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PROBIOTICS AND PREBIOTICS: MECHANISMS, BENEFITS, AND CHALLENGES - A NARRATIVE REVIEW

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ABSTRACT: The human gut microbiota harbours numerous microbiota which includes archaea, fungi, viruses and bacteria. A balanced and healthy gut microbiota is essential for maintaining optimal physiological functions and thus the overall health and well-being. The state of a balanced gut microbiome is known as eubiosis, while dysbiosis is condition where an imbalances or disruptions in the gut microbiota, occurs. Dysbiosis has been associated with a range of diseases including gastrointestinal disorders, metabolic syndrome, neurological disorders chronic inflammation *etc*. The term probiotics refers to live microorganisms that, when ingested in adequate amounts, confer health benefits. The emergence of using probiotics therapeutically to repopulate the gut with eubiotic microorganisms and improve health introduces many new concepts. On the contrary, prebiotics are food components that promote the growth or metabolism of beneficial microorganisms (e.g., bacteria & fungi). They can alter the gut microbiome makeup. Both probiotics and prebiotics have been effective in a variety of diseases. Nevertheless, concerns over standardization and safety dictate rigorous assessment of strains/formulations. New innovative therapeutic strategies are emerging due to recent advances in the understanding of Postbiotics activity and novel concepts such as symbiotics. This review highlights the existing literature regarding the mechanisms of probiotics and prebiotics in general, their health effects on various diseases as evidenced by animal models or intervention studies, also drawing attention to some controversies linked with these agents, which are still under investigation or revisiting after new high-quality evidence emerged mainly related to metabolic features such as weight loss.

INTRODUCTION: The gut microbiome is a diverse community comprising bacteria, fungi, viruses, and archaea [1, 2, 3]. The microbial diversity is shaped by various factors, such as age, gender, and antimicrobial agents leading to differences in bacterial populations [4, 5]. The initial colonization of the gut begins during gestation and extends until around 18 months to 3 years after birth. During this period, a distinct bacterial signature forms within the distal small intestine and colon, signifying the development of a mature microbiome. In humans colonization of the gut by *Lactobacillus* and *Bacteroides* occurs during early stages of infancy. Subsequently, environmental influences, breastfeeding, psychological factors, medications, and the maternal diet during and after pregnancy play significant roles in shaping the gut microbiota. By the age of four, these microbial communities typically stabilizes [6, 7, 8, 9, 10].

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They spread throughout the body with the digestive system harbouring the largest concentration [6]. The human body provides a nutrient-rich environment where these microorganisms metabolise nutrients into metabolites [11], interacting with the host immune system and affecting human health.

Dysbiosis is a condition when an imbalance occurs between harmful and beneficial bacteria, and this can lead to many diseases including autoimmune diseases, psychological diseases, and other health issues *etc* [5, 6, 12]. For instance, the rise in BMI is associated with an increase in specific kinds of intestinal bacteria (*Firmicutes*/*Bacteroidetes*) and (*Prevotella*/*Bacteroidetes*), which are main indicators of gut microbiota composition. Moreover, certain bacteria such as *Eubacterium ventriosum* are linked with obesity, while others like *Oscillospira spp* are related to leanness [3]. Bacterial population density vary in individuals, with approximately five hundred species in the oral cavity, one thousand and twelve bacteria per gram in the colon, and over hundred per gram in the small intestine and stomach, including *Bifidobacterium*, *Clostridium*, *Eubacterium*, *Faecalibacterium*, and *Peptococcus* [12, 13].

Numerous studies have confirmed the interaction of gut bacteria with the different organs via several axes including the axis of microbiota-gut-brain, the axis of microbiota-gut-liver, and the axis of microbiota-gut-lung, the axes of microbiota-gut-immune and other axes [14, 15]. They can produce essential vitamins, support the proliferation of epithelial cells, and enhance the metabolism of bile acid, fibres, proteins and fats changed into short-chain fatty acids and simple sugars. Besides this, they influence innate and adaptive immunity. In order to recognize the dynamics of gut microbiota in health management, researchers use a wide range of state-of-the-art research methods. These include DNA-based techniques, which enable the accurate identification and quantification of microbial species. Molecular biology methods such as polymerase chain reaction (PCR) are strain-specific and hence useful in recognizing the expressions of different species.

The 16S rRNA sequencing is a comparatively novel technique of microbial ecology that enables the detection of bacterial communities by examining the expression of the conserved 16S ribosomal RNA gene [13]. Researchers employ these technologies to define the diversity of microbial flora within the gut and its effect on human health. As we learn more about the different factors that affect gut health, it is necessary to expand our knowledge beyond probiotics and prebiotics. We have to research more into other dietary supplements like symbiotics and Postbiotics. All of these supplements have different effects on the composition and functionality of the gut microbiota and may influence overall health in different ways.

Probiotics: Probiotics are defined as living microorganisms that on ingestion in sufficiently large numbers, can have beneficial effects for the host. They are particularly renowned in relation to the promotion of bile production and, therefore, overall intestinal health and well-being [12, 13, 14]. They include *Saccharomyces boulardii*, and strains of *Lactobacillus*, *Bifidobacterium*, *Streptococcus thermophiles*, *and Enterococcus faecalis* etc [16]. The biological effect of probiotics is that they can influence the production of cytokines, inhibit the translocation of microorganisms from the gut lumen across the epithelial layer, suppress pathogenic bacteria by competition for resources and change the pH level [14, 15, 17, 18]. Prebiotics, on the other hand, are non-digestible food substances, which selectively encourage the growth of the friendly gut bacteria thereby, potentiating the effects of probiotics. They foster the development of constructive genera like *Eubacteria*, *Bifidobacteria* and *Lactobacilli* and suppress pathogenic species like *Clostridium* by providing the base for the fermentation by the normal flora [15, 19, 20].

The discovery of probiotics initially dependent on identifying beneficial bacteria in a healthy individual that could provide health benefits when administered to those with a health issue. However, Russian scientist E´lie Metchnikoff pioneered a novel approach by exploring the relationship between fermented foods and their health benefits [21]. He suggested that Western diets negatively impacted gut health by promoting harmful bacteria, which adversely affected overall health. Metchnikoff developed the theory that introducing beneficial bacteria could alter the gut microbiota and improve human health [22]. This concept led to various definitions of probiotics.

The World Health Organization (WHO) defines probiotics as live microorganisms [12, 23] used as nutritional supplements to promote human health and growth by restoring intestinal bacterial balance [23, 24, 14]. Parker was the first to use the term "probiotics" in this context, referring to nutritional supplements that support animal growth [25]. Several probiotic bacterial strains and genera are known, although the most common are those of the Lactic acid bacteria (LAB) like *Lactobacilli*, *Enterococci*, *Heterotrophic bacteria*, *Escherichia*, *Streptococcus Bacillus* and *Propionibacterium*. However, some fungal strains *Saccharomyces* (non-pathogenic yeasts) [23, 24], and some non-spore-forming, non-flagellated *Coccobacilli* [24] have also been used. Related terms have recently appeared that include postbiotics, meaning "non-viable microorganisms or their by-products biological activity". Another term, pharmabiotics, defines human microbial cells or their products having demonstrated roles in health or disease including psychobiotics and immunobiotics. Of these, next-generation probiotics (NGP) hold a special position. They are live microorganisms identified by comparative microbiota analyses which when administered in adequate amounts confer a health benefit on the host. Other related terms include Paraprobiotics, Probioceuticals / Probiotaceuticals, and Live biotherapeutic products (LBP) [26].

