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PROBIOTICS AND PREBIOTICS IN PERIODONTICS

Dental Science

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ABSTRACT

Over the years it has been evident that bacteria play an important role in various functions such as for the development and control of the immune system, metabolism of macronutrients, synthesis of vitamins, energy balance as well as defense of their territory against pathogenic bacteria. Probiotics are dietary supplements that contain potentially beneficial bacteria which help in stimulating beneficial flora while suppressing pathogens which initiates and spreads diseases. They are administered in different quantities that allow for colonization of the colon and mainly include Lactobacillus sps. and the Bifidobacterium sps. Probiotics have shown encouraging results in the control of chronic diseases such as gingivitis, periodontitis, dental caries and recurrent problems like halitosis and candida infections. Prebiotics are components of food that are not easily digested by humans which promote the growth and proliferation of beneficial bacteria in the digestive system. This article reviews the use of probiotics/prebiotics for the prevention of various oral diseases as well as the risks associated with their prolonged use. With the development of increased resistance to antibiotics, probiotics may provide a promising area in the field of research in oral health.

KEYWORDS

probiotics, prebiotics, Lactobacillus, Bifidobacterium, periodontitis

INTRODUCTION

A diverse population including 700–1000 species of bacteria are estimated to be present in the oral cavity spreading over the gingiva, inner cheeks, tongue, teeth, palate and tonsil. The oral cavity also accommodates various viruses and fungi in addition to these bacteria. It has been proposed that oral resident bacteria are an important factor influencing oral health in addition to age, health, life style and nutritional status of an individual [1].

Probiotic—"For life".
Probiotics—"Good microbes and bacteria".
Prebiotics—"Foods that feed good microbes and bacteria".

DEFINITION

According to the World Health Organization (WHO) and Food and Agriculture Organization (FAO) (2001), probiotics can be defined as "live microorganisms which when administered in adequate amount in food or as dietery supplement confer a health benefit on the host" [2]. Their mechanism of action is by increasing the number of beneficial microflora, competing with pathogenic species to inhibit their growth and multiplication and preventing further occurrence of a disease [3]. Oral administration of probiotic may also play an important role in modulating mucosal immunity in the oral cavity [4]. They help in combating various factors concerned with inadvertent use of antibiotics and antimicrobial resistance [5]

Prebiotics can be defined as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" [6]. They are selectively fermented ingredients that bring about specific changes in the composition and activity of microflora in the GIT which results in beneficial effects on the health and wellbeing of the host. A prebiotic will be effective only if it escapes digestion in the upper GIT so that it can be released in the lower tract and utilized by beneficial microorganisms in the colon mainly Bifidobacteria and Lactobacillus [7].

The effect of prebiotics mainly depends on the solubility, distribution, branching, length of the chains of molecules and through the metabolism of bacteria they promote. They have been found to be capable of altering the composition of intestinal microflora towards more protective intestinal bacteria and thereby altering the systemic and mucosal immune responses of the host. They can also modify the luminal or systemic aspects of the host defense [8].

HISTORY

In 1877, Pasteur and Joubert noticed that growth of E. coli was probably supressed by the presence of anthrax bacilli in cocultures with common bacilli. In 1907, Elie Metchnikoff found out that the microorganism Lactobacillus bulgaricus normally contained in yoghurt was able to displace pathological intestinal microbiota [9]. Later Henry Tissur observed that children with diarrhea had low number of Bifidobacteria in their stools which were more in number in healthy children. Therefore, he proposed that these bacteria could be given in patients with diarrhea in order to restore a healthy gut flora. A German physician, Alfred Nissle, used an isolate of E. coli to treat chronic ulcerative colitis. In 1965, Lilly and Stillwell proposed probiotics as substances produced by microorganisms that encourage the growth of other microorganisms [10]. In 1989, Fuller described probiotics as live microbial feed supplement that beneficially influences the host by improving its intestinal microbial balance [11].

Synbiotics

Promoting colonization of selective bacterial strains by providing them with nourishment competition has resulted in combined administration of probiotics with their preferred prebiotics giving rise to concept of synbiotics or eubiotics [12]. Synbiotics can be defined as mixtures of probiotics and prebiotics that beneficially affects the host by enhancing the implantation and survival of live microbial dietary supplements in the GIT of the host [13]. Therefore, the desired combination of prebiotics and probiotics helps in survival as well as facilitates inoculation of the administered probiotics. Prebiotics serve as a selective growth substrate for the probiotic strain during fermentation, periods of storage as well as during its passage through the gut. This combination confers live microbial dietary supplements and provides a congenial environment for their survival in gut flora [14]. Therefore, an additive and synergistic effect may be provided by synbiotics in improving oral health conditions.

