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PROBIOTICS AND THEIR ROLE IN HUMAN HEALTH

Sandhya Priya Parthasaradhi[1]*, Nagammagari Kusuma[2] and Mohan Pakala[3]

[1]Lecturer, Dept. of Microbiology, S.V. Arts College, Tirupati- 517502, Andhra Pradesh, India.

[2]Student, Dept. for Sustainable Development and Ecological Transition, Italy.

[3]Lecturer, Dept. of Biotechnology, S.V. Arts College, Tirupati- 517502, Andhra Pradesh, India.

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***Corresponding Author**
Sandhya Priya Parthasaradhi
Lecturer, Dept. of Microbiology, S.V. Arts College, Tirupati- 517502, Andhra Pradesh, India.

ABSTRACT

The objective of this comprehensive review is to study the probiotics and their role in human health. Probiotics are beneficial organisms normally found in the human gastrointestinal tract. These organisms work through several interrelated mechanisms and ensure to promote health at molecular level. They conquer potentially harmful organisms in intestine, reduces the risk of infection or toxin-mediated diseases. They regulate immune responses against infectious organisms and help to suppress inflammation. Probiotics promote the function of intestinal inner lining and enhances its ability to act as a barrier for the entry of potentially dangerous organisms and chemicals. These actions depend on the biochemical signals between intestinal bacteria and human cells. They are widely used in the production of different dairy and fermented dairy products. Due to their remarkable role, probiotics are now emerged as vital category of supplements and found in conventional, medicinal and dietary products etc.

KEYWORDS: Probiotics, Colonization, Adhesion, Colonization resistance, Gut microbiota.

1. INTRODUCTION

1.1 Definition of Probiotics

Probiotics are beneficial organisms normally found in the human gastrointestinal tract which help to maintain healthy gut, so called "good" or "helpful" bacteria. In Latin, the preposition “pro,” which means “for” and in Greek “biotic” means “bios” or “life”.[1] Therefore, these are

"live microorganisms that give health benefits to the host when administered in adequate amounts.[2]

1.2 History of Probiotics

The history of probiotics was well known by Greeks and Romans. For consumption, they used cheese and fermented products. In mid-1990s, people have wanted to know more about probiotics and their health benefits. The climatic conditions during that ancient time led to the development of different types of traditional soured milk or cultured dairy products like Kefir, Koumiss, karnemelk, Leben and Dahi.

Elie Metchnikoff (1907, 2004) proposed that in the large bowel putrefactive or proteolytic bacteria like *Clostridia* produce toxins such as phenols, indole and ammonia.[3] These toxins cause "intestinal auto-intoxication," which lead to the aging process.[4] Milk fermented with lactic-acid bacteria lowers the pH due to the fermentation of lactose which inhibits the proteolytic bacterial growth.

Probiotics are considered to be "live microorganisms that give health benefits to the host when administered in adequate amounts.[2] "Probiotics are also defined as beneficial microbial supplements which enhance microbial balance in different parts of the human and animal species. They increase host immune system and protect from viral infections, chemotherapy, hypocholesterolemia properties, food borne diseases, mutagenic and carcinogenic infections *etc.* The term "probiotic" originally known as microorganisms which show effects on other microorganisms *i.e.*, substances secreted by one microorganism stimulated the growth of another microorganism by Lilly and Stillwell.[5] Parker defined the concept as, "organisms and substances that have a beneficial effect on the host by contributing intestinal microbial balance".[6]

Fuller described probiotics as a "live microbial supplement which positively affects the host animal by enhancing intestinal microbial balance" and mentioned two important points *i.e.*, the viable nature of probiotics and the ability to help with intestinal balance.[7] In the following decades, intestinal *Lactobacillus* species with suspected health beneficial properties have been introduced as probiotics, including *Lactobacillus rhamnosus*, *Lactobacillus casei*, and *Lactobacillus johnsonii*.[8]

1.3 Identification of Probiotic bacteria

Henry Tissier isolated *Bacillus bifidus communis* from a breast-fed infant (1900), and was later renamed to the genus *Bifidobacterium.*[9] He found that in gut flora of breast-fed babies *Bifidobacteria* are dominant and by treating diarrhea in infants with *Bifidobacteria* observed clinical benefits. Bifidobacterial displacement of the proteolytic bacteria causing the disease was the claimed result. In 1917, during shigellosis outbreak, Alfred Nissle isolated a strain of *Escherichia coli* from the feces of a soldier who was not affected by the disease.[10] Nissle used the *E. coli* Nissle 1917 strain in acute gastrointestinal infectious like salmonellosis and shigellosis. As antibiotics were not available in that period, different methods were used in treating infectious diseases.

