

# Probiotics as a Sustainable Approach in Health Enrichment

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## Abstract

In recent years, the scientific community has paid closer attention to the dynamics involved in metabolic and inflammatory diseases. Clinicians and researchers are confronting new challenges as a result of these rapidly spreading diseases with epidemic dimensions. A unique strategy that might shift the gut microbiota's composition, improve food absorption, and modify the immune system in a way that would alleviate the disease was required to avert these dysbiotic conditions. The therapeutic effects of conventional probiotics were enhanced by the concurrent administration of prebiotics, synbiotics, and postbiotics. The sustainability characteristics of probiotic formulations lead to their use in a wide range of human health conditions, from digestive problems to cognitive impairment. Probiotics were created as a long-term approach to healthcare to increase individual well-being.

**Keywords:** Probiotics, Prebiotics, Synbiotics, Postbiotics, Psychobiotics, Probiogenomics

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## INTRODUCTION

Probiotics are live bacteria that, when provided in adequate amounts, can benefit the host's health. Probiotics have a long history that dates back to the start of civilisation, when people began eating fermented foods.<sup>1</sup> When commonly administered antibiotics fail to treat diseases, probiotics are the second-most effective immune defense method.<sup>2</sup> *Bifidobacterium*, *Enterococcus*, and *Lactobacillus* are among the beneficial intestinal bacteria that contribute to gut microbiota stability. Probiotics can assist several aspects of human health, including antimicrobials, lactose intolerance, diarrheal disorders, ulcer treatment, immunological activation, food preservation, colon cancer, and others.<sup>3</sup> Bacteriocins are ribosomally produced antimicrobial peptides that have an antagonistic spectrum against pathogenic bacteria such as *Bacillus*, *Clostridium*, *Listeria*, *Staphylococcus*, and others.<sup>4</sup> Bacteriocins from probiotic bacteria have become more important due to their safe application in foods, medicines, veterinary, and human treatments.<sup>5-7</sup> Lactic acid, organic acids, acetic acid, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and bacteriocins which are derived from probiotics can suppress foodborne pathogens like *Escherichia coli*, *Listeria monocytogenes*, and *Salmonella* spp. Furthermore, probiotic bacteria can release substances known as postbiotics such as butyrates, which may benefit the host.<sup>8</sup> *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Synergistetes*, *Fusobacteria*, and *Verrucomicrobia* are the dominating bacterial phyla in the gut. Fungi and Archaea represent up to 1% of the species of the human gut microbiota. *Bacteroides* sp., *Blautia* sp., *Bifidobacterium* sp., *Clostridium* sp., *Faecalibacterium* sp., *Prevotella* sp., and *Ruminococcus* sp. are highly abundant bacterial genera in breast-fed infants.<sup>9</sup> All of these probiotic strains with prognostic effects on various diseases were produced as viable candidates, with the expectation of a long-term strategy for disease care.

### Benefits of Probiotics

*Lactobacillus* and *Prevotella*, two vaginal-associated microorganisms, predominate in the gut of vaginally delivered newborns. Preterm infants

have delayed gut colonisation with commensal anaerobic microorganisms like *Bifidobacterium* or *Bacteroides*. Instead, they have much more *Enterobacteriaceae*, *Enterococcus*, and other opportunistic pathogenic microorganisms in their faeces than full-term neonates.<sup>10</sup> *Limosilactobacillus reuteri* (*L. reuteri*) DSM 17938 is the most thoroughly explored probiotic for paediatric functional abdominal pain problems. In the clinical trials, both the probiotic and placebo groups had a significant reduction in pain frequency. In comparison, only the probiotic group experienced a substantial reduction in pain severity.<sup>11</sup> *L. reuteri* DSM 17938 could alleviate infantile colic in breastfed infants. *Lactocaseibacillus rhamnosus* GG can effectively treat paediatric functional constipation.<sup>12</sup> The probiotics *Lactobacillus acidophilus*, *Lactobacillus crispatus*, *Lactocaseibacillus casei*, *Limosilactobacillus fermentum*, *Lactobacillus gasseri*, *Limosilactobacillus reuteri* RC-14, *L. rhamnosus*, and *Ligilactobacillus salivarius* are the most frequently utilized for modifying reproductive dysbiosis. Clinical studies have demonstrated that these probiotics can effectively treat bacterial vaginosis (BV) and regenerate vaginal microecology.<sup>13</sup> A topical gel containing *L. rhamnosus* Lcr35 has already shown promising results in the treatment of vulvovaginal candidiasis.<sup>14</sup> Probiotics such as *L. rhamnosus* GG or *Saccharomyces boulardii* are recommended for reducing antibiotic-associated diarrhoea (AAD). If probiotics are used to prevent diarrhoea caused by *Clostridioides difficile*, *S. boulardii* is recommended.<sup>15</sup>

Several approaches including *in vitro*, *in vivo*, and genomics approaches, were developed to find novel probiotic strains successfully. Following *in vitro* or *in vivo* testing, suitable probiotics are chosen based on their effects on fundamental host functions such as bile tolerance or the acidic environment of the stomach, as well as more complicated host functions such as immunological development, metabolism, or gut-brain interactions. Genome sequencing will make it possible to quickly identify and eliminate potentially dangerous strains due to the presence of virulence or antibiotic-resistance genes.<sup>16</sup> *L. reuteri* is a probiotic strain that was found to be an adjuvant of standard medications in the control