Ideal requirement for a probiotic

- It should exert a beneficial effect on the host [15].
- It should be nontoxic and nonpathogenic.
- It should contain a large number of viable cells.
- It should be capable of survival and metabolizing in the gut.
- It should be able to adhere to salivary-coated surfaces.
- It should remain viable during storage and use.
- It should be isolated from the same species as its intended host.
- It should be alive when administered.
- It should contain a taxonomically defined microbe including genus, species and strain.
- It should have good sensory properties.
- It should withstand gastrointestinal juice and should be delivered in adequate dose through the end of shelf life.
- It should have the capacity to influence local metabolic activity.

Probiotics can be incorporated in products either as culture concentrate added to beverages or food such as fruit juice, inoculated into

prebiotic fibers; inoculants incorporated into milk-based foods such as milk, yoghurt, cheese, etc.; and as concentrated and dried cells packaged as non-dairy products such as powder, capsules and gelatin tablets [16].

MECHANISM OF ACTION (ORAL)

It prevents the binding of pathogens to the host tissue. Initially it competes with oral pathogens for adhesion site and later colonizes the oral surface. After their initial aggregation on the oral surface, probiotics compete with pathogens for nutrients and growth factors and also produce antimicrobial compounds including hydrogen peroxide, organic acids, carbon peroxide, low-molecular-weight antimicrobial substances, bacteriocins and adhesion inhibitors [17–24].

Stimulation and modulation of mucosal immune system which can be brought about by reducing the production of pro-inflammatory cytokines through actions on NFkB pathways, increasing production of anti-inflammatory cytokines such as IL-10 and host defense peptides such as β-defensin 2, enhancing IgA defenses and promoting dendritic cell maturation.

Inhibition of collagenases and reduction of inflammatory associated molecules and modulation of pro-inflammatory pathways induced by pathogens.

Enhancement of intestinal barrier integrity and improving mucin production.

Modulation of cell proliferation and apoptosis through cell responses, e.g.microbially produced short-chain fatty acids.

Interferes with plaque formation and ecosystem by competing and disturbing the bacteria to bacteria attachments and disrupts binding of microorganisms to proteins.

Competing and acquiring essential nutrients and substrates from invading pathogens and impairing their colonizing ability.

Inhibiting the expression of virulence factors by altering the gene expression programme of pathogens.

It has been identified to create antioxidants which has been found to nullify permitted electrons that are needed for the formation of calculus.

Systemic effects of probiotics

- Prevention of diarrhea caused by Clostridium difficile [25].
- Prevention of colon cancer.
- Reduction of liver toxicity.
- Reduction of blood cholesterol levels.
- Enhances and improves calcium absorption.
- Reduces progression of AIDS.
- Helps in regulation of immunity.

Prebiotics

They are non-digestible oligosaccharides that influence the proliferation of resident commensal bacteria which may provide beneficial effects on the host. Examples are pectin, lactulose, cellobiose, manno-oligosaccharides, fructo-oligosaccharides and galacto- oligosaccharides of which fructo-oligosaccharides is the most common form. Prebiotics are naturally available in fruits and vegetables like asparagus, garlic, tomato, onion wheat and bananas [26].

Mechanism of action

- Enhances and encourages the growth of commensal gut bacteria like Bifidobacteria and Lactobacilli.
- They have a direct effect on the host by stimulating expression of interferon –Y and interleukin IL-10, enhancement of IgA secretion and modulation of inflammatory response in pathogens.
- Cellobiose plays an important role in downregulating virulence factors of Listeria monocytogenes [27–29].

Microorganisms used as prebiotics

- Lactobacillus sps.: L. acidophilus, L. casei, L. gasseri, L. salivarious, L. reuteri, L. fermentum, L. bulgaricus.
- Bifidobacterium sps.: B. bifidum, B. breve, B. infantis, B. lactis, B. adolescentis, B. longum.
- Streptococcus sps: S. lactis, S thermophiles, S. salivarious, S. intermedius, S. cremoris.
- Saccharomyces sps.: S. boulardii.
- Miscellaneous: B. cereus, E. coli.

