IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
March 2021 Vol.:20, Issue:4

Prospects for Probiotic Approach in the Management of the Oral Ailments: A Review

IJPPR
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ISSN 2349-7203
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Submitted: 09 February 2021
Revised: 28 February 2021
Accepted: 20 March 2021

www.ijppr.humanjournals.com

Keywords: Probiotics, Oral cancer, Dental caries, Gingivitis, Periodontitis, Halitosis, Dental plaque

ABSTRACT

The term ''Probiotic'' is composed of words pro, representing ''for'' and biotic, implying ''life''. Probiotics are live microorganisms when consumed in suitable quantity, avails the host with desired health benefits. Previously, Probiotics and their entire health benefits were limited to gastrointestinal tract infection. However, mounting interest in the field of probiotics lets investigators explore the clinical benefit of probiotics in oral ailments and reveal the indication that probiotics could be a novel natural therapy over the existing allopathic practice. Microbiota present within the oral fissure offers an outstanding opportunity and maybe the world of interest for researchers, scientists and the pharmaceutical sector for a more clinical trial. Several *in-vitro* studies and clinical evidence have supported and justified the inherent role of probiotics in the control of oral ailments. Further studies incorporating safety aspects of an individual or combination of strain may be conducted to establish and formulate a suitable probiotic delivery system for oral application. This review furnishes the most recent scientific evidence on oral probiotics for a more robust understanding regarding the prospects of probiotics in oral ailments.

INTRODUCTION

The term "Probiotic" is composed of words pro, representing "for" and biotic, implying "life". Expressly, Probiotics are live microorganisms when consumed in a suitable quantity counters the pathogenic microbes and avail the host [1]. According to the Food and Agriculture Organization (FAO) /World Health Organization (WHO) (2001), Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host". However, a conference held by the International Scientific Association for Probiotics and Prebiotics (ISAPP, 2013) with a panel of experts strengthened the definition with grammatical revision and designated as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [2]. In 1908, Prof. Metchnikoff assumed that the rationale behind the potential longevity of the Bulgarians was due to the consumption of an enormous quantity of fermented milk that comprises beneficial microbes opposing the pathogenic microflora. Nevertheless, Lilly and Stillwell (1965) proposed the word "Probiotics" [3].

The microorganisms dwell within the oral cavity are attributed as oral microbiome. As per the HOMD (Human Oral Microbiome Database), solely 54% of the bacterial species are officially acknowledged, 14% of microbes are cultivated but remained unrecognized while the remaining species yet to be cultured [4]. The oral cavity is profoundly complex and loaded with organic stuff with distinct specialties that attract several microbial communities. Every niche contributes to a unique ecosystem with suitable conditions and nutrients for microbial establishment. As a result, microbes can comfortably thrive and establish in each surface (tongue, teeth, gums, saliva, cheeks, and tongue) of the oral cavity [5]. Although plenty of microorganisms appear to be harmless, a fraction of the species is capable of developing dental plaque and oral disorders like Cavity, Gingivitis, Periodontitis, Endodontic infection, and Oral cancer/tumors [6].

Probiotics have confirmed their clinical ability to control the outgrowth of microorganisms. Previously, probiotic use was focused and confined to gut health. The number of clinical investigations conducted was limited to the microorganism found in the Gastrointestinal Tract (GIT) as well as GIT associated ailments. Previously, probiotics have demonstrated its clinical potential and proved its clinical significance in the management of traveler's diarrhea, cardiovascular disease, urogenital infection, and intestinal tumors. However, in recent times, several researchers have well-recognized probiotics roles in oral diseases [7,8].

Probiotics may be bacteria, molds, or yeast, but bacterial species are predominant. The most ordinarily employed in probiotic preparation and Generally Regarded as Safe (GRAS) principally originates from two genera *Lactobacillus* and *Bifidobacterium* species [9,10,11]. It is imperative to disclose that the impact of probiotics on oral health is strain-specific. Since the recommended mechanism and clinical effectiveness of individual strain may vary from another, therefore the identification of each strain should be scientifically verified to establish their possibility and aptness for industrial production [12].

Antibiotics are principally preferred and exercised frequently for the treatment of oral disease. Repeated use of antibiotics develops resistance to antibiotics and provokes alterations in the normal ecology of microbes. Consequently, the call to reduce the employment of antibiotics and acquire simple, low-cost, and receptive novel approaches in the treatment of oral ailments is the recent issue of interest. Accordingly, the utilization of probiotic bacterial strain with associated benefits can be a promising approach [13,14].

The motive of this review is to study published literature in several journals concerning probiotics and explore the clinical evidence to support the efficacy of probiotic therapy in oral health and furnish the most recent information for a more robust understanding of the potential good thing about probiotics in oral diseases.

