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Review Article

Investigation of the Potential Benefits and Risks of Probiotics and Prebiotics and their Synergy in Fermented Foods

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Abstract

Fermented foods are consumed throughout the world and produced as a means of preserving perishable products when other options of refrigeration/pasteurization were unavailable. The microorganisms that carry out the fermentation process can improve the nutritional quality of food by increasing the amount and availability of in nutrients. Moreover, microorganisms themselves contain cellular enzymes and biologically active components. Fermented foods are considered as functional foods thought to provide benefits beyond basic nutrition and may play a role in minimizing the risk of certain diseases. Prebiotics (substances that induce the growth or activity of microorganisms) and probiotics (microorganisms that are believed to provide health benefits when consumed) are proven to promote gastrointestinal health and immune function. Probiotics, prebiotics and synbiotics are functional components able to exert positive effects on human health. This is achieved by different mechanisms of actions to remediate the health problems of the host such as allergy reduction, immunity production, cholesterol level reduction and help to reducing cancer. However, there is a little and mildcomplications encountered from these products when they are consumed without the recommended dosage. The dynamic relationship between the gut microbiota, substrate utilized and the host has been described as a symbiosis. Therefore, proper utilization of fermented products, prebiotics and probiotics are suggested to improve the healthinessand the cost dispense through biological medication.

Key words: Fermented foods, gut biota, prebiotics, probiotics, synbiotics

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INTRODUCTION

In recent years, scientists have become aware of human microbiota in general and gut microbiota, in particular that play a major role in human health and diseases[1]. Since the beginning of human civilization there has been an intimate companionship between the human being and the fermentative activities of microorganisms[2]. Fermentation is an ancient form of food preservation, which also improves the nutritional content of foods. In many regions of the world, fermented foods have become known for their health-promoting attributes[3]. Fermented foods have a long history of use in Africa and in recent years efforts have been made to identify the microbial strains and propagate them as probiotics to confer additional health benefits[4]. Fermentation in food processing is the conversion of carbohydrates and other macromolecules using yeast and/or bacteria, under anaerobic conditions[5]. Fermentation is one of the classic methods to preserve foods where Lactic Acid Bacteria (LAB) and yeasts take the leading position[6]. The weight of the microorganisms in the food is usually small, but their influence on the nature of the food, especially in terms of flavor and other organoleptic properties is profound[7]. The foremost precondition for survival is to secure food. To assure food security, humans rely on resources that are close by and available method of preservation. Therefore, the most important concept with fermented food is storage, or preservation and health benefits of the consumers[8].

A food that contains biologically active components which beneficially affects one or more target functions in the body along with its nutritional effects is known as "Functional foods". Among these foods or beverages that are fortified through addition of exogenous functional compounds (i.e., prebiotics) or using microorganisms that produce biogenic compounds or have probiotic features (probiotics) and their combinations (symbiotic)[9]. A functional food with new ingredients gives an additional function to human health. Above their basic nutritional value functional foods deliver enhanced benefits and their industry is growing rapidly in recent years[10]. Some food components exert beneficial health effects beyond basic nutrition, leading to the concept of functional foods and nutraceuticals[11]. A nutraceutical is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food[12]. Furthermore, some functional food components influence the growth and/or metabolic activity of the gut microbiota and thereby, its composition and functions[13]. It is difficult to separate functional and conventional foods in appearance. Functional food can provide the needs of the body with the required amount of vitamins, fats, proteins, carbohydrates, etc., for healthy survival[14,15]. In addition improving the health and well-being of consumers, production functional foods with probiotics as in dairy products are attractive for marketing, providing new economic opportunities[16]. Moreover, the functional foods must remain as foods (not capsules, etc.) and they must also reveal their effects in amount that can usually be expected to be consumed in the diet. The demand for functional foods is growing rapidly all over the world due to the increased awareness of the consumers on the benefits of designer foods on health[17]. Today, over 60% of functional food products are directed towards intestinal health, with prebiotics and probiotics probably being the most common, worldwide. Currently, traditional fermented products, spontaneously and uncontrolled are receiving new attention for their health promoting, valuable source of LAB and disease preventing or probiotic significance[18].

Probiotics and prebiotics and both together termed synbiotics are bioactive components attracting much attention nowadays, although their use as fermented foods containing beneficial microbes, particularly LAB have been used by humans for thousands of years[19]. Probiotics are living bacteria that, when administered in adequate amounts, confer a health benefit on the host[20]. Lactic acid bacteria from food sources, such as dairy-based products, fermented fish, meat and vegetables are reported to possess antagonistic activity against food-borne pathogens[21,22]. Probiotics are a live microbial feed supplement which is beneficial to health and the most commonly used dietary method of influencing the gut flora composition[23]. The positive effects of probiotics and prebiotics on human health are being widely promoted by health and nutrition professionals in today's scenario. Their treatment has been shown to be a promising therapy to maintain and repair the intestinal environment[24]. A number of health benefits have been claimed for probiotic bacteria and more than 90 probiotic products containing one or more groups of beneficial organisms are available worldwide[17]. They involved in various health benefits of Inflammatory Bowel Disease (IBD), colon cancer, diarrhea, allergy, diabetes and infection and liver diseases etc.[25]. In contrast to their benefits, probiotic side effects are uncommon, but if they do occur they tend to be mild. Digestive symptoms occur as a result of probiotic side effects possibly are bloating or flatulence and unhealthy metabolism[26]. Prebiotics are non-digestible carbohydrates and selectively stimulate the growth and/or activity of beneficial bacteria[27]. The rationale behind prebiotic use is to promote the indigenous beneficial bacterial strains including lactobacillus and bifidobacterium[28].

