Futuristic Trends in Medical Sciences

 IIP Proceedings

 Chapter … Microbiology

**Future of probiotics and prebiotics**

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**Abstract**:- Probiotics and prebiotics are the emerging topics in today’s world. For some decades now, bacteria known as probiotics have been added to various foods because of their beneficial role for human health. Traditionally, probiotics have been associated with the gut health, and the oral consumption of probiotic microorganisms produces protective effect on the gut flora. Recent research have observed the use of probiotics in other mechanisms as well as on gut health. Prebiotics are the compounds in food that helps in growth and activity of the beneficial microorganisms such as bacteria and fungi. In this chapter, the author will elaborate on the various kinds of probiotics and prebiotics which will help the food and pharmacological market to grow in the world. However the interested reader is also referred to the references listed at the end of this chapter for developing a more holistic notion of this subject.

**Keywords**:- Next generation Probiotics, Emerging prebiotics, β-hydroxybutyrate, genetically modified bacteria, Ketogenic diet

**I. Introduction**

**1.Probiotics**

### The term Probiotics is derived from a Greek word meaning “for life” and used to define living non-pathogenic organisms and their derived beneficial effects on hosts. The term “Probiotics” was first introduced by Vergin, when he was studying the detrimental effects of antibiotics and other microbial substances, on the gut microbial population. He observed that “probiotika” was favourable to the gut microflora. Probiotic were then redefined by Lilly and Stillwell as “A product produced by one microorganism stimulating the growth of another microorganism”. Subsequently the term was further defined as “Non-pathogenic microorganisms which when ingested, exert a positive influence on host’s health or physiology” by Fuller. The latest definition put forward by FDA and WHO jointly is “Live microorganisms which when administered in adequate amounts confer a health benefit to the host”.

The idea that probiotics function in ways that might act beyond affecting the colonizing microbiota opens the door to a wider range of probiotic possibilities, encouraging innovation in the field. Some of the popularly used probiotic microorganisms are Lactobacillus rhamnosus, Lactobacillus reuteri, bifidobacteria and certain strains of Lactobacillus casei, Lactobacillus acidophilus-group, Bacillus coagulans, Escherichia coli strain Nissle 1917, certain enterococci, especially Enterococcus faeciumSF68, and the yeast Saccharomyces boulardii. Mostly probiotics are found in fermented products. New genera and strains of probiotics are continuously emerging with more advanced and focused research efforts.

**1.2 Future of probiotics:**

Probiotics are traditionally used for development of beneficial microorganisms at gut microbiota but today there are numerous probiotics undergoing various mechanisms that can be used in the future in our foods as well as in our medical sciences. Hereby elaborating the various mechanisms with the newly found probiotics in the recent studies.

**1.2.1 Stress management and probiotics**

Sedentary lifestyle has been the major cause for stress in today’s scenario. Stress is describe as a non-specific response and physiological consequence of the body to adversity with the feeling of emotional or physical tension (1). It originates from any life’s event or thinking that affects emotions or mood of an individual. The recent study shows that probiotics species belonging to Lactobacillus fermentum NMCC-14 and spores of Bacillus clausii (Enterogermina®), were evaluated for their role in treating acute and subacute restraint-stressed mice. Stress has a connection with cortisol and ACTH. The release of ACTH triggers the adrenal glands to produce cortisol, the “stress hormone,” and androgens. Cortisol slows down the “fight-of flight” mechanism in the body.

In the study, behavioural paradigms, i.e., EPM (Elevated Plus Maze), LDB (Light dark box/Dark light box), and OFT (Open field test) with other tests used like High-performance liquid chromatography and quantitative polymerase chain reaction and hemotoxylin as well as eosin-strain hippocampal slides were used for determining monoamine levels and prevalence of neurodegeneration respectively. probiotics suppressed the symptoms of stress in acute and subacute restraint-stressed mice in The study showed that the time spent in open arms of EPM, time spent in light compartment of LDB, and movable time and time spent in centre of OFT were significantly increased in probiotic-treated restrain-stressed mice. The study also showed stress in mice was reduced or suppressed by decreasing the serum cortisol and ACTH levels, increasing the monoamine (serotonin, dopamine, and NE) levels, and increasing the mRNA expression of dopamine (D1 and D2) receptors and synaptophysin in the mice. Moreover, enhancement in neurological arborization was also observed with neurodegenerative effects and pyknosis caused by restraint stress in the mice (2). The neurological aborization is essential for connectivity between neurons that helps in normal brain function. Thus this study demonstrated that probiotics may be help in managing stress at today’s scenario.