MECHANISM OF PROBIOTIC ACTION

The mechanism by which probiotics offer health benefits within the oral cavity has been motivated by previous studies carried out within the GIT. Although several theories are available to describe how probiotics contribute health benefits within the oral cavity, the exact mechanism is yet unknown [15,16]. Probiotics in the oral cavity fight against the oral pathogens for the adhesion site at the epithelial cell. Once the probiotic bacteria adhere to the surface competes for the nutrients and produce antimicrobial compounds (Organic acids, Short-chain fatty acid, Hydrogen peroxide, and Bacteriocins) that suppress the pathogenic microbes and helps to modulate the composition of bio-film and maintain oral health condition [17]. Several studies elucidated that the probiotic bacteria triggers both adaptive and innate immune function by interacting with immunocompetent cells (Macrophages). Thereby inducing phagocytosis, IgA secretion, altering T-cell response, improving Th1 response, and weakening Th2 response [12]. Although specific mechanisms for an individual strain are present. No strain may comprise the entire as presented in Figure 1.

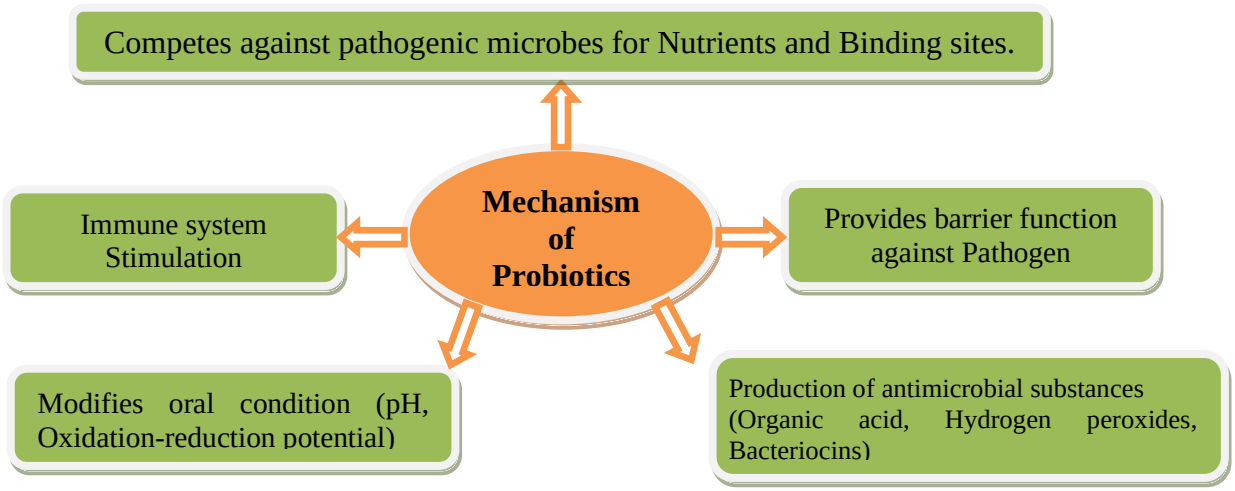


Figure No. 1: Possible mechanism of probiotics action for oral health benefits [7][18]

SELECTION OF STRAIN

Attributes that may be useful while selecting the probiotic strain had been described in the given figure 2. The selection of probiotic strain is a crucial facet. Therefore, safety entries regarding the origin, strain identification, production, application, and potential health benefit in the host should be taken into consideration. Probiotic strain characterization aid in obtaining information and the appropriate mechanism through which probiotic strain benefits the host. As per the FAO/WHO guidelines, the health benefits of probiotics are strain-specific. Therefore, it is recommended to be characterized at genus, species, and strain level and suggests employing phenotypic and genetic techniques to achieve identification and classification. The non-pathogenic and non-toxic strain referred to as Generally Recognized as Safe (GRAS) should be selected [20]. Additionally, a study of the phenotype and genotype stability, epithelial attachment characteristics, production of bacteriocins, antibiotic resistance ability, immunomodulation properties, ability to adhere to the target tissue, and inhibition of the growth of the pathogenic microorganism is a must while selecting the probiotic for oral health care [21]. A systemic approach or strategy relevant to that, as presented in figure 3 can be exercised during the selection of probiotic bacterial strain.

