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THE LIVING THERAPEUTICS-GLADIATORS OF THE PERIODONTIUM

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ABSTRACT

Microbiota play a key role in various body functions, as well as in physiological, metabolic, and immunological processes, through different mechanisms such as the regulation of the development andor functions of different types of immune cells in the intestines. Evidence indicates that alteration in the gut microbiota can influence infectious and noninfectious diseases. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefits on the host. They have been used to directly modify the resident oral microbiome and proposed to modulate immune responses. In dentistry, probiotics have been employed as useful adjuncts for the reduction of caries development, suppressing oral Candida infection and controlling halitosis and periodontal disease. Traditional treatment modalities of periodontal disease include nonsurgical andor surgical management, with an emphasis on mechanical debridement. Currently many studies have been reported on probiotic therapy to prevent or treat gingivitis and periodontitis. Oral administration of probiotics is an effective adjunct in reducing pathogenic bacteria and improving clinical signs of disease. Probiotics may serve as adjunct or replacement therapy substitute antibiotics in managing human periodontal infections in future.

KEYWORDS: Probiotics, Oral Health, Bacterio Therapy & Periodontal Disease

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Original Article

INTRODUCTION

The multifarious ecosystem of human gastrointestinal micro flora consists of roughly 300–500 bacterial species. These microbiota implements several important functions in the human body such as enflaming undigested energy substrate, strengthening the immune system, protection against the growth of the pathogenic bacteria, promoting gut development, production of vitamins (such as Vitamin K and Biotin) and hormones. The equilibrium of our gut bacteria can be altered in many ways, with the slow process of isolating new antibiotics coupled with the emergence of resistant bacteria, it has become imperative to enhance the use of living therapeutics. Bacterio therapy and Probiosis (Microbial interference therapy**)** is an alternate and promising way to fight infections by using harmless bacteria to displace pathogenic microorganisms. This therapy is based on the Hippocratic quote “let food be thy medicine and medicine be thy food.” The assuring results of probiotics in oral and general health have been used in the treatment of Crohn’s disease, irritable bowel disorders, acute diarrhoea, urogenital infections and cancers. However, till date, their potential benefits in the treatment of oral pathologies have not been established. The main purpose of this review is to throw some light on the overall benefits of probiotics in general and oral and periodontal health.

History

Ukrainian bacteriologist and Nobel Laureate Ilya Metchnikoff (1908), established theory that senility is caused by poisoning of the body by the products of some of the bacteria. The term probiotic (Greek word), which literally means "for life" was originally proposed in 1960 by Lilley and Stillwell. In 1974, Mann and Spoering discovered benefits of fermented yogurt in reduction of blood serum cholesterol. Dairy products such as ker, koumiss, liben and curd were often used therapeutically before the existence of microorganism was recognized. The introduction of the first probiotic species *Lactobacillus acidophilus* and *Bifidobacteriumbifidum* into research were by Hull *et al*. in 1984 and by Holcombh *et al*. in 1991 respectively.

Definition

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 [1]. The other definitions of probiotics are given in Table 1 below.

Table 1: Showing Various Definitions of Probiotics

1953 Kollath	Active substances that are essential for a healthy development of life
1965 Lilley and Stillwell	Growth promoting factors produced by microorganisms
1971Sperti	Tissue extracts that stimulate microbial growth
1973 Fuji and Cook	Compounds that build resistance to infection in the host but do not inhibit the growth of microorganisms *invitro*
1996 Salminen	A live microbial culture or cultured diary product that beneficially influences the health and nutrition of the host
1997 Charteris *et al*.	Microorganism which, when, ingested, may have a positive effect in the prevention and treatment of a specific pathogenic condition
2001 UN/WHO/FAO	Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host
2002 Marteau et al	microbial preparations or components of microbial cells that have a beneficial effect on health and well-being
2004 Fuller	Preparation of viable micro organisms that is consumed by humans or other animals with the aim of inducing beneficial effects by qualitatively or quantitatively influencing their gut microflora and/or modifying their immune status

