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Review Article

Role of Probiotics against Human Cancers, Inflammatory Diseases, and Other Complex Malignancies

Hammad Naeem,[1] Hammad Ul Hassan,[1] Muhammad Shahbaz,[1] Muhammad Imran,[2] Anjuman Gul Memon,[3] Ammarah Hasnain,[4] Shamas Murtaza,[1] Suliman A. Alsagaby,[5] Waleed Al Abdulmonem,[6] Muzzamal Hussain,[7] Mohamed A. Abdelgawad,[8] Mohammed M. Ghoneim,[9] and Entessar Al Jbawi[10]

[1]*Department of Food Science and Technology, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan*
[2]*Department of Food Science and Technology, University of Narowal, Narowal, Pakistan*
[3]*Department of Biochemistry, College of Medicine, Qassim University, Buraydah, Saudi Arabia*
[4]*Department of Biotechnology, Lahore University of Biological & Applied Sciences, Lahore, Pakistan*
[5]*Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Al-Majmaah 11932, Saudi Arabia*
[6]*Department of Pathology, College of Medicine, Qassim University, P.O. Box 6655, Buraidah 51452, Saudi Arabia*
[7]*Department of Food Sciences, Government College University Faisalabad, Faisalabad, Pakistan*
[8]*Department of Pharmaceutical Chemistry, College of Pharmacy, Jouf University, Sakaka 72341, Saudi Arabia*
[9]*Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Al Diriyah 13713, Saudi Arabia*
[10]*Agricultural Extension Directorate, MAAR, Damascus, Syria*

Correspondence should be addressed to Entessar Al Jbawi; dr.entessara@gmail.com

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Probiotics have growing medical importance as a result of their potential in the prevention and therapeutic support of several complex diseases, including different types of cancers. The anticarcinogenic properties of probiotics are attributed to various mechanisms, including alterations in the composition of the intestinal microbiota, suppression of cell proliferation, stimulation of apoptosis, inhibition of NF-kB, reduction in levels of H2AX, 8-hydroxy-deoxyguanosine, RIG-I, downregulation of IL-17, and TNF signaling pathway. Furthermore, probiotics have demonstrated significant advantages in the prevention and management of other complex diseases, including diabetes, obesity, and cardiovascular diseases. Probiotics had a considerable effect in reducing inflammatory infiltration and the occurrence of precancerous lesions. Additionally, the administration of probiotics led to a decrease in the appearance level of genes related to proinflammatory pathways, including NF-κB, IL-17, and TNF signaling pathways. However, further research studies are required to comprehend the processes via which probiotics exert their effects and to authenticate their potential as alternative therapeutic interventions.

1. Introduction

Probiotics refer to bacteria that, when ingested in enough amounts, confer a positive impact on the well-being of the host organism. The definition was formulated by the collaborative efforts of a consensus council assembled by the International Scientific Association for Probiotics and Prebiotics (ISAPP). A diverse array of microorganisms comprises the category known as "probiotics." It is important to understand that individuals are identified by their genus, species, and strain classifications [1]. To take *Lactobacillus rhamnosus* GG, for example, the taxonomic name involves three levels: genus-species, species (and subdivision)-strain. To constitute a probiotic. In addition, for

a given species, the health benefits shown in one strain will often not carry over to another. It might be that several of these pathways are shared among different strains and thus would result in similar clinical effects [2]. A large number of commercially available probiotics are a blend of many bacterial strains from various species, rather than just one. Using many strains of probiotic products is thought to increase their overall efficacy and improve their ability to provide health benefits, which may clarify their actions. The possibility that these strains will work together in a synergistic or additive manner is also being investigated by researchers [3].

In the worldwide market, the prevailing probiotics consist of species such as *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, and *Enterococcus*. *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, among other bacterial strains, are often not inherent components of the gut microbiota. Nevertheless, they are categorized as probiotics owing to their application as starter cultures in the production of dairy goods [4]. Currently, probiotics are classified and subject to regulation within three distinct categories. First, there are foods; more especially, fermented foods that have been GRAS-approved because they include *Lactobacillus*, *Bifidobacterium*, or *Lactococcus*. Dietary supplements, which are frequently available naturally, make up the second group. The third group includes pharmacological medications. The categorization of probiotics depends on the makers' choices, the intended uses, and the standards established by various regulatory agencies [5]. Numerous clinical studies have confirmed the safety of probiotics, as evidenced by the absence of any toxic effects observed across various populations. These populations include (i) healthy adult volunteers; (ii) women in the later stages of pregnancy and their infants in the early stages of infancy; (iii) infants and children aged 0–2 years; (iv) children who are hospitalized; (v) children who are critically ill; and (vi) patients with compromised immune systems. Probiotics are inherently nonpathogenic, indicating that they are not anticipated to induce or worsen diseases in people, irrespective of whether they are obtained via food or over-the-counter pills [6]. The principal sources of probiotics can originate from human biological systems, including the large intestine, small intestine, or breast milk. It may also originate from animal sources and other dietary habitats, such as unpasteurized milk or fermented food items. Probiotic bacterial strains derived from the human microflora have a higher likelihood of safety due to their enhanced adherence to the intestinal epithelial barrier. These strains are known to exert a pivotal influence on cholesterol reduction and its metabolic pathways. Additionally, they exhibit the ability to colonize the intestinal, respiratory, and urogenital tracts, thereby contributing to the maintenance of a healthy microbial balance in these regions. Furthermore, their presence can inhibit the development of carcinogenesis, either directly or indirectly, by stimulating the immune system. Moreover, these strains are involved in lactose metabolism, calcium absorption, and have the potential for vitamin synthesis. They also possess reductive properties that can combat yeast and vaginal infections, as well as provide relief from rheumatism [7]. Scientists have also identified *Lactobacillus* sp. strains from human breast milk and investigated their acid and bile tolerance, as well as their susceptibility to antioxidants and antibiotics. In addition, it has been found that the *Lactobacillus* isolates that were evaluated had efficacy against cervical cancer cells, indicating potential probiotic qualities. The studies have demonstrated the potential probiotic properties of *Bacillus subtilis* HMNig2 and *Bacillus subtilis* MENO2, which were isolated from honey and bee gut. These strains exhibited promising *in vivo* modulations, including the enhancement of the immune system and defense against *Salmonella typhimurium* infection. Furthermore, they were found to mitigate the effects on the liver, such as inflammation and hepatic infiltration [8]. Health benefits of probiotics presented in Figure 1.

Probiotics also have a beneficial effect on allergies by restoring the digestive system. This intervention leads to a reduction in inflammation, stabilization of the immune system, and reinforcement of the intestinal epithelial barrier. Allergies manifest as hypersensitivity responses that are initiated by immunological processes. Probiotics can change the arrangement of antigens, resulting in a reduction in their ability to induce an immune response. This, in turn, leads to a decrease in intestinal permeability and the group of proinflammatory substances [9]. These symptoms are frequently reported by people with different types of allergies. Evidence suggests that the probiotic bacteria *L. rhamnosus GG* can alleviate food allergy symptoms and reduce the severity of allergic reactions. In addition, research indicates that probiotics and their derivatives can lower blood pressure through mechanisms such as lowering total and low-density lipoprotein cholesterol levels. Managing the renin-angiotensin system, lowering blood glucose, and increasing insulin resistance are all correlated with elevated blood or serum cholesterol levels. Those who suffer from hypertension may find relief from their symptoms by including probiotics in their diet. Probiotics such as *Streptococcus thermophiles*, *Lactobacillus delbrueckii* ssp., *Bulgaricus*, and *Lactobacillus kefiri* are commonly used in hypertension control [10]. It is safe to say it is impossible to lead a healthy life without probiotics. This paper includes the collection of recent research-based evidence of the beneficial role of probiotics in the management of cancers and other complex diseases.

It is worth mentioning here that the authors have carefully selected papers from previous years for the readers to truly understand step by step research process involving probiotics against various cancers and other complex diseases. Most of the recent review papers on similar topics encompass the general information of the reported research, but the unique property of this paper is that each study reported has been carefully summarized for the reader to understand what the study was, how it was performed, and what the results were. This accumulation of data is specifically beneficial for pharmacists, doctors, clinical researchers, bioinformatics researchers, pharmacogenomics researchers, and all the scientific personnel involved in the treatment and research associated with cancers and other complex diseases. The data reported in

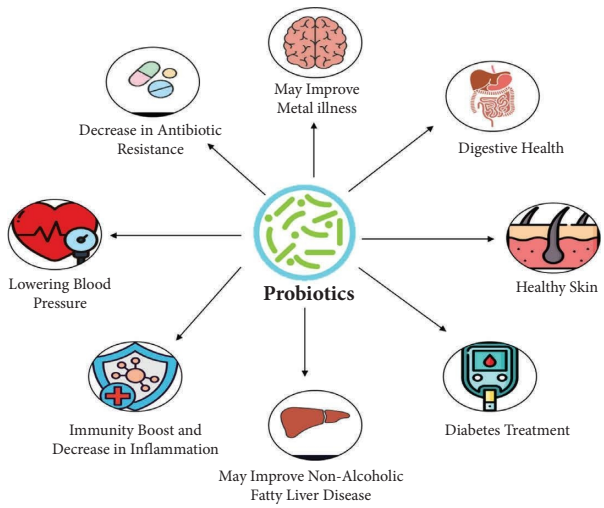

Figure 1: Health benefits of probiotics.

this paper will allow all of the above personnel to fully grasp the extent of research already done, which will help in the advancement of cancer and other disease-related research. For logical progression, the paper is mainly divided into three parts: part one: probiotics against cancers, part two: role of probiotics in inflammatory bowel diseases and diarrhea, and part three: probiotics against diseases outside of the gastrointestinal tract.

2. Probiotics against Cancers

Probiotics, which are microorganisms with potential health benefits, can be found in various fermented food products such as yogurt, kefir, and sauerkraut. Additionally, they can be ingested through the utilization of nutritional supplements [11]. Despite the advancements in cancer treatment, challenges and side effects continue to be hurdles, even with targeted, traditional approaches like surgery, chemotherapy and radiation. These treatments still damage healthy tissues. Chemotherapy is a double-edged sword. It can lead to nausea, vomiting, hair loss, and debilitating fatigue which significantly impacts quality of life. Surgery is curative in some cases but it carries risks of infections, scarring as well as functional loss. Radiation causes burns, fatigue, and long-term effects as in organ dysfunction. In addition, cancer cells are adaptable and develop resistance to treatments, thus rendering the treatments ineffective. Beyond physical discomfort, cancer treatments also have adverse effects on mental health, like anxiety, depression, and fear of recurrence. Scientists are exploring therapies with enhanced selectivity, also harnessing the immune system's power and are trying to minimize treatment-associated adverse effects [12, 13]. The recognized role of probiotics in the field of cancer inhibition resides in their capacity to modulate the intricate ecosystem of the gastrointestinal microbiota, thereby exerting a profound influence on the intricate network of inflammatory mediators, engendering the production of antimicrobial agents that possess cytotoxic properties against malignant cells, eliciting an immunological response against neoplastic cells, and facilitating the biosynthesis of antioxidant molecules that confer cellular protection against deleterious offenses. Multiple experimental studies have yielded substantial evidence substantiating the notion that probiotics exhibit the capability to attenuate the incidence of colorectal cancer, thereby implying their prospective utility in the domain of cancer prevention and therapeutic intervention. The consumption of a probiotic supplement over three years was related to a noteworthy decrease of 45 percent in the threat of developing colorectal cancer, in comparison to individuals who did not partake in the aforementioned supplementation. Numerous empirical investigations have consistently demonstrated that the incorporation of probiotics into one's diet holds promising potential as a prophylactic intervention in mitigating the risk of breast carcinogenesis. The investigation revealed that female subjects who incorporated a probiotics into their daily diets for twelve months demonstrated a statistical decrease of 33% in the probability of developing breast carcinoma, relative to those individuals who did not partake in the consumption of the said supplement. Emerging research suggests that probiotics may conceivably exert a contributory influence on the prophylaxis of prostate cancer, and the male individuals who incorporated a probiotic supplement into their daily diet for a year exhibited a noteworthy decrease of 25% in the probability of developing prostate cancer, in comparison to their counterparts who did not partake in such supplementation [14]. Studies showed that the individuals who consume probiotic supplement regularly for one year demonstrated a noteworthy reduction of 20% in the probability of developing lung cancer, as compared to their counterparts who did not partake in such supplementation. Scientific evidence also supports the possible positive role of probiotics in the prevention of head and neck cancer [15]. Based on the findings of research studies, individuals who incorporated a probiotic supplement into their daily diet for twelve months demonstrated a noteworthy decrease of approximately 15% in the emerging neck and head cancer, as compared to their counterparts who did not partake in the consumption of the said supplement. The utilization of probiotics exhibits the potential to ameliorate the probability of acquiring distinct manifestations of neoplastic disease and augment the prognosis of therapeutic interventions for cancer [16].

