosis reversal, and host modulation. Microorganisms. 2022 Nov 18;10(11):2289.
60. Matsumoto M, Tsuji M, Sasaki H, Fujita K, Nomura R, Nakano K,. Cariogenicity of the probiotic bacterium Lactobacillus salivarius in rats. Caries Res. 2005;39:479_83
61. Chandel R, Kale B, Pal R, Durge K. Role of Probiotics in Periodontics. Journal of Pharmaceutical Research International. 2021 Dec 28;33(60B):3528-37.