COMPOSITION AND DELIVERY SYSTEMS

Probiotics can be yeast, bacteria or moulds and they can contribute ominously to the health benefits when used in adequate quantity. They are obtainable as conventional pharmaceutical systems (beads, capsules and tablets) and non-conventional commercial formulations (cheese, yogurts, creams, chocolates and milk). By using probiotics in dairy products, acidic conditions can be neutralized. Some of the commercially available probiotics have been shown in Table 2. The promotion of the first probiotic specifically formulated to fight periodontal disease instigated as Sunstar (Etoy, Switzerland).Gum Perio Balance (a patented combination of 2 strains of *L. reuteri)* is marketed specially selected for their synergistic properties in fighting cariogenic bacteria and periodonto pathogens. Each dose of lozenge contains at least 2×10^8 living cells of *L.reuteriprodentis.*

Table 2: Commercially Available Probiotics

Worldwide Commercial Probiotic	
Microorganism Genus/Species	**Strain/Brand Name**
L. casei	Shirota (Yokult)
	DN-114001 (Immunitis)
L. reuteri	ATCC 55,730 (PROTECTIS)
	RC-14
Lactobacillus salivarius	WB21 (Wakamate D)
B. coagulans	BC30
Probiotics In India	
L. rhamnosus	GR-1
L. reuteri	RC-14
B. coagulans	SNZ-1969

L.casei: *Lactobacilluscasei, L.reuteri: Lactobacillus reuteri,*
B.coagulans: *Bifidobacteriumcoagulans,*
L.rhamnosus: *Lactobacillusrhamnosus*
L.acidophilus: *Lactobacillus acidophilus,*
B.coagulans: *Bacilluscoagulans*

To be called a living therapeutic, the candidate bacterial strain must be fully depicted and identified by their spectrum of resistance to antibiotics, their metabolic and hemolytic activities, their capacity to produce toxins, their infectious power in immune suppressed animal models and their side effects in humans according to internationally accepted methods, and its nomenclature corroborated by reference to the Approved Lists of Bacterial Names[2-3]. The most common probiotic strains belong to the genera *Lactobacillus* and *Bi fido bacterium (Acidogenic and aciduric)*. Some of the bacterial species, strains and their functions are given the Table 3. Ideal probiotic products should show the valuable effects on the host animal by being non-pathogenic, nontoxic, and should be capable of surviving and metabolizing in the gut environment by being low pH resistant, remain viable under storage for the duration, present as viable cells, preferably in large numbers, stable and capable of remaining viable for periods under storage and field conditions. For adequate amount of health benefits, a dose of 5 billion colony forming units (CFUs) a day (5×10^9 CFU/day) has been recommended, for at least 5 days.[4]

Table 3: Mechanism of Action of Probiotics in General Health

Bacterial Species	Bacterial Strains	Function
Lactobacillus species	*L. acidophilus acidophillus. Lactobacillus johnsonii, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus gasseri, L. rhamnous, L. brevis, L. casei* and *Lactobacillus reuteri. 0ver 100 species identified*	1. production of enzymes which digest and metabolise proteins and carbohydrates 2. Synthesis of vitamin B and vitamin K and facilitate the breakdown of bile salts. 3. Enhance innate and acquired immunity as well as cause inhibition of pro- inflammatory mediators. 4. *Lactobacillus paracasei*ssp. *paracasei* and *L. rhamnosus* had a high capacity to antag- onize important oral pathogens, including *Streptococcus mutans*a nd *Porphyromonasgingivalis*.[5] 5. Superior capacity to adhere to the surface of teeth and oral mucosa.
Weissellacibaria (formerly classified in the genus *Lactobacillus*),		1.Secretes hydrogen peroxide and bacterioc in 2. Coaggregate with *Fusobacteriumnucleatum* and adhere to epithelial cells. 3. Colonize the oral cavity and limit the proliferation of pathogenic bacteria[6-7]
Bifidobacterium	*B. bifidum, B. longum,*	1. Metabolisation of lactose, generation of lactic ions