2.1. Role of Probiotics in Colorectal Cancer. Colorectal cancer (CRC) ranks as the second most common disease among women and the third most common cancer among men worldwide. There has been an increasing prevalence of colorectal cancer (CRC) detected in Asian countries, such as Korea, affecting both males and females. The development of colorectal cancer (CRC) involves a complex genetic process, wherein a majority of cases, namely over 70%, originate from premalignant adenomas. The prevalence of hereditary types of colorectal cancer (CRC) is less than 5% among all reported cases [17]. Probiotics mostly inhabit the intestinal region and play a vital part in the breakdown of undigested food particles, as well as the processing of intestinal and digestive secretions, and the shedding of colon cells [18]. Probiotics can contribute to the inhibition and cure of colorectal cancer (CRC) through three separate pathways,

with colonization resistance being the initial mechanism. Probiotics exert inhibitory effects on pathogen colonization through many mechanisms, with the release of antimicrobial peptides, the reduction of luminal pH, and direct interactions with pathogens, such as competition for resources and spatial occupation, as well as the formation of coaggregates. Probiotics have been found to exhibit specific immunomodulatory effects that can effectively mitigate inflammation in the colon. These effects include the initiation of dendritic cells (DCs), the reduction of T-helper 17 (Th17) cells, the growth in regulatory T cell (Treg) expression, and the transformation of macrophages into the M2 subtype. Conversely, probiotics can also improve the immune response against tumors by promoting the production of Th17 cells and suppressing Treg expression at a systemic level. Additionally, they can reduce the appearance of CXCR4 and major histocompatibility complex class 1 (MHC-1) in tumors. It is important to note that the specific species and strains of probiotics chosen can determine whether these immunomodulatory effects are observed [19].

To study anti-colon cancer effects of probiotics, a randomized controlled experiment was done, involving a cohort of 78 patients diagnosed with colorectal adenocarcinoma. The participants were allocated into two cohorts: an experimental group receiving oral probiotics of *Lactobacillus brevis* Mk05 in a 2×1 regimen, commencing on the third day after surgery and continuing for thirty days. Subsequently, they received a maintenance dose of 1×1 for two weeks each month for one year. The control group did not get regular probiotic treatment. Except for ileus, all problems were shown to be more common in the group of patients who did not get probiotics. According to the result of the study, the administration of probiotics to individuals who have had surgical treatment for colorectal adenocarcinoma yields notable advantages, improving gut health, reducing the rate of postoperative complications, and enhancing immune function [20]. Researchers also investigated the possible impact of probiotic intervention on the manifestation of aggression in chemically induced colon cancers in animal models. A cohort of 25 male (Fisher 344) rats, each weighing an average of 250 g, were given unrestricted access to both food and water. The rats were subsequently allocated randomly into five groups, with each group including five animals. GControl, which received no therapy; GTumor, which was subjected to tumor induction; GTumor+5FU, which received 5-fluorouracil supplementation; GTumor + Prob, which received probiotics; and GTumor + 5-FU + Prob, which received both. For four weeks, 20 mg/kg of 1,2-dimethylhydrazine was injected intraperitoneally to induce tumors. After 15 days, the same method was repeated for four weeks. Patients received 5-fluorouracil (15 mg/kg, weekly) and a commercial probiotic (1×10^9 CFU daily by gavage) five weeks following the previous cancer-causing dose. The management of GTumor, GTumor + Prob, and GTumor + 5-FU + Prob had a moderating impact on the aggressiveness of colorectal cancers. This was proved by a decrease in the number of cancerous growths and abnormal cell clusters in the GTumor + Prob and GTumor + 5-FU + Prob groups, respectively. In the GTumor + Prob group, 40% had low-grade tubular adenoma, 40% had carcinoma in situ, and 20% had low-grade adenocarcinoma. The GTumor + 5-FU + Prob group had 40% low-grade tubular adenoma and 60% carcinoma. The study demonstrated the clear potential of probiotic supplements in reducing the development of aberrant crypts and mitigating cancer aggressiveness in colonic segments. Additionally, these supplements were found to enhance the anticancer effects of 5-fluorouracil chemotherapy [21].

Similarly, researchers evaluated the influence of heat-killed *Enterococcus faecalis* on the NLRP3 inflammasome in THP-1-derived macrophages *in vitro*. Macrophages were pretreated with 10% (w/v) heat-killed *E. faecali* cells or siRNA NLRP3 inflammasome and then exposed to fecal debris or commensal bacteria such as *P. mirabilis* or *E. coli*. Pretreatment with *E. faecali* or siRNA NLRP3 prevented the activation of the NLRP3 inflammasome and the production of IL-1β as evidenced by lower levels of caspase-1 activity and mature IL-1. These findings show that *E. faecali* interferes with phagocytosis and, by extension, the complete activation of the NLRP3 inflammasome. Researchers have shown that *E. faecali* can lessen intestinal inflammation in live animal experiments. The findings of the study suggest that inactivated *E. faecali* as a probiotic may be an effective and safe method for preventing NLRP3-mediated colitis and inflammation-induced colon carcinogenesis [22].

Another research investigation was carried out to demonstrate the influence of a probiotic combination on the proliferation and metastasis of colorectal cancer in animal models. Several assays, such as those using probiotics and cell coculture, cell counting kits, wound healing, colony formation, and migration/invasion, were used to assess the CT26 cell line. Moreover, the inoculation of CT26 cells into BALB/c mice was performed to generate an animal model that mimics tumor transplantation. The mice were partitioned into two distinct cohorts, specifically a control group and an experimental group that underwent intragastric administration of a probiotic combination (*B. longum*, *B. bifidum*, *L. acidophilus*, *L. plantarum*, resistant dextrin, isomalto-oligosaccharides, fructose oligosaccharides, and stachyose). Hematoxylin and eosin (HE) mark and immunohistochemistry (IHC) labeling was used to examine tumor progression and immune cell infiltration in tumor or spleen tissues after 21 days. The probiotic combination showed an important reduction in proliferation, incursion, and passage of CT26 cells when associated with the control cells. The findings demonstrated that the administration of the probiotic combination resulted in a notable decrease in tumor volume among the mice, in contrast to the control group. The mice that were visible to the probiotic combination had an increased abundance of apoptotic cells and infiltration of immune cells into their tumor tissues, as associated with the control group [23].

In the light of the recent studies, probiotics can help in the management and prevention of colon cancers. Not only that, probiotics can also enhance the efficiency of chemical anticancer agents, which implies that milder doses of these agents can be used to treat colon cancers and milder doses will in turn exert reduced side effects. It is also noteworthy

that probiotics can boost the immune system to fight colon cancer cells. Probiotics also show great potential in reducing the already-developed tumor volumes in colon cancers.

2.2. Role of Probiotics in Gastric Cancer. Gastric cancer (GC) is a significant contributor to global cancer-related mortality and is responsible for 10% of newly diagnosed cancer cases. Despite a decrease in the prevalence rate of gastric cancer (GC) in recent years, the five-year survival rate for this neoplasm remains below 25%, exhibiting regional differences. Gram-negative bacteria, *Helicobacter pylori* possess the ability to disturb the acid mucus barrier and establish colonization within the stomach epithelium. The study demonstrates the observed inhibitory effects of several probiotic strains, including *B. bifidum*, *L. acidophilus*, *L. rhamnosus*, *L. salivarius*, and others, on *H. pylori* infection in many animal models [24]. This particular carcinogen, classified as a class I carcinogen, plays a significant part in the beginning of gastric carcinogenesis. It achieves this by inducing heightened inflammation and gradual alterations in both the structure and function of the gastric mucosa. The gastric microbiota can be distinguished from the oral and/or esophageal microbiota due to the presence of a unique microbial environment within the stomach [25]. Probiotics have demonstrated the capacity to enhance the gut barrier and reduce the susceptibility to gastrointestinal cancer. Probiotics have an impact on the integrity of the gastrointestinal barrier and have the potential as a preventive measure against cancer. Research has demonstrated that probiotics can enhance the intercellular connections inside the intestine, stimulate the synthesis of defensive mucins, and modulate the arrangement and equilibrium of gut microbiota. These mechanisms contribute to the maintenance of intestinal barrier integrity and prevent the translocation of potentially hazardous substances into circulation. According to researchers, the potential of probiotics to mitigate the risk of cancer lies in their ability to mitigate systemic inflammation and safeguard the gastrointestinal tract against detrimental agents [26].

In a recent study, two groups of male INS-GAS mice, one infected with *H. pylori* and the other uninfected, were randomly selected for investigation. Following 4 weeks, a probiotic combination including *Lactobacillus salivarius* and *Lactobacillus rhamnosus* was delivered by drinking water for 12 weeks. Stomach samples were obtained for RNA sequencing analysis, and afterwards, the identified genes exhibiting differential expression were confirmed by the use of RT profiling PCR array. The study utilized 16S rRNA gene sequencing as a method to evaluate changes in the structure of the gut microbiota. The management of probiotics has a considerable effect on alleviating gastrointestinal pathology generated by *H. pylori*, including a notable reduction in inflammatory infiltration and a decreased occurrence of precancerous lesions. The data from the RNA sequencing analysis demonstrated that the administration of probiotics led to a decrease in the appearance level of genes related to proinflammatory pathways, including NF-κB, IL-17, and TNF signaling pathways. Following the administration of probiotics, the group afflicted with *H. pylori* exhibited an augmentation in microbial diversity. The stomach of the *H. pylori*-infected group exhibited an enrichment of gastric cancer-associated genera, including *Lactobacillus* and *Staphylococcus*. Conversely, mice treated with probiotics had a higher profusion of useful bacteria that have short-chain fatty acids, such as *Bacteroides*, *Alloprevotella*, and *Oscillibacter*. Furthermore, the administration of probiotics effectively reversed the decrease in the presence of the anti-inflammatory bacteria *Faecalibaculum* in the gastrointestinal tract generated by *H. pylori*. [27]. According to the research, it is likely that probiotic treatment offers protection against *H. pylori*-associated carcinogenesis by modulating the composition of the gastrointestinal microbiota. This modulation subsequently inhibits the malignant transformation of host cells.

Another investigation was conducted to examine the potential anticancer properties of *S. boulardii* supernatant (SBS), namely its ability to induce apoptosis and decrease the appearance of the survival gene in gastric cancer cells. The assessment of cell viability was conducted by examining the effects of SBS exposure on apoptotic induction and alterations in alive gene look in the EPG85-257P (EPG) and EPG85-257RDB (resistant to daunorubicin, RDB) cell lines at 24, 48, and 72 hours. The findings of the study indicate that exposure to SBS resulted in a decrease in cell viability, the induction of apoptosis, and a decrease in the appearance of the survival gene in both EPG and RDB cells. The important IC_{50} values for EPG and RDB cells were determined to be 387 and 575 μg/ml, respectively, after 72 and 48 hours of treatment [28]. It is thus evident that SBS was more effective in inducing apoptosis in EPG cells compared to RDB cells.

In an interesting clinical study, a probiotic combination consisting of *Bifidobacterium infanti*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus* was employed to mitigate the physiological disorders caused by gastrectomy. This was accomplished by observing the blood index and microbial diversity through the utilization of high-throughput sequencing techniques. The findings of the study demonstrated that the probiotic combination exhibited a significant reduction in inflammatory markers, namely leukocyte levels. Additionally, the probiotic combination considerably improved immune markers, such as lymphocyte levels, as well as nutrition markers, including albumin and total protein levels. Furthermore, the presence of gastric cancer significantly impacts the microbial diversity within the GI tract by promoting the proliferation of pathogenic bacteria such as *Streptococcus*, *Peptostreptococcus*, and *Prevotella*, while concurrently decreasing the abundance of the beneficial probiotic *Bifidobacterium*. The intestinal microbial diversity was significantly altered by partial gastrectomy. However, the administration of the probiotic combination resulted in a substantial decrease in the *Firmicutes*/*Bacteroidetes* ratio at the phylum level, in comparison to patients who did not receive any probiotics. At the taxonomic rank of genus, the administration of the probiotic combination resulted in a notable increase in the abundance of the probiotic bacteria *Bacteroides*, *Faecalibacterium*, and *Akkermansia*, while concurrently reducing

the diversity of *Streptococcus* [29]. Hence, it can be inferred that the administration of the probiotic combination leads to a notable improvement in the immunological response of individuals and a decrease in the severity of the disease through changing the composition of the gut microbiota.

2.3. Role of Probiotics in the Liver Cancer. Liver cancer exhibits the sole yearly percentage rise in frequency among the top five most fatal malignancies. Lung cancer is widely recognized as the important reason for cancer-related mortality globally and ranks as the fifth most prevalent cancer in the United States. Hepatitis B and C viruses, nonalcoholic fatty liver disease, cirrhosis caused by alcohol consumption, tobacco use, excess body fat, diabetes, high iron levels, and other dietary and environmental exposures are all contributors to liver disease progression [30]. Probiotics offer a range of health advantages, such as the ability to regulate microbial communities, inhibit the growth of harmful microorganisms, modulate the immune system, promote the growth of epithelial cells, and enhance the development of the epithelial barrier. Probiotics have a crucial role in the management of microbiome-related conditions but are partial to cancer prevention, liver disease treatment, immune system enhancement, and detoxification of environmental toxins. Furthermore, the significant relevance of probiotics in cancer biology lies in their antiproliferative and proapoptotic functions [31].

