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## REVIEW ARTICLE

# PROBIOTICS: A BIOTHERAPY FOR RESOLVING ORAL INFLAMMATION

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**ABSTRACT**

The purpose of this study is to critically analyse studies that are related to the use of probiotics to manage common oral diseases like dental caries, gingival and periodontal diseases as well as oral malodour. There is considerable evidence available supporting the fact that oral health has impact on general health and vice versa. Therefore, oral care is an important consideration in maintaining quality of life. Due to the increasing resistance to antibiotics, there is a need to minimise antibiotic use and develop novel treatments for oral diseases that do not involve conventional antimicrobial agents. Preventive approaches based upon the restoration of the microbial ecological balance, rather than elimination of the disease associated species, have been proposed. Thus, there is a desire for more 'natural' therapies. Probiotics form the cornerstone of such biotherapy. Probiotics have potential to prevent and control these diseases by more effectively addressing the host-microbial interface to restore homeostasis that may not be achieved with conventional treatments. While this beneficial effect was originally thought to stem from improvements in the intestinal microbial balance, there is now substantial evidence that probiotics can also provide benefits by modulating immune functions. Thus, an accurate characterization of the disease systems and mechanisms of inflammation will not only enable us to measure the impact between multiple diseases and develop new therapeutics, but will also help to develop a "personalized" treatment approach specifically targeting the susceptible individual rather than prescribing the same treatment to all subjects regardless of the underlying cause.



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## INTRODUCTION

Wound healing is a complex process involving three sequential, yet overlapping phases: inflammation, proliferation and remodeling. Phagocytic cells release growth factors, and produce cytokines to regulate the subsequent proliferative phase. The proliferative phase involves the formation of granulation tissue and revascularization, regulated by fibroblasts and endothelial cells. During the final maturation stage, the extracellular matrix is remodeled, leading to the tissue repair. Aberrations in any step of the reparative process are likely to result in impairment, with the potential for development of chronic wounds and ulcers, especially inflammation. Chronic inflammation delays epithelialization (wound closure) and interferes with the remodeling phase that results in poor wound outcome such as increased fibrosis and scarring.( Bruno S Herrera *et al*., 2015) There is evidence that specific microbes are associated with the progressive forms of the disease; however, the presence of these microorganisms in individuals with no evidence of disease progression suggests that the disease is the net effect of the immune response and the inflammatory processes, not the mere presence of the bacteria. Regulation of immune inflammatory mechanisms governs patient susceptibility and is modified by environmental factors (Ali Cekici *et al*., 2000). Periodontal disease results from excess inflammation and may be considered a failure of resolution pathways. Accordingly, inadequate resolution and failure to return tissue to homeostasis results in neutrophil-mediated destruction and chronic inflammation, with destruction of both extracellular matrix and bone, and scarring and fibrosis. Scarring and fibrosis in periodontitis prevent the return to homeostasis (Ali Cekici *et al*., 2000).

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### Inflammation and Immune Response

Inflammation, which is initiated as a protective response to pathogens, foreign bodies or an injury is characterized by vascular dilation, enhanced permeability of blood capillaries, increased blood flow and leukocyte recruitment into tissues (Hatice Hasturk, 2015). The host's immune response depends on the activity of leukocytes. Phagocytes (macrophages and neutrophils) are a group of leukocytes that are immediately available to combat a wide range of pathogens without prior exposure as key cells of the innate immune response.

Many infections are handled successfully by the innate immune response and cause no disease, however an infection, which cannot be resolved by innate immunity, triggers adaptive immunity to overcome it. Lymphocytes mediate the adaptive immune response. Oral inflammatory diseases can be considered as an adverse outcome of the protection efforts of the host against the invading pathogens. Inflammation should resolve in a timely manner to prevent tissue injury, and maintain health. The rapid and complete elimination of invading leukocytes from a lesion is the ideal outcome following an inflammatory event. Inadequate resolution and failure to return tissue to homeostasis results in neutrophil-mediated destruction and chronic inflammation (Hatice Hasturk *et al*., 2012).

If the host is unable to neutralize the pathogens, then acute inflammation would become chronic with consequences such as destruction of ECM and bone, scarring, and fibrosis (Hatice Hasturk *et al*., 2012). Resolution of inflammation is an active process leading to coordinated, temporal clearance of pro-inflammatory cells facilitating healing. The coordination between pro inflammatory and pro-resolving processes actively prevents damage to self. Damage to self occurs in non-resolving inflammation that is associated with chronic diseases, such as arthritis, periodontal disease, diabetes and cardiovascular diseases.

