

PROBIOTICS AND PREBIOTICS

Pradip Kumar Dutta ¹ Arup Dutta ² Md Nazrul Islam ³ Pranab Kumar Chowdhury ⁴ Sankar Kumar Ghose ⁴

Summary

Thousands of species of bacteria colonize gut. The number of microbes is ten times that of total human body cells. The intestinal microbiota is not always harmful, sometimes it is beneficial for human health. If the growth and activity of the intestinal microbiota is perturbed, it may lead to various diseases such as irritable bowel syndrome, autoimmune diseases, infections, colon cancers, gastric ulcers, cardiovascular disease and obesity. Restoration of the gut microbiota may be done by the use of probiotics (beneficial bacteria). Prebiotics, on the other hand, are the food substrate for probiotics. This review article describes uses and harms of probiotics and prebiotics in the body and their rationale for using in diet.

Key words

Probiotics; prebiotics; microbiota

Introduction

About 10¹⁴ microorganisms (3.3 million genes) belonging to 500 species of bacteria herb in the intestine, they altogether is called 'Microbiota' or 'Normal Flora'. 90% of bacteria belong to different phyla like Bacteroidetes, Firmicutes, and Actinobacteria. [1–3]. According to the World Health Organization (WHO) probiotics are "living organisms which, when administered in adequate amounts, confer a health benefit on the host" [4]. Microorganisms include bacteria, viruses, and yeasts the most common probiotics are certain types of bacteria. The microbiota includes both beneficial and harmful bacteria. Dysbiosis (alteration or imbalance) of microbiota produces diseases like inflammatory bowel disease, antibiotic-associated diarrhea, colon cancer, hypercholesterolemia, and others expected to be prevalent in 21st century [5].

The most common probiotics are Lactic acid bacteria (Lactobacillus and Bifidobacterium). These bacteria are now used as "Probiotics" These along with prebiotics (usually oligomers consisting of 4-10

monomeric hexose units, usually undigestible soluble fibres) and synbiotics (probiotics and prebiotics administered together) are used for disease treatment and preventions [5]. Most of the studies recommend uses of probiotics for general gut health, antibiotic-associated diarrhea, and immunity [6]. Emerging therapy of probiotics focuses on autism and gut-brain connection [5].

A new born baby has sterile gut. Later on the baby acquires microbes from mother and environment. When the baby weans to solid food the microbiota changes, further changes occur when dietary change occurs in adult [7, 8].

Colonic microbes help in the structural integrity. They secrete butyrate (a short chain fatty acid) which induces mucin secretion, antimicrobial peptides and other factors which prevents transformation of cells to neoplastic phenotype and maintains microvasculature of microvillus [9-12]. The gut bacteria also produce vitamin B, synthesize amino acids and causes biotransformation of bile which is required for metabolism of glucose and cholesterol [13-14].

The gut bacteria competes with pathological bacteria for nutrition and attachment to the mucosa and reduces production of lipopolysaccharides and peptidoglycans which are harmful for host [15]. They also give signals for production of T helper type 1, 2 and 17 cells. The short chain Fatty acid butyrate inhibits NF-κB (Nuclear Factor- kappa B) in ulcerative colitis producing immunomodulatory response [16, 17]. Probiotic Lactobacillus reuteri promotes TNF (Tumour Necrosis Factor) induced apoptosis in human myeloid leukemia-derived cells by down regulation of NF-kappaB and enhancing MAPK (Mitogen Activated Protein Kinase) signalling [18].

Dysbiosis of intestinal microbiota causes various immune mediated diseases like Inflammatory bowel disease and atopic disorder. To re-establish microbial homeostasis probiotic and prebiotics are used [19, 20]. They are used as food, dietary supplement and commercial delivery forms (oral and non-oral) [5]. Three international organizations named 'Internal Scientific Association for Probiotics and Prebiotics', 'International Probiotic Association' and 'World Gastroenterology Association' lead the researches and formulate the guidelines for probiotics and prebiotics [21].

