International Journal of Dental Sciences
www.dentaljournal.in
E-ISSN: 2663-4708, P-ISSN: 2663-4694
Received Date: 12-11-2018 Accepted Date: 13-12-2018; Published: 13-01-2019
Volume 1; Issue 1; 2019; Page No. 14-17

Probiotics: A review

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Abstract
Dental caries is one of the most widespread and common infectious diseases of childhood. *Mutans Streptococci* (MS) has been implicated as a primary etiological agent of dental caries and plays a decisive role in development of dental caries. Therefore, preventing the proliferation of MS in the microflora of the oral cavity is an important step to decrease the incidence of dental caries. Different methods were applied to control dental caries but it continues to be the single most prevalent oral infectious disease worldwide. To overcome the shortcomings an alternative therapy, Probiotics may be used. Probiotics is defined as live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host. Various studies have come up in recent past exploring probiotics in fields of caries, periodontal diseases and few other areas and the results showed the beneficial effects of probiotics on oral health and on whole body in general. Given these recent developments, this paper reviews the background and conceptual framework of the use of these agents for improving oral health.

Keywords: probiotics, denal caries, mutans streptococci, live microorganisms

Introduction

Probiotics have emerged as a fascinating scientific area, health-related and commercial target for the last two decades. There is a long history of health claims concerning living microorganisms in food, particularly lactic acid bacteria. Commonly, most of the species ascribed as having probiotic properties belong to the genera *Lactobacillus* and *Bifidobacterium*. Those bacteria are generally regarded as safe because they can reside in the human safe body causing no harm and also they are involved in milk fermentation and food preservation and used as such since long ago [1].

History of probiotics

There is reference to sour milk or fermented cultures as far back as the Bible but Elie Metchnikoff is regarded as the grandfather of modern probiotics. He pioneered research in immunology leading to the discovery of intercellular digestion in a flatworm. For his work, he was awarded the Nobel Prize for medicine in 1908. He observated that the regular consumption of lactic acid bacteria in fermented dairy products was associated with enhanced health and longevity.

In his book The prolongation of life which was published in 1907, the rationale for the health benefit of lactic acid bacteria was provided. According to him few bacterial organisms present in the intestine were toxi that can contribute to illness and aging. Hence he suggested that it is possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes. To test the hypothesis on the health benefit of consuming lactic acid bacteria, he himself introduced in his diet sour milk fermented with the bacteria and found his health benefited [2]. With the discovery of antibiotics may have triggered abandoning Metchnikoff's concept was abandoned.

Definitions of probiotics

- Substances secreted by one organism which stimulate the growth of another. [Lilly and Stillwell 1965]
- Organisms and substances which contribute to intestinal microbial balance. [Parker 1974].
- Live microbial supplements which beneficially affects the host animal by improving its microbial balance. [Fuller 1989].
- First probiotic species the lactobacillus acidophilus was found by Hull in 1984.
- Holcombh identified bifidobacterium bifidum in 1991.

Canadian Research and Development Centre for Probiotics gave the definition of probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host". This is now the widely used and accepted definition as it embraces all applications of live microbes, not just those for intestinal benefits [21].

Micro-organisms commonly used as Probiotics

Lactobacillus: acidophilus, casei, plantarum, delbreukii sp, bulgaricus, reuteri, gasseri, fermentum Salivarius.

Lactobacilus rhamnosus strain GG, ATCC 53103 was originally isolated from the human intestinal flora in 1985 and named after the discoverers, Sherwood Gorbach and Barry Goldin.

Pediococcus Pentosaceus, Saccharomyces cerevisiae boulardii, Bifidobacterium, *Enterococcus Faecium*, Bacillus subtilis cereus, Aspergillus oryzae are the other commomly used probiotics [3].

Ideal properties of Probiotics

1. Probiotic should exert a beneficial effect on the host
2. Contain a large number of viable cells
3. Capable of surviving and metabolizing in the gut
4. Remain viable during storage and use have good sensory properties
5. Be isolated from the same species as its intended host.
6. It must not cause disease itself or otherwise predispose the host to other disease states by disrupting the ecosystem in which it resides.
7. Should possess a high degree of genetic stability.[1]

Probiotics vehicles[1]

1. A cultured probiotic organism added to a beverage or food (such as a fruit juice).
2. Inoculants into a milk-based food, Yogurt drink, cheese.
3. As concentrated and dried cells packaged as dietary supplements non-dairy products. Such as powder, capsule, gelatin tablets, Inoculated into prebiotic fibres.

General applications of Probiotics

1. Treatment and prevention of acute diarrhea and antibiotic-induced diarrhea.
2. Prevention of cow milk–induced food allergy in infants and young children.
3. Prevention of traveler's diarrhea, relapsing Clostridium difficile–induced colitis, and urinary tract infections.
4. Prevention of respiratory infections in children, dental caries, irritable bowel syndrome, and inflammatory bowel disease.