A deficiency in resolution of inflammation molecules likely plays a role in disease pathogenesis. Active resolution of inflammation is mediated by the local biosynthesis of endogenous specialized pro-resolving lipid mediators (SPMs), which include the lipoxins, resolvins, protectins and maresins. SPMs are enzymatically synthesized and induce diverse actions on a variety of cells through specific receptors. Target cells for the SPMs are not confined to the immune system; they also include the cells of structural tissues, such as bone. Resolvins (Rv) are derived from the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), while lipoxins (LX) are from the omega-6 arachidonic acid. They effectively resolve inflammation in periodontal diseases, asthma, and colitis (Bruno, 2015). Resolvins stimulate the resolution of inflammation through multiple mechanisms, including preventing neutrophil penetration, the phagocytosis of apoptotic neutrophils to clear the lesion and enhancing the clearance of inflammation within the lesion to promote tissue regeneration (Ali Cekici *et al.,* 2000)

## COMPLEXITIES INVOLVED IN INFLAMMATION

The oral cavity is one of the most ecologically complex microenvironments in the human body where interactions between the host and microbes define health and disease (Hatice Hasturk *et al*., 2012). Another major issue in understanding inflammation as an entity is the communication between distant organs. While it is plausible that inflammatory processes in one organ could directly lead to the pathologies in another organ or tissue, communication between distant parts of the body and their inflammatory states is mediated by common signaling mechanisms via cells or soluble mediators (Hatice Hasturk and Alpdogan Kantarci, 2000). To this end, research has provided evidence of an oral and systemic connection in several diseases such as diabetes, cardiovascular diseases, and pathological conditions such as pre-term birth.[2] Therefore, there are potentially two mechanisms; through which the immune system and inflammatory process may play role in affecting distant organs:

- Direct migration and colonization of periodontal microbial species to distant organs eliciting an inflammatory reaction distant from the point of invasion. Theoretically, all microbial organisms and their products can travel throughout the body via the circulation. Sepsis or septicemia is the pathological result of bacteremia, which involves the presence of bacteria in blood and its compartments. Since bleeding is a common sign and symptom of periodontal inflammation, every time the periodontal pocket bleeds, microbial communities or single species enter into the blood circulation. This can be the result of disease activity or may arise due to periodontal procedures such as probing or scaling.
- Systemic inflammation as a result of metastatic periodontal inflammation or activated soluble inflammatory pathways by blood-borne periodontal bacteria. Periodontal disease is a chronic inflammatory condition that shares common mechanistic pathways with other systemic inflammatory diseases. To this end, strong evidence is accumulating for comorbid associations between periodontitis and other inflammatory diseases such as diabetes, cardiovascular diseases, adverse pregnancy outcomes, and rheumatoid arthritis. To a lesser extent, periodontal infection and inflammation are regarded as risk factors for chronic obstructive pulmonary diseases, inflammatory bowel disease, and chronic kidney disease (Hatice Hasturk and Alpdogan Kantarci, 2000).

### Impact of systemic inflammation on Periodontal Tissues

A classic example where a systemic inflammatory disease impacts the periodontal tissues is diabetes. Hyperglycemia presents a major stress on mammalian tissues and can result from a variety of conditions such as genetic defects where the intake of glucose may not be counteracted by the hormonal actions of insulin and glucagon regulation or as a function of acquired conditions such as obesity or toxicity by drugs where the production of insulin and the function of the pancreas may not be sufficient to eliminate the increased levels of glucose. In both cases, the outcome is increased levels of glucose in blood and circulating through the tissues, and if prolonged, the chronic exposure of cells to glucose results in pathological consequences. One well-defined mechanism is through the activation of advanced glycation endproducts (Hatice Hasturk and Alpdogan Kantarci, 2000). Other systemic inflammatory diseases such as haematological diseases could result in aggravation of periodontal inflammation. Systemic diseases caused by viruses or other microbes also affect periodontal diseases and inflammation. In the case of HIV infection, periodontal pathologies result directly from the systemic immune deficiency, notably necrotizing periodontal diseases (Hatice Hasturk and Alpdogan Kantarci, 2000).

### Oral cavity: A Complex microenvironment

In the oral cavity, a diverse population has been estimated to include more than 700–1000 bacterial species spread on the tongue, teeth, gum, inner cheeks, palate and tonsils. Streptococci form about 20% of these bacteria, in addition to viruses, fungi and some archaea. Finally, just as there are bacterial species associated with oral diseases, there are also species that seem to be associated with oral health (Stingu *et al*., 2008 and Riep *et al*., 2009).

