CHAPTER 2

REVIEW OF LITERATURE

Review of Literature

Microorganisms have played an important part in the human diet since the dawn of civilization. For the improvement of food quality, people knowingly or unknowingly incorporated microorganisms into food until the idea of probiotics evolved from a theory proposed by Elie Metchnikoff, who related longevity of Bulgarian people to the consumption of fermented milk products. According to him, bacteria present in those fermented products consumed by the Bulgarian people might play an important role in the modulation of colonic bacterial structure and overall human health and well being [1].

2.1. Definition of probiotics

The word "probiotics" was derived from the Greek words "pro" and "biotos" which means "for life" [2]. How different researchers used the term in probiotics can be found in the table 2.1. The first widely accepted definition of probiotics was proposed by a FAO/WHO working group on the evaluation of probiotics in food (2002) as "live microorganisms which when administered in adequate amounts confer a health benefit on the host". In 2014, Hill et al. gave a consensus definition of probiotics which includes a broad range of microbes and applications that summarizes the differences between live microorganisms with other health- beneficial compounds that are produced by microorganisms [3]. They also clarified that those live microorganisms which were isolated from fermented food might qualify as "probiotics", if they show evidences of health benefits. These evidences could be drawn from taxonomic and functional comparisons.

2.2. Technological properties of probiotics

Prior to probiotic selection, a microorganism must pass some technological and physiological tests so that they could maintain a viable count of 10^7–10^9 CFU/ml during food processing and at the time of delivery [1]. Different technological properties have been described for probiotics; these are as follows:

Table 2.1. Definition of probiotics

Year	Definition	Reference
1953	Those organic and inorganic supplements which are required to restore health in case of too much use of refined food	[4]
1954, 1955	Those substance which can restore the normal microbiota of the body after antibiotic treatment	[5], [6]
1965	Probiotics are substances produced by one microorganism that promoted the growth of another micro- organism	[7]
1971, 1973	Compounds that either stimulate microbial growth or improved the immune response of the host without inhibiting the growth of the culture *in vitro.*	[8], [9]
1974	Organisms and substances, which contribute to intestinal microbial balance.	[10]
1992	A live microbial feed supplement, which beneficially affects the host animal by improving its intestinal microbial balance	[11]
1999	Probiotics are microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host	[12]
2002	Live microorganisms which when administered in adequate amounts confer a health benefit on the host	[13]
2014	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host	[3]

2.2.1. Oxidative stress tolerance

During the time of delivery, probiotics may have to withstand the deleterious effects of reactive oxygen species. Most of the lactic acid bacteria lack cytochromes or catalase, however the presence of flavoproteins like NADH- oxidase makes lactic acid bacteria resistant to oxidative stress [14].

2.2.2. Heat and osmotic stress tolerance

Probiotics must express heat shock proteins to circumvent heat and osmotic stress conditions prevailing in food processing plants. Lactic acid bacteria express a number of chaperon complexes which enables them to adapt heat stress as much as 52°C for 15 min [15]. The authors also reported that this much of heat stress was beneficial to the bacteria to survive under high salt conditions.

2.2.3. Tolerance to storage conditions

Probiotic must maintain good survivability during storage at low temperature and freeze- dried conditions. Freeze drying is a common process for the storage of microorganisms in dehydrated form. When incorporated with a food matrix, probiotics has to show good viability at low temperature for longer period [16, 17, 18]. Microencapsulation or the use of cryoprotectant such as skim milk, trehalose or ascorbate also increases the shelf life of probiotics [19, 20]

2.3. Functional properties of probiotics

2.3.1. Acid tolerance

The upper gastrointestinal tract is known to be acidic which plays as a barrier for pathogen's entry into the digestive system. Moreover, the proteases present in the stomach also act at an acidic pH of 2-4 [21]. Therefore probiotics have to survive in these conditions during gastric transit and reach the small intestine.

2.3.2. Bile tolerance

The intestinal mucosa is the site for probiotic colonization and for that they have to withstand the high pH of the intestine as well proteolytic enzymes. Resistance to bile concentration of 0.15-0.3% is recommended for probiotic strains [22].

2.3.3. Adherence to intestinal mucosa

Probiotics must adhere to the intestinal mucosa to overcome the intestinal flow of digesta and impart the health beneficial effects. The probiotics adhesion is normally assessed in intestinal tissues [23], cell lines [24] or mucus [25]. Cell adhesion involves complex interaction between bacterial cell wall and host epithelium and cell surface hydrophobicity plays the most important role [26].