1. Professor of Nephrology
Chittagong Medical College, Chittagong
2. Assistant Professor of Paediatrics
Cox's Bazar Medical College, Cox's Bazar
3. Associate Professor of Nephrology
Dhaka Medical College, Dhaka
4. Assistant Professor of Paediatrics
Chittagong Medical College, Chittagong

Correspondence : Dr Pradip Kumar Dutta
email : duttaprd@gmail.com

Materials and methods

Electronic databases from 2001-2012 using pubmed and google scholar were visited by selecting words "Probiotics, Prebiotics and Synbiotics." References of the selected articles were also reviewed.

Probiotic history [22]

History of Probiotics has been around for thousands of years. According to history, The prophet Abraham's long life was believed to be due to drinking soured milk. The Romans used fermented milk to treat intestinal gas. History told that chronic diarrhoea of Francis I of France (king during the 1500's) was cured by yogurt prescribed by a doctor sent to him by the Ottoman sultan . Elie Metchnikoff, won the Nobel Prize in Medicine in 1908, for discovery of bacteria *Lactobacillus bulgaricus* in yogurt which he attributed for long life of peasants in Bulgaria .

Probiotic foods and supplements [23]

Food sources of probiotics include the followings: Yogurt , Kefir (a cultured drink that is similar to yogurt), *Acidophilus* milk, Buttermilk, Sour cream, Aged cheeses (Gouda, Swiss, etc.), Cottage cheese that contains active cultures, Miso (a fermented soybean paste), Tempeh (a fermented soybean product) and Sauerkraut.

Other foods that may contain added probiotics are certain varieties of cereal, juice, frozen yogurt, and even candy. Foods that have added probiotics usually contain *Lactobacillus* or *Bifidobacterium* bacteria, or *Streptococcus thermophilus*. If a food contains added probiotics, on the package one will get phrase "Live and Active Cultures". Some foods may contain more than one type of probiotic. For example, yogurt in the United States must be made with two types of bacteria, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. Stonyfield Farm yogurt contains four other strains : *L. acidophilus*, *Bifidus*, *L. casei*, and *L. rhamnosus*. Probiotics are also available as capsules, tablets, powders, and liquids. Like other dietary supplements, probiotics are not regulated by the US Food and Drug Administration (FDA).

Prebiotics [24]

Prebiotics are indigestible soluble fibres that serve as food substrate for probiotics. Since humans don't digest prebiotics, these nutrients pass through the digestive system until they are fermented in the large intestine by bacteria. Prebiotics may have some properties of their own, including the following:

i) Enhancing absorption of minerals, such as calcium, iron, and magnesium

ii) Promoting healthy bowel function and regularity
iii) Inhibiting growth of cancerous lesions in the digestive tract

iv) Improving the functioning of the immune system
v) Lowering blood cholesterol levels. The following foods are good sources of prebiotics: Asparagus, Bananas, Onions, Garlic, Wheat bran, Oatmeal and Barley.

Prebiotics may also be added to foods like cottage cheese, yogurt, yogurt drinks, cereals and pasta. Like probiotics, prebiotics are available as supplements, usually in capsule or powder form. There is no established daily dose of prebiotics, usually 5-15gms/day [25].

Clinical uses of Probiotics, Prebiotics & Synbiotics:

1. Lactose intolerance

Lactose intolerance occurs due to deficiency of enzyme 'lactase' The patient complains of abdominal cramping or pain, gas, bloating, nausea, or diarrhea. The *Lactobacillus* genus of bacteria (which includes many different species) present in yogurt or acidophilus drink converts lactose into lactic acid and relieves patient [26].

2. Antibiotic associated Diarrhoea (AAD) and infections of urogenital system [27]

Antibiotics kill off non-pathogenic bacteria throughout the body, including the digestive tract, the urinary tract, and reproductive organs. As a result, antibiotic-induced diarrhea (caused by pathogenic *Clostridium Difficile*) or a yeast infection in the mouth or vagina ensues. Different meta analysis have shown that Probiotics (especially formulation containing *Lactobacillus rhamnosus*) has been shown to reduce antibiotic-induced diarrhea. Some may be helpful for women who get vaginal yeast infections whenever they take an antibiotic .A probiotic yeast called *Saccharomyces boulardii*, along with antibiotics, may also help prevent recurrent *C. diff* infection [28]. Caution should, however, be exercised when administering probiotic supplements to immunocompromised individuals or patients who have a compromised intestinal barrier [29].