	and *B. infantis.* *Over 30 species identified*	from lactic acid and vitamin synthesis. 2. Ferment indigestible carbohydrates and produce beneficial short-chain fatty acids 3. Reducing antibiotic associated diarrhoea and traveller's diarrhoea. They relieve constipation, alleviate inflammatory bowel disease and prevent DNA damage 4. May prevent or delay the onset of cancers[12-13]
Streptococcus thermophillus and Lactobacillus bulgaricus		1. Chief cultures used in yogurt production. 2. Metabolisation of lactose, improvement in lactose intolerance, and antimicrobial activity[9]
Streptococcus	*S. salivarius*K12	Ability to produce BLIS, which inhibit the ability of other undesirable bacteria to grow
Saccharomyces boulardii- non-colonising lactic acid producing yeast		1. Checks or treats antibiotic-associated diarrhoea, *C. difficile* related disorders, acute diarrhoea, traveller's diarrhoea in tube-fed patients. 2. Beneficial in AIDS-associated diarrhoea and in preventing relapse of Crohn's disease 3. Secrete proteases that breakdown bacterial enterotoxins and hinder their binding to intestinal receptors.

***L. acidophilus*:** *Lactobacillus acidophilus,* ***L. fermentum*:** *Lactobacillus fermentum,* ***L. plantarum*:** *Lactobacillus plantarum,* ***L. rhamnosus*:** *Lactobacillus rhamnosus,* ***L. salivarius*:** *Lactobacillus salivarius,* ***L. paracasei*:** *Lactobacillus paracasei,* ***L. gasseri*:** *Lactobacillus gasseri,* ***L. reuteri*:** *Lactobacillus reuteri,* ***B. bi dum*:** *Bi dobacterium bi dum,* ***B. longum*:** *Bi dobacteriumlongum,* ***B. infantis*:** *Bi dobacteriuminfantis,* ***B. coagulans*:** *Bacillus coagulans,* ***S. salivarius*:** *Streptococcus salivarius,* **BLIS:** Bacteriocin like inhibitory substances

ROLE OF PROBIOTICS IN GENERAL AND ORAL HEALTH

The gastrointestinal tract probiotics may prerequisite some superfluous properties when used as oral probiotics. Factors necessary for oral application of probiotics are, that the candidate microorganism should resist the oral environment conditions, boost defense mechanism and should be able to adhere to the saliva coated surface. They must be able to colonize and grow in the mouth thereby inhibiting oral pathogens. Generally they are used for prevention or treatment of gastrointestinal infections (Hatakka and Saxelin.2008) and for upper respiratory tract infections (Lehtoranta et al. 2014). *Lactobacillus rhamnosus* GG has been used meritoriously in preventing and treating rotavirus diarrhoea, atopic eczema and upper respiratory infections (Isolauri and Salminen 2008, Floch et al. 2011,Kumpu et al. 2012), and also have shown favourable effects on microbial aberrancies, inflammatory diseases of the GI tract, *Helicobacter pylori* infection, and other infectious diseases as well as treatment of urogenital infections. Various mechanisms of action of probiotics in general health are shown in Figure1 and Table 4 and in oral health is shown in Figure 2. Most probiotics are in dairy forms that contain high calcium, thereby possibly reducing demineralization of teeth. It is seems to act as biofilm to keep pathogens away and occupy a space that might otherwise be occupied by a pathogen. Some of the hypothetical probiotic effects are its direct interaction in the dental plaque formation, competing and intervening with bacterial attachments on its complex ecosystem and involvement in binding of oral microorganisms to proteins. Probiotic candidate species and their health benefits in the oral cavity (results from clinical trials) are shown in Table 5.