Consumption of beneficial probiotic bacteria combined with oligosaccharides (symbiotic) enhance colonic bacterial composition and improve internal health[29]. Recently they are proposed as new therapeutic option in pediatric surgery, digestive organ surgery, liver disease and systemic inflammatory response syndrome[25]. Probiotics and prebiotics target the host gut by distinct as well as complementary mechanisms of actions[30]. Modes of action of the gut microbiota are: Preventing the attachment of pathogenic bacteria, eradicating some pathogens from the stools, secretes antimicrobial substances known as bacteriocins, development of immune system and production of different enzymes to mediate diarrhea[31]. They also down regulate inflammatory response, modulate host gene expression and deliver functional proteins or enzymes[32]. Food allergic disorders are contributing a serious health complication in the developed as well as developing world[33]. Food hypersensitivity or food allergy is a prevalent health problem associated with the developed and developing countries. Approximately 6% of infants and 3.7% of adults with an age less than 3 years have been reported to be prone of food hypersensitivities[34]. Genetic and environmental predisposition plays key role in the prevalence of the food hypersensitivity reactions in the susceptible individuals[35]. Several studies suggest the role of prebiotics and probiotics in curing allergic diseases[33]. Antibiotic resistance with the emergence of multiple resistant strains is an increasingly important global problem. This causes destruction of beneficial bacteria leaving resistant ones, pathogenic. Of late, it has been realized by health care professionals and prompted them to seek alternative therapeutic options. One such alternative is the use of beneficial bacteria, the probiotics which stimulate health promoting indigenous flora and reverting back the change[36,37].

Generally, this study assesses the potential role of probiotics and prebiotics as well as their combined effect on the health benefits of the host and in the possible treatment of diseases. Moreover, considering the side effects and higher price of allopathic medicines, to recommend the use of prebiotics and probiotics.

PROBIOTICS AND PREBIOTICS

Today's consumers are increasingly interested and conscious about their health and the food that they eat need to be healthy or even capable of preventing illness. Probiotics, prebiotics and synbiotics are the new concepts that have been developed to modulate the target gastrointestinal microflora balance[38]. Both probiotics and prebiotics are thought to work largely through direct or indirect effects on the gut microbiota and environment and/or on host function. Prebiotics enhance the growth of the endogenous microbiota or possibly stimulate the growth of probiotics when provided concomitantly[30]. Probiotics and prebiotics as commensally organisms act on and interact with the host by two main modes of action or a combination of actions. Probiotic and prebiotics are aimed at modulating the intestinal microbiota, promoting intestinal health, enhancing immunity and thereby improving general well-being and quality of life[39]. Thus, probiotics and prebiotics share many common mechanisms of action mediated through an impact of microbes on the host and these are discussed below.

Concept of probiotics: Probiotics were first described by Metchnikoff in 1908 based on his observations on the longevity of individuals who lived in a certain part of Bulgaria and which he attributed to their ingestion, on a regular basis of a fermented milk product. Probiotics, derived from the Greek and meaning "For life" are defined as live organisms that, when ingested in adequate amounts, exert a health benefit to the host[40]. Several lactococci, lactobacilli and bifidobacteria are held to be health benefiting bacteria but little is known about the probiotic mechanism of gut microbiota. Probiotics can be typically naturally occurring microbes, those used in foods or isolated from humans, animals or microbes that have been genetically altered for a specific effect[32]. Although, many of them are considered to be live cultures, the terms are not synonymous. Live cultures but not all probiotics are associated with foods as food fermentation agents[41]. However, live cultures have not necessarily been tested for health benefits. Similarly, the term probiotic is not synonymous with native commensal bacteria, although they may be isolated from the same source[41]. In order to be considered a probiotic, the native commensal bacteria must be shown to have a health benefit when administered to humans. The most common types of probiotics are lactic acid bacteria that include specie from the *Lactobacillus*, *Pediococcus* and *Bifidobacterium* genera. Various species including *Lactobacillus rhamnosus* and *Bifidobacterium* have mainly been used as probiotics over the years[42]. Factors, which technically support and influencing the function of probiotics are strain characteristics, stability, fermentation technology, target prebiotics, viability and non-viability, micro encapsulation etc. From Fig. 1, it can be easily assayed how probiotic functionality influenced by different technical factors.

Prebiotics concepts: Prebiotics are non-digestible food ingredient which beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improving host

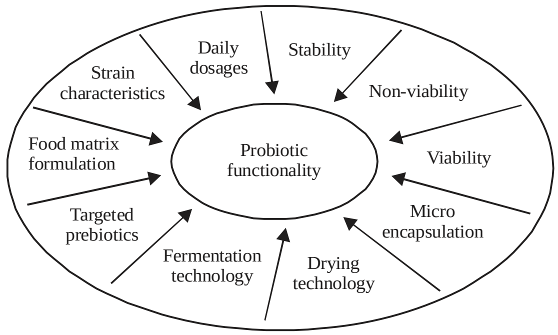

Fig. 1: Influencing technological factors for functionality of probiotics, Source: Bandyopadhyay and Mandal[38]

health. Prebiotics are an alternative for probiotics or their cofactors[43,25]. The concept of prebiotics essentially has the same aim as probiotics, which is to ameliorate host health via modulation of the intestinal flora, acting by a distinctive mechanism[36,44].

They specifically target the flora of the large intestine. They are considered to be a functional food and were first identified and named by Roberfroid[45]. Prebiotics pass through the digestive system without being broken down by the digestive enzymes i.e., reach the large intestine in an intact form and serve as a feast for the probiotic bacteria that live there[38]. They are dietary short-chain carbohydrates (oligosaccharides) specifically utilizable by intestinal microflora. They have been referred to as the bifidus factor, because they support the growth and/or activities of probiotic microorganisms in the gastrointestinal tract[46]. They are a source of carbon and energy for the friendly strains of bacteria already inhabiting in the colon, where bacterial fermentation processes of some nutrients occurs[47]. Prebiotics of proven efficacy are able to modulate the gut microbiota by stimulating indigenous beneficial flora while inhibiting the growth of pathogenic bacteria therein. They are normally commercially extracted from fruits and vegetables through enzymatic hydrolysis of polysaccharides from dietary fibers or starch. Potential prebiotic carbohydrates include fructooligosaccharides (FOS), galactooligosaccharides (GOS), lactulose, lactosucrose, soybean oligosaccharides, isomaltooligosaccharides, palatinose, xylooligosaccharides and glucooligosaccharides[48]. The most researched prebiotics are non-digestible oligosaccharide molecules, containing 3-10 monosaccharide residues connected by glycosidic linkages. Most of them occur naturally as native components in plants e.g., raffinose and stachyose in beans and peas, OF and inulin in chicory, garlic, artichoke, onion and leek[29]. Prebiotic oligosaccharides taking interest amongst food researchers and are getting more global attention than other functional foods because of their multipronged beneficial effects including gut health, higher mineral absorption, lowering of cholesterol, immune system stimulation, pathogen exclusion, etc.[49,50].