**Saliva as biomarker**

Interleukins (IL) comprise a second major class of investigated biomarkers, each of which has also been measured in saliva, but not in an obese adolescent population. Specifically, IL1b is associated with periodontal inflammation ; IL-6 has been measured in periodontitis patients; IL-4, IL-10, IL-12 and IL-17 are related to Sjogren's syndrome; IL-10 is reduced in periodontitis patients; IL-8 is related to dental caries in adolescents and oral cancer; IL-13 is identified in the sputum of asthmatics; IL-17 is lower in patients with periodontal disease ; and interferon c (IFN-c) is higher in the saliva of control subjects without Sjogren's syndrome (J. Max Goodson1 *et al*., ?).

**Probiotics**

Probiotics can be defined as living microbes, or as food ingredients containing living microbes, that beneficially influence the health of the host when used in adequate numbers. According to World Health Organization, the definition of probiotics refers to "live microorganisms which when administered in adequate amounts, confer benefits to the health of the host"[59]. International Life Science Institute Europe suggests a definition according to which a probiotic is "a live microbial food ingredient that, when consumed in ample volume, exerts health-benefits on the consumer (Rangare Lakshman Anusha *et al*., 2015). Probiotics by definition are the non-digestible food ingredient that confers benefits on the host by selectively stimulating the growth and/activity of one bacterium or a group of bacteria in the colon, and thus improve the host health. Oligosaccharides in the group of fructo-oligosaccharides and galactosaccharides are the commonly studied probiotics. They escape digestion in the upper gastrointestinal tract so that they can be released in the lower tract and used by beneficial microorganisms in the colon, mainly bifidobacteria and lactobacilli (Pavitra Rastogi *et al*., 2011). Prebiotics are generally defined as not digestible food ingredients that beneficially affect the host by selectively stimulating the growth and⁄or activity of one or a limited number of bacterial species already established in the colon, and thus in effect improve host health (Gibson and Roberfroid, 1995).

These prebiotics includes inulin,fructo oligosaccharides, galacto oligosaccharides and lactulose. The concept of prebiotics essentially has the same aim as probiotics, which is to ameliorate host health via modulation of the intestinal flora, albeit by a distinctive mechanism (Rangare Lakshman Anusha *et al*., 2015). Synbiotics are outlined as concoctions of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastro-intestinal tract of the host (Agarwal *et al*., 2011). Probiotics can improve patient condition in medical disorders such as diarrhea, gastroenteritis, short-bowel syndrome and inflammatory intestinal diseases (Crohn's disease and ulcerative colitis), cancer, immunodepressive states, inadequate lactase digestion, pediatric allergies, growth retardation, hyperlipidemia, liver diseases, infections with *Helicobacter pylori*, genitourinary tract infections and others (Bermudez-Brito *et al*., 2012). Research results have confirmed the positive activity of probiotic lactic acid bacteria in prevention and treatment of antibiotic associated diarrhea rota virus infections and many gastrointestinal diseases ( Vandenplas *et al*., 2015).

The most commonly used probiotic bacterial strains belong to the genera Lactobacillus and Bifidobacterium (Saxelin *et al*., 2005). These bacterial genera are regarded as a part of the normal human microbiota (Anna Haukioja, 2010). Probiotics can alter the immune response to vaccines. There is evidence that some specific probiotics can alter monocyte and natural killer cell function in the blood. Evidence is also accumulating that taking some specific probiotics can boost antibody responses to oral and systemically administered vaccines. This area needs further investigation (Nymphea Pandit Inder kumar Pandit *et al*., 2013).

**Features of a good probiotic**

- It should be a strain, which is capable of exerting a beneficial effect on the host animal, e.g., elevated growth or hindrance to disease.
- It should be nonvirulent and non-pathogenic.
- Preferred to be present as viable cells in large numbers.
- It should be capable of surviving and metabolizing in the gut environment, e.g., endurance to low pH and carbon-based acids, and should be able to maintain genetic stability in oral microflora.
- It should be stable and adept of permanently viable for periods under storage and field conditions (Rangare Lakshman Anusha *et al*., 2015)

**Probiotic delivery system**

They are provided in four basic forms: Beverage or food (fruit juice), Prebiotic fibers, Milk-based products, Dried cell packages such as powder, capsule, gelatin tablets.[76]

**Mechanism of action of probiotics**

The general mechanism of action of probiotics can be divided into three main categories

- Normalization of intestinal microbiota
- Modulation of the immune response and
- Metabolic effects(Pavitra Rastogi, Himani Saini, *et al*., 2011).

Probiotics do not always colonize the intestinal tract to exert their effects. For example, some probiotics like *Bifidobacterium longum* become part of the human intestinal microflora, whereas others like *Lactobacillus casei* indirectly exert their effects in a transient manner as they pass through by remodeling or influencing the existing microbial community. The following are the major mechanisms of action of probiotics on the host.[80]

Major probiotic mechanisms of action include enhancement of the epithelial barrier, increased adhesion to intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microorganism substances and modulation of the immune system (Bermudez-Brito *et al*., 2012).

