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Review Article

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Probiotics as promoters of human health

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Abstract

Numerous common human disorders, including cancer, high blood pressure, high cholesterol, inflammatory bowel diseases, obesity, and oral health issues, have been linked to changes in the composition and activity of the gut microbiota. This review aimed to highlight the significance of probiotics due to their positive impacts on gut microbiota, overall human health, cancer prevention, and production of bioactive compounds. Therefore, modifying the gut microbiota's balance can be highly beneficial for maintaining the human health. Probiotics are live microbial supplements, when consumed with meals; they help the host by harmonizing his/ her intestinal microflora. Supplements containing these good bacteria can be used up, or they can be added to dairy-free or non-dairy foods and drinks. Probiotics are mainly categorized into two main genera; mainly *Lactobacillus* spp. and *Bifidobacterium* spp. Probiotics are vital for maintaining a healthy microbiota; especially in cancer patients. They enhance the production of anticancer enzymes, apoptosis, autophagy, immunology, and other processes. Additionally, probiotics produce various bioactive molecules such as short-chain fatty acids, enzymes, vitamins, and exopolysaccharides with antibacterial attributes. Consequently, probiotics are utilized in food technology to develop the functional foods that promote the human health.

Keywords: Functional food, Microbiota, Bioactive substances, Probiotics, Cancer

1. Introduction

Nowadays, probiotics are frequent elements the in functional meals, whether in food or supplements. They have attracted the economic interests because of their possible health benefits (Hamad *et al*., 2022). Werner Kollath invented the term "probiotic" in 1953; combining the Latin "pro" and the Greek word "cιo," which means "for life." Moreover, Kollath defined probiotics as living microorganisms that are essential for promoting the general human health (Gasbarrini *et al*., 2016). Later, Food and Agriculture Organization (FAO) and the World Health Organization (WHO) defined probiotics as "live microbes that when consumed in adequate amounts, provide health benefits to their host" (Munir *et al*., 2022). Numerous microbial genera are thought to be viable candidates for probiotics, including *Lactococcus*, *Enterococcus*, *Streptococcus*, *Propionibacterium*, and *Bacillus* (Hamad *et al*., 2022). Frequent strains of *Bifidobacterium* and *Lactobacillus* play important roles in promoting the human health by detoxifying the environmental pollutants and xenobiotics, converting mycotoxins in food, and generating vitamin K, riboflavin, and folate (Hamad *et al*., 2022). By lowering the binding sites on the mucosal epithelial cells, probiotics improve the integrity of the intestinal barrier, suppress the pathogenic bacteria, and alter the host immune system. Probiotics have been shown to positively impact gut microbiota, alleviate lactose intolerance symptoms, enhance absorption of essential nutrients, and reduce allergic reactions in liable people (Roobab *et al*., 2020). These beneficial bacteria can be used up as supplements or become incorporated into dairy or non-dairy foods and beverages. Many probiotic strains are naturally present in fermented foods, which can enhance their nutritional value and functionality by converting substrates into bioactive end products (Marco *et al*., 2017). The recommended effective daily dose of probiotics is approximately 10^{-9} colony-forming units (cfu) (Hill *et al*., 2014). The food industry has been incorporating probiotics into various products such as drinks, yogurt, ice cream, bread, and more; ensuring the optimal dosage is maintained. A key challenge in utilizing probiotics in food production is their sensitivity to gastrointestinal irritants and processing conditions. Despite of this, consumer's demands for probiotic products remain high due to their perceived health benefits (Konuray and Erginkaya, 2018). Advances in technology, including genetic modification and nano-encapsulation enabled the development of probiotics that can withstand processing conditions and gastrointestinal stressors. The objectives of this review were to present various aspects of probiotics, emphasizing their importance in maintaining a healthy gut microbiota, enhancing human immunity, treating cancer, inducing apoptosis, and reactivating tumor suppressor genes. Additionally, probiotics produce a range of bioactive compounds such as antimicrobial compounds, EPSs, enzymes, and vitamins, making them valuable for functional food applications.

2. Proper probiotics and microbiota

2.1. The importance of gut microbiota in human health

The progress of treatments aimed at specifically restoring or enhancing beneficial activities of microbiota has garnered significant interests because of the critical roles that the microbiota plays in host healthiness. This interest is evident in academic research as well as emerging and established companies (Sorbara and Pamer, 2022). Since its discovery, various reports have highlighted the importance of microbiota in health and disorders. Depending on the particular regions, the microbiota can be divided into four groups: gut, oral, respiratory, and skin microbiota. According to Azad *et al*., (2018), living in symbiosis with their hosts, microbial populations support immune system regulation and homeostasis maintenance. The gastrointestinal tract contains 150 times more genes than the human genome and is a home for 10^{-13}-10^{-14} different types of

bacterial species. The adult gut microbiota is made up of around 1000 distinct species and over 7000 distinct bacterial strains (Elvers *et al*., 2020). According to the findings of Vivarelli *et al*., (2019), the human genome encodes 100 times fewer genes than the gut microbiota, which represents the entire genome of the host's gut microbiota. Despite the longstanding belief that the majority of intestinal microbes are un-culturable, recent advancements have enabled the cultivation of a significant portion of the microbiota *in vitro*. This feature has permitted the genetic and metabolic analysis of various symbiotic bacterial strains, demonstrating significant varieties within the bacterial families, genera, and species (Renwick *et al*., 2021).

These days, it is thought that the host's gut microbiota regulates its overall health. Microbes have colonized almost every part of our bodies, indicating various interactions with our organs. With the advancement of molecular tools and methodologies (e.g. metagenomic, metabolomic, lipidomic, and meta-transcriptomic), the complex interactions between different bacteria and their hosts are gradually being understood. Deviations from the normal gut microbiota are now linked to wide range of illnesses, including type 2 diabetes, obesity, hepatic steatosis, inflammatory bowel disorders (IBDs), and several cancers. Consequently, it is possible that different pathways related to energy, cholesterol, glucose, and immunology become affected (De Vos *et al*., 2022). Due to identification of the correlations that exist between microbiota compositions and disease susceptibility as well as our growing knowledge of the effects of symbiotic microorganisms and their metabolites on human health, we are getting closer to the development of targeted therapies that can optimize microbiota composition and enhance disease resistance (Peled *et al*., 2020).