The genes that have been associated with the development of carcinogenesis were investigated in a cohort consisting of 38 bulb/c mice. The subjects were divided into four discrete groups, one of which comprised the control group, including individuals who were in good health and did not use probiotics. In another study, azoxymethane was administered to mice. Mice that received azoxymethane (AOM) treatment were allocated into two distinct cohorts: the first cohort was administered *Lactobacillus acidophilus*, while the second cohort was administered *Bifidobacterium bifidum* (IV). Subsequently, an analysis was conducted on the levels of expression for four distinct microRNAs and their respective target genes. The study's results indicated that the treatment of azoxymethane, a very potent colon carcinogen, led to the increased expression of miR-221 and miR-155 in the circulatory system. Furthermore, the therapeutic intervention resulted in an upregulation of Bcl-w and KRAS gene expression, concomitant with a downregulation of miR-122, PTEN, and PU.1 gene expression in the bloodstream. Nevertheless, there was no substantial effect observed on the expression of miR-18a in the hepatic tissue. The use of probiotics led to a significant upregulation of miR-122 and PU.1 in the circulatory system, suggesting a substantial overexpression. In contrast, the ingestion of probiotics resulted in a reduction in the levels of miR-221, miR-155 (in the bloodstream), Bcl-w, and KRAS [32]. It is implied that probiotics can exert influence on the progression of cancer by obstructing the metastatic process, alleviating inflammation, and regulating the expression of oncogenes as well as tumor suppressor genes/microRNAs.

In another research, a retrospective analysis of a cohort consisting of 1267 persons who were diagnosed with hepatitis B virus infection was performed. A comparison analysis was undertaken to evaluate the probability of hepatocellular carcinoma (HCC) occurrence in two separate cohorts. The initial group comprised 449 participants who regularly used probiotics, with a cumulative consumption of prescribed daily doses (cDDD) that equaled or exceeded 28. The second cohort consisted of 818 participants who abstained from probiotic use, with a total consumption of less than 28 cDDD. The utilization of propensity score matching (PSM) was implemented to address the potential impact of confounding variables and reduce bias. The results obtained from the multivariate regression analysis revealed that the utilization of probioticsmay reduce the risk of hepatocellular carcinoma. The incidence of hepatocellular carcinoma (HCC) was shown to be considerably lower among those who received probiotics following propensity score matching (PSM), in comparison to those who did not get probiotics (adjusted hazard ratio (aHR): 0.70, 95% confidence interval: 0.59–0.83). The study provided adjusted hazard ratios (aHRs) for cumulative defined daily doses (cDDDs) of probiotics. The aHRs were found to be 0.58, 0.28, and 0.12 for cDDDs ranging from 28 to 89, 90 to 180, and over 180, respectively. The increasing rate of hepatocellular carcinoma was found to be 8.7%, 4.7%, and 3.0% for cDDD ranges of 28–89, 90–180, and greater than 180, respectively [33].

In another study, two mice models were employed to investigate the impact of *Bifidobacterium pseudolongum* on nonalcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC) produced by diethylnitrosamine. The first model involved mice fed a diet rich in both fat and cholesterol, while the second model utilized animals fed a high-fat diet lacking in choline. The metabolic examination of *B. pseudolongum* utilized germ-free mice. Mice fecal samples, portal vein specimens, and liver tissue samples were collected to conduct nontargeted and targeted metabolomic investigations. While two cell lines derived from human nonalcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC), namely HKCI2 and HKCI10, were subjected to coculturing using conditioned medium derived from *Bacteroides pseudolongum* (B.p CM). Additionally, a potential metabolite was also included in the coculturing experiment. The study's results revealed that *B. pseudolongum* demonstrated the most significant depletion among the bacterial species seen in mice with nonalcoholic fatty liver disease and hepatocellular carcinoma. The oral administration of *B. pseudolongum* by gavage has shown a significant inhibitory impact on the progression of hepatocellular carcinoma associated with nonalcoholic fatty liver disease in two distinct animal models. The simultaneous cultivation of cells with NAFLD and HCC in the presence of B.p CM led to a significant reduction in cell proliferation, hindered progression from the G1 to S phase of the cell cycle, and triggered apoptosis. The primary metabolite produced by *B. pseudolongum* in B.p CM was determined to be acetate, and this discovery was later validated in germ-free mice. Cell lines associated with HCC in individuals with NAFLD have established the restraint

results of acetate on cell proliferation and its capacity to trigger cell death. *Bifidobacterium pseudolongum* demonstrated the capacity to restore a harmonized structure of the gut microbiota and improve the performance of the intestinal barrier. The route by which acetate produced by *B. pseudolongum* is delivered to the liver involves its passage through the portal vein. In the liver, acetate binds to the G-protein coupled receptor 43 (GPR43), which is situated on hepatocytes. The findings indicated that the inhibition of the IL-6/JAK1/STAT3 signaling pathway via GPR43 activation had a decelerating effect on the progression of hepatocellular carcinoma in individuals afflicted with nonalcoholic fatty liver disease. *Bifidobacterium pseudolongum* also demonstrated its protective effects against hepatocellular carcinoma (HCC) in the context of nonalcoholic fatty liver disease (NAFLD-HCC) via the gut-liver axis [34]. Research findings have indicated that *B. pseudolongum* has efficacy as a probiotic in combating HCC associated with NAFLD. Similarly, recent research studies have shown us that probiotics can reduce the probability of HCC. It is also implied that probiotics aid in the treatment of HCC and associated disorders by improving overall health markers.

2.4. Role of Probiotics in Lung Cancer. Lung cancer is an important form of cancer and the largest contributor to cancer-related death in the country of China. Lung cancer is distinguished by the proliferation, infiltration, and dissemination of malignant cells. Beneficial bacteria have been found within the gut flora, which, when consumed in enough amounts, can have advantageous effects on the host and serve as probiotics. Probiotics have been suggested to possess potential benefits in terms of restoring the reliability of the intestinal barrier, mitigating infection in the gastrointestinal tract, and preserving the equilibrium of the gut. In particular, the probiotic strain known as *Clostridium butyricum* (*C. butyricum*) has been documented to modify gut homeostasis, diminishing inflammation, and decreasing the occurrence of diarrhea in conditions such as inflammatory bowel disease (IBD). Consequently, *C. butyricum* has been employed as a therapeutic intervention for gastrointestinal syndromes, including IBD and antibiotic-associated diarrhea [35]. Potential pleiotropic health benefits of probiotics in inducing antimicrobial and antitumor effects encompass the potential to impede tumor progression, enhance host immunity (both innate and adaptive), sequester and degrade diverse mutagens through competitive binding, ameliorate the adverse effects of chemotherapy by enhancing metabolic activity, directly inhibit food-borne pathogens through competitive mechanisms, and contribute to the mitigation of postoperative complications. Microorganisms might exert a detrimental influence on cancer prognosis by producing toxins and metabolites that can induce oncogenic effects [36].

An investigation focused on elucidating the role of *Clostridium butyricum* in individuals undergoing chemotherapy treatment. A cohort of 41 individuals diagnosed with lung cancer were recruited and allocated at random to receive either *C. butyricum* (CB) or a placebo in a 1 : 1 ratio, resulting in 20 participants receiving CB and 21 people receiving the placebo. During the three-week intervention, blood and stool samples were gathered and examined on both the initial and final day. The investigation of stool flora involved the utilization of 16S ribosomal RNA sequencing. The CB group had a lower occurrence of diarrhea caused by chemotherapy than the placebo group. Both the total number of lymphocytes and the platelet-to-lymphocyte ratio (PLR) were also different. Neutrophil-to-lymphocyte and peripheral lymphocyte-to-neutrophil ratios (NLR and PLR) were both lower in the CB group. At week 3, the CB group was shown to have a higher lymphocyte/monocyte ratio (LMR) than the placebo group. There was no appreciable contrast in albumin (ALB) or body mass between the two groups. At the three-week mark, there was no observed decline in the overall diversity of flora in either group. The distribution of phyla in the CB group exhibited slight variation while seeing a notable drop in the placebo group. While there was a tendency for an increase in the abundance of genera that produce short-chain fatty acids in the CB group, there was a corresponding decrease in the abundance of pathogenic genera. This trend was in stark contrast to the observations made in the placebo group. When comparing the CB group with the placebo group, the analysis of operational taxonomy units proved a statistical rise in the abundance of beneficial microorganisms, namely the genera *Clostridium* and *Lactobacillus* [35]. According to the results, *C. butyricum* resulted in a reduction in chemotherapy-induced diarrhea in individuals diagnosed with lung cancer. Additionally, it was observed that the use of *C. butyricum* led to a decrease in the systemic inflammatory response and facilitated the restoration of homeostasis.

In another study, probiotics from the MIYAIRI 588 strain of *Clostridium butyricum* reduced antibiotic-induced dysbiosis and associated symptoms. Probiotic *Clostridium butyricum* treatment may have affected immunocompromised bacteria (ICBs) therapeutic effectiveness. Immune checkpoint inhibitors were evaluated in progressing large-cell lung cancer patients. The results of the propensity score analyses confirmed that the use of probiotic CBT considerably increased both progression-free survival and overall survival. Patients who have been treated with antibiotics benefit greatly from probiotic CBT [37]. The results suggest that probiotic cognitive behavioral therapy (CBT) may increase the efficiency of immune checkpoint blockade (ICB) in cancer patients.

3. Probiotics against Breast Cancer

Breast cancer (BC) is the most often identified tumor among women, ranking as the second most frequent disease globally and 2nd biggest reason of cancer-related deaths. Approximately, 12.5% of women who reach the age of 85 may experience the occurrence of breast cancer at some point in their lives. Breast cancer (BC) prevention and treatment using probiotics has been the topic of several in vitro and animal investigations. In several studies involving animals, probiotics are useful in preventing and treating breast cancer (BC).

Probiotics are being studied for their potential use in reducing the side effects of chemotherapy and in preventing and treating breast cancer. The function of probiotics in breast cancer has been observed in research including humans, animals, and in vitro models. Based on findings from in vitro investigations, it has been observed that probiotic intervention leads to the induction of apoptosis and the inhibition of cancer cell growth. In experimental animal models, the administration of probiotics resulted in the suppression of tumor development and a reduction in tumor size. Additionally, probiotics exhibited immunomodulatory effects, as well as displayed features that hindered angiogenesis and metastasis. The findings from human research studies demonstrate a decrease in the occurrence of breast cancer with the intake of *Lactobacillus casei shirota*. Additionally, an inverse relationship was shown between the consumption of fermented milk products and yogurt and the incidence of breast cancer [38]. Researchers induced mice with breast cancer, a suspension of *Lactobacillus acidophilus* orally for 30 days, starting two weeks before the tumor was transplanted. The mice that received *L. acidophilus* had a significantly longer survival time than the control group [39]. This suggests that *L. acidophilus* may have significant anticancer properties.

The researcher investigated a particular strain of *Lactobacillus*, which was found through the use of 16S rRNA gene sequencing. This strain was provisionally named *Lactobacillus brevis* MK05. Biochemical studies confirmed that this strain had the greatest probiotic potential since it was resistant to acid and bile salts and had antibacterial activity. In the case of *L. brevis* MK05, the existence of antibacterial metabolites other than organic acids may account for the antimicrobial action against *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* subsp. *aureus* (ATCC 25923). The researchers employed the MTT test to assess the biological efficacy of the partly purified secretory proteins from this particular strain against MCF-7 cancer cells and normal fibroblast cells. The partly purified cell-secreted proteins of this strain, known as Lb-PPSPs, exhibited an anticancer and apoptosis-inducing effect that was dependent on both time and dosage. The viability of MCF-7 cells exhibited a significant decline after 48 hours when exposed to doses equal to or exceeding 0.5 mg/mL [40]. The study demonstrates that the cytotoxic activity and induction of apoptosis by Lb-PPSPs in MCF-7 cells are supported by alterations in the expression of three factors associated with the apoptosis pathway, namely BAX, BCL-2, and BCL2L11.

In another study, the effects of *S. boulardii* supernatant (SBS) on cell survival are investigated in MCF-7 and MCF-7/MX human breast cancer cells, both non-drug-resistant and multidrug-resistant. This is achieved via triggering apoptosis and reducing survival gene expression. The IC_{50} value of SBS against MCF-7 cells was determined to be 1037, 542, and 543 g/mL after treatment durations of 24, 48, and 72 hours, respectively. Furthermore, the aforementioned result about the inhibition of MCF-7/MX cells was measured at 1242, 616, and 444 g/mL following exposure durations of 24, 48, and 72 hours, correspondingly. The inhibition of survivin gene expression has been recognized as a key molecular mechanism for inducing apoptosis in breast cancer cells, hence exerting an anticancer effect. The efficacy of SBS in inhibiting cancer growth was observed to be higher in MCF-7 cells compared to MCF-7/MX cells [41]. The study proposes the utilization of SBS as a promising therapeutic agent for the management of human breast carcinoma, with possible anticancer properties.