3. Immune function and infections

Some strains of Lactic acid bacteria (LAB) may compete with pathogens for growth, improve immune function by increasing the number of IgA-producing plasma cells, increasing or improving phagocytosis as well as increasing the proportion of T lymphocytes and Natural Killer cells [30,31]. Clinical trials have demonstrated that probiotics may decrease the incidence of respiratory tract infections,

rota virus infection, traveller's diarrhoea in adults and dental caries in children [31,32]. Probiotics maintain immune system activity damaged by antibiotics (Antibiotics kill off good bacteria) [33].

4. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder producing frequent and recurrent alternating bouts of constipation and diarrhoea. Probiotics containing bacteria 'Bifidobacterium infant' seems to help with bloating, pain, and bowel regularity. Sometimes multibacterial probiotic reduced diarrhea in people with IBS [34].

5. Urinary tract infections (UTI)

E. Coli is the commonest aetiological agent causing UTI. Women and diabetic patients are more prone to UTI. Probiotics containing two specific strains of bacteria Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 has been shown to reduce the incidence of both UTIs and vaginal infections[35].

6. Inflammatory bowel disease

Some strains of LAB may modulate inflammatory and hypersensitivity responses by regulating cytokine function [30]. They can prevent recurrences of inflammatory bowel disease in adults probably by modulating the response of T lymphocytes to pro-inflammatory stimuli [30,36]. One study showed equivalence of Mutaflor and mesalazine (5-ASAs) in preventing recurrence of ulcerative colitis[37].

7. Blood pressure

Although not a confirmed effect, some studies have indicated that consumption of milk fermented with various strains of LAB may result in modest reductions in blood pressure, an effect possibly related to the ACE inhibitor-like peptides produced during fermentation [38].

8. Allergy and Atopic diseases of children [39-45]

Aberrant immune responses to environmental allergens lead to atopic disease in children [5]. Atopic dermatitis is a common allergic skin disease in children. Children suffering from AD have higher number of S. aureus and Clostridium in their colon and lower number of Enterococcus, Bifidobacterium, and Bacteroides [5]. Probiotics (like Lactobacillus GG, L. Rhamnosus, L. fermentum and Bifidobacterium) play potential role in improving atopic dermatitis in children. Probably they did it by reduction of IFN- and IL-10, so decreasing intestinal inflammation.

9. Obesity and metabolic syndrome

The gut microbiota of Diabetic and obese persons differ from that of normal persons [5]. Patients with diabetes mellitus had a lower number of 'Faecalibacterium prausnitzii' and an increase of inflammatory markers [5]. The Bifidobacteria population (and most other organisms in the group of Firmicutes) is slightly lower in individuals with obesity than in lean people and diabetic than non-diabetic patients[46]. Using probiotics containing different LAB and prebiotics containing arabinoxylan and inulin-type fructans showed decreased fat mass, risk of type 2 Diabetes and insulin resistance [47]. Probiotics probably increase Angiopoietin related protein 4 (Angptl4), a lipoprotein lipase inhibitor which inhibits the uptake of fatty acids from circulating lipoproteins and prebiotics prevent the over expression of certain host genes related to adiposity and inflammation[5,48]. Though different meta analysis failed to show significant reduction of serum cholesterol by giving yogurt (probiotic), but they noted significant increase in HDL from 50mg% to 62%.[49,50].

10. Cancer prevention

Different studies reported probiotics with LAB, especially combination of probiotics and prebiotics (5-15% inulin or oligofructose) reduced colonic cancer [5]. The suggested mechanism are either probiotics combine with heterocyclic amine (which are carcinogenic) or they inhibit beta glucuronidase (which generates carcinogens)[38,51]. Different strains of LAB are now in phase III trial for uterine cervical cancer and some other strains are now being used for radiation and chemotherapy induced diarrhoea [5].