Areas of future interest for the application of probiotics include colon and bladder cancers, diabetes, and rheumatoid arthritis [4].

A randomized, double blind, placebo-controlled human clinical trial involving 30 healthy adults was performed to investigate the effect of a fermented product containing Lactobacillus species were used. The study showed no adverse effects and the strains were isolated from their feces at a relatively high level. Additionally, the oral administration of the probiotic strains led to an improvement of parameters such as the production of short chain fatty acids, the fecal moisture and the frequency and volume of the stools. As a result, the volunteers assigned to the probiotic group perceived a clear improvement in their intestinal habits [2].

Application of probiotics to oral health

Conference paper by Anderson MH, Shi W, A Probiotic Approach to Caries Management concluded that probiotic strategies are part of the continuing evolution of the treatment of oral infection that produces the clinical manifestations of dental caries. We are slowly moving away from the purely surgical approach to diagnose and treat the infection before it causes damage. The application of probiotic strategies may, in the not-distant future, provide the end of new cavities in treated populations [5]. The research on the oral clinical implications has mostly used probiotic lactobacilli that are known to enhance gut microbiota and the immunological response from the immunological parts of the intestine. However, the desired properties on probiotic bacteria that are aimed for use in the oral cavity may be different from those for their use in the lower parts of the GIT. It has been shown that good adhesion to intestinal mucus does not correlate with good adherence to oral surfaces [6].

Probiotic resistance to oral defence mechanisms

Saliva

Ingested probiotics are exposed first to saliva which mediates the contact with hard and soft oral tissues. As the first contact with the probiotic micro-organism occurs at mouth survival and resistance to environmental factors in the mouth are of paramount importance [7].

For an oral probiotic, it is desirable that the bacteria have the ability to survive in saliva and studies by Haukioja *et al*. have shown that different strains of probiotic bacteria have this ability [6].

Stamatova I conducted an in vitro studies testing probiotic survival in saliva have shown that Lactobacilli and Bifidobacterium strains cannot grow in saliva but remain viable after 24hrs of incubation. Lysozyme pretreatment has been observed to significantly reduce the adhesion of L. *rhamnosus* GG, L. *rhamnosusLc705* and L. *caseishirota*. However the adhesive properties of L. johnsonni Lal and B. Lactic 612 remain unaffected. These results emphasize the strain specific response to proteolytic enzyme and its feature needs to be considered when selected probiotics for the oral cavity.

For evaluating establishment of probiotics in the mouth co-aggregation with saliva is very important. Aggregation ability is related to cell adherence properties. The mechanisms of adhesion in lactobacilli involve hydrophobicity and surface charge, as well as specific carbohydrate and/or proteinaceous components.

Auto-aggregating strains shows cell surface hydrophobicity which isneeded for colonization. Organisms able to co-aggregate with other bacteria, for example pathogens, may have greater advantages over non-coaggregating organisms which are easily removed from the mouth. To emphasize the role of aggregation, recent results have shown that *L. salivarius*W2431 was unable to form a biofilm when incubated as a monoculture in a microplate model, whereas when the species was added simultaneously with the inoculum of other commensal oral microorganisms, it established itself irrespective of pH. Similar findings were observed with *L. plantarum*SA-1 and *L. rhamnosus* ATCC 7469 that failed to form substantial biofilms in mono-culture but biofilm mass increased when co-cultured with *A. naeslundii* [7].

Adhesion as a prerequisite for probiotic establishment

Bacterial ability for adhesion to the surface of teeth considered an important virulence factor. Therefore, prevention of bacterial adhesion helps in minimizing tooth decay [8]. The ability of probiotics to adhere to surfaces of the oral cavity can avoid or at

least reduce rapid exclusion from the environment. In the mouth adhesion is a necessary phenomenon in the microbe-saliva interactions [7].

A study by Haukioja and colleagues to assess the survival in saliva and adherence to oral surfaces of various probiotics used by the dairy industry (specifically, species of both Lactobacillus and Bifidobacterium) showed they varied widely in their capacity to adhere to the surface of teeth and oral mucosa. Moreover, it has been reported that people who have consumed yoghurt *containing* L. rhamnosus on a daily basis host this microorganism in the saliva for up to 3 weeks after discontinuing yoghurt consumption [6]. However, contradictory results were obtained by Yli- Knuuttila H, Snall J, Kari K, Meurman JH. and colleagues. They reported that a strain of L. rhamnosus colonized the oral cavity only temporarily and that consistent consumption of the probiotic would be necessary for long-term beneficial effects [9].