3.1. Role of Probiotics in Brain Cancer. Tumors originating in the central nervous system (CNS) are a significant contributor to mortality associated with cancer, affecting individuals across many age groups, including adults and newborns. The age-adjusted yearly incidence rate of both malignant and nonmalignant brain and other central nervous system (CNS) cancers was found to be 24.25 per 100,000 persons, with around 29.1% of these tumors being classified as malignant. The most often documented cancers were meningiomas (39.0%), followed by pituitary tumors (17.1%) and glioblastomas (14.3%) [42].

Probiotics refer to bacteria that are not harmful and do not cause diseases. When consumed in enough amounts, these microbes play a significant role in promoting health benefits for the host. The predominant categorizations of probiotics include bacterial isolates, including lactic acid and nonlactic acid bacteria, as well as yeasts. Prominent bacterial probiotics commonly utilized include *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, and *Enterococcus*. These include the binding, degradation, and inhibition of mutagens by probiotics, as well as the prevention and conversion of procarcinogens into less harmful substances [43].

Researchers used a sample size of 158 individuals, including 101 patients diagnosed with brain tumors (65 benign and 36 malignant cases) and 57 healthy controls (HCs) who were matched in terms of age and sex. The gastrointestinal microbial population is defined and its relationships to clinical features are examined using 16S rRNA gene amplicon sequencing. Patients diagnosed with brain tumors demonstrated a notable decrease in both microbial ecosystem diversity and balance in comparison to individuals without any health conditions. The community structure of the gut microbiota saw notable changes within the brain tumor group, characterized by an elevated presence of pathogenic bacteria, including *Fusobacteriota* and *Proteobacteria*, and a reduced abundance of probiotic bacteria, such as *Bifidobacterium* or *Lachnospira*. Furthermore, the findings of the study indicate that the cohort diagnosed with malignant brain tumors had a higher degree of meaningful associations and aggregation of infections. The analysis of the Kyoto Encyclopedia of Genes and Genomes (KEGG) yielded findings indicating the presence of hazardous compounds and deviations from normal physiological pathways within the cohort of brain tumor subjects [44]. The findings of the study indicate that there may be variations in host-microbe interactions between brain tumor patients and healthy individuals, with a particular emphasis on those diagnosed with malignant brain tumors.

The combination of *Lactobacillus acidophilus* and *Bifidobacterium infantis* (LB) was administered daily from embryonic day 16 (E16) until weaning to pregnant C57/BL6J mice. This maternal LB supplementation was found to have a significant suppressive effect on postnatal peripheral proinflammatory insult-induced systemic inflammation. Additionally, it was observed that the supplementation normalized compromised blood-brain barrier permeability and restored the expression of tight junction proteins in the offspring during the preweaning stage. Furthermore, exposure to maternal LB (lipopolysaccharide) has been found to alter markers associated with leukocyte transendothelial migration, extracellular matrix damage, and neuroinflammation. Activation of astrocytes and microglia was reduced, and transcriptional regulators CCAAT enhancer binding protein delta (CEBPD) and inhibitor of B cells (IB) were downregulated when LB supplements were given to pregnant women, resulting in a decrease in neuroinflammatory activity. Furthermore, the administration of maternal LB supplementation was found to enhance the formation of neuronal and oligodendrocyte progenitor cells [45]. The research provides evidence for the efficacy of maternal LB supplementation in regulating inflammation in the systemic and central nervous systems, while also facilitating the formation of neural/oligodendrocyte progenitors in offspring. The findings indicate that the administration of probiotics to mothers may be a viable and secure approach to improve neurological outcomes in their kids.

Another research used the probiotic supplement ProBiotic-4 including the bacteria *Bifidobacterium lactis*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus acidophilus*. Using the senescence-accelerated mouse susceptible 8 (SAMP8) mouse model, researchers examined the impact of ProBiotic-4 on the microbiota-gut-brain axis and cognitive impairments. One further goal of the investigation was to figure out what molecular process was at work here. Nine-month-old SAMP8 rats were given ProBiotic-4 by mouth for 12 weeks. Memory was enhanced, additional damage to brain cells and connections was averted, glial cell activation was dampened, and the mice's feces and brains had a different microbial composition after being fed ProBiotic-4. It appears that ProBiotic-4 helped slow down the aging process by strengthening the intestinal barrier and the blood-brain barrier. The mRNA and protein levels of interleukin-6 and tumor necrosis factor were lowered as a consequence. In addition, ProBiotic-4 therapy resulted in a decreased concentration of lipopolysaccharide (LPS) in plasma and brain tissues. Furthermore, it inhibited nuclear translocation of NF-kB in the brain. Levels of H2AX, 8-hydroxydesoxyguanosine, and RIG-I are all reduced [46]. The studies exhibit the potential of probiotics against brain cancers. Probiotics can positively modulate cellular pathways to prevent and aid in the treatment of such cancers. Figure 2 presented the downregulation of inflammatory factors leading to cancers by probiotics.

3.2. Probiotics against Blood Cancer. The majority of hematopoietic cancers, sometimes referred to as blood cancer, arise within the bone marrow, the site responsible for the production of blood cells. The use of probiotics has been shown to have potential in the treatment of cancer. Probiotics are alive bacteria that, when consumed in enough quantities, have the potential to provide health benefits. Certain amounts, dosages, methods of administration, and active components have shown efficacy and safety for treating a variety of conditions, including intestinal inflammation or infection, ischemic heart disease, urogenital infections, respiratory ailments, and cancer [47]. The prevailing composition of probiotic products on the market consists mostly of lactic acid bacteria (LAB) derived from species of the *Lactobacillus* and *Bifidobacterium* genera. The investigation focused on examining the origins, safety, and efficacy of probiotics, as well as their mechanisms in preventing and treating different kinds of cancer, such as leukemia and melanoma. This examination has been conducted across three levels of research: in vitro, animal, and clinical surveys. Numerous mechanisms have been postulated to account for the prophylactic and antitumor properties of probiotics. These include the generation of short-chain fatty acids, modulation of colonic motility and transit time, modification of tumor cell differentiation, exertion of anticarcinogenic effects, possession of antimutagenic properties, regulation of the inflammatory response, suppression of bacteria involved in the conversion of procarcinogens to carcinogens, modulation of tumor gene expressions, and reduction of intestinal pH to mitigate tumor gene expressions [48].

Researchers investigated the production and application of fungal exopolysaccharides (EPS) in response to the growing utilization of natural biopolymers. The objective was to examine the possible antiproliferative and antioxidant properties of extracellular polymeric substances (EPS) derived from *Rhodotorula mucilaginosa* sp. GUMS16 on BCR-ABL-positive cells, namely K562 cells. To assess the potential mortality of cancer cells, many experimental techniques were employed, including cytotoxicity tests, colony formation assays, and measurements of lactate and dehydrogenase (LDH) activity. To clarify the antiproliferative mechanism associated with EPS, a cell cycle study was conducted subsequent to real-time PCR, which was utilized for the assessment of gene expression. EPS had a significant inhibitory impact on the vitality of K562 cells, as evidenced by its IC_{50} value of 1500 g/ml. Notably, this reduction in cell viability was seen without any discernible toxicity towards normal cells. Moreover, treatment with EPS resulted in a significant decrease in both the size and quantity of colonies formed by the treated group. The LDH levels exhibited a significant rise, being 2.75 times higher than the control group. In the experimental group, an upregulation of apoptotic genes and a downregulation of antiapoptotic genes were observed in comparison to the control group. Furthermore, the DPPH scavenging activity exhibited by the EPS in the treated cells was found to be considerably higher than that in the control group. The EPS derived from the

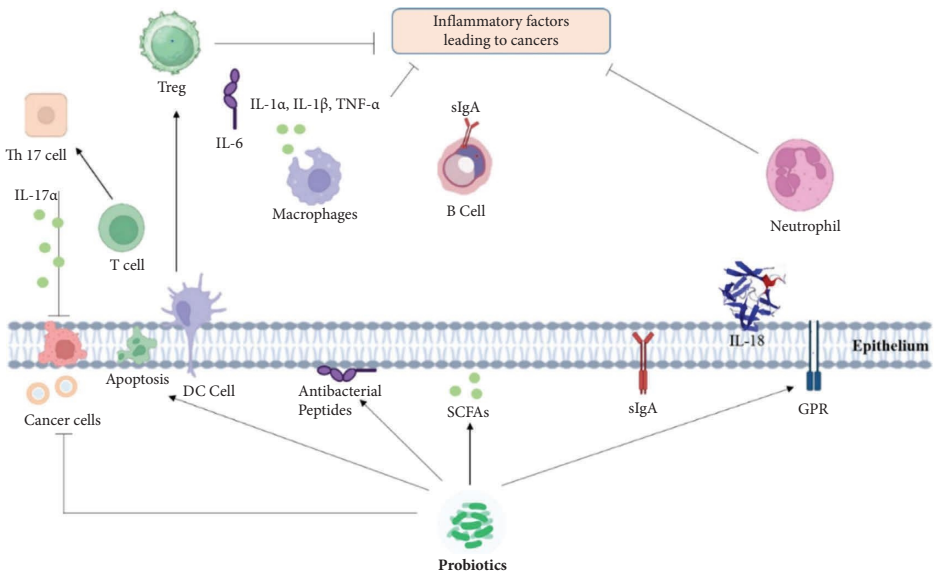

Figure 2: Downregulation of inflammatory factors leading to cancer by probiotics.

GUMS16 strain has antioxidant capabilities and demonstrates the capacity to impede the growth of K562 cells [49].

According to a study, the therapeutic effect of heat-inactivated *Lactobacillus casei* and *Lactobacillus paracasei* on the K562 cell line, is associated with chronic myeloid leukemia. A specific medium was utilized to cultivate bacteria in an environment devoid of oxygen, followed by the subsequent termination of cellular activity by exposure to a temperature of 100°C. The process of lyophilization was employed to remove moisture from deceased cells, then followed by sterilization using autoclaving. Subsequently, a series of heat-inactivated bacterial suspensions were made, each with varying concentrations (125, 250, 500, 1000, and 2000 g/ml). The MTT test was employed to assess the in vitro anticancer properties of heat-killed bacteria at three different time points: 24, 48, and 72 hours. The findings indicated that heat-killed cells of *L. casei* and *L. paracasei* exhibit anticancer activities in K562 cells. Furthermore, the concentration of cells that have been eradicated by heat is directly proportionate to their antitumor activities [50]. It can be said that heat-inactivated *Lactobacillus* exhibits promising promise as a viable option for further exploration in the realm of therapeutic interventions for chronic myeloid leukemia.

Another interesting study was conducted by researchers on the fecal microbiota of dogs affected with non-Hodgkin lymphoma (NHL). The research encompassed an examination of the fecal microbiome in a cohort comprising six canines in good health, eight canines diagnosed with non-Hodgkin lymphoma (NHL) during their initial presentation, and four canines with NHL who had undergone chemotherapy induction phase (involving cyclophosphamide, vincristine, and prednisone) and were subsequently treated with probiotics (containing *Lactobacillus* sp. and *Bifidobacterium* sp.). The investigation was performed via quantitative polymerase chain reaction (qPCR) tests that were designed to target certain bacterial groupings. The study revealed a significant increase in the presence of *Bifido bacteria*, *Lactobacillus*, *Faecali bacterium*, *Bacteroidetes*, and *Fusobacterium* in the fecal samples of healthy canines compared to those with non-Hodgkin lymphoma (NHL). A comparative analysis was performed to assess the relative abundances of various bacterial species, including total bacteria, *Bifido bacteria*, *Lactobacillus*, *Faecali bacterium*, *Bacteroidetes*, *Fusobacterium*, *Escherichia coli*, *Blautia*, *Ruminococcaceae*, and *Clostridium perfringens*, before and after the administration of chemotherapy in a cohort of four canines [51]. The findings of the study revealed that there were no statistically significant disparities identified in the abundances of the aforementioned bacterial species.