1.4 Properties of Probiotic Strains

- Provides efficient health characteristics.
- Adherence to the mucosal epithelial cells leads to the improvement and protection of intestinal ecology.[11]
- Shall not attack host intestinal tissues.
- Shall be capable to stay alive during transportation in the gastro intestinal tract.
- Shall be free of different side effects.
- Shall maintain stability during shelf life of usage
- Shall be with appropriate quantity of viable cells to confer health benefit.

1.5 Mechanism of action of probiotics

Oelschlaeger stated that the probiotics effects may be classified in three ways.[12]

(i) Probiotics might be able to modulate the innate and the acquired immune system. This mode of action is for the prevention and treatment of infectious diseases like (chronic) inflammation of the digestive tract or parts thereof. Probiotic action could also be important for the eradication of neoplastic host cells.

(ii) Probiotics have a direct effect on commensal and pathogenic microorganisms. This principle is for the prevention and treatment of infections and reestablishment of the microbial equilibrium in the gut.

(iii) Lastly, probiotic effects may be established on actions affecting microbial products like toxins and host products, *e.g.,* bile salts and food ingredients. These activities may contribute to the inactivation of toxins and the detoxification of host and food components in the intestine. The same author also specified that the probiotic

effectiveness depends on its metabolic properties, the molecules presented at its surface or on the components secreted and also integral parts such as DNA or peptidoglycan. The individual combination of such properties can be useful to determine a specific probiotic action and as a result it's effective application for the prevention and/or treatment of a certain disease.

1.6 Probiotic Mechanisms

- Enhancement of epithelial barrier
- Increased adhesion to intestinal mucosa
- Inhibition of pathogen adhesion
- Competitive exclusion of pathogenic microorganisms
- Production of anti-microbial substances like lactic acid, acetic acid and propionic acid lower the pH and inhibit the growth of pathogenic bacteria
- Modulation of immune system
- Modification in activity of other bacteria, affecting the "ecosystem" of the gut.[13 & 14]

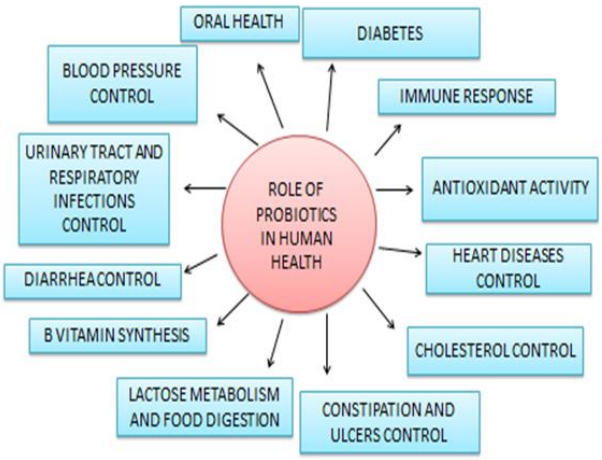

Fig. 1: Role of probiotics in human health.

Probiotics have applications in many different fields. They play a major role in Human Health, Food and Beverages, Animal Feed and Aquaculture *etc.*[15]

2. Significant Probiotic Bacteria

Lactobacillus and *Bifidobacterium* are the main probiotic groups.[2]

In living organisms, the common probiotic organisms are *Lactobacillus acidophilus, L. salivarius, Bifidobacteria, L. crispatus, L. brevis, L. casei, L. delbrueckii, L. fermentum, L. gasseri, L. johnsonii, L. paracasei, L. plantarum,L. rhamnosus, L. reuteri, L. ruminis, L. sakei, L.*

vaginalis, L. curvatus and *L. fructovorans*.