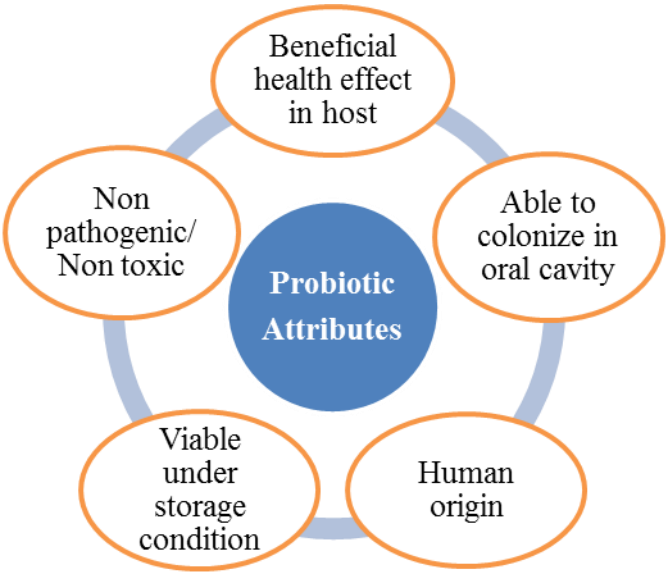
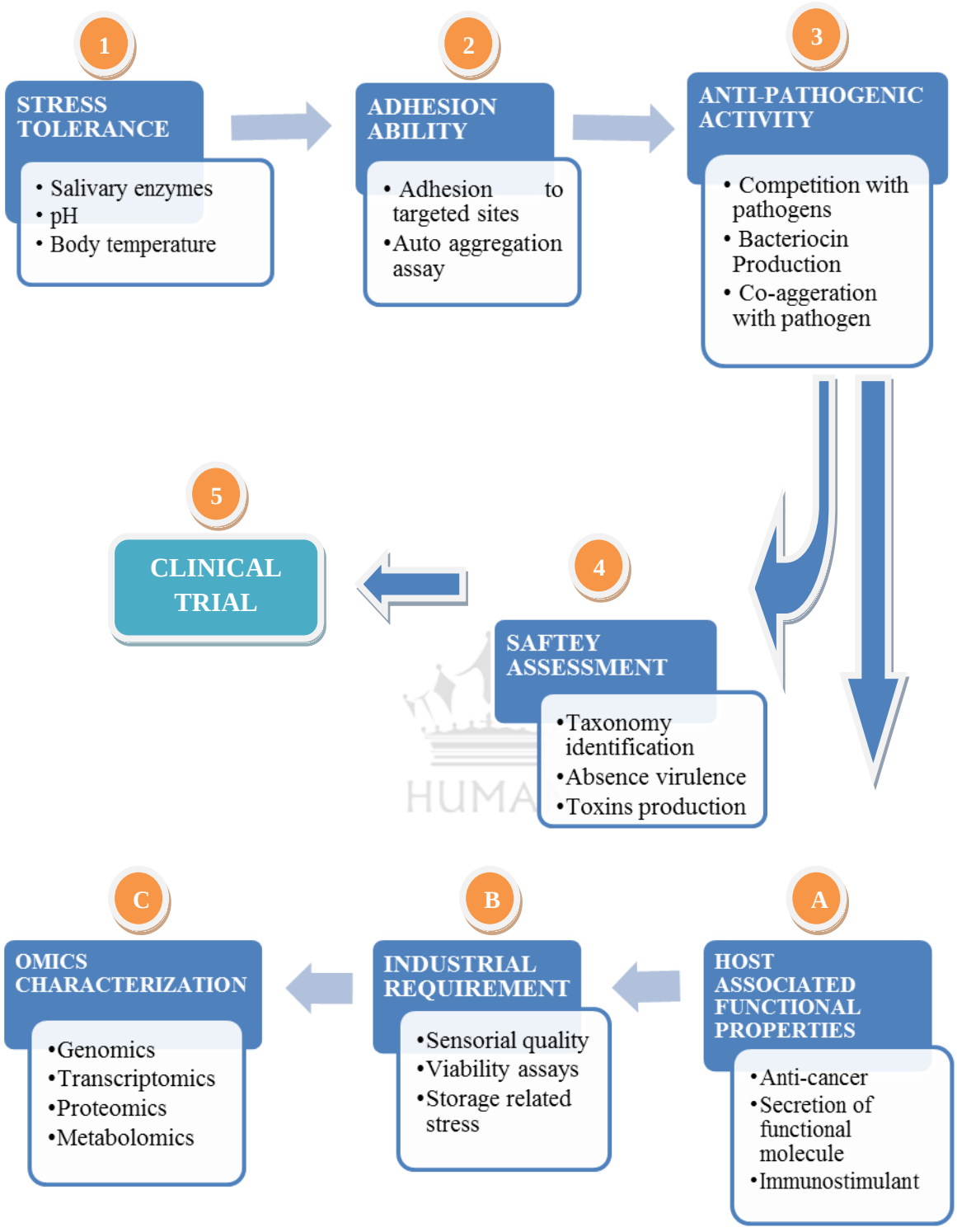


Figure No. 2: Attribute to be considered during the selection of probiotic strain [19]



1-5 → WHO and FAO recommended

A-C → Alternative requirement

Figure No. 3: WHO/FAO recommended screening strategies for the characterization of the bacterial strain [22]

CLINICAL EVIDENCE OF PROBIOTICS IN THE MANAGEMENT OF ORAL AILMENT

The initial portion of this paper is the preface to the probiotics introduction, potential mode of action, and its selection criteria. This portion summarizes the treatment strategies and the demonstrated potential and effectiveness of probiotics in the management of oral ailments. The information in this section displays prior contributions. So, for the thorough review, the scholars are requested to refer to the reference publications.