3.3. Role of Probiotics in Inflammatory Bowel Diseases and Diarrhea. In Western populations, Crohn's disease (CD) and ulcerative colitis (UC), which are categorized as inflammatory bowel diseases (IBD or IBDs), are chronic inflammatory conditions affecting the gastrointestinal (GI) tract. The combined mortality rate of these conditions is 450 per 100,000 individuals [52]. From the buccal cavity to the anus, every portion of the digestive tract may be impacted by Crohn's disease. It is discontinuous, with areas of inflammation and noninflammation occurring in alternation. The modifications influence every layer of the intestinal mucosa. Ulcerative colitis is characterized by a continuous kind, like Crohn's disease. Alterations in inflammation spread throughout the inner mucosa and are limited to the colon. Environmental and genetic coexistence, immunological imbalance, gastrointestinal barrier permeability, and microbiome health all significantly influence the onset and progression of the disease [53]. Although the use of antibiotics to eliminate potentially inflammatory bacteria may appear feasible, their application is limited. Alternative treatment consists of administering probiotics, which can reduce inflammation by restoring the intestinal

microbiome's stability. Probiotics refer to living microorganisms that are meant to offer beneficial effects. Several animal models have demonstrated the efficacy of probiotic therapy for patients with inflammatory bowel disease (IBD). When ingested, probiotics can modify the constitution of the bowel by inhibiting the proliferation of potentially pathogenic bacteria, which has positive effects on human health [54]. Probiotics may potentially provide benefits via various mechanisms, including their ability to stimulate anti-inflammatory cytokines, inhibit inflammatory cytokines, enhance the intestinal barrier, and exert an antagonistic effect on pathogens. Both *in vitro* and *in vivo* models have been used to study these pathways extensively [55].

Researchers evaluated the efficacy of a multistrain probiotic in treating inflammatory bowel disease and quality of life issues in asymptomatic UC and CD patients. A randomized, placebo-controlled, single-center, double-blind study of adults without symptoms of inflammatory bowel disease was conducted. Every participant received a daily dosage of 1 ml/kg of probiotic or placebo for four weeks. Primarily, the effectiveness was measured at week 4 by comparing the two groups' changes in the IBD Quality of Life Questionnaire (QoL). The results showed that out of 500 individuals selected, 81 patients with UC and 61 patients with CD were randomized and managed to finish the clinical trial. The IBD-QOL scores of the placebo and probiotic groups did not differ significantly. Similarly, the laboratory data exhibited no remarkable variations. Nevertheless, the disparities in FCAL (fecal calprotectin) among UC patients before and after probiotics compared to placebo were statistically significant. The FCAL levels of UC patients who received the probiotic as opposed to the placebo were significantly decreased [56]. It was implied that probiotics improved the health conditions of the patients by limiting the negative effects of the diseases. Researchers investigated the potential impact of probiotics on ulcerative colitis (UC) patients' quality of life (QoL). A total of twenty-four patients diagnosed with UC were enrolled in the research and were assigned at random, three times daily for six weeks, to either the probiotic group (probiotic capsules containing five *Bifidobacterium* species and nine *Lactobacillus* species) or the placebo group (consisting of a polysaccharide supplied in an identical package). Using an early inflammatory bowel disease questionnaire (SIBDQ), researchers compared the two groups' quality of life before and after the treatment. Participants given probiotics had higher scores on the social, mental, bowel, and overall SIBDQ variables compared to those in the placebo group. Additionally, among the SIBDQ subscales, the probiotic group exhibited notably improved scores on the systemic, social, gastrointestinal, emotional, and overall scales when comparing pretreatment to posttreatment. UC patients' quality of life was substantially enhanced through the administration of probiotic therapy comprising *Lactobacillus* and *Bifidobacterium* species [57].

Patients with mild to moderately active UC were studied to examine the influence of probiotic administration on clinical disease activity and biochemical markers. In a double-blind, randomized study, thirty patients with mild to moderate ulcerative colitis were chosen at random to receive either a placebo or 3×10^{10} probiotic capsules containing nine species of *Lactobacillus* and five species of *Bifidobacterium* as treatment. The result was carried out for the intention-to-treat analysis. After 24 volunteers who followed the procedure were included, the research was considered to be effective. Both groups had their biochemical markers and clinical disease activity assessed at the start and finish of the study. According to the results, the probiotic group had a significant reduction in the partial Mayo score (PMS), which is a measure of remission. A significant decrease was seen in the frequency of feces (0.00 ± 0.00 vs. 1.17 ± 1.19), general assessment and total PMS score. Average and percentage changes from pre- to posttreatment values for hemoglobin, hematocrit, and red blood cell levels, as well as C-reactive protein, showed substantial improvements in the probiotic group. In addition, the probiotic group showed a significant drop in IgA levels and an accompanying rise in IL-10 levels compared to the placebo group [58]. Thus, it is concluded that probiotics not only enhance the quality of life of patients of IBD but also aid in the treatment itself. Probiotics also improve overall health and are positive immunomodulators.

In another interesting study, probiotic therapy was compared to a placebo in terms of oxidative stress values and clinical manifestations in patients with inflammatory bowel disease. Study included forty patients that had previously been diagnosed with inflammatory bowel disease (IBD). These patients were randomized to receive probiotics or a placebo over ninety days. Participants were evaluated for their overall oxidant capacity (d-ROMs test) and antioxidant response (BAP test) in both groups. The results were presented at three time points: baseline, after one month, and after three months. Additional information was also disclosed across the study as a result of anamnesis and hematological investigation. The results obtained from the d-ROM assay unequivocally demonstrated a substantial improvement in the values observed in the test group, resulting in nonpathological oxidative stress levels. The increasing BAP values in the test group confirmed that probiotic administration resulted in general health improvements for the patients [59]. The effectiveness and safety of the probiotics were established in patients with IBD through oral administration. Probiotics not only aid in the treatment of IBD but also reduce inflammations by reducing oxidative stress at a cellular level. Figure 3 shows the anti-inflammatory role of probiotics at the cellular level.

In light of these recent studies, researchers have suggested that probiotics can help manage, prevent, and treat inflammatory bowel diseases effectively. One of the main benefits of taking probiotics is the prevention of the onset of IBDs. As reported by researchers, probiotics are excellent at preventing/reducing inflammations by reducing oxidative stress. Another interesting finding reported in many studies is that probiotics significantly enhance the quality of life of patients with IBDs. Probiotics help treat the main causes of the disease thereby reducing the effects and adverse symptoms associated with the disease while improving the biochemical, histopathological, and immunological markers and overall health of the individuals.

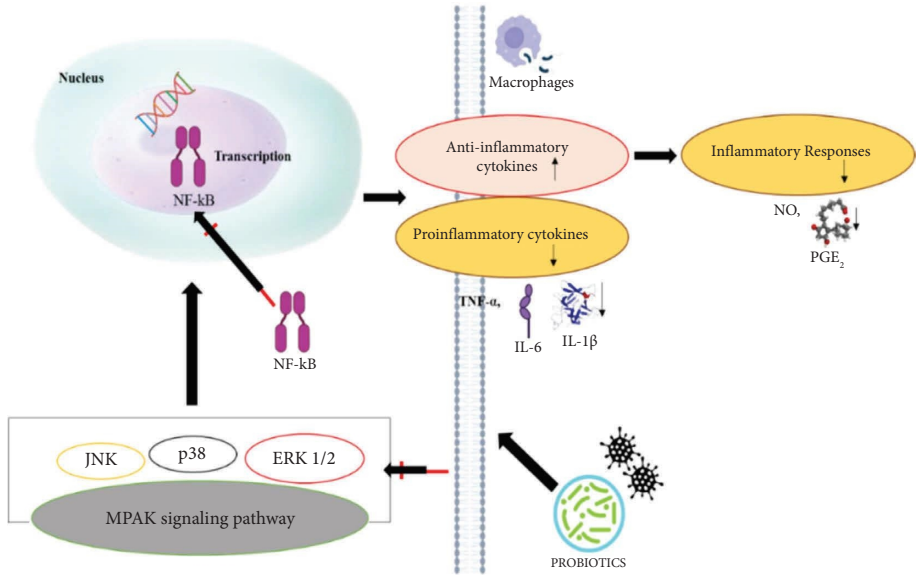

Figure 3: Anti-inflammatory role of probiotics at the cellular level.

3.4. Role of Probiotics in Ulcers. Ulcers are painful and inflammatory sores that appear on the skin's surface. The condition is categorized as mild, significant, or herpetiform based on its clinical characteristics. The etiology of the condition remains uncertain and subject to debate, with several explanations proposed, such as immunologic abnormalities, environmental and psychological stress, and viral infections. The administration of probiotics in adequate quantities has been found to have a positive impact on the health of the host. The modulation and enhancement of the immune system through the utilization of probiotics contributes to the mitigation of illness. Probiotics are capable of generating several compounds, including organic acids, bacteriocins, and peptides, among others. As a result, the probability of colonization by dangerous bacteria is reduced. The analgesic effects of tetracyclines can be attributed to their ability to restrict oxidative activation, reduce prostaglandin production, block collagenase and gelatinase activities, and suppress leukocyte activity [60].

There are several classifications of ulcers.

3.4.1. Oral Ulcers and Role of Probiotics. Oral ulcers are a highly widespread oral condition characterized by a significant level of complexity, diversity, and frequency. Oral ulcers can arise due to several etiological reasons, including infectious agents, traumatic events, and allergic reactions. Mouth ulcers are characterized by the loss of connective tissue and the creation of crater-like depressions caused by chronic disruption or damage to the integrity of the mouth epithelium. Probiotics are microorganisms that are both innocuous and resistant to pathogens. They have the potential to provide health advantages to the host, including enhancing immune function, preventing infection by battling pathogenic bacteria, and facilitating nutrient assimilation through improved digestion. They play a role in regulating immune function and modulating tissue healing. The utilization of fucoidan (FD), a prebiotic derived from marine sources, has the potential to enhance the efficacy of probiotics in facilitating the process of ulcer healing [61]. Probiotics can form a biofilm within the mouth cavity, which can effectively compete with carcinogenic and periodontal bacteria. Also, they exert modulation on the immunological response of the host, enhance the functionality of the immune system, and subsidize to the inhibition of illnesses. The utilization of oral probiotics is correlated with a notable enhancement in oral well-being [62].

Local administration of oral probiotics is being studied by researchers to determine if it might help patients with recurrent aphthous ulcers and oral candidiasis improve their oral health. The research encompassed a cohort of 80 individuals who had been clinically diagnosed with regular aphthous ulcers and oral candidiasis. Group A comprised a cohort of 40 individuals who were orally supplied with probiotics as an adjuvant, whereas Group B comprised 40 individuals who did not receive probiotics. The participants were organized into two categories, namely AU and BU, which represented regular aphthous ulcer, AC and BC, which represented oral candidiasis. The clinical signs and symptoms were assessed at the beginning and conclusion of the trial. The probiotic utilized in the research was *Bacillus clausii*. On the fifth day of the study, individuals were assigned to a group who showed an exhibited noteworthy enhancement in erythema, pain alleviation, reduction in oral candidiasis, and alleviation of stinging sensation in the oral cavity. However, on the tenth day, there was no statistically significant disparity seen between the groups. The findings support the effectiveness and speed of the oral probiotic intervention in managing aphthous ulcer and oral candidiasis. Hence, the utilization of probiotics as a supplementary treatment in the management of several oral illnesses has been documented [62]. The development of bioactive oral ulcer dressings involved the creation of calcium alginate composite hydrogels that incorporated probiotics, which was achieved through scientific study. The hydrogels with

a well-defined structure demonstrated remarkable adherence to wet tissues, appropriate swelling and mechanical characteristics, prolonged release of probiotics, and excellent stability during storage. Moreover, the composite hydrogel demonstrated enhanced cyto/hemocompatibility and antibacterial characteristics, as evidenced by in vitro biological experiments. In direct comparison to commercial oral ulcer patches, bioactive hydrogels exhibit notable advantages in terms of therapeutic efficacy for the promotion of ulcer healing in vivo. These advantages include the enhancement of cell migration, the stimulation of epithelial formation and organized collagen fiber deposition, as well as the facilitation of neovascularization [61].

3.4.2. Stomach Ulcer and Role of Probiotics. The word "peptic ulcer" denotes the occurrence of acid-induced damage to the digestive system, resulting in the rupture of the submucosal mucosa. Peptic ulcers are commonly observed in the gastric region or the proximal duodenum; however, they may also manifest in the esophagus or Meckel's diverticulum. Peptic ulcer disease pertains to the occurrence of peptic ulcers in the stomach or duodenum. The major risk factors associated with gastric and duodenal ulcers are the presence of *H. pylori* infection as well as the utilization of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin [63]. Probiotics are beneficial bacteria that, when consumed in adequate amounts, contribute to the promotion of host well-being. Probiotics have the potential to enhance the barrier function. The gastric mucosa of the stomach possesses an acid and mucous barrier, which serves as the primary protective mechanism against harmful germs. Certain probiotics can enhance the upregulation of fitted connected proteins and stimulate the production of mucin and mucus, therefore reinforcing the mucus secretion process, and augment the protective function of the stomach mucosal barrier. Additionally, some strains of probiotics can produce antimicrobial compounds, including lactic acid, short-chain fatty acids (SCFAs), hydrogen peroxide, and bacteriocins. Lactic acid and short-chain fatty acids (SCFAs) exhibit partial dissociation characteristics, and the dissociated states of these organic acids have deleterious effects on *H. pylori* [64].