**1.2.2. Probiotics and photo-aging effect by UV light**

In recent times, interest has significantly expanded beyond the gut microbiome to include the skin microbiome. Topical probiotics have shown beneficial effects for the treatment of certain inflammatory skin diseases such as acne, rosacea, psoriasis and also found to have a promising role in wound healing.

A study conducted by Lee et al. on effects of *Bifidobacterium animalis* subsp. *lactis MG741* (*B. lactis MG741*) against skin photo-aging induced by UVB exposure. UV light has mixed effects on the skin. As positive effect, UV light is helpful in synthesis of Vitamin D. But there are numerous negative effects like skin cancer and other environmental skin disorders. Photo-aging is another negative factor which causes wrinkles, increased epidermal thickness and rough skin. The study showed that *B. lactis* MG741 has reduced wrinkles and skin thickness by downregulating the molecular mechanisms of dermal aging like MMP-1 and MMP-3, phosphorylation of ERK, and c-FOS in fibroblasts and hairless mice used in the study (3). It also inhibited the expression of NF-κB, an inflammation-related factor in UVB-irradiated dorsal skin. Probiotics can show a promising approach in the dermal sector with more research and studies.

**1.2.3. Probiotics in Cow’s milk allergy**

Cow’s milk allergy is a common diagnosis in infants and children. Cow’s milk contains more than 20 proteins but the significant allergens belonging are casein protein(4) and whey proteins(5). If an individual has an allergy to milk, the body’s immune system responds to a specific milk protein, triggers an immune response, to an extent that histamine and other immune mediators are released.

Cow’s milk protein allergy (CMPA) is a type of food allergy that is most common in infants and children under the age of three. The most common symptoms are dermatitis, urticaria or oral allergy syndrome, and gastrointestinal (GI) disorders such as changes in stool frequency and consistency, mucous or blood spots in stools, infantile colic, nausea, vomiting, and gastroesophageal reflux .

The recent study by Keddar et al. demonstrated that probiotic bacteria from human milk, specifically the SL42 strain, have the potential to reduce the allergic response to cow’s milk casein in rats. *Limosilactobacillus reuteri Protectis DSM* 17938 (formally known as *Lactobacillus reuteri*) was the reference strain from breast milk supplied by the PEDIACT laboratory BioGaia (Asnières-sur-Seine, France). SL42 is an isolated strain from the breast milk of a healthy young mother and SL42 was identified by partial sequencing of 16S rRNA genes. Various other tests were performed for both bacteria strains used in the in vivo part of this study to confirm it as a probiotic, where the SL42 isolate was compared with the probiotic strain of DSM 17938 taken as reference. The tests performed were pH and Bile Tolerance Assays, detection of Antimicrobial Activity(using seven pathogenic indicator bacteria and one fungus, Candida albicans), Hydrophobicity, hemolytic Activity, cholesterol Uptake and antibiotic Susceptibility.

The results confirms that supplementing juvenile rats with *L. rhamnosus* SL42 induces tolerogenic responses with lowering the level of casein-associated allergy parameters. Its effects were similar to those expressed by the probiotic strain of *L. reuteri DSM* 17938. The SL42 strain showed positive results like decreased histamine levels, milk casein-specific IgE levels, eosinophil numbers, S100A8/9 levels, and cytokine concentrations with also increasing LAB and Clostridium species in the gut microbiota. They also inferred protective effect when histologically analysed of the jejunum. The study identified a potential role of breast milk in ameliorating casein allergy effect by consumption of cow’s milk.