Probiotics: Mechanism of Action [10]

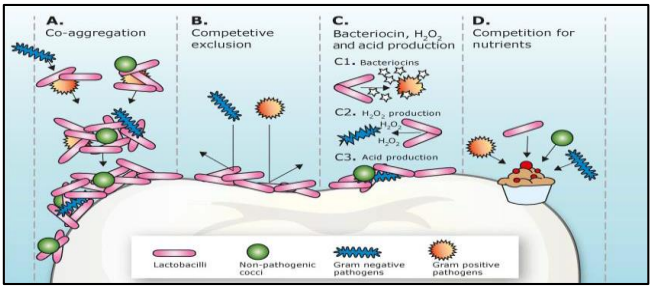

Fig 1

1. Prevention of adhesion of pathogens to host tissues [11, 12]
2. Improvement of intestinal barrier integrity and upregulation of mucin production [11]
3. 3.Killing or inhibition of growth of pathogens through production of bacteriocins or other products, such as acid or peroxide, which are antagonistic towards pathogenic bacteria.[13]
4. Involvement in binding of oral microorganisms to proteins (biofilm formation). Action on plaque formation and on its complex ecosystem by competing and intervening with bacteria-to-bacteria attachments. Involvement in metabolism of substrates (competing with oral microorganisms of substrates available) [13].

Theoretical adverse risks of probiotics

1. Transmigration potential.
2. Bacteremia and endocarditis potential.
3. Antibiotic-resistance transfer.
4. Gastrointestinal toxicity studies.

Safety of probiotics

Regular consumption of probiotic bacteria like Lactobacilli, bifidobacteria, and lactococci is considered as 'generally regarded as safe' by health authorities around the world. There are other probiotic organisms, such as *Enterococcus, Bacillus*, and other spore-forming bacteria, as well as streptococci, that are not GRAS but have been used as probiotics, their use is associated with increased risk of Bacteremia and endocarditis development. Human populations in which *Lactobacillus* GG has been studied and have shown evidence of safety include pregnant women, premature neonates, elderly individuals, children with rotavirus diarrhea, children and adults hospitalized with diarrhea, malnourished children from Peru, patients with rheumatoid arthritis, adults with Crohn's disease, adults with *Helicobacter pylori* infection, and adults with *Clostridiumdifficile*–associated diarrhea [14].

There are only few studies were reported in relation to safety of probiotics. A case was reported by Mackay *et al.* after a dental extraction in a 67 year old man with mitral regurgitation who was taking probiotic capsules daily. The patient developed Lactobacillus endocrditis. Lactobacilli have a long history of safe use in foods and dairy products. There is a natural association of lactobacilli with human flora, and lactobacilli are found in animals as well as plants. Rarely, lactic acid bacilli will cause infection in humans, which has manifested as either bacteremia or endocarditis, particularly in immunocompromised hosts [14, 15].

Genetically engineered probiotics

Genetic modification of probiotics has been undertaken to increase certain physiologic or immunologic properties within the organism and to use the probiotic as a mucosal delivery system or a vaccine vector. The use of these genetically engineered products has been quite limited to date [15].

Steps to monitor safety of probiotics

Safety of probiotics as they are introduced and increasingly used around the world should be monitored regularly. A population-based surveillance for the isolation of probiotic bacteria from patients with infection should be done. There should be knowledge of the susceptibility profile for any strain used in clinical trials. Caution is necessary in any trial of probiotics, concern about toxicity should not preclude their study. Rather, each study should be evaluated on a case-by-case basis, examining the risk benefit and potential toxicity. Caution might be warranted among those with immune compromise, premature infants, those with short bowel syndrome, those with central venous catheters, elderly patients, and those with cardiac valvedisease [15].

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Competence stimulating peptide approach to achieve probiotic effects

Several pathogenic properties of *S. mutans* are regulated by quorum sensing mechanism involving Competence Stimulating

Peptide (CSP) as the signaling molecule. With addition of a high concentration of CSP signaling events of *S. mutans* can be changed and the death of the bacteria induced thus exhibiting a potential beneficial effect against dental caries [3].

Targeted antimicrobial therapy via a novel STAMP technology

According to Eckert *et al*. with the exception of a limited number of pathogens, the majority of indigenous oral microorganisms are benign or beneficial. Indiscriminate killing of all microbes by these conventional antimicrobials disrupts the ecological balance of the indigenous microbiota with unknown clinical consequences. These investigators formulated a new class of antimicrobials called Specifically Targeted Anti-Microbial Peptides (STAMPs).

A "Stamp" is a fusion peptide with two moieties

- A killing moiety made of a nonspecific antimicrobial peptide
- A targeting moiety containing a spp. specific binding peptide.

The targeting moiety provides specific binding to a selected pathogen and facilitates the targeted delivery of an attached antimicrobial peptide [3].

Conclusions

The currently available literature is not sufficient to recommend probiotics but neither exclude the possibility that probiotic bacteria interfere with the oral biofilm. Any clinical recommendation would be premature. Large-scale clinical studies are still lacking.

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