**Enhancement of the Epithelial Barrier**

The intestinal epithelium is in permanent contact with luminal contents and the variable, dynamic enteric flora. The intestinal barrier is a major defense mechanism used to maintain epithelial integrity and to protect the organism from the environment.

Defenses of the intestinal barrier consist of the mucous layer, antimicrobial peptides, secretory IgA and the epithelial junction adhesion complex. Mucin glycoproteins (mucins) are major macromolecular constituents of epithelial mucus and have long been implicated in health and disease. Probiotics may promote mucous secretion as one mechanism to improve barrier function and the exclusion of pathogens. Several *Lactobacillus* species increase mucin expression in human intestinal cell lines (Bermudez-Brito *et al*., 2012). Probiotics are capable of influencing many of the components of epithelial barrier function either by decreasing apoptosis of intestinal cells or increased mucin production. *Lactobacillus rhamnosus* GG was able to prevent cytokine-induced apoptosis in intestinal epithelial cell models by inhibiting tumor necrosis factor (TNF) (Vijaya K Gogineni *et al*.).

**Increased Adhesion to Intestinal Mucosa**

Adhesion to intestinal mucosa is regarded as a prerequisite for colonization and is important for the interaction between probiotic strains and the host. Adhesion of probiotics to the intestinal mucosa is also important for modulation of the immune system and antagonism against pathogen. Thus, adhesion has been one of the main selection criteria for new probiotic strains and has been related to certain beneficial effects of probiotics. Lactic acid bacteria (LABs) display various surface determinants that are involved in their interaction with intestinal epithelial cells (IECs) and mucus. IECs secrete mucin, which is a complex glycoprotein mixture that is the principal component of mucous, thereby preventing the adhesion of pathogenic bacteria. Additionally, lipids, free proteins, immunoglobulins and salts are present in mucous gel. This specific interaction has indicated a possible association between the surface proteins of probiotic bacteria and the competitive exclusion of pathogens from the mucus (Bermudez-Brito *et al*., 2012).

Probiotic bacteria compete with invading pathogens for binding sites to epithelial cells and the overlying mucus layer in a strain-specific manner. Surface layer proteins purified from *L. helveticus* R0052 inhibited enterohemorrhagic *Escherichia coli*O157:H7 adherence and the subsequent rise in permeability, without altering the growth of the pathogen. *S. boulardii* secretes a heat-labile factor which has shown to be responsible for the decreased bacterial adherence (Vijaya K Gogineni *et al*.,), Probiotic strains can also induce the release of defensins from epithelial cells. These small peptides/proteins are active against bacteria, fungi and viruses. Moreover, these small peptides/proteins stabilize the gut barrier function. Defensins comprise a major family of membrane-disrupting peptides in vertebrates. The interaction is non-specific and mainly by binding to anionic phospholipid groups of the membrane surface through electrostatic interactions. This interaction creates defensin pores in the bacterial membrane that disrupt membrane integrity and promote lysis of microorganisms (Bermudez-Brito *et al*., 2012).

**Competitive Exclusion of Pathogenic Microorganisms**

The mechanisms used by one species of bacteria to exclude or reduce the growth of another species are varied, including the following mechanisms: creation of a hostile microecology, elimination of available bacterial receptor sites, production and secretion of antimicrobial substances and selective metabolites, and competitive depletion of essential nutrients.

Specific adhesiveness properties due to the interaction between surface proteins and mucins may inhibit the colonization of pathogenic bacteria and are a result of antagonistic activity by some strains of probiotics against adhesion of gastrointestinal pathogens. Exclusion is the result of different mechanisms and properties of probiotics to inhibit pathogen adhesion, including the production of substances and the stimulation of IECs. Competitive exclusion by intestinal bacteria is based on a bacterium-to-bacterium interaction mediated by competition for available nutrients and for mucosal adhesion sites. To gain a competitive advantage, bacteria can also modify their environment to make it less suitable for their competitors. The production of antimicrobial substances, such as lactic and acetic acid, is one example of this type of environmental modification. Some lactobacilli and bifidobacteria share carbohydrate-binding specificities with some enteropathogens, which makes it possible for the strains to compete with specific pathogens for the receptor sites on host cells. In general, probiotic strains are able to inhibit the attachment of pathogenic bacteria by means of steric hindrance at enterocyte pathogen receptors.

