

# Probiotics in Health and Disease: A Review of Emerging Evidence of Potential Benefits and Harm

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**Abstract** Emerging multi-drug resistant pathogens are the main driving force behind the efforts to find an alternative treatment approach such as probiotics. Probiotics are considered living drugs that can reduce the consumption of conventional antibiotics and improve human and animal health. Particularly, bacterial origin probiotics became increasingly popular during the last two decades as a result of the continuously expanding scientific evidence pointing to their beneficial effects on human and animal health. In recent years, there has been an increase in the application of probiotics for the treatment of different infectious diseases and to alleviate the symptoms of many others, including metabolic disorder-related illnesses and cancer. More specifically, diseases and ailments such as diarrhea, urogenital infections, ulcerative colitis, irritable bowel disease, and a host of others have experienced an increase in the use of certain probiotic bacteria. There are several possible mechanisms by which probiotic bacteria can inhibit the effect of other pathogenic microorganisms. This review, therefore, provides an overview of the current status of bacterial probiotics with special emphasis on therapeutic purpose, mechanisms of action, and their selection criteria. It also highlights the emerging pieces of evidence concerning the role of probiotics in health and disease, and the potential limitations and challenges of probiotic development as a novel therapeutic agent.

**Keywords:** bacteria, drug-resistance, novel therapeutics, probiotics, mechanisms of action, health, diseases

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## 1. Introduction

Humanity's continued success is dependent on its future ability to prevent and treat diseases. The current dissemination of antibiotic resistance genes into pathogenic bacteria calls into question the future efficacy of today's antibiotic repertoire [1]. Antibiotics, substances that either prevent the growth of or kill a living organism, are considered miracle drugs. Antibiotics can enhance human and animal lives by treating or preventing diseases [2]. However, a major public health threat is the resistance to antibiotics or the increased capability of bacteria to stay alive in the presence of antibiotics. A rise in media reporting on the increase in antibiotic resistance has led many consumers to seek innovative and alternative measures to treat infectious diseases or this led scientists to shift the paradigm of treatment from specific bacteria elimination to altering bacterial ecology by use of probiotics [3,4].

It became clear that intestinal microflora has metabolic functions, such as fermenting indigestible dietary residues and endogenous mucus, saving energy, production of

vitamin K, and absorption of ions [5]. Moreover, some microorganisms (probiotics) are considered living drugs that can reduce antibiotic consumption and increase human health development [6]. Looking back through history, the concept of using live bacteria called probiotics, beneficial to health has been revived and has now come under intensive research using modern study designs and methods [2]. Probiotics refer to harmless live normal flora/microorganisms that provide a health benefit on the host when administered in adequate amounts and it also leads to having a therapeutic advantage [7].

Probiotic is a phrase of the modern era, the denotation "for life" and is in use to name bacterial association with beneficial effects on human and animal health. In the early nineties, Metchnikoff expressed probiotics in a scientific context as modification of floral/microbial diversity in human bodies and replacing the harmful microbes with useful ones [8]. The preventive and therapeutic role of probiotics on several diseases has been established via several mechanisms including modulation of gut microbiota, enhancement of gut barrier functions, degradation of potential carcinogens, and enhancement of immune system [9].

Several health benefits are associated with the consumption of products containing probiotics. Probiotics are known for the improvement of the intestinal transit of foods and facilitate digestion, relieve lactose intolerance symptoms, increase the immune response, and decrease diarrheal episodes. They also have a great contribution to the stabilization of intestinal microbiota following antibiotic consumption. Furthermore, it has a potential role in the reduction of the population of pathogenic microbes through the production of lactic acid, bacteriocins, and other antimicrobial compounds. According to some pieces of evidence, probiotics also involve the prevention or suppression of colon cancer and reduction of blood cholesterol. It is also reported that probiotics can also alleviate allergic reactions and are used for the treatment of infections of the respiratory tract [10].

Following their promising treatment effect, probiotics have been considered as an alternative therapeutic approach for the treatment of different diseases since recent times. However, the specification of microbial groups as a probiotic and the mechanism of action they use need further illustration. More importantly, there is a paucity of information regarding challenges and limitations to developing probiotics as effective chemotherapy.

Therefore, the objective of this review was to highlight the current status of bacterial probiotics in the treatment of different diseases. We also review the commonly used bacteria as probiotics, selection criteria, and their mechanisms of action. Furthermore, this review discusses the major challenges during the selection and development of probiotics as a therapeutic agent.

## 2. Definition and Historical Aspects of Probiotics

The definition of probiotics has a long evolutionary history. As defined by Lilley and Still, probiotics are all those substances, generally secreted by a microorganism, that facilitate the growth of another microbe. Later probiotics were used to describe tissue extracts that stimulated microbial growth and animal feed supplements exerting a beneficial effect on animals by contributing to the balance of their intestinal flora [11]. Since then, with a minor grammatical change, the definition of probiotic had evolved and today, probiotic is defined as any substance containing live organisms that, when ingested in adequate amounts improves the health of the host [12].