11. Renal failure

value of probiotics in the nephrectomised animals has already been demonstrated in different studies which showed reduction of blood urea nitrogen and ultimately prolonged life span [52]. A 6-month randomized, double-blind, placebo controlled, and crossover trial in CKD stage 3 and 4 patients in four countries with probiotic (LAB) showed decreased BUN levels in 29 patients (P < 0.05), decreased creatinine levels in 20 patients (no statistical significance), and improved quality of life (P < 0.05) [53].

12. Hepatic encephalopathy

Minimal Hepatic encephalopathy (MHE) is a chronic liver disease due to gut-derived-nitrogenous substances (ammonia) derived primarily from increased urease activity by enteric bacteria.

Gram negative bacteria mainly produce urease and in MHE level of Bifidobacteria is substantially reduced. Probiotics cause reduced concentration of gram negative bacteria, increase concentration of LAB, decrease bacterial urease activity, and overall reverse MHE in 50% of cases [5,54].

Emerging fields of Probiotic research :

1. Myocardial Infarction (MI)

Bacteria in intestine by leptin production promotes myocardial infarction. Vancomycin kills bacteria and reduce MI. LAB like *L. plantarum* 299v decreases leptin production and reduces MI more than Vancomycin [55,56].

2. Psychotropic Properties

Probiotic formulation consisting of *Lactobacillus helveticus* RO052 and *B. longum* RO175A reduces stress induced gastro-intestinal discomfort. In human volunteers they are also shown to reduce anxiety, stress, depression, chronic fatigue syndrome and coping strategies. Suggested mechanisms are :

- i) Microbiota is responsible for gut-brain signalling and probiotic by their action in the digestive system aids in psychological distress.
- ii) By the anti-inflammatory properties of these good bacteria probiotics may modulate the activity of brain structures involved in the processing of emotions related to anxiety, mood and aggression.
- iii) Probiotics produce neurotransmitters that act directly or indirectly on specific targets in the central nervous system.
- iv. Probiotics regulate glycemic control thereby glucose tolerance, and glucose intolerance has been linked to the risk of depression.
- v) probiotics reduce substance P in stomach which is a neurotransmitter associated with pain and inflammation, and linked to anxious, depressive and aggressive behaviours [57,58].

Drug interactions of probiotics [5]

Probiotics interact with warfarin. Antibiotics kill off some beneficial bacteria when given together. Antifungal also reduces the efficacy of probiotics. Use of Probiotics with immunosuppressants, such as cyclosporine, tacrolimus, azathioprine, and chemotherapeutic agents is contraindicated because of pathogenic colonisation in immunosuppressed condition.

Safety of Probiotics

The use of probiotics in children, elderly, pregnant women and immunocompromised patients (like AIDS) is not studied. Probiotic foods are more safe than supplements. Probiotic are also not safe in organ failure and ICU patients [59]. Dutch Pancreatitis Study Group, the consumption of a mixture

of six probiotic bacteria found increased death rate of patients with predicted severe acute pancreatitis with probiotics [60]. Probiotics cause lactobacillus septicaemia in lowered immune systems [61].

Safety of Prebiotics

Prebiotics are generally considered to be safe. Common side effects include gas, bloating, and cramps. Prebiotics themselves do not affect blood glucose level, if they've been added to a food that contains carbohydrate, they may slow or otherwise change the digestion of that food's carbohydrate [62].

Conclusion

Probiotics, prebiotics and synbiotics are now increasingly used in digestive disorders like IBS, traveller's diarrhoea and AAD. Promising results are also seen in Psychiatric disorder, Hypercholesterolemia, obesity, Chronic Kidney disease and cancer. Besides children, pregnant women and immunocompromised patients their use were found to be safe. Newer tools for identifying human microbiome opened an exciting chapter for identification of individual microbiome and diagnose association of individual disease with probiotics.

Disclosure

All the authors declared no competing interestes.

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