Researchers evaluated the effect of triple therapy with probiotics on *Helicobacter pylori*-induced peptic ulcers. The control group included 90 patients who were administered quadruple therapy for two weeks. This therapy included the use of a proton pump inhibitor, namely ilaprazole enteric-coated tablet, in addition to two antibiotics, namely amoxicillin dispersible tablet and metronidazole tablet. Furthermore, patients in the control group also got a colloidal bismuth pectin capsule as part of their treatment regimen. The trial group consisted of 90 patients who were given the quadruple treatment stated above, along with orally provided live probiotics including a combination of *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* capsules, for two weeks. Subsequently, a comparative analysis was conducted between the two cohorts to assess the Hp clearance rate, recurrence rate, levels of gastrointestinal hormone producers, and advanced responses. After a two-week period posttreatment, the study group exhibited a notably higher clearance rate of *Helicobacter pylori* (87.79%) associated to the control group (78.89%). Additionally, the study group had a considerably lower overall recurrence rate (6.67%) in contrast to the control group (13.37%). In comparison to the control group, there was a notable decrease in serum gastrin and motilin expressions, although somatostatin expressions exhibited a considerable increase [65]. Thus, it can be said that the utilization of quadruple therapy in conjunction with probiotics for the management of peptic ulcers caused by *Helicobacter pylori* has been found to enhance the eradication rate of *Helicobacter pylori*, reduce the likelihood of *Helicobacter pylori* reoccurrence, and enhance the levels of gastrointestinal hormones, while maintaining an acceptable level of safety.

H. pylori-infected individuals participated in a randomized, placebo-controlled study for this project. Two groups were chosen at random to receive either a 7-day or 14-day course of high-dose PPI-bismuth-containing triple therapy. Some patients in each group also received a probiotics supplement, while others were given a placebo. Each pill of the probiotic supplement included 37.5 mg of the beneficial bacteria *Lactobacillus reuteri*. The subjects were given two pills every day. In addition, tests for antibiotic susceptibility and CYP2C19 genotyping were performed. The operational definition of *H. pylori* eradication was a negative result on the 13C-urea breath test, which was performed at least four weeks following the end of therapy. A total of 100 people, including 72 women and 28 men, were included in the analysis. The mean age of the people who took part was calculated to be 54. Antibiotic resistance was shown to be 15.6% prevalent in clarithromycin, while 34.1% prevalent in metronidazole. Based on CYP2C19 genotyping results, researchers may infer that 13% of the population are poor metabolizers, 50% are intermediate metabolizers, and 37% are rapid metabolizers. There was a statistically significant difference between the eradication rates for 7-day and 14-day probiotic regimens (from 68% to 96%). All patients who were identified as poor and rapid metabolizers and who adhered to the treatment plan for 14 days were completely cured. A probiotic program of 14 days can eliminate resistance to the antibiotics clarithromycin, metronidazole, and the combination of clarithromycin and metronidazole. When compared to the placebo group, those taking probiotics experienced significantly fewer episodes of nausea, vomiting, stomach pain, and bitter taste. *H. pylori* may be effectively treated with a 14-day course of high-dose proton pump inhibitor (PPI)-bismuth-containing quadruple therapy supplemented with a probiotic, and this treatment has been shown to have a remarkable cure rate regardless of CYP2C19 genotype and antibiotic resistance patterns [66]. Thus, it was concluded that when probiotics were added to the treatment, both adverse events and noncompliance dropped significantly.

3.4.3. Diabetic Ulcers and Role of Probiotics. Lesions and abrasions in people with diabetes mellitus are characterized by the loss of epithelial tissue, making them easily

identifiable as ulcers. Diabetic foot ulcers exhibit delayed healing attributed to various molecular and cellular characteristics inherent in the healing process. Furthermore, these factors can encompass the excessive formation of advanced glycation end products (AGEs), insufficient neoangiogenesis, inadequate levels of growth factors, an imbalance between metabolism and nutrient delivery, cellular abnormalities, and dysregulation of gene expression regulators [67]. Probiotics have garnered significant attention in the realm of treating several metabolic illnesses owing to their notable antibacterial, antioxidant, anti-inflammatory, antidiabetic, and immunomodulatory properties. Probiotics play a role in regulating the levels of short-chain fatty acids, gastrointestinal hormones, and the endocannabinoid system in individuals with diabetic foot ulcers (DFU). These mechanisms contribute to the maintenance of glucose homeostasis, the reduction of inflammation, and the enhancement of immune response in DFU patients [68].

Researchers used lyophilized conditioned medium with extracellular probiotics since earlier publications showed that probiotics aided in wound healing in animal models. The biological activity of cefotaxime, clindamycin, and the lyophilized conditioned medium *Lactobacillus acidophilus* (LCMLa) against bacteria obtained from diabetic foot ulcers was assessed using the turbidimetric technique. Furthermore, alongside the examination of the colonies at a macroscopic level and the utilization of an atomic force microscope for morphological study, the determination of the Gram type and oxygen needs for bacterial development was conducted. Three strains were obtained from diabetic foot ulcers. Isolates 1 and 3 had a bacillus-like morphology and showed susceptibility to cefotaxime and the lyophilized conditioned media of *L. acidophilus*. Cefotaxime exhibited significant bacteriostatic effects on the bacteria derived from diabetic foot ulcers across all tested dosages, suggesting a pronounced level of toxicity through impeding their development. The strain denoted as Strain 1 exhibited the highest level of sensitivity, as evidenced by the observed inhibitory percentages of 85%, 87%, and 88% at dosages of 0.15 g/mL, 0.25 g/mL, and 0.5 g/mL, respectively [69]. Researchers examined the effects of probiotics on wound healing and metabolic status in people with diabetic foot ulcers (DFUs). Patients between the ages of 40 and 85 participated in this randomized, double-blind, placebo-controlled experiment. Everyone in the study had diabetic foot ulcers of grade 3. The 60 people who participated were split evenly between two groups of 30 who were given probiotics and another thirty who were given a placebo. The length of this intervention was 12 weeks. During a 12-week intervention, ulcer length (1.3 to 0.8 cm), width (1.1 to 0.7 cm), and depth (0.5 to 0.3 cm) were significantly reduced when probiotic supplements were compared to a placebo. Fasting plasma glucose levels were also observed to be lower after taking probiotic supplements as were insulin levels and hemoglobin A1C levels. Probiotics significantly decreased serum total cholesterol high-sensitivity C-reactive protein and plasma malondialdehyde. Total antioxidant capacity concentrations increased, and plasma nitric oxide levels increased [70]. It can be concluded that patients with diabetic ulcers can have dramatic improvements after taking probiotics. The positive effects include reduced ulcer size, improved glycemic control, lower total cholesterol, high-sensitivity C-reactive protein, lower plasma nitric oxide, and increased total antioxidant capacity.

3.5. Probiotics and Antibiotics-Associated Diarrhea. Antibiotic-associated diarrhea (AAD) is an often-seen and unanticipated adverse consequence resulting from the use of antibiotics. The condition is characterized by disruptions in the gut microbiota, reduced levels of short-chain fatty acids (SCFAs) in the intestines, buildup of luminal carbohydrates and colonic bile acids, changes in water absorption, and eventually the manifestation of diarrhea [71]. Diarrhea commonly occurs as a side result of systemic antibiotic treatment. Antibiotic-associated diarrhea (AAD) has been seen to impact a range of people, with prevalence rates ranging from 5% to 39% throughout therapy and persisting for a period of up to two months thereafter. The justification for providing probiotics to individuals with gastrointestinal diseases lies in their potential to restore equilibrium to an unbalanced gut microbiota. Probiotics have been shown to improve gut health, and there are several theorized processes by which this occurs. Immune system activation, nutritional competition, blocking pathogen attachment to epithelial and mucosal surfaces, blocking epithelial invasion, and the synthesis of antimicrobial compounds are all examples of these methods. A wide range of probiotic species have been examined, with particular emphasis on those classified under the genera *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*. Probiotics have demonstrated efficacy in the prevention of antibiotic-associated diarrhea (AAD), notably among youngsters [72].

They investigated the potential of a tannic acid and ferric ion-based coating, referred to as "nano armor" to protect bacteria against the impacts of antibiotics. The nano armor protected against six therapeutically important antibiotics for both Gram-positive and Gram-negative microorganisms. The mutual interactions between nano armor and antibiotic molecules facilitated the efficient absorption of antibiotics by nano armor. The study also provided evidence of the colonization capacity of armored probiotics in the gastrointestinal tracts of levofloxacin-treated animals. Antibiotic-associated diarrhea (AAD) was greatly reduced by treatment with levofloxacin, and some of the preinflammatory symptoms brought on by AAD were alleviated [73]. Thus, the nano armor technique serves as a reliable framework for augmenting the effectiveness of therapeutic bacteria within the gastrointestinal tracts of patients undergoing antibiotic treatment, while also mitigating the occurrence of gastrointestinal adverse effects associated with antibiotics.

In a randomized precise clinical trial, the efficiency of the probiotic alkali *Halobacillus clausii* 088AE, which is both genetically and phenotypically safe, was assessed for its potential to alleviate antibiotic-associated diarrhea (AAD) in individuals across different age groups. The study included children (2–10 years old) as well as adolescents and adults. A

seven-day administration of *A. clausii* 088AE was conducted, with a daily dosage of 4 billion probiotic units (PE) and 6 billion acidophilus units (AA). The evaluation of main and secondary endpoints was placed throughout several sessions. The administration of *A. clausii* 088AE demonstrated an important development in the diarrheal conditions of individuals across several age groups, including children, adolescents, and adults, when compared to the corresponding placebo groups. This improvement was shown in terms of both the time elapsed since the last occurrence of unformed stool and the frequency of diarrhea. The administration of *A. clausii* 088AE resulted in a reduction in the severity score of acute antibiotic-associated diarrhea (AAD) at visit 5 in the pediatric (0.12 0.33, and 12.39-fold drop), adult and adolescent (0.54 0.36, 2.34-fold decrease), and placebo groups [74]. It can be concluded that the strain *A. clausii* 088AE demonstrated good tolerability, with no significant changes in vital and clinical safety indicators. Also, no side effects or severe adverse responses are associated with it. *A. clausii* 088AE is both safe and therapeutically effective in the treatment of AAD.

Scientists have performed a study to establish the safety and viability of a probiotic drink for patients in the intensive care unit (ICU). The study recruited patients who had received antibiotics in the intensive care unit (ICU) and matched them with a control group of patients who had not received antibiotics but were otherwise similar in terms of relevant characteristics. The participants in the trial were administered a daily dosage of two flasks of a beverage containing 10 billion *Lactobacillus casei* via enteral feeding. The study documented the occurrence of AAD, the emergence of unfavorable outcomes, and the level of tolerance towards probiotics and enteral nutrition. The incidence of *Clostridium difficile* infection (CDI) was observed during 30 days after the administration of antibiotic therapy. The findings indicated that a total of thirty-two participants were involved in the study. In the group receiving probiotics, no instances of serious adverse effects were seen, in contrast to the control group where three such incidents occurred. The presence of AAD was seen in 12.5% of the individuals in the probiotic group, whereas it was found in 31.3% of the individuals in the control group. It was shown that the incidence of *Clostridium difficile* infection (CDI) was lower in the probiotic group, with only one patient developing CDI, as opposed to three patients in the control group [75].

A randomized, double-blind, placebo-controlled clinical trial of antibiotics was conducted with hospitalized patients. Participants were randomly assigned to receive either a placebo yogurt containing *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*, a probiotic yogurt containing those same strains in addition to *Bifidobacterium animalis* subsp. *lactis*Bb-12 and *Lactobacillus casei* subsp. *casei*Lc-01, or no yogurt at all (an unblinded control). This phase began during the first 48 hours of initiating antibiotic medication and may have continued for up to 5 days after the final dose was taken. Diarrhea prevalence was determined by following subjects for 30 days. The average age of the 314 people who took part in the study was 76. There is a 95% confidence interval (CI) ranging from 15.4 to −4.7 for the absolute risk reduction of 5.35 percent. Diarrhea occurred in 23.0 percent of the probiotic group and 17.5 percent of the placebo group. The incidence of gastroenteritis was not significantly different between the unblinded external control group and the blinded study group. There was no statistically significant difference between groups in terms of hospitalization time, total number of BMs, or peak BM count owing to diarrhea. The death rates among the different groups were not significantly different. Hospitalized patients using the probiotic strains LA-5, BB-12, or LC-01 did not have a lower rate of antibiotic-associated diarrhea [76].