HEALTH BENEFITS OF CONSUMING PROBIOTICS AND PREBIOTICS

Bacteria have a reputation for causing disease, but a growing body of scientific evidence suggests that one can treat and even prevent some illnesses with foods and supplements containing certain kinds of live bacteria. For example, Metchnikoff related the longevity of Bulgarians to the presence of *Lactobacillus bulgaricus* in the souring milk yogurt[51]. Infectious diseases are the biggest problem to humans. Every year gastrointestinal infections lead to significant morbidity and mortality worldwide[52]. The WHO[53] estimates that more than 4 billion episodes of diarrheal disease occur annually and those 2.2 million deaths were attributable to enteric infection, making it the 5th leading cause of death at all ages worldwide. Consumption of food containing live bacteria in the form of fermented products is the oldest and still most widely used way to increase the number of advantageous bacteria called probiotics in the intestinal tract[54].

Probiotics have established their efficacy as dietary factors that can regulate gastrointestinal functions, thereby imparting health benefits to consumers. Alleviation of lactose intolerance, prevention of diarrhea and urogenital infections, cholesterol reduction, reduction of atopic diseases and modulation of the immune system are some of the functions attributed to probiotics[55,56]. Other benefits include prevention of cancer, particularly colon carcinoma and food allergy[57]. The competitive exclusion of pathogens and the reduction in number as well as metabolic activities of harmful organisms by probiotics have been demonstrated *in vitro*[56]. Dysbiosis occurs when there is an alteration in the normal balance of micro-flora or organisms of the human body. Thus, it becomes imperative to control dysbiosis by fortifying the body with "Good bacteria" known as probiotics[58].

There are large numbers of probiotic containing foods that date back to ancient times. These mostly originated from fermented foods, as well as cultured milk products[59]. The quest to find food ingredients with valuable bioactive properties has created interest in LAB with probiotic attributes such as antimicrobial activity against pathogenic microorganisms[60]. In Ethiopia there is few studies have been conducted on the health benefits and risks of probiotics and prebiotics. Their role as antagonism or as biological control methods from Ethiopian traditional fermented borde and shamita was reported by Anteneh *et al.*[61]. Here are some of the health benefits of probiotic and prebiotic containing food products.

Experimental evidence indicates that probiotics are effective in treating atopic eczema in infants[62]. It has also been shown that the incidence of allergies in infants with a high risk of allergy can be halved with the consumption of certain probiotics by their mothers during pregnant and by the infant after birth. It is thought that consumption of probiotics helps to form a normally functioning immune system, preventing allergies[63]. Similarly they involved in the treatment of peptic ulcers[27]. *Helicobacter pylorus* is pathogenic bacterium that causes peptic ulcers and other gastric problems. The *H. pylorus* is normally treated with antibiotics. This treatment is expensive and has negative side effects. The consumption of probiotics with antibiotics is thought to be the most effective and safest treatment[64]. Diarrheal reduction and prevention is also the role of probiotics and prebiotcs. Evidence indicates that probiotic bacteria in foods can help prevent and treat diarrhea in children. Rotavirus infections are a common cause of diarrhea in children. In clinical trials, infected children who consumed probiotic fermented milkhad lower rates of diarrhea. Probiotic treatments have also been used to effectively treat antibiotic associated diarrhea[65].

Milk is fermented by bacteria and the protein in the milk is hydrolyzed into smaller peptides. The peptides are absorbed in the small intestine. Consumption of these peptides in milk and yogurt has been shown in clinical studies to lower blood pressure in some individuals[66]. The consumption of probiotics reduces the transit time for the movement of wastes through the intestines. This results in reduced constipation and may help prevent colon cancer. Prebiotics also decrease transit time through the intestines because they are a form of fiber. Probiotics and prebiotics are reducing infections in sick and postoperative patients. Since the use of antibioticsreduces the population of intestinal bacteria, using probiotics and prebiotics to repopulate the beneficial intestinal organisms in the digestive tract[65]. On top of this, lactose digestion, HIV/AIDS retardation and immune function are known health benefits of probiotics. Individuals with lactose intolerance are missing an important digestive enzyme, lactase. Probiotic bacteria make the lactase enzyme and consumption of these bacteria can help lactose digestion[67]. Recently the role of probiotics to slow down the progression of AIDS has been postulated by Lin[68]. Some *Lactobacillus* strains produced proteins capable of binding a particular type of sugar called mannose found on HIV envelope. Consumption of probiotics can enhance natural immune functions[65].

Protective role from *Mycobacterium tuberculosis* and *Mycobacterium bovis*, prevention of necrotizing entero colitis, cancer prevention and cholesterol assimilation/hyperlipidemia are some tips on the positive benefits of probiotic and prebiotic consumption. The simultaneous presence of indigenous LAB in *Mycobacterium* contaminated milk is believed to confer protective effect when the milk is adequately fermented[69]. The NEC is a challenging clinical disease entity, which is a complication of very low birth weight infants and is often fatal. Several clinical studies showed that the use of probiotics significantly reduces mortality[70]. Another benefit of probiotics is serum lipid reduction. They have role to play in the cholesterol lowering mechanism. Cholesterol level keeps increasing leads to cardiac diseases. These cholesterol levels can be brought down using probiotics[71]. Probiotics are preventing cancer by reducing DNA damage by carcinogens[67]. Prebiotics, being indigestible have been associated with improved bowel functions and metabolisms of the distal colon, including a reduced risk of colon cancer[68]. Finally, assisting vitamin and mineral uptake and other potential health benefits of probiotics and prebiotcs are to increase the bioavailability of vitamins and protein in the GI tract as a result of increased acidification of the gut pH by the lactic acid produced by bacterial strains[72]. Some experimental animal and human suggest probiotics may reduce the risk of heart disease by their beneficial effects on blood lipid levels and blood pressure[73], alleviate kidney stones[74], decrease inflammation associated with arthritis[75] and protect against dental caries.