2.4. Desirable physiological properties of probiotics

2.4.1. Cholesterol metabolism

Elevated blood cholesterol level leads to hypercholesterolemia and ultimately cardio-vascular diseases (CVDs). Pharmacological agents such as statins are available for the treatment of hypercholesterolemia. Statins are the most used drugs for the treatment of hypercholesterolemia which inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase required for the cholesterol synthesis. However, statins are often associated with severe side effects such as myalgias and muscle weakness, increased fatigue, reduced energy, deteriorating hyperglycemia and risk of new onset diabetes [27]. The most well- known mechanism by which probiotics decrease cholesterol accumulation is through the production of the enzyme bile salt hydrolase (BSH). Many probiotic bacteria produce BSH which has the capability to deconjugate bile salts [28] which are less soluble and get excreted with feces. In case of the probiotic yeasts, cholesterol lowering is achieved through cholesterol uptake by growing cells and the production of short chain fatty acids which decreases the production of hepatic cholesterol [29, 30].

2.4.2. Antagonism towards gastrointestinal pathogens

Gastrointestinal tract is a pool of both beneficial and harmful microbiota. From both *in vivo* and *in vitro* evidences it could be summarized that probiotics could be very effective in the removal of pathogens from the gastrointestinal tract. Probiotics augment pathogen inhibition by the host body by decreasing the luminal pH, secretion of bacteriocins and bacteriocidal peptides or by the stimulation of defensin production by the epithelial cells [31and 32]. Probiotics also inhibit the binding of pathogens by blocking the receptors present on the intestinal epithelia or by stimulating the mucin production which form a protective barrier along the epithelia [33]. Enteric pathogens often disrupt the epithelial barrier integrity which could be restored by probiotic treatment [34]. The mechanism of action by which probiotics prevent pathogen interaction with the intestinal lumen is explained schematically in the fig. 2.1.

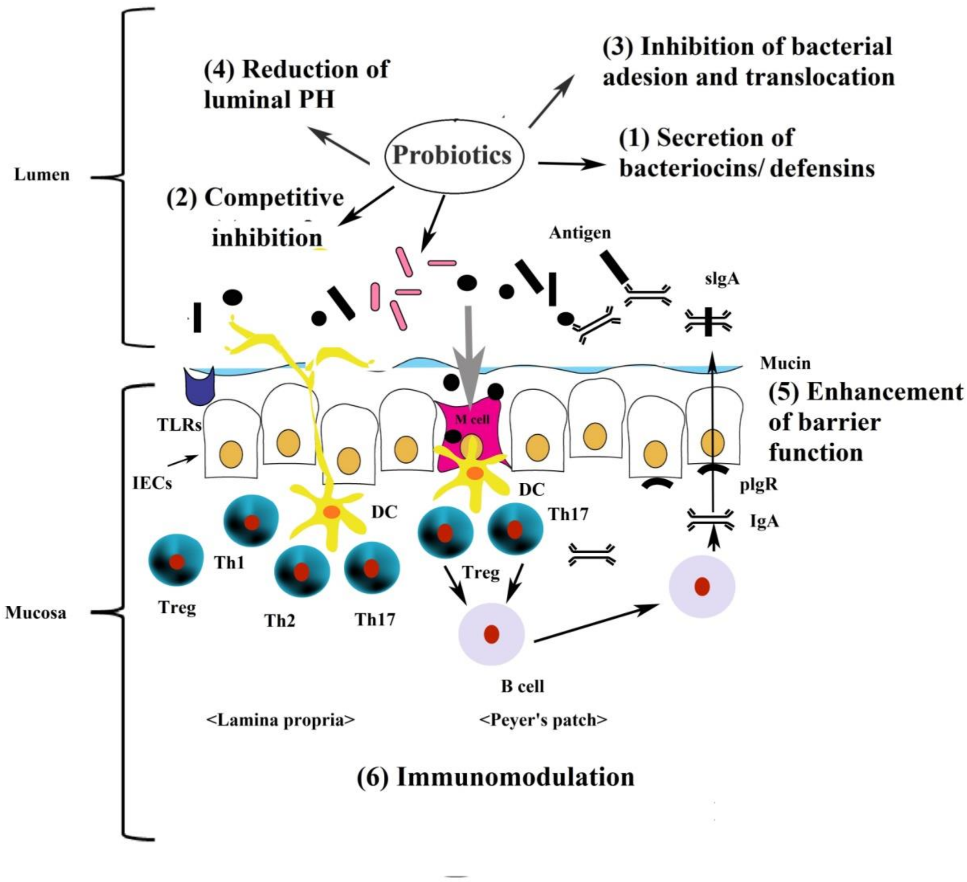

Fig. 2.1. Mechanism of action of probiotics; adapted from Ng et al. [32].