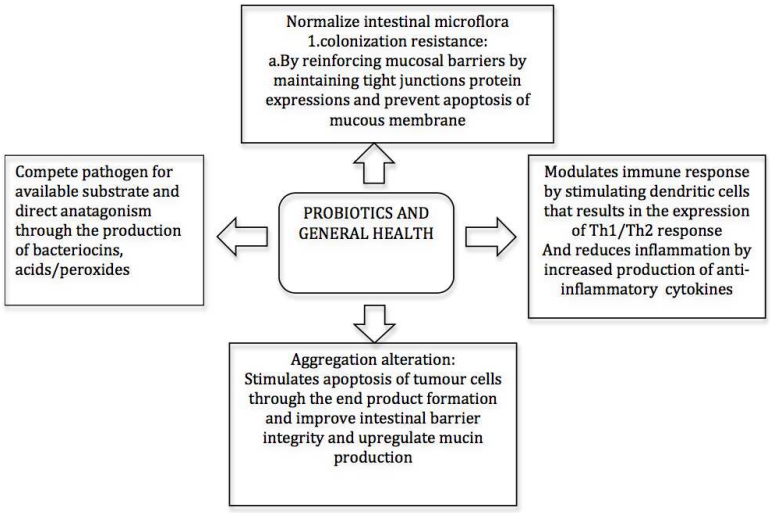

Figure 1

Table 4: Probiotics and Oral Health

Bacterial Genus/Species/Strains	Mode of Action	Available Forms of Administration	Reference
L reuteri ATCC55730	Salivary *s.mutans* reduced	Lozenges, straw and tablet	Caglar et al 2006, 2008[22]
L.rhamnosus GG, ATCC 53103	Highest level of reduction of s.mutans	Milk,cheese	Nase et al 2001[24]
Bifidobacterium DN-173 010	s.mutans,streptococci	yoghurt	Caglar et al 2005
L.reuteri	Reduction of gingivitis and plaque	Probiotic formulation	Krasse et al 2006[26]
L.caesi	Remission after treatment of chronic generalized periodontitis	Periodontal Dressings	Volozhin et al 2004[27]
L.rhamnosus GG(ATCC 53103),*L.rhamnosus* LC705	Reduction in growth of candida and positive effect on hyposalivation	cheese	Hatakka et al 2007[28]
Bifidobactrriumanimalis DN 173010	Alternative storage of avulsed teeth	Transport medium	Cagler 2015[22]