**1.2.4.Probiotics and colon disease**

Colitis is a common disease of the colon that is very difficult to treat. Probiotic bacteria could be an effective treatment. The probiotic *Escherichia coli Nissle 1917 (EcN)* was engineered to synthesize the ketone body (R)-3-hydroxybutyrate (3HB) for sustainable production in the gut lumen of mice suffering from colitis(6). The growth of probiotic bacteria, especially *Akkermansia* spp, increased from 2% to 31% in the microbiome due to the presence of 3HB in mouse guts. As a result, the engineered EcN termed EcNL4 ameliorated colitis induced via dextran sulfate sodium (DSS) in mice. Oral EcNL4 uptake demonstrated better effects on mouse weights, colon lengths, occult blood levels, gut tissue myeloperoxidase activity and pro-inflammatory cytokine concentrations than oral administration of 3HB only . Thus, a promising live bacterium was developed to improve colonic microenvironments and further treat colitis.

**1.2.5. Inflammatory Bowel Disease(IBD) and probiotics**

Inflammatory bowel disease (IBD) is a chronic or remitting/relapsing inflammatory disease of the intestinal tract, including ulcerative colitis (UC) and Crohn’s disease (CD)(7). Among the recent therapies, anti-tumor necrosis factor α (anti-TNFα) agents are the most recognizable providing improved health outcomes and decreased need for surgical intervention (8). However, anti-TNFα agents have shown adverse effects like serious infections, autoimmune reactions and also fails to works in many individuals. To fulfil this gap, researchers have come across a new strategy by introducing genetically modified bacteria. Some of the genetically modified bacteria are ***Engineered Escherichia coli***, ***Engineered Lactococcus lactis, Engineered Lactobacillus paracasei***, ***Engineered Bifidobacterium longum***, ***Engineered Bacteroides ovatus*** are tested in mice.

Apart from the study on genetically engineered bacteria for treating IBD,there is also another next generation probiotic i.e *Akkermansia muciniphila*. Another study by Henry et al. showed that the regulatory mechanism among *A. muciniphila*, a transcription factor cAMP-responsive element-binding protein H (CREBH), and microRNA-143/145 (miR-143/145) in intestinal inflammatory stress, gut barrier integrity and epithelial regeneration.By his study he inferred that outer membrane protein of *A. muciniphila*, Amuc\_1100, can be expressed in mammalian cells which may lend support to pharmaceutical development focusing on gut bacterial components (e.g., membrane proteins) instead of whole bacteria for the treatment of IBD and other human diseases.

**1.2.6. Obesity and insulin resistance with probiotics**

A body mass index (BMI) over 25 is considered overweight, and **over 30** is obese by WHO. Obesity is a triggering factor for diabetes associated with insulin resistance. In individuals who are obese, higher amounts of non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines that could participate in the development of insulin resistance are released by adipose tissue. Besides, endoplasmic reticulum stress, adipose tissue hypoxia, oxidative stress, lipodystrophy, and genetic background have a role in insulin resistance.

Earlier, the administration of different strains of Lactobacillus rhamnosus, plantarum, curvatus or gasseri in diet-induced obese (DIO) mice has been associated with a multitude of benefits like reduction in weight and visceral fat as well as a decrease in glucose, insulin and triglyceride levels, also reduction in insulin resistance (IR) and pro-inflammatory cytokines, as well as a concomitant increase in interleukin-10 (IL-10) and an improvement in fatty liver indices was shown in the study. Various studies on human with different strains of bacteria like L. gasseri BNR17 and L. rhamnosus CGMCC1.3724 strain also showed reductions in visceral fat  and reductions in weight.(9,10,11,12,13,14)

Recent advent of the polymerase chain reaction (PCR) of the 16 S rRNA gene, as well as next-generation sequencing (NGS) and the use of bioinformatics help us to accurately identify various bacterial strains. There are numerous emerging probiotics like Akkermansia muciniphila, Faecalibacterium prausnitzii, Eubacterium hallii (recently reclassified into Anaerobutyricum hallii and Anaerobutyricum soenhgenii , Bacteroides uniformis, Bacteroides coprocola, Parabacteroides distasonis, Parabacteroides goldsteinii, Hafnia alvei, Odoribacter laneus and Christensenella minuta have been proposed as NGPs, which can be potentially effective in treating obesity and obesity-associated disorders (15,16,17).