of *Helicobacter pylori* infections. *L. reuteri* can colonize the gastric mucosa despite the bile and acidic environment of the stomach.<sup>17</sup> This species can block the growth of a range of pathogenic bacteria via numerous ways, hence maintaining the microbiota's homeostasis. Reuterin and reutericycline have antibacterial activity.<sup>18</sup> Lactic acid bacterial species in kefir is *Lentilactobacillus kefir*. Several *L. kefir* strains are tolerant of the harsh gastrointestinal environment, and lack transmissible antibiotic resistance genes.<sup>19</sup> Numerous scientific studies have demonstrated the possibility of enhancing the safety of dairy probiotic meals by using innovative probiotic strains generated from conventional fermented foods. Incorporating *Lactococcus lactis* strains from fruits, herbs, and vegetables into cheese successfully inhibits *Listeria monocytogenes*, a well-known food borne pathogen. Similarly, *Weissella cibaria* D30, which was isolated from Korean kimchi, was successfully used as a biopreservative in cottage cheese.<sup>20</sup> *Lactiplantibacillus plantarum* HD1 isolated from Korean kimchi has the potential to be employed to prevent mycotoxin development and fungal rot in the food. Multiple strains of *Lb. plantarum* isolated from Korean kimchi were discovered to have anti-cavity and anti-metabolic disorder properties.<sup>21</sup> Two probiotics isolated from pickles, *Pediococcus acidilactici* 004 and *Lb. plantarum* 152, have greater antidiabetic scores than *L. rhamnosus* GG, indicating that these two strains could be promising anti-diabetic probiotics.<sup>22</sup> Next-Generation Probiotics (NGP) will need to possess in-depth knowledge of the diseases they are targeting as well as bacterial genetic and physiological aspects, such as growth dynamics and antibiotic susceptibility patterns.<sup>23</sup> Furthermore, it's essential to understand the underlying molecular ameliorative pathways. To accomplish this, it is necessary to perform strict functional validation of the novel probiotics following screening and isolating the NGP using cutting-edge next-generation sequencing (NGS) and bioinformatics technology platforms.<sup>24</sup> In addition to *Lactobacilli* and *Bifidobacterium*, which have the most probiotic strains, *Akkermansia muciniphila*, *Eubacterium hallii*, and *Faecalibacterium prausnitzii* have emerged as candidates for next-generation probiotics (NGPs), which hold great promise for the

prevention and treatment of dysbiosis-related ailments (Table 1 & Figure 1).<sup>25</sup> Despite the absence of endotoxemia, *Akkermansia muciniphila* is an aerotolerant anaerobic bacterium with Gram-negative features. Several metabolic and inflammatory disorders, including obesity, type 2 diabetes (T2D), and inflammatory bowel syndrome, have been linked to a reduction in *A. muciniphila* in the gut.<sup>26</sup> *A. muciniphila* can reduce the gut barrier integrity due to its mucin-degrading nature.<sup>27</sup> *Faecalibacterium prausnitzii* is an anaerobic, mesophilic, Gram-positive bacterium with the ability to produce a diverse range of short-chain fatty acids (SCFAs) such as acetate, butyrate, formate, and D-lactate via the glycolytic pathway from the digestion of insoluble carbohydrates and dietary fibres.<sup>28</sup> *F. prausnitzii* has been discovered to stimulate the creation of mucin and tight-junction proteins. This demonstrates the degradation of gut mucosal integrity in subjects with low levels of this bacterium.<sup>29</sup> *Eubacterium hallii* is a Gram-positive, strictly anaerobic bacterium found in both human and mouse faeces. This bacterium can produce butyrate from lactate and acetate in a low-pH environment.<sup>30</sup> Because lactic acid buildup is linked to a variety of intestinal diseases, this bacterium plays an important function in maintaining intestinal metabolic equilibrium.<sup>25</sup> The most significant and well-established health benefits of probiotics are their ability to prevent diarrhea and constipation, alter the conjugation of bile salts, increase antibacterial activity, and function as an anti-inflammatory component. In addition, probiotics are known to exert anti-oxidative activity in the form of intact cells or lysates and help increase nutrient bioavailability.<sup>31</sup> Probiotics have also been beneficial in treating the symptoms of allergies, cancer, AIDS, lung infections, and urinary tract infections. Their positive effects on aging, fatigue, autism, osteoporosis, obesity, and type 2 diabetes (T2D) have been reported infrequently.<sup>32</sup> Several mechanisms are assumed to be linked to the therapeutic benefits of probiotics, as demonstrated below: a) production of inhibitory compounds such as H<sub>2</sub>O<sub>2</sub>, bacteriocins, organic acids, etc. b) preventing pathogenic microorganisms from adhering to specific receptors by blocking them, c) competition for nutrition with the pathogenic bacteria, d) toxins being broken down and toxin

**Table 1.** Impact of Next-Generation Probiotics (NGP) on the human diseases

Species	Mode of Action	Diseases treated	Ref.
<i>Akkermansia muciniphila</i>	Increases enterocyte monolayer integrity by promoting colonic mucus turnover and lowering LPS uptake.	Inflammation	[117]
	It negatively correlated with intestinal permeability, metabolic endotoxemia, inflammatory biomarkers and low grade induced metabolic disorders such as type 2 diabetes and insulin resistance with additional increased macrophage infiltration into the adipose tissue and hepatic steatosis.	Metabolic disorders	[118]
<i>Faecalibacterium prausnitzii</i>	Ameliorates metabolic endotoxemia-induced inflammation (via restoration of the gut barrier endotoxemia); Reduction of the expression chemokines and the adhesion molecules MCP-1, TNF- $\alpha$ , and ICAM-1, along with decreased aortic infiltration of macrophages.	Atherosclerosis	[119]
	Increases fatty acid oxidation, hepatic adiponectin signaling and insulin sensitivity.	Diabetes/Obesity	[120]
	Reversed effect of Concanavalin A, through the decrease of pro-inflammatory cytokines (IL-2, IFN- $\gamma$ , IL-12p40) and hepatocellular apoptosis.	Hepatic Diseases	[121]
	Negative correlation with intestinal inflammatory disorders.	Inflammation (IBS, IBD, Crohn's disease, ulcerative colitis)	[122]
<i>Eubacterium hallii</i>	Positive correlation explained by the increased abundance of <i>F. prausnitzii</i> F6 in atopic dermatitis.	Skin Diseases	[123]
	Negative correlation in chronic heart failure older patients.	Cardiac diseases	[124]
	Butyrate and propionate production.	Inflammation of the gut	[125]
<i>Bacteroides fragilis</i>	Reduces PhIP bioavailability.	Colon detoxification	[126]
	Improves insulin sensitivity. Increases energy expenditure.	Diabetes/Obesity	[127]
	PSA boosts CD4+FoxP3 T cells after direct interaction with APC cells like plasmacytoid dendritic cells.	Inflammatory diseases like abscesses, neuro-inflammations, and cancers.	[128] [129] [130]
<i>Bifidobacterium</i> spp	Enhance DC and CD8 <sup>+</sup> T cells functions.	Enhance the efficacy of immune checkpoint inhibitors in cancer therapy.	[131]
<i>Prevotella copri</i>	Production of succinate, a TCA cycle intermediate.	Ameliorate prediabetes syndromes.	[132]

receptors being blocked, and e) immune responses being regulated.<sup>31</sup> According to recent studies, probiotics may be used to treat irritable bowel syndrome (IBS), diabetes, cancer, and human immunodeficiency virus infection, among other illnesses.<sup>33</sup>