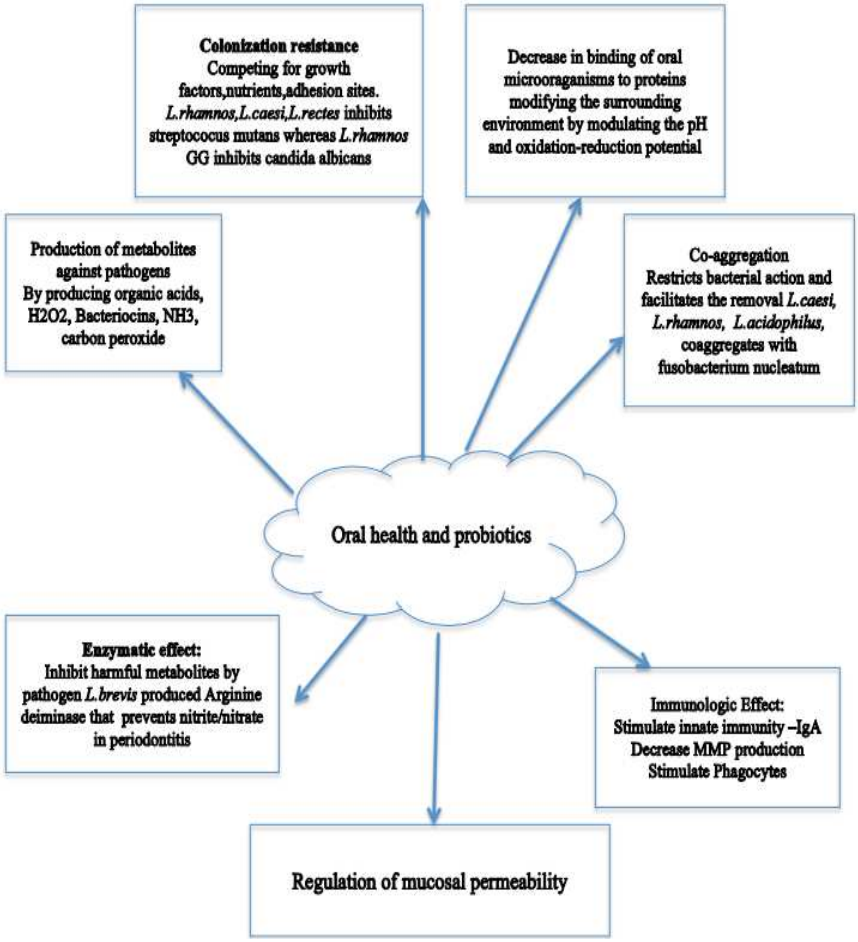

Figure 2

Table 5: Probiotics and Its Various Applications

Applications	Mechanism of Action	Studies
Dental caries:	*S.thermophilus* and *L.bulgaricus* have Bactericidal effect	Amitet al [29]
Halitosis	*W.cibaria* to inhibit the production of volatile sulphur compounds, hydrogen peroxide proliferation by *F.nucleatum.*	Kang et al[40]
Candidiasis	Reduction in anti-candida IgA. Possibly due to competition between the yeasts rather than by specific secretory immune response stimulation	Santos AL[19]
Orthodontic patients	Short-term daily consumption of fruit yogurt containing *Bifidobacteriumanimalis* subsp. *lactis* DN- 173010 may reduce the levels of mutans streptococci in saliva during orthodontic treatment with fixed appliances.	Sule Kavaloglu et al[21]
Lactose insufficiency	Microbial galactosidase in the (fermented) milk product, delayed gastrointestinal transit, positive effects on intestinal functions and colonic microflora, and reduced sensitivity to symptoms	De verse et al [30]

Allergic disease	Enhance intestinal permeability and reduced inflammation in the gut.	Sonia et al [31]
Anticholesterolaemic	Formation of certain tripeptides that are inhibitors of ACE (Angio-tension-converting enzyme)	Fulleria et al [41]
Atopic disease	Ability of lactobacilli to reverse increased intestinal permeability, enhance gut-specific IgA responses, promote gut barrier function through the restoration of normal levels of microbes, and enhance transforming growth factor-β and interleukin-10 production as well as cytokines that promote the production of IgE antibodies	Zuccoti et al [32]
HIV	Compete for nutrients and epithelial and mucosal adherence, inhibit epithelial invasion, counteract the inflammatory process by stabilizing and strengthening the gut microbiota responsible for the intestinal barrier integrity, prevent microbial translocation, lower mucosal and systemic inflammation, stimulate production of antimicrobial substances and intestinal immunoglobulin A responses to improve the immunological barrier function.	Lin Tao and colleagues (2008)[38]
Oral cancer	Interference with chromosomal and DNA damage	Haukioja A (2010)[25]