**Production of Antimicrobial Substances**

One of the proposed mechanisms involved in the health benefits afforded by probiotics includes the formation of LMW compounds (<1,000 Da), such as organic acids, and the production of antibacterial substances termed bacteriocins (>1,000 Da). Organic acids, in particular acetic acid and lactic acid, have a strong inhibitory effect against Gram-negative bacteria, and they have been considered the main antimicrobial compounds responsible for the inhibitory activity of probiotics against pathogens. The undissociated form of the organic acid enters the bacterial cell and dissociates inside its cytoplasm. The eventual lowering of the intracellular pH or the intracellular accumulation of the ionized form of the organic acid can lead to the death of the pathogen. Many LAB produce antibacterial peptides, including bacteriocins and small AMPs. Bacteriocins produced by Gram-positive bacteria (usually LAB, including lactacin B from *L. acidophilus*, plantaricin from *L. plantarum* and nisin from *Lactococcus lactis*) have a narrow activity spectrum and act only against closely related bacteria, but some bacteriocins are also active against food-borne pathogens. The common mechanisms of bacteriocin-mediated killing include the destruction of target cells by pore formation and/or inhibition of cell wall synthesis. For example, nisin forms a complex with the ultimate cell wall precursor, lipid II, thereby inhibiting cell wall biosynthesis of mainly spore-forming bacilli.

Subsequently, the complex aggregates and incorporates peptides to form a pore in the bacterial membrane[81] . Microcins (produced by gram negative bacteria), on the other hand, can target the inner membrane, enzymes that are involved in DNA or RNA structure and synthesis, or protein synthesis enzymes (Vijaya K Gogineni *et al*.,).

Intestinal bacteria also produce a diverse array of health-promoting fatty acids. Indeed, certain strains of intestinal bifidobacteria and lactobacilli have been shown to produce conjugated linoleic acid (CLA), a potent anti-carcinogenic agent. Finally, probiotic bacteria are able to produce so-called de-conjugated bile acids, which are derivatives of bile salts. De-conjugated bile acids show a stronger antimicrobial activity compared to that of the bile salts synthesized by the host organism (Bermudez-Brito *et al*., 2012).

Probiotics either by inducing host cells to produce peptides or by directly releasing peptides interfere with pathogens, and prevent epithelial invasion. Defensins (hBD protein) and cathelicidins are the antimicrobial peptides expressed constitutively by the intestinal epithelial cells and display antimicrobial activity against a wide variety of bacteria, fungi and some viruses. Certain probiotic strains like *E. coli* strain DSM 17252 G2 (one of the three Symbioflor 2 genotype strains) and several Lactobacilli species have shown to express certain defensins. Probiotics have been shown to suppress pathogen growth through the release of a variety of antimicrobial factors like defensins, bacteriocins, hydrogen peroxide, nitric oxide, and short chain fatty acids (SCFA), such as lactic and acetic acids, which reduce the pH of the lumen (Vijaya K Gogineni *et al*.,).

**Interference with quorum sensing signaling**

Bacteria communicate with each other as well as with their surrounding environment through chemical signalling molecules called auto-inducers. This phenomenon is called quorum sensing. The use of this cell-to-cell signaling mechanism facilitates the regulation of important traits of enteric microbes that allow them to successfully colonize and/or start infection in their host. Medellin-Pena *et al*. demonstrated that Lactobacillus acidophilus secretes a molecule that inhibits the quorum sensing signalling or directly interact with bacterial transcription of E. coli O157 gene, involved in colonization and thus, bacterial toxicity is opposed80.

**Probiotics and Oral Health**

In respect to commensal oral microbes, several aspects support the idea that it may be possible to find bacteria that could be useful in prevention or treatment of oral diseases. In fact, it has been suggested that some observed probiotic effects are not just properties of a few well-studied strains but common to several species (Haukioja *et al*., 2006; Cosseau *et al*., 2008 and Haukioja *et al*., 2008). Indeed, it is recognized that most new strategies to deal with oral cavity diseases are based on manipulating microbial activities through use of beneficial probiotics inhibitory activities against pathogens including cariogenic and gingivitis causing microbiota (Alok *et al*., 2017; Laleman and Teughels, 2015 and Collado *et al*., 2008). Probiotic bacteria seem to affect both oral microbiota and immune responses. On the other hand, the extent to which bacteria in food or in food ingredients can influence relatively stable oral microbiota is difficult to predict (Anna Haukioja, 2010).

