Progress in Microbes and Molecular Biology

HH PUBLISHER

Review Article

Expanding Horizons of Probiotic Research: Postbiotics, Precision Therapies, and Emerging Clinical Applications

Siew Mei Tan[1], Achuth Jayakrishnan[2], Ying Hui Loke[1], Siti Munirah Md Noh[1], Phei Er Kee[1], Muhammad Redza Fahmi Mod Razif[1], Vinie Xian Ying Tan[1], A.B.M. Helal Uddin[3], Hui-Suan Ng[4*], Jui-Jen Chang[5,6*], Kai Bin Liew[1*]

Article History

Received: 16 October 2026;

Received in Revised Form: 20 November 2026;

Accepted: 24 November 2026;

Available Online: 26 November 2026

[1]Faculty of Pharmacy, University of Cyberjaya, Persiaran Bestari, 63000 Cyberjaya, Selangor, Malaysia; siewmei.tan@cyberjaya.edu.my (SMT), lokeyinghui@cyberjaya.edu.my (YHL), sitimunirah@cyberjaya.edu.my (SMMN), kpe0731@gmail.com (PEK), muhammadredza@cyberjaya.edu.my (MRFMR), vinie9988@gmail.com (VXYT)

[2]Department of Microbiology, Hindusthan College of Arts & Science, Coimbatore, Tamil Nadu, 641028, India; achuth.j@hicas.ac.in (AJ)

[3]Faculty of Pharmacy, International Islamic University Malaysia, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia; abmhelal@iium.edu.my (ABMHU)

[4]Smart Bioresource Recovery and Formulation Laboratory, Department of Chemical Engineering and Materials Science, Yuan Ze University, Chungli, Taoyuan 320, Taiwan

[5]Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan, R.O.C

[6]Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan, R.O.C

*Corresponding authors: Kai Bin Liew; Faculty of Pharmacy, University of Cyberjaya, Persiaran Bestari, 63000 Cyberjaya, Selangor, Malaysia; liewkaibin@cyberjaya.edu.my (KBL); Jui-Jen Chang; Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan, R.O.C; lance@twbio.com.tw (J-JC); Hui-Suan Ng; Smart Bioresource Recovery and Formulation Laboratory, Department of Chemical Engineering and Materials Science, Yuan Ze University, Chungli, Taoyuan 320, Taiwan; grraceng@saturn.yzu.edu.tw (H-SN)

Abstract: The development of microbiome-based therapeutics has expanded beyond conventional probiotics to include next-generation probiotics (NGPs), engineered live biotherapeutic products, synbiotics, postbiotics, paraprobiotics, and microbially based peptides. Although these approaches offer diverse mechanisms for modulating host-microbiome interactions, their therapeutic promise is not consistently supported by clinical evidence. This review critically evaluates the biological mechanisms, formulation, and delivery strategies, and emerging therapeutic applications of these microbial interventions, with particular emphasis on the gap between mechanistic potential and clinical translation. It

examines how microbial strains, cellular components, and bioactive peptides influence epithelial barrier integrity, immune signalling, pathogen virulence, and host metabolism, while assessing the contributions of formulation technologies, including microencapsulation and targeted delivery, to product stability and therapeutic performance. Evidence from preclinical investigations and human studies is critically appraised, distinguishing mechanistic plausibility and preliminary safety or pharmacodynamic findings from demonstrated clinical efficacy. Emerging applications in chronic kidney disease, iron deficiency anaemia, mental health, and metabolic disorders are considered, alongside potential differences in therapeutic responses across paediatric and geriatric populations. The review further identifies key translational barriers, including heterogeneity in product composition and dosing, inadequate standardisation, variable clinical outcome measures, and regulatory challenges across product categories. Microbiome profiling and multi-omics approaches may support patient stratification and precision-based interventions, although their clinical utility requires prospective validation. Therefore, advancing microbial therapeutics towards clinical application will require product-specific characterisation, appropriately designed and adequately powered clinical trials, validated biomarkers, and evidence of sustained clinical benefit. This critical synthesis provides a framework for evaluating the maturity of emerging microbial interventions and identifying the evidence needed to translate mechanistic advances into clinically meaningful outcomes.

Keywords: Next-generation probiotics; postbiotics; live biotherapeutic products; precision microbiome therapeutics; targeted probiotic delivery; SDG 3 Good health and well-being

1. Introduction

Probiotic research was originated from interest in fermented foods and the beneficial effects of live microorganisms on intestinal health. Its scope has progressively expanded towards the development of microbial-based interventions targeting specific biological functions and clinical indications. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as live microorganisms that confer a health benefit when administered in adequate amounts. This definition establishes viability and demonstrates health benefits as essential characteristics of probiotics. As a result, studies performed for a particular strain, formulation, or patient population could not be necessarily extrapolated to other microbial products or clinical settings [1]. Beyond gastrointestinal health, research has increasingly explored extraintestinal applications, including the gut-skin axis and strain-specific probiotic approaches to atopic dermatitis [2,3].

Alongside conventional probiotics, several emerging microbial-based approaches have broadened the scope of microbiome-targeted interventions. Synbiotics combine live microorganisms with substrates selectively utilised by host microorganisms, with a

demonstrated health benefit from the combination [4]. Postbiotics refer to preparations of inanimate microorganisms and/or their components that confer a health benefit, although purified microbial metabolites alone do not meet the ISAPP definition [5]. Other terms, including paraprobiotics and proteobiotics, have also appeared in the literature to describe inactivated microbial preparations and microbially based peptides investigated for antimicrobial or antivirulence activities, respectively [6,7]. More recently, next-generation probiotics (NGPs) and engineered live biotherapeutic products have attracted interest because of their potential to deliver more targeted and function-specific therapeutic effects. Despite these developments, the expanding terminology also reflects differences in product composition, mechanisms of action, manufacturing requirements, and regulatory considerations. These distinctions are important because the evidence required to establish safety, biological activity, and clinical benefit varies considerably between product categories.

Despite encouraging mechanistic findings and increasing clinical investigation, an important translational gap remains between the biological potential of microbiome-based interventions and their demonstration of clinically meaningful benefits. Early human studies illustrate both the opportunities and limitations of this emerging field. For example, a pilot study investigating *Akkermansia muciniphila* reported improvements in selected metabolic parameters following administration of its pasteurised preparation for adults with overweight or obesity and insulin resistance [8]. Although these findings support further investigation, the limited scale and exploratory nature of the study do not establish efficacy across broader patient populations or clinical indications. Similarly, a first-in-human study evaluated the safety and pharmacodynamic activity of an engineered *Escherichia coli* Nissle strain designed to metabolise phenylalanine in the gastrointestinal tract [9]. However, early-phase safety and pharmacodynamic findings should not be interpreted as evidence of therapeutic efficacy. Furthermore, the clinical performance of microbial interventions may be influenced by interindividual differences in baseline microbiome composition and host characteristics. A human study demonstrated that mucosal colonisation following administration of a probiotic mixture varied according to baseline host and microbiome features, highlighting the importance of understanding host-microbiome interactions when developing precision-based interventions [10]. In addition, formulation and delivery remain important considerations, particularly for live microbial products, as encapsulation strategies may help preserve microbial viability during gastrointestinal transit [11].

These challenges highlight the need to evaluate emerging microbiome-based interventions beyond their proposed mechanisms of action and early clinical signals. In

particular, the translation of these approaches requires stronger evidence of clinical benefit, well-characterised and standardised products, appropriate formulation, and delivery strategies, and a clearer understanding of host-specific responses. Although existing reviews have discussed individual microbial approaches and their therapeutic applications, an integrated assessment of the relationship between mechanistic evidence, early-phase clinical findings, product development, and the requirement for clinical translation remain important. This is particularly relevant as research expands towards chronic and multifactorial conditions, for which microbial interventions may have different therapeutic implications across patient populations.

Accordingly, this review critically examines the development and therapeutic potential of next-generation probiotics, engineered live biotherapeutics, and non-live microbial preparations, including postbiotics and other microbially based bioactive components. It evaluates their emerging applications in chronic kidney disease, iron deficiency anaemia, mental health, and metabolic disorders, with particular consideration of paediatric and geriatric populations. In addition to discussing proposed mechanisms and available preclinical and clinical evidence, this review considers the challenges associated with product standardisation, formulation and delivery, regulatory classification, and microbiome profiling. Importantly, it distinguishes mechanistic findings and early human studies from established clinical benefits, thereby identifying the evidence gaps and research priorities that should be addressed to advance these emerging interventions towards clinical application.

2. Beyond Conventional Probiotics: Expanding the Definitions

2.1. Probiotics vs. Synbiotics vs. Postbiotics vs. Paraprobiotics vs. Proteobiotics

The landscape of microbiome therapeutics has expanded beyond traditional probiotics to include diverse microbial interventions, including synbiotics, postbiotics, paraprobiotics, and proteobiotics, each with distinct mechanisms of action and therapeutic benefits. Although these approaches share the objective of modulating host-microbe interactions, they differ considerably in their composition, viability requirements, mechanisms of action, and levels of supporting evidence [5]. Understanding these distinctions is essential for interpreting experimental findings and evaluating their therapeutic applicability.