The recommended daily intake of probiotics for consumers varies depending on the individual's bacterial environment, typically ranging between(108 and 109 colony-forming units (CFU)) [22, 24, 27]. Probiotics are added to many food products such as milk and milk products, cheese, meat products, juices, bread and fruits. The quality and quantity of probiotics, however, may vary during manufacturing and storage. Also, some probiotic products contain only a single strain or one type of bacteria while others preparations have contain a mixture of numerous strains or types of bacteria [28].

Mechanisms of Action of Probiotics: Understanding how probiotics work is important in order to appreciate their potentials and limitations. Studies have identified many mechanisms of actions based on in vitro or ex vivo, rodent and human examples. However, not all the mechanisms are definitive because probiotic can act on multiple pathways of host physiology simultaneously diversifying the influencing factors and increasing the complexity. Probiotics modulate the gut microbial community by increasing the population of beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli*, while reducing pathogenic microbes [29]. They can influence the host metabolism and energy balance by the metabolites they produce or providing necessary nutrients for metabolism through cross-feeding and carbohydrate metabolism [18, 22, 30, 31]. This section elaborates on the ways through which probiotics exert their effects on the host.

Modulation of Gut Microbiota: One of the fundamental roles of probiotics is the modulation of the gut microbiota composition. It does this by the following mechanism:

Promotion of Beneficial Bacteria: Probiotics enhance the population of beneficial bacteria, such as *Lactobacillu*s and *Bifidobacterium*. These bacteria ferment dietary fibers to produce short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate. By lowering the pH of the gut environment SCFAs inhibit pathogenic bacteria and promote the growth of commensal microorganisms [17].

Inhibition of Pathogenic Bacteria: Probiotics produce antimicrobial substances, including bacteriocins, hydrogen peroxide, and organic acids, which suppress the growth of harmful bacteria. By competing for nutrients and adhesion sites on the intestinal mucosa, probiotics also prevent pathogens from establishing themselves in the gut [23].

Enhancement of Gut Barrier Function: Probiotics play a critical role in maintaining and enhancing the integrity of the intestinal barrier:

Tight Junction Integrity: Probiotics enhance the expression of tight junction proteins, such as occludin and zonulin, which are essential for maintaining the tight junctions between epithelial cells. This reduces intestinal permeability and prevents the translocation of harmful substances into the bloodstream.

Mucus Production: Probiotics stimulate the production of mucin, the primary component of mucus, which forms a protective layer on the intestinal lining. This barrier prevents pathogens from coming into direct contact with the epithelial cells. Probiotics interact with host microorganisms through various macromolecules of cell surface. These include protein molecules like LPxTGbinding proteins, and non-protein molecules like peptidoglycan, lipoteichoic, and exopoly-saccharides that affect mucin production, intestinal cells, and dendritic cells. Consequently, probiotics can extend their transit times within the gut and help fortify, the intestinal mucosal barrier [14, 18, 32, 33] by enhancing gene expression involved in junction signalling and mucin-glycoprotein production. This support contributes to the repair of the gut barrier following damage. For example, *Staphylococcus thermophilus* and *Lactobacillus acidophilus* significantly inhibited the adherence of enter invasive. *Escherichia coli* to HT29 cells, and increased transepithelial resistance in Caco-2 cells. Mucins play a crucial role in immune system support. For example, *lactobacilli* stimulate the secretion of MUC5AC mucin in human intestinal cell lines like HT29 through adhesion to monolayers [29, 34, 35].

Production of Antimicrobial Substances: Probiotic bacteria secrete antimicrobial peptides that serve multiple functions, including signalling to the immune system or microbiota, directly eliminating other microbiota. For instance, certain bacterial strains produce ribosomally synthesized peptides known as bacteriocins.

These are proteinaceous toxins produced by probiotic bacteria that inhibit the growth of similar or closely related bacterial strains. Bacteriocins can target specific pathogens without disrupting the overall microbiota balance and can act as preservatives in probiotic-treated foods and inhibit both Gram-positive and Gram-negative microorganisms [22]. One such antimicrobials peptide, Low Molecular Weight Bacteriocin (LMWB), functions by either disrupting cell wall synthesis or forming pores to lyse target pathogenic cells. Additionally, probiotic bacteria secrete acetic and lactic acids, which acidify the environment and inhibit pathogens like Salmonella sop. Probiotic also release chemicals known as microcins, which penetrate target cells and disrupt cellular functions by binding to iron siderophore receptors. This action leads to the inhibition of enzymes, such as ATP-synthase, RNA polymerase, and DNA gyrase, ultimately resulting in the death of pathogenic organisms [29]. Probiotics contribute to the synthesis of various biologically active compounds, including amino acids, small peptides, phenols and lactanes through fermentation of proteins. These compounds play an important role in immunomodulation by promoting the production of antioxidants and inflammatory mediators that target and eliminate harmful organisms. Probiotics also produce vitamins such as vitamin K, also vitamin B12 and propionic acid, with "*Propionibacterium shermani*" being a notable producer of propionic acid. Enzymes produced by Probiotic bacterial hydrolyze proteins to create peptides with immune-modulating and anti-inflammatory properties [15]. These peptides stimulate the production of immunoglobulin A (IgA) and interleukin-10 (IL-10), affecting immune responses and inflammatory gene expressions. The production of IgA enhances immune-modulation and the clearance of pathogenic microorganisms by activating dendritic cells, naive T cells, and B cells [36, 37].

Furthermore, probiotics can enhance antioxidant defences by increasing the activities of enzymes like glutathione S-transferase, catalase, and glutathione peroxidase. This enhancement helps reduce oxidative stress and protect cells from damage caused by carcinogens [38]. Probiotics produce organic acids, including lactic acid and acetic acid, which lower the pH of the gut. This acidic environment is inhospitable to many pathogenic bacteria, thereby preventing their proliferation [29].

TABLE 1: THE MOST IMPORTANT VITAL COMPOUNDS PRODUCED BY PROBIOTICS

Bioactive Compounds Produced by Probiotics	Role of Bioactive Compounds
Bacteriocins [39]	Antimicrobial peptides synthesized by ribosomes, produced by certain types of bacteria; have antiviral roles and help form bacterial communities.
Amino acids, small peptides, phenols, lactones, and indoles [22]	Created from the fermentation of proteins; help combat harmful germs and achieve energy balance by exhibiting immunomodulatory, anti-inflammatory, and antioxidant actions.
Organic acids and short-chain fatty acids (SCFAs) [40]	Reduce the stomach's pH and activate antimicrobial responses by creating an environment where pathogenic bacteria are less likely to thrive.

Vitamins [28]	Vitamin B6 (pyridoxine) produced by *Bifidobacteria*; Vitamin B12, propionic acid, and other beneficial metabolites produced by *Propionibacterium shermani*; Vitamin K promotes the development and proliferation of beneficial gut bacteria.
Exopolysaccharides (EPS) [41]	Synthesized through the action of glycosyltransferase and glycantransferase enzymes from sugar nucleotide precursors; EPS has been extracted from *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Lactobacillus rhamnosus*.
Enzymes [32]	Microbial enzymes, such as β-galactosidase and bile salt hydrolase, improve human blood lipid profiles and lactose digestion, respectively.