The mechanism of action of probiotic bacteria in the oral cavity could be analogous to that described in the gut. The bacterial biofilm formation in the oral cavity is considered to be the principal etiological agent in many pathological conditions in the mouth. Once oral biofilm reaches maturity a dynamic interplay between the host and microbial species is established. The inflammatory byproducts, along with bacterial endotoxin and metabolic products are mainly responsible for periodontal destruction. Probiotic therapy could be considered as a means of inhibiting oral biofilm development and reducing the cascade of harmful immune-inflammatory reactions (Pavitra Rastogi *et al*., 2011). Strains belonging to the Lactobacillus, Streptococcus and Bifidobacterium genera are most commonly investigated as regards probiotics (Devine and Marsh, 2009). Other strains of probiotics in the oral cavity include: L. acidophilus, L. casei Shirota, L. paracasei, L. casei, L .johnsonii, L. reuteri, propionibacterium, W. cibaria ( Meurman and Stamatova, 2007). Several studies suggest that consumption of products containing probiotic lactobacilli or bifidobacteria could reduce the number of mutans streptococci in saliva.( Näse *et al*., 2001; Ahola *et al*., 2002; Nikawa *et al*., 2004; Caglar *et al*., 2005; Caglar *et al*., 2006; Caglar *et al*., 2007; Caglar *et al*., 2008; Caglar *et al*., 2008 and Cildir *et al*., 2009). Some probiotic Lactobacillus and Streptococcus strains are able to colonize the oral cavity of some people during the time that products containing them are in active use. L. rhamnosus GG and two different L. reuteri strains have been reported to colonize the oral cavity of 48–100% of volunteers consuming products containing them.( Krasse *et al*., 2006; Yli-Knuuttila *et al*., 2006; Meurman *et al*., 1994 and Caglar *et al*., 2009). In addition, S. salivarius K12, used for treating oral malodour, temporarily colonizes the oral cavity for a short time after use (Horz *et al*., 2007).

The various means of administration of probiotics for oral health purpose that have been studied are lozenges, tablets, cheese, yoghurt, mouth rinse, capsule, liquid.( Meurman and Stamatova, 2007). Recently, oral lactic acid bacteria and bifidobacteria have been isolated and characterized for various oral health purposes, including caries, periodontal diseases, and halitosis(Simark-Mattsson *et al*., 2007; Simark-Mattsson *et al*., 2007; Sookkhee *et al*., 2001; Kang *et al*., 2005; Kang *et al*., 2006; Strahinic *et al*., 2007 and Koll *et al*., 2008).

**Probiotics and Dental Caries**

Caries is a bacterially-mediated process has been known for more than 115 years. Currently, the host, bacteria and nutrients are required for fermenting the product of organic acids and the subsequent demineralization activity. According to this model all the three elements must be present to initiate the disease. To overcome the limitation of traditional caries management strategies, the use of probiotics has been tried to treat caries by preventing oral colonization of cariogenic pathogens. Several studies suggest that consumption of products containing lactobacilli or bifidobacteria could reduce the number of *Streptococcus mutans* in the saliva. Strains of Lactobacillus rhamnosus, L. casei, L. reuteri and Bifidobacterium spp. have all demonstrated the potential to alter colonisation of cariogenic bacteria and thus prevent dental caries (Meurman and Stamatova, 2007). Genetically modified microbes bring a new dimension to the concept of probiotics. 'Replacement therapy' based upon biotechnological approaches has also been investigated.

Techniques used include gene inactivation to remove harmful metabolites and the incorporation of genes to encode for antimicrobial compounds, for example bacteriocins (Robert *et al*., 2017). One approach is to reduce the harmful properties of pathogenic strains naturally colonizing the oral cavity. The modified strain could then be used to replace the original pathogen. One ambitious and promising example is the generation of an S. mutans strain with a complete deletion of the open reading frame of lactate hydrogenase and thus significantly reduced cariogenicity ( Hillman *et al*., 2007). It has been suggested that this S. mutans clone (SMaRT Replacement Therapy product has recently been developed by Oragenics Inc.) could provide a lifetime of protection in

humans against dental caries, but may require occasional re-application (Robert *et al*., 2017).

**Effect on periodontitis**

Periodontal diseases (periodontitis and gingivitis) are a group of inflammatory pathologies of the periodontium that lead to loss of teeth principally due to dysregulated, immune-mediated destruction of the periodontal ligaments and tooth supporting structures (Chapple *et al*., 2017 and Hajishengallis, 2015). A dysbiotic oral microbiota is associated with periodontitis and in the most common forms of this disease namely, chronic and aggressive periodontitis is thought to play an active role in the pathogenesis by promoting chronic dysregulated inflammation which in turn sustains the dysbiotic microbial ecology (Hajishengallis *et al*., 2012 and Nibali, 2015). PDL cells are highly specialized fibroblasts with unique involvement in the regeneration of soft and hard tissues of the periodontium lost to disease. The goal of regenerative therapies for periodontitis is enhancement of wound healing and restoration of tissue integrity. As such, PDL cells play a critical role for regeneration of the periodontal tissues as the primary target in tissue engineering (Melcher, 1976). Fibroblasts are involved in collagen production, wound healing, and tissue repair. Fibroblasts are responsive to the surrounding inflammatory environment and cytokine activity. PDL cells are a highly specialized phenotype of fibroblasts with unique functions important to regeneration of the attachment apparatus between the hard tissues of teeth and alveolar bone, including the production of extracellular proteins such as basic fibroblast growth factor (bFGF), platelet-derived growth factor and epidermal growth factor. PDL cells also produce several types of collagen, including type V collagen, which is involved in tissue repair and regeneration.