PROBIOTICS AND PERIODONTAL HEALTH

Periodontitis is a multifactorial disease affecting the soft and hard tissue and initiating an inflammatory response and immune response. *Porphyromonusgingivalis, Treponemadenticola, Tannerella forsythia* and *Aggregati bacteractinomycetemcomitans are* considered as key pathogens in the pathogenesis of periodontal disease. A dysbiotic oral microbiota plays a dynamic role in the pathogenesis by promoting chronic dys regulated inflammation. Probiotic bacterium helps in re-modelling the periodontal ecosystem by its property of adherence, co-aggregation with Fusobacterium, inhibition of A.a (Aggregaterbacteractinomycetumcomitans), P.gingivalis (Porphyromonousgingivalis) and P.intermedia (Prevotellaintermedia) thereby preventing plaque formation, production of lactic acid, hydrogen peroxide, bacteriocin or bacteriocin like substance, used to regularise immune response by boosting immunity and modulating pathogen induced inflammation via toll-like receptors regulated signalling pathway *L.rhamnosus and L.paracasei*, shows hydrophobicity which correlates with adhesive property. They prevent adherence of other bacteria by binding and degrading the salivary protein. Figure 3 shows the role of probiotics in periodontal health maintenance. More comprehensive ecological surveys using proven high quantity 16S rDNA sequencing platforms in the literature overcomes the limitation of the current understanding into the nature of community-wide changes exerted by the probiotic strains in the periodontal niches during treatment. Table 6 shows various probiotic strains from clinical trials. Concentration of lactoferrin decreased with the intake of probiotics along with PGE2, interferon –γ and MMP activity in saliva. Probiotic strains included in periodontal dressings at optimal concentration of 108 CFU/ml have been shown to diminish the periodontal pathogens[12]

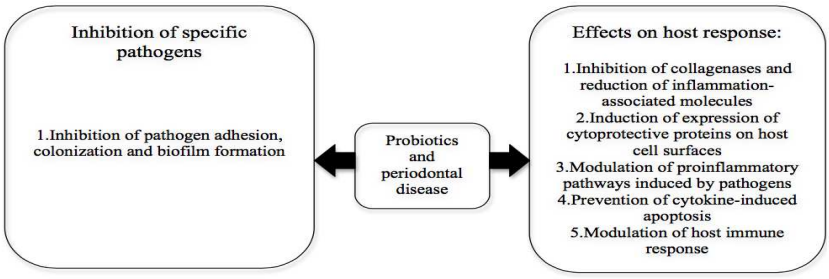

Figure 3: Probiotics and Periodontal Disease

Table 6: Probiotics and Periodontal Health Maintenance

Species/Strains	Mechanism of Action	Form of Administration	Reference
L.caesi	Periodontal microbiota is reduced and remission period is extended	Periodontal dressings	Volozhin et al 2004[27]
L.acidophilus	Shift in local microbiota towards gram positive cocci and lactobacilli	Tablet-Acilact	Puzharitskala et al 1994
*L.salivarius*wb21	Improvement of clinical parameters in smokers and non-smoker patients.	Tablet taken thrice daily	Shimouchi et al 2008
S.sanguis,S.salivarius	Inhibitory effect for *Aa* and its recolonization	Invitro effect on epithelial cells	Teughels et al 2007[39]

L.caesi-Lactobacillus caesei, L.acidophilus-Lactobacillus acidophilus, L.salivarius-Lactobacillus salivarius, S.sanguis-Streptococcus sanguis

PREBIOTIC CONCEPT

The prebiotic concept was introduced by Gibson and Roberfroid in1995. They are defined as the fermented ingredients that allow specific changes, both in the composition and in the activity of the gastrointestinal microflora that bestow benefits upon host wellbeing and health. In order to be effectual, a prebiotic must escape digestion in the upper gastrointestinal tract so that it can be released in the lower tract and used by beneficial microorganisms in the colon, mainly *Bifidobacteria* and *Lactobacilli*. The oligosaccharides, the fructo-oligosaccharide and galactooligosaccharide groups can be considered currently as prebiotics. They are naturally found in certain fruits such as bananas, asparagus, garlic, tomato, onion and wheat and are not destroyed when ingested in the body. They modify the composition of the intestinal microbiota towards more protective intestinal bacteria and subsequently alter systemic and mucosal immune responses of the host and are not affected by heat or bacteria. Synbiotics /Eubiotics are defined as mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbes in the form of dietary supplements in the gastrointestinal tract of the host (Gibson and Roberfroid, 1995). Some of the commonly used prebiotics is shown in the Table 7.