Etymologically the term probiotic is derived from the Greek language meaning "for life". The definition of probiotics has evolved simultaneously with the increasing interest in the use of viable bacterial supplements and concerning the progress made in understanding their mechanisms of action [13]. According to the Food and Agriculture Organization (FAO) of the United Nations and World Health Organization (WHO) report (2002), probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The International Life Science Institute (ILSI), Europe, suggests a definition, according to which a probiotic is a live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer beyond the basic nutrition [2].

Over a century ago, Elie Metchnikoff postulated that lactic acid bacteria (LAB) offered health benefits, capable of promoting longevity. He suggested that due to aging, there is a possibility of disturbances in the intestinal microbiota. This can be prevented by modifying the gut microbiome, wherein the harmful microbes that generate toxic substances like phenols, indoles, and ammonia from the digestion of proteins are replaced by the beneficial ones. He developed a diet involving milk fermented with a bacterium that was called "Bulgarian Bacillus" [14].

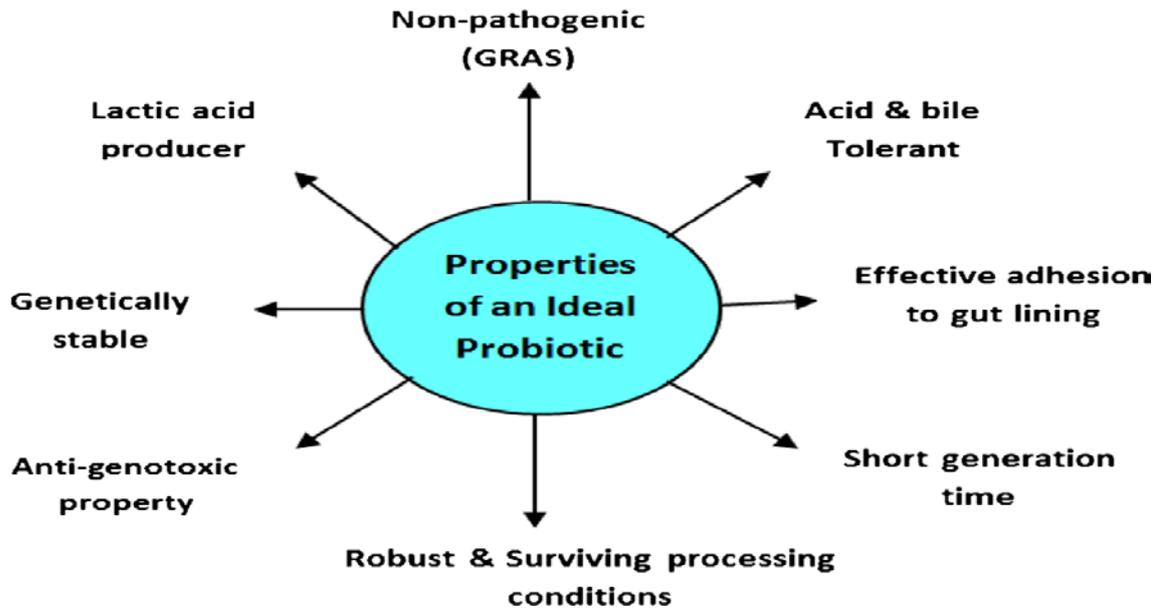
Other early developments of this concept ensured that disorders of the intestinal tract were frequently treated with viable nonpathogenic bacteria to change or replace the intestinal microbiota. Even before the discovery of antibiotic penicillin from *Penicillium* fungus by Sir Alexander Fleming, in the year 1917, a German scientist named Alfred Nissle identified a nonpathogenic strain of *Escherichia coli* in the feces of a First World War soldier. It was noted that the soldier never developed enterocolitis even during the severe outbreak of shigellosis. The resulting *Escherichia coli* strain named "Nissle 1917" is one of the few examples of a non-LAB probiotic [15].

Consequently, Henry Tissier isolated a *Bifidobacterium* from a breast-fed infant intending to administer it to infants suffering from diarrhea presuming that this bacterium could potentially replace harmful bacteria responsible for diarrhea. Similarly, in Japan, Minoru Shirota isolated *L. casei* strain Shirota to battle diarrheal outbreaks. A probiotic product with this strain has been marketed since 1965 [16].

## 3. Microorganisms Used in Probiotics and Their Characteristics

Numerous microbial species like yeast, bacteria, and molds have been used as probiotics. Nevertheless, probiotics are most commonly prepared using bacterial species. Probiotics are composed of one or more beneficial microbes. Human and animal probiotic microorganisms belong mostly to the following genera, including *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, and *Enterococcus* [17]. Despite being considered as two of the most commercially important LAB, and playing a significant role in the food industry, especially in the category of dairy products, they are not complete probiotics by nature. Moreover, strains of Gram-positive bacteria belonging to the genus *Bacillus* and some yeast strains belonging to the genus *Saccharomyces* are commonly used in probiotic products [18].

