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Probiotics: Role of bioactives in foods and dietary supplements

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Abstract
Bacteria in the human gut play a significant role in the host's metabolic functions. These bacteria's metabolites have an impact on the host's physiology and health. The gut flora is subjected to a multitude of environmental factors, including way of life, strain, antibiotics, host genetics, and diseases. When a disease pathogenesis occurs, the intestinal microbial composition changes which results in a diseased state. This stage is caused by bacterial pathogen colonization in the intestinal environment. Probiotic strains can be injected into the intestinal environment to treat the pathological condition. Medicinal compounds produced by probiotic strains include amino acids, vitamins, bacteriocins, enzymes, immunomodulatory compounds, and Short-Chain Fatty Acids (SCFAs). This review describes latest proofs of the effect of bioactive components produced by probiotic bacteria on food and host wellbeing while having no impact on good bacteria sharing the same niche.

Keywords: Probiotics, gastrointestinal disease, pathogenesis, immunomodulatory compounds

Introduction
Metchnikoff, a Russian scientist and Nobel Prize winner, pioneered the idea of probiotics in the early twentieth century. The scientist believed that these probiotic bacteria benefit the host by enhancing intestinal microbial stability and reducing gastrointestinal diseases. Probiotics are presently defined as live microorganisms that, once given in therapeutic levels, provide health benefits to the host (Indira *et al.*, 2019) [20]. Customers are becoming more aware of the link between nutrition and health, which has urged science studies into the revelation of foods and food constituents with beneficial health effects. The growth of functional foods, which are foods or food components, has a positive effect on consumer health and reduces the risk of chronic diseases. To be good for human body, probiotic products must contain more than 108 to 109 cfu/ml of microbes. Probiotics must be strong enough to withstand the harsh environments found in the body's intestinal system (Syiemlieh & Morya, 2022) [46]. Probiotic bacteria are used in the production of a variety of functional foods, including dairy and non-dairy products. The amount of potential probiotic cells needed in a probiotic food for an obvious effect is 108-109 CFU each day, based on the host's bacterial and physiological changes. Probiotics provide health advantages through a variety of mechanisms encompassing a diverse range of bioactive compounds. Probiotics' mechanisms of action involve inhibitory activity of pathogenic bacteria replication by adjusting the pH and lowering oxygen levels, resulting in less desirable intestinal environments, non-competitive suppression by making bacteriocins, formulation of essential micronutrients such as vitamins, amino acids, and enzymes, and improving the bioavailability of dietary nutrients, enhancement of the host immune system, and improvement of the metabolic process (Chugh & Kamal, 2020) [8]. It is significant to mention that the health advantages offered by probiotic bacteria seem so to be strain-specific rather than species- or genus-specific. Neither of the strains, not even strains of the same species will have all of the potential advantages, nor will not all strains of the same species be beneficial against specified health conditions (Baek & Lee, 2009) [2].
Gut microbiota affects human health by influencing the gut defensive system barrier, immune function, and nutrient absorption, as well as possibly by immediate signaling with the gastric epithelium (Collado *et al.*, 2009) [10]. In the gastrointestinal system, approximately 10 trillion microbes of 500-1000 different bacterial communities invade and occupy and maintain a complex equilibrium. *Bacteroides*, *Lactobacillus*, *Clostridium*, *Fusobacterium*, *Bifidobacterium*, *Eubacterium*, *Peptococcus*, *Peptostreptococcus*, *Escherichia*, and *Veillonella* are few examples.