Probiotics and Dental caries

Although the incidence of dental caries in western countries declined yet it is familiar across the world, especially in developing countries [23]. Dental caries recognized as a cavity or tooth decay is the progressive demineralization of teeth and root surface resulting from metabolic events in a biofilm. Dental caries recognized as a cavity or tooth decay is the progressive demineralization of teeth and root surface resulting from metabolic events in a biofilm. These biofilms contain acidogenic bacterial species that are exceptionally stable at low pH. They convert carbohydrates into lactic acid that makes the environment more acidic leading to demineralization and erosion. The initial demineralization progressively penetrates more profoundly through the layer that ultimately converts into decay. A rise in the count of streptococci is a strong indicator of the mounting risk of dental caries [17,24]. In an account of the crucial role of *Streptococcus mutans* in dental caries development, several *in-vitro* studies have revealed that probiotic strains and acknowledged probiotic candidates inhibit the growth of *S. mutans* and other species with cariogenic properties [25,26]. In dental caries, Probiotic bacterial strain encounters with the microbes present in the oral cavity to adhere to the dental surface and colonize to develop a biofilm that results in the decline of the pathogenic as well as cariogenic bacterial count [27].

Nase *et al.* (2001) conducted the foremost randomized, double-blind, placebo-controlled study on 594 children of 1 to 6 years of age who consumed milk containing a probiotic strain of *L. rhamnosus* GG for 7 months and published the result which concluded that children of 3 to 4 year of age had shown a potential reduction in salivary *S. mutans* count and significantly lower incidence of caries [28]. Yadav *et al*. performed a double-blinded study, which revealed that *Lactobacillus casei Shirota* potentially reduced dental caries development that affirms its ability to adhere to the dental surface and inhibit biofilm development by pathogenic microbes [29]. According to Rodriguez *et al*. (2016), the probiotic milk

supplemented with probiotic strain *L. rhamnosus* SP1 demonstrated that the prevalence of caries incidence in children consuming the probiotic group was lower than in the placebo group [30]. Several oral probiotic strains evidencing its effectiveness in the management of dental caries have been enlisted in Table 1.

Table No. 1: List of strain and type of study carried out to elucidate the effectiveness of probiotic strain in the prevention and management of caries

S. No.	Probiotic strain	Type of study	Result	Ref.
1.	*L. acidophilus*	*In-vivo*	Reduction in salivary *S. mutans* count	[31]
2.	*L. rhamnosus GG*	*In-vivo*	Reduction in salivary *S. mutans* count	[32]
3.	*L. reuteri ATCC 55730/L. reuteri ATCC PTA 5289*	*In-vivo*	Reduction in salivary *S. mutans* count	[33]
4.	*L. paracasei*	*In-vivo*	Reduction in salivary *S. mutans* count	[34]
5.	*L. salivarius* strains WB21	*In-vitro*	Reduction in salivary *S. mutans* count	[35]
6.	*B. lactis Bb-12*	*In-vivo*	Reduction in *S. mutans* count	[36]
7.	*Bifidobacterium DN-173 010*	*In-vivo*	Reduction in *S. mutans* count	[37]
8.	*L. reuteri*	*In-vivo*	Reduction in *S. mutans* count	[38]

Probiotics and Dental plaque

The diverse colony of micro-organism encompassed within an extracellular polymeric matrix found on the surface of the tooth can be recognized as dental plaque [39]. Plaque may offer suitable conditions for the growth and nourishment and serve as a reservoir for micro-organism. It is one of the major contributing factors in tooth decay, periodontitis, and other oral diseases [40].

In 2002, Comelli *et al*. concluded that the probiotic strain of *Streptococcus thermophilus* and *Lactococcus lactis* was able to adhere to hydroxyapatite beads coated by saliva. *L. lactis* NCC2211 completely encompassed into a biofilm, in the same manner imitating the dental plaque and was able to reduce the colonization of *Actinomyces naeslundii* OMZ745, *S. sobrinus* OMZ176, *Streptococcus oralis* OMZ607 and *Veillonella dispar* OMZ493 [41].

Several oral probiotic strains evidencing its effectiveness in the management of dental plaque have been summarized in Table 2.

Table No. 2: List of strain and type of study carried out to elucidate the effectiveness of probiotic strain in the prevention and management of dental plaque

S. No.	Probiotic strain	Type of study	Result	Ref.
1.	*Lactobacillus paracasei* and *Lactobacillus rhamnosus*	*In-vitro*	Anti-pathogenic activity	[42]
2.	*L. plantarum* strain 299v	*In-vitro*	Antimicrobial activity seems to be strain-specific and pH-dependent, Alters *S. mutans* growth and biofilm formation.	[43]
3.	*Lactobacillus acidophilus*	*In-vitro*	Reduction in biofilm formation	[44]