2.1 Probiotic bacteria

Probiotic bacteria are defined as "live microorganisms that give health benefits to the host when administered in adequate amounts".[2] The predominant probiotics are *Lactobacillus*, *Bifidobacterium* and *Saccharomyces boulardii*. *Lactobacillus* and *Bifidobacterium* are Gram-positive, rod shaped, obligated facultative anaerobes whereas *S boulardii* is yeast[14], but products having strains from other genera such as *Propionibacterium, Enterococcus* and *Escherichia*.[16] Probiotics signify over 65% of the functional food market.[17] In the year, 2008 more than 2000 probiotic products were launched.[18] Probiotics are considered as "helpful bacteria" to humans. Traditionally, probiotics were yields of the pharmaceutical industry, but currently they belong to the health food sector and once again making Hippocrates statement "Let food is your medicine".

2.2 Lactobacillus

Lactobacillus, also known as Doderlein's *Bacillus*, they belong to the phylum Actino bacteria, Gram- positive, rod shaped facultative anaerobic or micro aerophilic bacteria with a high percentage of guanine and cytosine bases in their genome. Taxonomically, the *Lactobacillus* genus is diverse and it contains at least twelve separately phylogenetic groups. In *Lactobacillus* genus more than 150 species have been named, which were isolated from human and animal GITs and mucous membranes and from plant surfaces.

Lactobacillus species are the most widely used probiotics in a large variety of food products throughout the world.[19] Some strains are used in the fermented dairy products preparation and in the production of sauerkraut, pickles, and silage. Propionic bacteria are commonly used as starter culture in Swiss-type cheeses, and are only fewer reports on their probiotic properties compared to *Lactobacillus* and *Bifidobacterium* strains.[20] Certain *Lactobacillus* strains have been known residents of the human gut[21] and found to have beneficial effects on human health and therefore used as probiotics. *Lactobacillus* involves in food fermentation and can also be found in the GI system of humans and animals in variable quantities based up on the species, host age and location within the gut.[22] *Lactobacillus plantarum* KLDS1.0391 whole genome was sequenced and will be useful for its applications in food industry.[23]

Various *Lactobacillus* strains are used in the preparation of fermented dairy products as well as sauerkraut, pickles, and silage production. Some *Lactobacillus* strains have been found to

show health benefits on human health, and hence used as probiotics.[24]

These organisms convert lactose and other sugars to lactic acid. In humans, they are present in the gastrointestinal tract, where they form a small portion of the gut flora.[2] and the vagina.[25] They are commonly not harmful, except in the mouth where they have been associated with cavities and tooth decay (dental caries). The production of lactic acid makes the environment acidic, which leads to the inhibition of harmful bacteria.

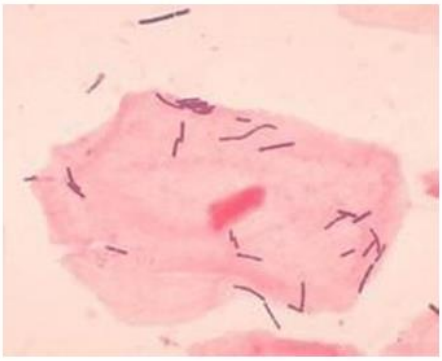

Fig. 2: *Lactobacillus* (https://en.wikipedia.org/wiki/*Lactobacillus*).

3. Role of Probiotics in Human health

3.1 Lactobacillus role in gastrointestinal tract

Lactobacillus is a known species that occurs in oral cavity as well as intestinal tracts of humans. *L. salivarius* retains bacteria levels balanced in the small intestine.[26] Benno in 1996 reported the stimulatory effects of Probiotics that the consumption of probiotic *Lactobacillus rhamnosus* GG increased fecal *Bifidobacterial* number.[27 & 28] Probiotic *Streptococcus thermophilus* ATCC 19258 and *L. acidophilus* ATCC 4356 have been shown to interfere with the adhesion and invasion of enteroinvasive *Escherichia coli* in human intestinal epithelial cells *in vitro*.[29] Probiotics attach to the gut and prevent pathogens from occupying the living space (colonization resistance).[30] *E. coli Nissle* 1917 and a few *Lactobacillus* strains induce defense in antimicrobial peptide production and strengthen innate defense mechanisms in the host.[31] Injuries in the epithelial cell barrier, induced by enterohemorrhagic *E. coli* were prevented by *L. rhamnosus* GG.[32] *In vitro*, probiotic strain *Propionibacterium freudenreichii* subsp. *Shermanii* has been shown to have anti- inflammatory effects during *H. pylori* infection.[33]

