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Review Article

PRELIMINARY ORAL PROBIOTICS BACTERIAL PROFILE IN NEONATAL AND PEDIATRICS AND ITS CLINICAL EVALUATION

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ABSTRACT

Probiotics are live bacteria that are consumed or administered to the body to provide health advantages. They are in yoghurt and other fermented food consumer, as well as dietary supplements and cosmetics too. After birth, the mouth of the infant is richly colonized immediately. The different probiotic microorganisms present in infants are *Bifidobacterium, Streptococcus salivarius, Streptococcus albicans, Lactobacillus crispatus, Lactobacillus gasseri*. Some of these can exhibit some powerful anti-inflammatory capabilities. For the novel application of probiotics in pediatric nutrition, there is a new concept in the composition of the microbiota. In probiotic food, it contains healthy microorganisms, which helps in the safe gut association with lymphoid tissue in infants. Traditionally, probiotics have been associated with gut health, and most clinical interest has been focused on their use for the prevention or treatment of gastrointestinal infections and diseases; however, during the last decade, several investigators have also suggested the use of probiotics for oral health purposes. The aim of this review is to examine the potential mechanisms of probiotic bacteria in the oral cavity and summarize the observed effects of probiotics with respect to oral health. The research focuses on probiotic lactobacilli and its genera that are most used in various probiotic products. Due to this reason, the idea of the usage of probiotics is leading the way to new therapeutic perspectives.

Keywords: Oral Samples, Neonatal cases, Pediatrics cases, Probiotic, Bacteria

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INTRODUCTION

Probiotics are defined as live microorganisms that are isolated from human and animal intestinal tracts and then administered through oral route or through feeding tubes as live cultures. Research has demonstrated that probiotics provided in adequate amounts can help to promote health benefit to the host [1]. The gut-associated immune tissue constitutes approximately 80% of immunologically active cells in the human host [2]. Microbial flora is responsible for the abundance and activation of the mucosal immune system in healthy individuals [3]. The intestinal microflora profoundly influences the development of specific and nonspecific cellular and humoral gut mucosal immune responses [4]. The gut needs exposure to bacteria to develop its immune defense and appropriate (nonexaggerated) immune responses, which support host health. The mechanisms of host-bacteria interaction are increasingly being unraveled and, in great part, explain the clinical effects certain ingested (probiotic) bacteria have on improving host health, including enhancing defense mechanisms (such as against viral infections), as well as modulating host immune response (such as in allergic disease) [5]. The oral microbiota is heterogeneous and diverse, and its imbalance leads to the onset of major oral diseases such as periodontitis and dental caries.

Probiotic-based intervention strategies are widely used for intestinal diseases but not yet for oral diseases due to the limited scientific evidence of usefulness. Probiotics can outcompete pathogenic bacteria and increase the proportion of beneficial bacteria in the mouth, thereby contributing for the prevention and therapy of oral diseases [5]. The advent of new sequencing technologies, mainly based on the 16S ribosomal RNA genes, and the development of sophisticated bioinformatics tools, the characterization of gut microbiota is being advanced, leading to the understanding of the composition and function of bacterial populations throughout the intestine and to the influence of fluctuations in the diversity of gut bacterial populations (known as dysbiosis) in the development of diseases [6-8]. This knowledge has been translated in great interest in those therapeutical strategies to directly or indirectly influence gut microbiota to obtain clinical benefits, such as the use of probiotics, prebiotics, and other food supplements or fecal transplantations [9-11].

Literature review

The beginning of probiotics

In 20th century, Russian scientist and noble laureate Elie Metchnikoff were the first one to suggest the possibility to modify the gut microflora by replacing the harmful microbes with useful microbes. Metchnikoff observed that certain rural populations in Europe, for example, in Bulgaria and the Russian steppes who mainly depended on milk fermented by lactic acid bacteria for their sustenance had comparatively longer lives [12]. Bifidobacteria was the first isolated probiotic bacteria. Henry Tissier (1905) isolated it from a breast-fed infant. Tissier (1906), a French pediatrician, observed a low number of Bifidobacteria in the stool of infants with diarrhea as compared to healthy infants [13]. The probiotics have been shown to have prominent physiological and immune effects; they may be classified as functional foods [14]. Since early reports in the mid-1960s, scientific interest has grown dramatically in probiotics [15].