Probiotics represent the foundational category, defined by ISAPP as “live microorganisms that, when administered in sufficient quantities, confer a health benefit to

the host" [6]. These live microorganisms must retain viability during processing, storage, and gastrointestinal transit. Conventional probiotics exert their effects via competitive exclusion of pathogens, synthesis of bioactive metabolites, modulation of host immune responses, and enhancement of intestinal barrier integrity [12]. Importantly, safety assessments and regulatory requirements depend on the intended application and jurisdiction, whereby Generally Recognised as Safe (GRAS) and Qualified Presumption of Safety (QPS) status should not be interpreted as universal regulatory approval or proof of clinical efficacy.

Synbiotics are targeted combinations defined as "a mixture comprising live microorganisms and substrate(s) selectively utilised by host microorganisms, conferring a health benefit to the host" [13]. They are broadly categorised into complementary synbiotics, in which probiotics and prebiotics independently provide health benefits, and synergistic synbiotics, in which the substrate is specifically selected to support the administered microorganism. By combining microbial supplementation with substrate availability, synbiotics may improve microbial activity and metabolic functionality via substrate-driven support, potentially addressing limitations of standalone probiotic use. However, the benefits of these formulations cannot automatically be attributed to the combined intervention, as the individual contributions and potential interactions of their components require appropriate experimental evaluation.

Postbiotics are defined by ISAPP (2021) as "inanimate microorganisms and/or their components that confer a health benefit on the host" [14]. Unlike conventional probiotics, postbiotics do not require viable microorganisms to exert their biological effects. Their composition may include inactivated microbial cells, cellular components, and associated bioactive constituents. Although microbial metabolites and cell-free supernatants may contribute to biological activity, isolated metabolites alone should not automatically be classified as postbiotics under the ISAPP definition [15]. The absence of viability requirements may improve formulation stability, facilitate quality control, and reduce concerns associated with administering live microorganisms, although these advantages depend on the manufacturing process and the stability of the active constituents [5].

Paraprobiotics, also known as ghost or inactivated probiotics, are defined as "non-viable microbial cells (intact or fragmented) or crude cell extracts that, when administered in sufficient quantities, confer a health benefit" [6]. These preparations may contain structural molecules, including exopolysaccharides, peptidoglycans, and cell-wall-associated proteins or glycoproteins [16], which interact with host immune and epithelial pathways. However, the terminology overlaps substantially with the broader ISAPP definition of postbiotics, and

paraprobiotics are not universally recognised as an entirely separate regulatory or scientific category. As a result, their classification should be based on the composition and characteristics of the preparation rather than terminology alone. Although comparative studies have reported greater antioxidant and anti-inflammatory activities of certain inactivated strains than their viable counterparts in experimental models of ulcerative colitis, these findings are model- and strain-dependent and cannot establish the general superiority of paraprobiotics or demonstrate equivalent benefits in humans [17].

Proteobiotics are a less established category of microbial-derived bioactive compounds, generally referring to antimicrobial peptides and proteinaceous metabolites produced by selected probiotic strains, including species of *Lactobacillus*, *Lactococcus*, and *Bifidobacterium* species [7]. These compounds may exert antimicrobial and antivirulence activities by interfering with pathogen adhesion, inhibiting toxin production, suppressing virulence-associated gene expression, and disrupting quorum-sensing pathways. Distinctive with whole-cell probiotics, proteobiotics can potentially provide more targeted antimicrobial activity without requiring the administration or establishment of viable microorganisms. However, their composition, classification, and proposed mechanisms remain less standardised than those of established probiotic and postbiotic preparations, warranting further characterisation and validation.

2.2. Regulatory Landscape and Challenges

The regulatory framework for microbiome-based therapeutics remains fragmented because of inconsistent terminology, differences in product classifications, and variations in regulatory requirements across jurisdictions [18]. The regulatory pathway is generally determined by product composition, intended use, health claims, and the jurisdiction in which the product is marketed. For example, probiotics intended for general consumption may be regulated as foods or dietary supplements, whereas products intended to prevent or treat specific diseases may be subjected to more stringent requirements applicable to biological products or live biotherapeutic products (LBPs) [19]. GRAS and QPS frameworks provide safety-related assessments within their respective jurisdictions but do not replace product-specific evaluations of clinical efficacy.

LBPs intended for disease prevention or treatment are subjected to rigorous regulatory evaluation, including preclinical investigations, clinical trials, and manufacturing quality requirements. In the United States, the Food and Drug Administration (FDA) regulates investigational LBPs under the relevant drug and biological product frameworks, with particular emphasis on product identity, purity, potency, safety, and manufacturing

consistency. Good Manufacturing Practice (GMP) requirements are essential for ensuring batch-to-batch reproducibility, microbial identity, genetic stability, and contamination control [20,21]. However, the capacity of conventional manufacturing and quality-control frameworks to address strain-specific genetic variation, microbial adaptation, and the potential acquisition or transfer of antimicrobial resistance determinants remains an important consideration for microbial therapeutics.

Regulatory uncertainty is also evident for postbiotics and paraprobiotics, for which the absence of universally harmonised product classifications complicates the evaluation of composition, biological activity, and safety [14,22]. Depending on the jurisdiction and intended claims, these preparations may be assessed under existing food, supplement, novel food, or medicinal product frameworks. Their non-viable nature may reduce certain risks associated with administering live microorganisms. However, inactivation does not directly link to establish safety, as residual bioactive components, impurities, manufacturing-related contaminants, and immunological responses still require evaluation. Furthermore, the distinction between postbiotics, paraprobiotics, and other microbial-derived preparations is not consistently reflected in regulatory terminology.

Synbiotics introduce additional regulatory and scientific complexity because they contain multiple components with potentially independent and interactive effects. Therefore, the identity, safety, quality, and functionality of both the microbial and substrate components must be established. Demonstrating that the combined formulation provides a health benefit beyond that of its individual components may also require appropriately designed comparative studies [4,23]. Proteobiotics face further challenges because their molecular composition, production processes, mechanisms of action, and pharmacological properties are not yet supported by widely accepted classification or regulatory standards [7].

Beyond product approval, regulatory fragmentation has important consequences for scientific evidence synthesis. Differences in product definitions, microbial strains, inactivation methods, formulation compositions, dosage specifications, and outcome measures can result in substantial methodological heterogeneity across studies. For example, preparations described as postbiotics may differ considerably in their cellular composition and metabolite content, while paraprobiotic studies may use different microbial inactivation techniques and characterisation criteria. Such inconsistencies make it difficult to determine whether studies are investigating comparable interventions, even when similar terminology is used. Consequently, pooling results across heterogeneous preparations may introduce

substantial clinical and methodological heterogeneity, limiting the reliability of meta-analyses and potentially obscuring genuine differences in therapeutic efficacy.

These challenges also hinder the translation of preclinical findings into clinical practice, as differences in product characterisation and quality control procedures may compromise reproducibility and complicate comparisons between clinical trials. International initiatives, including the FAO/WHO and Codex Alimentarius frameworks, provide important foundations for improving harmonisation of food-related microbial product standards [24]. However, further agreement on standardised definitions, minimum characterisation requirements, manufacturing specifications, and clinically relevant outcome measures remains necessary. Such harmonisation would facilitate meaningful cross-study comparisons, strengthen evidence synthesis, and support the development of reproducible and clinically translatable microbiome-based therapeutics. Table 1 below summarises the definitions, viability, regulatory considerations, and strength of clinical evidence of the microbiome-based therapeutic interventions.

Table 1. Comparison of microbiome-based therapeutic interventions according to definition, microbial viability, regulatory considerations, and strength of clinical evidence.

Category	**Definition and composition**	**Microbial viability**	**Regulatory considerations**	**Strength of clinical evidence**
Probiotics	Live microorganisms that confer a health benefit when administered in adequate amounts.	Viable; requires maintenance of viability throughout processing, storage, and administration.	Relatively established frameworks for food and supplement applications; disease-related claims and LBPs require more stringent regulatory evaluation.	Most established among the five categories, with human clinical evidence available for selected strains and indications. However, efficacy remains strain-, dose-, and indication-specific.
Synbiotics	Combinations of live microorganisms and substrates selectively utilised by host microorganisms to confer a health benefit.	Contains viable microorganisms and a selectively utilised substrate.	Requires characterisation and safety assessment of both components, as well as evidence supporting the combined health benefit.	Human clinical studies are available for selected formulations and indications, but findings are heterogeneous and the contribution of individual components is not always established.