These bacteria invade and occupy the human gut from birth and are ultimately revealed to foreign microbial communities and antigens obtained from digested foods (Misra *et al*., 2019) [30]. The interaction of the host microbiota with external agents may disrupt or change the normal microbial stability or action in the gastrointestinal system. The pathogenesis of various diseases is linked to changes in microflora. Pathogens that cause enteric diseases include *Escherichia coli*, *Salmonella*, *Shigella*, and a variety of other food-borne pathogenic strains such as *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, and *Vibrio cholera* (Burkholder & Bhunia, 2009) [5]. They have the potential to cause infections in two stages. Pathogens may bind to the surfaces of intestinal epithelial cells via specific adhesive receptors such as glycoproteins and glycolipids in the first step of the infection cycle, and later in the second step they induce direct cytotoxic injury, intracellular migration, and eventually interrupt the epithelial tight junctions, resulting in mucosal infection (Sears, 2000) [45]. By preventing the growth of infective or opportunistic pathogenic organisms, probiotics encourage gastro intestinal homeostasis and accelerate the growth of indigenous beneficial gut microbiota. As a result, probiotics are suggested as a potential bio-therapeutic agent for intestinal pathogenic infections. These may function through a range of techniques, including antimicrobial compound production, competition for nutrient substrates, competitive exclusion, intestinal barrier function improvement, and immunomodulation (Lobo *et al.*, 2010) [26].

Bioactive Compounds Produced by Probiotic Bacteria

Bacteriocins

Bacteriocins are antimicrobial peptides which are synthesized ribosomally made by one organism that kills other organisms (Indira *et al.*, 2019) [20]. These are produced by two, including bacteria and some archaea. Bacteriocins are produced by both gram-positive and gram-negative bacteria in the bacterial community (Indira *et al.*, 2018) [19]. Bacteriocins are grouped into four categories based on molecular mass, thermostability, enzymatic sensitivity, presence of post-transationally modified amino acids, and mechanism of action. Types of bacteriocins are shown in below table (Nishant *et al.*, 2011) [32].

Table 1: Classification of Bacteriocins

Class	Example	Characteristics
Class I	Nisin, Lantibiotics, Sub-group Ia, Sub-group Ib	Small peptide. Inhibitors, screw-shaped, amphipathic, tiny cationic peptides that generate voltage-dependent pores via an unknown interaction with the target cell's membrane. Globular shaped anionic or neutral peptides.
Class II	Class IIa, Class IIb, Class IIc	Heat-stable peptides with molecular masses less than 10 kDa and no altered amino acids. Anti-listerial peptides in Group IIa have the consensus sequence YGNGV at their N-terminal sequence. Have a high potential for use in food preservation as well as medical applications. For activity, class IIb bacteriocins require two distinct peptides. Class IIc have a broad spectrum of effects on membrane permeability, cell wall forming, and target cell pheromone actions.
Class III	Antibiotics	Heat labile proteins. Have a molecular weight higher than 30 kDa.
Class IV	Glycoproteins, Lipoproteins	Need non-protein moieties for their activity.

The American Food and Drug Administration have granted GRAS status to Nisin, a bacteriocin created by several strains of Lactococcus lactis, and it is widely used in food safety. Bacteriocins are beneficial against a variety of human infectious diseases due to their ability to kill multiple pathogens. Nisin, for example, can be used to cure Streptococcus pneumonia-related pneumonia, meningitis, and sepsis. In mice, the cyclic bacteriocin griselimycin was capable of curing tuberculosis. A few bacteriocins, such as pediocin PA-1 and lactocin AL705, have been shown to have anticancer and anti-inflammatory properties (Tiwari, 2022) [47].

Short-Chain Fatty Acids (SCFAs)

Organic acids, primarily short-chain fatty acids, are created in millimolar amounts in the gastrointestinal system and are particularly abundant in areas dominated by anaerobic bacteria. SCFAs are volatile saturated fatty acids with 1-6 carbon atoms in the aliphatic chain and can occur in a straight or branched conformation. They are the primary carbon source from the diet to the host microflora. The creation of these acids is fairly well understood and explained. The most popular are acetic acid, propionic acid, and butyric acid, which account for 90 percent to 95 percent of the SCFAs found in the human colon, with formic acid accounting for a lower percentage (Markowiak-Kopeć & Śliżewska, 2020) [28]. In both the small and large intestines, the human body contains 100 trillion microbes. A few enzymes involved in carbohydrate digestion are missing from the host cells. Even so, probiotic bacteria ferment these undigested carbohydrates and generate energy, which the host uses to perform numerous purposes. Probiotic bacteria coexist with colonocytes, forming a mutually beneficial relationship between gut flora and humans (Chatterjee *et al.*, 2017) [7]. These indigestible sugars are transformed by the probiotic bacteria into SCFAs such as butyrate, acetate, and propionate, as well as other reaction products such as heat and gases like methane, carbon dioxide, and hydrogen (LeBlanc *et al.*, 2017) [25].

