Probiotics: The Forth Coming Oral Health Alternative Therapy

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Abstract

Probiotics, live cells having various health-promoting effects and benefits to the host, have been, and still are, under extensive investigations. These "friendly microorganisms" are usually isolated from the human intestine and traditionally-fermented foods of plant and animal origin. They are recognized for their positive effects on the intestinal flora among many other direct and indirect benefits eliciting better human body functioning. Studies are being conducted in the last decade o substantiate the real role played by these exotic microorganisms and to ascertain the safety of its use being of probiotic potential.

The concept of disease prevention, rather than treatment, is most appealing to health providers and clinical settings world-wide. Dentistry is not an exception; preventive oral medicine is a significant pillar in modern dental practices. In fact, a large proportion of every day dental care, in addition to clinical treatments, aims at preventing oral diseases, including caries, gingivitis, periodontitis and halitosis. Based on varying results of so many clinical trials using different types and formulas of experimental oral probiotics and to shed some light on the questionable role and effectiveness of probiotics on the prevention and treatment of oral diseases, this mini review is presented. We believe that exploring the possible mechanisms of action of probiotic bacteria in the oral cavity and identifying specific potential uses of probiotics in preventive dentistry and stomatology is eminent and needs further investigations pertaining to developing a safe, efficient and reliable general and perhaps designer oral probiotics..

Keywords: Probiotics, Oral health, Microbiology, Preventive dentistry.

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Introduction

The word "Probiotics" was originally derived from the Greek "pro bios" meaning "for life" (Soccol *et al*, 2010). The currently agreed upon definition is "live microorganisms which, when taken in sufficient amounts, confer health benefits on the host" (FAO/WHO, 2001). The idea was first introduced by Nobel laureate Eli Metchinkoff in 1907. He recommended the use of soured milk fermented by "Bulgarian Bacillus" for intestinal, kidney and skin problems (Metchinkoff, 1907). It was not until 1953 that Weiner Kollath, a german scientist, used the term "probiotika" to refer to "active substances

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essential for healthy development of life" (Guarner *et al*, 2005). (Lilly and Stillwell 1965) later took the word "probiotic" to be the antonym of "antibiotic" and defined it as "a substance produced by one microorganism stimulating the growth of another microorganism".

The most commonly employed probiotic bacterial strains are members of the genera *Lactobacillus* and *Bifidobacterium* (Holzapfel *et al*, 1998). However, historically, *Lactobacillus* species found in the oral cavity were implicated in dental caries (Munson *et al*. 2004; Keller and Twetman, 2012; Karuppaiah *et al*, 2013). This is related to the fact that *lactobacilli* usually produce acids and lower the pH of their surrounding environment (Rodrigues *et al*, 2011; Sohi *et al*, 2011). The currently accepted models in cariology state that acids produced by cariogenic bacteria are the single most important cause for cavity progression (Grover and Luthra, 2011; Somat and Badet, 2013). Moreover, both genera are usually found in carious dentine and epidemiologic studies link them to dental caries (Munson *et al*. 2004).

Nevertheless, Keller and Twetman (2012) showed that there was no significant increase in the acidity of plaque after co-culture with selected probiotic strains. Furthermore, numerous reports have emerged in the recent years suggesting that these genera, in addition to several others under investigation, are actually useful in the prevention of oral disease **(**Sohi *et al*, 2011 Sugano, 2012, Tong *et al*, 2012; Shah et al, 2013**)**. Research results showed that the most commonly isolated *Lactobacillus* species from saliva include *Lactobacillus plantarum, Lactobacillus salivarius, Lactobacillu paracasei* and *Lactobacillu rhamnosus* (Hojo*et al*, 2007). *Bifidobacterium* species isolated from the oral cavity include (*B.) dentium, (B.)--- bifidum and (B). longum* (Beighton *et al.* 2008).