Most of the proven health effects that probiotics elicit are in the gastrointestinal tract (GIT) and can be roughly divided into luminal, mucosal and submucosal effects.[34] A numerous of

microbes are colonized in GIT, whose balanced composition and activity are vital for human health.[35] Probiotics consumption encourages the GIT homeostasis and stimulates the growth of indigenous beneficial gut microbes and inhibits the growth of pathogenic or opportunistic pathogenic microbes.[36] *In vitro* studies, Pathogenic or opportunistic pathogenic microbes are inhibited by bacteriocins and lactic acid. For example, probiotic *L. rhamnosus* GG inhibited pathogenic *Salmonella enterica* by producing lactic acid and other secreted antimicrobial molecules.[37] *Lactobacillus acidophilus* and *Lactobacillus casei* antibacterial activity, against methicillin-resistant *Staphylococcus aureus* were studied.[38] *Bifidobacterium longum* become part of the human intestinal microflora, whereas *Lactobacillus casei* indirectly exert their effects in a transient manner and they do not always colonize the intestinal tract.[39]

Probiotic bacteria have useful health effects to prevent gastrointestinal infections.[40] Probiotics showed immune modulatory effects on intestinal tract.[41] *In vitro Propionibacterium freudenreichii* subsp. Shermanii has been shown to have anti-inflammatory effects in *Helicobacter pylori* infection.[33] Probiotics restore micro flora balance and help in passing cellular communications with other healthy bacterial population of the body.[42]

Probiotics replace micro flora balance and help in cellular communications transfer with other healthy bacterial population of the body.[42] The lining of gastrointestinal tract has the largest surface area and interface between body and the external environment, if the intestinal flora is imbalanced, signals from the detectors such as nerve cells, endocrine cells and immune cells affect tissues and organ functions throughout the body especially in gastrointestinal tract. These detectors are influenced by the composition of intestinal microbial population. When probiotics are used as dietary supplements, these helps in promoting most vital systems of health in the body.[42] Inflammation and programmed cell death of the intestinal epithelial cells lining have shown to be prevented by *Lactobacillus rhamnosus GG.*[43] They also exert mitogenic effects and enhance mucosal regeneration.[44]

In stomach and upper two-thirds of the small intestine, due to acidic conditions and faster peristaltic movements the survival of *Lactobacilli* is less where as in the distal small intestine, ileum and large intestine, because of the neutral pH and slow peristaltic movements increases the survival.[45] *L. acidophilus* break down large amount of substrate for the ATP generation for its growth and metabolism, the transportation of nutrients is through PEP- PTS and permease system. It acts as a competitor for enteric pathogens in binding mucosal surfaces of

the gastrointestinal tract.[46] The regulation of induced inflammation of colon by *Lactobacillus acidophilus* deficient in lipoteichoic acid was studied.[47] To prevent and also to treat diarrhea and respiratory infections *L. rhamnosus* GG, *B. lactis* BB-12 have been used.[48&49] To prevent and treat rotavirus diarrhea, atopic eczema and upper respiratory infections *Lactobacillus rhamnosus* GG seems to be effective.[50,51&52] In premature babies, *L. acidophilus* is used to treat necrotizing Enterocolitis and in preterm infants, decrease the symptoms related with crying and fussing.[53] Antibiotic treatment results sometimes in Diarrhoea *etc*, it helps in reducing diarrhoeal diseases and also eliminates food poisoning toxins from the body. Studies showed that *L. salivarius* help to improve irritable bowel syndrome, an intestinal disorder.[54&55] *L. rhamnosus* GG and *B. lactis* BB-12 together have efficiency to prevent and treat allergic disorders, acute respiratory infections and acute otitis media.[56, 57&58] Probiotic are considered to be effective because of their capacity to survive in the GI tract and resistance to gastric acids, exert clear profits in the host and the lack of any transferable antibiotic resistance genes.[59] By metabolizing bile salt or emphasizing the missing digestive enzyme functions, probiotics strains can improve digestion in the host.[60&61]