Side effects or risks of probiotics: Most of the significance of probiotics mentioned has a beneficial role on the host. However, there is another side to this therapy. They are usually used by patients suffering fromindigestion, diarrhea or heartburn. While probiotics alleviate some of these problems, they also cause similar kind of complications when it is not taken as per prescription. The national center for the complementary and alternative medicine describes the potential gastrointestinal side effects of probiotics. The most common side effects of probiotics are gas and bloating. In more serious and rarer instances, probiotics can cause infections, especially in immune-compromised people[76]. Recently, probiotics are known to react with certain drugs like sulfasalazine. They cause faster metabolism of these drugs and thereby causing higher quantities of them in the body. In some cases the genetically modified strains increases the mortality rate of patients with acute pancreatitis. In a clinical trial conducted at the University of Western Australia, aimed at showing the effectiveness of probiotics in reducing childhood allergies, those given the good bacteria were more likely to develop sensitivity to allergens compared to placebo treatment[77]. Some individuals may experience side effects related to the ingestion of probiotics due to the death of pathogens in the gut environment, as they release toxic cell products ("Die-off reaction"). In such cases, one should persist in the use of probiotics for which there is improvement in symptoms. There is also slight increase in gas production, abdominal discomfort and even, in rare cases, diarrhea associated problems of probiotics which resolved spontaneously by time[78].

Generally, probiotics side effects tend to be mild and digestive problem (such as gas or bloating). More serious effects have been seen in some people. The Food and Drug Administration (FDA) has special labeling requirements for dietary supplements and treats them as foods, not drugs. No Complementary and Alternative Medicine (CAM) therapy should be used in place of conventional medical care or to delay seeking that care. They can interact with commensal bacteria and can also have a direct impact on the host. Disentangling these interactions is one of the key challenges for future research. Other key challenges are to understand their mechanisms of action to elucidate more specifically which probiotic strains can offer which health benefits and to define the intake levels needed to achieve those effects[30].

Beneficial effects of prebiotics: Prebiotic influences the content of Volatile Fatty Acids (VFA), lactic acid concentrations and ammonia concentrations in the gut[79]. Increased concentrations of Short Chain Fatty Acids (SCFA) stimulate natural bacterial activity and abundance of bifidobacteria and LAB. The production of butyrate is a dominant energy source for enterocytes to increases. The mannanoligosaccharides are important because they modify the microbial gut ecosystem by binding to the receptors present in the intestinal epithelium, thereby preventing the colonization of bacterial pathogens[80]. Use of this type of additives has a beneficial effect on the production results, animal's equalization, reduce mortality and morbidity and lower treatment costs.

Probiotics suppress the growth of *E. coli*, *Salmonella typhimurium*, *Clostridium botulinum* and *C. sporogenes* and conversely stimulate the growth of *B. longum*, *L. casei*, *L. acidophillus* and *L. delbrückei*[81]. Mannan-oligosaccharides from the yeast cell wall stimulate the local immune system by increasing the activities of macrophages and T-lymphocytes. Bifidogenic effects of galactooligosaccharide (GOS), fructooligosaccharide (FOS) and soybean oligosaccharides have been repeatedly confirmed by many *in vitro* and *in vivo* experiments, where they selectively interacted with the intestinal bacterial ecosystem[82,83]. Observed an increase in *Bifidobacterium* and *Lactobacillus* genera numbers in the intestine, a concomitant increase in SCFA concentration and improved small intestine morphology[46]. Dietary supplementation with inulin has a positive effect on SCFA production, sufficient height of intestinal villi and stimulation of natural microflora and improvement of efficiency parameters[81].

Generally, prebiotics have effects on bifidobacteria proliferation and reduction of the proliferation of harmful microorganisms, increasing animal performance, removing harmful enzymes and toxic metabolites, lowering blood cholesterol level, lowering blood pressure, preventing the processes of carcinogenesis, affecting the synthesis of vitamins B1, B2, B6, B12, folic acid and nicotinic[84]. Since the commercial oligosaccharides increase carbohydrate fermentation, they also increase gas formation. The main side-effects are flatulence and bloating. These effects may be present with the intake of 5 g in sensitive persons, but may be absent with the intake of 40 g in tolerant persons. In other words, the side-effects are due to the type of oligosaccharide and the tolerance of the host[27].

MOLECULAR CHARACTERIZATION AND IMMUNOLOGIC ROLE OF PROBIOTCS

The immune system of mammals includes a complex array of cells and molecules, which interact to provide protection from challenge by pathogenic microbes (bacteria, viruses, parasites). Antigens are often components of invading microbes. Various organs participate in this immune response. For example, bone marrow, thymus, spleen, lymph nodes and mucosal lymphoid tissue. As most antigens penetrate the body through the mucosa, the mucosal immune system of the host plays a key role in the defense response to pathogens[85].

Probiotics can modulate systemic and mucosal immune function, improve intestinal barrier function, alter gut micro ecology and exert metabolic effects on the host. Epithelial cell signaling pathways are stimulated by whole microbes, structural components and microbial-produced metabolites[86]. Probiotic inhibition of pathogen adherence to epithelial cells is mediated partially by competition for lectin binding sites on glycoconjugate receptors on the brush border surface[87]. Probiotics also express microorganism-associated molecular patterns (MAMPS) that bind to the same pattern recognition receptors as pathogens do, thus preventing access via competitive exclusion[88]. Probiotics also induce mucus secretion, which would aid in preventing pathogenic bacteria adhesion[89].