Mechanisms of Probiotic Effects in the Oral Cavity

Broadly speaking, probiotics are thought to produce their positive effects in the gut through one of three general approaches:

- Immediate antagonism to pathogenic microorganisms, whether through the production of antimicrobial substances, competitive exclusion and prevention of adhesion, or competition for nutrients.
- Immune modulation and stimulation of the immunity, through, for example, enhancement of the generation of dendritic cells.
- Metabolic effects, such as enzymatic the breakdown of lactose.

The mechanisms postulated for probiotic action in the oral cavity are probably analogous to those in the intestines (Hankioja, 2010). More specifically, it seems that local effects of the probiotic bacteria, rather than systemic, are the ones responsible for their actions in the oral cavity. In that regard, local colonization is considered crucial for the probiotic strains exert their effects (Ravn *et al*, 2012).

Probiotic bacterial strains are hypothesized to have direct and indirect interactions with the pathogenic strains in the oral cavity (Grover and Luthra, 2011). Direct interactions include prevention of protein binding of oral pathogens, competition for adhesion and production of chemicals that inhibit these pathogens.

On the other hand, indirect actions proposed include modulating both local and systemic immune functions, as well as other defense mechanisms such as barrier functions and regulation of permeability of mucosal lining.

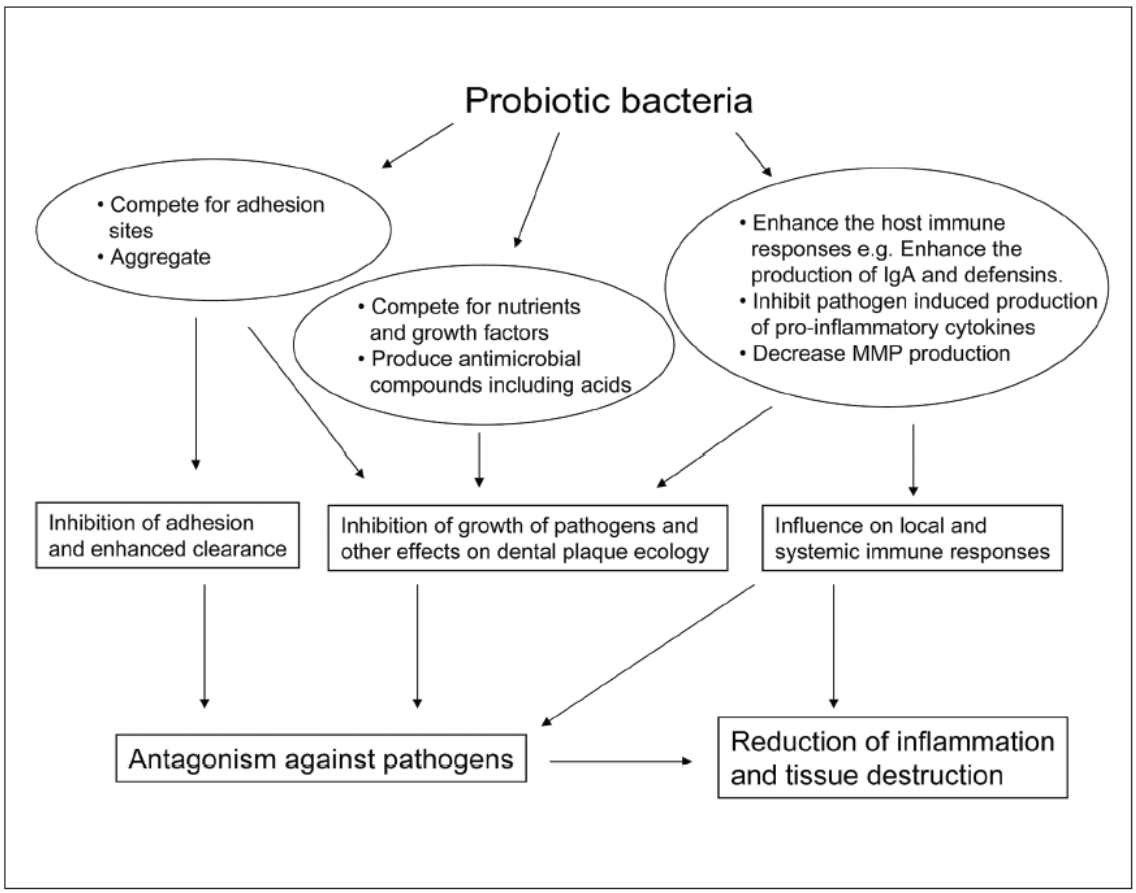

Fig. 1. Potential mechanisms by which probiotic bacteria could affect oral health (Hankioja, 2010)

Probiotics and Dental Caries

Dental caries are defined as localized destruction of the hard tissue of teeth through acidic by-products that result from bacterial fermentation of the carbohydrates present in food (Featherstone, 2008). The destruction in dental tissues is termed demineralization, and is a result of an imbalance between protective and pathogenic factors.