### Nutritional Aspects of Probiotics and Prebiotics

Some organic acids, for instance, are the main by-products of host microbes' fermentation of dietary fiber or non-digestible carbohydrates. Acetate (C2), propionate (C3), and n-butyrate (C4) are the primary short chain fatty acids (SCFAs) produced primarily in the colon (in humans) and caecum (in rodents) as a result of numerous bacterial metabolic pathways. These SCFAs are essential for intestinal health, and as a result, their activity can impact areas outside the gut. Different SCFAs serve different purposes.<sup>34</sup> Prebiotics can assist in providing sufficient nutrients to the disturbed microflora. It can promote the growth of beneficial microorganisms, which favourably impacts health.<sup>35</sup> According to research on neonates, the presence of some fructo- and galactooligosaccharides aids the multiplication of *Bifidobacteria* and lactobacilli in their stomach.<sup>36</sup> Prebiotics can aid patients with

irritable bowel syndrome (IBS) by keeping the altered microbiota in balance, which helps to alleviate symptoms. Patients with IBS experience reduced stomach pain, bloating, and flatulence when prebiotics with probiotics, also known as synbiotics given as part of a diet.<sup>37</sup> Modifying lipid metabolism can enhance calcium absorption, which benefits both the intestinal and immune systems. Because of their structure and chemistry, they can be used by specific bacteria as a carbon and energy source.<sup>38</sup> Several models that demonstrate the prebiotic effect in diverse bodily locations have been developed. Regulation of the hepatic lipogenic enzyme can increase the output of SCFAs like propionic acid and butyric acid from fermentation.<sup>39</sup> Fiber fermentation is regulated by an individual's microbiota as well as the existence of keystone species. People who did not contain *Ruminococcus bromii* in their microbiota had a decreased ability to ferment the additional resistant starch.<sup>40</sup> Prebiotics nourish beneficial microbes, making it more difficult for pathogens to adhere to the epithelium.<sup>41</sup> SCFAs are produced as a by-product of glucose metabolism, which can also result in pathogen-inhibiting metabolites and a decrease in intestinal pH.<sup>35</sup> Individuals with small intestine (SI) diseases who



**Figure 1.** Mode of action of Next Generation Probiotics

**Table 2.** Different lactic acid bacteria involved in colon and cervical cancer treatment

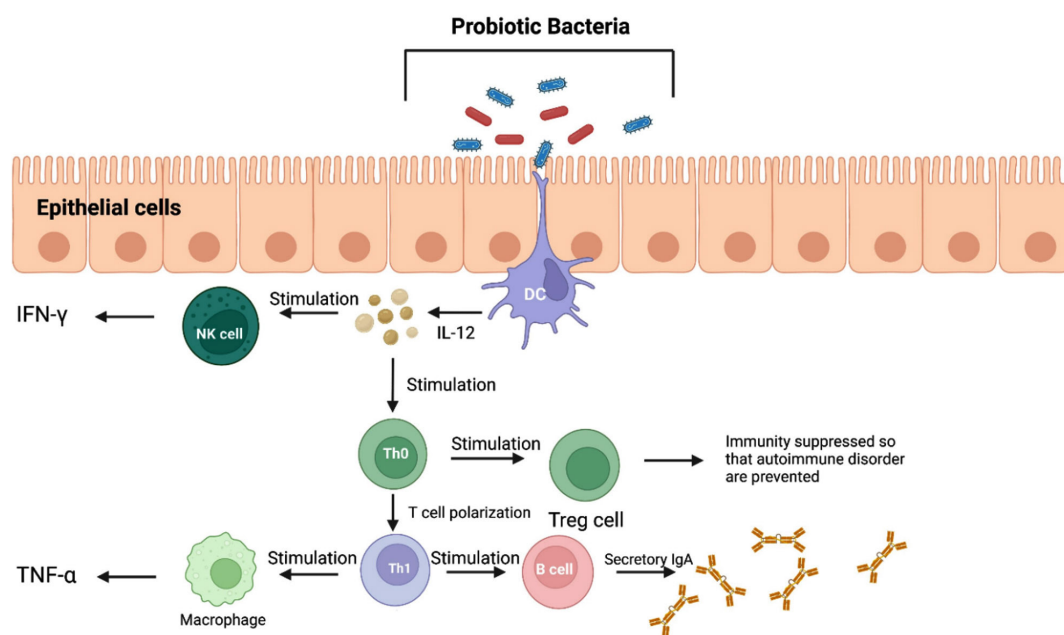
Lactic acid Bacteria	Research conducted on	Type of Cancer	Mechanism/Outcome	Ref.
<i>Lactocaseibacillus rhamnosus</i> GG	Caco-2 cell line.	Colorectal	Levels of IL-8 decreased	[133]
<i>Lactocaseibacillus casei</i> ATCC393	CT26(murine colon carcinoma cell lines); HT29 (human colon carcinoma cell lines)	Colorectal	Anti-proliferative activity. Live <i>L. casei</i> induced apoptotic death of CT26 and HT29 cells.	[89]
<i>Lactobacillus acidophilus</i>	Rats DMH-induced CRC model	Colon	Decreasing the incidence, number and size of tumors. Significant reduction in DNA damage. Increased TLR-2 expression and decreased TLR-4 expression, caspase 3, COX-2, and $\lambda$ -catenin	[134]
<i>Lactiplantibacillus plantarum</i>	Wistar albino rats HeLa cell line	Colon Cervical cancer	Reduced concentration of bile acid and bacterial enzymes. Increased level of TNF-alpha in the serum and the number of bacteria of the <i>Lactobacillus</i> genus. Suppression of proliferation and induction of apoptosis	[135] [136] [137]
<i>Bacillus coagulans</i>	COLO 205 cell line	Colorectal cancer	Cytochrome release and caspase-3 activity increased.	[138]
<i>Streptococcus thermophilus</i>	HT-29 cell line	Colorectal cancer	Increase in folate	[139]
<i>Enterococcus faecium</i> RM11	Caco-2 cell line	Colorectal cancer	Cell apoptosis	[140]
<i>Bifidobacterium bifidum</i>	Rats	Colon	Increased TLR-2 expression and decreased TLR-4 expression, caspase 3, COX-2, and $\lambda$ -catenin	[135]

have poor absorption have distinct microbiome profiles. Firmicutes, Collinsella, Actinobacteria, and Bacteroidetes were reduced in *inflammatory bowel disease* (IBD) children.<sup>42</sup> The microbiome absorbs nutrients, especially lipids, which can lead to over- or under-nutrition.<sup>43</sup> Diets rich in polyphenols, fibre, and whole plant sources are associated with higher quantities of commensal bacteria in the microbiome and higher levels of biodiversity in faecal samples.<sup>44</sup>