Competitive Exclusion of Pathogens: Probiotics compete with pathogens for resources and adhesion sites in the gut. In the 1970s, research demonstrated that introducing a diverse array of adult intestinal microorganisms could significantly enhance resistance to diseases, such as Salmonella infections, in newly hatched Chicks [42]. This led to the development of the concept of "competitive exclusion" which involves maintaining a balance of microorganisms in the digestive system. This balance is achieved by reducing the concentration of harmful organisms primarily aerobic bacteria while preserving a greater number of beneficial anaerobic bacteria [29, 42]. Competitive exclusion operates through several mechanisms: it reduces harmful bacteria by altering the gut environment to make it less hospitable. This is achieved by decreasing the oxygen levels or adjusting the pH of the intestinal environment [23]. Additionally, competitive exclusion includes nutrients competition and preventing the pathogen adhesion. Probiotics consume available nutrients in the gut, limiting the resources that pathogenic bacteria need to grow and thrive [29].

Probiotics adhere to the intestinal mucosa, occupying the binding sites that pathogens would otherwise use to attach and colonize. This competitive exclusion helps prevent infections and supports a healthy microbiota. Probiotics contribute to these processes by secreting biosurfactants, disrupting receptors through enzymatic activity, and producing receptor analogues, thereby impeding pathogen attachment [18, 14, 29, 33].

Immune system Modulation: Probiotics interact with the host's immune system to modulate immune responses.

Enhancement of Innate Immunity: Probiotics activate macrophages, dendritic cells, and natural killer cells, enhancing the body's first line of defence against infections. They stimulate the production of immunoglobulins, particularly IgA, which plays a crucial role in mucosal immunity.

Regulation of Inflammatory Responses: Probiotics modulate the production of cytokines, promoting an anti-inflammatory environment. They can decrease the levels of pro-inflammatory cytokines like TNF-α and IL-6 while increasing anti-inflammatory cytokines such as IL-10.

Probiotics enhance both adaptive and innate immunity [42]. They increase production of antibodies and stimulate macrophages and natural killer (NK) cells activity. This occurs through the interaction of the system humoral immunity with probiotics via toll-like receptors (TLR) [6]. For example, "*Lactobacillus casei shirota*" boosts natural killer cells (NK) activity and cytokine IL12 production [43]. Probiotics also inhibit the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [2, 8], which reduces the activation of B cells, induces T-cell apoptosis and increased levels of anti-inflammatory cytokines such as interleukin-10 (IL-10) while decreasing interleukin 8 (Il-8)[15]and tumour necrosis factor alpha (TNF-α) [2, 15]. Additionally, Probiotics downregulate TLR expression, which helps to suppress intestinal inflammation [44] TLRs, such as TLR2 and TLR 6 are essential in immune regulation processes, and several probiotics, including "*L. plantarum ccfm634*", "*L. plantarum ccfm734*", "*L. Fermentum CCFM381*", "*L. acidophilus ccfm137*", and "*S. thermophilus ccfm218*" [43].

Regulatory T cells are crucial for promoting oral tolerance and immunity to infections and allergies, benefit from new probiotic strains. Immunological effects of probiotics are primarily associated with the initial resident bacteria rather than prolonged probiotic presence.

Research indicates that the immunological effects of probiotics are primarily associated with the initial resident bacteria rather than prolonged probiotic presence [8]. Among the most significant probiotic species are lactic acid bacteria (LAB**)** [19]. "*Lactobacillus rhamnosus GG*", identified in 1985, was the first probiotic used in the dairy industry and has been shown to enhance the immune system by increasing IgA levels and the number of immunoglobulin-releasing cells in the intestinal mucosa [23, 19] (LAB) also utilize toll-like receptor (TLR2) to activate Interleukin 6 (IL-6) and Transforming growth factor-beta (TGF-B) from dendritic cells (DC), promote Interleukin 12 (IL-12) synthesis, and enhance antibody formation and cytokine regulation to boost host defence [29].

Metabolic Effects: Probiotics influence host metabolism in several ways. Certain probiotics synthesize essential vitamins, such as B vitamins and vitamin K, which are crucial for various metabolic processes in the host (Poindexter B *et al*., 2021). By fermenting dietary fibers, probiotics produce SCFAs that serve as an energy source for colonocytes. SCFAs also have systemic effects, including anti-inflammatory properties and the regulation of lipid and glucose metabolism [17].

Neurological Effects: Emerging research highlights the impact of probiotics on the gut-brain axis neurotransmitter Production: Some probiotics produce neurotransmitters like serotonin and gamma-aminobutyric acid (GABA), which can influence mood and behaviour. These neurotransmitters can affect the central nervous system *via* the vagus nerve or through systemic circulation.

Modulation of the HPA Axis: Probiotics can influence the hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress responses. By modulating this axis, probiotics can potentially alleviate stress and anxiety [45, 46, 47, 48].

The multifaceted mechanisms of action of probiotics underline their potential benefits in promoting gut health, enhancing immune function, and even influencing mental well-being. However, understanding these mechanisms also helps in identifying the limitations and potential side effects of probiotic use. Comprehensive knowledge of how probiotics work is essential for their effective application in clinical practice and for maximizing their health benefits while minimizing risks.