2.4.3. Immunomodulation

Gut associated lymphoid tissue (GALT) is the largest lymphoid organ in the human body where lymphocytes are scattered throughout. Intestinal antigens including both commensal and enteropathogenic bacteria are processed by the dendritic cells (DCs) [32]. Intestinal DC population is the most important component of both innate and adaptive immunity and probiotics play an important role in the maturation and cytokine production in dendritic cells [35]. There are reports of induction of IL-12, TNFα and IL-10 in variable amounts [36]. DCs can differentiate between pathogens and probiotics using pattern recognition receptors such as toll- like receptors (TLRs). Probiotics have the ability to form a non- inflammatory and tolerogenic patterns through the induction of regulatory T cells. On the other hand, DCs in the Peyer's patches capture pathogenic bacteria and antigens internalized by M cells (Fig. 2.1). The primary antibody involved in the neutralization and clearance of antigens is IgA. IgA secretion is mediated by polymeric Ig receptor (pIgR) which secrets IgA in the form of secretoty IgA (sIgA). It was found that the IgA production is maintained by probiotic commensal bacteria, through Th17- mediated response [37].

In case of autoimmune diseases such as inflammatory bowel disease (IBD), which is triggered by the loss of tolerance to the intestinal microflora , leads to the production of inflammatory cytokines such as TNF-α and IL-1β. Because certain probiotics has the ability to balance the intestinal microflora and mucosal barrier integrity randomized controlled clinical trials were performed. It was found that certain probiotics were able to maintain remission in case of ulcerative colitis [38 and 39].

2.4.4. Anticancer properties

Malignant cancer cells are known to produce pro inflammatory cytokines and proteolytic factors due to which acute phase reactions initiate and ultimately cancer cachexia arises leading to weight loss and death. Due to malignancy, patients are at an immunocompromised state which can be restored by the use of probiotics. During some drug induced cancer, the oxidative DNA damage is the most preliminary step. Probiotics are known to produce compounds such as exopolysaccharide (EPS) which involve in scavenging of reactive oxygen species (ROS), superoxide anions and hydrogen peroxide [40]. Probiotics are also involved in triggering apoptosis in colorectal cancer cells through intrinsic and extrinsic pathways [41].

2.4.5. Prevention of antibiotic associated diarrhea

Due to antibiotic treatment, the indigenous microflora gets disturbed and *Clostridium dificale*, which is a microorganisms normally present in the intestine increase in number and produce toxins which is the prime cause of antibiotic associated diarrhea. The administration of exogenous probiotics is required to restore the balance of the colonic microflora to outnumber C. *dificale* population and therefore reduce the toxic effects of the same in the formation of diarrhea. Oral administration of probiotics in infants resulted in reduced risk of diarrhea [42].

2.5. Evaluation of yeast as probiotics

Unlike lactic acid bacteria and *Bacillus*, assessment of probiotic properties of yeasts started very recently, although yeasts such as *Saccharomyces cerevisiae* have a safe history of use as starter cultures for fermentation. Probiotic efficacy of different yeast strains is given in the table 2. The first ever yeast, which was used for the treatment of intestinal infections was *Saccharomyces boulardii*. Yeasts other than *S. boulardii* were investigated for probiotic properties by Psomas et al. [45] for the first time. In 2006, *S.boulardii* was compared with probiotic *Lactobacillus* strains in preventing acute diarrhea and it was found that *S. boulardii* showed comparable efficacy. Probiotic yeasts were also investigated for *in vitro* and *in vivo* cholesterol lowering properties [46, 49, 51].