Probiotics and Gingivitis

Gingivitis is an oral ailment generally described as the initiation and accrual of bacterial biofilm around the teeth and soft tissue or gums followed by the invasion of gingival epithelial cells resulting in the stimulation of an immune-inflammatory response. Gingivitis can be characterized by gingival index (GI) and Bleeding on probe (BOP). *Porphyromonas gingivalis* is the causative organism for the development of gingivitis and may further escalate to periodontitis [45,46]. Even though Mechanical removal of plaque is a valuable and promising means in the management of gingivitis, Mechanical removal of plaque remains inadequate to control plaque aggregation and gingivitis. Inhibiting plaque accumulation and gingivitis in the oral cavity, Probiotic therapy may symbolize as a natural breakthrough way in the management of plaque and gingivitis by balancing the microbiota in the oral cavity. *Lactobacilli* and *Bifidobacterium* produce metabolites that act against oral pathogens. A study carried out by Howell *et al*. in the beagle dog revealed that a commercially accessible antibacterial peptide Nisin secreted by *Lactococcus lactis* was efficient in controlling the accumulation of plaque and gingivitis [47,48]. To assess the influence of probiotic strain *L. reuteri* on plaque accumulation and to evaluate its

effectiveness in the treatment of gingivitis, Krasse *et al.* carried out the foremost randomized, double-blind placebo-controlled clinical trial in 59 patients with severe to moderate gingivitis for 14 days. The study concluded that the strain *L. reuteri* reduced both the plaque as well as gingivitis [49]. Several oral probiotic strains evidencing its effectiveness in the management of dental caries have been summarized in Table 3.

Table No. 3: List of strain and type of study carried out to elucidate the effectiveness of probiotic strain in the prevention and management of Gingivitis

S. No.	Probiotic strain	Type of study	Result	Ref.
1.	*L. rhamnosus ATCC 9595*	In-vitro	Prevents *P. gingivalis* induced inflammation	[50]
2.	*Bifidobacterium animalis subsp. lactis DN-173010*	In-vivo	Reduction in GCF volume, lesser BOP, Lower PI and GI	[51]
3.	*L. ruteri*	In-vivo	Reduction of pro-inflammatory cytokines in gingival crevicular fluid (GCF)	[52]
4.	*L. casei Shirota*	In-vivo	Reducing the effects of plaque-induced gingival inflammation	[53]
5.	*L. plantarum* 44,048 and NC8	In-vitro	Growth inhibition of *P. gingivalis*	[54]
6.	*L. ruteri*	In-vivo	Reduction in the number of Periodontal pathogens in the subgingival microbiota	[55]

Probiotics and Periodontitis

Periodontitis can be referred to as plaque-induced inflammation of the soft and hard tissue holding the teeth, damage of periodontal ligament, and loss of bony support. It is considered the foremost reason for tooth loss and prevails worldwide as one of the biggest threats in the oral health system [56,57]. Substantial evidence concludes that *P. gingivalis*, *A. actinomycetemcomitans*, and *T. forsythia* are the most prevalent causative micro-organism correlated with the development of chronic periodontitis [58]. Invasion of the periodontal pathogen may also lead to complications in pregnancy and originate preeclampsia [59].

Several studies on probiotic strains and periodontal health disclose that probiotics strain such as *L. ruteri*, *L. Brevis, L. rhamnosus,* and *L. salivarius* WB2I are useful in the management of periodontal diseases. These probiotic strains reduce the Gingival Index (GI) as well as Plaque Index (PI) and assist in the treatment of chronic periodontitis. They reduce the discharge of

Nitric oxide, deactivate salivary matrix metalloproteases, and suppress the T-cell receptor resulting in compromised immunity. There is a considerable reduction in the gingival index (GI), plaque index (PI), and improvement in bleeding on probing (BOP). Peptides produced by strain *Lactobacillus helveticus* helps in the formation of bone and also inhibit the resorption of bone [60,61,62]. Maekawa and coworker carried out an *in-vivo* study intending to assess the influence of *Lactobacillus brevis* CD2 in the management of bone loss and periodontitis in mice. The result elucidated that *L. brevis* CD2 notably reduced the bone loss, suppressed the inflammatory responses in the gingiva, and the periodontal microbiome as compared to the placebo group [63]. S. Tsubura *et al*. carried out an *in-vivo* study, which revealed that the strain *Bacillus subtilis* in a mouth rinse was able to treat periodontitis. The study demonstrated its effectiveness in improving the Gingival Index (GI) and Bleeding on Probing (BOP) [64]. A randomized, double-blind, placebo-controlled clinical study carried by Teughels *et al*. (2013) unveiled that lozenges containing *L. reuteri* significantly reduced the pocket depth. Also, there was a significant reduction in *P. gingivalis* in the test group as compared to the placebo group [65]. Several oral probiotic strains evidencing its effectiveness in the management of dental caries have been summarized in the Table 4.

Table No. 4: List of strain and type of study carried out to elucidate the effectiveness of probiotic strain in the prevention and management of periodontitis

S. No.	Probiotic strain	Type of study	Result	Ref.
1.	*Lactobacillus brevis (CD2)*	*In-vivo*	Antagonize the growth of specific periodontopathic pathogens	[66]
2.	*L. fermentum*	*In-vitro*	Antagonistic activity against the growth of *S. mutans* and *S. pneumonia*	[67]
3.	*L. reuteri*	*In-vivo*	Effective in plaque inhibition, anti-inflammatory properties, and antimicrobial effects	[68]
4.	*Lactobacillus salivarius WB21*	*In-vivo*	A decline in the mathematical sum of five periodontopathic microbes in subgingival plaque	[69]