Several data confirm that gut microbiota is engaged in a dynamic interaction with the intestinal innate and adaptive immune system, affecting different aspects of its development and function. Butyric acid, a byproduct of bacterial fermentation of fiber has been shown to nourish colonic enterocytes enhancing mucosal integrity[90]. The DNA of probiotic organisms may also inhibit apoptosis of entero colitis. This is the most common and serious acquired intestinal disorder. The LAB also demonstrated a host of properties in preventing colorectal cancer development by inhibiting initiation or progression through multiple pathways. Colorectal cancer (CRC) is one of the major health challenges, representing the second cause of cancer deaths. Cellular and molecular mechanisms of LAB in CRC prevention including apoptosis, antioxidant DNA damages, immune responses and epigenetic are discussed by Zhong *et al.*[91]. Apoptosis is a form of genetically programmed cell death, playing a key role in the regulation of cell numbers. An important pathogenetic event in many types of cancers is the reduced ability to trigger apoptosis associated with alteration of control processes of cell proliferation. The regulation of cell survival and death at molecular level on the apoptotic process can have a huge chemo preventive and therapeutic potential. The LAB can play a role in the regulation of cell apoptosis via intrinsic and extrinsic pathways which are potentially critical mechanisms in the prevention of CRC. The metabolic antioxidant activities of LAB may be assigned to Reactive Oxygen Species (ROS) scavenging, enzyme inhibition and reduction activity or inhibition of ascorbate autoxidation in the intestine by neutralizing free radicals. The term "Epigenetics" is used to describe those mechanisms which are able to modify the expression levels of selected genes without necessarily altering their DNA sequences, including DNA methylation, histone tail modifications, chromatin remodeling, as well as mechanisms mediated by non-coding RNA molecules. Epigenetic modifications are often induced by environmental factors. Currently, there is a growing interest in the consumption of probiotic foods due to their reported health benefits. Probiotcs specially, *Bifidobacterium* and *Lactobacillus* decreases the inflammatory cells and also helps in raising the immune system efficiency and has a remarkable effect on IgM and IgE[92] as shown in Fig. 2a-d. Identification of lactobacilli has previously been based on culture dependent methods and recently molecular techniques involving gene sequencing are now the gold standard[93]. Phylogenetic analysis of rRNA genes, amplified by PCR, has been used as a rapid and efficient strategy to investigate the biodiversity of intestinal bacteria and revealed many novel species[94]. A 460 bp fragment could be obtained as a result of amplification of the 16S rRNA gene in both *Lactobacillus* and *Bifidobacterium* using the primers[95]. The 16S rRNA sequence is used for phylogenetic studies as it is highly conserved between different species of bacteria.

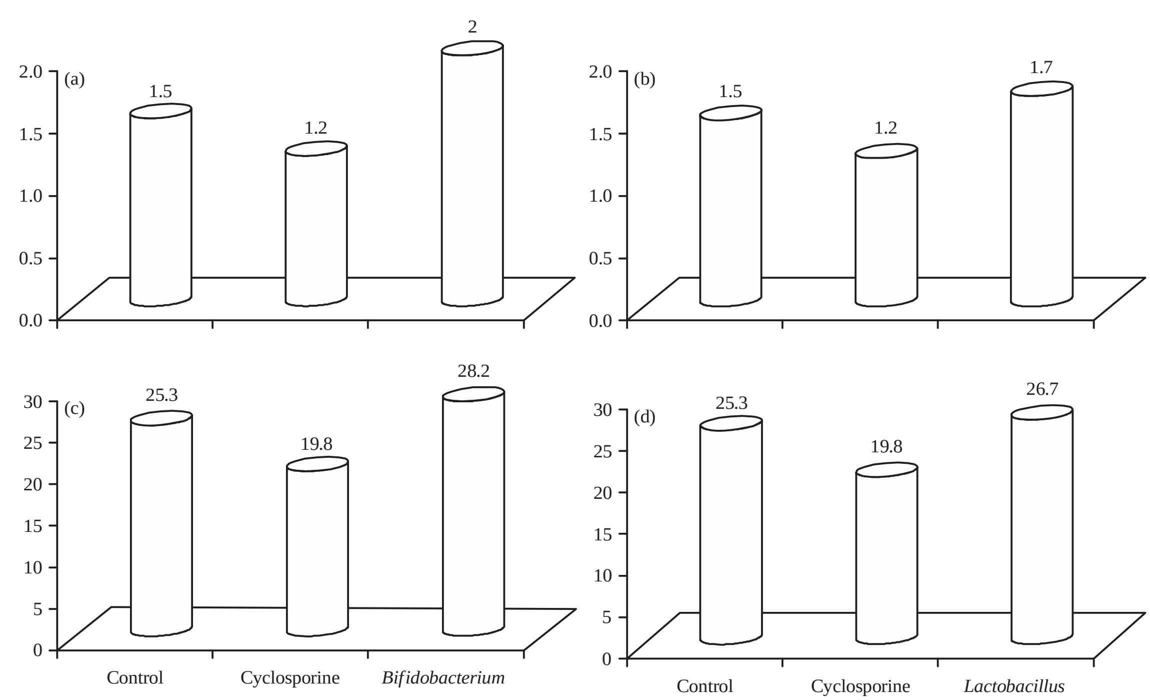

Fig. 2(a-d): Immunological role of some selected probiotics, IgE levels after treatment with (a) Cyclosporine and *Bifidobacterium*, (b) Cyclosporine and *Lactobacillus*, IgM levels after treatment with (c) Cyclosporine and *Bifidobacterium* and (d) Cyclosporine and *Lactobacillus*

Several studies have demonstrated that *Lactobacillus* is able to boost the immunity of the host by producing the strong colonies in the intestinal tract, so that pathogenic bacteria are not able to create any destruction in the host body. This is to mean that *Lactobacillus* produces a large number of viable beneficial bacterial cells with the capacity to compete with pathogenic one. Meanwhile, probiotics are the viable microorganisms, which upon digestion exert health-promoting effects on host[74]. As a fact, a key requirement for probiotic strains is that they should not carry transmissible antibiotic resistance genes[96] and this was the case for the strains used in the present study. The amelioration observed in the ulcerative colitis may be partially due to the action of probiotics given to the mice as it may serve as a protector against the pathogens in the intestine and meanwhile results in vital benefits for developing healthy gastrointestinal function[51]. Probiotics containing for example, *Bifidobacterium bifidum* and *Streptococcus thermophilus* when administered in children with rotaviral diarrhea, results in faster sero-conversion within IgA and IgM antibodies accompanied by growth of cells producing IgM antibodies[97]. Enzymatic hydrolysis with the participation of probiotics increases the bio accessibility of lipids and proteins and reduces allergen city of foodstuffs[98]. There is increase in the level of folic acid, niacin and riboflavin up to 20 folds by the application of probiotics.

SYNBIOTIC FOODS

Synbiotic food is defined as a food which is a mixture of probiotics and prebiotics that beneficially affects the host by (1) Improving the survival and implantation of live microbial dietary supplements in the gastro-intestinal tract and (2) Selectively stimulating the growth and activity of one or a limited number of health-promoting bacteria and thus improving host health and welfare[29]. The best synbiotic combinations currently available include bifidobacteria and FOS, *Lactobacillus* GG and inulins and bifidobacteria and lactobacilli with FOS or inulins. Prebiotics are complementary and synergistic to probiotics, thus presenting multiplier on their isolated actions[99]. This combination should enable the survival of probiotic bacteria in food and conditions of the gastric medium. Allowing its action in the large intestine and the effects of these ingredients can be added or synergistic[100].