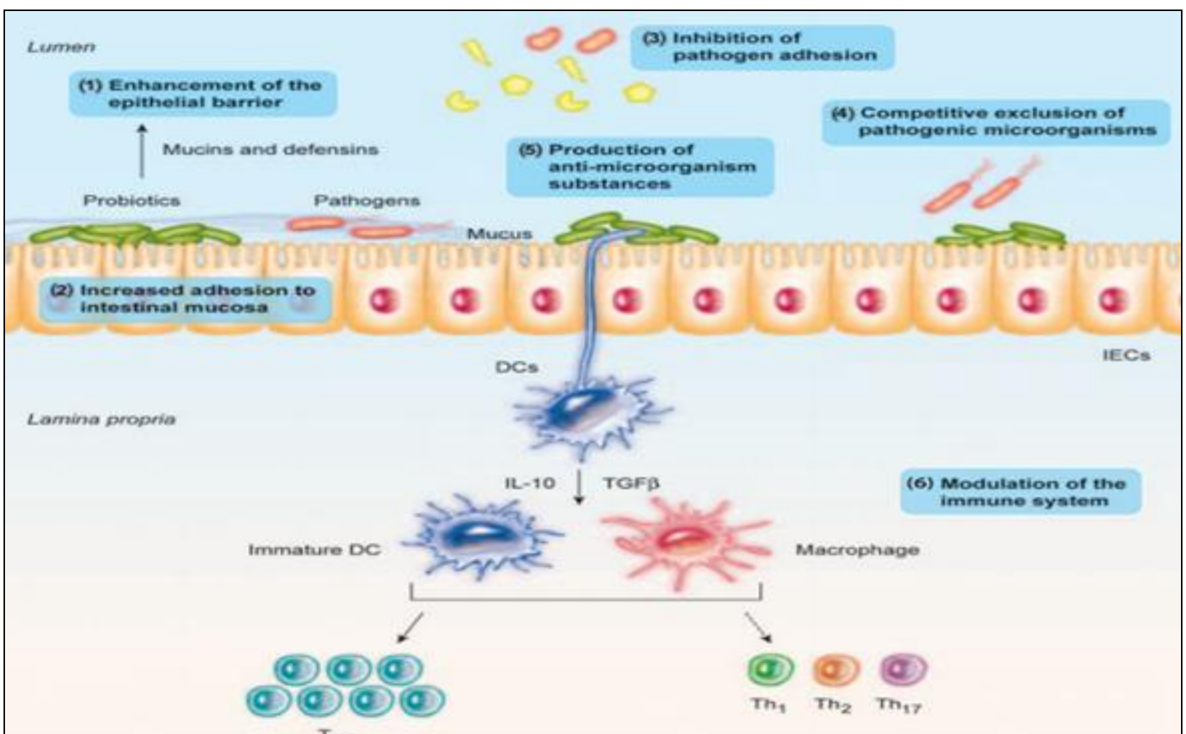

FIG. 1: GENERAL MECHANISMS OF PROBIOTICS [49]. DCs: Dendritic cells; IECs: Intestinal Epithelial Cells; IL-10: Interleukin 10; TGF-β: Transforming Growth Factor β; Th1: Type 1 T helper; Th2: Type 2 T helper; Th17: T helper 17; Treg: regulatory T cells.

Probiotics for Health and Diseases Management: Probiotics have become an integral part of modern health management due to their wide-ranging benefits. They contribute to maintaining and enhancing health by supporting various bodily systems, including the digestive, immune, and genitourinary systems. They aid in preventing and managing a variety of conditions, from gastrointestinal disorders and infections to mental health issues and many chronic diseases. This section delves into the impact of probiotics on health and disease management, examining their therapeutic potential and the safety standards essential for their effective use. Research has demonstrated that probiotics play a crucial role in protecting the genitourinary system and reducing infants and neonatal mortality, particularly with strains such as "*Lactobacillus GG(ATCC53103)*" and "*Lactobacillus rhamnosus*". By maintaining a balanced vaginal flora, these probiotics may help lower the risk of sexually transmitted infections, a key benefit of *lactobacillus* species. Additionally, the strain "*Banimalis*", has been shown to alleviate the severity of cirrhosis, mucosal candidiasis and to ease gingival pain. Probiotics have also been effective in managing allergy-related conditions like asthma and dermatitis, as well as certain mental health disorders such as depression and anxiety [23]. In severe illnesses like COVID-19, research indicates that diverse beneficial bacteria can mitigate inflammatory symptoms, potentially improving patient outcomes [49]. Probiotics have been proven effective in reducing symptoms associated with gastrointestinal disorders, cancer, heart disease, constipation, depression, and various autoimmune diseases.

TABLE 2: ROLE OF PROBIOTICS IN DISEASES

Diseases	Probiotics	Function of Probiotics
Skin diseases like allergic reactions, eczema, rosacea, acne, and atopic dermatitis [50,51,52,53]	*Bifidobacteria* and *Lactobacilli*	Probiotic cosmetics boost the growth of beneficial bacteria and suppress pathogenic species, effectively treating several skin conditions.
Acute gastroenteritis [31]	*Bifidobacterium lactis* Bb12, *Lacticaseibacillus reuteri*, *Lacticaseibacillus casei*, *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, and *Enterococcus faecium* SF68	Reduce the duration of rotavirus diarrhea and effectively avoid or alleviate antibiotic-associated diarrhea (AAD).
Diarrhea[54]	*Saccharomyces boulardii*	Prevention of Vavelle'sdiarrhea.
Constipation [31,52,55]	*Bifidobacteria*, *Bacteroides*, and *Clostridia*	Probiotic supplements and dietary fiber help constipation sufferers by altering fecal microflora, reducing discomfort, and normalizing stool type.
Inflammatory bowel disease [22,31]	Lactic acid bacteria, *Lactobacillus salivarius* UCC118, a strain of *E. coli* (Nissle), and *Saccharomyces cerevisiae*	Reported to reduce the signs of inflammatory bowel disease (IBD) and provide relief from Crohn's disease.
Helicobacter pylori infection [56]	Probiotics isolated from various sources, like fermented food	Control or mitigate the effects of *Helicobacter pylori*.
Oral health [57]	Probiotic-containing products like mouthwash	Reduces periodontitis, dental caries, and maintains a healthy oral environment and plaque ecology.
Rheumatoid arthritis [58]	*Lactobacillus casei* 01	Decreases levels of TNF-α, IL-12, and IL-6, while increasing IL-10.
Colorectal cancer [44,59]	*Lactobacillus rhamnosus*, probiotic lactic acid bacteria	Reduces the incidence of colorectal cancer; inhibits feces putrefaction product production, and increases short-chain fatty acid concentrations.
Mental health: Depression, stress, and anxiety [3,20,33,45,46,60]	*Lactobacillus*, *Lacticaseibacillusparacasei* YIT 9029, *Bifidobacterium adolescentis* NK98, *Lactobacillus rhamnosus*	Improves depression severity; reduces anxiety and depression through the microbiota-gut-brain axis.
Cardiovascular disease (CVD) and oxidative stress [61]	Lactic acid bacteria (LAB), *Lactobacillus rhamnosus*	Withstands reactive oxygen species (ROS) and shows significant antioxidant activity under high physical stress.

Hypercholesterolemia [61]	Probiotic yogurt containing *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus* LA-5, and *Bifidobacterium animalis* BB12	Significantly reduces total cholesterol, LDL cholesterol, and HDL levels.
Candidiasis [30]	*Saccharomyces cerevisiae* CNCM I-3856, *Bifidobacterium* species	Effective against oropharyngeal candidiasis, vaginal mucosal infections, and reduces the severity of gastrointestinal candidiasis.
Women's urogenital health [50,62]	Probiotic *Lactobacilli*	Supports women's genitourinary health; can be taken as supplements, vaginal suppositories, or used as a gel.
Anorexia Nervosa (AN) [63]	*Lactobacillus bulgaris* and *Streptococcus thermophilus*	Exhibits immune modifications contributing to the treatment of anorexia nervosa through the digestive system.
Multiple Sclerosis [47]	*Bacillus coagulans*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and others	Increases IL-10 and reduces levels of inflammatory markers such as IL-17 and TNF-α.

Quality and Safety Standards of Probiotics: Selecting the optimal bacterial strain and ensuring safety are critical when using probiotics. Researchers emphasize the need to consider various factors, including bacterial mutations, environmental stability, bile resistance, survivability, adhesion and antimicrobial production and bacterial identity [19, 64, 65].

Studies should address these aspects to select the appropriate strain and assess its qualities and functions, including its survival during storage and transfer [19]. In 2002, the World Health Organisation established guidelines for probiotics use, emphasizing the need for extensive clinical trials, cell lines and animal models testing, adherence to high-quality standards, and understanding *in-vivo* mechanisms. It is also important to develop probiotics that can be used in protective vaccines and other health applications [23, 66]. Key quality standards include maintaining the properties and purity of probiotic products [31].