Antimicrobial properties are seen in the SCFAs generated as byproducts of saccharolytic fermentation. Organic acids are six carbon components that aid in the host's defense against microbial infections (Ciarlo *et al.*, 2016) [9]. Short chain fatty acids, especially butyrate, have been shown to be beneficial in the treatment of a variety of diseases, including IBD, antibiotic-associated diarrhea, colon cancer, and cardiovascular disease (Tominaga *et al.*, 2018) [48]. A past research discovered that short-chain fatty acid receptors (GPR43) are connected to the energy metabolism of microbes. These receptors retained homeostasis in host cells by managing the host's usage of energy. Furthermore, they discovered that GPR43-deficient mice are obese on a normal diet when particularly in comparison to GPR43 overexpression mice (Kimura *et al.*, 2013) [24].

Exopolysaccharides

Microbial polysaccharides are extracellular polymeric compounds which are either soluble or insoluble and are produced by bacteria, yeast, algae, fungi, and other organisms. They are regarded as value-added compounds and are used for a variety of purposes. Exopolysaccharides are microorganism's metabolic remnants. They are high-molecular-weight substances made up of carbohydrates and proteins, DNA, phospholipids, and non-carbohydrate substituents like acetate, glycerol, pyruvate, sulphate, carboxylate, succinate, and phosphates. EPS formed by probiotic lactic acid bacteria has been preferred for various uses among microbial polysaccharides since it is usually considered to be safe and can be used for biological functions *in vitro* and *in vivo* (Angelin & Kavitha, 2020) [1].

The EPSs most likely contribute in the attachment and transitory colonization of the intestinal mucosa by the producing bacteria in this niche. EPSs generated by lactic acid bacteria have been asserted to have health advantages with respect to their physiological role and technological usage, such as defense against gastric ulcers, a prebiotic impact, cholesterol-lowering action, and the role in shaping the immune response and thus assert anti-tumor activity (Ruas-Madiedo *et al.*, 2010) [42].

Oligosaccharides

The indigestible cross-linked polymers made up of monosaccharide units are known as oligosaccharides. The number of units and the category of glycosyl moieties in an oligosaccharide define its characteristics (Indira *et al.*, 2019) [20]. Oligosaccharides have a huge potential for enhancing growth of bacteria and the development of bioactive substances like antibodies, SCFAs, and organic acids. As a result, modulating intestinal flora attains homeostasis in the intestinal environment (Pan *et al.*, 2009) [34]. Inulin, fructooligosaccharides, glucooligosaccharides, and xylooligosaccharides are examples of oligosaccharides (Yoo & Kim, 2016) [51]. Researchers conclude that glucooligosaccharide plays a defensive part in the growth and spread of tumors (Pericleous *et al.*, 2013) [37]. Galactooligosaccharides' laxative impact alleviates the symptoms of chronic constipation and irritable bowel syndrome in the elderly (Rao *et al.*, 2015) [40]. Through the ingestion of prebiotics, oligosaccharides encourage mineral uptake. A latest review discovered that prebiotics boost iron and calcium uptake from the colon (Baye *et al.*, 2017) [3].

Enzymes

Since probiotic bacteria create enzymes such as lipases, esterases, and amylases, they can perform a variety of metabolic functions (Markowiak & Śliżewska, 2017) [27]. Lactose intolerance evolves in people who lack the enzyme lactase. Lactase, an enzyme created by probiotic bacteria, metabolizes lactose in milk and transforms it to glucose and galactose. These sugars are then transformed into SCFAs (Den *et al.*, 2013) [14]. Lactose intolerance is reduced by some lactic acid bacteria species via their enzyme –galactosidase (Montalto *et al.*, 2006) [31]. Amylases and peptidases created by probiotic cultures contribute in host metabolism biochemical processes. Lactic acid bacteria and Bifidobacteria are the genera that generate these enzymes (Savaiano, 2014) [44].