Among the functions of symbiotic strains, increased resistance against pathogens is the best characterized. The use of probiotic cultures excludes potentially pathogenic microorganisms by the production of organic acids and bacteriocins and enhancing natural defense mechanisms. The use of symbiotic has shown a promising alternative for its use in combination with antibiotics or isolated. Re-establishing the micro environment enhances gastrointestinal absorption and increases the immunity of patients[101]. The use of functional foods, particularly symbiotic has been incremented by diet therapy with the intention of improving the health status of patients with certain cancers. It is common the occurrence of changes in the composition of the human gastrointestinal flora which can be altered by environmental and dietary factors favoring preoperative infections[102]. The reasons why these patients are more susceptible to infections than other surgical patients are multi factorial. Among them, bacterial translocation is considered the leading cause of postoperative infection[103]. Physiologic interactions between gut epithelium and its abundant indigenous bacteria create an important basis for intestinal homeostasis. In addition, bacterial pathogens have developed several mechanisms to manipulate the enterocytes functions for their own survival[104].

Studies show that treatment with symbiotics may be good strategy in the prevention and reduction of postoperative infections. The magnitude of the effect depends on the type of synbiotic preparation and concentration of the microorganism in the compound[102]. Hernandez-Hernandez *et al.*[105] have shown that prebiotic carbohydrates can enhance the survival of beneficial probiotic bacteria during exposure to gastric conditions. Probiotics and their suitable prebiotics can be designed into food products to improve metabolic activities and stimulate the growth of the probiotic bacteria through their synergistic effects[106]. Using prebiotics and probiotics in combination is often described as a synbiotic, although the Food and Agricultural Organization (FAO) recommends that the term synbiotic be used only if the net health benefit is synergistic, or that the prebiotic be shown to increase the population and/or function of the probiotic it is paired with Pineiro *et al.*[107].

The main health promoting actions of prebiotics is because of their capacity to increase the growth and metabolic activity of probiotic microorganisms, it was thought to administer both of them simultaneously. Such a product contains live cells of the beneficial bacteria (probiotic) and a selective substrate (prebiotic). When combined product is administered, the bacterial cells which survive their transit through the stomach grow quickly and competitively because of the presence of the selective substrate (prebiotic) and that helps their establishment and their predominance[108]. Since the word 'synbiotics' refers to synergism, this term should be used for products in which the prebiotic compound selectively favors the probiotic microbe, e.g., FOS in combination with strains such as *B. infantis*, *B. longum*, etc. As the prebiotic component of the synbiotics improve the survival of the probiotic bacteria crossing the upper part of the GIT, their effects are enhanced in the large bowel[108]. While probiotics act in the small intestine, prebiotics are specifically targeted to act on the flora in the large intestine[109]. The two thus work synergistically.

The combination of suitable prebiotics with probiotic/s has been found (from both *in vitro* and *in vivo* experiments) to stimulate the survival and activity of the organism, for example a FOS in conjunction with a *Bifidobacterium* strain or lactitol in conjunction with *Lactobacillus*. Besides the synergistic effect in which the growth of beneficial bacteria (existing strains) in the colon is promoted, synbiotics also act FOS in conjunction with a *Bifidobacterium* strain. The combination of *Bifidobacterium* and oligofructose (OF) has been found to act synergistically and retard colon carcinogenesis in rats compared to either given individually[26]. Another investigation demonstrated that the consumption of *B. lactis* and resistant starch was able to enhance the apoptotic response to azoxymethan in rats, which was suggested to be due to the resistant starch acting as a metabolic substrate to provide optimal activity of the probiotic species. Roller *et al.*[110] have demonstrated that synbiotic (combination of oligofructose-enriched inulin, *L. rhamnose* and *B. lactis*) use prevented azoxymethane-induced suppression of NK-cell activity in Peyer's patches, an effect not noted in the individual pro-and prebiotic treatments. These studies indicated that synbiotics may have a role in colo rectal cancer treatment[111]. Liong[26] has mentioned a lesser number of tumours in rats treated with carcinogens when they were given cereal bran. He also concluded that synbiotics produced increased benefits compared to the administration of either probiotic or prebiotic alone.

Generally, synbiotic is a combination of probiotic and prebiotic having synergistic action, which contains live cells of the beneficial bacteria and a selective substrate. An ideal synbiotic supplement should contain an appropriate combination of prebiotics with probiotics where the former selectively favors the later should exhibit synergistic relationship between viable beneficial bacteria and their selective substrate and should produce additive or synergistic effect.

MECHANISMS OF ACTION OF PRO, PRE AND SYNBIOTICS

The principal mechanism of action is competitive exclusion or competitive colonization in which bacteria in the gastrointestinal environment, produce substances which inhibit growth of pathogenic microorganisms and compete with them for a place in the intestinal epithelium[112]. This is described as the creation of probiotic bacteria in the human intestine, which acts as a vital barrier to invasion by pathogens in the gastrointestinal tract of the human host. Over 90% of the total cells in the body are present as bacteria in the colon, about 10^{12} for every gram of large intestinal contents[113]. Under natural conditions, a protective gut microflora develops and there is no need for a bacterial supplement Shanta-Retenly[114] but the changing food habits and lifestyle force us to take processed food, which affects our access to and colonization, by probiotics. Moreover, we also consume antibacterial substances ranging from vinegar to antibiotics. The second mode of probiotics action is to stimulate the efficiency of immune system. Infant is born with a sterile digestive system. Therefore, the use of probiotics due to their ability of adhesion to the intestinal mucosa, allows creating a natural barrier against potential pathogens and thus enhances immunity. The stimulation of the immune system manifested by increased production of immunoglobulin, increased activity of macrophages and lymphocytes and stimulates the production of γ-interferon[115] as shown in Fig. 3.

Probiotics, prebiotics and synbiotics are the new concepts that have been developed to modulate the target gastrointestinal microflora balance. Indeed synbiotic combinations are considered to have more beneficial effects on human health than probiotics or prebiotics alone. Recent studies established that synbiotics improve the intestinal microbial environment and activate host immune function, leading to prevention of bacterial translocation[38]. Like probiotics, the possible anticarcinogenic activity of synbiotics is not clearly understood. As shown in Table 1, prebiotic oligosaccharides are fermented by the probiotic bacteria and other bacteria that reside.