Category	Definition and composition	Microbial viability	Regulatory considerations	Strength of clinical evidence
Postbiotics	Preparations of inanimate microorganisms and/or their components that confer a health benefit.	Non-viable; may contain intact or fragmented cells and associated cellular components.	Regulatory classification varies according to composition, intended use, and jurisdiction; standardised characterisation and safety requirements remain important challenges.	Predominantly preclinical evidence, with emerging human studies; clinical validation remains limited and preparation specific.
Paraprobiotics	Non-viable microbial cells, intact or fragmented, and cellular components retaining biological activity.	Non-viable.	No universally harmonised classification as a distinct category; frequently overlaps with postbiotics in terminology and regulatory interpretation.	Mainly supported by in vitro and animal studies; comparative clinical evidence demonstrating superiority over viable probiotics remains insufficient.
Proteobiotics	Bioactive peptides and proteinaceous metabolites produced by selected probiotic microorganisms, with potential antimicrobial and antivirulence activities.	No viable microorganisms are required when purified or isolated bioactive compounds are administered.	Specific regulatory frameworks remain poorly established; molecular characterisation, toxicological evaluation, and efficacy assessment are required.	Predominantly experimental evidence, with limited clinical validation and substantial opportunities for further investigation.

2.3. Functional Distinctions and Unique Therapeutic Potential

Although probiotics, synbiotics, postbiotics, paraprobiotics, and proteobiotics share the potential to modulate host-microbe interactions, their therapeutic effects arise through distinct biological mechanisms [5]. Importantly, the available evidence is not equally established across these categories, with much of the reported therapeutic potential being derived from *in vitro* investigations and animal models rather than adequately powered human clinical trials.

Conventional probiotics exert their biological effects through several complementary mechanisms, including competitive exclusion of pathogens, production of short-chain fatty acids (SCFAs) and vitamins, modulation of immune responses, and reinforcement of intestinal epithelial barrier integrity through interactions with pattern recognition receptors. Strain-specific investigations have demonstrated anti-inflammatory, metabolic, and physiological effects. For instance, *Lactobacillus paracasei* MSMC39-1, *L. sakei* Probio65, *and L. paracasei* NB23 have exhibited beneficial effects in experimental models investigating inflammatory responses, metabolic regulation, and exercise performance [25–27]. However, these findings should not be generalised across probiotic species or strains, as biological activity is highly strain dependent. Furthermore, scientific validation in animal and *in vitro* models does not necessarily establish clinical effectiveness in human populations.

Synbiotics aim to enhance microbial functionality by combining selected microorganisms with substrates that support beneficial microbial activity. Their proposed mechanisms include improved microbial survival or activity, increased SCFA production, and modulation of intestinal and systemic immunometabolic responses. Potential applications have been reported in inflammatory bowel disease (IBD) and oncology, suggesting their relevance to intestinal health and disease-associated microbiome modulation [28,29]. However, the clinical interpretation of these findings is complicated by differences in microbial strains, prebiotic substrates, intervention duration, and patient populations. In particular, the relative contributions of the individual components remain difficult to establish without appropriately designed factorial or component-controlled clinical trials.

Postbiotics offer an alternative approach by utilising inactivated microorganisms and their components to modulate host responses without requiring microbial viability. Proposed mechanisms include activation of anti-inflammatory signalling pathways, enhancement of epithelial barrier function, and interactions with host immune cells through microbial structural components and associated bioactive molecules. Extracellular vesicles derived from microorganisms may also contribute to host-microbe communication and intestinal physiological regulation. Experimental studies have demonstrated beneficial effects of heat-killed *L. plantarum* FRT4 and *Pediococcus acidilactici* pA1c® in models of hepatic steatosis and hyperglycaemia, while extracellular vesicles from *Escherichia coli* Nissle 1917 have been investigated for their effects on intestinal peptide transport [30,31]. Other experimental investigations have reported protective effects against colitis and mucositis [32,33]. Although some preparations have demonstrated comparable or superior effects to their viable counterparts, these findings are specific to the tested preparations, experimental conditions,

and outcome measures. They should therefore not be interpreted as evidence that postbiotics are generally more effective than conventional probiotics or that equivalent benefits have been established in humans.

Paraprobiotics similarly exert biological effects through non-viable microbial cells and their structural constituents. Their proposed mechanisms include interactions between microbial cell-wall components and host pattern recognition receptors, modulation of inflammatory signalling, antioxidant activity, and maintenance of epithelial barrier function. Studies involving UV-C-inactivated *Lacticaseibacillus casei* 39 and cellular fragments of *L. plantarum* and *L. reuteri* have reported anti-inflammatory and protective effects in experimental models of colitis and mucositis [34–36]. However, differences in microbial inactivation methods, residual cellular integrity, and the composition of the resulting preparations may substantially influence their biological activity. Furthermore, because these interventions overlap conceptually with postbiotics, distinguishing their therapeutic contributions requires more rigorous compositional characterisation and standardised terminology.

Proteobiotics provide a potentially more targeted approach to microbiome modulation through antimicrobial peptides and proteinaceous metabolites. Their mechanisms include disruption of pathogen-host interactions, inhibition of bacterial adhesion, suppression of toxin production, and interference with quorum-sensing pathways that regulate microbial virulence. For example, proteobiotic preparations derived from *L. acidophilus* have been investigated for their ability to reduce enterohemorrhagic *E. coli* colonisation and mitigate *Clostridioides difficile*-associated virulence [37]. Unlike broad-spectrum antimicrobial approaches, such targeted interventions may offer opportunities to control pathogenic activity while minimising disruption to beneficial microbial communities. However, their selectivity, stability, susceptibility to gastrointestinal degradation, potential toxicity, and effectiveness in clinically relevant settings require further investigation.

3. Next-Generation Probiotics: Redefining the Microbial Arsenal

Probiotics are widely used in daily life nowadays and can be found in a variety of products, including dietary supplements and fermented foods like yogurt and kombucha. Originally, the term “probiotics” was used to refer to substances and microorganisms that promote intestinal microbial balance. The definition has changed over time, and the joint Food and Agriculture Organisation (FAO) and World Health Organisation (WHO) group currently defines probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” [38,39].

Probiotics are believed to offer a number of significant health advantages to humans. For example, to support digestive health and general well-being, different probiotic strains are frequently added to fermented foods. However, recognition of their broader therapeutic potential has driven growing interest in research. According to recent research, probiotics can now be found in oral health products that aim to prevent dental cavities in addition to the gastrointestinal tract [40]. The development of new formulations and novel opportunities for probiotic research are being driven by these findings, which show that the advantages of probiotics extend beyond gut health.

In contrast to conventional probiotics, next-generation probiotics (NGPs) comprise emerging microbial candidates, frequently identified through comparative microbiome analyses and selected for their potential to provide specific health benefits [38,41]. Advances in next-generation sequencing, metagenomics, and bioinformatics have facilitated the identification of previously underexplored microorganisms associated with health and disease. Unlike conventional probiotics, which have an established history of use in fermented foods and dietary supplements, many NGP candidates are being investigated for disease-specific applications and targeted therapeutic effects [38,42,43]. However, the designation of a microorganism as an NGP does not necessarily indicate established clinical efficacy, standardised safety, or regulatory approval. Most candidates remain at different stages of preclinical and clinical development, and their therapeutic potential requires strain-specific validation. Table 2 summarises the distinguishing characteristics of NGPs and conventional probiotics, including the current uncertainties associated with their development and clinical translation [38,42,43,44].

Table 2. Comparative characteristics, developmental status, and translational uncertainties of next-generation and conventional probiotics.

Aspects	Next Generation Probiotics (NGPs)	Conventional Probiotics
Origin	Frequently identified from human microbiome studies, comparative microbiota analyses, and functional screening of emerging microbial candidates.	Commonly derived from food, fermented products, and human or animal microbiota, with established histories of use.
Identification and Development	Identified through metagenomic sequencing, bioinformatics, functional screening, and disease-associated microbiome analyses. Many candidates remain under preclinical or early clinical investigation.	Developed through conventional isolation, screening, and characterisation approaches, with a relatively extensive history of commercial use.