The most commonly used strains belong to the Lactobacillus and Bifidobacterium sps. That are frequently found in the oral cavity [30].These probiotic species were the first ones to be introduced into research (Lactobacillus acidophilus by Hull et al. in 1984 and Bifidobacterium bifidum by Holcombg et al. in 1991 [10]). Probiotic bacteria including Lactobacilli and Bifidobacteria are known to be good colonizers of the GIT, oral cavity and vagina in humans which widens the prospective of biotherapy [31]. Certain conditions have also shown the beneficial effects of species such as Saccharomyces species, Streptococci, Enterococci and E. coli [32].

Dysbiosis

Dysbiosis is a condition characterized by a change in the normal balance of microflora present in the GIT. A diseased dysfunctional or disordered microflora develops that alters immune and metabolic responses of the body. Dysbiosis can occur in the oral cavity and vagina [33]. The common causes include antibiotics, high-carbohydrate diet, food-borne pathogens, changes in lifestyle, stress, hypochlorhydria and achlorhydria. Consequences of dysbiosis includes halitosis, adrenal stress, diarrhea, candidiasis, leaky gut syndrome, colon and breast cancer [34].

Replacement therapy

This concept involves the use of live bacteria for the treatment of infectious disease. Otherwise known as “bacteriotherapy” or “bacterial interference”, this concept was put forward by Hillman and co-workers. This therapy involves inoculation of genetically engineered effector strain of S. mutans that will replace the cariogenic strain which helps to arrest caries and promote remineralization of tooth surfaces that have been remineralized but not cavitated. A genetically modified effector strain of S. mutans known as BCS3-L1 has been used in replacement therapy in order to prevent dental caries. Recombinant DNA technology has been used in BCS3-L1 to delete gene encoding lactate dehydrogenase rendering it incapable of producing lactic acid [35].

The following criteria's were used to differentiate it from prebiotics [36]:

- Effector strain is neither ingested nor applied directly at the site of infection.
- Essential colonization of the site by the effector strain.
- Should provide a long-term change in the indigenous microbiota and involves either displacing or preventing colonization of pathogen.
- Should have a minimal immunological impact.

Microbial populations associated with oral disease

Most common oral diseases which occur due to alteration in the balance of resident microflora are dental caries and periodontal disease. Probiotics should be a part of the oral biofilm and adhere to the dental tissues to fight with cariogenic and periodontopathogenic bacteria. An increase in acidogenic and acid-tolerating species such as S. mutans, Lactobacilli, Actinomyces, Bifidobacterium and Veillonella have been found to be associated with caries [37, 38].

In periodontitis, an increase in plaque mass and shift towards obligatory anaerobic and proteolytic bacteria can be observed. Damage to the host may be due to synergistic effects of subgingival biofilm and alteration in host response to the diverse bacterial populations in the oral cavity [39, 40].

Oral indications of probiotics

- Gingivitis
- Periodontitis
- Halitosis
- Caries management
- Candidiasis
- HIV
- Orthodontic therapy.

Probiotics in the management of gingivitis

The beneficial effects of L. reuteri in the management of gingivitis

were assessed by Krasse and colleagues. Patients with moderate to severe gingivitis were selected for the study. Scaling and root planning of the root surfaces was followed by administration of L. reuteri strains. After 2 weeks, clinical parameters were improved in the group-consuming probiotic chewing gums, and three plausible possibilities were suggested [41, 42].

L. reuteri has been found to secrete two bacteriocins, namely, reuterin and reutericyclin, that inhibit a wide variety of pathogens.
L. reuteri has strong ability to adhere to the host tissues, thereby competing with pathogenic bacteria.

L. reuteri has anti-inflammatory effects on the intestinal mucosa that leads to inhibition of secretion of pro-inflammatory cytokines [60].

Staab et al. noted reduction of MMP-3 elastase activity in 50 students with plaque-induced gingivitis after having probiotic milk for 8 weeks containing L. casei species [43].

Haukoja et al. reported that probiotic Lactobacilli such as L. casei and L. rhamnosus may influence oral ecology by specifically preventing the binding of other bacteria and modifying the protein composition of salivary pellicle. Ishwaka et al. reported that daily intake of L. salivarius isolated from healthy individuals leads to decrease in the number of black pigmented rods [44].