### Genomics of Probiotics and Prebiotics-Probiogenomics

Several probiogenomic projects have been undertaken to characterise the genetic and metabolic properties of a subgroup of the species *Bifidobacterium*. The genomic sequencing of *Bifidobacterium longum* subsp. *infantis* ATCC 15697 reveals features that explain this strain's ability to digest certain human milk oligosaccharides (HMO).<sup>45</sup> A gene cluster that encodes different glycosyl hydrolases and carbohydrate transporters required for importing and metabolizing HMOs is found explicitly in the *B. longum* subsp. *infantis* ATCC 15697 genome. The genome of this microbe

also includes genetic loci that encode fucosidases and sialidases in addition to a complete urease operon. This operon is believed to be involved in the metabolism of urea, an essential source of nitrogen for milk.<sup>46</sup> The complete decoding of the *B. bifidum* PRL2010 genome revealed fresh information on the metabolic mechanisms used by this strain to digest mucin-derived sugars.<sup>47</sup> These data support the existence of different *B. bifidum* metabolic pathways involved in host-derived glycan consumption. The procedures involve enzymes which eliminate sialic acid and fucose groups from galacto-N-biose (GNB) and its extended derivatives found in different mucin O-glycans.<sup>46</sup> The genome sequencing of *B. breve* UCC2003 provided information about its genetic flexibility to colonization and persistence in the human gut by means of the generation of type IVb (or Tad) pili-family structures that mimic fimbria.<sup>48</sup> An array of genes encoding enzymes specific to the metabolism of typical milk-derived sugars and other carbohydrates can be found in the genomes of the usual milk-adapted *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Lactobacillus helveticus*. The occurrence of a bile salt hydrolase



**Figure 2.** Modulation of host immune system by probiotics. NK cell- Natural Killer cell, IFN-γ – Interferon-γ, DC – Dendritic cell, Th – T-helper cell, TNF-α – Tumor Necrosis Factor-α, Treg – T-regulatory cell, IgA – Immunoglobulin-A

(BSH) gene in intestinal *Lactobacillus* supports unique adaptation to the human gut. The genome of *L. plantarum* WCFS1 showed many secreted proteins that are thought to play a role in adhesion to mucins and collagen found in the host.<sup>46</sup> AI-2, an interspecies signalling molecule produced by *Bifidobacteria*, is a quorum-sensing molecule.<sup>49</sup>

### Probiotics in Oral Health

The potential use of probiotics in treating dental disorders and preserving oral health is an increasing topic of attention. Lactobacilli and *Bifidobacteria*, the natural occupants of the gut, have been discovered to be active against a wide range of oral disorders. Apart from the classic probiotic contenders, several other bacterial species were found to be effective against oral diseases. For instance, *Streptococcus salivarius* has been shown to be effective against *Streptococcus pyogenes*, the primary causative agent of bacterial pharyngitis. Additionally, studies have shown that *S. salivarius* effectively treats halitosis, pharyngitis, and tonsillitis by lowering their frequency.<sup>50</sup> *Candida albicans* development in the oral compartment was reported to be inhibited by *S. salivarius*.<sup>51</sup> Antimicrobial drugs that induce gastrointestinal side effects due to broad-spectrum antibiotics, bacterial resistance, and allergic responses may be required to treat specific conditions or their consequences.<sup>52-53</sup> Probiotic activity in more widespread indigenous oral strains related with the tongue should be evaluated to aid in colonisation and preserve healthy tongue ecology.<sup>54</sup> Probiotics may benefit in the control of microorganisms associated with dental caries and periodontitis by generation of NO in oral cavity through nitrate reduction and upregulation of synthase activity. However, the role of NO is both advantageous as an antibacterial agent and detrimental concerning its inflammatory effects if present in large amounts. *Bifidobacterium* spp., *Lactocaseibacillus casei*, *L. rhamnosus*, and *Limosilactobacillus reuteri* have been found to have the ability to modify the colonisation of cariogenic bacteria and prevent dental caries.<sup>55</sup>

### Probiotics in Gut-Liver Axis -Non-Alcoholic Fatty LiverDisease

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent cause of chronic liver disease

in children and adults in industrialized countries.<sup>56</sup> The intimate anatomical and physiological connection between the liver and the gastrointestinal system is called the gut-liver axis. Transferring molecules linked with intestinal microbiota (IM) to the liver is part of the two organs' interaction.<sup>57</sup> Probiotic bacteria seem to be shielded by the microencapsulated structure, in which they are confined in a coating substance until they reach the gut targets.<sup>56</sup> Numerous physiological investigations have demonstrated that, depending on the situation, probiotics may enhance or alter intestinal barrier function. For instance, the activation of tight junction (TJ) proteins by *Streptococcus thermophilus* and *Lactobacillus acidophilus* helps to avoid the emergence of a condition termed "leaky gut".<sup>58</sup> *L. rhamnosus* GG can suppress inflammation of intestinal epithelial cell lining through alteration of expression of the TJ proteins occludin and zonula occludens (ZO).<sup>59</sup> The intestinal barrier's function may be restored by administering probiotics such as *L. casei* DN-114001 and VSL#3 (a combination of pre- and probiotics) through over expression of ZO-2 and protein kinase C in TJs.<sup>56</sup> VSL#3 (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, and *Streptococcus salivarius* subsp. *thermophilus*) significantly decreased oxidative damage, protein nitrosylation, and tissue TNF- $\alpha$  level in rats with high-fat diet (HFD)-induced NAFLD and increased the expression of peroxisome proliferator-activated receptor (PPAR), indicating that it can control inflammation and oxidative damage. The probiotic may reduce dietary fat absorption because the treatment significantly reduced blood and liver triglyceride concentrations, which were connected to a reduction in body fat mass but not hepatic fat mass.<sup>60</sup> Probiotics and synbiotics can help persons with NAFLD by restoring gut microbiota (GM) balance and reversing dysbiosis. Probiotics and synbiotics reduce inflammation by modulating nuclear factor kappa B (NF- $\kappa$ B) and tumour necrosis factor (TNF) (Figure 2). The antifibrotic effects are mediated by the modulation of transforming growth factor- $\beta$  (TGF- $\beta$ ) and collagen expression. Hepatic lipid deposition, endotoxemia, and oxidative stress are other mechanisms by which