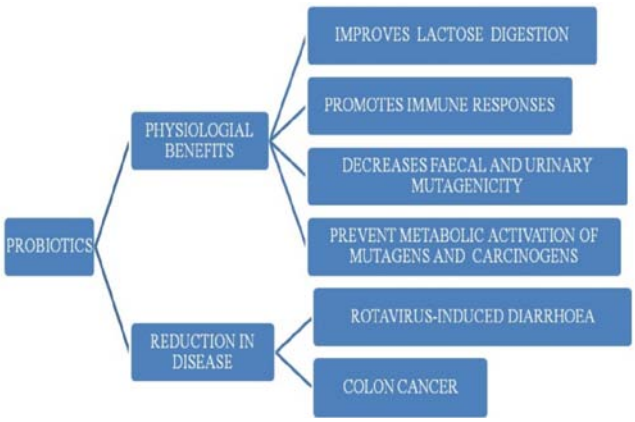

Fig. 1: Probiotic as a functional food [14]

Probiotics: basic concept and characteristics

Intestinal microflora is composed of both well-established resident microbes and those ingested orally, which transiently occupy the gastrointestinal (GI) tract. Probiotics are generally defined as nonpathogenic organisms in the food supply (ingested microbes) that are capable of conferring a health benefit to the host by modifying gut microbial ecology [15]. The main focus of this review will be on probiotic bacteria in the oral cavity. A body of evidence demonstrates that probiotic bacteria have immunomodulating properties, regulate inflammation in a number of ways, and enhance the epithelial barrier function to prevent chronic inflammation in the gut [16, 17]. Probiotic bacteria confer anti-inflammatory responses by modulating different signaling pathways Different anti-inflammatory effects at the intestinal level have been described with probiotics, for example, enhancement of the epithelial barrier function in the gut attenuation of barrier dysfunction due to pro-inflammatory cytokines or modulation of intestinal anti-inflammatory responses such as the expansion of the T-regulatory response, which may be relevant for its use in chronic inflammatory disease [18-21]. Prebiotics are usually in the form of oligosaccharides, which may occur naturally but can also be added as dietary supplements to foods, beverages, and infant formula.4Although indigestible by humans, their presence in the digestive system selectively enhances the proliferation of certain probiotic bacteria in the colon, especially *Bifidobacteria* species. Prebiotic oligosaccharides often contain fructose chains with terminal glucose and typically consist of 10 or fewer sugar molecules. Examples of prebiotic oligosaccharides include fructooligosaccharides (FOSs), inulin, galactooligosaccharides (GOSs), and soybean oligosaccharides. Inulin is a composite oligosaccharide that contains several FOS molecules.

Table 1: Characteristics of probiotic bacteria [22, 23]

Characteristics that define probiotic bacteria
Probiotics are microbial organisms
Probiotics remain viable and stable after culture, manipulation, and storage before consumption
Probiotics survive gastric, biliary, and pancreatic digestion
Probiotics are able to induce a host response once they enter the intestinal microbial ecosystem
Probiotics yield a functional or clinical benefit to the host when consumed.

How do probiotics function in body?

- Inhibit growth or reduce the activity of bad bacteria in the intestine by colonizing the gut.
- Having antimicrobial activity and aid in increasing our immunity by making our body more resistant to diseases and infections.
- Improve the secretion of digestive enzymes and helps in proper digestion.
- Increase the production of lactic acid and regulates pH balance in the intestine and other parts of body.
- Promote acidic pH, which facilitates the absorption of protein and minerals like calcium, copper, magnesium, iron and manganese.
- Having anti-inflammatory properties
- It could ferment fructo-oligosaccharides which thereby results in reduced pH balance. This increases acidity in gut, thereby enabling better absorption of calcium and allow it to get into the blood stream [24].