To ensure safety, stool samples are analyzed using selective media or advanced techniques such as 16s rRNA sequencing, Polymerase chain reaction (PCR), optical enumeration and flow cytometry to identify and quantify intestinal bacteria [8, 65]. Emerging technologies, including microarray analysis and bioinformatics platforms have led to the development of , Next generation probiotic (NGPs), which include Gram-positive anaerobic bacteria like "*Clostridium butyricum*", "*Bacteroides ovatus*", "*Bacteroides xylanisolvens*", "*Bacteroides fragilis*", "*Akkermansia muciniphila*", and "*Faecalibacterium prausnitzii*" [27, 67]. Integrating this data provides a comprehensive view of microorganisms and their interactions with the host, guiding effective treatment approaches [27].

Monitoring the presence of these organisms in faeces over several weeks to months helps, assess their ability to proliferate and establish themselves in the gastrointestinal tract [68]. Probiotic preparations should contain at least ($5*10^9$ CFU) and be used for a minimum of five days [23]. Safety standards include testing for bacterial toxicity, potential for systemic infections, and metabolic byproducts [64]. Probiotic support the immune system, resist bile and hydrochloric acid, reduce permeability and adapt to intestinal conditions [22]. Currently, the most common genera of probiotics in the market are lactic acid bacteria, including: *Lacyobacilli*, *Bifidobacteria*, and *Streptococci* [25].

Prebiotics: Prebiotics are useful in synthesizing other beneficial metabolites of the gut microbiota and work to establish a healthy state of the gut microbiome where it contributes to the generation of short-chain fatty acids (SCFAs) [69, 70]. This study also demonstrates that probiotics and prebiotics have significant outcomes in disease control and prevention of chronic illnesses such as IBD [71], CVD [61, 72], and mental illnesses[20].The total genome of the gut bacteria is of the least one hundred-fold of the genome size of a human. These bacteria participate in metabolism through SCFAs, tryptophan metabolites, amino acids and glycans, which are required for bacterial growth in the gut and modulation of the host's inflammation [11]. Research has also shown that host genome may play a role in transmitting other bacterial families for instance Christensenellaceae which may transact with other genetic families and methanogenic archaea [4]. The concept of "prebiotic" was defined by Gibson and Roberfroid in (1995) as "a selective non-digestible food component". The more recent definition by the International Scientific Association for Prebiotics and Probiotics (ISAPP) as a "substrate" that is selectively used by gut bacteria only [15,20]. Prebiotics are food ingredients that must resist acidity in the stomach, remain undigested in the gut, and not hydrolysable by endogenous enzymes. Prebiotics can be classified based on their structure and fermentation properties. Some of them are carbohydrates [73], others are fibres that a certain degree of polymerization turn into carbohydrates [69]. Normally, prebiotics are taken in small quantities in diet [70].

Based on the level of fermentation, prebiotics can be divided into two major categories, partially digested or non-digested. Thus, they can be either poorly fermented by oral microbiota or well fermented by gut microbiota [74]. Phytochemicals like polyphenols, carotenoids and organosulfer compounds also act as prebiotics[75,76]. Glycomacropeptide (GMP), which contains a variety of amino acids, is another example of a prebiotic [77]. Resistant starch, whole grains, pectin that forms pectic oligosaccharides or (POS), and fructans, which include inulin and a fructo-oligosaccharide are some of the commonly used prebiotics [15, 23, 69]. Other prebiotics include, isomaltooligosaccharides, xilooligosaccharides, lactobionic acid, psyllium and galactomannan [70].

Functions of Prebiotics in the Body: Because of the disruption of the immune barrier and metabolic function there may be low-grade endotoxemia, and many inflammatory mediators such as Lipopolysaccharide (LPS) in the gut are transported into the bloodstream leading to various diseases [29]. Such conditions can be treated with prebiotics because affect the type and/or number of bacterial species in the large intestinal and its environment by changing the pH that is preferred by acid-sensitive bacteria. Most of the prebiotic fermentation materials like bacteroids are acids [50]. Chen & Liu, 2018 claimed that the chain length of bacteria may influence the type of fermented prebiotics among the species. For instance, activities with polysaccharides having DP ≤ 60 can only be conducted by a few species of fructans such as inulin. Inulin decreases the risks associated with oxidative stress that is associated with some inflammatory biomarkers and prevents the effects of lipid peroxidation in the stomach through the use of certain dietary antioxidants [69]. G protein receptor is found to regulate the immune system, the population density of beneficial bacteria and metabolism which is changed and influenced by prebiotics found in the gut-associated lymphoid tissue (GALT) [5]. Cross-feeding is also observed in the functioning of probiotics. A complex prebiotic ferments and produces a by-product that serves as a substrate for another microbe. For instance, *Ruminococcusbromii* can ferment resistant starches and *lactobacilli* and *bifidobacteria* utilize dietary fibers [70].

Specific investigations in monoculture have revealed that *Bifidobacteria* are surpassed by other bacterial species when it comes to assimilation of inulin-type fructans (ITF). It was also established that *Bifidobacteria* species differ in their versatility towards the different chain lengths of inulin-type fructans (ITF). While *Bifidobacteria* have a very fast growth rate [78] in the presence of Fructo-oligosaccharides (FOS) and gives out lactate and acetate, which is considered to be good sources of energy [70]. *Eubacterium halliu* cannot grow in vicinity of Fructo-oligosaccharides (FOS) [78]. Another major characteristics of prebiotics is specificity for microorganisms, and the ability to enhance the growth of good bacteria to overcome pathogenic ones besides enhancing the formation of fermentation products essential for immunity. The prebiotic fermentation results the in short chain fatty acid (SCAFAs) such as acetate, propionate, and butyrate [70]; these change the stomach pH and influence acid-sensitive bacterial forms like *Bacteroids*, while stimulating *Firmicutes* to produce butyrate referred to as the butyrogenic effect [69].

Other functions of prebiotics include regulation of, cytokines synthesis, which is a way to immune system regulation as well. Namely, rat mesenteric lymph nodes (LNs) and cell cultures were shown to elevate the synthesis of the anti- inflammatory cytokines interferon gamma (IFN-g) and Interleukin 2 (IL2) and the production of the suppressor of the pro-inflammatory cytokines acetate and propionate. These prebiotics enhance the quantity of *lactobacilli* in the large intestine; therefore benefiting probiotics by increasing cytokines synthesis of Interleukin 10 (IL10) and Interferon gamma (IFN-g) in relation to intestinal immunity through (DP16, DP8, and DPG4). Inulin or beta-glucan Immunosuppressive polysaccharides can affect the innate immunity of fish in the way that ly50 also increases activity of neutrophil, phagocytosis and lysosome activity [48]. Studies have established that prebiotics are useful in the moderation of the incidence of allergic atopic dermatitis and urticaria in infants with the long-chain Fructo-oligosaccharides (FOS) and Galactooligosaccharide (GOS) [29]. Short chain fatty acids (SCAFs) control hormones and bowel movements prebiotic carbohydrates are responsible for the softening stool because of their water retention property. Studying has further confirmed that a ratio of Galactooligosaccharide (GOS) and fructans of 9:1 lowers respiratory tract infections in new-borns [32]. A study done on elderly people taking Galactooligosaccharide (GOS) revealed enhanced phagocytosis, and NKCA and valuable microorganisms [29].