the protective effects of probiotics and synbiotics are reduced.<sup>61</sup>

### Psychobiotics in Gut-Brain Axis

The gut microbiota affects the brain, albeit the exact process is unknown. In one experiment, the fecal microbiotas from depressed patients were transferred to germ-free (GF) rats. These rats later expressed a dysregulated microbiota and exhibited anxious behaviors, indicating a sort of 'transplanted' depression in these rats.<sup>62</sup> An improvement in psychosocial behavior was reported in a fat mass surplus group of people who underwent weight loss dietary treatments involving psychobiotics.<sup>63</sup> Reports indicate that psychobiotics may be chronically administered to normalize behaviors associated with anxiety and depression. *B. longum* 1714 strain was found to have beneficial effects on cognition, behavior, and physiological response in stressed mice.<sup>64</sup> Apart from this, *L. rhamnosus* JB-1 was found to reduce the corticosterone levels induced by anxiety in mice. Psychobiotics can be used to treat patients with Autism Spectrum Disorder (ASD), which has been linked to a deviation in the microfloral proportions, particularly levels of *Prevotella*, and *Clostridium*.<sup>65</sup> In addition, Tourette's syndrome, a neurological condition marked by uncontrollable, repeated movements and vocalizations known as "tics," and attention deficit hyperactivity disorder (ADHD) may both benefit from psychobiotic treatment. A recent study found that fecal transplantation may help a patient with Tourette's syndrome, but further research is still essential.<sup>66</sup> Psychobiotics function by involving the vagus nerve and numerous metabolites such as SCFAs, enteroendocrine hormones, cytokines, and neurotransmitters such as  $\gamma$ -aminobutyric acid (GABA), and glutamate.<sup>67</sup> The gut-brain axis is a bidirectional signaling pathway that connects the gut and the brain. The neuroendocrine system, neuroimmune system, autonomic nervous system (sympathetic and parasympathetic arms), enteric nervous system (ENS), and gut microbiota are some of the communication pathways between the gut and brain/central nervous system (CNS).<sup>62</sup> Gut microbiota constantly interacts with the brain via various pathways, including immune regulation, metabolism of neurotransmitters, SCFAs, and vagal afferents.<sup>68</sup> Furthermore, the

gut microbiota influences stress response by modulating the hypothalamic-pituitary-adrenal axis (HPA axis), and various probiotics modulate stress cortisol responses.<sup>69</sup> Butyrates are required for the integrity of the intestinal barrier and have an effect on the CNS through modulating the expression of brain-derived neurotrophic factor (BDNF). These SCFAs have been discovered to be less prevalent in psychiatric illnesses, such as depression.<sup>68</sup>

### Probiotics in Women and Urogenital Health

Lactobacilli protect the vagina against pathogenic microorganisms through secretion of organic acids, bacteriocins, and  $H_2O_2$ , and production of a biofilm on the surface of the vaginal mucosa.<sup>70,71</sup> Probiotics can be taken orally as a probiotic food supplement, delivered intravaginally as vaginal suppositories, or administered externally as a paste to replace the vaginal microbiota and modulate the local mucosal immune response. Probiotic bacteria have been shown to have inhibitory activity for bacterial vaginosis (BV) and aerobic vaginitis (AV). *L. acidophilus* GLA-14 has the most significant antagonistic effects against anaerobic strains such as *Gardnerella vaginalis* and *Atopobium vaginae*.<sup>72</sup> The most common bacteria to be isolated from a healthy human vagina are those belonging to the genus *Lactobacillus*, including *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners*, and *Lactobacillus jensenii*.<sup>73</sup> These vaginal lactobacilli have been proposed as a means of preventing pathogen invasion by limiting their population. However, the disruption of the vaginal ecology promotes the development of microorganisms that result in severe vaginal illnesses such as vulvovaginal candidiasis (VVC), bacterial vaginosis, and sexually transmitted infections (STIs).<sup>74</sup> A growing number of investigations have established the primary probiotic benefits of *Lactobacillus* against pathogens colonizing in the oral cavity, epidermal layer, GI tract, and vagina. It has been demonstrated that *L. acidophilus* KS400 produces bacteriocin by fermentation and inhibits the growth of pathogens that affect the urogenital system, including *Gardnerella vaginalis*, *Streptococcus agalactiae*, and *Pseudomonas aeruginosa*.<sup>75</sup> A bacteriocin from vaginal *L. rhamnosus* (Lactocin 160) was also able to form temporary holes on

the cytoplasmic membrane of *G. vaginalis* by collapsing the pathogen's chemiosmotic potential. Numerous investigations have also demonstrated that the vagina frequently harbors microorganisms that cause inflammatory vaginitis and cause aerobic vaginitis (AV), including *Escherichia coli*, *Enterococcus faecalis*, *S. agalactiae*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*.<sup>76</sup> Drug resistance may occur due to prolonged vaginal treatment with antimicrobial treatment. As a result, substantial research is being conducted on a probiotic lactobacilli-based technique as a potential substitute for current antibiotic therapy.<sup>77</sup>

### Probiotics in Obesity and Weight-Loss

Due to the modern lifestyle, obesity is a severe public health issue spreading globally. By 2030, 20% of adults are predicted to be obese, with 38% of adults being overweight. Numerous factors contribute to the development of obesity, which has a wide variety of etiologies. Through direct connections with proximal organs or indirect contacts with distant organs via metabolic products (mostly SCFAs), the gut microbiota contributes to the development of obesity.<sup>78</sup> Regulating the gut microbiota through varied diets and supplementation with probiotics and dietary fibres is a promising treatment and prevention strategy for obesity. A potential strategy for managing and preventing obesity involves altering the gut microbiota through dietary changes, probiotic supplementation, and dietary fiber intake.<sup>79</sup> Firmicutes/Bacteroidetes (F/B) ratio contributes significantly in maintaining healthy gut homeostasis. Dysbiosis is either an increase or reduction in the F/B ratio; the former is typically seen with obesity and the latter with inflammatory bowel illness (IBD).<sup>80</sup> With the help of various biochemical and molecular biology techniques, predominantly 16S rRNA gene amplification, studies have looked at the F/B ratio in lean and obese humans and animals. The dysbiotic F/B ratio can be restored, and obesity can be treated or prevented by altering the gut microbiota with various dietary supplements. Probiotics can modify the gut microbiota and lower obesity, whether taken as foods or supplements. The majority of the bacteria in probiotics that have the potential to lower the F/B ratio in obesity are from the