Dental plaque, or biofilm, is considered one of the most complex microbial communities in the human body, consisting of hundreds of bacterial species. The oral microflora is extremely variable, and especially so between healthy and diseased individuals (Belda-Ferre *et al*. 2012). The greater majority of these bacteria are non-pathogenic.

Some of the bacteria present in dental plaque, collectively designated as cariogenic, such as *Streptococcus mutans*, *Streptococcus sobrinus* and *Lactobacillus* species, produce weak organic acids which would result in a drop of local pH, leading to demineralization.

In the demineralization process, acids

penetrating through dental hard tissues would eventually lead to leaching out of calcium and phosphate ions. Should this continue, cavitation will follow. Tooth brushing is in fact a mechanical method to prevent these bacteria from adhering and therefore reduce their chances of producing acidic by products

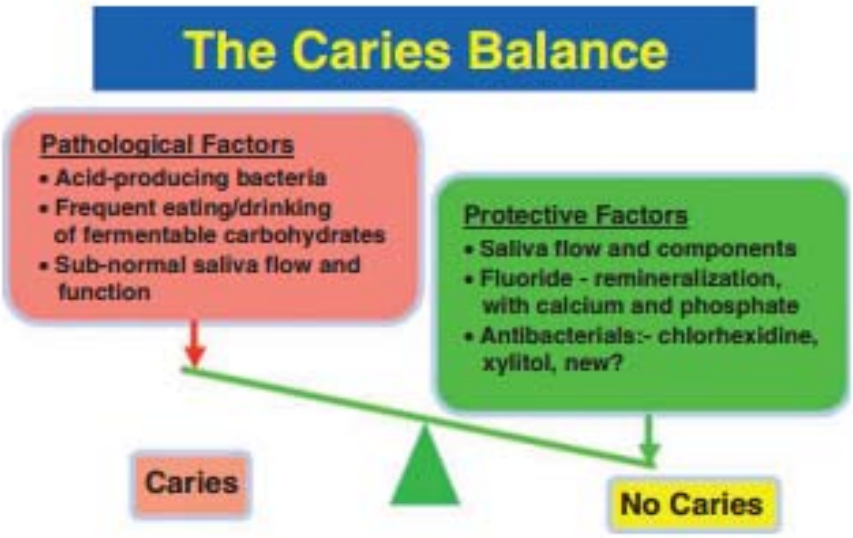

Fig. 2. The caries balance concept. (Featherstone, 2008)

The rationale behind the use of probiotic bacteria to prevent caries is fairly straight forward. If these bacteria would adhere to the tooth surfaces in the biofilm, they would prevent the attachment of cariogenic bacteria. Moreover, it was also suggested that these beneficial strains produce antimicrobial substances in the plaque.

Encouraging a shift in the oral microbial ecology has been suggested as a probiotic approach (He *et al*. 2009). The use of bacterial strains that naturally occur in the dental biofilm, such as *Streptococcus salivarius*, to inhibit *Streptococcus mutans* would both reduce caries and not pose a health risk issu (Wang *et al*. 2012).