3.6. Probiotics against Diseases outside of the Gastrointestinal Tract

3.6.1. Role of Probiotics in Upper Respiratory Tract Infections. The upper respiratory tract (URT) is continuously exposed to ventilation from the external environment. On a daily basis, an estimated range of 104 to 106 bacterial cells per cubic meter of air are breathed concomitantly with the inhalation of air. The microenvironments of the upper respiratory tract (URT), which encompass the nasal cavity, sinuses, nasopharynx, and oropharynx, are determined by these aforementioned elements in conjunction with the anatomical characteristics. Various external and internal variables, including age, illnesses, immunological responses, olfactory function, and lifestyle habits such as smoking, have been identified as contributing factors to upper respiratory problems [77]. Probiotics refer to living microorganisms that, when provided in sufficient quantities, have possibility to provide a positive impact on the fitness of the host organism. Various species of bacteria and yeasts, such as *Lactobacillus*, *Bifidobacterium*, *Leuconostoc*, *Pediococcus*, and *Enterococcus*, are employed as probiotics. The gastrointestinal system harbors a diverse array of microorganisms, among which are species that fall under the genera *Lactobacillus* and *Bifidobacterium*. These particular species are considered to be part of the normal microflora of the gastrointestinal tract. Probiotics offer several health advantages, encompassing the management of gastrointestinal infections, enhancement of lactose metabolism, possession of anticarcinogenic and antimutagenic qualities, lowering of cholesterol levels, stimulation of the immune system, and amelioration of inflammatory bowel disease. Probiotics can enhance both the innate and acquired immune response. This is achieved through several mechanisms, including the stimulation of secretory and systemic IgA production, promotion of phagocytosis, modulation of T-cell responses, and maintenance of the balance between Th1 and Th2 activities. Specifically, probiotics have been found to increase Th1 responses while decreasing Th2 responses [78].

To explore the impact of probiotics on the manifestation of upper respiratory tract infection (URTI) signs, a group of researchers conducted a placebo-controlled experiment with overweight or obese adults. The main goal of the study was initially centered on weight loss. In addition to the observed benefits of weight loss and improvements in specific metabolic parameters, the individuals who participated in the

study and were administered probiotics had a noteworthy reduction of 27% in symptoms associated with upper respiratory tract infections (URTIs) associated to the control group. Furthermore, it is worth noting that the reduction in URTI symptoms was more pronounced among participants aged 45 years or more and those with a body mass index (BMI) of 30 kg/m^2 or higher. The amelioration of symptoms becomes apparent within a fortnight of probiotic use. The diversity of the gut microbiome in patients who received probiotic treatment remained consistent throughout the trial. The aforementioned findings provide evidence that more research is necessary to assess the possible role of probiotics in the inhibition of viral upper respiratory tract infections (URTI), with a specific focus on overweight and obese persons [79]. Researchers conducted a scientific investigation involving a double-blind, randomized, parallel-group, placebo-controlled design to measure the impact of a probiotic-based supplement on the occurrence and period of symptoms related to upper respiratory tract infections (URTI) in a population of healthy school children aged 3 to 10 years. The study spanned six months. The intervention was the daily ingestion of a probiotic supplement containing 12.5 billion colony-forming units of *Lactobacillus acidophilus* CUL21 and CUL60, *Bifidobacterium bifidum* CUL20, and *Bifidobacterium animalis* subsp. *lactis* CUL34, as well as 50 milligrams of vitamin C. A placebo that closely resembled the probiotic supplement was used as a control. The analysis had a total of 171 teenagers, with 85 participants assigned to the placebo group and 86 participants assigned to the active group. The prevalence of wheezing in children who got the active intervention was significantly lower (16%) compared to those who received the placebo. There were no notable disparities seen in the prevalence of additional upper respiratory tract infection (URTI) symptoms. The group that engaged in physical activity had a significantly lower likelihood of encountering five specific symptoms associated with upper respiratory tract infections within 24 hours. The active group exhibited significant reductions in both school absenteeism (−16%) and antibiotic usage (−27%). The results of the study indicate that a six-month diet of daily administration of the Lab4 probiotic and vitamin C has the potential to decrease instances of wheezing, absenteeism, and antibiotic use among children between the ages of 3 and 10 [80]. Scholars compared the efficacy and safety of *Streptococcus oralis* 89a and *Streptococcus salivarius* 24SMBc for preventing URTIs in children as part of the study. 91 children (47 boys and 44 girls) were included in the research because they were experiencing symptoms of respiratory tract infections (RRIs). Participants' averaged age was 7.4±2.3 year. At first, the youngsters were given nasal sprays containing *Streptococcus salivarius* 24SMBc and *Streptococcus oralis* 89a twice a day for seven days every month. Three months passed during treatment. Both one month (T1) and three months (T3) after starting therapy, the efficacy of the treatment was evaluated. During the evaluation, fever, wheezing, bronchospasm, rhinorrhea, and otalgia were checked to see if any were present. Researchers evaluated the number and types of adverse events (AEs) recorded during treatment to determine the probiotic's safety and tolerability. Treatment with *Streptococcus salivarius* 24SMBc and *Streptococcus oralis* 89a significantly reduced symptoms such as fever, wheezing, bronchospasm, rhinorrhea, and otalgia in children compared to the baseline. In individuals with a positive family history of atopy and children with atopic disorders, the medicine significantly reduced the incidence of fever, cough, bronchospasm, rhinorrhea, otalgia, and cough. When children were divided into subgroups based on whether or not they had a positive or negative family history of atopy, whether or not they were atopic themselves, whether or not they had been exposed to secondhand smoke, and so on, no statistically significant differences in symptoms were found. In the subgroup analysis, it was shown that children between the ages of 1 and 3 years saw a positive change in all symptoms. In contrast, the therapeutic effectiveness demonstrated a steady and statistically significant improvement starting from the initial month of treatment among children aged 3–6 and 6–12 years. No participants were excluded from the trial as a consequence of adverse events. However, it is worth noting that nine children did encounter nasal irritation, leading to discontinuation of the medication. Research suggests that the administration of *Streptococcus salivarius* 24SMBc and *Streptococcus oralis* 89a is both harmless and potentially beneficial for the short-term management of respiratory tract infections (RRIs) [81]. The study employed cocultures utilizing transwell inserts to investigate if the secretion of soluble compounds by the two *Streptococci* strains may impede the production of biofilms by the chosen pathogenic strains. To investigate the necessity of direct touch for inhibiting biofilm development, mixed-species biofilms were generated. The investigation of biofilm development was conducted using a spectrophotometric test and confocal laser scanning microscopy. According to the findings, it has been shown that *S. salivarius* 24SMB and *S. oralis* 89a possess the ability to hinder the capability of some pathogens to build biofilms, as well as disperse biofilms that have already been created. The antibiofilm action has been demonstrated to be mediated by diffusible compounds that are released by two strains of streptococci, as well as a reduction in the pH of the surrounding medium. According to the research, *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a have favorable attributes as probiotics in the context of managing and preventing upper respiratory tract infections [82].

3.7. Probiotics against Autoimmune and Allergic Conditions. Probiotics can potentially mitigate or manage allergies, such as atopic dermatitis and allergic rhinitis, along with autoimmune illnesses, including inflammatory bowel disease and multiple sclerosis. The prevalence of food allergies has experienced a significant increase over the last twenty years, affecting around 1-2% of adults and 5–7% of adolescents. There is a growing consensus among researchers that exposure to microorganisms throughout early childhood, including the use of probiotics, has been recognized as a means to stimulate antigen-presenting cells (APCs). This activation of APCs leads to the establishment of immunological homeostasis and subsequently contributes to the

decrease of allergies. Probiotics can selectively activate the immune system to produce both pro- and anti-inflammatory cytokines, with the specific response depending on the strain of probiotic used. Atopic dermatitis is a persistent inflammatory cutaneous condition that typically impacts newborns and toddlers. During the acute stage of atopic dermatitis, there is a prevailing presence of Th2 cells (specifically, IL-4, IL-5, and IL-13) and Th22 cells. However, in the chronic stage, Th1 cells (IFN-gamma and IL-12) become prominent, leading to the manifestation of atopic dermatitis. Multiple sclerosis (MS), Alzheimer's disease, and Parkinson's disease are all examples of neurodegenerative illnesses, and it is widely accepted that they share the characteristic of continuous inflammation. An adult's mucosal immune response and systemic immunological response can be affected by taking probiotics. This has beneficial effects on autoimmune illnesses and allergy responses because it alters immunological homeostasis and the immune profile [83].

The investigational study was designed as a double-blind, placebo-controlled, randomized experiment involving 415 pregnant women who participated in the Probiotics in the Inhibition of Allergy in Offspring. Participants were split into two groups; one received a placebo, while the other ingested probiotic milk with varying concentrations of *Lactobacillus rhamnosus* GG, *Bifidobacterium animalis* subspecies *lactis*Bb-12, and *L. acidophilus*La-5. This intervention occurred at the time of nursing, from the 3rd trimester (week 36) of pregnancy to the third month after giving birth. The baseline appearances of the females and their offspring did not differ significantly between the two groups. Researchers looked for controlling T cells and other subsets of T helper cells including Th1, Th2, Th9, Th17, and Th22 in the peripheral blood of 3-month-old infants. In marginal plasma models taken at three months of age, researchers saw a significant reduction in Th22 cells in the probiotic group associated with the placebo group (median 0.038% vs 0.064%). There was a significant increase in Th22 cells between those who developed atopic dermatitis (AD) and people who did not do it (0.090% vs. 0.044%; P 0.001). The reduction in Th22 cells was a major mediator of probiotics' protective effect against AD. Analysis of the V3-V4 region of the 16S rRNA gene of salivary bacterial DNA was performed using an Illumina sequencing technique on a group of bacterial DNA samples from the mouths of 54 patients with ulcerative colitis (UC), 13 patients with Crohn's disease (CD), and 25 healthy individuals. PCoA was performed on the OTU profile and KEGG pathways to identify distinct sample clusters based on illness or health condition. Returning samples after 2 months of treatment were found to have, as predicted, moved closer to the healthy cluster than the initial samples [84].

The analysis revealed that *Streptococcaceae* (*Streptococcus*) and *Enterobacteriaceae* were administered in individuals with ulcerative colitis (UC), while *Veillonellaceae* (*Veillonella*) were enriched in individuals with Crohn's disease (CD). Additionally, there was a reduction of *Lachnospiraceae* and *Prevotella* in UC, and *Haemophilus* and *Neisseriaceae* (Neisseria) in CD. These findings align with previous studies that have observed similar variations in the gut microbiota of individuals with inflammatory bowel disease (IBD). Regarding changes in white blood cells, the presence of microbes linked to inflammatory bowel disease resulted in decreased proportions of essential metabolic processes, while simultaneously increasing the production and transportation of chemicals that promote oxidative stress and virulence. Furthermore, it was revealed that two strong ecotypes existed within the UC or CD populations, which were not particular to demographics or severity. This analysis successfully revealed types that aid as indicators of ulcerative colitis (UC) and Crohn's disease (CD). The research aims to explore the impact of probiotic medication administered during the neonatal period or adulthood on the destruction of experimental ovalbumin- (OVA-) induced asthma [85]. Neonatal or adult mice were subjected to OVA-induced allergies after receiving orally delivered probiotic bacteria. Both cohorts underwent assessment for asthma-like symptoms, analysis of microbiota composition, and determination of the frequencies of total CD4+ T lymphocytes and CD4 + Foxp3+ regulatory T (Treg) cells. The delivery of probiotics to newborns, as opposed to adults, was both necessary and effective in completely preventing allergen-induced sensitization in animals. The findings indicate that tolerance acquired during the neonatal period, which can be transferred to adult recipients who have not received probiotics, is linked to changes in the composition of gut bacteria, advanced stages of butyrate in the cecum, and specific accumulation of regulatory T cells in the airways. The results suggest that there is an interaction among a diverse microbiota and specific structures of neonatal T cells, specifically in the Treg cell subset [86]. This interaction may contribute to the positive impact of exposure to probiotic bacteria during the perinatal period on the establishment of long-term tolerance to allergens.

3.8. Probiotics against Diabetes. Diabetes mellitus is a persistent metabolic disorder categorized by a range of severe consequences, mostly driven by glycemic indicators. Moreover, diabetes has been recognized as a prominent contributor to disability-adjusted life years (DALYs), with the actual burden surpassing anticipated levels in certain geographical areas [87]. Type 1 diabetes (T1D) is a persistent autoimmune disorder distinguished by the immune-mediated death of pancreatic beta cells responsible for insulin secretion [88]. There is a growing body of research indicating a positive correlation between the intake of probiotics and the metabolic profile of individuals with diabetes. One of the suggested main pathways might potentially include the augmentation of glucagon-like peptide 1 (GLP-1) production from enteroendocrine L-cells to improve carbohydrate metabolism, mitigate the harmful effects of excessive glucose levels, and raise the responsiveness of target cells to insulin. Additional proposed pathways for the impact of probiotics on diabetes including anti-inflammatory, antioxidant, and immunomodulatory properties, and changes in the expression of genes associated with diabetes. Furthermore, the ingestion of probiotics has been shown to affect the composition of the gastrointestinal

microbiota, potentially leading to enhanced integrity of the intestinal epithelium, compromised immunological responses, and reduced activation of the toll-like receptor 4 pathway. Consequently, this can result in a decrease in proinflammatory signaling and an improvement in insulin sensitivity. The probiotics exhibit diverse effects depending on factors such as dose, length of therapy, and mode of delivery. The gut microbiota's impact on metabolic diseases, such as diabetes, and its ability to improve the host's metabolism have led to a growing interest in the manipulation of the gut microbiota in recent times [87].