Aspects	Next Generation Probiotics (NGPs)	Conventional Probiotics
Biological Characteristics	May possess specialised metabolic, immunomodulatory, or disease-associated functions. However, proposed benefits require strain-specific functional validation.	Beneficial properties are also strain-specific and include competitive exclusion, metabolite production, and modulation of host responses.
Safety Profile	Often have limited human exposure data. Strain-level safety assessment, antimicrobial resistance screening, virulence characterisation, and long-term tolerability remain important.	Several commercially established strains have documented safety records, although safety cannot be generalised across all species or strains.
Therapeutic Applications	Primarily investigated for disease-specific applications, including metabolic disorders, inflammatory conditions, and targeted microbiome modulation. Clinical effectiveness remains under evaluation.	Commonly used in food and dietary supplements, with selected strains investigated or established for specific health indications.
Regulation Status	Regulatory classification depends on composition, intended use, and jurisdiction. Some candidates developed for therapeutic indications may be regulated as LBPs or biological products. No universal NGP-specific regulatory classification exists.	Regulated according to intended use and jurisdiction, including food, dietary supplement, or medicinal product frameworks.
Strain Specificity	Requires detailed strain-level characterisation because biological functions, safety profiles, and therapeutic effects may vary considerably.	Therapeutic effects are also strain-specific, despite the longer history of use of certain strains.
Clinical Evidence and Translational Uncertainty	Predominantly preclinical or early clinical evidence for many emerging candidates. Limited sample sizes, surrogate endpoints, variable formulations, and insufficient long-term follow-up restrict conclusions regarding clinical efficacy.	Relatively more extensive human evidence for selected strains and indications, although clinical effectiveness varies across products, populations, and conditions.
Key Developmental Challenges	Limited cultivation and formulation technologies for certain anaerobic species, incomplete safety characterisation, manufacturing consistency, host-microbiome interactions, and long-term ecological effects.	Maintaining strain viability, formulation stability, product quality, and reproducibility of strain-specific clinical benefits.

3.1. Non-traditional Strains (Akkermansia muciniphila, Faecalibacterium prausnitzii, and engineered probiotics)

Advances in microbial genomics, sequencing technologies, and bioinformatics have facilitated the identification and characterisation of microorganisms with potential therapeutic properties [38,45]. These approaches enable researchers to identify microbial candidates associated with specific physiological conditions and investigate their potential mechanisms of action. However, associations between microbial abundance and health outcomes do not necessarily establish causality or demonstrate that supplementation with the corresponding microorganisms will produce therapeutic benefits. Therefore, the selection of NGP candidates requires further functional characterisation, safety assessment, and clinical validation [38]. Figure 1 shows the flow chart of identifying and isolating potential NGPs [38].

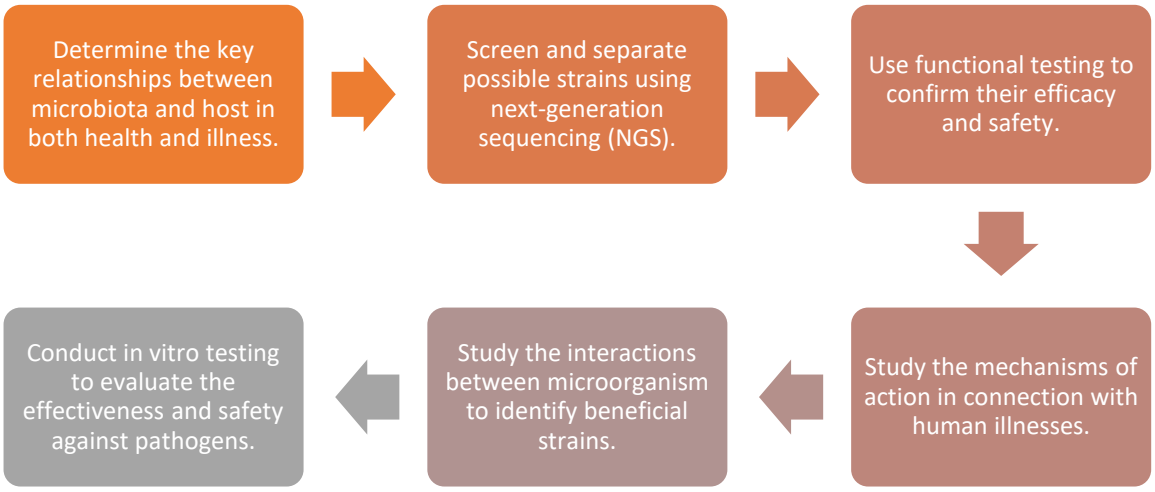

Figure 1. Process of Identification and Isolation of Potential NGPs.

3.1.1. Akkermansia muciniphila

Akkermansia muciniphila (A. muciniphila), which belongs to the Akkermansiaceae family, is an emerging NGP candidate initially identified in 2004. It is an oval-shaped, oxygen-tolerant anaerobic bacterium commonly found in the human gastrointestinal tract, generally accounting for approximately 1–5% of the intestinal microbiota in healthy individuals [42,46]. This microorganism primarily utilises mucin as an energy source and contributes to intestinal metabolic and immunological homeostasis through the production of short-chain fatty acids (SCFAs), particularly acetate and propionate [47–49]. Additionally, *A.*

muciniphila has been associated with enhanced intestinal barrier integrity, modulation of immune responses, and stimulation of antimicrobial peptide production [48,50,51].

Despite these promising biological characteristics, the therapeutic potential of *A. muciniphila* requires cautious interpretation. Associations between its intestinal abundance and favourable metabolic or inflammatory profiles do not necessarily establish a causal relationship, as microbial abundance may also be influenced by dietary patterns, host metabolic status, disease conditions, and other members of the gut microbiota. Furthermore, its mucin-degrading activity presents a potentially complex biological interaction, as mucin utilisation may contribute to beneficial host-microbe interactions but could also have different consequences depending on microbial abundance, intestinal conditions, and mucus-layer integrity.

Preliminary human investigations have provided encouraging evidence for the therapeutic potential of *A. muciniphila*, particularly in metabolic health. However, the pilot clinical trial discussed in the introduction should be interpreted in the context of its limited sample size and reliance on surrogate metabolic endpoints. Although improvements in selected metabolic parameters provide preliminary evidence of biological activity, these findings do not establish long-term clinical benefits or demonstrate efficacy in preventing or treating metabolic diseases. The limited number of participants also restricts statistical power and the generalisability of the findings to broader patient populations. Consequently, larger, adequately powered randomised controlled trials with longer follow-up periods and clinically meaningful endpoints are required to establish its therapeutic efficacy, optimal dosage, and long-term safety.

Another important consideration is the distinction between viable and non-viable *A. muciniphila* preparations. Investigations involving pasteurised *A. muciniphila* suggest that certain biological benefits may be retained following inactivation, indicating that its therapeutic effects may not exclusively depend on microbial viability. However, findings obtained using different preparations should not be considered interchangeable, as viability, cell integrity, and bioactive components may influence host responses. Overall, although *A. muciniphila* is a promising NGP candidate, its clinical application remains at an emerging stage and requires further investigation into strain-specific mechanisms, formulation characteristics, and long-term safety.

3.1.2. Faecalibacterium prausnitzii

Faecalibacterium prausnitzii (F. prausnitzii), classified under the Firmicutes phylum, is a Gram-positive, rod-shaped, strict anaerobe frequently found in the human intestinal

microbiota [48,52]. In healthy individuals, it may constitute up to approximately 5% of the faecal microbiota. Its potential contribution to intestinal homeostasis is primarily associated with butyrate production, which provides an important energy source for colonocytes and supports intestinal epithelial function [48,52]. Furthermore, *F. prausnitzii* has demonstrated anti-inflammatory properties through the modulation of host cytokine responses. For instance, its metabolites have been associated with increased production of the anti-inflammatory cytokine interleukin-10 (IL-10) and reduced secretion of pro-inflammatory cytokines, including interleukin-12 (IL-12) and interferon-gamma (IFN-γ), in human peripheral blood mononuclear cell (PBMC) cultures and experimental colitis models [48,53]. Its culture supernatant has also shown potential to reduce inflammation and improve intestinal barrier function by modulating epithelial paracellular permeability [48,54].

Despite these promising findings, the evidence supporting the clinical translation of *F. prausnitzii* remains less established than its biological mechanisms might suggest. Much of the current evidence is derived from observational microbiome studies, *in vitro* investigations, and experimental animal models. Although reduced abundance of *F. prausnitzii* has been associated with inflammatory and metabolic disorders, such associations do not establish whether microbial depletion contributes directly to disease development or occurs because of altered intestinal conditions. Similarly, the anti-inflammatory effects observed in cell cultures and animal models cannot be directly extrapolated to therapeutic efficacy in humans.

A major challenge in developing *F. prausnitzii* as a live therapeutic is its strict anaerobic nature, which presents substantial difficulties in cultivation, large-scale manufacturing, formulation, storage, and maintenance of viability during gastrointestinal delivery. These requirements may complicate product standardisation and reproducibility compared with more robust conventional probiotic strains. Moreover, differences in strain characteristics, butyrate-producing capacity, and other metabolic functions may influence therapeutic outcomes. Consequently, the reported health benefits of this species should not be generalised across all strains.

Future investigations should prioritise strain-level characterisation, optimisation of anaerobic manufacturing and delivery systems, and rigorous safety evaluation. Human clinical studies are also needed to establish its tolerability, effective dosage, and therapeutic efficacy across specific disease indications. Until such evidence becomes available, *F. prausnitzii* should be considered a promising but clinically under-validated NGP candidate rather than an established therapeutic microorganism.

3.1.3. Engineered probiotics

Advances in genome sequencing and genetic engineering have enabled the development of engineering have enabled the development of engineered probiotics with potentially enhanced or precisely controlled therapeutic functions [55,56]. Genetic modification approaches have evolved from homologous recombination to programmable gene-editing technologies, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats-associated protein systems (CRISPR-Cas) [55,57].