Probiotics in the management of periodontitis

Periodontitis is a multifactorial disease characterized by destruction of the hard and soft tissues by microbial colonization, inflammatory responses and adaptive immune responses. Periodontitis is mainly initiated by dental plaque, and probiotics has been shown to inhibit plaque formation. This is done by reducing the salivary ph, so that associated bacteria cannot form plaque [45]. Predominantly gramnegative anaerobic microorganisms such as P. gingivalis, T. forsythia, T. denticola, A. actinomycetemcomitans and E. corrodens have been most commonly associated with subgingival plaque and contribute to gingival inflammation. Various studies were conducted in order to evaluate the influence of probiotics in periodontitis patients. Riccia and colleagues studied the anti-inflammatory effects of L. brevis in a group ofchronic periodontitis patients. They also evaluated the antagonistic effects of L. brevis leading to reduced plaque formation and gingival index. According to the authors, anti-inflammatory effects of L. brevis could be attributed to its capacity to prevent nitric oxide production, thereby halting release of PGE2 and activation of MMPs induced by nitric oxide [46, 47]. During fermentation of milk, L. helveticus produces short peptides that acts on osteoblast and increases their activity in bone formation. These bioactive peptides thereby helps in reducing bone resorption associated with periodontitis [48].

Teughels et al. noted that subgingival application of bacterial mixture containing S. sanguis, S. mitis and S. salivarius following scaling and root planning significantly reduced the recolonization of P. gingivalis and P. intermedia [49].

Twetman et al. used chewing gums containing L. reuteri in 42 healthy patients and evaluated its effects on crevicular fluid volume, cytokine levels (IL-1β, IL-6, IL-10 and TNF-α) and bleeding on probing. They noted that crevicular fluid volume, cytokine levels of IL-6 and TNF-α and bleeding on probing were notably reduced [50]. Shimauchi et al. noted a beneficial effect of Lactobacillus salivarius WB21, contained in probiotic tablets in the treatment of periodontitis patients [51].

An in vitro study conducted by Ishiwaka et al. with L. salivarious isolated from healthy human showed inhibitory effect on P. intermedia, P. gingivalis and P. nigrescens after coculturing for 6–12 hours [44]. A study furnished by Vivekananda MR using L. reuteri ProDentis lozenges showed its plaque reserve, antimicrobial and anti-inflammatory effects. The study showed that probiotics can be a valuable tool in the management of periodontitis especially in cases where SRP is contraindicated [52].

Another therapeutic approach evaluated the combined application of L. casei and collagen in a periodontal dressing after SRP in periodontitis patients (Volozhin et al.). The results showed a combined reduction in major periodontal pathogens and extended remission time for more than 12 months [53]. A chewing gum containing combination of two strains of L. reuteri known as “Periobalance” was specifically selected for their synergistic properties in fighting periodontopatho gens and cariogenic bacteria. Users were instructed to use a lozenge everyday, either after a meal or in the evening after brushing to allow the probiotics to spread through the oral cavity and attach to various surfaces. Additional studies are however required to evaluate the long-term effects of this product.

A combination of S. salivarius, S. sanguis and S. mitis were found to be effective in inhibiting periodontal pathogen colonization by means of direct interbacterial interactions, interaction with epithelial cells and environmental conditioning.

Immunological benefits of probiotics Activate local macrophages to increase antigen presentation to B-lymphocytes and increase secretory IgA production both locally and systemically.

Modulate cytokine profiles.

Probiotics stimulate dendritic cells resulting in expression of Th-1/Th-2 response which regulates immunity. Probiotics enhance innate immunity and modulate pathogen-induced inflammation via toll-like receptors present on the dendritic cells. Intracellular pathogens are phagocytised by Th-1 response,while extracellular pathogens are neutralized by Th-2 response. The advantage is probiotics can mimic response similar to a pathogen but without causing periodontal destruction [36].

Dosage of probiotics

There is no consensus regarding the minimum number of microorganisms that should be ingested or contained in a probiotic in order to obtain the desired effect[37]. The most common carriers of probiotics are milk and milk products. Milk contains calcium lactate and other organic and inorganic compounds with known anticariogenic properties [38]. Probiotics are usually supplied along with prebiotics as powder, gelatin capsules or suspension.

