

## Review Article

# PROBIOTICS IN ORAL HEALTH: A REVIEW

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**Abstract:** The term probiotics is a relatively new word meaning “for life” and is currently used to name bacteria associated with beneficial effects for humans and animals. The development of resistance to range of antibiotics by some important pathogen has raised a possibility of return to pre antibiotic dark ages. So there was need of new treatment paradigm to be introduced to treat periodontal diseases. This need was fulfilled by the introduction of probiotics. Probiotics are counterparts of antibiotics thus are free from concerns for developing resistance, further they are body's own resident flora hence are most easily adapted to host. The buzz about probiotics has become a roar but despite great promises, probiotics work is limited to gut. Periodontal works are sparse and need validation by large randomized trials. It can be said probiotics are still in “infancy” in terms of periodontal health benefits, but surely have opened door for a new paradigm of treating disease on a nano molecular mode. Novel species are likely to be added in the future as research data accumulate. In-depth understanding of the intrinsic microbial ecological control of commensal microbiota may introduce new putative species to this discussion.

**Key Words:** Probiotics, Oral health, Periodontics, Beneficial bacteria.

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### INTRODUCTION:

The term probiotics is a relatively new word meaning “for life” and is currently used to name bacteria associated with beneficial effects for humans and animals<sup>1</sup>

The Food and Agriculture Organization (FAO) and World Health Organization (WHO) define probiotics as 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host'.

The development of resistance to range of antibiotics by some important pathogen has raised a possibility of return to pre antibiotic dark ages.<sup>2</sup> So there was need of new treatment paradigm to be introduced to treat periodontal diseases. This need was fulfilled by the introduction of probiotics. The concept of probiotics evolved at the turn of 20<sup>th</sup> century from a hypothesis first

proposed by nobel prize winning Ukrainian bacteriologist Elie Metchnikoff working at the Pasteur institute in Paris, who laid down the scientific foundations of probiotics.<sup>3</sup> Taking into account the two major treatment strategies against periodontal diseases, namely the elimination of specific pathogens and the suppression of a destructive host response, the probiotic approach may add value in achieving these treatment goals.<sup>4</sup> Probiotics provide an effective alternative way which is economical and natural to combat periodontal disease. Thus a mere change in diet by including probiotic food may halt, retard, or even significantly delay the pathogenesis of periodontal diseases, promoting a healthy lifestyle to fight periodontal infections.

Research surrounding probiotics has historically focused on digestive health. Over recent years, scientists have been investigating the potential immune benefits of probiotics, as well as other benefits beyond the recognized area of gut.<sup>5</sup> However, in the past few years probiotics have also been investigated in the oral health perspective. To be able to exert probiotic properties in the oral cavity, however, it is essential for the microorganism to resist the oral environmental conditions and defense mechanisms, to be able to adhere to saliva-coated surfaces, to colonize and grow in the mouth, and to inhibit oral pathogens. The putative probiotic species also needs to be safe for the host.<sup>3</sup>

Probiotics are broadly categorized in two genus *Lactobacillus* and *Bifidobacterium*. While other microorganism also classified in to this group includes yeast and moulds eg. *Saccharomyces cerevisiae*, *Aspergillus niger*, *Aspergillus oryzae*, *Schizosaccharomyces boulardii*.<sup>2</sup> Probiotics enhances innate immunity and modulate pathogen induced inflammation through “Toll like receptors” on dendritic cells. Probiotics can mimic response similar to a pathogen but without periodontal destruction.<sup>2</sup> Similar to their better known actions in the gastrointestinal tract, probiotics exert their effect in many ways in the oral cavity.<sup>5</sup> Mechanisms of action explaining beneficial probiotic effects include modulation of host immune response leading to strengthening of the resistance to pathogenic challenge, alteration of the composition and metabolic activity of host microbiota at the specific location.<sup>3</sup>

Probiotics bacteria can provide health benefits to the host by:

- 1.) Enhancement of the non-specific and specific immune response of the host<sup>3</sup>
- 2.) Production of antimicrobial substances and competition with pathogens for binding sites<sup>3</sup>
- 3.) Degradation of toxins<sup>5</sup>
- 4.) Competing directly with the pathogens<sup>4</sup>

Probiotics are counterparts of antibiotics thus are free from concerns for developing resistance, further they are body’s own resident flora hence are most easily adapted to host. The buzz about probiotics has become a roar but despite great promises, probiotics work is limited to gut. Periodontal works are sparse and need validation by large randomized trials. It can be said probiotics are still in “infancy” in terms of periodontal health benefits, but surely have opened door for a new paradigm of treating disease on a nano molecular mode.

Novel species are likely to be added in the future as research data accumulate. In-depth understanding of the intrinsic microbial ecological control of commensal microbiota may introduce new putative species to this discussion.

#### **ANTICIPATED MECHANISMS OF PROBIOTIC ACTIVITY:**

An intricate interplay between periodontal pathogens and host cells is needed for the development of periodontal disease. There is evidence to show that periodontal pathogens, when in contact with periodontal tissues, may invade epithelial cells, endothelial cells and fibroblasts, prompting evasion of host immune defense mechanisms and disease progression. It is not known if probiotic species interfere with the metabolism and / or growth of the putative periodontal pathogens, thus affecting host-microbe interactions.<sup>4</sup>

#### **I. Inhibition of pathogen adhesion, colonization & biofilm formation:**

Different *Lactobacillus* sps. vary greatly in their adherent capacity to saliva-coated surfaces in a test model system mimicking oral cavity conditions.<sup>6</sup> Consequently, there is a need to identify the best putative probiotic strains and species for different purposes. *Lactobacilli* may also interact with other microorganisms, such as *Fusobacterium nucleatum*.

A probiotic candidate bacterium should be able to adhere to and successfully establish itself in the oral biofilm to exert health

effects. Consideration of the highly sophisticated organization of biofilms, with their primitive circulatory systems, quorum sensing, and spatially and functionally organized species composition, is of key importance for the putative probiotics to be able to integrate into the biofilm structure. They also need to compete for binding sites or to coaggregate with other microorganisms to remain viable in the mouth.

The ability of probiotics to adhere to saliva-coated surfaces varies among species and it has been reported that *L. rhamnosus* and *L. paracasei* strains possess strong binding activity (more than 20%). It is recognized that high values of cell-surface hydrophobicity correlate with superior adhesive properties.<sup>7</sup>

## II. Inhibition of pathogen growth:

Tailoring the composition of the biofilm could be an interesting approach to modulate bacteria-host interactions, thus affecting the disease progression. Eventually, if a species binds well to structures of the oral biofilm, it could be anticipated that this might affect the pathogenic potential of the species based on antimicrobial activity, which, in fact, is another evaluation criterion for probiotics.<sup>8</sup> Antimicrobial activity has been validated through various in vitro and in vivo studies. Strong species dependent and strain-dependent activities against primary periodontal pathogens have been observed. Ishikawa et al. reported that daily intake of *L. salivarius* isolated from healthy humans led to a decreased number of black-pigmented anaerobic rods, with facultative heterofermentative lactobacilli being the strongest inhibitors of *A. actinomycetemcomitans*, *P. gingivalis* and *P. intermedia*.<sup>9</sup>

## III. Modulating the host inflammatory response:

The mechanisms by which probiotics modulate immunity have been broadly studied on gastrointestinal structures.

Probiotic species have shown their ability to alter the balance of pro-inflammatory and anti-inflammatory cytokines secreted by epithelial cells. Elevated levels of tumor necrosis factor- $\alpha$ , interleukin-1, interleukin-6 and interleukin-8 are regarded as hallmarks of the inflammatory response in the intestine.