ZFNs and TALENs introduce double-strand break at specific genomic locations, which are subsequently repaired through cellular mechanisms such as homology-directed repair (HDR) or non-homologous end joining (NHEJ) [55,58,59]. However, their application may be limited by off-target modifications, variable editing specificity, and the complexity of designing and constructing functional editing systems [55,60,61]. In comparison, CRISPR-based technologies offer greater flexibility and accessibility for targeted genome modification [55]. These systems can facilitate gene knockout, activation, and repression through approaches such as CRISPR knockout (CRISPR-KO), CRISPR activation (CRISPRa), and CRISPR interference or inhibition (CRISPRi) [55,62,63].

These technologies provide opportunities to develop microorganisms capable of producing therapeutic molecules, modifying metabolic pathways, sensing disease-associated signals, and delivering bioactive compounds at specific sites. However, the development of engineered probiotics introduces additional biosafety, ethical, and ecological considerations that extend beyond those associated with conventional microbial supplementation. One major concern is the potential unintended persistence or dissemination of genetically modified microorganisms following administration. Depending on their biological characteristics, engineered strains may interact with resident microbial communities, transfer genetic material to other microorganisms, or undergo genetic changes during gastrointestinal residence. Horizontal gene transfer, particularly involving antimicrobial resistance determinants or engineered genetic elements, is an important biosafety concern. Furthermore, unintended genetic modifications or evolutionary adaptations could alter the intended therapeutic function, potentially resulting in unpredictable host-microbe interactions.

Containment strategies are therefore essential for minimising environmental dissemination and unintended persistence. Potential approaches include auxotrophic designs, inducible kill switches, biological containment systems, and genetic safeguards that limit microbial survival outside defined conditions. However, these approaches require rigorous

validation because containment mechanisms may undergo evolutionary instability, acquire mutations, or lose functionality under selective pressure. Their effectiveness should therefore be assessed under physiologically relevant conditions and across extended experimental periods.

Ethical considerations also arise from the administration of genetically modified microorganisms to human populations, particularly regarding informed consent, long-term monitoring, environmental release, and potential effects on individuals who may be exposed indirectly. These concerns are particularly relevant when engineered organisms are designed to persist or interact extensively with the host microbiome. Accordingly, responsible development requires transparent risk assessment, appropriate regulatory oversight, post-administration surveillance, and consideration of the potential ecological consequences of microbial release.

Thus, although genetic engineering provides opportunities to enhance the precision and therapeutic functionality of probiotics, these advantages should not be considered established without evidence demonstrating predictable biological activity, genetic stability, effective containment, and acceptable long-term safety. Future development should integrate therapeutic efficacy with biosafety-by-design principles to ensure that engineered probiotics can be translated into clinical applications without introducing unacceptable risks to human health or the environment.

3.2. Live Biotherapeutic Products (LBPs)

Live biotherapeutic products (LBPs) are biological products containing live microorganisms intended for the prevention, treatment, or management of diseases [64,65]. In contrast to conventional probiotics generally marketed as foods or dietary supplements, LBPs are developed for specific therapeutic indications and are subjected to more stringent regulatory requirements. As living biological systems, they can actively interact with their host and resident microbial communities, presenting unique development challenges related to viability, host immune responses, microbial competition, and product consistency [66–68].

LBPs can broadly be categorised according to their composition into: (1) single-strain products, comprising one naturally occurring microbial strain; (2) composite products, containing multiple microbial strains; and (3) engineered products, incorporating genetically modified microorganisms. Examples include *Christensenella minuta* (Xla1), which has been investigated for its potential effects on metabolic regulation, hepatic lipid accumulation, bile acid metabolism, SCFA production, and intestinal barrier integrity in experimental models [69–71]. Composite products such as Vowst™ have demonstrated clinical applications in

preventing recurrent *Clostridioides difficile* infection through restoration of intestinal microbial diversity and bile acid-mediated colonisation resistance [66,69]. Additionally, engineered *Escherichia coli* Nissle 1917 has been investigated as a therapeutic platform for phenylketonuria by facilitating the conversion of excess phenylalanine into less toxic metabolites [69,72,73].

Despite these advances, the therapeutic development of LBPs involves challenges that extend beyond conventional pharmaceutical manufacturing. Maintaining microbial identity, viability, potency, and purity throughout production, storage, and administration requires carefully controlled manufacturing conditions. Furthermore, variations in host physiology, dietary patterns, baseline microbiome composition, and concomitant medication use may influence microbial colonisation, persistence, and therapeutic activity. Consequently, responses to the same LBP may differ substantially between individuals, complicating dose optimisation and clinical reproducibility.

Safety evaluation is particularly important because LBPs contain viable organisms capable of interacting with host tissues and resident microbial communities. Potential risks include unintended translocation, opportunistic infection in susceptible individuals, undesirable immune responses, and horizontal gene transfer. For composite products, interactions among constituent strains may further complicate the prediction of microbial behaviour and therapeutic outcomes. These considerations highlight the importance of strain-level characterisation, antimicrobial resistance screening, assessment of virulence-associated characteristics, and evaluation of potential interactions with the host microbiome.

The challenges are particularly pronounced for engineered LBPs, which introduce additional concerns regarding genetic stability, containment, and environmental dissemination. Although genetic safeguards and biological containment strategies may reduce these risks, their long-term reliability requires validation. Furthermore, post-administration monitoring may be necessary to assess microbial persistence, unintended ecological changes, and potential adverse effects following treatment, Regulatory evaluation should therefore consider not only immediate clinical safety and efficacy but also the potential consequences of administering viable microorganisms capable of replication and adaptation.

To summarise, LBPs is an important development in microbiome-based therapeutics, offering opportunities for targeted microbial interventions and disease-specific applications. However, their clinical translation requires a comprehensive assessment of manufacturing consistency, host-microbiome interactions, long-term safety, and ecological consequences. Further well-designed clinical trials and standardised regulatory approaches are necessary to

establish their therapeutic value and ensure that the proposed precision of these interventions is supported by reproducible clinical evidence.

4. Postbiotics and Paraprobiotics

Postbiotics and paraprobiotics have attracted increasing attention as alternatives to conventional probiotics because they utilise inactivated microorganisms or their components to modulate host physiological functions [74]. Their proposed biological activities include modulation of immune signalling, maintenance of epithelial barrier integrity, and antimicrobial effects. Potential clinical applications have been investigated in respiratory health, oral health, and gastrointestinal conditions, including antibiotic-associated disturbances of the gut microbiota. Although randomised controlled trials (RCTs) have reported encouraging findings, the available clinical evidence remains limited by relatively small study populations, short intervention periods, heterogeneous preparations, and reliance on surrogate endpoints [75,76]. Therefore, their therapeutic potential should be interpreted according to the composition of the preparation and the level of supporting evidence rather than extrapolated directly from mechanistic findings.

The development of postbiotics and paraprobiotics has partly addressed limitations associated with live probiotics, including maintaining microbial viability during storage and transportation and concerns regarding microbial translocation in susceptible individuals. Postbiotics are defined as preparations of inanimate microorganisms and/or their components that confer a health benefit on the host, whereas paraprobiotics generally refer to non-viable microbial cells or cellular fragments that retain biological activity. Importantly, isolated microbial metabolites, such as short-chain fatty acids (SCFAs), should not automatically be classified as postbiotics, as their classification depends on the nature and composition of the administered preparation. Similarly, the biological effects observed *in vitro* or in animal models do not necessarily establish clinical efficacy in humans. Differences in microbial strains, inactivation methods, and preparation characteristics further complicate comparison across studies.

4.1. Mechanisms of Action

4.1.1. Short-chain fatty acids (SCFAs) and metabolites

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are important microbial metabolites involved in intestinal homeostasis and host physiological regulation [77]. They are primarily produced through microbial fermentation of dietary fibres by intestinal microorganisms and may contribute to the biological activities of certain postbiotic preparations [78]. However, SCFAs should be distinguished from postbiotic

preparations themselves, as the administration of isolated SCFAs does not necessarily fulfil the established definition of a postbiotic. Their biological activities provide mechanistic evidence for the potential contribution of microbial metabolites to host health, rather than direct evidence of the clinical efficacy of postbiotic products.

One of their central roles of SCFAs is maintaining the integrity of the gut epithelial barrier. SCFAs enhance the expression of tight junction proteins such as claudins and occludins, thereby reducing intestinal permeability and preventing the leakage of harmful substances like endotoxins into systemic circulation [79]. Butyrate also serves as a vital energy source for colonocytes and supports intestinal epithelial homeostasis. Although butyrate enemas have been investigated as a therapeutic intervention in patients with ulcerative colitis, this approach represents the direct pharmacological administration of an isolated metabolite rather than the administration of a postbiotic preparation [80]. Therefore, these findings demonstrate the potential therapeutic relevance of butyrate-mediated mechanisms but should not be interpreted as clinical evidence supporting the efficacy of postbiotic products.