The current issue facing the biomedical research community is to use our understanding of microbiota to develop potent medical treatments. Modifying the gut microbiota's composition has the potential to significantly lower the prevalence and severity of a number of human illnesses and disorders. There are promising prospects for advancement of microbiota-based treatments starting from transplantation of fecal microbiota to delivery of well-defined and clinically verified symbiotic microbial consortia that improve disease resistance. These opportunities result from the use of ecological principles and machine learning, and our growing understanding of the symbiotic microbial species. The symbiotic microorganisms in the gastrointestinal tract enhance immunity against a range of diseases such as cancer, and reduce susceptibility to infections (Sorbara and Pamer, 2022). The development of colorectal cancer (CRC) that remains as one of the most frequent malignancies globally is significantly influenced by the gut microbiota. Additionally, CRC ranks the second globally in terms of cancer-related deaths and is the third most frequent type of cancer; with around 2 million new cases reported annually (Xi and Xu, 2021).

Important information concerning CRC screening, early detection and treatment results prediction come from the makeup of bacterial strains and the effects of location, race, sex, and diet on the microbiota. One of the most exciting new avenues in medicine to enhance individual health is microbiota control. It is imperative to conduct additional studies on the gut microbiota in oncology and CRC patients care, to ascertain the effectiveness of systemic medicines, reduce side effects, and raise survival rates (Rebersek, 2021).

The three primary roles of gut microbiota are metabolic, protective, and structural. Furthermore, the tumor microbiota adversely affects the gut microbiota, which limits the systemic therapeutic efficacy of immunotherapy, chemotherapy, and insufficient host immune system responses both locally and systemically (De Vos *et al*., 2022).

The role of gut microbiota in colorectal cancer carcinogenesis has drawn more attention in the last several years. The bacteria linked to colorectal cancer or the CRC microbiota are not the same as those bacteria found in a healthy gut microbiota. In addition, the recently identified bacterial strains that have been

connected to colorectal cancer also include strains that are individually linked to this disease, including *Bacteroides fragilis*, *Streptococcus gallolyticus*, *Enterococcus faecalis*, *Escherichia coli*, *Fusobacterium nucleatum*, *Parvimonas*, *Peptostreptococcus*, *Porphyromonas*, and *Prevotella*. CRC biomarkers may include elevated concentrations of these bacterial strains in tumor and fecal samples obtained from patients suffering from the disease (De Vos *et al*., 2022).

Interactions between hosts and microorganisms play a crucial role in activating the procarcinogen signaling pathways, leading to molecular alterations with subsequent occurrence of colorectal cancer. Regarding CRC, these mechanistic elements can be modified for preventive or therapeutic purposes (Wong and Yu, 2019). For CRC patients, bacteria's involvement in both of chemotherapeutic metabolism and immune-related colitis from immunotherapy underscores the importance of distribution and localization of bacteria in tumors for patient's prognosis and future treatment strategies (Rebersek, 2021).

Approximately 35 % of colon cancer cases may be related to dietary factors such as excessive or low intake of animal products; especially for processed meat, added sugars, fats, and refined carbs. Eating red and processed meats has been associated with a higher risk of CRC. Red and processed meats contain much iron that is broken down in the stomach to form N-nitroso compounds, which can damage the intestinal lining cells and elevate the cancer risk. N-nitroso compounds are produced when nitrates and nitrites which are frequently used as preservatives in processed meats decompose (Sharaf *et al*., 2018). Dietary fat is another element that affects the composition of gut microbiota and gastrointestinal functions. Diet is a key factor in determining the status of gut microbiota because of the symbiotic relationship that occurs during digestion between the gut microbiota and its host. The gut microbiota plays a significant role in food digestion and extraction of essential nutrients that the host cannot absorb. It has been demonstrated that dietary fiber; particularly fructans and galacto-oligosaccharides, suppresses tumors, modifies the composition of gut microbiota, fosters the growth of probiotics (*i.e*., *Bifidobacterium* and *Lactobacillus* spp.), and raises the amount of butyrate in feces (Wong and Yu, 2019).

2.2. Definitions and ideas of probiotics

With the introduction of new "biotic" terms such as pharmabiotic, psycho-biotic, post-biotic, symbiotic, and others into the global language, it is especially beneficial to define the minimal requirements needed for proper use of the term "probiotic" (Binda *et al*., 2020). Here, the word "probiotic" refers to more than simply conventional probiotics. Innovation will undoubtedly results in the extraction of promising probiotics from cutting-edge sources; with fascinating new health advantages and previously unknown functions. These so-called "next generation probiotics," which in certain circumstances may be regarded as live biotherapeutics, are not excluded by these criteria. However, the development of such probiotics must take into account proper safety, legal, and ethical considerations depending on their intended usage (Johansen, 2017).

The United States Food and Agriculture Organization and the World Health Organization (FAO/ WHO. 2001) developed the term "probiotic" that is used globally today. Rather to "antibiotics" that mean "against life," the phrase "probiotic" is "pro bios," which means "for life." These two organizations defined probiotics as living microorganisms that when provided in sufficient proportions, may have a favorable influence on the host organism's health.

Probiotics are appealing as a potential adjuvant therapy for preventing and/or minimizing gastrointestinal (GI) side effects associated with anticancer chemical drugs; therefore enhancing patient's compliance (Pino *et al*., 2020). Recently, studies have focused mostly on examining the culture conditions and viability of probiotic strains during processing and storage; mainly susceptibility to low

pH, gastric fluid, bile, pancreatic and intestinal fluids, intestinal and/or respiratory mucus; and adherence to the isolated probiotic strains (Barajas-Álvarez *et al*., 2021); despite the fact that the various characteristics of probiotics have been identified as main health boosters. The name *Weissella* was first assigned to the new probiotic bacteria by Collins *et al*., (1993) following taxonomic findings on typical *Leuconostoc*-like germs derived from fermented sausages made in Greece. In several biochemical assays, Collins *et al*., (1993) noted that these bacteria differ from other *Leuconostoc* spp. Moreover, it was revealed by molecular systematic analyses that *Leuconostocs* (L) could be divided into three separate genetic lineages, including genus *L. ensustricto*, *L. paramesenteroides* group (which included Lactobacilli as well), and the species that was formerly known as *L. oenos* (now categorized as *Oenococcusoeni*). Diversity of the new genus *Weissella* (W) and removal of these species that were formerly included in the genus *Lactobacillus*; mainly *W. confusa*, *W. halotolerans*, *W. kandleri*, *W. minor*, and *W. viridescens* have been revealed by recent investigations based on phenotypic, biochemical, and 16SrRNA gene examinations (Assamoi *et al*., 2016).

Additionally, one species that was previously classified under the genus *Leuconostoc* as *W. paramesenteroides* has now been reclassified under the newly created genus. These species which included a recently discovered isolate of *W. hellenica* with a morphological shape that was documented by Collins *et al*., (1993), all had strong sequence matches for the 16S RNA gene, which made them eligible for inclusion in the newly created genus *Weissella*. As reported by Collins *et al*., (1993), the *Leuconostocs* have a slightly lentil-like form; with tapering ends rather than a completely round appearance. This is known as their "typical irregular coccoid morphology."