*Lactobacillus plantarum*, *L. rhamnosus* GG (LGG) and *Lactobacillus lactis* could effectively reduce the levels of interleukin-8 before *Helicobacter pylori* infection of epithelial cells when the concentration of lactobacilli was  $10^{10}$  colony-forming units/ml. Probiotics also regulate immune responses by enhancing innate immunity and modulating pathogen-induced inflammation via toll-like receptor-regulated signaling pathways.<sup>10</sup> The enhancement of local immune responses, as well as of systemic immune response, by probiotics can offer new opportunities for probiotics in preventing infections at peripheral mucosal surfaces, such as those in the oral cavity and in the respiratory and urogenital tracts.<sup>11</sup> LGG cell free supernatants also have been shown to modulate macrophage activity by enhancing the phagocytic digestion of bacterial cells.

Despite the fact that most probiotics belong to the genus lactobacilli or bifidobacteria, some authors have developed the idea that probiotic therapy is equivalent to replacement therapy, thus allowing any species capable of affecting pathogen adhesion to be considered a probiotic. By adopting the latter concept, Teughels et al. have proven that repeated application of *Streptococcus sanguinis*, *Streptococcus salivarius* and *Streptococcus mitis* after root planing successfully reduced and maintained low levels of anaerobic species and black-pigmented bacteria.<sup>12</sup>

This study was the first to assess the role of commensal oral streptococci to modulate periodontal pocket recolonization. However, bacterial replacement, as such, does not meet the traditional criteria of probiotic therapy. As opposed to probiotics, in replacement therapy, the effector strain is

not ingested but is applied directly on the site of infection. Also colonization of the site by the effector strain is essential in replacement therapy. It involves dramatic and long-term change in the indigenous micro biota. Therapy is directed at displacing or preventing colonization of a pathogen & has a minimal immunological impact.

### **PROBIOTICS IN PERIODONTAL DISEASES:**

The oral micro biota is considered to be as complex as the gastrointestinal or vaginal micro biota. Moreover, dental biofilms are considered to be difficult therapeutic targets. The current view on the etiology of plaque-related periodontal inflammation considers three factors that determine whether disease will develop in a subject: a susceptible host; the presence of pathogenic species; and the reduction or absence of so-called beneficial bacteria. Because it is difficult to influence the host response without the risk of serious side effects (e.g. as a result of the use of cyclooxygenase-2 inhibitors), periodontal therapy especially envisages the reduction of the bacterial threat.

The worldwide treatment strategy applied for periodontal disease is based on mechanical sub-gingival debridement eventually including periodontal surgery to reduce the depth of the periodontal pocket improving the oral hygiene. This shifts the sub gingival flora to a less pathogenic composition, characterized by high proportions of gram-positive aerobic species. Although reductions in the total sub gingival micro biota of up to two-log values can easily be achieved, a re-colonization, primarily by less pathogenic bacteria, towards baseline numbers occurs within 1-2 weeks.<sup>13</sup>

The shift towards a less pathogenic micro-biota is only temporary, with the re-establishment of a more aggressive micro-biota within weeks to months. The dynamics of this re-colonization depends on the level of oral hygiene, the efficacy of the

sub gingival debridement and the residual probing depth. The use of antibiotics or antiseptics, either locally or systemically, does not really improve the long-term effect of periodontal therapy. Therefore, some authors have started to focus on the third etiological factor for plaque-related periodontal inflammation, namely the reduction or absence of so-called beneficial bacteria.<sup>14</sup>

### **Clinical evidence of probiotic effectiveness in Periodontal disease:**

Studies on probiotics and periodontal disease are particularly sparse and at present only a few clinical studies have evaluated the efficacy of probiotic species in this indication.