The WHO, FAO, and EFSA (the European Food Safety Authority) have made recommendations regarding the microbes that can be considered as probiotic microbes. They suggest probiotics must meet safety and functionality criteria, apart from their technological usefulness [19]. A microbe that is not known to be a causative agent of disease/non-pathogen and is not associated with antibiotic resistance is a candidate for probiotic. Functional aspects on the other hand define their survival in the gastrointestinal tract and their immunomodulatory effect [20].



**Figure 1.** Characteristics of an ideal probiotic microbe/s [6]. Copyright © Association of Food Scientists & Technologists (India) 2015

In addition, probiotic strains have to meet the requirements associated with the technology of their production, which means they have to be able to survive and maintain their properties throughout the storage and distribution processes. Probiotics should potentially have health benefits that are consistent with the strains currently used in a marketed product. The selection or promotion of microbial strains should not be rely on the data or scientific studies on other strains [21].

Overall, an ideal probiotic should have several potential characteristics such as being non-pathogenic and non-toxic, beneficial to the host animal, high viability, stable on storage and in the field, able to survive in or colonize the gut, and amenable to cultivation on an industrial scale [22]. In addition, a probiotic organism should be resistant to gastric acidity, bile, and pancreatic enzymes (PE). Furthermore, they should have a capacity to adhere into intestinal mucosa cells, with better colonization capacity thereby they can be kept itself alive for a long-time during transportation, storage, so they can effectively colonize the host; production of antimicrobial substances against pathogenic bacteria and absence of translocation [23]. The overall preferred characteristics of microorganisms to be considered as probiotics are illustrated in Figure 1.

## 4. Mechanisms of Action of Probiotics

Probiotics do not necessarily colonize in the intestinal tract to show their health-benefiting activities. This is evident by the fact that probiotics like *Bifidobacterium longum* became a part of the human and animal intestinal microflora, whereas the others like *L. casei* indirectly or transiently show their pro-health effects as they pass through remodeling or influencing the existing microbial community [24].

### 4.1. Production of Antimicrobial Substances

Probiotics may inhibit microorganism growth by secreting short-chain fatty acids and antibacterial substances. The

short-chain fatty acids such as acetic, propionic, and lactic acids are produced during the carbohydrate metabolism by probiotics and as consequence, the physiological PH of the body would be extensively dropped [25].

Alternatively, probiotics interfere with pathogens and prevent epithelial invasion either by inducing host cells to produce peptides or by directly releasing peptides [23]. Defensins and cathelicidins are the common antimicrobial peptides expressed constitutively by the intestinal epithelial cells and display antimicrobial activity against a wide variety of bacteria, fungi, and some viruses. Certain probiotic strains like *E. coli* strain DSM 17252 G2 and several *Lactobacillus* species have also been shown to express certain defensins [26].

### 4.2. Competition for Adhesion and Function as a Mucosal Barrier

The adhesion of pathogenic microorganisms to epithelial cells is important in determining the outcome of associated diseases. The ability of the bacteria to establish physical contact with the gastric epithelium is affected by several factors that include the influence of the epithelial mucosa, receptors associated with the adhesion of pathogenic microorganisms to the epithelium, and immune cells [27]. Probiotic bacteria compete with invading pathogens for binding sites to the epithelial cells and the overlying mucus layer in a strain-specific manner [28].

There are several possible mechanisms by which probiotic bacteria can inhibit the adhesion of pathogenic bacteria mainly lactic acid and bacteriocins [29]. Surface layer proteins purified from *L. helveticus* R0052 inhibited enterohemorrhagic *Escherichia coli* O157:H7 adherence and the subsequent rise in permeability, without altering the growth of the pathogen [30]. In the same way, *S. boulardii* secretes a heat-labile factor, survives at low pH, fights invading pathogens, shows immunomodulatory effects, secretes antimicrobial peptides that are responsible for the decreased bacterial adherence [30].

The mucosal surfaces can defend against toxic substances and pathogens found within the intestinal

lumen owing to the presence of mucins. These are large complex glycoproteins that protect intestinal mucosal surfaces from microbial pathogens by limiting access of environmental matter to their epithelial cells [31]. Probiotics are capable of influencing many of the components of epithelial barrier function either by decreasing apoptosis of intestinal cells or increasing mucin production [32].

In vitro studies involving *L. rhamnosus* GG have revealed that these microbes were able to inhibit and control cytokine-induced inflammation and apoptosis in the intestinal epithelial cell models. It was also noted that the tumor necrosis factor (TNF) was inhibited thereby favoring mitogenic effects and mucosal regeneration [16]. Some, Lactobacillus species have been shown to increase mucin expression in vitro in intestinal epithelial cells, thus blocking pathogenic *E. coli* invasion and adherence. This ability of the strains restores the mucosal permeability of gastric mucosa and inhibits the adherence of pathogenic bacteria [33].