Beyond intestinal barrier regulation, SCFAs influence host metabolic and immunological pathways [81]. They modulate glucose and lipid metabolism and may contribute to energy balance and the regulation of metabolic disorders, including obesity and type 2 diabetes [82]. Their anti-inflammatory activities are partly mediated through histone deacetylase (HDAC) inhibition and activation of G-protein-coupled receptors, including GPR41 and GPR43, which regulate metabolic and immune signalling pathways [83]. Furthermore, propionate administration has been investigated in human studies for its effects on appetite regulation and energy intake, suggesting potential metabolic applications [84]. However, such investigations involving directly administered SCFAs should be distinguished from clinical trials of whole postbiotic preparations. SCFAs may also promote regulatory T-cell differentiation and modulate the production of inflammatory cytokines, including TNF-α and IL-6, thereby contributing to immune homeostasis [85].

Collectively, these findings provide a mechanistic basis for understanding of the contribution of microbial metabolites to the intestinal, metabolic, and immunological health. However, much of the evidence originates from experimental models or investigations of individual metabolites. Further clinical studies using well-characterised postbiotic preparations are required to establish whether these mechanisms can be translated into reproducible therapeutic benefits in humans. In particular, the contribution of individual metabolites, their concentrations, and their interactions with other microbial components require further investigation.

4.1.2. Immune signalling and host defence

Paraprobiotics contain non-viable microbial components, including lipoteichoic acids, peptidoglycans, and exopolysaccharides, which can engage with host pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), on immune cells [86,87]. These interactions may activate innate immune responses involving macrophages and dendritic cells, resulting in the secretion of cytokines and chemokines that contribute to host defence. Certain preparations have also been investigated for their ability to enhance mucosal immunity through increased secretory immunoglobulin A (sIgA) production, which shows an important component of mucosal protection against pathogens [88]. These findings suggest that non-viable microbial components can retain immunomodulatory activity following inactivation.

In addition to innate immune activation, microbial components may influence immune homeostasis by modulating the balance among T-helper cell subsets, including Th1, Th2, Th17, and regulatory T cells (Tregs) [89]. They may also influence the production of host-derived antimicrobial peptides, including defensins, which contribute to mucosal defence [90]. However, these immunological effects depend on the structural composition, microbial origin, and preparation methods of the administered products. For example, differences in exopolysaccharide structure and production conditions may influence their interactions with host immune receptors [91].

Importantly, activation of immune signalling does not necessarily translate into clinical protection against infection or inflammatory diseases. Excessive or inappropriate immune stimulation may also produce undesirable inflammatory responses, depending on the host's physiological condition and the characteristics of the preparation. Therefore, the immunomodulatory effects reported in experimental models require further validation through human studies incorporating relevant immunological and clinical outcomes. Standardised characterisation of microbial components and dose-dependent assessment are also necessary to establish reproducible immunological responses.

4.1.3. Antimicrobial, anticariogenic and biofilm effects

Postbiotic molecules may contain antimicrobial compounds, such as bacteriocins, organic acids, and other microbial metabolites, which can interfere with pathogenic microorganisms. These compounds may inhibit the growth of harmful oral pathogens, including *Streptococcus mutans* and *Porphyromonas gingivalis*, as well as selected gastrointestinal pathogens [92,93]. However, the antimicrobial activity of isolated metabolites or microbial products should be distinguished from the effects of viable probiotic

microorganisms. For instance, the reported inhibition of antibiotic-resistant *Klebsiella pneumoniae* by selected live probiotic strains isolated from preterm infant stools shows evidence of probiotic-mediated antagonism rather than direct evidence of postbiotic efficacy [94]. The clinical challenge posed by antimicrobial resistance has also prompted development of antibiotics with activity against resistant pathogens [95].

Another proposed mechanism involves the disruption of microbial biofilms, which are structured microbial communities that enhance pathogen survival and resistance to host defence mechanisms and antimicrobial treatments [96,97]. Certain postbiotic-based compounds may interfere with microbial adhesion, biofilm formation, or biofilm-associated metabolic activity. Such effects could potentially contribute to the prevention of oral and gastrointestinal infections. However, the majority of scientific studies supporting these antimicrobial and antibiofilm mechanisms remains derived from *in vitro* investigations. Their effectiveness in complex host environments may differ because of interactions with resident microbial communities, host secretions, and tissue-associated factors. Therefore, clinical studies are required to establish whether these effects translate into meaningful reductions in infection incidence or improvements in oral and gastrointestinal health.

4.1.4. Others: oxidative stress and barrier function

Postbiotics may also influence oxidative stress and epithelial barrier function through microbial metabolites and interactions with host cellular pathways. Certain preparations have demonstrated the ability to reduce reactive oxygen species or enhance endogenous antioxidant enzyme activity, potentially limiting oxidative damage [98,99]. Furthermore, microbial components may support mucosal barrier integrity and reduce the translocation of endotoxins and pathogenic microorganisms across epithelial surfaces [100]. These effects have also been investigated in relation to metabolic regulation, including obesity, insulin resistance, and type 2 diabetes [101–103].

In this context, the evidence supporting these mechanisms should be interpreted according to the intervention investigated. For example, studies involving conventional probiotics in 5-fluorouracil-induced intestinal mucositis provide evidence of potential microbial intervention in epithelial injury but cannot be directly extrapolated to postbiotic or paraprobiotic efficacy [104]. Similarly, findings from antioxidant assays and experimental models do not independently establish clinically meaningful improvements in oxidative stress-related diseases. Further human investigations using chemically and biologically characterised preparations are needed to determine the relevance of these mechanisms and identify the components responsible for the observed effects.

4.2. Clinical Applications

Although experimental studies have identified several mechanisms through which postbiotics and paraprobiotics may influence host physiology, clinical evidence remains limited and varies across health conditions. Importantly, findings from trials involving specific strains, formulations, and populations should not be generalised to all postbiotic or paraprobiotic preparations. Differences in microbial inactivation, dosage, administration routes, intervention duration, and clinical endpoints may contribute to inconsistent outcomes across studies.

4.2.1. Respiratory health in the elderly

Elderly individuals are particularly vulnerable to respiratory tract infections (RTIs) due to immunosenescence, a natural decline in immune function with age, along with reduced mucosal immunity and the presence of chronic low-grade inflammation. Probiotics have been investigated as potential interventions for supporting mucosal immunity and reducing respiratory infection risk in this population. For instance, a randomised controlled trial involving heat-killed *Lactobacillus paracasei* B-240 reported increased salivary IgA levels and a reduction in upper respiratory tract infections among elderly participants [105]. Similarly, Akatsu and colleagues reported improvements in immune-related outcomes and reduced respiratory infection incidence following postbiotic supplementation in institutionalised elderly individuals [106].

Despite these encouraging findings, several limitations should be considered when interpreting the clinical evidence. First, the findings are associated with specific microbial preparations, particularly heat-killed *L. paracasei* B-240, and should not be generalised to other postbiotic strains or formulations. Second, the study populations were restricted to older adults, including institutionalised individuals, whose baseline immune function, comorbidities, and exposure to respiratory pathogens may differ from those of community-dwelling adults or younger populations. Third, salivary IgA represents a surrogate marker of mucosal immune activity and does not independently establish clinically meaningful protection against respiratory infections. Although reported reductions in infection incidence provide additional clinical information, the duration of follow-up and sustainability of these effects require consideration.

Furthermore, differences in study design, supplementation regimens, population characteristics, and outcome definitions complicate direct comparisons between trials. The available findings therefore support the potential of selected postbiotic preparations for respiratory health but do not establish a class-wide therapeutic effect. Larger, adequately

powered RCTs with standardised infection definitions, clinically relevant endpoints, and longer follow-up periods are necessary to determine the magnitude and durability of these benefits.

4.2.2. Oral Health

Postbiotics have also been investigated for their potential applications in preventing and managing oral diseases, including dental caries and periodontal disease. Their proposed mechanisms include modulation of the oral microbiome, suppression of cariogenic microorganisms such as *Streptococcus mutans*, inhibition of periodontal pathogens such as *Porphyromonas gingivalis*, and modulation of host mucosal immune responses [107,108]. Systematic reviews have reported reductions in *S. mutans* levels, promotion of enamel remineralisation, and improvements in overall oral health outcomes following the use of microbial-based preparations [109].

Clinical investigations have evaluated postbiotic-containing oral care products, including toothpaste formulations in children, with reported increases in salivary IgA levels [110]. Additionally, studies involving adults receiving periodontal treatment have investigated the use of postbiotic or synbiotic supplementation as an adjunct to conventional scaling and root planning, reporting improvements in periodontal indices, including probing pocket depth and inflammatory parameters [111]. However, the clinical interpretation of these findings requires consideration of the differences between preparations and study populations.