Gingival and PDL fibroblasts express a variety of different genes. PDL fibroblasts also express alkaline phosphatase, which plays a key role in the mineralization of bone and acellular cementum formation, indicating their osteogenic potential and capability for producing mineralized tissues (Manal Mustafa *et al*., 2013). The clinical manifestation of periodontal disease result from a complex interplay between the etiologic agents, specific bacteria found in the dental plaque and the host tissues. The oral bacteria lives in harmony with its host, but under specific conditions (increased mass and/or pathogenicity, suppression of beneficial bacteria and/or reduced host response), disease can occur. Periodontal diseases can be managed by either inhibition of specific pathogens or affecting the host response. New strategies for periodontal disease management have been emerging as more is learned about the role of the host response. Since the primary etiological factors for the development of periodontal disease are bacteria in supra- and sub-gingival biofilm, efforts for disease prevention and treatment are mainly focused on pathogen reduction and strengthening of the epithelial barrier; thus, contributing to decreased susceptibility to infection (Nymphea Pandit Inder kumar Pandit *et al*., 2013).

A probiotic that could alter the oral microbial ecology may be a useful tool in the clinical management of periodontitis, with the potential to offer two-fold benefits (Saha *et al*., 2012). Firstly, to combat dysbiosis by competitive inhibition of periodontal pathogens, and thereby reducing the overall immunogenicity of the oral microbiota. Secondly, to modulate active disease-associated immune/inflammatory pathways to reduce the destructive inflammation of periodontitis, and lead to immune homeostasis that could be maintained by the host in the long term. The systemic immunomodulatory effects of gut based probiotics may also have a protective effect in relation to periodontitis as demonstrated in a mouse model (Kobayashi *et al*., 2017 and McCabe *et al*., 2015). Patients with various periodontal diseases, gingivitis, periodontitis, and pregnancy gingivitis, were locally treated with a culture supernatant of a L. acidophilus strain. Significant recovery was reported for almost every patient. There has been significant interest in using probiotics in treatment of periodontal disease recently, too. The probiotic strains used in these studies include L. reuteri strains, L. brevis (CD2), L. casei Shirota, L. salivarius WB21, and Bacillus subtilis. L. reuteri and L. brevis have improved gingival health, as measured by decreased gum bleeding.( Krasse *et al*., 2006; Della Riccia *et al*., 2007 and Twetman *et al*., 2009). The use of probiotic chewing gum containing L. reuteri ATCC 55730 and ATCC PTA 5289 also decreased levels of pro-inflammatory cytokines in GCF,[41] and the use of L. brevis decreased MMP (collagenase) activity and other inflammatory markers in saliva (Della Riccia *et al*., 2007). Prevention and treatment of periodontal diseases mainly focuses on the reduction of bacterial load. Conventional treatment modalities include surgical and non-surgical management which emphasizes on mechanical debridement, often accompanied by antibiotics. Due to the emergence of antibiotic resistance and frequent re-colonization of treated sites with pathogenic bacteria, probiotics have emerged in the field of periodontics. Probiotics is based on the concept of bacterial interference, whereby one microorganism can prevent and or delay the growth and colonization of another member of the same or different ecosystem (Nymphea Pandit Inder kumar Pandit *et al*., 2013).

**Probiotics and Halitosis**

Halitosis is not a disease but a discomfort, although some oral diseases including periodontitis may be the underlying cause; however, in approximately 90% of cases, the origin can be found in the oral cavity,( Delanghe *et al*., 1997) and probiotics are marketed for the treatment of both mouth- and gut-associated halitosis. Intra-oral halitosis is a common condition, and is known to be associated with periodontitis with the putrefactive activity of the tongue microbiota playing a major role in producing volatile malodorous compounds in both pathological (disease associated) and physiological (transient non-disease associated)halitosis(Scully, 2008 and Bollen and Beikler, 2012). One of the earliest probiotic strains proposed to target oral malodour and fulfilling the above criteria was the bacteriocin producing strain S. salivarius K12, which reduced breath volatile sulfur compound (VSCs) concentrations in individuals who consumed the probiotic lozenges after pre-treatment with achlorhexidinerinse.( Wescombe *et al*., 2010 and Masdea *et al*., 2012).