genera lactobacilli and *Bacillus*, and yeasts from the genus *Saccharomyces*. *B. amylolique faciens*, *S. boulardii*, *L. paracasei*, *L. rhamnosus*, *L. sakei*, and *L. salivarius* are probiotics that are involved in reducing body weight and F/B ratio. *L. rhamnosus* GG and *Latilactobacillus sakei* NR28 treatment reduced the F/B ratio in obese mice. In addition, the two probiotic strains lowered epididymal fat mass, acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase-1 activity in the liver. *L. fermentum* KBL374 and KBL375 also reduced pro-inflammatory cytokine levels (IL-1, IL-4, IL-6, IL-13, IL-17A, IFN- $\gamma$ , TNF, CCL2, and CXCL1) while increasing anti-inflammatory cytokine levels (IL-10). Non-toxic commensal *Bacteroides fragilis* has been found as a viable probiotic candidate and provides significant health advantages to the host.<sup>78</sup>

Nonetheless, probiotics are not a panacea for obesity. As previously stated, not all probiotics demonstrated the ability to reduce body weight or provide anti-obesity advantages. Obesity and increased body weight, on the other hand, have been associated to *Limosilactobacillus reuteri*,<sup>81</sup> and certain *Bifidobacteria*.<sup>82</sup> Probiotic strains like *Lactobacillus pentosus* GSSK2 and *Lactiplantibacillus plantarum* GS26A can help reduce obesity.<sup>83</sup> Several studies have shown that the anti-obesity effects of probiotics differed between lyophilized bacteria and live bacteria, as well as between single-strain and multi-strain probiotics.<sup>84</sup> The lyophilized *L. casei* IMVB-7280 was found to have higher anti-obesity properties than the lyophilized *Bifidobacterium animalis* VKB and VKL strains, according to a number of investigations.<sup>85</sup> Additionally, when compared to lyophilized single-strain or multi-strains, the live multi-strains containing *Acetobacter*, *Bifidobacterium*, *Lactobacillus*, and *Propionibacterium* could more effectively reduce obesity, insulin resistance, the production of pro-inflammatory cytokines, and adiponectin levels.<sup>86</sup> It was found that by altering resistant starch with amylosucrase from *Deinococcus geothermalis*, the anti-obesity impact could be enhanced.<sup>85</sup> With regard to mouse models, the probiotic effect on body weight depends on both species and strain. Mice fed with *L. gasseri* SBT2055, *L. plantarum* LG42, *L. gasseri* L66-5, and simultaneous administration of *L. curvatus* HY7601

and *L. plantarum* KY103, were all found to have weight gain-reducing effects. Although several bacteria were studied for weight gain-reducing properties, only *L. rhamnosus* CGMCC 1.3724 delivered positive results for the particular study *in vivo*.<sup>87</sup>

### Probiotics in colorectal cancer

Live complete probiotic strains of *L. fermentum* RM28 and *Enterococcus faecium* RM11 from fermented milk were found to inhibit the proliferation of colon cancer cells in an *in vitro* experiment.<sup>88</sup> Therefore, both probiotics have potential applications in functional foods and CRC treatment and prevention (Table 2). Live *L. casei* ATCC393 and its constituent parts have been shown to have powerful anti-proliferative, growth-inhibitory, and pro-apoptotic properties.<sup>89</sup> It was demonstrated in an *in vivo* investigation by Jacouton et al. that giving C57BL/6 6–8-week-old female mice the dairy strain of probiotic live *L. casei* BL23 may have potential anti-inflammatory and anti-tumor benefits. The anti-proliferative function of *L. casei* BL23 is achieved by the up-regulation of Bik, caspase-7, and caspase-9, and the immunomodulatory potential is mediated by IL-22 cytokine down-regulation.<sup>90</sup> It was established that a potent carcinogen, 1, 2-dimethyl hydrazine, which causes colon tumors in male albino Wistar rats, might be reduced by *L. plantarum* AS1 isolated from fermented food. The synthesis of anti-mutagenic chemicals, possible carcinogen binding and degradation, host immune response development, and impacts on host physiology are some of the mechanisms through which *L. plantarum* AS1 can prevent colon cancer.<sup>91</sup> *L. acidophilus* in the gut stimulates NK cells, a powerful interferon-gamma (IFN- $\gamma$ ) generator crucial for anti-tumor immunity (Figure 2). Thus, *L. acidophilus* inhibits the formation of tumors by activating innate anti-cancer cells. To boost anti-cancer properties, anti-angiogenesis, and NK activity and determine *L. acidophilus*' overall impact on the cellular immune system, it creates IFN- $\gamma$  from splenocytes.<sup>92</sup> Compared to pure live bacteria, animals fed dead Nano-Sized *L. plantarum* showed much less expression of inflammatory markers, mediated the expression of apoptotic markers and the cell cycle in the colon, and increased fecal IgA

levels. Pure live and dead probiotics administered together significantly lowered pro-inflammatory cytokines, inflammatory gene up-regulation, and suppressive potentials compared to administering either group separately.<sup>88</sup> By generating SCFA in the culture media, *Propionibacterium freudenreichii* suppresses cell growth by causing cell death through apoptosis in the colon and stomach cancer cell line. Caspase 3 activation, the generation of free oxygen radicals, and mitochondrial membrane permeability were all detected during this cell death process.<sup>93</sup> The glycolysis pathway, which CRC cells use to generate energy, causes considerable lactate generation in the intestinal environment. *Propionibacterium* produces a lot of SCFA due to this mechanism, also known as aerobic glycolysis or the "Warburg effect," which employs an increase in extracellular lactate to prevent CRC cells from entering the sub-G1 stage.<sup>94</sup> These bacteria generate cytotoxic effects on cancer cells through secretion of certain compounds with cytotoxic effects, and positively regulating the C-fos and C-jun genes in HT-29 and HCT-116 cell lines.<sup>95</sup>