Several studies have shown that *W. paramesenteroides*, isolated from bee bread, can be used as a valuable biological tool for making fish silage. The pH drop in fish silages with encapsulated and non-encapsulated bacteria was compared. According to Libonatti *et al*., (2019), *W. paramesenteroides* has made a strong presentation on the advancement of biological fish silage uses. From a technological perspective, *Weissella* sp. is crucial to food fermentations using meat or vegetables as substrates, in addition to several fermentation processes such as creation of silage. In certain nations, fish silage waste is utilized to improve the nutrients found in fish waste. This practice has two advantages: it lowers the risk of contamination caused by untreated waste and lowers the price of food processing. *Weissella* is a genus of hetero-fermentative lactic acid bacteria (LAB) that is frequently associated with food. *Weissella* sp. inhabits diverse environments, including animal skin, milk, and excrement, human feces, saliva, breast milk, plants, vegetables, and several fermented foods such as Asian and European sourdoughs. *W. paramesenteroides* MN2C2 is also able to contribute to the higher-quality yoghurt production process, which in turn has produced a multitude of health-promoting bioactive substances. These findings proved that *W. paramesenteroides* MN2C2 as a probiotic is a highly promising microorganism for usage in variety of applications such as fermentation of cassava dough into attack, which is the major fermented plant food in Africa (Libonatti *et al*., 2019).

During natural fermentation of cassava roots, *Weissella* sp. as a LAB has shown to predominate over the other bacteria and yeasts. In addition to improving detoxification, this species also increases food safety and quality through making changes in its functional characteristics, including flavor development, cyanide reduction, and product preservation (Assamoi *et al*., 2016).

Acute diarrhea in children is the second most common illness after respiratory tract infections; it usually lasts less than two weeks and is caused by a variety of pathogens and factors. Diarrhea is characterized by increased frequency and consistency of stool and is often accompanied by fever, vomiting, and imbalances in electrolytes and pH; if not treated promptly and effectively, it can result in severe

dehydration and serious consequences. Probiotic supplementation is important because it can improve the intestinal microenvironment, promotes immunity, and enhances resistance in children with acute diarrhea due to imbalance of the intestinal bacteria. Further studies on probiotics led to the development of prebiotics, which are certain compounds that impact the gut microbial ecosystem but are not simply digested by humans. Prebiotics have a specific purpose in promoting the growth and activities of beneficial bacterial species in the gut. Some of the most well-known prebiotics include insulin, oligofructose, and fructo-oligosaccharides (FOS), which are synthesized from sucrose and contain galactose and xylose. These substances also have bifidogenic properties. Natural sources of prebiotics include the foods that we eat on a daily basis such as grains, vegetables, and fruits (Sanders *et al*., 2019).

Both probiotics and prebiotics are rapidly being included in a wide range of meals, beverages, and many other products. As a result, additional studies must be conducted on providing new health supplements, including novel probiotic, prebiotic and its bioactive compounds (Sanders *et al*., 2019). The intricate community of microorganisms known as the gut microbiota, which inhabits the gastrointestinal tract, is known as "the second brain" or "the forgotten endocrine organ", because it influences metabolic, oxidative, and cognitive status while playing a significant but an unidentified role in preserving the host's health and homeostasis. Conversely, several variables such as age and sex, and other aspects that can be changed, including nutrition, medication, and lifestyle, have an impact on the variety and richness of the gut microbiota (Donati-Zeppa *et al*., 2023).

Probiotics have an attractive role as a potential adjuvant therapy in preventing and/or reducing gastrointestinal side effects, due to anticancer treatment, improving patient compliance, and producing many anticancer and antioxidant bioactive compounds. Therefore, novel local probiotics and their bioactive substances are used to manipulate the gut microbiota for improving overall health outcomes for protection and therapy of many diseases. Probiotics are becoming more and more popular for both prophylaxis and therapeutics. The term "stable gut microbiota" refers to the functional role of bioactive agents produced by the microorganisms in each host. The vast majorities of these probiotics are oral and stay in the intestine (Sharifi-Rad *et al*., 2020).

Additionally, it has been demonstrated that probiotics can effectively reverse chronic intestinal dysbiosis disorders such cancer (Tsai *et al*., 2019). Probiotic use in managing intestinal disorders and diseases during chemotherapy, immunotherapy, and radiation therapy is also being investigated in an increasing number of clinical trials, with encouraging outcomes.

The development of symbiotics that are a blend of probiotics and prebiotics as a consequence of advances in microbial research has improved the survival and implantation of the living microbial food supplements in the gut. Growing scientific data indicates that the symbiotic interaction between probiotics and prebiotics has a key role in human wellness; thus, there has been a progressive increase in commercial interests in functional foods that contain symbiotics. The development of innovative meals that enhance wellbeing and aid in the prevention and treatment of illnesses is the current focus of recent studies in this field (Gibson *et al*., 2017). According to Gibson *et al*., (2017), conventional research and investigations have discovered that the individual recipient effects of probiotics, prebiotics, and symbiotics are far more potent than the unitary administration of these medications to date.

Postbiotics are metabolic byproducts or non-viable bacterial products that probiotic microorganisms make and that have biological functions in human. Postbiotics are useful bioactive substances produced within a matrix during anaerobic fermentation of organic nutrients such as prebiotics, in order to produce adenosine triphosphate (ATP), which is used as an energy source. Postbiotics are metabolic sequence's byproducts, which are low molecular weight soluble substances that are either secreted by

living microflora or released following lysis of microbial cells (Thorakkattu *et al*., 2022).

Short-chain fatty acids, microbial cell fragments, extracellular polysaccharides, cell lysates, teichoic acid, vitamins, etc. are few instances of postbiotics that have been extensively studied. The products that are now available in the markets include the prebiotics and probiotics; however postbiotics are also receiving considerable attention. In the near future, consumers demand for postbiotic supplements may rise due to the existence of many health benefits of these postbiotic components (Thorakkattu *et al*., 2022).

2.3. Immunity and probiotics

To sustain healthy immunological activity, commensal bacteria and immune cells in the human gut interact and communicate with one another continuously in a stable environment. The balance between immunological tolerance and immunogenicity is maintained through a complex network of pathways that are essential for immune system-microbiota cross-talk. Probiotic use may be a viable strategy for enhancing immune system capabilities, since probiotic bacteria have the ability to interact with intestinal immune cells and commensal microflora to control certain immunological functions and immune homeostasis. The positive immune modulatory effect of probiotics has not been extensively studied to date (Mazziotta *et al*., 2023).