#### 4.4. Inhibition of Bacterial Toxin Production

Bacteria present in the host grow and multiply, and along this course generate several metabolites that result in the damage of host cells/environment. It is important to inactivate and remove the toxins from the human body. Adsorption of the toxins, wherein the toxins adhere to the cell wall and reduce intestinal absorption is one of the mechanisms by which detoxification is initiated. Also evident is the ability of certain microbes to metabolize mycotoxins (e.g., aflatoxin) and therefore perform detoxification [34]. It should be noted that only a few microbial species with pro-health benefiting and detoxifying properties could act as probiotics. The effectiveness of some probiotics in combating diarrhea is probably associated with their ability to protect the host from toxins. The reduction of metabolic reactions leading to the production of toxins is also associated with the stimulation of the pathways leading to the production of native enzymes, vitamins, and antimicrobial substances [21].

### 5. Clinical Significance of Probiotics

#### 5.1. Probiotics and Gut Health

Bacterial agents are responsible for approximately 10% of diarrheal illnesses in industrialized countries. Infection with viruses that cause gastroenteritis among infants and community-associated food and waterborne gastroenteritis in adults assume increased significance. One of the main applications of probiotic microorganisms is in preventing or treatment of gastrointestinal disturbances [23].

Diarrheal diseases are caused by different microbes, and they do so by disrupting the normal intestinal environment. Probiotics, therefore, are beneficial in the management of diarrheal diseases since they help in reinstating the normal intestinal environment and controlling the disease. It was observed that Lactobacilli were safe and effective when administered to children

suffering from acute infectious diarrhea. *Clostridium difficile* induced traveler's diarrhea and recurring colitis were successfully treated with probiotics. Also, the consumption of high levels of certain strains of microbes as probiotics may shorten the duration or decrease the incidence of certain diarrheal illnesses [35].

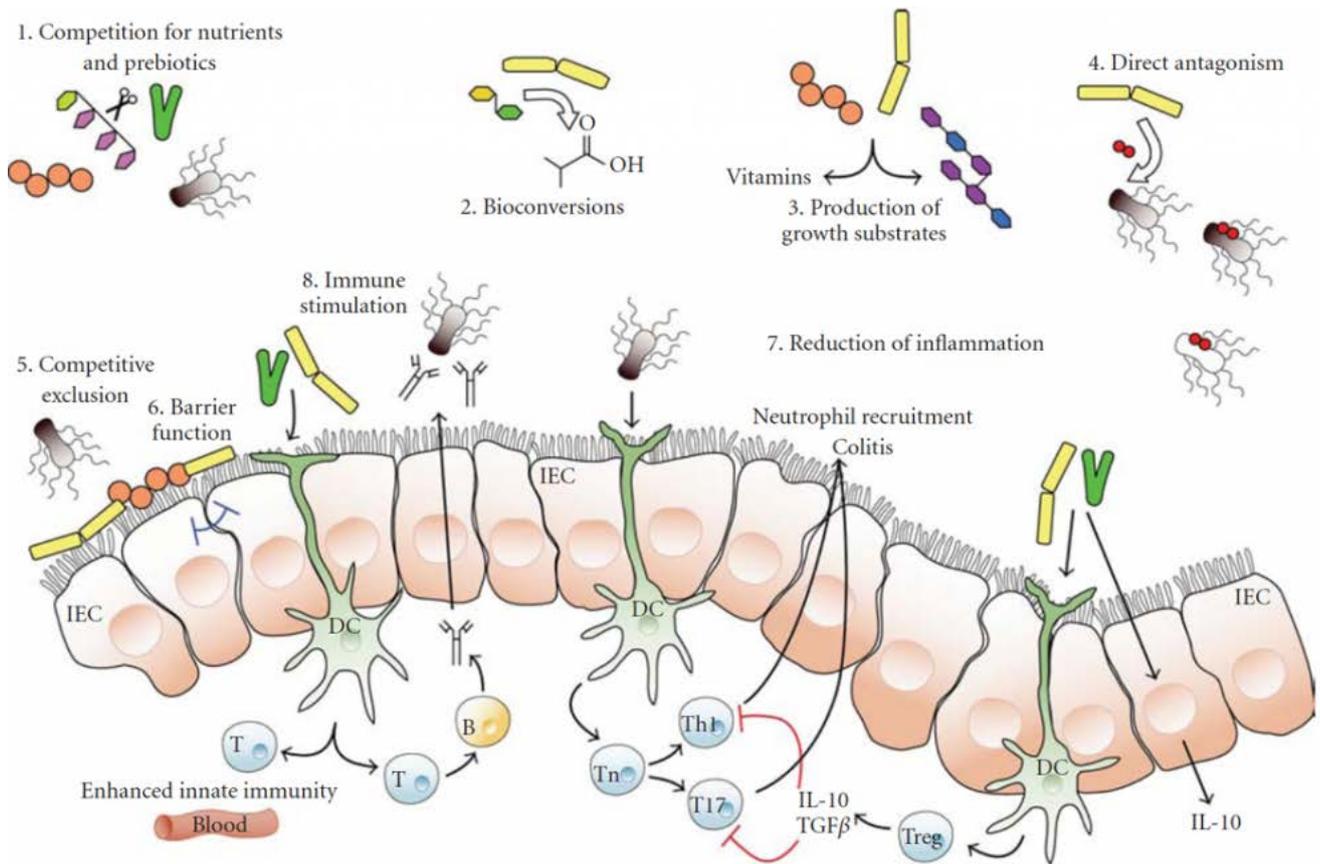
A significant effect was observed in a study carried out with patients who presented diarrhea caused by antibiotics, in which intake of a probiotic, containing *L. casei*, *L. bulgaricus*, and *S. thermophilus* reduced the incidence of diarrhea. Diarrhea is frequent in the critically ill, especially in cases with sepsis and hypoalbuminemia and during treatment with enteral nutrition. The treatment of choice in diarrheal cases includes rehydration, replacement of lost electrolytes, anti-diarrheal medication, and continuous enteral nutrition. The benefit of enteral supplementation with soluble fiber, probiotics, or prebiotics is not clear [36].