Probiotics are used to treat GI illness like Traveler's diarrhea, antibiotic associated diarrhea and acute diarrhea in children, IBS, IBD, atopic dermatitis.[14] They help in the digestion of food and absorption of nutrients to make skin healthy and glowing. Single probiotic at a low dose and short treatment duration seems to be more effective in treating Irritable Bowel Syndrome.[62] When multiple species of probiotics were consumed, they reduce body weight and Body Mass Index i.e., BMI.[62] In patients with Parkinson Disease the consumption of fermented milk with multiple probiotic strains and prebiotic fiber was higher to placebo in improving constipation.[63] A study summarizes the mechanisms and therapeutic efficacy of *Lactobacilli*, it concluded that the determination of sufficient amount of bacteria to be supplied is necessary to achieve the best clinical efficacy decreasing side effects.[64] In adults, clinical practice guidelines for IBS found to be evident that multi-strain probiotics in combinations considerably improve IBS symptoms, pain, and bloating compared with placebo.[65]

The probiotic functions of *L. reuteri* are strain-dependent. By combining different strains of *L. reuteri*, the beneficial effects can be maximized.[66] In patients with irritable bowel syndrome, some probiotics can produce lower gastrointestinal symptoms.[67] Probiotics have been studied widely in infectious gastroenteritis, antibiotic-associated diarrhea, IBD and

IBS and the future probiotic research provides the exciting potential to effect conditions regarding health and disease.[68] *L. acidophilus* surface layer protein addition exerts anti-inflammatory effects and inhibits inflammatory bowel diseases.[69] Some studies have demonstrated the effectiveness of probiotics in the treatment and prevention of immune associated diseases like inflammatory bowel diseases (IBDs).[70,71&72] The main mechanisms of action of probiotics were well studied.[73] Probiotic bacteria therapy has been shown to decrease both upper and lower respiratory tract infections.[74] Probiotics enhance immune activity and the clear respiratory tract infections. It is evident that they prevent COVID-19 by maintaining the human GI or lung microbiota.[75] The journey and factors affecting probiotic viability and their mucoadhesive properties in the gastrointestinal tract and various mucosadhesion-related proteins on the probiotic cell surface which facilitate colonization were studied.[76]

3.2 Neuro-psychiatric diseases

The intake of *Enterococcus faecium* along with inulin and *Bifidobacterium breve* A1 improved learning and memory skills, language, attention and orientation in the elderly people.[77] *L. acidophilus*, *B. bifidum*, *L. reuteri*, *Limosilactobacillus fermentum* and *L. salivarius* allowed an improvement in Parkinsons disease.[78&79] After the administration of *Lactobacillus* and *Bifidobacterium* showed improvement in behavioural abnormalities and reduction in the symptoms of depression in humans.[80]

The gut microbiota modulate brain activity and behaviour, plays an important role in the regulation of mood, emotions and in the interpersonal interactions and communications. Hence can be used in the treatment of neuropsychiatric disorders like autism spectrum disorders, depression *etc.* The mode of action of probiotic on behaviour and neuro-psychiatric diseases is still unclear, as in some cases symptoms improvement and amelioration are not related to a modification in gut microbiota. The improvement of anti-inflammatory, gastrointestinal disorders and neuro-behavioural symptoms was observed by microbial mixtures composed of several strains of *Bifidobacterium*, *Lactobacillus*, *Streptococcus* genera. *L. plantarum* PS128, *Limosilactobacillus reuteri* and *Lacticaseibacillus rhamnosus* GG. The effectiveness of *L. plantarum* PS128 showed best results on infants.[81]