Due to constant exposure to variety of pathogenic agents and antigens, the gut is a dynamic and complex ecosystem that has developed unique immune cells features over time (Zhou *et al*., 2020). Numerous intestinal immune cell types are crucial to the host's ability to fight off infections and control immunity to both ingested antigens and commensal microorganisms. However, intestinal commensal microorganisms with advantageous immunomodulatory qualities might influence immune cell functions and activities to a significant extent (Sharifi-Rad *et al*., 2020). Indeed, immunological homeostasis and regulation of both innate and adaptive immune responses depend on immune cells, commensal microbes, and nutrients interacting and responding to one another continuously in a stable environment (Lee *et al*., 2022).

The immune system is essential to the development, maintenance, and removal of many illnesses. Given that 70-80 % of immune cells reside in the gut, the local mucosal immune system, the intestinal epithelial layer, and the intestinal microbiota interact intricately. It is becoming more widely acknowledged that gut microbiota influences systemic immunity and local mucosal immune responses in the gut (Wiertsema *et al*., 2021).

Donaldson *et al*., (2015) stated that the gut-associated lymphoid tissue (GALT) is linked to the digestive tract and has significant immunological functions. GALT is the most extensive component of the entire immunological capability and is a member of the mucosa-associated lymphoid tissue (MALT) (Fig. 1). According to Donaldson *et al*., (2015), GALT is a vast source of T and B cells that travel to effector locations in order to trigger immunological responses. Additionally, GALT has a variety of dendritic cell (DC) populations. Peyer's patches, which are follicle-associated epithelia distributed throughout the intestinal epithelium and in secretory regions within the mucosa are another component of GALT. DCs are necessary for appropriate induction of adaptive immune responses. During inflammation, DCs migrate to lymphoid organs, where they mature and consume antigens to expose foreign material to naïve T cells. DCs cells get activated and can either differentiate into cytotoxic antibodies specific to a pathogen or into locally generated proteolytic-resistant antibodies in effector tissues. These antibodies are particularly significant for immune functions of the mucosal membrane (Rotondo *et al*., 2022).

IgAs have a role in mucosal immunity to protect mucosal surfaces by adhering to and neutralizing foreign antigens originating from poisons and pathogens. As a result, IgAs prevent microorganisms from adhering to and penetrating the intestinal

epithelial cells. Recent data; however, indicated that IgAs may now play a role in inflammation at both of mucosal and extra-mucosal sites. One of the most significant functions of probiotics is their immunomodulatory action (Fig. 1 and 2) (Maldonado-Galdeano *et al*., 2019). Scholars have redirected their focus towards comprehending the immunomodulatory impacts of probiotics, as they may be able to avert or mitigate specific illnesses where appropriate medical intervention is still lacking. The immune cells (*i.e*., T- and B-cells) have been scientifically proven to mediate adaptive immunity and give immunological protection through the development of pathogen-specific memory (Azad *et al*., 2018). Further findings indicated that LAB would be helpful as adjuvants to prevent mammary gland pathologies, including cancer and oral treatments, to shield the mucosal surfaces from intestinal and respiratory disorders (de Moreno de Leblanc *et al*., 2005).

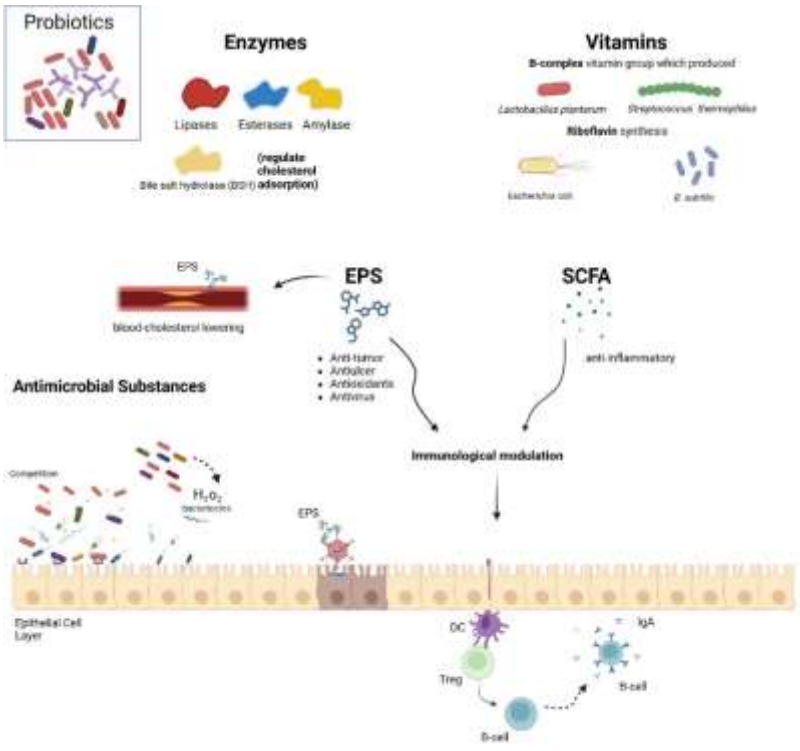

Fig. 1: Probiotics can produce bioactive compounds that play a beneficial role in combating certain infectious diseases in humans. The figure was adopted from https://www.biorender.com/

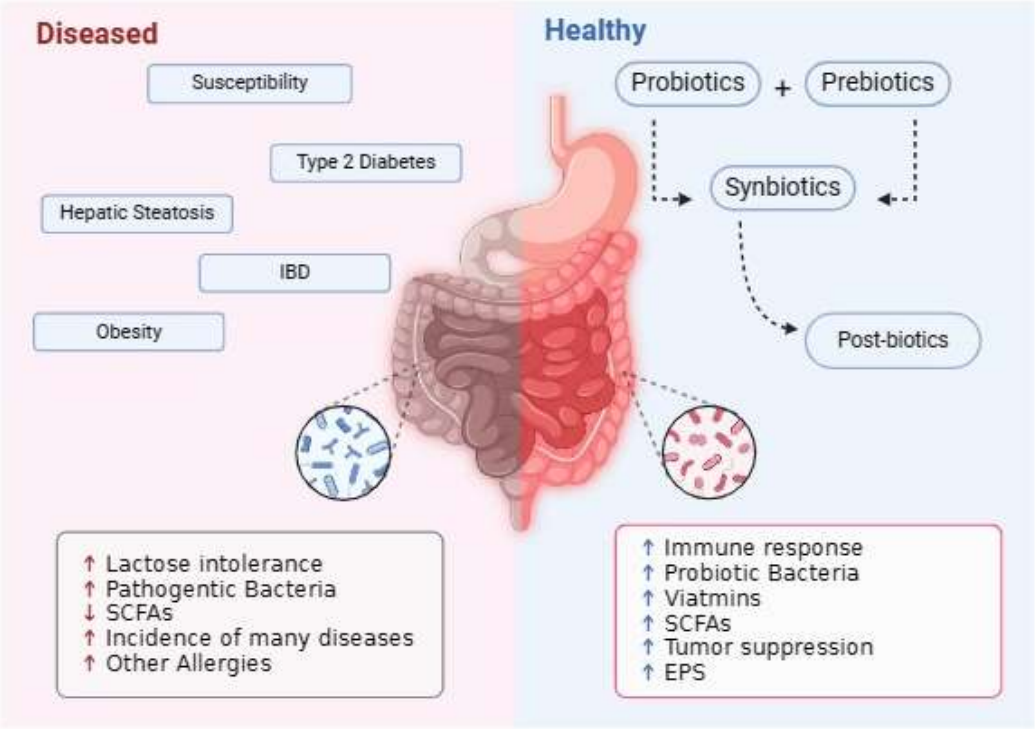

Fig. 2: Microbiota and probiotics play a crucial role in healing human serious diseases. The figure was adopted from https://www.biorender.com/