Inflammatory bowel disease (IBD) is a clinical condition that is characterized by abnormal immune responses against a luminal antigen of commensal bacteria. IBD could present as ulcerative colitis (UC), Crohn's disease (CD), and Pouchitis, and is common in genetically predisposed individuals. Mesalamine (5-Aminosalicylic acid) and corticosteroids are generally used to treat/manage IBD. A few clinical trial studies have shown the utility of selected probiotics, alone or in combination with prescribed medications, can prevent recurrent intestinal inflammation and possibly control IBD [37,38].

Probiotics can regulate T-cells and suppress inflammation-inducing effectors components of immune responses. Probiotics have the potential characteristics to interact with the mucosal immune system that does not arouse an inflammation-inducing innate response and the consequent induction of master inflammatory cytokines [24]. The non-pathogenic strain *E. coli* was found to be efficient in Crohn's disease maintenance therapy. This microorganism was able to adhere to intestinal epithelial cells in addition to its inhibitory effect observed against pathogenic strains isolated from patients with the disease [38, 39]. IBDs were noted to aggravate during alterations in the gut environment including infections [40]. The potential mechanisms by which the probiotics ensure better intestinal health are shown in Figure 2.

#### 5.2. Probiotics and Urogenital Infections

Bacterial vaginosis results from the abnormal multiplication of bacteria unusual for the vaginal environment. It presents as vaginal discharge and often is the consequence of disturbed vaginal Lactobacilli, a bacterium that forms the normal flora of the vagina and enables an acidic vaginal environment that is unsuitable for disease-causing microbes, thereby preventing infections. Urinary tract infections can be ascending or descending depending on the mode of entry of the microbes. Descending infections generally affect kidneys, ureters, and bladder, whereas ascending infections involve the urethra. Women frequently suffer from urogenital infections due to a change in the vaginal environment in which lactobacilli decrease in concentrations or are completely lost [7].



(1) competition for dietary ingredients as growth substrates, (2) bioconversion of, for example, sugars into fermentation products with inhibitory properties, (3) production of growth substrates, for example, EPS or vitamins, for other bacteria, (4) direct antagonism by bacteriocins, (5) competitive exclusion for binding sites, (6) improved barrier function, (7) reduction of inflammation, thus altering intestinal properties for colonization and persistence within, and (8) stimulation of innate immune response (by unknown mechanisms). IEC: epithelial cells, DC: dendritic cells, T: T-cells.

**Figure 2.** The action of probiotics by resisting infection by pathogens and immune modulation (Adopted from <https://www.customprobiotics.com/mechanisms-of-action>)

*Lactobacillus* spp. is the prominent microbial factor that governs the presence, growth, colonization, and persistence of non-endogenous microorganisms in the vagina. When the numbers of *Lactobacillus* spp. go down, the resident mucosa are prone to colonization and infection with uropathogens. The lactobacilli have been noted to form biofilms on the surfaces of urogenital cells, thereby preventing colonization of invading microbes. The role of Lactobacilli in preventing bacterial vaginosis is supported by positive results obtained in clinical trials. Probiotic capsules for example *L. rhamnosus*, *L. crispatus*, *L. gasseri*, *L. vaginalis*, *L. acidophilus*, *L. reuteri*, and *Streptococcus thermophilus* have been found effective for the prevention of recurrent bacterial vaginosis [42].

### 5.3. Probiotics for Better Circulation and Cardiovascular Health

Probiotic strains, particularly lactic acid microscopic organisms (bacteria) have a noteworthy part to play in cholesterol by bringing down the mechanism of cholesterol synthesis. The cholesterol levels can be cut down direct or indirectly by using probiotics. The direct mechanism involves inhibition of de novo synthesis or decrease in the intestinal absorption of dietary cholesterol [43]. The decrease in dietary cholesterol retention can be diminished in three ways, including assimilation, binding, or degradation [44]. Probiotic strains absorb the

cholesterol for their digestion, they can attach to the cholesterol particle, and they are capable of debasing cholesterol to its catabolic products. The cholesterol level can be decreased indirectly by deconjugating the cholesterol to bile acids, in this way lessening the aggregate body pool [45].