3.2 *Lactobacillus* and immunity

Various species of *Lactobacillus* have been shown to have efficacy as future vaccine adjuvants because they differentially regulate dendritic cells and enhance their ability to

initiate specific immune responses.[82] *L. salivarius* develops both natural and acquired immunity.[83] Daily intake enhances gut microbiota and immune response.[84] Probiotics sub mucosal effects include the effects on the host immune system by improving the intestine's immunological barrier functions and reduce the intestinal inflammatory response by immune activation, cytokine production, immunomodulation and inflammation.[85] The different mechanisms of action of probiotics and prebiotics are pathogenic bacteria inhibition, immune modulator effects, barrier and metabolic functions stimulation by which they impact human health.[86] A study illustrated that probiotics interact with host through receptors like toll-like receptors and nucleotide-binding oligomerization domain-containing protein-like receptors. They influence downstream pathways by modulating key signaling pathways and elicit measured antimicrobial responses with slight inflammatory tissue damage. Understanding of these mechanisms will allow suitable probiotic strain selection for specific applications.[87] It increases IL-10 and/or IFNγ[88] and decreases inflammatory markers such as hs-CRP, interleukins IL-6, IL-1β, TNFα and TGF-β.[89] Probiotics should not be used in critically ill or immune- compromised patients, during pregnancy and in infants their use should be advised. Before use the risks and benefits should be weighed though they are generally safe. In GI-related illnesses, Probiotics seemed to exert some beneficial effects. In non-GI illnesses the use of probiotics is not sufficiently supported by current data.[14]

The fermented milk containing selected probiotic strain like *Lactobacillus paracasei* N1115 could boost T cell mediated natural immune defense to decrease the acute upper tract infections.[90] Yogurt with *Lactobacillus paracasei* N1115 develops the T-cell-mediated natural immune defense mechanisms to express their anti-infective effects.[91] Due to daily intake of fermented milk with *Lactobacillus casei* strain Shirota, the risk of Upper respiratory tract infections in healthy middle-aged office workers may reduce due to modulation of the immune system.[92] A study demonstrated that probiotic strains of *Lactobacillus* exert early immune stimulatory effects that may be linked directly to the response of human macrophages initial inflammation.[93] A study revealed that some strains of *Lactobacilli* inhibited the progression of atherogenesis whereas other strains accelerated the atherogenesis. Treg cell activity up regulation is an important mechanism of anti-atherogenic effects of *Lactobacilli*. Several strains are found to increase the Treg cell activity. T-lymphocytes secreted inflammatory cytokines are also important in immune response network. Some strains upregulated pro-inflammatory cytokines as well as down regulated anti-inflammatory cytokines. Some other strains increased anti-inflammatory cytokines levels and some strains

at the same time increased pro-inflammatory cytokines and anti-inflammatory cytokines. So it became difficult to derive the *Lactobacilli effects* involved in atherogenesis.[94]

A study showed that for antibiotic-resistant bacterial infections, effective treatments are in shortage, to overcome this the intravaginal administration of *Lactobacilli* and Lactoferrin could be an efficient therapeutic approach and also to restore mucosal immune homeostasis.[95] A study stated that the research publications were insufficient on how probiotics induce immunomodulatory effects in the treatment of inflammation. It is needed to understand cytokine secretion by Th2 cells, DCs, monocytes, B cells, and Tregs to establish new strains of probiotics. Further studies can be recommended to determine the exact action of probiotics on inflammation because these findings will be useful in the medical sector and for human health.[96] The different adhesion mechanisms to the intestinal mucosa, antagonism against pathogens, stimulation and modulation of the immune system was well explained.[97]

3.3 *Lactobacilli* in Urogenital tract

In a healthy premenopausal female vagina, *Lactobacilli* are dominant. The predominant species in vagina are *L. crispatus, L. gasseri, L.* acidophilus, *L. jensenii* and *L.iners*. Glycogen content, pH, hormone levels and medical treatments are the factors affecting microbial colonization.[98] *Lactobacilli* acts against urogenital infections like Yeast vaginitis, Bacterial vaginosis or Urinary tract infections by the production of antimicrobial compounds, making the environment low pH and high redox potential. *Lactobacilli* colonization to the vaginal stratified squamous epithelium has a protective role against pathogens.[98] People prefer antibiotics to control urinary tract infections. Apart from antibiotics, *L. acidophilus* restores the vaginal *Lactobacilli* microflora and is proved to be effective against urinary tract infections. In a study single and mixed probiotics were tested on inhibition of biofilm formation. Biofilms were reduced equally by both single and multi-strains, but it seems to be dependent on pH.[99] Against microbial infection, *Lactobacillus* GG and *Lactobacillus rhamnosus* seem to be effective to protect the intestine and urogenital tract. The concept of treating and preventing urogenital infection in patients and care taker by instillating probiotic organisms has great appeal.[100] The probiotic combination of *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* GLA-14 strains have shown to be different microbicidal activity against the different strains tested and demonstrated the effectiveness of combined *Lactobacillus* strain treatment.[101] *In vitro, Lactobacillus casei Shirota, L. casei LC01, L. plantarum ST-III and L. paracasei LPC37* strains showed effects

on the composition of bacterial biofilms and inhibited the growth of multispecies biofilms, which shows they may have potential in the prevention of dental caries.[102]