Let’s discuss about the evolving and emerging prebiotics in the recent market of food and agriculture.

**2.PREBIOTICS**

Prebiotics are mostly fibers that are non-digestible food ingredients and beneficially affect the host’s health by selectively stimulating the growth and/or activity of some genera of microorganisms in the colon, generally *lactobacilli and bifidobacteria* spp(18).

An ideal prebiotic should be

1. Resistant to the actions of acids in the stomach, bile salts and other hydrolysing enzymes in the intestine
2. Should not be absorbed in the upper gastrointestinal tract.
3. Be easily fermentable by the beneficial intestinal microflora (19).

FAO/WHO defines prebiotics as a non-viable food component that confer health benefit(s) on the host associated with modulation of the microbiota. Some of the sources of prebiotics include: breast milk, soybeans, inulin sources (like Jerusalem artichoke, chicory roots etc.), raw oats, unrefined wheat, unrefined barley, non-digestible carbohydrates, and in particular non-digestible oligosaccharides. However, among prebiotics only bifidogenic, non-digestible oligosaccharides (particularly inulin, its hydrolysis product oligo-fructose, and (trans) galacto-oligosaccharides (GOS), fulfil all the criteria for prebiotic classification (20).

Prebiotics like inulin and pectin exhibit several health benefits like reducing the prevalence and duration of diarrhoea, relief from inflammation and other symptoms linked with intestinal bowel disorder and protective effects to prevent colon cancer (21). They are also implicated in enhancing the bioavailability and uptake of minerals, lowering of some risk factors of cardiovascular disease, and promoting satiety and weight loss thus preventing obesity (20).

Prebiotics can be divided in several categories according to their development and regulatory status. Inulin, galacto-oligosaccharides, fructo-oligosaccharides and lactulose are generally classified as well established prebiotics. Xylo-oligosaccharides, isomalto-oligosaccharides, chilto-oligosaccharides and lacto-sucrose are classified as “emerging” prebiotics, while raffinose , neoagaro-oligosaccharides and epilactose are “under development”. Other substances such as human milk oligosaccharides, polyphenols, polyunsaturated fatty acids, proteins, protein hydrolysates and peptides are considered as “new candidates”.

**2.1 FUTURE OF PREBIOTICS**

Disorder of the gut microbiome leads to chronic inflammation-related gut diseases. Classical prebiotics do not show significant inhibition of these diseases; thus, new prebiotics are urgently needed for the chronic inflammation-related gut diseases.

Poly-hydroxybutyrate (PHB), which increases 3-hydroxybutyrate (3HB) in the large intestinal lumen, can be used as a prebiotic to donate 3HB to microbiota. PHB increase the butyrate producing bacteria, release short-chain fatty acids that shows anti-inflammatory effects by activating regulatory T cells. In a study, circulating β-HB were significantly increased during CR(Calorie restriction) and KD(Ketogenic Diet). Moreover, the supplementation of β-HB extended the lifespan of *C. elegans* and longevity. β-HB diminishes senescence-associated secretory phenotype as well as senescent vascular cells in mammals. In addition, exogenous β-HB contributed to stem cell homeostasis and intestinal stem cell function for tissue regeneration. Therefore, β-HB could be regarded as a potential regenerative mediator as well as alleviate age-related diseases(22).

**2.2.AGE RELATED DISEASES:**

**2.2.1. Cancer**

Recent animal studies KD showed a therapeutic approach to tumor cells through selective metabolic oxidative stress, while simultaneously inhibiting primary tumorigenesis and systemic metastasis. They can be effectively used as adjuvant therapy with other therapies to improve quality of cancer patients’ life .