It has also been demonstrated that probiotics and their products can improve blood pressure through the mechanisms, including improving total cholesterol and low-density lipoprotein cholesterol levels [7]. Probiotics also have contributed to the reduction of blood glucose levels and insulin resistance. In addition, they involve in regulating the renin-angiotensin system and significant reduction takes place in blood or serum cholesterol when cholesterol is elevated [46].

The probiotics mediate the cholesterol-lowering effect along with the anti-inflammatory, anti-platelet, and antioxidant activities that minimize the chances for the development of cardiovascular diseases [47,48].

### 6. Immune Mechanisms: Probiotics and Immunologic Enhancement/Immune Stimulation

Probiotics have a biological effect on Immunological functionality. The immunological benefits of probiotics

can be due to activation of local macrophages and modulation of IgA production locally and systemically, to changes in pro/anti-inflammatory cytokine profiles, or the modulation of response towards food antigens [49]. The other mechanisms that the probiotics use to improve health are the stimulation/modulation of specific and nonspecific immune responses by T-cell activation, cytokine production, immunomodulation, and inducing phagocytosis. These collectively, modify T-cell responses, by enhancing Th1 responses and attenuating Th2 responses. This mode of action is most likely important in the prevention and therapy of infectious diseases [7].

The probiotic bacteria can interact with epithelial and dendritic cells (DCs) and with monocytes/macrophages and lymphocytes. In various strategies, they interact and modulate the immune system that benefits human health [13]. The immunological advantages of probiotics can be because of the modulation of response towards food antigens as noted by a previous study [50,51].

The intrinsic properties of lactobacilli modulate the immune system making them appealing for wellbeing applications [52]. The Proposed systems engaged with reinforcing nonspecific and antigen-specific defense against infection and tumors. They also have potentiated adjuvant impact in antigen-particular immune responses and modulate Th1/Th2 cells as well as the production of anti-inflammatory cytokines. Probiotics in particular modulate the immune system through improving phagocytic action of granulocytes, cytokine discharge in lymphocytes, and increasing immunoglobulin-emitting cells in the blood to scale up antibody production. These are ordinary reactions of probiotics, which are all demonstrative of changes in the immune system. An inflammatory immune response delivered cytokine-actuated monocytes and macrophages recruit cytotoxic particles fit for lysing tumor cells and pathogens in the body [53].

## 6.1. Probiotics in Allergic Diseases

Recent evidence suggests that exposure to bacteria in early life may exhibit a protective role against allergy and in this context, probiotics may provide safe alternative microbial stimulation needed for the developing immune system in young animals. Probiotics have been noted to improve mucosal barrier function, a property that contributes to controlling allergic responses [54]. The role of intestinal microbiota in allergy is evident from the fact that significant quantitative and qualitative differences were noted among children and infants suffering from allergic diseases [55].

Furthermore, *L. rhamnosus* GG was able to prevent the occurrence of atopic eczema in infants born to women who had a genetic predisposition or family members with atopic eczema, allergic rhinitis, or asthma. However, probiotics were not successful in alleviating symptoms of asthma. Food allergy is a result of exaggerated immunological response to dietary antigens, that may cause excessive intestinal inflammation and damage [56].

In a recent clinical study, a blend of probiotic microbes including LAB strains isolated from healthy human intestines (*Lactobacillus salivarius* AP-32, *L. acidophilus* TYCA06, and *L. reuteri* GL-104), and breast milk (*Bifidobacterium animalis* subsp. *lactis* CP-9, *B. longum* subsp. *infantis* BLI-02, *B. breve* Bv-889, *L. gasseri* AI-88 and *B. bifidum* Bf-688). Invitro, animal studies, and human clinical experiments have positively evaluated the antimicrobial activities, the proliferation of anti-inflammatory cytokines and peripheral blood mononuclear cells, wound-healing abilities of the probiotic microbial blend, among others [57]. This study had noted that the probiotic therapy could benefit patients suffering from atopic dermatitis.