Several bacterial strains were investigated for their probiotic effects against dental caries. A strain that was isolated from the oral cavity of caries-free individuals, called *Streptococcus oligofermentans*, was found to convert lactic acid to Hydrogen peroxide and therefore, inhibit the growth of *S. mutans (*Tong *et al. 2012)*. Also, a variant of *Streptococcus rattus*, deficient in lactate dehydrogenase, was reported to compete with *S. mutans* for its habitat on enamel and was, therefore, suggested as a potential probiotic for caries prevention (Rodríguez-Lozano *et al*. 2012).

In a recent randomized, double-blinded, placebo-controlled clinical trial, administration of *Streptococcus salivarius* in 100 children who had active dental caries reduced plaque scores and *S. mutans* counts, indicating that regular intake of *S. salivarius* could have oral benefits (Burton *et al.* 2013). Another species with antagonistic effects against *S. mutans*is

Lactobacillus lactis. *In vitro* competition studies revealed that *L. lactis*showed more effective colonization of tooth surfaces and significantly less caries in comparison with *S. mutans*, suggesting a potential strategy exploiting the application of *L. lactis* in the oral cavity as anticariogenic (Tong, Zhou *et al*. 2012).

The more classical probiotic bacterial Strains, such as Bifidobacterium and lactobacillus species, were also investigated. In a double-blinded, randomized crossover trial, Caglar *et al* reported that salivary *S.mutans* counts significantly declined after consumption of ice-cream containing *Bifido bacterium lactis* (Caglar *et al*, 2008).

Lee *et al*. found that *Bifidobacterium adolescentis* and *Bifidobacterium longum* inhibited both *Streptococcus mutans* and *Streptococcus sobrinus*, both reported as being cariogenic (Lee *et al*, 2011). Several lactobacillus species, including *L. plantarum*, *L. rhamnosus, L. Casei*, *L. paracasei*and *L. salivarius*, were reported to inhibit oral cariogenic bacteria (Teanpaisan *et al*. 2011).

Lactobacillus paracasei was found to specifically co-aggregate *Streptococcus mutans* (Lang *et al*, 2010). This characteristic enabled *L.paracasei* to decrease *S.mutans* in the biofilm and lower caries scores in rats (Tanzer *et al*, 2010). Moreover, *L.paracasei* significantly reduced salivary *S.mutans* in a double-blinded, randomized, placebo-controlled clinical trial (Chuang *et al*. 2010).

Drinking milk supplemented with *Lactobacillus rhamnosus* was shown to reverse primary root caries lesions in older adults (Petersson *et al*, 2011). Also, *Lactobacillus acidophilus* was reported to inhibit the adhesion of oral *S. mutans*on tooth surfaces (Tahmourespour and Kermanshahi, 2011).

Probiotics and Periodontal Disease

The periodontium is the supporting tissue for teeth. Periodontal diseases are comprised of two main types-gingivitis and periodontitis. Gingivitis is the inflammation of the gingiva, while periodontitis is a more destructive, irreversible disease that involves all of the periodontium, including the alveolar bone supporting the teeth. Around 500 species inhabit the periodontal pocket (Nayak *et al*, 2013). The principal pathogenic bacteria involved in periodontitis are *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerellaforsythia*, *Prevotella intermedia, Treponema denticola, Fusobacterium nucleatum* and *Eikenella corredens* (Zorca *et al*, 2011).

Periodontal disease, and analogous to the case of dental caries, is essentially a bacterial infection, and accumulated plaque is responsible for the initiation and progression of the disease. In case of imbalance between pathogenic and non-pathogenic bacteria, proportions of pathogenic microorganisms dominate (Gupta *et al*, 2011). These microorganisms release proteolytic enzymes that result in destruction of host tissues. The prevention strategies thought to be employed by probiotic strains against period onto pathogens are mainly through either inhibition of particular pathogens or by changing the host's immune responses (Elavarasu *et al*, 2012).