Constant intake of prebiotics can cause accumulation of the mentioned molecules and even the number of metabolites. Molecular dynamism in a diet containing arachidic acid, behenic acid, and oleic acid together with a novel prebiotic Galactooligosaccharide (GOS) was shown to affect approximately 21 receptors in a study. It was also established that difructose anhydrides (DFA) impacted on the bioavailability of the iron and blood calcium. Moreover, prebiotics increase the permeability of the intestinal membrane according to the molecule size and improve, nutrient absorption in the intestine and, therefore, the proliferation of different kinds of blood cells. From Channastriate fingerlings high percentage of fructo-oligosaccharide and manoligosaccharide enhanced the increase in hemoglobin and serum protein [48]. It should also be noted that prebiotics enhance feelings of fullness, decrease and prevent constipation and diarrhoea, and are beneficial for cardiovascular health [7].

Source of Prebiotics of Vegetable Origin and Their Biochemical Constituents: Many plants contain prebiotics in them because of the carbohydrate they possess. The examples are garlic, onions, wheat, asparagus, bananas, dandelion root, and many tubers. Pectin present in walls of these plants belongs to those Polysaccharides that can synthesize prebiotics. For example, Kiwi has bacterial polysaccharides content, which results into the formation of metabolites and alteration of colonic bacteria. Solutes such as polyphenols found in the food are metabolized with colonic bacteria or their distribution in the intestine. Some of the phenolic metabolites of low molecular weight can be produced through the metabolic activities of the gut bacteria, such as *Lactobacteria* and *Bifidobacteria* [78]. These interactions synthesise prebiotics; *Aspergillus brasiliensis* and *Aspergillusnidulans* are capable of fermenting rice husk carbohydrates into Xylooligosaccharides (XOS) at 37 °C, pH 4. 5–7, for five days. Enzymatic processes also create prebiotics; when cellobiose 2-epimerase is applied on milk, 50 °C for 24 hours lactulose and epilactose are generated [79].

TABLE 3: THE SOURCES OF PREBIOTICS

Sources of Prebiotics	Examples
Dietary fibers[7]	Fruits and vegetables including chicory root, garlic, leeks, onion, asparagus, banana, barley, oats, apple, and seaweeds
Fructooligosaccharides (FOS)[80]	Honey, banana, barley, tomato, asparagus, sugar beet, garlic, wheat, mushrooms, and rye
Xylooligosaccharides (XOS)[48]	Variety of fruits, vegetables, milk, bamboo shoots, and honey
Galactooligosaccharides (GOS)[48]	Bovine and human milk
Raffinose oligosaccharides[81]	Seeds of legumes, peas, lentils, beans, mustard, and chickpeas
Soybean oligosaccharides (SOS)[7]	Soybeans, which consist of raffinose and stachyose

Prebiotics are substances that can develop and enhance their presence in a variety of products such as rice, wheat, oats, barley and aloe vera. Coffee also restores prebiotics derived from roasted, dark, and ground coffee beans (*Anacardium occidentalel*), which significantly boosts lactobacillus species [7]. Additionally, biologically active peptides, vitamins and minerals in milk, which contain numerous prebiotics, are major sources of immune-boosting cytokines. Consequently, Prebiotics in milk, particularly in yoghurt, increase *Bifidobacteria*. Xylooligosaccharides (XOS) have been demonstrated to be more potent growth enhancers of probiotics than Fructo-oligosaccharides (FOS), stimulating the growth of *Bifidobacteria* and *Lactobacillus* [48].

Metabolic Profiling of Bioactive Compounds in Foods and Supplements: Bioactive compounds in foods and supplements can be directly assessed, and their effect on human health can be understood by measuring metabolic profile. This helps identify products resulting from the metabolism of short-chain fatty acid (SCFAs) which are produced after fermentation of dietary fibres by gut bacteria [12, 78]. Metabolic profiling involves techniques like "hydrogen nuclear magnetic resonance (H-NMR) spectroscopy" and "mass spectrometry", along with structural analysis experiments to study the composition of the microbiome. Combining metabolic profiling and structural analysis measurements allows fora deeper understanding of metagenomic and metabolic data, leading to a more accurate classification and comprehension of microbiome functions [78, 82].

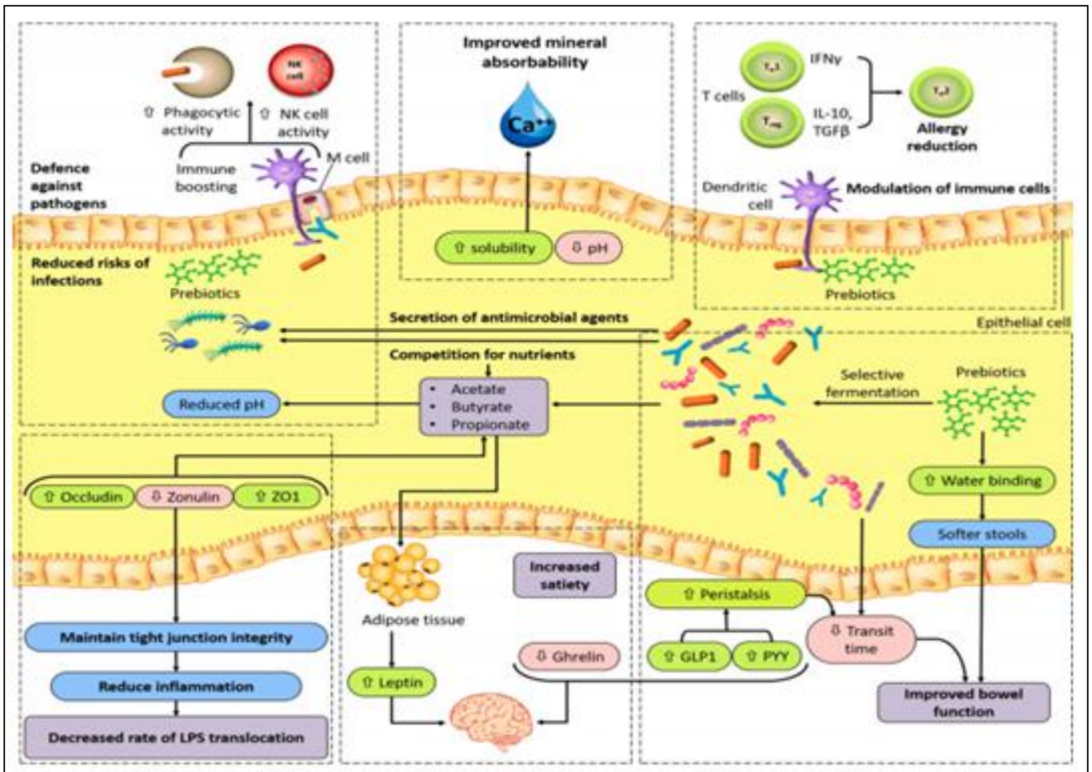

FIG. 2: ROLE PREBIOTICS IN THE GUT [29]. When prebiotics are used selectively in the gut, the microbiota expands to support immunity at many species and strain levels. For a healthy bowel movement, the bacterial cell wall and other biomass boost immunomodulation and faecal bulking. Organic acids and other metabolites lower the luminal pH, which is hazardous to pathogens but helps make minerals like calcium soluble and absorbable. They also have a favourable effect on hormone regulation and epithelial integrity. GLP1: glucagon like peptide1; IL-10: Interleukin 10; M cell: microfold cell; NK: natural killer; PYY: peptide YY; TGFβ: transforming growth factor-β; Th1: type 1 T helper; Th2: type 2 T helper; Treg: regulatory T cells; ZO1: zonula occludens 1.