In vivo, *L. fermentum* MG901 and L. *plantarum* MG989 have cleared Vulvo vaginal candidiasis.[103] In healthy people, *Lactobacillus* and *Corynebacterium* are predominant in urine and in patients with Neuropathic Bladder they can change into pathologic Enterobacteria. In future, Urinary microbiome studies should be conducted to provide new treatment strategies.[104] *In vitro* model of human cervix showed that supernatants from *L. acidophilus* GLA-14 and *L. rhamnosus* HN001 with lactoferrin exert a useful effect on cervix cells. In biotic and abiotic surfaces, both strains were showed aggregation and adherence properties. These aggregation and adherence properties are modulated and increased by lactoferrin to prevent and manage urogenital tract infections in women.[105] A study showed that the Squacquerone cheese as probiotic food able to prevent gynecological infections and promote the woman's health.[106]

3.4 In Dental caries

L. rhamnosus and *L. paracasei* subsp. paracasei occurred in all stages of caries progression as they are specialists in carious progression in primary molar deep caries lesions whereas other species were found only sporadically.[107] The oral microbiota composition is influenced by temperature, pH, nutrients and host genetics and defenses. The fluctuations in the oral environmental conditions change the balance between the host and the oral microbiota leads to an increased risk of disease.[108] A Study showed that Probiotic ice-cream with *B. lactis* BB- 12 and *L. acidophilus* LA-5 decreased *Streptococcus mutans* in saliva.[109] Studies have been conducted on *L. acidophilus* effect on the plaque formation of oral *Streptococci.*[110] *L. rhamnosus* LB21 or lozenges with *L. reuteri* DSM 17938 and ATCC PTA 5289 consumption did not affect *Streptococcus* mutans counts.[111& 112] Probiotics have been shown to decrease the risk of dental caries.[113] The early administration of *B. lactis* BB-12 in children did not affect *Streptococcus mutans* colonization.[114&115] Daily intake of Espar, a probiotic dairy product, decreased *Streptococcus mutans* counts in saliva.[116] When sugar rich diet is consumed frequently, *Streptococcus mutans* synthesize glucans from sucrose by using "Glucosyl transferase" enzyme. Attachment of *S. mutans* to the dental surfaces generates initiation and progression of dental caries.[117] *S. mutans* is capable of colonizing the oral cavity, survive in an acidic environment and form bacterial biofilm by attaching to a solid surface.[118]

In patients undergoing orthodontic treatment, Yoghurt containing *B. lactis* DN- 173010 did not affect either salivary or dental plaque levels of *Streptococcus mutans.*[119] *L. salivarius* consumption increased salivary buffering capacity significantly in the *L. salivarius* group compared to the xylitol group, but did not affect salivary pH.[120]

3.5 Probiotics role in oral health

Probiotics adhere to the oral mucosa and teeth and in *In-vitro* studies; they show different degrees of adhesion to saliva coated hydroxyapatite surfaces.[121]

Table 1: Mechanism of action of probiotics to reduce dental caries.[121]

Direct actions	In direct actions
Biofilm formation	Modulating systemic immune function
Modifying the external environment pH	Effect on local immunity, Regulation of mucosal Permeability
Antagonism of pathogenic organisms by the production of antimicrobial compounds, that inhibit oral bacteria	
Competes for pathogen binding and receptor sites, stimulate immune modulatory cells and produces lactase[122]	
Competing with oral microorganisms for available substrates	