In vitro studies investigating the antimicrobial activity of 66 probiotic strains against *Porphyromonas gingivalis* and

Fusobacterium nucleatum, two known periodontopathogenic species, showed that all experimented probiotic strains except one were able to inhibit *F.nucleatum*, and 52 strains inhibited the growth of *P.gingivalis* (Somat and Badet, 2013).

The findings that *Lactobacillus salivarius*, when co-cultured with *Porphyromonas gingivalis*, caused almost complete eradication of that periodontal pathogen, and that it was highly susceptible to low acidity, indicated that it was possible to use this strain to produce a healthy microflora and prevent the colonization of periodentopathic bacteria, without the fear of it being cariogenic, as other *Lactobacillus* species are thought to be (Sugano *et al*, 2012).

Oral administration *L.salivarius* tablets significantly lowered the numbers of periodontal pathogenic bacteria in plaque and improved periodontal health in two double-blinded, placebo controlled, randomized clinical trials (Shimauchi *et al*, 2008 and Mayanagi *et al*, 2009). The use of probiotic lozenges containing *Lactobacillus brevis* was recently reported to significantly improve the periodontal health of subjects with aggressive periodontitis, a very destructive form of periodontitis (Shah *et al*. 2013)

Lactobacillus reuteri improved the gingival index and reduced bacterial plaque (Krasse *et al*, 2006) and when administered in chewing gum, caused a decline in gingival bleeding and inflammatory mediators (Twetman *et al*, 2009**).** However, a randomized clinical trial in which *L.reuteri* was administered in tablets showed a decrease in the numbers of periodontopathogenic bacteria, but with no reflection on the clinical outcome (Iniesta *et al*, 2012).

Harini and Anegundi reported that the use of a probiotic mouth rinse reduced plaque scores and improved the gingival indices in children. The results were comparable to those obtained from Chlorhexidine mouth wash, a well-established antibacterial which is considered the most effective antiplaque agent in clinical practice (Harini and Anegundi 2010).

Probiotics and Halitosis

Halitosis, or oral malodor, is not a disease per se. It can be the result of several diseases such as periodontitis, but is more often caused by a disturbed equilibrium in the oral microflora (Meurman and Stamatova 2007). Specifically, halitosis is the result of volatile sulfur compounds produced by oral anaerobic bacteria such as *F. nucleatum* (Bonifait *et al*, 2009).

Interestingly, one species seems to be absent from the oral cavities of halitosis-sufferers, *Streptococcus salivarius*. This species is usually isolated from the dorsal surfaces of tongues of people who do not have the problem of bad breath. More specifically, a strain of the *S.salivarius*, called K12, was shown to produce bacteriocin, which exhibits antimicrobial activity against many bacteria implicated in halitosis (Masdea *et al*, 2012). This strain has also been commercialized for that purpose.

Also, a bacterial species usually isolated from fermented food, *Weissellacibaria*, was found to reduce halitosis when used in mouth rinses, and was postulated to co-aggregate with *F.nucleatum*, thereby improving periodontal health as well (Kang *et al*, 2006).

Oral administration of tablets containing

the probiotic bacteria *Lactobacillus salivarius* was shown to reduce halitosis in an open label pilot trial (Iwamoto *et al*, 2010).Also, in a randomized, double-blinded, placebo controlled clinical trial, chewing gum containing *Lactobacillus reuteri* had beneficial effects on halitosis when compared to placebo (Keller *et al*, 2012).

Probiotics and *Candida*

Candida albicans is naturally-occurring yeast in the oral cavity. Although, usually suppressed by the action of bacteria, Candidal infections, candidiasis, can happen as a result of the disturbance of the normal balance in the oral microflora, most commonly in states of compromised immunity, use of broad spectrum antibiotics, older age or xerostomia.