Effect of Prebiotics on Various Disease: Prebiotics play a very important role in the management of certain health disorders by intervening with gut microbiota and metabolic pathways. They can manage the raised levels of bile acid by supplementing with good bacteria in to enhance the metabolism of bile acids. These prebiotics inhibit the activity of enzyme that degrade hypoxanthine and short chain fatty acid (SCFAs) such as tryptamine, and thus relieve constipation [82]. Research has shown that in stool samples of people with obesity, there is generally a lower level of SCFAs. Short-chain fatty acids play an enormous role in the in stimulating the satiety hormone glucagon. Moreover, research has proved that a greater abundance of SCFA-producing bacteria can improve blood sugar level [16]. Vulevic, 2015, proved that when Galactooligosaccharide (GOS) prebiotics were given to the elderly, showed elevated levels of lactate, increased *Bifidobacteria* and *Bacteroids* were identified, an indication of an increased colic absorption and reduced excretion [78]. Changes in faecal metabolites were detected in the stool of irritable bowel syndrome patients [82].

Prebiotics were also reported to ameliorate to colon cancer. Butyrate is the main SCFA that affects the proliferation of epithelial cells growth in the colon and serves as an energy source. It also affects the production of anti-inflammatory propionate and acetate in the large intestine which will lower pH that will favour the multiplication, *Lactobacilli* and *Bifidobacteria* [3]. Butyrate has been shown to suppress Interleukin 12 (IL12), enhance Interleukin 10 (IL10) and Interleukin 14 (IL14) secretion, and inhibit the production of Interferon gamma (IFN-g) and Interleukin 2 (IL 2). Inhibiting colonic immune activation by inducing apoptosis and decreasing inflammatory signals, butyrate affects Interferon (IFN) signalling pathways including, specifically activator of transcription 1 (STAT1) and nitric oxide synthase (INOs) models. The induction of butyrate has shown decreased levels of the pro-inflammatory cytokines (IL6) and tumour necrosis factor-beta (TNF-B) in human studies [48]. Furthermore, Short chain fatty acid (SCFAs) are ligands for G-protein-coupled receptor 41 (GPR41) and G-protein-coupled receptor 43 (GPR43) on epithelial cells and therefore trigger immune responses to protect against infection by intestinal *Escherichia coli* [29]. Short chain fatty acid (SCFAs) affect the function of the colonic epithelium through the good absorption of various cations such as calcium (Ca+2), magnesium (Mg+2), and iron (Fe+2) [7].

Prebiotics appear to have beneficial effects in the management of type 2 diabetes. For example, β-glucans lower glycemic index and cholesterol levels. The intake of carbohydrates has an impact on the insulin and blood sugar responses and thus affects the intestinal microflora. Recently, scientific Studies have established a correlation between microbiome-brain axis with obesity, and diabetes among others [48].

In a study in children and women done over a wide span of 60 days or more, it was established that prebiotics extracted from orange juice, other than being fortified with hesperidin and naringen increased, substantially enhanced insulin regulation, lowered glucose levels, triglycerides, and the level of total cholesterol [29]. Prebiotics extracted from mushrooms have also demonstrated anticancer activities and activate the immune system [79].

TABLE 4: THE ROLE OF PREBIOTICS IN THE DISEASE

Disease	Prebiotic	Role of Prebiotics
Irritable Bowel Syndrome and Crohn's [83]	Fructo-oligosaccharides (FOS)	Raised the number of Bifidobacteria in the stomach and benefited those with Crohn's disease.
Necrotizing Enterocolitis [84]	Fructo-oligosaccharides (FOS), Galacto-oligosaccharides (GOS), or their combination	May increase the amount of fecal Bifidobacteria.
Immune System [69,85]	Adherence of mannose to Salmonella; Fructo-oligosaccharides (FOS) and Galacto-oligosaccharides (GOS)	Inhibits pathogen colonization. Improves the availability of lymphocytes and/or leukocytes in the Gut-associated lymphoid tissue (GALT).
Skin [86]	Alginate oligosaccharides (AOS) and Galacto-oligosaccharides (GOS)	Successfully prevents atopic dermatitis.
Cardiovascular System [72,87]	Inulin and Lactulose	Lowers the risk of cardiovascular disease (CVD).
Calcium Absorption [32]	Short-chain fatty acids (SCFA); Galacto-oligosaccharides (GOS)	Lowers luminal pH, making calcium more soluble and enhancing its passive uptake. Improves barrier function in vivo. Prebiotic intervention benefits human blood lipid profiles, inflammation, and glucose homeostasis.
Depression and Anxiety [60]	Short-chain fatty acids (SCFA), Galacto-oligosaccharides (GOS), and Fructo-oligosaccharides (FOS)	No positive effect of prebiotics on reducing depression and anxiety.
COVID-19 [49]	An increase in short-chain fatty acid	Aids in reducing inflammation and remodeling beneficial

	(SCFA) synthesis	bacteria in the gut, providing health benefits for COVID-19 patients.
Hypertension [88,89]	Dietary fibers; Short-chain fatty acids (SCFAs)	Reduces the risk of hypertension by raising acetate concentrations and intestinal Bacteroides levels. Alters the composition and structure of the gut microbiota, helping to regulate blood pressure.
Cancer [90]	Short-chain fatty acids and conjugated linoleic acid	Modifies the intestinal microbiota composition, metabolic activity, and production of compounds with anticarcinogenic activity.

AOS, Alginate oligosaccharides; CVD, Cardiovascular; COVID-19, Coronavirus disease 2019; FOS, Fructo-oligosaccharides; GOS, Galacto-oligosaccharides; GALT, Gut-associated lymphoid tissue; NEC, Necrotizing Enterocolitis; SCFA, Short-chain fatty acids.

Prebiotics Safety Levels: Production technologies for prebiotic involve isomerization, fructosyl-transfer, and hydrolysis, and microbial fermentation [79] to enhance physical and chemical properties [18]. Though the US Food and Drug Administration does not define prebiotics, the same are regulated and labeled as safe for consumption in countries like Japan, the Netherlands, and Sweden [83]. Microbial diversity in the gut varies between developed and underdeveloped regions due to environmental influences on gut flora composition [19].

Safety levels of prebiotics depend on acidity of the stomach, bile, the site of digestion mainly in the colon [15, 20]. Chain length is a vital aspect of prebiotics, and shorter chains can be fermented in the proximal colon, while the longer chain of prebiotics ferments more slowly in the distal colon with a negative influence on health. Common adverse effects due to excessive intake of prebiotics include osmotic diarrhoea and flatulence and have been reported to cause bacteremia and infections [69].

Insights from Ancient Systems of Medicine:

Indian System (Ayurveda): Ayurveda, the ancient Indian system of medicine, emphasizes the importance of gut health through the concept of "Agni" (digestive fire) [91]. A strong Agni is central to Ayurvedic philosophy, believed to be the cornerstone of good health by aiding in the proper digestion of food, experiences, and emotions.