Probiotics and Halitosis

Halitosis is generally known as bad breath, occurs due to dysbiosis in the oral microbiota. Food debris that adheres to the teeth or retains in the dorsal part of the tongue is degraded by the gram-negative and produces by-products as volatile sulfur compounds (VSC) such as hydrogen sulfide, methyl mercaptan, and dimethyl sulfide. Besides this hydrogen sulfide, methanethiol and dimethyl sulfide gases that originate from the upper and lower respiratory tract also assist in halitosis. A study carried out by Kazor *et al*. (2002) revealed that microbial species such as *Atopobium pavulum*, *Eubacterium sulci*, *Fusobacterium periodonticum*, *Dialister* species, and *Solobacterium moorei* were present in adequate amount patient with halitosis. Temporary management and improvement of halitosis may include the use of products such as toothpaste, mouth sprays, and chewing gums. Nevertheless, for the treatment of halitosis need to be focused on the eradication of microorganisms responsible for VSC generation [70,71,72]. It is well known that to exert a beneficial health impact in oral ailment, the selected or targeted probiotic strain should colonize at a particular niche. The niche-specific probiotic strain may not colonize effectively to the tongue as compared to other sites within the oral cavity. The etiology of oral halitosis is more discrete than in periodontitis. Therefore, probiotic utilization could aid in the management of halitosis [73,74].

Several studies demonstrate the rationale behind the implementation of probiotics in the management of halitosis. Recently, Soares *et al*. (2019) carried out a double-blinded, placebo-controlled, randomized clinical trial that discloses that probiotic strain *Lactobacillus reuteri*, *L. salivarius*, and *L. acidophilus* was capable in the reduction of halitosis [75]. Studies suggest that oral consumption of probiotic strain *Lactobacillus salivarius* WB21 in patients with oral malodor showed a notable improvement in halitosis and reduction in bleeding on probing (BOP) [76]. A study carried out by Suzuki *et al*. declared that the tablet accompanying *Lactobacillus salivarius* WB21 notably reduces the total VSC in probiotic patients compared to the placebo with oral malodor [77]. Several oral probiotic strains evidencing its effectiveness in the management of halitosis have been summarized in Table 5.

Table No. 5: List of strain and type of study carried out to elucidate the effectiveness of probiotic strain in the prevention and management of halitosis

S. No.	Probiotic strain	Type of study	Result	Ref.
1.	*S. salivarius K12*	*In-vivo*	Antimicrobial activities against halitosis inducing microbes	[78]
2.	*S. thermophiles*	*In-vitro*	The decline in oral malodor by inhibition of *P. gingivalis* growth and compensates VSCs with their metabolites or themselves.	[79]
3.	*Weissella cibaria*	*In-vitro* *In-vivo*	Reduction in the production of VSC in both *in-vivo* and *in-vitro* study	[80]
4.	*S. salivarius K12*	*In-vivo*	A notable decline in VSC level	[81]

Probiotics and Candida Infections

Almost 75% of an individual's oral cavity consists of candida species commonly responsible for the development of fungal infection. *Candida* species are non-pathogenic inherently. However, predisposing factors transform these species into pathogenic species. *C. Albicans*, *C. krusei*, *C. pseudotropicalis*, *C. guillermondii*, *C. Stellatoidea*, *C. parapsilosis*, *C. tropicalis*, *C. Glabrata* are the common *candida* species found in the oral cavity. Oral candidiasis occurs mainly due to the pathogenic agent *C. albicans* [59][82,83]. Application of probiotic bacteria strains in the oral cavity may overcome the symptoms as well as the pathogenicity of *Candida spp*. [84]. According to the literature, the elderly population is susceptible to Candida infection due to lower saliva production, lack of oral hygiene, medication, and disease condition. Rossonia *et al*. (2018) demonstrated that *lactobacillus* strain was able to inhibit the *C.albicans* biofilm and proved its antifungal activity against candida species. [85]. Matsubara *et al*. (2012) stated that bacterial strain *L. rhamnosus* and *L. acidophilus* notably reduced the concentration of *C. albicans* on the oral mucosal surface [86].

Probiotics and oral cancer

Cancer is the uncontrolled proliferation of a single or combination of cells generally manifested at the late stage of its development. It may radiate throughout the body (malignant) or may be restricted within the tissue or organ (benign). Alteration in DNA

replication due to numerous factors such as exposure to radiation, infectious agents, virulent agents, and personal oral hygiene progressively remodel normal cells toward the tumor state [87]. The commensal microbiome encountered in the oral cavity produces favorable metabolites with fancied effects to manage a disease like oral carcinoma [88]. A possible mechanism by which probiotics demonstrate its potential effect toward the carcinoma involves inhibition and destruction of the mutagen, anticarcinogenic metabolite production, suppression of the carcinogen inducing enzymes, stimulation/modulation of the immune response, and cancer cell apoptosis [89,90]. The antitumor strength of probiotics relies on the particular strain or species investigated [91]. Concerning available literature, the probiotic bacterial strain *L. salivarius* REN is competent to suppress the growth of an oral carcinoma [92]. The investigation led by Abbas Asoudeh-Fard *et al*. unveiled the molecular mechanism involved in the initiation of cancerous cell apoptosis and thereby considered probiotic strain *L. Plantarum* as a desirable candidate in the treatment of oral carcinoma [88].