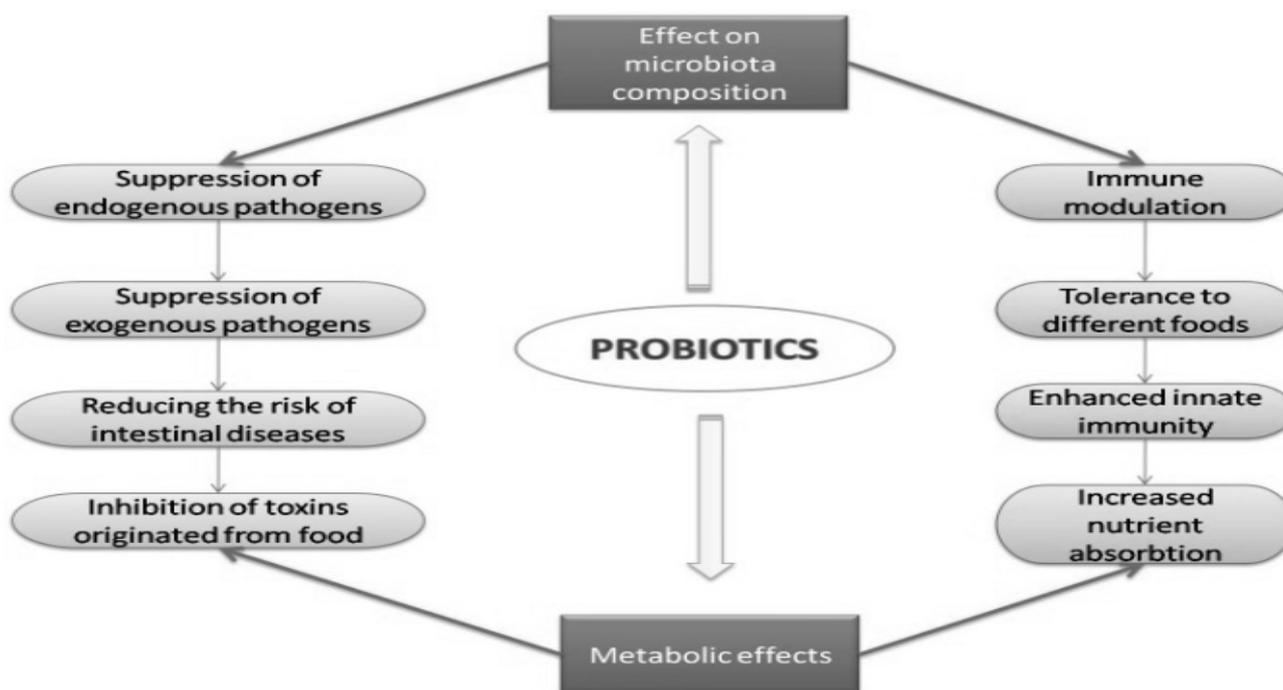


Figure 3. Immune modulation and mechanisms of action of probiotics [51]

## 7. Emerging Evidence of Benefits and Harms of Probiotics

The microbiota of the gut-liver and gut-lung axis has proven the significance of resident microbial flora in health and disease. Probiotics have now been recommended along with the prescribed medication in the treatment and management of diseases including the novel Coronavirus disease-19 (COVID-19) [58]. The probiotic prescription was suggested among COVID-19 patients to compensate for the gut microbial dysbiosis [59]. Also, it was found that the healthy intestinal microbiome facilitates pulmonary function through the gut-lung axis, exhibits antioxidant and anti-inflammatory properties, and improves/boosts immunity [60,61,62,63,64]. Given the complexity of the disease, COVID-19 patients are recommended probiotics as adjuvant therapy despite the scarcity of confirming evidence of the potential benefits among the infected patients [65,66,67,68,69].

Studies recently have suggested the role of probiotics in mental health. It was noted that the gut microbiome produces several metabolites that influence the brain and therefore could also impact the psychological well-being of humans [70,71]. Consumption of probiotics by mothers significantly influences the microbiome of breast milk and infant feces [72]. Application of probiotics in the treatment of Acne Vulgaris found favorable results with organisms like *Streptococcus salivarius*, *Bifidobacterium lactis*, *L. casei*, *L. bulgaricus*, *L. rhamnosus* GG, and *Streptococcus thermophilus*. These bacteria were noted to influence the glucose and fat metabolism, thereby benefiting people suffering from Acne vulgaris, and diabetes mellitus type 1 (non-insulin-dependent diabetes mellitus) [73].

Animal experiments have found the benefits of probiotics in the amelioration of cadmium toxicity. Although human clinical trials haven't yet proved the efficacy of probiotics, they have been considered as potential therapeutic interventions in treating cadmium toxicity [74].

The application of probiotics and prebiotics as supplements during regular therapeutic medications for respiratory tract infections was recently investigated. It was noted that although there was a clinical improvement with probiotics, the right concentrations of probiotics, their harmful effects need further confirmation [75].

The application of probiotics was positively evaluated in the management of bacterial vaginosis by a previous study [76]. This study noted that the patients treated with probiotics only had significant remission of BV, as compared to probiotics and antibiotics combined therapy. No adverse effects were found, and the long-term clinical benefits were apparent among the treatment groups. A positive effect on the overall health of the baby over 12 months after birth was noted among the mothers who in the third trimester were prescribed supplements and probiotics including *L. rhamnosus* and *Bifidobacterium lactis* [77]. This clinical trial had observed no ill effects of the probiotics and supplements.

Potential beneficial effects of probiotics were noted regarding the development of autism spectrum disorder [78]. The study involving ASD patients showed that there was a significant alteration in the gut microbiota, and

probiotic supplementation could minimize the symptoms. Therefore, it is suggested that pregnant women with probiotics and other supplementation could influence the development of ASD among infants.

Because humans and microbes have been co-existing in an atmosphere of mutual benefit, any disturbances in such microbiome dysbiosis could influence the immunological mechanisms/responses [79]. This phenomenon is evident by the previous reports which suggested the replacement of microbial community of the skin, the intestines, vagina, and other environments would resist colonization of pathogenic microorganisms [72,73,74].