### **Probiotics in growth inhibition of causal organisms of periodontal disease:**

The first study linking probiotics to periodontics was initiated in the late 1970s by Socransky's group at the Forsyth Institute in Boston (USA). This group of researchers found that sub-gingival plaque samples of healthy patients contained Organisms that could inhibit the growth of *A. actinomycetemcomitans* and other periodontopathogens.<sup>15</sup>

Sub gingival plaque samples from diseased sites of patients with localized juvenile periodontitis and patients with refractory periodontitis almost invariably lacked such inhibitory bacteria. Interestingly, sub gingival plaque samples from clinically healthy sites in these periodontitis patients contained inhibitory bacteria in proportions similar to those in sub-gingival plaque taken from healthy control patients. These micro-organisms that inhibited the growth of periodontopathogens were almost invariably identified, at that time, as *Streptococcus sanguis* and *Streptococcus uberis*. The basis for their inhibition of *A.actinomycetemcomitans* lay in the production of hydrogen peroxide. These findings, together with the strong negative association between *A. actinomycetemcomitans* and *S. sanguinis* in studies of the predominant culturable micro

biota in plaque from healthy and diseased periodontal pockets, encouraged these researchers to proceed to in vivo studies using *S. sanguinis* as an effector strain.<sup>16</sup>

### **Role of probiotics in the treatment of gingivitis:**

*Lactobacillus reuteri* and *Lactobacillus brevis* are among the species able to affect gingivitis and plaque composition positively as well as being specific markers for periodontal disease.<sup>17</sup> A significant decrease in gingival bleeding and a reduction in gingivitis were observed after a two-week intake of probiotic species. The observed improvement in clinical status may be attributed to the effective colonization of the probiotic bacteria within the oral cavity.

Research of the medical journals shows that *Streptococcus salivarius* K12 could be found in 2% of the population and it is seen that these individuals rarely became ill or suffered from other oral ailments such as halitosis. The study of the mechanism of how this bacterium was different then began in earnest.<sup>18</sup>

*S. salivarius* K12 makes two defense peptides (called BLIS - Bacteriocin like Inhibitory Substance) that the probiotic fired at encroaching invading bacteria. The probiotic recognises the closeness of these invading bacteria by sensing the voltage change along the cell wall of the invading bacteria. The BLIS peptide is fired at the invader, and the peptide punctures a hole in the cell wall allowing vital nutrients to leak out of the invading bacteria, thus causing its death. Thus *S. salivarius* K12 is able to maintain the status quo in oral health, by controlling many opportunistic bacteria.

Although this probiotic was found to be effective against many bacteria including *Streptococcus pyogenes* it is not a magic pill. The probiotic needs to be placed in a healthy mouth with a suitable mouth environment in order to colonize the tongue surface. The probiotic BLIS K12, cannot survive in an acid environment, and therefore, would not be able to colonize in a mouth high in acid, or lacking oxygen (as

smokers and alcoholics). The oral administration of a tablet containing *L. salivarius* WB21 was able to decrease the plaque index significantly, and the pocket probing depth markedly, in subjects who were smokers.<sup>19</sup> Another finding in this clinical trial was the ability of *L. salivarius* WB21 to successfully reduce the prevalence of periodontal pathogens. The latter study adds significant impact to the role of probiotics in periodontal disease pathogenesis because it evaluated both clinical and crevicular fluid markers of periodontal inflammation. The concentrations of lactoferrin in the gingival crevicular fluid correlate with the clinical parameters of periodontitis. The intake of lactobacilli showed gingival crevicular fluid values of lactoferrin that corresponded to values in the healthy state, suggesting that a probiotic intervention could be a useful tool for the treatment of inflammation and the clinical symptoms of periodontitis.<sup>4</sup>

W Teughels evaluated the inhibitory effect of *Streptococcus crista* (Sc) strains on the epithelial colonization by *Porphyromonas gingivalis* & concluded that Sc seems to inhibit Pg by interference with the initial adhesion. Therefore Sc can be considered as a probiotic species.<sup>20</sup>

Krasse et al. evaluated the effect of another lactobacillus strain, *L. reuteri*, in the treatment of recurrent gingivitis. The selection of this strain was based on anecdotal data, the reported reduction of salivary *S. mutans* levels and on the generally claimed health effects of lactobacilli. *L. reuteri* strain was delivered via chewing gum. It was concluded that *L. reuteri* is efficacious in reducing gingivitis and plaque scores.<sup>21</sup>