Changes in salivary IgA or bacterial abundance show intermediate biological outcomes and do not necessarily demonstrate sustained prevention of dental caries or periodontal disease progression. Similarly, improvements observed when postbiotic supplementation is combined with conventional periodontal treatment cannot be attributed exclusively to the postbiotic intervention without appropriate control groups. The inclusion of synbiotic preparations in several investigations further complicates attribution of the observed effects to postbiotic components alone. Therefore, although current findings suggest potential applications of postbiotics in oral healthcare, further well-designed clinical trials are needed to establish their independent contribution, optimal formulation, dosage, and long-term effectiveness. Standardised periodontal and caries-related clinical endpoints would also improve comparisons across studies.

4.2.3. Gut Microbiome Modulation During Antibiotic Therapy

Antibiotic treatment can disrupt the composition and functional activity of the intestinal microbiota, potentially resulting in dysbiosis, antibiotic-associated diarrhoea, and increased susceptibility to *Clostridioides difficile* (*C. difficile*) infection. Postbiotics and

paraprobiotics have therefore been investigated as potential adjunct interventions to support intestinal barrier function and modulate host-microbiome interactions during antibiotic therapy. Several clinical investigations have evaluated fermented inactivated microbial preparations and heat-killed probiotic products alongside antibiotic treatment, reporting potential benefits in reducing antibiotic-associated diarrhoea and supporting intestinal health [112,113]. However, the available clinical evidence remains limited, and differences in the microbial preparations, antibiotic regimens, patient populations, and clinical endpoints complicate comparisons across studies. In particular, studies demonstrating restoration of the gut microbiome following antibiotic exposure remains insufficient to establish that postbiotic supplementation can consistently prevent dysbiosis or restore microbial diversity in humans. In a separate gastrointestinal context, probiotics have also been explored for *Blastocystis*-associated gut disturbances, where the clinical significance of colonisation and its interactions with the gut microbiota remain uncertain [114].

Preclinical studies have additionally reported protective effects of postbiotic preparations against intestinal epithelial injury and improvements in barrier function [115]. However, these findings should be distinguished from human clinical studies, as improvements in experimental models do not necessarily establish prevention of antibiotic-associated complications in patients. Genomic surveillance of clinical *C. difficile* isolates provides additional information regarding antimicrobial resistance and pathogen diversity but does not directly show the therapeutic effectiveness of postbiotic interventions [116]. Similarly, investigations of microbiome modulation as an adjunct to antibiotic-based *Helicobacter pylori* eradication provide a broader context for microbial interventions but should not be interpreted as direct evidence of postbiotic efficacy unless the administered preparation meets the relevant postbiotic definition [117].

Overall, postbiotics and paraprobiotics may offer opportunities for supporting gastrointestinal health during antibiotic therapy, particularly through modulation of epithelial and immune responses. However, their ability to prevent antibiotic-associated diarrhoea, reduce *C. difficile* infection, or accelerate microbiome recovery requires further confirmation through adequately powered human clinical trials. Future studies should incorporate baseline and post-intervention microbiome characterisation, clinically relevant gastrointestinal outcomes, and appropriate antibiotic-treated control groups.

4.3. Randomised Control Trials (RCT) Status and Research Gaps

4.3.1. Current clinical evidence

Available RCTs provide preliminary studies supporting selected applications of postbiotics and paraprobiotics, particularly in respiratory and oral health. In the elderly, studies involving heat-killed *Lactobacillus pentosus* strain b240 have reported improvements in mucosal immune responses and reductions in upper respiratory tract infection incidence [105]. Akatsu and colleagues also reported beneficial immune-related outcomes among institutionalised elderly individuals receiving postbiotic supplementation [106]. However, these findings are based on specific preparations and populations, and differences in study design, follow-up duration, and outcome assessment limit generalisation across postbiotic products.

In dentistry, clinical investigations involving postbiotic-containing oral care products have reported changes in salivary IgA and selected oral health parameters. For example, Basir and colleagues conducted a triple-blind RCT evaluating postbiotic-containing toothpaste in children, using salivary IgA as an immunological outcome [118]. Although such findings provide preliminary clinical evidence, changes in immunological biomarkers should be distinguished from sustained reductions in dental caries or periodontal disease progression. Furthermore, clinical investigations involving postbiotic and paraprobiotic preparations for antibiotic-associated microbiome disturbances remain relatively limited, with much of the available evidence originating from pilot or proof-of-concept studies [119].

Collectively, the existing clinical literature suggests that selected postbiotic and paraprobiotic preparations may provide health benefits in specific populations. The overall studies and evidence remain insufficient to establish consistent therapeutic efficacy across different formulations and clinical indications. In particular, the relatively small number of human studies, limited follow-up periods, heterogeneous interventions, and inconsistent outcome measures restrict the ability to compare findings and draw broader clinical conclusions.

4.3.2. Research priorities and translational challenges

Several research priorities emerge from the limitations identified across mechanistic investigations and clinical applications. Firstly, standardisation of product composition and dosage is essential. Studies frequently employ different microbial strains, metabolites, and preparation methods, making it difficult to identify the active components responsible for reported benefits [120]. Future investigations should provide detailed characterisation of microbial identity, inactivation efficiency, residual cellular integrity, and relevant bioactive

constituents. Standardised dosage specifications and administration regimens are also required to facilitate reproducibility and meaningful comparisons between studies.

Secondly, long-term efficacy and safety require further investigation. Many existing RCTs involve relatively short intervention periods, leaving uncertainty regarding the persistence of therapeutic benefits after supplementation is discontinued and the potential occurrence of adverse effects during prolonged administration. Although non-viable preparations reduce certain risks associated with live microorganisms, their safety should not be assumed solely on the basis of inactivation. Residual microbial components, immunological responses, and potential manufacturing-related contaminants require appropriate evaluation [121,122].

Thirdly, the relationship between mechanistic findings and clinical outcomes remains insufficiently established. Although *in vitro* and animal investigations have identified potential mechanisms involving immune signalling, epithelial barrier regulation, antioxidant activity, and antimicrobial effects, corresponding data from human studies remains limited. Future clinical investigations should incorporate relevant biological measurements, such as inflammatory cytokine profiles, intestinal permeability markers, and microbiome-related functional changes, alongside clinically meaningful endpoints. This approach would help establish whether the proposed mechanisms contribute directly to observed clinical benefits.

Furthermore, population diversity and generalisability should be improved. Existing studies have predominantly involved selected Asian and European populations, frequently focusing on relatively healthy adults or specific patient groups. Scientific studies remain limited for children, immunocompromised individuals, individuals with multiple comorbidities, and populations from low- and middle-income countries (LMICs) and tropical settings [123]. Differences in dietary patterns, baseline microbiome composition, environmental exposures, and health status may influence responses to postbiotic interventions. Accordingly, future trials should include more diverse populations and investigate potential differences in treatment responses.

Finally, regulatory harmonisation and reporting standards require further development. Inconsistent definitions of postbiotics and paraprobiotics, variation in microbial inactivation methods, and inadequate reporting of preparation characteristics complicate the interpretation and comparison of published findings [124]. The distinction between whole inactivated microbial preparations, cellular components, and isolated metabolites should be clearly maintained. Establishing standardised definitions, characterisation procedures, manufacturing specifications, and reporting criteria would strengthen reproducibility and facilitate the growing of literature work. These measures are

also necessary to support the development of clinically validated postbiotic and paraprobiotic products.

4.4. Safety Advantages

Postbiotics and paraprobiotics have several safety and practical advantages over live probiotic preparations. Due to these products contain inactivated microorganisms or microbial components, they do not replicate or establish active microbial colonisation, thereby reducing concerns regarding uncontrolled microbial growth and microbial translocation [125]. These characteristics may be particularly relevant when considering interventions for immunocompromised individuals and other vulnerable populations. In addition, many inactivated preparations demonstrate improved storage stability and reduced dependence on cold-chain transportation, while their composition may be easier to standardise under controlled manufacturing conditions [126].

The absence of viable microorganisms also reduces certain risks associated with live microbial administration, including opportunistic infection and the potential transfer of antimicrobial resistance determinants by viable strains. Furthermore, inactivation may improve formulation consistency by reducing variability associated with microbial survival during storage and gastrointestinal transit [127,128]. However, these advantages should not be interpreted as evidence of absolute safety. Inactivation must be adequately validated to ensure the absence of viable organisms, while residual cellular components and bioactive molecules may still induce undesirable immune responses depending on their composition and dosage. Manufacturing-related contaminants and product-specific toxicological concerns also require evaluation.

In short, although postbiotics and paraprobiotics may provide practical and safety advantages over live probiotics, their clinical suitability should be established through preparation-specific quality control, toxicological assessment, and appropriately designed human studies. Their potential advantages should be considered in the context of their demonstrated safety and therapeutic efficacy rather than assumed solely from their non-viable nature.