### Synbiotics

The most widely utilized prebiotics include fructans, inulin, galacto-oligosaccharides (GOS), and xylooligosaccharides (XOS). These fibers are known as synbiotics when combined with probiotics to increase the viability of the probiotics. Synbiotic products benefit the host by boosting the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by particularly stimulating the growth and/or activating the metabolic processes of one or a small number of health-promoting bacteria. To help probiotics survive any potential pitfalls, synbiotics were created. The justification for using synbiotics appears to be supported by observations demonstrating an enhancement in the probiotic bacteria's survival during transit through the upper digestive tract. In synbiotic formulations, probiotic strains such *Bifidobacteria* spp.; *B. coagulans*, *Lactobacilli*, and *S. boulardii* are utilized. At the same time, the main prebiotics are fructo-oligosaccharides (FOS), xylooligosaccharides (XOS), inulin, and prebiotics from natural sources like chicory and yacon roots. Human consumption of synbiotics is

said to have the following health benefits: 1) higher abundance of *Lactobacilli* and *Bifidobacteria* levels in gut, 2) enhancement of liver function, 3) enhancement of immunomodulation, 4) lowering bacterial translocation and diminishing the risk of nosocomial infections in surgical patients.<sup>31</sup> Because probiotics are most active in both the small and large intestines, while prebiotics are predominantly absorbed in the large intestine, combining the two substances may have a synergistic impact. Prebiotics are primarily used as a selective medium for the development, the fermentation process, and gastrointestinal transit of probiotic strains. There are shreds of evidence in the literature that probiotic microbes become more resilient to environmental factors, including oxygenation, pH, and temperature in an organism's intestine due to prebiotics.<sup>96</sup> It was found that synbiotics containing *Bifidobacterium lactis*, *L. rhamnosus*, and oligofructose-enriched inulin may manage the intestinal microenvironment more efficiently than prebiotics or probiotics.<sup>85</sup> An example for a randomised clinical trial on the use of synbiotics was performed as: A synbiotic containing five probiotics (*Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactiplantibacillus plantarum*, *Lactobacillus delbrueckii* spp. *bulgaricus*, *L. rhamnosus*) and inulin as a prebiotic in adult subjects with NASH (non-alcoholic steatohepatitis) demonstrated a significant reduction of IHTG (intrahepatic triacylglycerol) within six months of administration.<sup>96</sup>

#### Development of probiotic food formulations

The most common method of including probiotics in a person's diet is by ingesting food products. Studies have looked into using yogurt, tablets, ice cream, and chewing gum as delivery systems for probiotics for applications related to oral health. Notably, intestinally-derived probiotics were the main focus of this research.<sup>50</sup> There is a plethora of information on the survival of *Bifidobacteria* and *Lactobacilli* under different feeding conditions, but little is known about the mechanistic connection between food matrix and probiotic viability. Sanders and Marco (2010) hypothesized that the generally held belief that probiotics are a functional element and that the food matrix is irrelevant when making active

claims was the reason behind it. Probiotics are functional elements that can be added to food matrices in one of two ways: (1) as a soluble solution or (2) as an insoluble dispersion. A range of intrinsic and extrinsic characteristics of food, such as pH, water activity, oxygen concentration, the presence of other ingredients within a food matrix, storage temperature, and type of packing materials, are related to the survival of probiotics in food during storage.<sup>50</sup> By producing specific metabolites that can alter the pH, moisture, and nutrient dynamics in a fruit or vegetable of interest, beneficial microbes can be used in bioprotection to effectively restrict the presence of pathogenic and spoilage microorganisms.<sup>97</sup> In addition to improving safety, safeguarding the sensory and nutritional properties of coated products, and acting as probiotic delivery vehicles, edible films, and coatings are bidirectional preservation techniques for fruits and vegetables. According to numerous research, using alginate as a probiotic carrier can enhance the quality, usability, and storage stability of fresh and minimally processed fruit and vegetables.<sup>98</sup> For long-term storage of probiotic preparations, alternative methods apart from cryopreservation have to be tested, and adopting various drying techniques is one of them. The drying technique typically influences the qualitative characteristics of dry cells, such as the number of living cells and their biological activity. Some methods include spray drying, freeze drying, vacuum drying, and fluid bed drying. Various innovative formulations, including nasal sprays, creams, and lotions, can be created using the obtained probiotic compositions.<sup>99</sup> Non-fermented and, more crucially, non-dairy food products can act as a matrix for probiotics in addition to fermented food products. Healthy probiotic food can be prepared while considering food preferences, allergies, and dietary requirements, as well as the end product's flavor and aroma. Non-dairy probiotic food items like cereals, fruits, vegetables, and meat-based products are also excellent providers of protein, vitamins, minerals, dietary fiber, antioxidants, and other bioactive compounds that may have additional health advantages.<sup>100</sup> It can also be made in a variety of ways and combine numerous advantageous effects. For instance, probiotic-enriched chocolate and hazelnut spreads have

been created that also have less fat and more beneficial triacylglycerols instead of fat. Because of its nutritious qualities, porous structure, low cost, and widespread availability, banana powder makes a tremendous probiotic matrix. After combining banana paste with several probiotic compositions, the freeze-dried banana powder was created. These formulations contained whey protein isolate, fructooligosaccharides, and a 1:1 mixture of both, along with *L. acidophilus* and *L. casei*.<sup>101</sup>

### Probiotics delivery system

Encapsulation is entrapping a substance in a material to create particles with a diameter of a few nanometers to a few millimeters. It can be a physiological, chemical, or mechanical process. The term “core material” refers to the substance that is encased. The matrix in which the core material is spread is referred to as the “coating” or “shell.” If the encapsulated product will be used in the food business, the food-grade carrier material is used. The carrier substance is designed in such a way that it can act as a barrier to safeguard the substance that is enclosed.<sup>102</sup> Due to their distinctive properties, biopolymers have been employed as encapsulation agents to pharmaceutical drugs. Probiotics have earlier been found to be effective in treating several ailments resulting from infectious diseases. Thus, effective delivery methods were the need of the hour. Encapsulation methods for probiotics have emerged as a resource to address multiple errors linked to probiotic formulations associated to their viability during manipulation, preservation, marketing, and incorporation in food and pharmaceutical products so that cell viability remains unaltered during transit and halt in the gastrointestinal (GI) tract. The numerous encapsulation methods developed can be given as: microencapsulation, spray-drying technique, lyophilisation, extrusion, emulsion, and spray-freeze-drying.<sup>103</sup>