**Oral fungal Infections**

Interactions between bacteria and fungi in the oral cavity environment are dynamic and usually drive the structure and behavior of the oral cavity community resulting in pathogenesis of the oral diseases (Vesty *et al*., 2007; Xu *et al*., 2015; Krom *et al*., 2017; Ghannoum *et al*., 2010).The diverse numbers of fungal genera including Candida, Saccharomyces, Pencillium, Cladosporium, Malasseezia and Fusarium with varying densities. However, species of Candida were dominant and they are known to be commensals in the oral cavity and

present in about 25%–75% of the microbiota of healthy individuals (Barros *et al*., 2016). These species are opportunistic pathogens and may under suitable conditions infect the oral mucosa causing infectious candidiasis(Jorgensen *et al*., 2017). The majority cases of candidiasis are associated with Candida albican isolates (Xu and Dongari-Bagtzoglou, 2015). Other Candida species such as C. krusei, C. tropicalis, C. glabrata, C. parapsilosis, and C. dubliniensis were incriminated and isolated from oral cavity infections (Melcher, 1976; Manal Mustafa *et al*., 2013; Pavitra Rastogi *et al*., 2011 and Rangare Lakshman Anusha *et al*., 2015 ). These dysbiotic infections could affect mucosal surfaces of the oral cavity and oesophagus, and may become systemic (Xu and Dongari-Bagtzoglou, 2015). It is also recognized that probiotics activity is highly host and strain specific, even at strain level (Mahasnehm 2017).

**Mechanism of action of probiotics in oral cavity**

The general mechanisms of probiotics can be divided into three main categories: normalization of the intestinal microbiota, modulation of the immune response, and metabolic effects.[18] Accumulating research results point to the following activities of probiotics in the human oral cavity: (1) Antagonism with pathogens; (2) Aggregation with oral bacteria; and (3) Interaction with oral epithelium (Mahasneh, 2017). The mechanisms of probiotic action in the oral cavity could be analogous to those described for the intestine. Some of the hypothetical mechanism of probiotics action in the oral cavity includes direct interaction in dental plaque by enmeshing in securing of oral micro-organisms to proteins, agility on plaque evolution and on its complex ecosystem by competing and intervening with bacterial attachments and engaging in metabolism of substrate and yielding of chemicals that inhibit oral bacteria. Indirect probiotic actions featured are based on modulating systemic immune function, effect on local immunity, eventuality on nonimmunologic defense mechanisms, regulation of mucosal permeability, probiotics function as antioxidants and also produce antioxidants, hampering plaque induction by neutralizing the free electrons. (Meurman, 2005; Huovinen, 2001 and Salminen *et al*., 2002). Within the oral cavity, mechanisms of probiotic action can possibly be suggested from previous gastrointestinal studies, whereby the introduction of microorganisms as a therapeutic tool for the control of oral and dental disease could act as follows (Meurman, 2005).

Direct interactions within dental plaque (colonisation resistance).This mechanism could possibly include the disruption of plaque biofilm formation through competition for binding sites on host tissues and other bacteria, and through competition for nutrients. The production of antimicrobial compounds by probiotic species that inhibit other oral bacteria may also be a significant mechanism. It is known that lactic acid bacteria produce a range of antimicrobial agents including organic acids, hydrogen peroxide, peptides, bacteriocins and anti-adhesion molecules (Meurman, 2005).

Indirect probiotic actions within the oral cavity, including the modulation of both innate and adaptive immune function. Within this context, it is possible that lactic acid bacteria can interact with immunocompetent cells, such as macrophages and T-cells, leading to an alteration in the production of cytokines and subsequent effects on overall immunity (Meurman, 2005). For example, lactobacilli are able to elicit a transient reduction in IL-8 secretion in the gingival crevicular fluid of subjects with mild gingival inflammation. Beyond the modulation of immune responses, some probiotic species are able to enhance mucin production and barrier function, upregulate host defence peptides, promote angiogenesis and wound healing (Devine *et al*., 2015).

**Conclusion**

Traditionally, probiotics have been associated with gut health, and most clinical interest has focused on the prevention or treatment of gastrointestinal infections and diseases. However, during the last decade, an increasing number of established and proposed health effects of probiotic bacteria have been reported, including enhancement of the adaptive immune response, treatment or prevention of urogenital and respiratory tract infections, and prevention or alleviation of allergies and atopic diseases in infants. This has resulted in the quest for a better understanding of how probiotics operate. Moreover, this has catalyzed an enormous interest in the molecular processes underlying host-microbe interactions. Gaining insight into the mechanisms of probiotic action may not only help to improve the credibility of the probiotic concept but also to foster the development of novel strategies for the treatment or prevention of oral diseases as well as other autoimmune diseases. On the contrary, much more scientific knowledge is needed about probiotics, including their safety and appropriate use. Hence, the full potential of probiotics can be realized only when their benefits can be established scientifically through more research in this area.

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