The dosage for probiotics varies with respect to the product and strain, although many products deliver in the range of 1–10 billion CFU/dose. Some products have been shown to be effective at lower doses, while some require substantially higher doses in order to obtain the desired effect. Therefore, a formulation of approximately 108 probiotic bacteria per gram or mililitre (108/ml) with a daily intake of 1.5–2 dl per day is recommended dose [39].

Since probiotics are provided in the live form, they are more prone to die off during the storage state. Therefore, probiotics are manufactured in overages so that at the end of product shelf life, potency level does not go down. A permissible and specific range of colony-forming unit is essential to reduce the loss of efficacy between the production and end of shelf life as well minimize the toxic effects oft the product [40,41].

Adverse effects

As a consequence of increased probiotics supplementation in different food products, safety measures are a major concern. It has been anticipated that repeated use of probiotics over a long period of time will encourage an increased level of lactic acid bacteria in the oral cavity. Systemically, gas formation and blotting have been noted in individuals consuming prebiotics for longer periods. It has been found that manufacturers of probiotic food products sometimes add a lot of sugar to enhance the taste which can ultimately confer an oral health risk.

Any viable microorganisms like Lactobacillus is capable of causing bacteremia especially in patients with severe underlying pathologies or immunocompromised conditions which can range from symptomatic to septic shock-like symptoms. Some cases of bacteremia and fungemia has been reported in immunocompromised individuals as well as with chronic disease associated with long-term probiotic use [42–44]. It has been reported that an individual on L. rhamnosus developed Lactobacillus endocarditis following dental treatment [45]. Probiotic strains of Lactobacillus have also been found to cause bacteremia in patients with short-bowel syndrome, mainly due to altered gut integrity. Care should be taken to see that these products should not be given in individuals who are hypersensitive to any component of a probiotic-containing product.

Lactobacillus preparations are contraindicated in persons with a hypersensitivityto lactose or milk, and S. boulardii is contraindicated in patients with history of yeast allergy.

Lactic acid bacteria and Bifidobacterium associated with food fermentation as well as level of infection attributed are generally considered safe for oral consumption as part of foods and supplements for the healthy population and at levels normally used. Introduction of newly isolated probiotics in other disease conditions is only acceptable after approval by an independent ethical committee.

Future prospects

Probiotics can be used as passive local immunization tool for the management of dental caries. Early mucosal colonization in newborns with E. coli bacteria stimulates mucosal immune mechanism in our body to produce non-specific immunoglobulins as well as specific antibodies. Many research activities are aimed at the reduction of occurrence and severity of intraoral mucosal lesions, specifically aphthous ulcers [46].

In the field of oncology, patients undergoing chemotherapy are more for systemic infections due to disturbances in the oropharyngeal and gastrointestinal microflora, impaired mucosal barrier functions and immunosuppression. Studies in animals subjected to chemotherapy showed an improvement in food intake and gain in body weight with probiotic L. plantarum 299v. Advancement in this field has led to newer techniques like quantitative polymerase chain reaction procedures which could be useful for defined disease-associated deviations in gut microbiota. Genetically modified lactic acid bacteria have been proposed as medium to deliver vaccines in the gastrointestinal tract [47].

Various processing techniques, such as microencapsulation, bacterial coating and addition of prebiotic compounds with probiotic organisms, have been found to provide optimal delivery and survival of strains at the site of action. The Given Imaging's Pill Cam is a tiny capsule which when swallowed takes photographs of the mucosal tissues as it passes through the host. Therefore, molecular, nano-level, microbiological, biochemical immunological and engineering sciences can function as an effective tool in the clinical application of probiotic and prebiotic products in the near future [48].

CONCLUSION

The use of probiotics in dentistry is emerging with a lot of current research being carried out in this field. Biotechnological advancements in the field of probiotics advocate valuable opportunity to treat diseases in a noninvasive and natural way. The use of probiotics should not be a substitute for oral hygiene methods but rather an adjunct for better oral health care. Despite our increasing knowledge regarding host pathogen interaction, the role of beneficial or useful bacteria in preventing the emergence of pathogenic species and oral health remains obscure.

Therefore, there is a great need to evaluate the role of oral beneficial microbiota to initially identify the beneficial bacteria and to conduct large-scale studies on the usefulness of probiotics to improve oral and systemic health.

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