Traditional Probiotic Preparations in Ayurveda:

Asava and Arishta: These are traditional fermented medicinal wines. Herbs and other ingredients are soaked in water or fruit juices and allowed to ferment naturally. These preparations are rich in beneficial microorganisms, including lactic acid bacteria and yeasts.

Takra (Buttermilk): Considered a digestive elixir in Ayurveda, takra is made by churning yogurt and adding water. It contains diverse probiotic strains such as Lactobacillus and Bifidobacterium species, which are known to support gut health.

Kanji: This fermented rice gruel is rich in prebiotics and naturally occurring probiotics. It has been traditionally used to prevent and treat diarrheal diseases.

Shukta: Various vegetables and fruits are fermented to create shukta preparations. These not only preserve food but also enhance its nutritional and medicinal properties [92].

Traditional Prebiotic Foods in Ayurveda:

Ginger: Known for its digestive properties, ginger is often used in Ayurvedic preparations to enhance digestion and support gut health.

Turmeric: This powerful anti-inflammatory spice is also considered a prebiotic, promoting the growth of beneficial gut bacteria.

Asafoetida: Commonly used in Indian cooking, asafoetida aids in digestion and helps maintain a healthy balance of gut flora.

Fenugreek: Rich in fiber, fenugreek seeds act as a prebiotic, supporting the growth of beneficial bacteria in the gut [93, 94].

Modern Research and Validation: Modern scientific research has validated many of these traditional practices. Studies have shown that Ayurvedic fermented foods often contain more probiotic strains than commercial products. Additionally, the use of prebiotic foods like ginger and turmeric has been supported by research for their role in promoting gut health [94, 95, 96, 97].

Chinese System (Traditional Chinese Medicine): Traditional Chinese Medicine (TCM) is one of the most important complementary and alternative therapies, which has played a major role over the years in treating or alleviating various diseases. TCM works to maintain gut health through Chinese plants and herbal compounds that produce prebiotics and some types of good bacteria.

Herbal Combinations in TCM: In one study, three herbs *Rheum palmatum, Coptis chinensis*, and *Scutellaria baicalensis* were combined in a traditional herbal formula administered to mice with Type 2 Diabetes Mellitus. This formula was found to improve the disease by modifying the intestinal microflora and producing new bacteria such as *Alloprevotella* and *Barnesiella* that contribute to the production of short-chain fatty acids (SCFAs) [17].

Both Ayurveda and Traditional Chinese Medicine have long recognized the importance of gut health and have utilized probiotics and prebiotics to promote well-being. Ayurveda, with its rich history of fermented foods and digestive spices, offers a holistic approach to maintaining gut health. Traditional Chinese Medicine complements this with its use of herbal compounds to modify gut flora and enhance health. Modern research continues to validate these ancient practices, highlighting their relevance in contemporary health and wellness. By incorporating these traditional practices, we can support our digestive health and overall well-being, leveraging the wisdom of ancient systems to complement modern scientific understanding.

Synbiotic and Postbiotics: Synbiotics are combinations of probiotics and prebiotics designed to synergistically improve gut health and overall well-being [6, 48, 98]. Probiotics are live microorganisms that confer health benefits to the host, while prebiotics are non-digestible substrates that promote the growth and activity of beneficial gut bacteria. Their combination provides a synergistic effect for better survival of probiotics, increased activity, improved integrity of the gut barrier and digestive health. Research involving humans, fish, and oysters has demonstrated that synbiotics are more effective than pre and probiotics for gastrointestinal health [67, 82].

Postbiotics are metabolic by-products produced by probiotic bacteria. These substances exert effects on the host either directly or indirectly [3, 6], Experimental evidence suggests that postbiotics can modulate the immune system [7] and are beneficial for various conditions including Alzheimer’s disease, multiple sclerosis, and SARS-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus). They also aid in managing allergic diseases by restoring the balance between helper T cells (type I and type II) and influencing physical fitness and activity. For example, recent research on rats has identified propionate, a postbiotic derived from lactic acid metabolism by the *Veillonella* genus, as having potential health benefits [6]. Additionally, postbiotics may interact with antibiotics such as tetracyclines, quinolones, and macrolides [29].

Challenges and Limitations of Probiotics: Despite the potential benefits, the effectiveness of probiotics remains debated. Systematic reviews and meta-analyses have highlighted inconsistencies in the results of probiotic studies. For instance, some studies have reported a decrease in C-reactive protein levels, while others have questioned the reliability of these findings due to limitations in study design and the need for more randomized clinical trials [99, 100, 101]. Furthermore, genetic factors, dietary differences, and variations in microbial composition can impact individual responses to probiotics, contributing to the variability in study outcomes. Research involving children, adults, and the elderly has shown mixed results regarding probiotics such as *S. boulardii* [31, 102, 103, 104] and various strains of *Lactobacillus*, particularly in treating conditions like acute intestinal inflammation and gastroenteritis [31].

In neonates, the efficacy of probiotics in treating sepsis and reducing mortality has varied based on factors such as birth weight, milk type, and the use of single versus mixed strains. For instance, probiotics like *L. plantarum PP 11-217* and prebiotics such as fructooligosaccharides (FOS) were effective in Indian infants, while *Bifidobacteriumbreve BBG-001* showed limited benefits in English infants fed pasteurized milk. Conversely, combining *Lactobacillus* and *Bifidobacteria* was effective in treating necrotizing enterocolitis (NEC) but not nosocomial sepsis [105, [106, 107, 108, 109, 110, 111]. A comprehensive review by the Southeast Asian Neurogastrointestinal Society (SEAGMA) on the clinical use of probiotics reported differed opinions on their effectiveness. Probiotics were found to be beneficial for treating acute gastroenteritis in children and reducing antibiotic-associated diarrhoea, but less effective for constipation or obesity in children. They were also noted to have limited efficacy in inducing remission for ulcerative colitis but helpful in maintaining remission for chronic bursitis. The review emphasized the need clinical trials to validate their efficacy [112].

Future Directions: The development of precision probiotics has numerous challenges. The two types of research studies involved in precision probiotics include observational and mechanistic studies, whereas the utilization of phenotypic screening with target-based discovery is still under development [21]. The high throughput strategies aim to describe molecular processes and host responses in more detail to design specific probiotic consumption strategies. Newer techniques like multi-omics technologies are helping in gaining better perspective for microbial associated community, bridging the gap in clinical diagnostics and improving the awareness of public regarding prebiotics, probiotics [82]. These advancements accompanied by the integration of nanotechnology have revealed enhanced product stability, as well as the effectiveness of the chemicals and structure of the probiotics and prebiotic [82, 91, 113, 114, 115, 116, 117] and is expected to become a powerful partner alongside drug therapies through advanced research [29, 118].

CONCLUSION: Ongoing research and technological innovations continue to advance the field of probiotics and prebiotics. Understanding bacterial strains, their mechanisms of action, and adherence to safety standards will be crucial for their integration into global healthcare systems. The growing body of evidence and increasing consumer awareness suggest that probiotics and prebiotics will play a significant role in future therapeutic and preventive health strategies.

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