Research was conducted to see if the probiotic *Escherichia coli* Nissle 1917 (EcN) may reduce the enlargement of the heart that is caused by diabetes. Five-week-old, 27119.4-gram male Wistar rats were given streptozotocin to cause diabetes. After that, for 24 days, the rats were fed EcN through oral gavage at a dosage of 109 cfu/day. To evaluate heart parameters, an echocardiogram was performed. Activation of the MAPK, ERK, and JAK2 signaling pathways was seen in streptozotocin-induced diabetic rats with IL-6 overexpression. Hypertrophy indicators such as atrial and B-type natriuretic peptides were also elevated due to the increased expression of calcineurin, NFATc3, and p-GATA4. Researchers found that when diabetic rats were given the probiotic EcN, IL-6 expression was significantly decreased. Additional research has shown that EcN supplementation in diabetic rats significantly attenuated eccentric hypertrophy and MAPK signaling (phosphorylated MEK, ERK, JNK, and p-38) [89]. The probiotic EcN may have cardioprotective effects when used to treat diabetes-related cardiomyopathies.

Researchers studied 14 different probiotics to determine how they could help people with diabetes. C57BL/Ks rats were utilized in the experiment. Control, metformin, liraglutide, low-dose probiotic, and high-dose probiotic groups were randomly allocated to the rats. Gas chromatography and quantitative real-time PCR were used to calculate the levels of microbiota and short-chain fatty acids (SCFAs). Hematoxylin and eosin (HE) staining and immunofluorescence were used for histomorphological research. Analysis of Bax, Bcl-2, caspase-3, and PI3K/AKT expression was performed using quantitative polymerase chain reaction (PCR) and western blotting. Blood glucose and cholesterol levels improved dramatically after probiotic supplementation, and there were also noticeable morphological changes in the pancreas, liver, and kidneys, as well as a growth in SCFA-generating microbes and SCFAs, and an upregulation of claudin-1 and mucin-2 expression. On the flip side, this resulted in a decrease in the concentrations of *Escherichia coli* and lipopolysaccharide (LPS). In addition, probiotics improved insulin secretion by increasing the activity of G protein-coupled receptor 43/41 (GPR43/41), proglucagon, and proconvertase 1/3. This was accomplished via stimulating glucose-induced production of glucagon-like peptide-1 (GLP-1). The PI3K/AKT pathway may be responsible for mediating this protective function [90]. The antidiabetic benefits of probiotics in mice may be attributable to the stimulation of GLP-1 production, the enhancement of intestinal barrier function, and the promotion of SCFA-producing bacteria.

The incidence of diabetes in nonobese diabetic (NOD) mice was significantly reduced in research examining the effects of a specific mix of probiotics with immunomodulatory capabilities targeting numerous inflammatory illnesses. These mice are widely accepted as a model for investigating human type 1 diabetes (T1D). Diabetes was significantly attenuated in NOD mice when they were given Immune Regulation and Tolerance 5 (IRT5), a probiotic mix including *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus reuteri*, *Bifidobacterium bifidium*, and *Streptococcus thermophiles*. Starting at the age of four weeks, this intervention was given six times weekly for a total of 36 weeks. The beta cell mass increased, and the insulitis score decreased after IRT5 administration. Injecting IRT5 did not alter the overall ratio of regulatory T cells in the body. The number of gut-homing regulatory T (Treg) cells, however, increased dramatically in both the pancreatic lymph nodes (PLNs) and the small intestine lamina propria (SI-LP). There was less of a bias toward Type 1 T helper (Th1) cells in the PLNs after IRT5 therapy [91]. It is suggested that IRT5 might be used as part of a probiotic cocktail to help treat or prevent type 1 diabetes.

3.9. Probiotics in the Prevention of Cardiovascular Diseases. Common cardiovascular diseases include atherosclerosis, cardiomyopathy, arrhythmia, venous thrombosis, and thromboembolic disease. Cardiovascular diseases (CVD or CVDs) are a growing worldwide health issue. In the year 2015, cardiovascular illnesses accounted for a total of 18 million deaths, or about one-third of all recorded causes of mortality. This figure reflects a notable rise of 12.5% compared to the statistics recorded in 2005. According to projections made by the American Heart Association, it is anticipated that by the year 2030, roughly 43.9% of the overall population of the United States will be affected by cardiovascular disease (CVD). At present, cardiovascular disease (CVD) has a prevalence of 92.1 million among adults in the United States. The formation and progression of atherosclerotic plaques in the arterial wall, which are mostly fueled by lipids, characterize the chronic inflammatory disease known as atherosclerosis [92].

Researchers isolated the *Lactobacillus plantarum* DMDL 9010 strain (CGMCC No. 5172) from naturally fermented mustard. Using an in vivo model, the potential advantages of this strain in reducing cholesterol were investigated. Results from the study showed that when *L. plantarum* DMDL 9010 was given to rats at a dose of 10^9 cells per day, total cholesterol (TC), low-density lipoprotein cholesterol content (LDL-C), and the atherosclerosis index (AI) were all significantly decreased by 23.03%, 28.00%, and 34.03%, respectively. However, there was no statistically significant change in blood triglyceride levels after *L. plantarum* DMDL 9010 dosing. *L. plantarum* DMDL 9010 treatment protected hepatocytes against steatosis in rats, as evidenced by morphological and pathological changes in the liver. *L. plantarum* DMDL 9010 was also found to significantly reduce hepatic cholesterol (33.20%) and triglyceride levels (40.86%) when given in large doses. Fecal cholesterol

Table 1: Potential of probiotics against cancers and other diseases.

Disease	Type of study	Intervention	Results	Reference
Brain cancer	*In vivo*; SAMP8 mouse model	Oral administration of probiotic supplement *Bifidobacterium lactis, Lactobacillus casei, Bifidobacterium bifidum,* and *Lactobacillus acidophilus*, for 12 weeks	Inhibition of NF-kB. Reduced levels of H2AX, 8-hydroxydesoxyguanosine, and RIG-I	[46]
Brain cancer	*In vivo*; pregnant C57/BL6J mice	*Lactobacillus acidophilus* and *Bifidobacterium infantis*. Daily; from embryonic day 16 until weaning	Reduced activation of astrocytes and microglia. Decreased neuroinflammatory activity	[45]
Lung cancer	Clinical	*Clostridium butyricum* along with chemotherapy	Reduction in chemotherapy-induced diarrhea and decreased systemic inflammatory response in patients	[35]
Gastric cancer	*In vivo*; male INS-GAS mice	*Lactobacillus salivarius* and *Lactobacillus rhamnosus* oral administration, 12 weeks	Down regulated NF-κB, IL-17, and TNF signaling pathway	[27]
Gastric cancer	Clinical	*Bifidobacterium infanti*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus*	Improved immunological response, improved immune markers, as in lymphocyte levels and decreased disease severity	[29]
Colorectal cancer	*In vivo*; CT26 cells inoculated into BALB/c mice	*B. longum*, *B. bifidum*, *L. acidophilus*, *L. plantarum*, resistant dextrin, isomaltooligosaccharides, fructose oligosaccharides, and stachyose	Induction of T cell-mediated immune response and reduced tumor volume	[23]
Colorectal cancer	*In vivo*; male fisher 344 rats	5-fluorouracil and *Lactobacillus acidophilus*, *Lactobacillus paracasei, Bifidobacterium lactis*, *Bifidobacterium lactis*, and *Bifidobacterium bifidum*. 10 weeks study	Reduced malignant neoplastic lesions and reduced development of aberrant crypts	[21]
Liver cancer	*In vivo*; Bulb/c mice	*Lactobacillus acidophilus, Bifidobacterium bifidum*, and azoxymethane	Reduced inflammation, and regulation of expression of oncogenes/oncomirs, tumor suppressor genes/ microRNAs	[32]
Liver cancer	*In vivo*; rat model	*Bifidobacterium pseudolongum*	Inhibited IL-6/JAK1/STAT3 signaling pathway via GPR43 activation	[34]
Breast cancer	*In vitro*; MCF-7 cells	*Lactobacillus brevis* MK05	Induction of apoptosis via Lb-PPSPs in MCF-7 cells, positive modulation in the expression of apoptosis pathway mediators, BAX, BCL-2, and BCL2L11	[40]
Blood cancer	*In vitro*; K562 cell line	*L. casei* and *L. paracasei*	Significant anticancer activity in K562 cells	[50]
Gastric ulcer	Clinical	Ilaprazole, amoxicillin, metronidazole *Bifidobacterium, Lactobacillus,* and *Enterococcus*	Higher clearance rate of *Helicobacter pylori* and lowered reoccurrence rate	[65]
Antibiotic-associated diarrhea	Clinical; children, adolescents, and adults	Alkali *Halobacillus clausii* 088AE	Reduction in the severity across all age groups	[74]
Diabetes	*In vitro*; C57BL/Ks rats	14 different probiotics included in diet	Improved insulin secretion via increased activity of GPR43/41, proglucagon, and proconvertase 1/3	[90]
Cardiovascular diseases	*In vivo*; rats model	*Lactobacillus plantarum* DMDL 9010 at 10^9 cell per day	Decreased blood and total hepatic cholesterol and triglyceride levels	[93]

SAMP8, senescence-accelerated mouse susceptible 8; GPR43/41, G protein-coupled receptor 43/41.

(+31.07%) and bile acid (+70.18%) were also significantly increased. A decrease in blood and total hepatic cholesterol and triglyceride levels and an increase in bile acid excretion via feces were seen following treatment with *L. plantarum* DMDL 9010. These results appeared to be dose-dependent upon *L. plantarum* DMDL 9010 [93].

In another study, rats were given oral doses of four different bacterial strains thought to possess probiotic qualities; these were *Bifidobacterium breve*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Lactobacillus acidophilus*. The dosage was 2106 CFU/mL. Isoproterenol was used to generate infarct-like myocardial damage in the rats after they had been given this treatment for 14 days. Researchers catheterized the right carotid artery and the left ventricle 24 hours after myocardial infarction to obtain blood pressure and cardiac parameters. The investigation culminated in histological, biochemical, and tumor necrosis factor-alpha (TNF-α) evaluations of the heart. This was shown by a higher LV end-diastolic pressure and lower LV systolic pressure, LV dp/dt max, LV dp/dt min, and blood pressure compared to rats with normal cardiac function. The use of live probiotics before treatment led to a decrease in lipid peroxidation and TNF- levels and an increase in cardiac function [94]. The facts demonstrate the cardioprotective effect of live probiotics in a rat model of infarct-like myocardial infarction by blocking TNF- and oxidative stress-induced damage. Supplemental usage of probiotics may help persons at risk of developing ischemic heart disease avoid its devastating effects. Table 1 shows the health potential of probiotics against cancers and other diseases.

4. Conclusion

In conclusion, probiotics, consisting of various microbes such as *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and others have demonstrated substantial potential in addressing a wide range of health conditions. This comprises SCFAs and inhibitory proteins such as polysaccharides and nucleic acids as well as the anticancer impact of probiotics. Several studies have indicated their effectiveness in countering cancers, antibiotic-associated diarrhea, alleviating upper respiratory tract infections, mitigating autoimmune and allergic conditions, various ulcers, and even preventing cardiovascular disease and diabetes. Studies have shown that probiotics can help the treatment of cancers via various pathways, i.e., inhibition of NF-kB, reduced levels of H2AX, 8-hydroxy deoxyguanosine, RIG-I, downregulation of IL-17, and TNF signaling pathway and more. In the context of antibiotic-associated diarrhea, studies have indicated the ability of probiotics to restore gut microbiota balance, ultimately reducing the prevalence and severity of diarrhea associated with antibiotic use. Also, in upper respiratory tract infections, probiotics have shown beneficial effects in reducing symptoms, particularly in children by enhancing immune response and modifying gut microbial composition. Probiotics have also displayed potential in managing autoimmune and allergic conditions like atopic dermatitis, multiple sclerosis, and allergies with mechanisms including immunomodulation and gut microbiota modification. Certain strains have demonstrated the ability to reduce cholesterol levels, protect hepatocytes, and decrease cardiovascular and atherosclerotic risk factors. Further research is needed to advance the understanding of intricate interactions between probiotics, the gut microbiota, and various physiological systems; the available *in vivo* and *in vitro* studies point to a promising future for probiotics as a valuable addition to healthcare strategies aiming to enhance human health and prevent cancer and other diseases [95–98].

Data Availability

The review data used to support the findings of this study are included in the article.

Conflicts of Interest

The authors reported that there are no conflicts of interest.

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