### **PROBIOTICS IN ORAL HEALTH:**

#### **Caries Management:**

The fact that caries is a bacterially mediated process has been known for more than 115 years. Since then, research has refined the process of caries development to a multifaceted disease process. Currently, we know that the host, bacteria and nutrients

are required to foment the production of organic acids and the subsequent demineralization activity. Because, according to this model, all three elements must be present for disease initiation and progression, the removal of anyone element leads to the interception of the disease process. To overcome the limitations of the traditional disease management strategies, a number of researchers are developing probiotic methods to treat the caries causing infection by interfering with the oral colonization of cariogenic pathogens.<sup>22</sup> *L. reuteri*, administered in lozenge, straw & tablet forms, *L. rhamnosus* in milk, *Bifidobacterium* in yoghurt have shown a reduction in salivary *S. mutans* levels.

For patients undergoing long-term probiotic treatment with lactobacilli (e.g. for gastrointestinal disorders, dental health should be monitored closely during the treatment and patients should be caries free prior to the initiation of the probiotic treatment.

## **PROBIOTICS AND GENERAL HEALTH:**

### **Applications in gastrointestinal disorders:**

Probiotics have traditionally been used to treat diseases related to the gastrointestinal tract. The most widely used species belong to the genera *Lactobacillus* and *Bifidobacteria*, although these species are not predominant in the gastrointestinal microbial ecology. The focus remains, however, on these species because these organisms are already produced in the dairy industry and because they are very rarely implicated in infections of humans. Therefore, they are categorized by the United States Food and Drug Administration as 'Generally Regarded as Safe (GRAS)'. Several gastrointestinal health claims have been made for probiotics, such as the relief of enzymatic maldigestion. Probiotic bacteria containing  $\beta$ -galactosidase can be added to food to improve lactose maldigestion.<sup>23</sup> Similarly, milk fermented

with *Lactobacillus delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus* is tolerated well by lactose maldigesters (deficient in lactase production)<sup>24</sup> compared with regular milk and helps to relieve symptoms such as loose stools and abdominal pain. A similar effect has been observed for sucrose deficient children, in whom the intake of *Saccharomyces cerevisiae* enhances the digestion of a sucrose load.<sup>25</sup>

The currently available data demonstrate that probiotics are more effective in preventing relapse of inflammatory bowel diseases than in suppressing active disease. There are various substantiated indications of probiotics in gastrointestinal disturbances. To name a few, replacement of milk with yogurt has been indicated in lactose indigestion. Freeze dried *S. boulardii* or *E. faecillum* SF 68 is indicated in antibiotic & *C. difficile* associated diarrhea. Rotavirus associated diarrhea in children can be fed with milk containing *L. rhamnosus* GG. *E. coli* Nissle 1917 is indicated in remission in ulcerative colitis. Prevention of relapse of chronic pouchitis is treated by a combination of *L. acidophilus*, *B. longum*, *L. casei*, *B. breve*, *L. plantarum*, *B. infantis*, *L. bulgaricus*, and *S. Thermophilus*.<sup>26</sup>

### **Urogenital infections:**

The dominant presence of lactobacilli in the urogenital micro biota of healthy women, and the obliteration of lactobacilli in patients who develop urinary tract infections, bacterial vaginosis and other genital infections, has led to a focus on lactobacilli as potential probiotics for the prevention of urogenital disease. In a recent Cochrane review<sup>27</sup>, pooled results showed an 81% reduction in the risk of genital infection with the use of probiotics.

### **ADMINISTRATION OF PROBIOTICS:**

Appropriate forms of administration of probiotic strains have been discussed in several articles. Dairy products supplemented with probiotics are a natural means of oral administration and easily

adopted in dietary regime. However, for the purposes of prevention or treatment of oral diseases, specifically targeted applications, formulas, devices, or carriers with slow release of probiotics might be needed.