While it seems very obvious that probiotics would be of great benefit in preventing candidiasis, very few animal studies and clinical trials have been done to confirm that. One explanation of this would be that candidal infections would happen in the case of immune system breach, and therefore, once evident, little can be done. However, prevention in high-risk patients is key. In one animal study, (Elahi *et al*. 2005) showed that when administered orally, *Lactobcillus acidophilus* was effective in enhancing clearance of *Candida albicans* from the oral cavities of mice (Elahi, *et al*. 2005).

In a randomized double-blinded, placebo controlled clinical trial, Hatakka *et al* showed that frequent consumption of cheese containing *Propionibacterium freu denreichii* subsp. *Shermanii* and *Lactobacillusr hamnosus* resulted in a 32% decrease in oral *Candida* in elderly subjects (Hatakka *et al*, 2007). Moreover, the authors noted a decrease in hyposalivation and discomfort in these subjects, even though they could not explain these outcomes.

Conclusion

The use of probiotics in oral medicine is emerging as an attractive field of research. There seems to be an increasing amount of evidence to support the notion that probiotic bacteria may actually have a role in preventive dentistry. In fact, several commercial products have already been marketed for that purpose.

However, it is important to understand that the level of salivary pathogens is a very poor indicator of the disease process of any of the conditions described here. In that sense, reduced levels of salivary bacteria does not equate disease control.

Furthermore, one should be careful when assessing the mode of application of the probiotic strain as well as its need for colonization in order to exert its effects. Here, one should bear in mind that mechanical plaque control practices, such as brushing and flossing, will surely remove both the “good” and the “bad” bacteria. Therefore, a hasty conclusion should not be made.

All in all, further work is needed to verify the encouraging benefits observed, as well as postulate and test for hypotheses to explain the mechanism underlying probiotic effects in the oral cavity.

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المحسنات الحيوية: المعالجة البديلة الواعدة لصحة الفم

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2- قسم الأحياء، كلية العلوم، الجامعة الأردنية.

الملخص

لقد كانت ولازالت المحسنات الحيوية مجالاً لدراسات مكثفة من حيث كونها خلايا كائنات حية دقيقة تحمل صفات عديدة جمة لصحة وفائدة العائل، وتعزل هذه الكائنات الدقيقة الرفيقة عادة من أمعاء الإنسان ومن المواد الغذائية حيوانية أو نباتية الأصل المخمرة تقليدياً وتعرف هذه المحسنات بأثرها الإيجابي على المحتوى الجرثومي للأمعاء من ضمن العديد من الفوائد الإيجابية المباشرة وغير المباشرة المؤدية لقيام الدسم بوظائفه بصورة أفضل. أجريت في العقد الأخير العديد من الدراسات لتمكين الدور الحقيقي الذي تلعبه هذه الكائنات الدقيقة المميزة إضافة للتأكد على دورها الحيوية. إن منع حدوث المرض مقابل المعالجة أمر جاذب للعاملين في الحقل الصحي بصورة عامة وعلوم رعاية الأسنان ليس استثناءً هنا حيث إن المعالجة الوقائية السنية تعد الأساس في الممارسة الحديثة وفي الواقع فإن جزءاً كبيراً من العناية السنية اليومية إضافة للمعالجة السريرية تهدف لمنع أمراض الفم شاملة التسوس والتهاب اللثة ومحيط السن وروائح الفم، وبناءً على نتائج مختلفة من الدراسات السريرية المتعلقة باستعمال أنواع وخلطات مختلفة من المحسنات الحيوية التجريبية ولإلقاء الضوء على الدور وفاعلية هذه المحسنات على منع ومعالجة أمراض الفم فإننا نقدم هذه المراجعة العلمية.

ونعتقد أن استكشاف الآليات الممكنة لعمل المحسنات الحيوية في المعالجة السنية الوقائية وعلوم الفم لأمر ذو أهمية قصوى ويحتاج لدراسات ضرورية لتطوير محسنات حيوية عامة ومتخصصة وتتمتع بأصول السلامة والفاعلية التي يعتمد عليها.

الكلمات الدالة: المحسنات الحيوية، المعالجة البديلة، صحة الفم.