Recent studies have come up on effects of prebiotics on colorectal cancer. The American Cancer Society has named colorectal cancer as the third leading cause of cancer-related death in the United States. Worldwide, CRC (Colorectal cancer) is the third most common type of cancer and the fourth cause of cancer-related deaths. The potential new varieties of prebiotics have been demonstrated to promote the growth of beneficial bacteria such as protein-oligosaccharide conjugates, human milk oligosaccharides (HMOs), and non-carbohydrate molecules including polyphenols, fats, and various plants and herbs .

Fructans are oligosaccharides that consist primarily of fructose and fructosyl units. The fructans group includes the prebiotics inulin, FOS, and oligofructose. Fructan prebiotics are primarily fermented by *Bifidobacteria* in the colon(23). These microbes efficiently work as importers for these molecules and enzymes that cleave and liberate fructose monomers. SCFAs are produced from *Bifidobacteria*  by-products of this metabolic process.(24)

Galactans are oligosaccharides derived from galactose and glucose monomers.They are  further designated as alpha-GOS or beta-GOS depending on the sugar linkages. Alpha-GOS is naturally occurring in foods, whereas beta-GOS is produced synthetically. *Bifidobacteria* are the strongest consumers of galactans prebiotics such as GOS and recently *Lactobacillus* numbers have also been observed to increase after GOS supplementation.(25,26). The specific ingredients such as chicory root, dandelion greens, Jerusalem artichoke, garlic, onions, leeks, asparagus, bananas, burdock root, yacon root, and jicama root, are listed as prebiotic ingredients based on their inulin/FOS content. Alpha-GOS can be found naturally in legumes and various grains. Beta-GOS is synthesized in an enzymatic reaction utilizing beta-galactosidase and lactose; it may be added to various foods or used in isolation as a supplement.

Human milk oligosaccharides (HMOs) are a group of over 200 carbohydrate compounds that are highly abundant in human milk and are being considered as a new class of prebiotics . There are three major HMO categories: fucosylated neutral HMOs, sialylated acidic HMOs, and non-fucosylated neutral HMOs. In vitro studies have shown that HMOs have anti-proliferative and growth arrest effects by directly interacting with epidermal growth factor receptors in the cultured CRC cells to activate ERK1/2-mediated cyclin B1 expression and promote the p53/p38/p21 cascade to arrest the cells at the G2/M checkpoint(27). HMOs also promote *Bifidobacteria (B. infantis)* and *Lactobacillus* growth that produce SCFAs.

Studies have found that HMOs prebiotics can act directly as inhibitors to microbial pathogen adherence through their structural similarity to epithelial cell glycoproteins. HMOs have been shown to inhibit *Campylobacter*, *Vibrio cholera*, *Shigella*, *Salmonella*, *E. coli* toxins, and caliciviruses from binding to host cells in vitro(29). HMOs also restrict the host dendritic cell response to antigens such as lipopolysaccharides by decreasing expression of TLR-4 and microbial pattern recognition receptors to maintain tolerance to gut microbes and avoiding destructive inflammatory responses.

Propionic acid and butyric acid SCFAs inhibit chemokine release by host cells and the adhesion of several pathogens to the gut epithelium. They also reduce the formation and release of NO, and IL-6 and TNF-alpha inflammatory cytokines, while increasing the release of IL-10 and IL-8 anti-inflammatory cytokine(30). SCFAs in the gut lumen bind FFA2 and HCA2 receptors (G protein-coupled receptors) of dendritic cells to initiate immunomodulation.

Activation of downstream pathways stimulates activity of transcription factor NF-κB which can promote the expression of anti-inflammatory cytokines. Dendritic cells subsequently release IL-10 which stimulates the proliferation and differentiation of Treg cells. Dendritic cells also release IL-8 which functions with IL-10 to resolve inflammatory states. B cells are also stimulated by dendritic cells to release IgA antibodies which are secreted into the gut lumen and function to eliminate pathogens.

**2.2.2. Neurological disorders**

Neurodegenerative diseases shows characteristic decline in mitochondrial metabolism, including attenuated ATP generation, increased ROS production, complex IV dysfunction in AD, and complex I dysfunction.