DOSAGE FOR THE USE OF SYMBIOTIC

The viable probiotic microorganisms that are administered have to be in adequate amounts to provide a health benefit to the host[108]. One to two billion colony forming unit per day of a mixed strain supplement probiotic are considered to be the minimum amount for the healthy maintenance of intestinal microflora. This huge number is required to compete with pathogenic bacteria and outnumber them. According to Earl Mindell, an expert on nutrition, healthy persons should take 2-5 billion CFU of probiotics per day and those with problems in the GIT can take up to 10 billion CFU per day. The current daily intake recommended

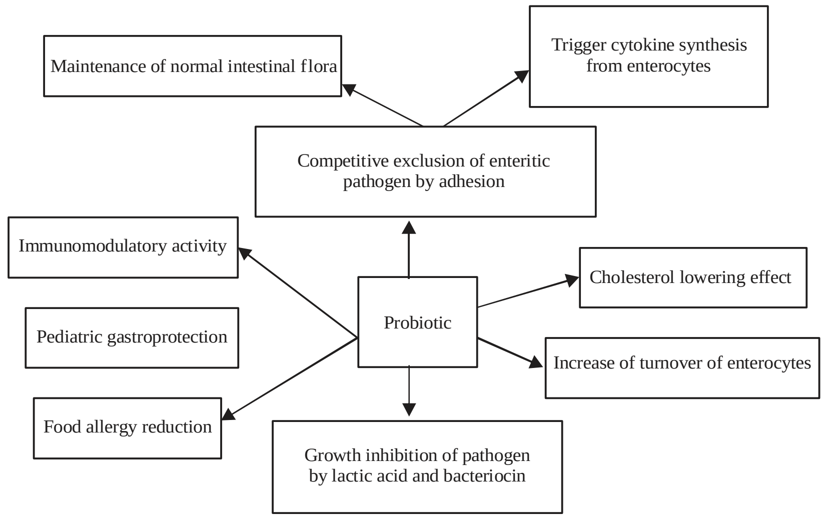

Fig. 3: Proposed mechanisms of action of probiotics, Source: Bandyopadhyay and Mandal[38]

Table 1: Mechanisms of action of pro, pre and synbiotics

Probiotics	Prebiotics	Synbiotics
Modification of the metabolic activities of intestinal microflora	Enhancement of growth of probiotic bacteria	Effects are synergistic
Alteration of physicochemical conditions in the colon	Enhancement of formation of the SCFAs and lactic acid as fermentation products	Stimulation of growth implantation, survival and activity of probiotic bacteria in the presence of selective prebiotic substrate
Binding and degrading potential carcinogens	Increase in the level of Ca and Mg in the colon	Prevention of AOM-induced suppression of
SCFA Production		NK-cell activity in
Formation of antitumorigenicor antimutagenic compounds	Modification of gene expression	Peyer's patches
Elevation of host's immune system		Modification of the composition of colonic bacterial ecosystem, leading to altered metabolic
Effects on the host's physiology		activity of the colon

Table 2: Recommended doses based on evidence of the most used probiotics

Strain	Amount
Lactobacillus casei	10^{10} CFU-2x day^{-1}
Lactobacillus acidophilus	10^{9} CFU-3x day^{-1}
Lactobacillus rhamnosus	10^{11} CFU-2x day^{-1}
Bafdobacterium lactis	10^{10} CFU-2x day^{-1}

Source: Adapted from Fooks and Gibson[118]

by the Natural Health Products Directorate of Canada, for prescription probiotics is 5-10 billion CFU. It is best to administer non-enteric coated probiotics with meals to take advantage of the lower gastric acidity during digestion and to aid in compliance[116]. According to the Technical Regulations 2005 ANVISA probiotic portion of a symbiotic must have minimum viable amount in the range 10^8-10^9 CFU in the daily recommendation of the product ready for consumption. The concentration of viable cells should be adjusted in the initial preparation, taking into account the survivability in order to reach the minimum of 10^7 CFU of intestinal contents as indicated[117] in Table 2.

For the prebiotic portion, 10 g day^{-1} of FOS and optimal dose is well tolerated but 4 g day^{-1} of FOS or inulin is the minimum required to promote growth of bifidobacteria. Moreover, the use of 14 g day^{-1} or more of inulin can cause intestinal discomfort[101]. Nowadays, FOS and inulins are available in nutritional supplements and in functional foods where their dose ranges from 4-10 g day^{-1}. It has been recommended that those who use more than 10 g daily of FOS or inulins should split the dosage throughout the day. Doses more than 30 g day^{-1} of FOS or inulins may lead to significant gastrointestinal discomfort (like flatulence, bloating, cramping and diarrhea[116]. The effect of synbiotics on faecal microflora of experimental animals demonstrated by increasing the counts of total anaerobes, aerobes, lactobacilli and bifidobacteria counts and decreasing in Clostridia, Enterobacteriaceae and *Escherichia coli* counts in the colon of rats. In humans, an overall increase in faecal bifidobacterial numbers in healthy volunteers after the consumption of synbiotic mix of inulin and *Bifidobacterium* spp. Studies in mammals showed that the combined use of probiotics and prebiotics have greater beneficial effects than if these two constituents were to be used alone as indicated in Table 3.

GUT MICROFLORA AND FUNCTIONS

A newborn baby has a sterile gut that is soon colonized by bacteria from the mother and from the baby's environment[120]. An adult human has 10 times more bacterial cells on and in the entire body as compared to the total human cells. Evidence is accruing that the early colonization of the neonatal gut is important for the development of gut flora and the immune system of the growing child[121]. It has been further suggested that the composition of the gut microbiome is connected to many physiological states, diseases and conditions in both early and later life[122]. The human microbiome is highly complex and diverse. Its composition and number varies from the nose and mouth to the distal colon and rectum. The compositions and complexities of the gut microbiota changed when the baby is weaned to solid foods. Dietary changes in adulthood are also greatly responsible for the composition of gut microbiota. Development of 16S ribosomal RNA (rRNA) gene-sequence-based metagenomic methods has led to major advances in defining the total microbial population of the gut[123]. This technique has been used to show that 90% of the bacteria belong to two phyla, namely, the Bacteroidetes and Firmicutes[12].