3. The ways in which probiotics aid in cancer treatment

Many cancer patients are able to survive due to chemotherapy; however there are hazards associated with its side effects. Medication combinations and drugs such 5-fluorouracil, irinotecan, oxaliplatin, methotrexate, and others can cause intestinal mucositis, which can lead to or cause anorexia, discomfort, diarrhea, weight loss, systemic infections, and even death. Strategies targeted toward altering the intestinal microbiota may be helpful to mitigate and prevent the terrible effects of chemotherapy-induced intestinal mucositis and diarrhea, as dysbiosis is a characteristic of both conditions (López-Gómez *et al*. 2023).

The findings that have been obtained so far however are encouraging. In the near future, intestinal mucositis should hopefully have less effect on the cancer patient with the help of these medications (López-Gómez *et al*., 2023). Probiotics generate biofilms, which have antibacterial properties against oral infections. On the meantime, prebiotics can promote growth and boost probiotic benefits. Furthermore, according to Mohd-Fuad *et al*., (2023), postbiotics have antibacterial, anticariogenic, and anticancer activities.

Probiotics have the ability to modulate cancer through a number of mechanisms, including: (a) inducing apoptosis; (b) the variability and strain-dependent nature of probiotic activity impairs an anti-mutagenic properties against the different

mutagens (Massoud, 2023); (c) downregulating oncogene expression; (d) enhancing autophagy; (e) inhibiting kinases (An *et al*., 2023); (f) reactivating tumor suppressors; and (g) preventing metastasis.

3.1. Probiotics' induction of apoptosis

Pfeffer and Singh, (2018) reported that apoptosis is a good target for cancer therapy. Tumor necrosis factor (TNF), caspases, and β-cell lymphoma (Bcl)-2 is inhibitor of apoptosis proteins, while the *p53* gene is one of the genes implicated in apoptosis. According to Karimi-Ardestani *et al*., (2019), probiotics affect caspases and *Bax/Bcl-2* to cause cancer cells to undergo apoptosis by upregulating the expression of *Bax*, *IFN-γ*, and *TNF-α*. In the same trend, *L. acidophilus* and *B. bifidum* demonstrated higher cytotoxic effects against breast and colon cancer cell lines.

3.2. Oxygen and autophagy

Double-membrane autophagosomes trap organelles or parts of the cytoplasm fuse with lysosomes for further breakdown by resident hydrolases during the self-degradation process known as autophagy (Li *et al*., 2020). The removal of aging proteins and organelles or damaged cells depends on autophagy. Furthermore, it has been suggested that autophagy deficiencies have a role in tumor suppression by causing DNA damage and malignancy (Tran *et al*., 2021). There is a dearth of studies on the use of probiotics to induce autophagy and reduce tumor growth. According to Wang *et al*., (2019), an autophagy-linked protein called microtubule-associated protein 1 light chain 3 has a change in its levels caused by a surface protein from *L. acidophilus*, which led to death of HCT116 cells (Wang *et al*., 2019). Furthermore, by initiating Beclin1/GRP78-mediated autophagy activation, LAB have facilitated induction of apoptosis in the presence of 5-fluorouracil (Śliżewska *et al*., 2021). Beclin-1, lysosome-associated membrane protein, damage-regulated autophagy modulator 1, and *p53* are among the significant genes and proteins involved in autophagy (Bednarczyk *et al*., 2018). Chaperone-mediated autophagy, selective autophagy, mega autophagy, and micro autophagy are the four forms of autophagy (Yim and Mizushima, 2020). Depending on number of variables, including age and kind of cancer, autophagy may either stimulate or hinder the growth of tumors (Bednarczyk *et al*., 2018).

3.3. Potential anti-mutagens in probiotics

Numerous substances have the potential to harm and mutate DNA, which can ultimately result in cancer (Golemis *et al*., 2018). An additional aspect of probiotics and their anti-mutagenic properties is their potential for successful dietary integration. Thus, survivability is a crucial feature of probiotics found in the functional meals. Yogurt is one of these functional product categories. Given that yogurt should have at least 10^6 cfu/ g of probiotics at the time of use, it's a great matrix for delivering probiotics, which depends on a number of variables, including pH, water activity, oxygen, strain type, and other strains (Han *et al*., 2021).

Several approaches, including microencapsulation of probiotics, addition of enzymes, and use of prebiotics, may reduce the negative impacts of probiotics (Taherian-Esfahani *et al*., 2016). Probiotics have an anti-mutagenic effect that has been extensively studied in the previous literatures. The probiotics' hydrophilic interaction with mutagens is mediated by lipids, proteins, carbohydrates, and teichoic acids that make up their cell wall. Amino acids known as heterocyclic aromatic amines (HCA) have the ability to damage DNA and raise the risk factors for colon cancer. To bind and detoxify the action of HCA, try to use *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. helveticus*, and *L. plantarum* (Pithva *et al*., 2015b).

3.4. Reactivation of tumor suppressor genes mediated by probiotics

Tumor suppressor genes control a variety of molecular processes, including invasion, migration,

apoptosis, and cell proliferation (Kaur *et al*., 2022). Oncogenes are modifications of these genes that cause cancer cells to develop (Kontomanolis *et al*., 2020). Probiotics may be utilized possibly as a unique targeted biotherapy for cancer and numerous clinical trials have been being conducted to find out more (Vivarelli *et al*., 2019).

According to Sharma and Shukla, (2016), probiotic-produced short-chain fatty acids can target tumor cells by controlling the expression of oncogenes and tumor suppressor genes through epigenetic regulation. Without affecting the original DNA sequence, epigenetic processes modify the expression of genes. Furthermore, according to Vedham and Verma, (2014), these processes are reversible, heritable, and involve modifications to histones, short noncoding microRNAs (miRNAs), and DNA methylation. By up-regulating expression of the tumor suppressor gene *p53*, meta-biotics isolated from the probiotic *L. rhamnosus* MD prevent colorectal cancer (Sharma and Shukla, 2020). In an experimental conducted using colon carcinogenesis model caused by 1,2-dimethylhydrazine, it has been demonstrated that *L. rhamnosus* MD 14, *L. acidophilus*, and *L. rhamnosus* GG up-regulate the expression of tumor suppressor genes (Sharaf *et al*., 2018).