Lactobacilli may inhibit caries causing microorganisms by producing antimicrobial substances like organic acid production or bacteriocins at a low pH.[123,124,125&126] *In vitro* studies showed that *L. rhamnosus* strains can attach better to saliva- coated hydroxyapatite.[127,128 & 129] Stamatova[130] found that *L. rhamnosus* GG strains were able to inhibit *P. gingivalis* and *F. nucleatum Lactobacilli*, Heat-killed *L. paracasei* DSMZ16671 able to coaggregate with oral *Streptococci.*[131,132&126] *S. mutans* growth was inhibited by *L. rhamnosus* GG without affecting the pH.[133] Different *L. reuteri* strains had major inhibitory effects on peri odontopathic bacterial growth and the formation of *S. mutans* biofilms.[134] In biofilm experiments, heat-inactivated *B. lactis* BB-12 has reduced *S. mutans* cariogenicity.[135] and different *Lactobacilli* have reduced the growth, biofilm formation of *Streptococcus mutans.*[136, 137& 138] *L. reuteri* has an inhibitory effect against *S. mutans.*[139] The role of *Streptococcus mutans*-derived extracellular matrix is to provide bacterial binding sites and holding microbial cells together in cariogenic oral biofilms.[140] A study showed probiotic role

in the bacterial number reduction in periodontitis and halitosis. A study revealed that specific strain recognition is required with probiotic activity for each infectious oral disease to determine exact dose, treatment period and ideal vehicles.[141] Studies show synthesis of monofluoro phosphate internal polysaccharide in *Streptococcus mutans.*[142] A study revealed management of oral health through novel probiotics.[143] A multi- centered clinical trial with enough statistical power, the use of analytical tools is needed to establish the role of probiotics on oral health.[144]

3.6 Obesity

Gut microbiota plays an important role in controlling body weight, energy homeostasis and inflammation. A study revealed that administration of fermented milk containing *Lactobacillus gasseri* SBT2055 (200 g/day) showed reduction in visceral and subcutaneous fat, body weight and BMI (Body Mass Index) in adults. The consumption of yogurt supplemented with capsules, containing 109 CFU of *Lactobacillus amylovorus* and *L. fermentum* to overweight participants, led to a reduction in total body fat mass.[145] A combination of probiotics, prebiotics and vitamins A, E and C for 8 weeks, reduced BMI, waist circumference, waist/hip ratio, LDL cholesterol and triglycerides.[146] Third trimester of pregnancy showed reductions in total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol and serum triglyceride concentrations by the administration of 200 g/day of yogurt containing *S. thermophilus, L. delbrueckii subsp. bulgaricus, L. acidophilus* LA-5 and *B. animalis* BB12.[147]

3.7 Diabetes

The microbiota of diabetic patients is poorly populated by probiotics like *Bifidobacterium*, which have anti- inflammatory activity, are butyrate-producing and are promoters of low intestinal permeability. Diabetes is closely linked to food choices and habits i.e., active lifestyle could improve insulin resistance, taking foods rich in fibers, largely represented by prebiotics. *L. reuteri* DSM 17938 to patients with type 2 diabetes showed increased insulin sensitivity and improvement of microbial diversity.[148] *L. paracasei* HII01 (50 × 109 CFU/day) was administrated into 50 type 2 diabetes mellitus patients and observed that fasting blood glucose (FBG) levels were significantly decreased.[149] *L. paracasei* HII01 could play a potential role in type 2 diabetes as it reduced the pathogenic microorganisms and improved beneficial bacteria. Treatment with *L. rhamnosus* reduced fasting blood glucose

(FBG) levels, lowered insulin resistance, alleviated metabolic lipopolysaccharide- related inflammation and relieved hepatic oxidative stress.[150]

4.0 CONCLUSION

It is very important to learn and discuss the role of probiotics in human health, as this is emerging topic and still, we need to research and learn more about these good microbes. Probiotics have many important characteristics that could achieve most of the human elementary nutritional supplementation requirements. They have been shown many positive activities in human systems like Gastro intestinal tract, Immune system, Central nervous system, Uro genital tract *etc*., these microbes also showed positive responses in treating Obesity, Diabetes, Cancer, Dental Health and diseases related to pathogenic microbes. They are used in therapeutic purpose for Colitis, Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD) *etc*., Probiotic strains are also used in the production of different dairy and fermented products.

Therefore, the applications of probiotics in biomedical and clinical research have been used to explore their role in improving human health.

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