Table 7: Clinical Evidence of General Prebiotic Effectiveness

Prebiotic	Health Benefit	Type of Study	Duration of Prebiotic Intake	Reference
Oligosaccharides in a liquid formula	Improvement of the low-noise inflammatory process in elderly	Prospective-randomized, double-blind controlled study	12 weeks	Schiffrin et al 2007[37]
Psyllium	Effective in treatment Crohn's disease	Prospective open trial	13 months	Fujimori et al 2007[36]
Insoluble and soluble multifibre supplement	Decrease in acute phase response	Randomized prospective double blinded controlled clinical trial	48 hours	Karakan et al 2007[35]
Inulin, Linseed and soya fibre	Enhanced levels of carotenoids and antioxidative capacity in the plasma	Randomized parallel study	5 weeks	Seidel et al 2007[34]

Bacteriotherapy/Replacement Therapy

The use of probiotics in antibiotic resistance is termed microbial interference therapy/replacement therapy or bacterio therapy. Although both methods use live bacteria for the inhibition or management of infectious disease, there are a few differences. The difference between bacterio therapy and replacement therapy is given in Table 8.

Table 8: Difference between Replacement Therapy and Probiotic Therapy

Replacement Therapy	Probiotic Therapy
Effector strain is not ingested, rather is applied directly on the site of infection.	Probiotics are generally dispensed as dietary supplements.
Involves dramatic and long-term change in the indigenous microbiota.	Hardly a dramatic and long-term change in the microbiota.
Colonization of the site by the effector strain is crucial.	Probiotics are able to exert a beneficial effect even without permanently colonizing the site.
Effector strain is not ingested, rather is applied directly on the site of infection.	Probiotics are generally dispensed as dietary supplements.

Safety Measures

Due to increased combination of live probiotic bacterial supplementation of different food products, safety measures are a major concern. Probiotics are often considered as dietary supplements rather than as pharmaceutical or biological products. The results from antibiotic susceptibility tests claim that the tet- (W) and tet- (S) genes in some probiotic *Lactobacilli* and *Bifidobacteria*strains are responsible for sulfamethoxazole, gentamycine, polymyxin B and tetracycline resistance.[13] Bacteraemia and fungaemia associated with probiotic use have been reported in those suffering from chronic disease.[14] Reports developing Lactobacillus endocarditis following dental treatment in Finland was reported due to prior consumption of *L. rhamnosus* in a probiotic preparation.[15]

Future Application

Wider application of probiotics in general health can increase its demand. In future, probiotics application can be extended to cure many health related problems. The critical steps in wider application will be to make products available that are safer and clinically proven in a specific formulation, which should be easily accessible to physician and consumers. The term “Patho-Biotechnology” was introduced by Sletor and Hill. It has three basic approaches towards the use of attenuated bacterial pathogens as vaccine, isolation and purification of pathogen specific immunogenic protein for direct application and equipping probiotics bacteria with genetic element necessary to overcome stress outside host, inside host and antagonize invading pathogens.The modified probiotic strains designed for such specific functions are termed as “designer probiotics”. Sporolac (*Sporolactobacilli)* is a commonly used probiotic in India. And *Bacillus mesentricus* is used as an alternative to B-complex.[16]Capsules coated with biosensors that can ascertain the favourable conditions for release of probiotic contents are on the horizon in macromolecular research. Genetically modified lactic acid bacteria have been proposed as a vehicle to deliver vaccines in the gastro- intestinal tract.[17] Probiotics are already administered as passive local immunization vehicles against dental caries in oral immunology.[18]

CONCLUSIONS

In this new era of life, where creation of a harmonious relationship with our environment is well within the realm of possibility, the use of probiotics (live bacteria) that have beneficial characteristics is the perfect solution to microbial disharmony afflicting the human population. The development of data on oral living therapeutics and their ability to

transform the immune response in the oral cavity has been suggested to be a topic of research in the future. Therefore, more methodical in vitro and in vivo studies are needed to substantiate collaborations of probiotic species, with periodontal pathogens in oral biofilms, also to understand its effects on periodontal host tissue interactions. Thereafter, appropriately controlled, randomized, long-term clinical trials and histological studies have to be performed using the most promising strains to authenticate the use of probiotics in oral health.

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