HUMANS AS MICROBIAL DEPOTS

It has been known from the history of microbiology, the gut of people and other animals is inhabited by microbial species, mostly bacteria. Studies developed innovative techniques for cultivating extremely oxygen-sensitive bacteria that inhabited the proximal gut of ruminants, the importance of these anaerobic bacteria in the rumen fermentation and the reliance of the ruminant host on microbial metabolic products for nutritional well-being[124]. It is well documented that the large intestine is one of the most densely populated ecosystem in nature consisting of over 500-1,000 different species of bacteria[29]. The adult human body contains 10^{14} cells of which only 10% compose the body proper and 90% are accounted for by members of the microflora. The intestinal microflora plays a crucial role in the health of humans and animals. Approximately 70% of the immune function is derived from the gut, being composed of the mucosal barrier, sub mucosal glands and the mucosa-associated lymphoid tissue[125]. The collection of microorganisms that live in peaceful coexistence with their hosts has been referred to as the microbiota, microflora or normal flora[126,127]. It is estimated that the human microbiota contains as many as 10^{14} bacterial cells, a number that is 10 times greater than the number of human cells present in our bodies[128] as shown in Fig. 4. By far the most heavily colonized organ is the gastrointestinal tract (GIT), the colon alone is estimated to contain over 70% of all the microbes in the human body. The human gut has an estimated surface area of a tennis court (200 m^2) and as such a large organ, represents a major surface for microbial colonization. Additionally, the GIT is rich in molecules that can be used as nutrients by microbes, making it a preferred site for colonization (Table 4).

Function of the microflora of the gut: The functions of the normal flora have been called Microflora Associate Characteristics (MAC) by several researchers. These MAC (Fig. 4) include digestion of metabolizable substrates, colonization resistance, vitamin production, mucosal cell development, immune system stimulation and intestinal transit regulation.

FACTORS AFFECTING THE GUT FLORA

Prior to birth, micro-organisms are absent from the GI tract but quickly colonies it during and after birth. Exactly

Table 3: Combined use of probiotics and prebiotics (height in μm and density in cm^{-2})

Variables	Basal	*Antibiotic	Probiotic	Prebiotic	Symbiotic
Height					
Duodenum at day 7	0.88	0.75	0.76	0.67	0.87
Duodenum at day 14	0.70	0.75	0.87	0.75	1.05
Density					
Jejunum at day 7	98.3	82.0	86.4	94.90	100.60
Jejunum at day 14	86.4	89.5	101.8	98.50	100.20

*Zinc bacitracin, Source: Budino *et al.*[119]

Table 4: Composition of the intestinal flora of adult humans

Aerobes or facultative anaerobes	Stomach	Jejunum	Ileum	Colon
Enterobacteria	0-10^2	0-10^3	10^2-10^7	10^4-10^{10}
Streptococci	0-10^3	0-10^4	10^2-10^6	10^5-10^{10}
Lactobacilli	0-10^3	0-10^4	10^2-10^5	10^6-10^{10}
Bifidobacteria	Rare	0-10^4	10^3-10^9	10^8-10^{12}
Streptococci	Rare	0-10^3	10^2-10^6	10^{10}-10^{12}

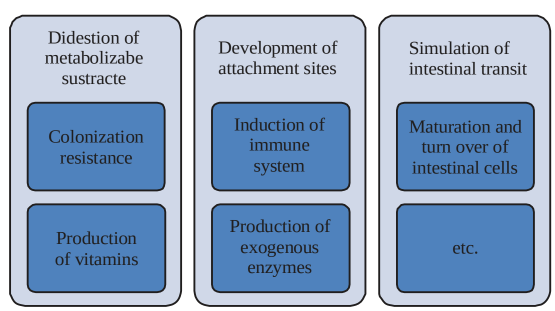

Fig. 4: MAC relating to different functions of the normal intestinal microecology, Source: McFarland[129]

which microbiota develops is dependent on factors such as the method of delivery and the environment in which birth takes place, the mother's microbiota and the manner of feeding[30]. Many factors can harm the beneficial members of the GIT flora, including antibiotic use, psychological and physical stress, radiation, altered GIT peristalsis and dietary changes. This study will focus exclusively on the interactions of antibiotics, stress and diet with the gut flora. Disruptions to the normal balance between the gut microbiota and the host have been associated with obesity[130], malnutrition[131], Inflammatory Bowel Disease (IBD), neurological disorders Gonzalez *et al.*[132] and cancer. Understanding how the gut microbiota affects health and disease requires a shift in focus from individual pathogens to an ecological approach that considers the community as a whole. Once the adult microbiota is established, by the age of about 2-3 years, it is relatively stable within an individual but nevertheless subject to influence by diet, disease, use of medication (particularly antibiotics) and ageing[30]. Therefore, knowledge of the gut microflora and its interactions may lead to the development of dietary strategies that serve to sustain or even improve normal gastrointestinal microbiology[38].

CONCLUSION

Fermented foods are those foods subjected to the action of microorganisms or enzymes so that desirable biochemical changes cause significant modification in the food. The growing in understanding of the relationship between diet and health increased the demand for food with specific benefit beyond their basic nutrition. Probiotics used as dietary supplement that contains potentially beneficial bacteria or yeast with lactic acid bacteria is being increasingly accepted for its therapeutic benefits world over. Prebiotics are non-digestible carbohydrates those get away digestion in colon and stomach, reach the large intestine and selectively stimulate the growth of bacteria that are beneficial to health. Probiotics and prebiotics share a unique role in human nutrition. The risk of probiotics and prebiotics are very mild if applied in the recommended manners. Probiotic organisms can have a significant influence on the treatment and prevention of disease. Combining probiotics with prebiotics could improve the survival of the bacteria crossing the upper part of the gastrointestinal tract, thus enhancing their effects in the large bowel. Moreover, probiotic and prebiotic effects might be additive or even synergistic. Growth and activity of probiotics are effectively stimulated by prebiotic preparations. Between prebiotics and probiotics a mutual correlation exists. Animal diet may be supplemented with both of these components by using synbiotic preparations. Using appropriate dosage and combinations of substrate with live bacteria are very important to achieve the require health of the host. The gut microbiota plays an important role in the maintenance of health. The functions gained from the intestinal microbiota are disrupted by natural and environmental factors.

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