Amino acids

The intestinal flora synthesizes numerous amino acids from scratch and represent as precursors for the production of SCFAs (Feng *et al.*, 2018) [15]. The SCFAs generated aid in the fermentation of indigestible carbohydrates. Amino acids and short-chain fatty acids change the host's physiology (Den *et al.*, 2013) [14]. Aromatic amino acids primarily serve as substances for the production of a variety metabolites (Dai *et al.*, 2015) [12]. Probiotic microbes in the intestines ferment these amino acids, generating phenols and indole. Because of immune signals, they sustain energy balance and opposition to infectious pathogens (Rowland *et al.*, 2018) [41]. Probiotic bacteria generate amino acids that are crucial in the treatment of a variety of illnesses. D-tryptophan functions as an immunomodulator, lowering hyperactivity in adverse reactions (Kepert *et al.*, 2017) [22]. Intestinal flora generates small molecules that aid in biofilm development and quorum sensing. These are acylhomoserine lactones and auto inducer peptides obtained from S-adenosyl methionine, a key integrator in the biosynthesis of the amino acid methionine (Dai *et al.*, 2011) [11].

Vitamins

Vitamins are usually categorized as fat soluble (A, D, E, and K) or water soluble (C, vitamin H or B7, and a series of B vitamins). Whereas fat soluble vitamins are important constituents, water soluble vitamins function as coenzymes that transfer particular chemical groups. Because humans are unable to produce most vitamins, they must be acquired exogenously. The use of vitamin producing microbes could be a more natural and consumer friendly substitute to chemically synthesized pseudo vitamins for fortification (Gu & Lee, 2016). Vitamin is an essential nutrient that aids in human growth, development, reproduction, red blood cell formation, antibody production, and lactation. It is needed by the body to perform multiple metabolic functions involving amino acids, fatty acids, carbohydrates, and nucleic acid production. Pyridoxine and iron are assimilated in the intestinal system due to riboflavin, which increases uptake and aids in the upkeep of red blood cells (LeBlanc *et al.*, 2017) [25]. Pyridoxine is a vitamin that aids in the initial development of the nervous system and embryonic growth. This vitamin serves as a link between one carbon metabolism and antioxidative activity (Dalto & Matte, 2017) [13]. Bifidobacterium is the primary source of this vitamin (Patel *et al.*, 2013) [35]. *Salmonella typhimurium* contains numerous genes for the de novo synthesis of vitamin B12. Transferring these genes to *E. coli* enables industrial production of vitamin B12 (Fang *et al.*, 2017). Another organism, *Propionibacterium shermani*, is able to generate vitamin B12, propionic acid, and other important industrial metabolites (Piwowarek *et al.*, 2018) [38]. A probiotic *E. coli* strain Nissle 1917 was created via genetic engineering for the production of β-carotene. This probiotic microbe enhances vitamin A levels in the gastrointestinal system of malnourished children. Vitamin generation by bacteria in the human intestine is a natural process of vitamin advancement in humans (Miller *et al.*, 2013) [29].

Immunomodulatory compounds

Probiotic microbes in the intestinal mucosa influence the host's immune system. The immune system is modulated by probiotic bacteria, which control the antibody production, interleukins, cytokines, and lymphocytes (Indira *et al.*, 2019) [20]. Immunity is modulated by probiotic bacteria, and inflammatory gene expression results in the formation of interleukins such as IL-1 and IL-8 (Plaza-Diaz *et al.*, 2014) [39]. According to a latest report, the generation of IgA antibodies stimulated by IL-10 in host mucosal sites is a host protective mechanism against pathogens. Anti-inflammatory mediators such as IL-10 and IL-12 made by genetically engineered *Lactococcus lactis* strains lowered dextran sodium sulfate-induced colitis in mouse models (Kawashima *et al.*, 2018) [21]. A further analysis revealed that there is a decrease in IgE levels in illnesses. As a result, immunomodulation via probiotics is a substitute effective therapy for a variety of diseases (Özdemir, 2010) [33].