MARKETED PROBIOTIC FORMULATION

Several *in-vivo/in-vitro* studies have confirmed the effectiveness of probiotics in the management of oral ailments. Globally, many probiotic formulations have successfully marketed to provide beneficial oral health effects. A wide range of formulation such as tablets, hard gelatin capsule, sachets, suspension, oral rinse/mouth wash is available to deliver the probiotic strain. Dosage forms like Oral-rinse, ODT tablet, lozenges, chewing gum, chewing tablet, and toothpaste (Listed in Table.6) are promising in the treatment of oral diseases due to an exclusive effect on the oral cavity [93,94]. Since the oral probiotic market is expanding daily, the more stable oral probiotic formulation must be in the pipeline to enter the market.

Table No. 6: Commercially marketed probiotic formulation with their proposed use

S. No	Product Name	Probiotic Strain	Dosage form	Health benefit claim	Mfr.
1.	Gum PerioBalance	*L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 5289	Lozenge	Helps to endorse and maintain normal ecology of beneficial bacteria in the oral cavity	Sunstar Americas, Inc.
2.	Advanced oral probiotics (Great Oral Health)	*L. reuteri*, *L. alivarius*, *L. paracasei*, *L . acidophilus*, *L. thermophilus* and *Streptococcus salivarius*-BLIS K12, BLIS M18	Chewable tablet	Inhibits pathogenic microbes, Reduces halitosis	Probi USA
3.	Pro-Dental	*L. paracasei*, *Lactobacillus sakei*, *L. reuteri*, *L. salivarius*, *S. salivarius* M18	Chewable tablet	Suppresses halitosis, Prevents dysbiosis, and soften biofilms	Hyperbiotics
4.	Jarro-Dophilus Oral Probiotic	*Lactobacillus brevis* CECT 7480 and *Lactobacillus plantarum* CECT 7481	Lozenge	improves malodor, maintain gums and teeth healthy	Jarrow Formulas
5.	NatureWise Oral Health Chewable Probiotics	*Lactobacillus reuteri*, *Lactobacillus salivarius*, *Lactobacillus paracasei* Lpc-37, *Lactobacillus plantarum*, *Lactobacillus casei subsp. casei*, *Streptococcus*	Chewable tablet	Offer continues fresh breath and guards oral health	Nature Wise

		salivarius BLIS-M-18, *Streptococcus thermophilus*, *Streptococcus salivarius* BLIS-K-12, *Bifidobacterium infantis*, *Bifidobacterium breve* Bb-03			
6.	ProbioRinz	*Lactobacillus* species	Oral rinse /mouth-wash	Inhibits plaque formation, maintain a healthier oral cavity and prevents halitosis	Probio Care Crisal
7.	Activated charcoal probiotic toothpaste	*L. paracasei*	Toothpaste	promotes fresh breath and maintains normal oral flora	Hyperbiotics Probiotics
8.	E.N.T. Biotic BLIS K12® Probiotic	*S. salivarius* BLIS K12	Lozenge	prevents halitosis and maintain healthy oral microbes	Trade Scout, LLC
9.	LavaRox™ Probiotics for oral health	*S. salivarius* K12	Tablets	Maintain and Promotes oral health	AOR Inc., USA
10.	PerioBiotic Probiotic Toothpaste	*L. paracasei*	Toothpaste	Promote healthy gum and prevents teeth	Designs for Health

SAFETY ISSUES

The safety issue is a fundamental factor in the perspective of "Consumer Protection Law" [95]. To promote oral health via probiotics. A high number of viable bacterial strains need to be administered for an extended period. Devoid of any adverse effects in human health, the use of probiotic bacterial strains as a dietary supplement has demonstrated their safety from

ancient times [96]. Although probiotics have been consumed from ancient times, the specific mechanism through which each strain avails the host remains unsettled. Therefore, it is critical to understand the pathophysiology to estimate the risk-benefit relationship. *In-vitro/In-vivo* studies should monitor the safety of each strain or the combination before entering in a dietary supplement or medical formulation [95].

With safety concern, a study revealed that even HIV infected individuals could consume viable bacterial strain *L. reuteri* exclusive of clinically significant safety or tolerance problems [97]. A comprehensive review carried out by the Southern California Evidence-based Practice Centre funded by the Agency for Healthcare Research and Quality (AHRQ) concerning the safety of probiotics reported that the presently available literature has not satisfactorily evaluated the safety issue [98,99]. In an explanation of the AHRQ report, Wallace and MacKay [100] pointed out that lack of evidence for adverse events throughout the studies reinforces the argument that probiotics are safe. They suggested the scientific community to make their efforts on assessing the safety of probiotics by risk-benefit analysis method rather than anticipating literature that include drug-induced adverse effects and toxicity. According to FAO/WHO (2002), the possible risk observed on the host includes genetic transfer, destructive metabolic action, extreme immune stimulation, and systemic infections [95]. Mechanistic Omics tools can be employed to assess the safety of probiotics since a particular strain has reported the production of harmful metabolites and shown antibiotic resistance [22].