The probiotics in oral cavity

More than 700 bacterial strains were identified in the oral cavity, and the microbial flora is different from subject to subject. Everyone can count on a bacterial population composed by an average of 30-100 species that constitute a custom ecosystem, making the flora of the oral cavity an essential part of the biological uniqueness of individuals. This uniqueness is for during a time process in which genetics, bacterial exchange with the mother, age, dietary habits, use of drugs, diseases, play an important role.

The efficacy of probiotics cannot set aside the biological individuality of the patient [25-27]. There are many variables that can affect the permanence in the oral cavity of new bacterial strains. First, it should be considered that in the mouth the composition of the bacterial flora tends to remain stable over time. In the saliva, for example, the microbiome composition in individuals was constant during the periodic analysis carried out in an arc of 7 y [28].

Among the many bacterial species present in the saliva, *Streptococcus mutants* (SM) is universally considered as the most important pathogen for the initial development of tooth decay, while Lactobacillus has an important role in the progression of tooth decay. The main characteristics of virulence of the Streptococcus mutants are their acidogenicity, ability to survival in acidic environments, the ability of biofilm formation and adherence to the tooth. Various hypotheses have been proposed regarding the mechanism of action of probiotics, including the production of antimicrobial substances, in antagonism with the pathogenic agents, preventing cell adhesion, invasion, and the modulation of both local and systemic immune actions. From an emerging understanding of the gut–lung axis wherein probiotic microbial species in the digestive tract can influence systemic immunity, lung immunity, and possibly viral pathogenesis and secondary infection co-morbidities [29].

Probiotics in neonatal and pediatrics

Over the past few years, witnessed an explosion of new information pertaining to the possible role of gut microbiota in health and disease. This has led to an interest in the development of strategies aimed at manipulating bacterial colonization, including the administration of probiotics; these products are currently gaining worldwide popularity and are increasingly being used in the pediatric population and preterm infants. Preterm infants are often cared for in intensive care units and receive broad-spectrum antibiotics, which further contribute to differences in colonization patterns. While the possible consequences to health are not known, it has been speculated that abnormal patterns of colonization in preterm infants may contribute to increased susceptibility to infections and the pathogenesis of necrotizing enterocolitis (NEC) [30]. The UNICEF 2010 report showed that the global burden of under-five mortality was reduced by one-third compared with 1990s; however, progress in reducing neonatal mortality has been slow Almost 40% of under-five deaths occur during the neonatal period, out of 135million births each year, 3.1million have died within the neonatal period and nearly 35% of these deaths occur in preterm neonates. Probiotics have been shown to significantly reduce the risk of NEC, all-cause mortality, LOS and facilitate feed tolerance in preterm very low birth weight (VLBW) neonates [31-33].

Table 2: Probiotic bacteria in immunogenic uses

Probiotic bacteria (strain)	Infection	Mode of action	Reported medicinal effects	References
Lactobacillus brevis (KB290)	Influenza virus	Increased IFN-α production and augmentation of influenza-virus-specific immunoglobulin A production	Reduced risk of infection	[34]
Lactobacillus rhamnosus (GG)	Influenza virus	Increased IFN-γ production in serum	Reduced risk of infection	[35]
Lactobacillus bulgaricus (OLL1073R-1) and Streptococcus thermophiles	Rhinovirus	Increased IFN-γ production in serum	No significant difference	[36]
Lactobacillus rhamnosus (GG)	Rhinovirus	Not determined	Reduced incidence of respiratory tract infections (RTIs)	[37]
Lactobacillus casei (DN-114001)	Rhinopharyngitis, influenza virus	Increased expression of defensins	Decreased duration of common infectious diseases	[38]
Bacillus subtilis (OKB105)	Transmissible gastroenteritis virus	Inhibition of virus entry by competing with viral entry receptors	Reduced viral entry *in vitro*	[39]
Bifidobacterium animalis	Rhinovirus	Inhibition of CXCL8 response upon viral infection	Decreased viral titres in nasal lavage and viral shedding in the nasal secretions	[40]

DISCUSSION

The community of microorganisms that colonizes the mouth and forms the dental plaque mainly plays a protective role against pathogens. Dental plaque consists of bacterial cells (mainly streptococci and lactobacilli), bacterial metabolites/products/toxins, salivary polymers/proteins, and food debris. Probiotic lactobacilli may inhibit the adhesion of pathogenic bacteria to the oral tissues, reducing the amount of biofilm formed [41]. On the other hand, lactobacilli probiotics may potentiate dental plaque acidogenicity and increase the load of acid-tolerant bacteria such as S. mutants and viridians streptococci, making the dental biofilm more pathogenic.