3.5. Probiotics down-regulate oncogene expression

Proto-oncogenes are natural and non-mutated forms of oncogenes, while oncogene expression cause cells to exhibit characteristics of tumor cells. According to Brown, (2021), proto-oncogenes are the antecedents of oncogenes that undergo mutation to become oncogenes. One of the goals that can be used to treat cancer is to down regulate its genes (Wang *et al*., 2021). Because of their structural similarity to retroviral oncogenes, a number of proto-oncogenes have been found in many microorganisms (Kontomanolis *et al*., 2020). According to Pithva *et al*., (2015a), some of the key proto-oncogenes in humans are *β-catenin*, *HER2*, *Myc*, *cyclin D*, *cyclin E*, and *MITF* (microphthalmia-associated transcription factor). *L. crispatus* and *L. rhamnosus* are two probiotic bacteria, which modify malignancies by modifying the Wnt/β-catenin pathways and mTOR-related gene expression (Taherian-Esfahani *et al*., 2016).

It has been demonstrated by Azam *et al*., (2014) that *L. acidophilus* and *L. crispatus* culture supernatants can down-regulate cancer-testis gene expression *in vitro*. Celecoxib; a non-steroidal anti-inflammatory medication together with probiotics can also down-regulate the Kirsten rat sarcoma (KRAS) proto-oncogene, hence lowering the incidence of colon cancer (Sharaf *et al*., 2018). Heydari *et al*., (2019), found that probiotic ingestion has down-regulated *miR-221*, *miR-155* (in blood), *Bcl-w*, and *KRAS* and significantly overexpressed *miR-122* and *PU.1*. According to Heydari *et al*., (2019), probiotics can therefore aid in regulation of advancement of cancer by delaying the metastatic process, decreasing inflammation, and up- and down-regulating oncogenes/ oncomirs and tumor suppressor genes/ microRNAs, respectively.

3.6. Probiotics' function in stopping metastasis

Tumor cells that have been separated from their original tumor and spread to the other body areas are referred to as metastatic processes (Fares *et al*., 2020). Years after the main tumor has diagnosed, cancer patients may experience metastases. The primary cause of metastases is the epithelial-mesenchymal transition (EMT) of cancer cells. This is a physiological process that provides the epithelial cells with several morphological and physiological traits of mesenchymal cells (Yang *et al*., 2020). There are five stages that occur during the spread of cancer cells: (1) invasion of the basement membrane; (2) infiltration into the surrounding lymphatic system or vasculature; (3) enduring in the bloodstream; (4) extravasation to adjacent tissue; and (5) colonization at sites of secondary tumors (Hapach *et al*., 2019). Certain LAB can prevent colon cancer from spreading. By down-regulating

the VEGF/MMPs signaling pathway, the cell free supernatants (CFSs) of *L. Rhamnosus*, *L. casei*, and *L. plantarum* have expressed positive effects on metastasis of CRC cells (Yue *et al*., 2020).

3.7. Probiotics inhibit kinase

Phosphatases and kinases are enzymes that add and remove phosphate groups, respectively. According to Kannaiyan and Mahadevan, (2018), Phosphorylation modifies proteins by adding the terminal γ-phosphate group of ATP to serine, threonine, and tyrosine residues. Several studies have shown that probiotics and their metabolites have kinase inhibitory potential as treatments for diarrhea that follow cancer therapy (Secombe *et al*., 2020). In a previous study, Seth *et al*., (2008) have shown that probiotic secretory proteins; *via* a mechanism dependent on protein kinase C (PKC) and MAPK, shield the intestinal epithelial tight junctions and barrier functions from damage caused by hydrogen peroxide. According to Asoudeh-Fard *et al*., (2017), *L. plantarum* causes apoptosis *via* up-regulating phosphatases and down-regulating the mitogen-activated protein kinases (MAPKs). By generating tumor necrosis factor-associated apoptosis-inducing ligand (TNFAIL); a ligand that stimulates apoptosis in prostate cancer cell lines, *L. plantarum* increases the activity of natural killer cells.

4. Probiotics' bioactive components

For a number of different reasons, colonizing probiotic bacteria have positive effects on the host cells, by enhancing their resistance to new colonization and eliminating potential harmful bacterial species. These bacteria have a high metabolic rate, producing beneficial substances, including vitamins that promote health, bacteriocins that combat pathogens and immune-modulatory chemicals that regulate the host's immune system (Jandhyala *et al*., 2015).

By generating oligosaccharides, probiotics also support a healthy environment (Gill *et al*., 2018). The microbial composition is changed by these beneficial microorganisms, and this has been linked to a therapeutic strategy to fight pathogenic bacteria in the intestinal niche (Martín and Langella, 2019). These probiotic bacteria produce bioactive substances, including exopolysaccharides (EPSs), bacteriocins, enzymes, vitamins, amino acids, antimicrobial substances (acids), SCFAs, and immune-modulatory agents (Thorakkattu *et al*., 2022). Probiotic foods typically contain 10^{-8}-10^{-9} cfu/ d, depending on the host and bacteria's physiological parameters (Sanders *et al*., 2018). However, the benefits of probiotic microorganisms differ depending on the species, the number of bacteria consumed, and the host's physiological state (Bernatek *et al*., 2022).

4.1. Antimicrobial materials

One of the main requirements for probiotic strains is their antimicrobial activity against pathogenic microorganisms. Probiotics exhibit strain-specific antimicrobial potential, and their interactions with pathogens can be categorized into four main types: 1) competition through adhesion at the host site; 2) competition for substrates and limited resources; 3) synthesis of antimicrobial agents (*i.e*., organic acids, H_2O_2, bacteriocins, etc.); and 4) reduction of toxin expression in pathogens. Additionally, probiotics combat pathogens by acidifying the intestinal microenvironment, storing organic acids, or secreting antimicrobial substances. Colonization resistance is observed in the luminal material and mucosal surfaces of the gastrointestinal tract. The most abundant metabolite produced by all LAB is lactic acid (LA). However, only hetero-fermentative LAB produce acetic acid and other acids.