2.6. Incorporation of probiotics into functional foods

"Functional foods" are those foods which can provide physiological benefits such as reduction the risk of chronic diseases apart from their nutritional benefits [52]. Addition of probiotics to functional foods began soon after the health beneficial effects of probiotics were revealed. The most commonly used matrix for probiotic growth was milk, which provides a good environment for growth of most of lactic acid bacteria and bifidobacteria. As mentioned in the previous chapter, since lactose intolerance is pretty much common is the population of East Asia, therefore, selection of milk- based functional foods may not be a suitable option for probiotic delivery in this region. This reinforces the advent of vegetable- based functional foods. For this primary aim was to isolate bacteria with potential probiotic properties from non-dairy origin (Table 2.3).

Table 2.2. Probiotic efficacy of different yeast strains

Year	Probiotic properties shown by yeasts	Reference
1994	Treatment of *Saccharomyces boulardii* significantly decreased *Clostridium dificale* disease in clinical trial	[43]
1996	Effect of *Saccharomyces boulardii* against experimental oral infection with *Salmonella* typhimurium and *Shigella flexeneri* in *conventional* and gnotobiotic mice	[44]
2001	Growth at 37 °C and acid and bile tolerance	[45]
2003	*In vitro* Cholesterol assimilation	[46]
2006	Efficacy of *S. boulardii* in prevention of acute diarrhoea in clinical trials	[47]
2010	*Saccharomyces cerevisiae* protection against bacterial translocation and immunomodualtion	[48]
2015	*In vivo* hypolipidemic and antioxidant properties by probiotic *Pichia kudriavzevii*	[49]
2015	Protective activities of *S. boulardii* against *B. Anthracis* LT Toxin	[50]
2017	*In vivo* cholesterol assimilation by *Saccharomyces cerevisiae* and *Saccharomyces boulardii*	[51]

After ensuring that probiotic bacteria can grow in non- dairy substrates, they were incorporated into various finished products as mentioned in the table 4.After establishing survivability of probiotics in food matrices it is important to find out the health beneficial effects in individuals. After feeding with probiotic enriched food products, probiotic were recovered from excreta of individuals and also influenced the intestinal microbiota positively and antagonized enteropathogenic bacteria [75 and 76].

Although milk based matrices are the most predominant vectors for probiotic delivery, fermented milk products are becoming limited in some population groups due to lactose intolerance, cholesterol metabolism or milk protein allergies. There are studies which reported that vegetable- based matrices provide support to the probiotics while passing through the gastrointestinal tracts [77]. The viability also has been improved by techniques such as encapsulation.

Table 2.3. Isolation of different probiotic bacteria from non- dairy fermented products

Strain	**Product**	**Probiotic trait**	**Reference**
Lactococcus lactis	Sauerkraut	Production of nisin	[53]
Lactobacillus plantarum	Fermented cucumber	Production of plantaricin	[54]
Lactobacillus brevis	Chinese cabbage	Production of brevicin	[55]
Pediococcus pentosaceus	pickled cabbage	Protection of *Salmonella* invasion in mice	[56]
L. plantarum and *Lactobacillus acidophilus*	pickled cabbage	Cell adhesion, biotic stress tolerance, antimicrobial	[57]
Bacillus amyloliquefaciens	Fermented soyabean	Enzyme production, acid and bile tolerance, hydrophobicity	[58]

Table 2.4. Incorporation of probiotic bacteria into functional foods

Food product	Probiotic organism	Reference
Minimally processed products	*Lactococcus lactis, Lactobacillus rhamnosus*	[59], [60]
Chocolate	*Lactobacillus acidophilus and Bifidobacterium lactis*	[61]
Prickly pear juice	*Lactobacillus fermentum*	[62]
Clarified apple juice	*Lactobacillus paracasei*	[63]
Sonicated pineapple juice	*Lactobacillus casei*	[64]
Chestnut extract	*Lactobacillus rhamnosus,Lactobacillus casei, Streptococcus thermophilus, Enterococcus durans*	[65]
Pomegranate juice	*Lactobacillus plantarum, Weissella cibaria, Pediococcus acidilactici, Pediococcus pentosaceus*	[66]
Juçara and Ubá mango juice	*Lactobacillus rhamnosus*	[67]
litchi juice	*Lactobacillus casei*	[68]
dried yacon	*Lactobacillus casei*	[69]
Peanut yoghurt	*Lactobacillus brevis, Lactobacillus casei , Lactobacillus fermentum , Lactobacillus fermentum , Lactobacillus plantarum Enterococcus faecalis*	[70]
Blanched cabbage	*Lactobacillus paracasei*	[71]
Fermented olive	*Lactobacillus pentosus, Lactobacillus plantarum*	[72]
Sauerkraut (Fermented cabbage)	*Leuconostoc mesenteroides Lactobacillus plantarum*	[74]
Cereal based fermented food	*Pichia kudriavzevii*	[49]