1. **Capsule & Liquid form:** Montalto et al (2004) administered probiotic mix both in capsules and in liquid form without observing statistically significant difference, however, in the *S.mutans* counts between the two test groups.

2. **Chewing gum:** A recent invention for caries prophylaxis is a chewing gum containing *L. reuteri* Prodentis. Consumed twice daily this was marketed to regulate *S.mutans* counts in the oral cavity. The average content of *L. reuteri* was  $10^8$  CFU/ml. However, the most suitable means of delivery and dosages of probiotics for various oral health purposes have not been defined.

3. **Tablet:** *L. acidophilus* contained in a tablet named Acilact was first clinically tested by pozharitskaia et al in 1994 and they found improved clinical parameters in periodontitis patients and shifts in local microflora towards gram positive cocci and lactobacilli. Later in the year 2002 Grudianov et al also carried out a clinical study where they obtained a probiotic mix in the tablet forms, viz Acilact and Bifidumbacterin and found normalization of micro flora and reduction of signs of gingivitis and periodontitis. In Russia, probiotics have been officially adopted as a preventive means for oral candidal infections and recommended to dental practitioners.<sup>28</sup>

#### **NATURAL PROBIOTIC SOURCES:**

To get the health benefits of probiotics, it's not necessary-to reach for a pill. There are a variety of foods that contain probiotics naturally - offering a supplement-free way to benefit from these good bacteria.

#### **FOODS THAT CONTAIN PROBIOTICS**

One of the most popular foods that contain probiotics is yogurt. When choosing yogurt as a source of probiotics, it's important to

pick one that contains live bacterial cultures. Not all of them do. Some yogurt is exposed to heat after the fermentation process is complete which destroy the good probiotic bacteria. To avoid eating a yogurt that's been heat treated, look for one that has a "live and active cultures" seal on it. This ensures that the yogurt contains at least 100 million cultures per gram. Not all yogurts are created equal from a probiotic standpoint. Other dairy sources of probiotics include aged, fermented cheese and kefir. Kefir is a milk product made by combining milk and kefir grains. It is easily digested and contains both pro biotic bacteria and yeast - which helps ward off *Candida*. Kefir can be found at most health food stores and natural food markets. An inexpensive source of probiotics that can be found at any grocery store is buttermilk, which can be used in place of regular milk on cereal or in smoothies. Using it in coffee or other hot liquids should be avoided since this could destroy the probiotic bacteria.

#### **REGULATION OF PROBIOTICS:**

There is a need for properly designed prospective clinical trials to evaluate probiotics for therapeutic uses. In general, characteristics desirable in such clinical studies include a high quality product and placebo, enrollment of a well-defined population (or population subset) of consenting subjects, broad sampling of host microbiota, use of validated testing instruments in determination of clear, clinically meaningful, endpoints, and adequate statistical power. It should be noted that placebo effects can be very strong in trials of probiotics, particularly with respect to products in the self care market, a category in which most current probiotic formulations fit.<sup>29</sup>

#### **CONCLUSION:**

Probiotics are gaining importance because of the innumerable benefits, from treating lactose intolerance, hypercholesterol problem, cardiac diseases and managing cardiac problems like atherosclerosis and arteriosclerosis. Today probiotics are

available in a variety of food products and supplements. With the current focus on disease prevention and the quest for optimal health at all ages, the probiotics market potential is enormous. Health professionals are in an ideal position to help and guide their patients toward appropriate prophylactic and therapeutic uses of probiotics that deliver the desired beneficial health effects. Finally, possibilities to genetically modify or engineer potential probiotic strains may offer all new vision.<sup>30</sup> In recent years, there has been an upsurge in research in probiotics as well as growing commercial interest in the probiotic food concept. This increased research has resulted in significant advances in our understanding and ability to characterize specific probiotic organisms, which has resulted in an increasing amount of evidence indicating health benefits by consumption of food containing probiotics.

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