Both Gram-positive and Gram-negative bacteria are broadly inhibited by the combination of lactic acid and acetic acid as well as pH drop. Inhibition of lactic and acetic acid is dependent on several factors such as the dissociation constant (pK value), molar concentration in the surrounding environment, and

acidic pH (Tsai *et al*., 2019). LAB produce oxygen metabolites that have a strong oxidizing effect on the bacterial cells that results in breakdown of cell proteins and nucleic acids, which has bactericidal effects on yeast and both of Gram-positive and Gram-negative bacteria. Additionally, all LAB generate hydrogen peroxide (H_2O_2) through a flavin enzyme electron transport. In the presence of H_2O_2, superoxide anions form damaging hydroxyl-radicals, which cause membrane lipid peroxidation and increased membrane permeability (Tsai *et al*., 2019).

4.1.1. Polysaccharides other than exo-polysaccharides (EPS)

Glycosyl-transferases and glycan transferases are enzymes that convert sugar nucleotide precursors to EPSs. These EPSs are produced in large quantities by various probiotic bacterial genera such as LAB, which are considered Generally Recognized as Safe (GRAS) bacteria (Indira *et al*., 2016). These bacteria are known for their immune-stimulatory, anticancer, antioxidant, and blood cholesterol-lowering attributes. Recently, microbial EPSs have gained significant attention due to their potential health benefits. In addition, EPSs from *W. paramesenteroides* MN2C2 have shown anticancer efficacy against the colon *Caco-2*, breast *MCF-7*, and liver *HepG-2* cancer cell lines, and expressed antiviral activity against Coxsackie virus (CVB3) (Amer *et al*., 2021). Additionally, these EPSs showed good emulsifying properties, which are essential for food applications. Furthermore, LAB-derived EPSs have various roles such as immunological modulation, antiulcer, and cholesterol-lowering properties, thus providing medical benefits and other industrial applications (Julendra *et al*., 2017). Li *et al*., (2015) studied the antitumor activity of *L. helveticus* MB2-1 cell-bound EPSs against colon (*HT-29*), stomach (*BGC823*), and liver (*HepG-2*) cancer cells.

By directly destroying tumor cells and exhibiting flexible indirect immunity, EPSs produced from LAB have anti-tumor efficacies. For instance, *HepG-2*, *BGC-823*, and *HT-29* tumor cells' ability to proliferate can be inhibited by an EPS derived from *L. plantarum* 70810 (Wang *et al*., 2014), while HT-29 tumor cells can also be inhibited by an EPS derived from *L. plantarum* YW32 (Wang *et al*., 2015). Although LAB have shown antiviral properties against gastrointestinal and upper respiratory tract viral infections; however, their most significant antiviral activities appear to be related to immune response regulation, production of antiviral metabolites, and direct interaction with the viral particles (Ögel and Öztürk, 2020).

Leuconostoc spp. produce EPSs that have demonstrated antiviral properties against HSV-1 (Zikmanis *et al*., 2020). With a 97-99 % reduction in viral adsorption, penetration, and particle formation, these EPSs have demonstrated strong virucidal activity. Furthermore, by inhibiting viral adsorption to the host cells, the EPSs reduce the infectivity of viral offspring (Biliavska *et al*., 2019). This family's member, *EPS 26a*, has shown to have inhibitory effects on Human Adenovirus Type 5 (*HAdV-5*) replication, resulting in the production of viral progeny that are not infectious (Biliavska *et al*., 2019).

4.1.2. Short-chain fatty acids (SCFAs)

An important source of short-chain fatty acids (SCFAs) is fermentation of non-digestible complex carbohydrates, which is facilitated by some commensal anaerobic bacteria found in the intestinal lumen (Cong *et al*., 2022). According to Akhtar *et al*., (2022), SCFAs are defined as those that have six or fewer carbon atoms. Examples of SCFAs are formate (C1), acetate (C2), propionate (C3), butyrate (C4), valerate (C5), and caproate (C6). Acetate, propionate, and butyrate are the main SCFAs that are most prevalent in the colon (Zhang *et al*., 2019). While members of phylum Bacteroidota primarily manufacture acetate and propionate, members of the Firmicutes phylum primarily synthesize butyrate (Zhang *et al*., 2022). After being created in the colon, SCFAs are discharged into the bloodstream

and travel to far-off tissues, where they are able to perform their advantageous functions (Hanus *et al*., 2021). As being mediators between gut microbiota and immunology, SCFAs have unique anti-inflammatory and immune-modulatory qualities and are essential to gut homeostasis (Gill *et al*., 2018).

4.1.3. The enzymes

Probiotics produce various enzymes such as lipases, esterases, and amylases, which have multiple metabolic activities. In the gastrointestinal lumen, probiotics interact with bile acids to alter bile acid metabolism, which in turn affects cholesterol absorption. The majority of recognized probiotics and bacterial species belonging to various genera that are linked to the gastrointestinal tract generate the enzyme bile salt hydrolase (BSH), which may take part in the first de-conjugation reaction of biliary salts (Plaza-Diaz *et al*., 2019).

The extracted enzyme data have illustrated various clinical states and also revealed the important functions that probiotic bacteria play in regulating the mechanisms of cell development. Polyamines play a role in the differentiation and multiplication of cells. Although about half of cancer cases have responded well to classic anticancer treatments, including radiotherapy, chemotherapy, and surgical resection; however, some nonspecific techniques are useless and have numerous unfavorable side effects. The alteration or replacement of generic and invasive traditional treatment methods is also taken into consideration in cancer therapy studies; especially those that specifically target the cancer cells. Therefore, all these strategies are based on enzyme therapy, which provides more targeted and effective cancer care (Górska *et al*., 2019). The use of particular enzyme forms that can deplete the cells from a certain type of amino acid required for tumor cell growth but not necessary for normal cell survival is the basic notion underlying these enzyme techniques (Górska *et al*., 2019).

In fact, it's known that focusing on a specific amino acid deficit may be a successful cancer treatment approach. Deregulation of polyamine production and transport in human malignancies leads to elevated levels of polyamines (Vivarelli *et al*., 2019). Early studies have highlighted the relationship among probiotic activity in carcinogenesis, tumor growth, and polyamine biosynthesis. The mechanisms by which probiotics can inhibit cancer are still poorly understood, However, it is thought that enzymes that break down amino acids, including L-asparaginase, arginase, L-glutaminase, and methioninase, can prevent the growth of some tumor cell lines. Both arginine and asparagine are non-essential human amino acids because they can be synthesized in the normal cells and tissues, but they are essential for tumor cell development. The enzyme's antitumor inhibitory activity is primarily based on the depletion of arginine and asparagine stocks as essential nutrients (Górska *et al*., 2019). These enzymes that catalyze the irreversible conversion of L-asparagine (substrate) to L-aspartate and ammonia (products) can be utilized in chemotherapy procedures. Following the asparaginase model, L-arginase converts L-arginine to ornithine and urea. Over fifty years ago, L-asparaginase was shown to be a useful enzyme in the treatment of juvenile leukemia, paving the way for the pioneering use of amino acids in cancer therapy (Broome, 1961).