Alginate-based biopolymers have been imparted emphasis for the development of probiotics delivery systems. Specialised delivery devices are essential for ensuring adequate probiotic distribution into the large intestine and colon. This is because uncased probiotics are susceptible to the harsh conditions prevailing in

the GI tract. Microencapsulation is an efficient technique that could be adopted as a potential probiotics delivery system.<sup>104</sup> Numerous natural polymers were employed as candidates for microencapsulating delivery vehicles, such as pectin and starch derivatives, kappa-carrageenan, alginate, xanthan, gum arabic, gellan, and animal proteins.<sup>105</sup> Researchers were drawn to alginate because of its distinct physicochemical and mechanical qualities, which include a simple structure and ingredients, low toxicity, gentle processing, and ease for creating a gel matrix around bacteria. The form in which alginate is used for these encapsulations can be natural, chemically modified, or physically modified.<sup>33</sup>

### The chemically modified forms comprise

- (i) Chitosan forms a positively charged layer around the probiotics, followed by a negatively charged alginate layer, creating a bilayer.<sup>106</sup>
- (ii) Proteins: Usually, whey proteins are combined with alginate to form a rigid structure.<sup>33</sup>
- (iii) Wild Sage Seed Mucilage (WSSM): WSSM is a galactomannan with a stiff rod-like structure that has a lot of potential as a stabilizer, thickener, or emulsifier in food items. It is thought to be an excellent prebiotic. Probiotics can be effectively shielded from the unfavorable gastrointestinal environment by using WSSM in the alginate microcapsule structure to increase the integrity and stability of the microcapsules.<sup>33</sup>

### The physically modified forms consist of

- (i) Starch: Mixing alginate with starch increases the complexity of the matrix network, thereby increasing the encapsulation efficiency.<sup>33</sup>
- (ii) Polyvinyl alcohol: Electrospinning is regarded as an effective way for nanoencapsulating probiotics among the several approaches.<sup>107</sup> Toxic-free materials and higher solubility and strength must be used for the electrospinning process to be successful. Probiotic bacteria were loaded into sodium-alginate and polyvinyl alcohol-based nanofibers that were used as a nanocarrier. Some pathogenic bacteria could not grow on these nanofibers.<sup>108</sup>
- (iii) Polystyrene: The alginate hydrogel beads were placed between two polystyrene (PS) mats using the electrospinning technique.

The probiotic bacteria's stability, chemical, and heat resistance, as well as their rate of leaching were all improved through this layer-by-layer microencapsulation technique.<sup>109</sup>

- (iv) Carboxymethyl pachymaran: In the gastrointestinal tract, carboxymethyl-pachymaran (CMP) gels exhibit great pH sensitivity, according to earlier investigations. The fact that CMP can reduce cell damage during freeze-drying is more significant and raises the possibility that it might be a new cryoprotective agent.<sup>33</sup>

### Side Effects of Probiotics

Systemic infections, excessive immunological stimulation in susceptible people, detrimental metabolic impacts, or gene transfer may all be brought on by probiotics. The intestinal bacteria may relocate for several reasons, including mucous membrane damage, abnormalities in the intestinal microflora, or a deterioration of the host's immune system. Various clinical publications have named probiotic bacteria as inadvertent causes of dental caries, endometritis, urinary tract infections, meningitis, and spleen abscesses. Since newborns do not have a completely formed immune system at birth, probiotic therapy delivered to preterm infants and neonates should be carefully examined as the risk of fungemia or bacteremia after probiotic administration considerably increases.<sup>110</sup> After ingesting *L. rhamnosus* GG, a 17-year-old adolescent with ulcerative colitis developed *Lactobacillus* bacteremia. The *L. rhamnosus* strain obtained from the patient's blood and the ingested probiotic strain shared 99.78% of the same 16S rRNA genes. According to this evidence, the *Lactobacillus* strains may increase the risk of bacteremia in persons with ulcerative colitis.<sup>111</sup> Peptide-glycan-polysaccharides, which make up the bacterial cell wall of the *Lactobacillus* genus, are capable of causing adverse reactions, including fever or arthritis. In healthy individuals, probiotic bacteria may favor phagocytosis; however, this effect may be the opposite in allergic individuals.<sup>112</sup> The dose of the probiotic is also a critical factor in determining the immunomodulatory effects.<sup>113</sup> In the small bowel, probiotic bacteria deconjugate and dehydroxylate bile salts, which may cause diarrhea and intestinal ulcers. Because probiotic

bacteria can manufacture bile salt hydrolase (BSH), the gut microbiota may accumulate deconjugated bile salts and convert them to harmful secondary bile acids.<sup>110</sup> The risk of cholestasis and colorectal cancer may rise as a result of the build-up of these cytotoxic substances in the enterohepatic circulation.<sup>114</sup> D-lactate generation by probiotic bacteria is an additional detrimental metabolic impact. Destructive metabolic processes may also influence potential adverse effects from probiotic use, such as mucin breakdown.<sup>115</sup> The potential for the transmission of antibiotic-resistance genes between probiotics and other commensal or pathogenic bacteria found in the gastrointestinal system is another factor pertaining to the safety of bacteria used as probiotics.<sup>116</sup> Over 68% of probiotic bacteria have been shown to be resistant to two or more antibiotics. Furthermore, certain probiotic *Bacillus* strains have extremely high resistance levels. Some antibiotics are naturally resistant to lactic acid bacteria. Apart from *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *L. johnsonii*, and *L. crispatus* several lactobacilli strains inherently resist vancomycin.<sup>110</sup>

### CONCLUSION

Through immune system stimulation and pathogen inhibition, probiotic bacteria have a sustainable beneficial impact on human health. Probiotics and prebiotics have drawn much attention in the medical community and consumer goods due to their numerous health advantages. But just a few probiotics and prebiotics have been addressed in extensive study data. Innovative methods involving genetic manipulation, multi-omics, system biology, nanotechnology, and immunotherapy must be applied to completely understand the makeup and functions of the microbiota in relation to probiotics, prebiotics, synbiotics, and postbiotics. With regard to probiotic therapy for cancer, only a few species have been identified to date as effective candidates, and the horizon for further potential candidates remains wide open, which is yet to be traversed. Probiotics, prebiotics, and synbiotics should be examined further to determine the most effective dosages and durations of treatment for each in terms of preventing or controlling specific inflammatory diseases and how they help reduce inflammatory

biomarkers in the gut and throughout the body. This, in turn, helps to alleviate disease symptoms and enhance the sustainability of these products in maintaining human health.

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#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

#### AUTHORS' CONTRIBUTION

AR and AS conceptualized the study and collected the data. AR and IC wrote the manuscript. IC reviewed and edited the manuscript. All authors read and approved the final manuscript for publication.

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#### DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

#### ETHICS STATEMENT

Not applicable.

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