Safety of Probiotics in Foods and Dietary Supplements

It is thought that certain beneficial microbes ingested within the human body through food can affect the health of consumers by modifying their intestinal flora. In the meantime, a link between excessive numbers of good bacteria and advantageous biological effects in the intestinal flora remains unknown (Khan *et al.*, 2021) [23]. The use of live microbes, particularly lactic acid bacteria in food, has an ancient legacy of preserving and enhancing human health. A Roman historian once suggested that fermented milk products can be used to treat gastroenteritis. In 1900, Elie Metchnikoff proposed that eating yoghurt containing lactobacillus would decrease toxigenic bacteria in the gut, thus boosting the host's life cycle. It has now been demonstrated that increasing the amount of Lactobacilli in the gut wall reduces the number of gram-negative anaerobic bacteria, Enterobacteriaceae, and sulfite-reducing clostridia (Peivasteh-Roudsari *et al.*, 2019) [36]. The process of probiotics' advantageous impacts on human gut health is still unknown. In general, probiotics hinder the growth of harmful bacteria in the gastrointestinal system through attachment and incorporation, enhance gut microbial balance, and improve the function of the gastrointestinal mucous barrier. Probiotics regulate the propagation of food antigens and enhance the host's systemic and mucosal immune systems. They have the ability to remove carcinogens (Hareesh & Varghese, 2006) [18]. There are numerous frameworks to support probiotics' capacity to safeguard the host from digestive diseases. "Colonization resistance" refers to all methods in which bacteria hinder the invasion and incorporation of other bacterial species in the body. Several Bifidobacteria species have been shown to be resistant to pathogenic microorganism's colonization in the large intestine (Peivasteh-Roudsari *et al.*, 2019) [36].

The safety of probiotic strain-containing products indicates that they are progressively supporting customers with immunocompromised systems or vulnerable individuals, such as the aged, youngsters, and individuals with impaired immune systems. This mindset elevates concerns about the safety of probiotics. The probiotic strains ought to be totally pathogen-free and not injurious to the host. It is difficult to obtain evidence for this statement (Wassenaar & Klein, 2008) [49]. The human digestive system naturally includes a lot of Lactobacilli and Bifidobacteria (Guarner, 2006) [17]. Lactic Acid Bacteria are frequently harmless and are widely accepted as safe (Salminen *et al.*, 1998). Even so, as said before, certain Lactobacillus species are linked to opportunistic infections (Cannon *et al.*, 2005) [6]. The safety of all members of a species or genus alone is not a problem (Bernardeau *et al.*, 2006) [4]. There are no regulatory definitions in location worldwide to evaluate the safety of probiotic-containing functional foods. As a result, before being used, microbes or a mixture of bacteria or yeast must be formally recognized as a probiotic additive (Wright, 2005) [50]. This evaluation seeks pre-sale authorization as well as an accurate risk analysis of strain and its impacts on human health. Based on the final customer, the target species, the environment, and worker safety during manufacturing or implementation, safety factors are considered to be in contact with the microbe (Wassenaar & Klein, 2008) [49].

Conclusion

Some initiatives, such as the administration of probiotic microorganisms, can be used to modulate the intestinal flora in order to restore host health. This review focused on the data concerning the relation between bioactive molecules created by probiotic bacteria and their effect on food and host wellbeing. This is an exciting new phase of investigation for developing probiotic bacterial compositions to modulate the human immune response for disease prevention and diagnosis. In the coming years, recognizing new variants and ingesting novel synthetic probiotics may be a good way to promote good health. As a result, probiotics can be advised as an alternate solution as bio-therapeutic agent for the treatment of different ailments and can be added to food.

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