Probiotics are also expected to influence innate and adaptive immune responses through the gut mucosal immune system, which may indirectly mediate their health benefits against cancer proliferation. Several probiotic strains have the ability to influence innate defense mechanisms by enhancing phagocytosis and cytotoxic potential of natural killer (NK) cells (Vivarelli *et al*., 2019).

4.1.4. Vitamins

Vitamins are essential elements for growth and development of the multicellular organisms. Humans no longer have the ability to synthesize vitamins internally, resulting in deficiencies, starvation, and

stunted growth from infancy to old life. These vitamins can be gained through food sources. Vitamins are classified as either water-soluble or fat-soluble (Ofoedu *et al*., 2021), which are produced through microbial fermentation processes. Many bacteria create B-group vitamins, which are water-soluble and absorbed in the stomach, while fat-soluble vitamins are absorbed in the digestive tract using lipids as micelles.

Dairy products rich in B-complex vitamins are significant sources of vitamins (Hanna *et al*., 2022). Both plants and animals naturally provide vitamins, although some vitamins can be synthetically produced. Vitamin-producing LAB strains such as *L. plantarum* CRL2130 and *Streptococcus thermophilus* CRL808 have been isolated from various ecological environments. Folate-producing bacterial strains have been utilized to enhance vitamin levels in yogurts (Fayemi *et al*., 2023). Vitamins are essential for human development, reproduction, red blood cell creation, antibody production, and lactation. They are required for a variety of metabolic processes in the body, including the production of amino acids, fatty acids, carbohydrates, and nucleic acids. Riboflavin improves pyridoxine and iron absorption in the digestive tract, hence protecting the red blood cells (LeBlanc *et al*., 2017). Riboflavin synthesis has been intensively investigated in plants, bacteria, and filamentous fungi, with more focus on *B. subtilis* and *E. coli*.

5. Use of probiotic products in functional foods and nutraceuticals

Foods containing bioactive chemicals (matrices that have good impacts on human health) have been acknowledged for their health advantages in preventing certain illnesses (Requena *et al*., 2018). Functional foods; often known as nutraceuticals, are substances or meals that promote health. The pace of life and changes in eating habits is rapid; with well-being and longevity becoming new priorities. Vitamins, minerals, amino acids, and fatty acids are examples of "nutrients," which occur naturally in our diets and have been linked to a variety of health advantages (Chen *et al*., 2018). Most vegetables, whole grains, dairy products, fruits, meat, and chicken have vitamins that can help you manage diabetes, cancer, cataracts, heart disease, stroke, and other illnesses (Asif, 2014). Beneficial minerals found in plants, animals, and dairy products are used to treat anemia and osteoporosis, build bones, teeth, and muscles, and improve nerve signals and heart rhythm. The word "nutraceuticals" embraces a wide range of chemicals (Atlante *et al*., 2020), including vitamins, minerals, plant-based products, antioxidants, polyunsaturated fatty acids, prebiotics, and probiotics.

Probiotic food items have been much more widely available in recent years; there are already over 500 products available worldwide, and this number is continually rising. Scientists and the general public are both interested in probiotic foods, which are derived from fermented fruits, vegetables, grains, and animal products (Rezac *et al*., 2018). Nowadays, probiotics can be found in a wide range of commercial foods, including meat products, ice cream, milk, sour milk, fruit juices, mayonnaise, cheese, and dips made with cheese. During the production process, probiotic bacteria are added to these foods (Terpou *et al*., 2019). According to Aspri *et al*., (2020), infants who were given probiotic supplements that included the *L. casei* bacterial strain had elevated levels of circulating immunoglobulin A, which was linked to a reduced duration of diarrhea caused by rotavirus.

Food must have the minimum viable microbial count at the time of ingestion in order to provide the suggested health advantages of probiotics. The recommended level of 10^6 cfu/ ml at the time of consumption is generally followed by the food sector (Cristofori *et al*., 2021). Depending on the quantity ingested and the storage conditions, individuals need to be exposed to a daily dose of 10^8 to 10^9 probiotic bacteria in order to experience their beneficial probiotic effects (Zhao *et al*., 2015).

6. The forthcoming

Many diseases are influenced by the gut microbiota and modifying it may result in novel and effective therapies. Probiotics and prebiotics produce therapeutic metabolites such as propionate and butyrate, which are beneficial gut microbial byproducts generated by bifidobacteria or lactobacilli. Identifying bacteria with unique metabolic abilities beyond the traditional probiotics is a promising avenue. Additionally, anti-adhesive compounds and carbohydrates that reduce microbial virulence offer potential benefits. These components could complement existing prebiotic approaches by providing non-selective substrates. Additional meticulously planned randomized controlled studies are required to validate the influence of gut microbiota alterations on illness prevention and treatment. The field of microbiota research is expanding; with increasing awareness of variations in disease states, attributed to the accessibility and cost-effectiveness of high-throughput sequencing technologies. Advances in metabolomic analysis tools and databases are crucial for enhancing clinical translation. Understanding the functional ecology of the gut and its systemic health implications is essential. Ultimately, probiotics, prebiotics, and their bioactive compounds have significant potential to enhance human health, revolutionize patient care, and reduce disease risk.

Conclusion

Probiotics have been suggested as a potential treatment for a number of gastrointestinal and other disorders based on data collected from carefully executed clinical trials. Probiotics' physiological effects and their precise modes of action are well-established. However, further researches are necessary to fully understand how they promote health and prevent diseases. Even though some of the molecular mechanisms underlying the beneficial effects of probiotics are now understood, there is still a lack of clinically established efficacy for many inflammatory and autoimmune illnesses. It is crucial to translate the findings obtained from animal studies into human applications. Currently, lactic acid bacteria that have been modified by commensal microorganisms produce essential health-promoting compounds. However, most researches on genetically engineered microorganisms focus on vaccination strategies. Genetically modified bacteria offer a promising avenue for exploring new methods of delivering bioactive compounds to mucosal tissues. To analyze the effects of probiotics on the immune system and determine the safety, effectiveness, and limitations of these supplements, comprehensive and repeatable researches are urgently needed.

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Conflict of interest

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Ethical approval

None applicable in this study, because it did not involve any research studies on humans or living animals.

Author's Contributions

Conceptualization: M.N.A., M.M.K. and A.A.M; Investigation and Methodology: S.R.S., M.M.S., O.A.A.M., S.R.S., M.M.S., M.N.H.A., M.M.H.M.; Supervision: M.N.A. and H.M.A; Roles/Writing - original drafts: M.N.A., M.M.K. and A.A.M; Reviewing, and editing: M.N.A. and H.M.A.

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