The dental plaque accumulation in children was significantly reduced after 14 d of tablet consumption containing *Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum and Streptococcus boulardii,* and after three weeks of intervention. In a study, administration of *Streptococcus salivarius* M18 to children for 3 mo caused a significant decrease in dental plaque scores. Non-target microorganisms*, Streptococcus salivarius*, *Lactobacillus spp*., hemolytic streptococci and Candida spp. levels were not changed during the study. Despite a high adhesion rate (>80%), only 22% of the children were colonized by *Streptococcus salivarius* M18 and this lasted until 4 mo after discontinuation. *Streptococcus mutans* counts were reduced, especially in colonized children, suggesting that *Streptococus salivarius* M18 may have anti-cariesactivity and that colonization helps the probiotic effect. A significant reduction of salivary *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis and Streptococcus mutans* counts, and the total number of microorganisms was achieved in children after 2-weeks of ingestion of Petit-Suisse (cream cheese) with *Lactobacillus casei*. However, the reduction of the total number of microorganisms and *Streptococcus mutans* was attributed to Petit-Suisse alone as it occurred in both the probiotic and control groups [42-44].

CONCLUSION

The use of probiotic bacteria is an expanding area of research in dentistry. Oral probiotics are safe, influence the oral microbiota favorably and provide benefits to the oral ecosystem in periodontal diseases, cariology, halitosis, orthodontics and management of oral mucositis resulting from cancer treatment. The areas in which probiotics should be further developed are endodontics, dental traumatology, and the healing of chronic oral wounds. Probiotics likely act without colonization or by transient colonization of the oral cavity, so a daily intake is advised. In addition, synergistic combinations of probiotic bacteria should lead to higher clinical efficacy than any individual probiotic agent.

Before recommending probiotic use in daily dental practice and considering probiotics as a self-management preventive strategy or adjuvant/alternative therapy, additional large-scale, long-term, randomized, placebo-controlled clinical trials studies are needed to determine the most effective probiotic strain combinations, the most suitable probiotic, and the most appropriate dosage and frequency of administration. Further research is also needed on product compliance and acceptance by different age groups.

Finally, a better understanding of the mechanisms of action of probiotics and of the host response to probiotics is needed. Algorithms matching person-specific data and known factors interfering with probiotic efficacy will allow the identification of the optimal probiotic modality for stratified populations or individuals [45]. There is scientific evidence that specific strains of probiotic microorganisms confer benefits to the health of the host and are safe for human use. However, considerable work is required to affirm the benefits of probiotics. Probiotics are, nevertheless, a new, interesting field of research in oral microbiology and oral medicine.

The research is still in the initial stage. The idea of probiotics casts new light on the connections between diet and health, including oral health. The complex interplay with respect to the mechanisms of probiotics' actions in the development of microbial colonies as well as oral biofilms is yet to be known [46]. Further studies on the combined effect of different probiotics and prebiotics should be carried out to authenticate the possible additive, cumulative, or competitive modes of action in the oral environment. So far, little has been known about the possible naturally occurring resident probiotics of the mouth. In this regard, it might be interesting to conduct studies on patients with lichen planus, pemphigus vulgaris, cicatricial pemphigoid or apthous stomatitis. Probably, different probiotics are needed for therapy in oral mucosal diseases as there is the difference in the microbial attachment sites on the keratinized and non-keratinized epithelium [46].

In order to assess the best means of administering probiotics, randomized controlled trails are needed. In addition, variation in the dosage for different preventive or therapeutic purposes are also to be studied carefully in order to avoid ill effects of the species that ferment sugar and lower oral pH that are detrimental to the teeth. Apart from this, general safety aspects such as those related to potential invasiveness and antibiotic resistance genes must be screened [47, 48].

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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