2.7. Antibiofilm properties of probiotics and probiotic- derived metabolites

Many food-borne pathogens are known to form biofilms on various biotic and abiotic surfaces which have severe economic and health consequences. Biofilms are known as microbial cell assemblies formed on nutrient- rich surfaces enclosed within an extrapolymeric matrix [78]. The extrapolymeric matrix, also known as extracellular polymeric substances (EPS) consists of different substances ranging from polysaccharide, proteins, and phospholipids to nucleic acids [79]. Microbial biofilms are common in food processing units which are well- structured microbial communities and often known for causing problems during food processing operations. Apart from the food processing surfaces, microbial biofilm formation is also frequent in food surfaces such as beef surfaces, chicken skins [80] and ready-to-eat (RTE) fruits and vegetables. RTE products are more preferred by the consumers for nutritional benefits, but sometimes the qualities of these products are compromised due to microbial contamination and different episodes of outbreaks related to them are reported. These microbial biofilms are very hard to remove using conventional cleaning systems since they are far more resistant towards sanitizers and environmental changes than the planktonic bacteria [79]. In industrialized countries, people afflicted by food- borne diseases are nearly 30% and 60% of the infections are due to transfer of bacteria from food contact surfaces to the processed foods [81]. Antibiotic resistance is a major concern of the present century which is triggered by the excessive use of chemotherapeutic agents. Therefore, alternative strategies are getting underway and probiotic treatment is one of the most accepted measures to eliminate biofilm of pathogenic bacteria.

The most important bacterial species associated with food borne infections are *Salmonella enterica*, *Listeria monocytogenes*, *Escherichia coli*, and *Staphylococcus aureus*. *Salmonella enterica* and *Listeria monocytogenes* were found to show hydrophobic interactions with solvents, a property similar to probiotic bacteria which indicate that these bacteria are equally capable of forming biofilm [82]. When cocultured, probiotic strains could decrease the biofilm formation of *Salmonella enterica* and *Listeria monocytogenes* on polystyrene microtitre plates. Moreover, released exopolysaccharides produced by probiotics were reported to reduce the biofilm formation by the enterohemorrhagic *Escherichia coli* O157:H7 by affecting the genes related to biofilm formation and chemotaxis [83]. Probiotic strains *L. fermentum* and *L. plantarum* were able to disrupt the biofilm of *Staphylococcus aureus* and inhibited the expression of genes related to biofilm formation. [84]. Probiotics also have a great contribution towards the inhibition of oral pathogens such as *Streptococcus mutans*. The probiotic strains *Lactobacillus rhamnosus*, *L.*

acidophilus and *L casei* could decrease the biofilm formation in a cariogenic model and could decrease the expression of *gtfs* gene of *Streptococcus mutans.* [85]. One of the mechanisms by which probiotics decrease biofilm formation is through the expression of lectin like proteins [86] which have affinities towards sugar molecules present on the cell walls of pathogenic bacteria.

2.8. Antifungal properties of probiotics

Food spoilage is deleterious to food industries in which the contributions of yeasts and moulds are very common. Both yeasts and moulds produce different mycotoxins and virulence factors accompanied with known and unknown health hazards. The most known fungal contaminants are *Penicillium, Aspergillus, Fusarium* sp. that produce arrays of mycotoxins. Different physical and chemical techniques are employed for the removal of fungal contaminations from food such as freeze drying, modified atmospheric storage, treatment of organic acids and antifungal agents [87, 88]. However, similar to their bacterial counterparts, yeasts and moulds which cause food spoilage as well as infections are increasing becoming resistant to those traditional treatments. Moreover, due to change in the virulence patterns, pathogenicity of yeasts has changed. For instance, Candida non- albicans sp., which were once considered as non- pathogenic have emerged as potential pathogens [89]. Therefore, in addition to the abovementioned factors, consumer's demand for minimally processed foods also plays an important role for selecting alternative agents for the removal of contaminating fungal strains from foodstuffs and the use of biopreservatives such as probiotics is now-a-days a trend.

2.9. Bibliography

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