Applications of probiotics in health have previously been documented about the microbiota of the skin and intestines. It was suggested that replacement and/or manipulations of the microbiome imbalances of the human skin or the intestinal tract (fecal transplantations) could benefit patients [80,81]. This was evident from the clinical benefits observed among the COVID-19 patients [82].

There have been reports emerging from both human research and animal experiments on the constitution of the gut microbiome affecting neurological health [83,84,85]. This is evident by the microbiota-gut-brain axis, a relation that is established between the gut microbiota and the brain, when disturbed can result in neurological diseases like Parkinson's, Alzheimer's, multiple sclerosis, and other diseases [86,87,88].

Metagenomic studies have observed that the pre-term born infants had ill-formed gut microbiome. Therefore, such infants are predisposed to serious intestinal inflammations, infections, suffer from late-onset sepsis, and may at a later age suffer from immunological disorders like hypersensitivity, asthma, and psychological disorders [89]. Also, noted were the variations in the types of gut microbiomes with the age and specific geographical regions. Six clusters of *Lactobacillus* types with three clusters being dominated by *L. delbrueckii*, *L. ruminis*, *L. casei* were noted. Variable trends in the numbers of Lactobacilli with increasing age were observed in different geographical regions. The numbers of Lactobacilli in the gut showed an increasing trend in North America and Europe in contrast to a decreasing trend among people in other geographical locations [90]. Association of the variability in the gut Lactobacilli correlated with the age, gender, and development of obesity, diabetes, hypertension, IBD, among others. The relationship of the gut microbiome with the development of type 1 diabetes was also previously established [91].

Influences of gut microbiota in the development of cancers were previously assessed [92,93]. The dysbiosis in the gut microbiome was found to influence the breast microbiome and in turn, may result in breast diseases.

Given the potential of probiotics in reducing the incidences of diarrhea is well established, it was not sure if they benefit people in reducing the duration and incidences of respiratory tract infections [94]. Therefore, further metagenomic, transcriptomic, proteomic, and metabolomic studies were suggested to evaluate the role of gut microbiota in the development of intestinal and extra-intestinal diseases [95].

Although several studies have supported the beneficial effects of probiotics, the American Association for

Gastroenterology (AAG) has not recommended the use of probiotics in the treatment and management of patients. This comes in the light of no consensus regarding the type of microbes used, the dosage, duration of therapy, and several other factors [96,97].

Risks involved in using live microbial species as probiotics were addressed by suggesting the role of non-viable and heat-killed strains. The drawback of live microbes includes but is not limited to the translocation of bacteria from the intestines to other locations of the body, cellular invasion, and development of resistance to antibiotics [98].

Given the increasing popularity and on-the-counter availability of probiotics, and due to the uncertainty over the potential harm posed by them, there is a need for caution while using probiotics. Further studies are needed to understand the behavior of microbes that are consumed as probiotics, their interactions with the endogenous microbiome, and the long-term consequences of their presence to the human physiological constitution [99].

## 8. Limitations of Bacterial Probiotics

Even though there are numerous advantages and health benefits of probiotics or probiotic food products, there are different risks potentially associated with their use. These risks are mainly concerning safety in vulnerable target groups such as immunocompromised individuals (pregnant women, babies, and elders) or critically ill or hospitalized patients [100]. Probiotics can interact with commensal bacteria and can also have a direct impact on the host. Understanding these interactions is one of the key challenges for the therapeutic applications of probiotics. Other key challenges are associated with understanding their mechanisms of action and elucidation of effective microbial strains with their correspondent health benefits and the level of intake to achieve the desired therapeutic effect effects [101].

Therefore, it is an urgent need to conduct clinical, mechanistic, and omics studies for better understanding regarding the interface between the microbes, host cells, mucus, and immune defenses, and to ultimately ensure efficacious interventions [102,103,104,105].

Such studies should include molecular examination of the intestinal (not only fecal) flora and long-term (5-10 years) effects of probiotic microorganisms [106].

Alternatively, some probiotic microbes may pose problems. The *Enterococcus* group of bacteria harbor transmissible antibiotic resistance determinants. *Bacillus cereus* is also known to produce enterotoxins and an emetic toxin. Theoretically, probiotics may be responsible for four types of side-effects that include systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, and gene transfer [24].

## 9. Conclusions

Emerging microbes and multi-drug resistant pathogens are the main driving forces behind the efforts to find an

alternative solution in the form of probiotics. Probiotics are considered living drugs that can reduce antibiotic consumption and increase human health development. Health benefiting microbes in the form of probiotics have assumed increasing significance. Several human diseases are attributed to the disturbances in the resident microbial flora, be it the skin, intestine, lungs, vagina, and other organs of the body. There is a shred of ever-increasing evidence pointing to the beneficial effects of probiotics on human health. Nevertheless, the clinicians treating patients are unsure of the dosage, timing of probiotics, and potential ill effects of probiotics. Therefore, further focused research in this direction could identify some more beneficial microbes which can be successfully used as probiotics in health and disease.

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