β-HB have some positive inferences like promoting mitochondrial metabolism via multiple mechanisms such as inducing mitochondrial turnover, reducing oxidative stress and impairment of mitochondria, as well as serving as an alternative energy substrate. Moreover, β-HB supplementation may resist neuro-inflammation through inhibiting pathologic microglial activation and regulating NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome pathways. β-HB could prevent the toxicity of neurotoxins.

A study conducted on rats who were fed prebiotics and was examined on their sleep/awake cycle. Rats that ate prebiotics, more quickly realigned their sleep-awake cycles and core body temperature and resisted the alterations in gut flora that often come with stress. The researchers found that those rats on the prebiotic diet hosted an abundance of several health-promoting microbes, including Ruminiclostridium 5 and Parabacteroides distasonis. They also had a substantially different “metabolome,” the collection of metabolic by products churned out by bacteria in the gut(31).Prebiotics may show more promising approaches in lowering neurological disorders.

#### **2.2.3. Cardiovascular Diseases**

Both morbidity and mortality of cardiovascular diseases (CVDs) increase with age, which is the central risk factor of many forms of major diseases. The beneficial effects of a prebiotic complex based on fermented wheat bran and prebiotic chitosan oligosaccharides on heart failure and CHD are partially attributed to the rebalancing of gut microbiota dysbiosis and promoting the growth of different probiotic species.

SCFAs including acetate, propionate, and butyrate are the main end-products of prebiotic fermentation by the gut bacteria. These metabolites show health-promoting functions, including lowering glycaemic levels and body weight and improving intestinal membrane integrity. Another function of SCFAs is to inhibit histone deacetylase. Histone deacetylase inhibitors (HDACs) can regulate chromatin structure to activate transcription factor and downstream gene expression. SCFAs play a role in appetite regulation and energy intake to protect against obesity. Glucose homeostasis can also be modulated by SCFA through improved insulin sensitivity via ameliorated gut barrier function and increased anti-inflammatory and antioxidant abilities (32,33,34,35).

**2.2.4. Muscle dysfunction**

Age-related muscle dysfunction is characterized by progressive sarcopenia and atrophy of skeletal muscles, which is related to frailty, muscle weakness, and disability in the elderly (36). Recently, β-HB show anti-catabolic, anabolic, and regenerative potential has been demonstrated by therapeutic ketosis in human skeletal muscle atrophy under an inflammatory microenvironment(37,38). β-HB has also been proved to potentially slow muscle loss with myopathies by maintaining mitochondrial respiration and morphology within muscle tissue (39). HDACs with age-related muscle dysfunction, has shown roles in regulating metabolic processes in skeletal muscle (40). β-HB, which is one kind of HDAC inhibitor, could be a promising target to treat sarcopenia clinically.

**3.2.5. Inflammation and metabolic syndrome**

β-HB is now considered a modulator of inflammation and immune cell function, yet various research still needed (41). β-HB administration help to promote anti-inflammatory actions, involving the regulation of NLRP3 inflammasome in neutrophils and macrophages and the declining production of inflammatory molecules.

It also inhibit inflammasome formation, lipid accumulation, and oxidative stress by binding to specific HCARs, and inhibiting HDACs, FFARs, and NLRP3, to suppress ER stress, suggesting the beneficial effects of β-HB supplementation on liver steatosis and restoration of liver functions in aging progression .

**II. Discussion**

Many new prebiotics and probiotics are coming up in the medical science and microbiology field. Researchers and scientists need to keep themselves updated continuously of these new pre and probiotics. With the emerging study in the pre and probiotics can navigate a pathway for cost effective treatment in numerous diseases which is the need of the hour. With time, more new novel prebiotics and probiotics will emerge in the world.

**III. Concluding remarks :-**

New tests on human are the need of the hour as in most cases the experiments are conducted over mice or rats. Despite the promising results in preclinical models and other tests, one must consider that the mice microbiota is radically different from the human one and several encouraging preclinical approaches have failed when translated to humans. New research based on human microbiota is the need of the hour.Laboratory scientists need to research more on various mechanisms in vivo and in vitro for new probiotics and prebiotics in food technology,microbiology and medical sciences.

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