REGULATORY ISSUES

Globally, Probiotics are marketed under different groups and regulated by their regulatory authority that makes confusion and complexity regarding the regulatory requirement for the marketing and manufacturing of the probiotic product [101]. Safety, Efficacy, Quality, and Health claim regulations are the regulatory aspects that must be considered for each probiotic product. Probiotic products are categorized as pharmaceutical products or medical products if the individual product described and claim regarding prevention, diagnosis, treatment, mitigation, or cure. The Majority of the probiotic preparations are categorized as dietary/food supplement since they are unable to make drug or disease-specific claim [102]. According to the USFDA, Probiotic preparation offered as a drug for intended use is also a biological product. If the probiotic product meets the criteria as mentioned in section 201(p) of the FDC Act, categorize as New drug. The FDA needs an Approved Biologics License Application

and regulatory requirement of Investigational New Drug Application (IND) for the safety and efficacy of the product [103]. The labeling requirement for the probiotic product recommends by the International Scientific Association for Probiotics and Prebiotics (ISAPP). According to ISAPP, the label must specify the genus, species, and strain of the microorganism used in the product. Probiotics manufacturers are requested to denote the quantity of each bacterial species employed and justify the efficacy of the product throughout their shelf life and clarify the doses utilized in clinical trials to claim any health benefits [104]. To place a probiotic food/dietary supplement in the market, the manufacturer does not need FDA approval. Instead, the manufacturer should notify FDA. As per the regulation of USFDA, A Probiotic food/dietary supplements manufacturer needs to follow and comply with the Current Good Manufacturing Practice (CGMP) guidelines to ensure the safety and quality of the product [105]. There is still a lack of established framework across the world regarding the regulation of probiotics since this regulation varies from country to country [102]. Probiotic products have been described and regulated according to their intended use or label claim by different countries that have been summarized in Table 7 [106].

Table No. 7: Categorization of Probiotic product across the globe along with their concerning regulatory bodies

S. No	Country	Regulatory body	Category	Reference
1.	USA	Dietary Supplement Health and Education Act (DSHEA)	Dietary supplements	[103]
		U.S. Food and Drug Administration (USFDA)	Biological products	
			Drugs	
			Medical food	
			Food or food ingredient	
2.	EUROPE	Functional Food Science in Europe (FUFOSE)	Functional foods	[93]
3.	JAPAN	MHLW, Foods for specialized health use (FOSHU)	Functional foods	[107]
			Nutraceuticals	
4.	BRASIL	National Health Surveillance Agency (ANVISA)	Functional foods	[108]
5.	CHINA	State Food and Drugs Administration (SFDA)	Functional foods	[109]
6.	NEW-ZEALAND AND AUSTRALIA	Food Standards Australia New Zealand (FSANZ)	Functional foods	[106]
7.	INDIA	Prevention of Food Adulteration (PFA)	Functional foods	[110]
		Food and Drug Administration (FDA)	Drugs	
8.	CANADA	Health Canada	Natural health products	[104]

FUTURE ASPECT

Regarding oral health, there is an outstanding opportunity for the researchers to develop a well-established novel strain with fancied effects which can be suitable for both dietary as well as therapeutic use. At present, some queries remained opened regarding the safety of

probiotics. It is expected that a thorough clinical investigation will be performed to address the issues raised concerning the safety of probiotics and acquire clinically safe and effective probiotics followed by a suitable delivery system. Since biological activity and health benefits of probiotics are strain-specific, issues associated with using combination and single strain also anticipate further research soon.

CONCLUSION

Oral ailments make an impact on one's personal as well as social life. The primary reason for the initiation of oral diseases is due to the disturbance in the normal ecology of microorganisms, i.e. "Dysbiosis". Previously, the clinical health benefit of probiotics was within the human GIT only. However, rising interest in the field of probiotics lets researchers discover the clinical benefits of probiotics in oral ailments and disclose the indication that probiotics use may be used as novel natural therapy over existing allopathic treatment. Several studies have reported that probiotic use suppresses pathogenic microorganisms and helps to maintain the oral microbial environment. This study appraises the doable health benefits of probiotics in the management of oral ailments ranging from dental plaque, periodontal diseases, halitosis, and other oral infections. But the precise mechanism by which probiotics exert their action has not been justified. Several *in-vitro* and *In-vivo* studies with bacterial strain and their ability to deliver health benefits in oral ailments have set up a new horizon in the field of oral diseases and probiotic strain. Modification in genetic material of the existing microorganisms to enhance the potential therapeutic properties and to develop targeted probiotics has magnetized the researcher involved in this field. The development of an appropriate delivery system and delivering microorganisms in the oral cavity by tackling formulation associated challenges and pursue a regulatory paradigm is a matter of great concern.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors have no conflict of interest to reveal.

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