5. Proteobiotics: The Next Frontier

Proteobiotics are naturally occurring bioactive oligopeptide metabolites produced during the growth of specific probiotic bacteria, including *Lactobacillus*, *Lactococcus* and *Bifidobacterium* spp. [129]. They have been proposed as a distinct class of microbiota-derived bioactive compounds, particularly because some exhibit antimicrobial effects through

interference with bacterial communication and virulence-associated pathways rather than through direct inhibition of bacterial growth.

Proteobiotics have therefore attracted interest as a potential approach to attenuating pathogen virulence. Proposed mechanisms include interference with quorum-sensing pathways and downregulation of virulence-associated genes [130], which may reduce pathogen adhesion, biofilm formation and toxin production [131]. However, the studies supporting these effects are predominantly from *in vitro* and animal work. Hence, proteobiotics should be regarded as an emerging preclinical strategy rather than an established antimicrobial intervention. Furthermore, the suggestion that targeting virulence rather than bacterial viability may impose less selective pressure for antibiotic resistance, which remains a theoretical advantage. The validation of this approach in reducing the emergence of resistance under clinically relevant conditions has yet to be established.

Several experimental studies have provided preliminary support for this concept. For example, bioactive molecules from *L. acidophilus* La-5 suppressed virulence-associated pathways in enterohaemorrhagic *Escherichia coli* (EHEC) O157:H7, including downregulation of locus of enterocyte effacement (LEE) genes, with reductions in bacterial adhesion and colonisation in cell culture and mouse models [132]. In studies involving *Clostridioides difficile*, La-5-derived bioactive molecules reportedly reduced toxin A and B expression, epithelial cell cytotoxicity and bacterial adherence. Extracts from *L. acidophilus* GP1B were also reported to interfere with autoinducer-2 (AI-2)-associated signalling, suggesting a potential role in quorum-sensing modulation [133]. These findings provide mechanistic evidence for virulence attenuation, but their clinical relevance remains uncertain because efficacy, effective concentrations, delivery to infection sites and safety have not been adequately established in human studies.

Other investigations have explored virulence regulation and microbial products as potential antimicrobial targets, For example, the SarA regulator in *Staphylococcus aureus* has been investigated in relation to virulence and biofilm formation [134]. Separately, genome sequencing of *Streptomyces pluripotens* MUM 16J identified candidate biosynthetic pathways associated with glycopeptide antibiotic production [135], while genome analysis of *Streptomyces sp.* MUM 178J identified biosynthetic gene clusters for further investigation in a strain exhibiting *in vitro* activity against multidrug-resistant *Vibrio parahaemolyticus* [136]. These studies may inform broader antimicrobial discovery and microbial antagonism research. However, they should not be considered direct evidence for proteobiotics unless the active peptide compounds and their relevant mechanisms are specifically demonstrated.

Beyond antimicrobial and anti-virulence effects, microbiota-derived bioactive preparations have also been investigated for their immunomodulatory properties. Proposed activities include modulation of cytokine expression, regulation of innate and adaptive immune responses, and maintenance of epithelial barrier function [137,138]. For example, *L. plantarum* cell-free culture supernatant altered cytokine responses in human macrophages, including changes in IL-10 and TNF-α expression, suggesting immunomodulatory potential [139]. However, cell-free culture supernatants contain a mixture of secreted products and should not automatically be classified as proteobiotics without studies identifying the active oligopeptide components. Similarly, a study in broiler chickens reported that postbiotic supplementation reduced inflammatory responses, improved intestinal lesion scores and decreased pathogen burden following *Clostridium perfringens* challenge [140]. Although this finding supports the broader potential of non-viable microbial preparations in animal health, it does not establish the efficacy of proteobiotics specifically.

Potential applications of proteobiotics have been proposed in functional foods, animal health and, prospectively, pharmaceutical development [141,142]. However, the current commercial examples identified in this field are directed towards veterinary use rather than human healthcare. Nuvio (MicroSintesis Inc.) was developed to support piglet health during the post-weaning period. Studies reported that *L. acidophilus*-derived proteobiotics reduced clinical signs associated with enterotoxigenic *E. coli* (ETEC) infection, faecal shedding and ileal colonisation in piglets [143]. MicroSintesis has also introduced YGIA14 for companion animals, with the intended purpose of supporting gastrointestinal health in dogs [144]. These products demonstrate commercial interest in animal health applications, but their availability does not establish efficacy, safety, or regulatory acceptance for human use. Findings from veterinary studies also cannot be directly extrapolated to human populations because of differences in host physiology, microbiota composition, disease context, and product administration.

To summarise, proteobiotics show a potentially interesting approach to microbial virulence modulation, but their development remains at an early stage. Further research is required to identify and chemically characterise the active peptide components, establish their mechanisms of action, determine dose-response relationships, and evaluate stability, bioavailability and delivery to relevant sites of infection. Importantly, well-designed human studies are needed before their therapeutic efficacy and safety can be assessed in clinical settings. Hence, proteobiotics should be discussed as a promising preclinical concept with emerging veterinary applications, rather than as an established or near-term class of human antimicrobial therapeutics. Studies investigating live *Streptomyces* sp. MUM 195J strains as aquaculture feed interventions against *Vibrio parahaemolyticus* provide additional examples

of microbial approaches to animal health but are distinct from proteobiotic interventions and should be discussed separately if retained [145]. A separate review of live probiotics in shrimp farming examined growth-related outcomes and proposed mechanisms involving microbial metabolites and digestive function [146].

6. Advanced Formulation & Delivery: Improving Probiotic Stability and Targeted Administration

The therapeutic potential of probiotics is influenced not only by the characteristics of individual strains but also by their ability to remain viable during manufacturing, storage and gastrointestinal transit, and to reach the intended site of action. Exposure to gastric acid, oxygen, heat, and moisture can compromise probiotic viability, while intestinal adhesion and persistence may vary according to the strain, resident microbiota, and host characteristics [147]. Advanced formulation and delivery strategies have therefore been investigated to improve microbial stability, gastrointestinal survival, and controlled release. However, improved delivery performance does not necessarily translate into improved clinical outcomes, and the clinical value of these technologies requires further evaluation.

6.1. Encapsulation and Co-delivery Strategies

Conventional encapsulation approaches, including spray-drying, freeze-drying and extrusion, are widely investigated because of their relative simplicity and potential for large-scale production [148]. However, their protective performance varies, with limitations relating to particle-size uniformity, release control, and survival under gastrointestinal conditions [149,150]. More recently, emulsion-based and layer-by-layer systems have been explored to improve control over capsule composition, thickness, and release characteristics [151–153].

Other emerging platforms include electrospun nanofibres, liposomes, and biopolymer-based hydrogels. For example, coaxial poly-lactic acid nanofibres containing *Lactobacillus plantarum* and fructooligosaccharides improved probiotic viability under simulated gastrointestinal conditions [154], while other nanofibre systems have demonstrated protective effects under harsh environmental conditions [155]. Liposomes offer a biomimetic carrier approach, although lipid oxidation, production costs, and limited storage stability remain challenges [156,157]. Similarly, pH- or enzyme-responsive hydrogels have been investigated for site-specific release, particularly in the intestine [158]. Despite promising laboratory findings, these platforms require further assessment of manufacturing scalability, batch consistency, storage stability, cost, and performance under variable human gastrointestinal conditions [159–164].

Co-encapsulation of probiotics with prebiotics or polyphenols has also been investigated to combine microbial protection with complementary biological activities [165]. For example, co-encapsulation of *Lactiplantibacillus plantarum* LM19 with inulin improved viability compared with single-component encapsulation [166]. Polyphenols, including curcumin, resveratrol and catechins, may provide antioxidant and anti-inflammatory effects, although their concentrations and antimicrobial properties can influence probiotic survival [167,168]. Prebiotics such as inulin, fructooligosaccharides and galactooligosaccharides may act as microbial substrates and protective excipients, but their effects depend on strain-substrate compatibility [169,170]. Accordingly, co-delivery systems require formulation-specific optimisation rather than assuming that combining multiple bioactive components will consistently produce synergistic effects.

6.2. Personalised and Computationally Guided Delivery

Personalised delivery is an emerging concept intended to account for inter-individual differences in microbiome composition and gastrointestinal physiology. Technologies such as three-dimensional food printing have been investigated to control the spatial distribution and release of probiotics within food matrices. Experimental studies have showed that printed structures can influence probiotic survival and release under simulated gastric conditions [171,172]. However, these findings remain primarily at the proof-of-concept stage.

Artificial intelligence (AI) and machine learning (ML) have also been explored to identify microbial combinations, predict strain-environment interactions and support formulation optimisation [173,174]. Computational approaches, including microbiome modelling and digital-twin concepts, may eventually assist in predicting individual responses to microbiome-based interventions [175–177]. However, their clinical utility depends on the quality and representativeness of the underlying datasets, external validation and demonstration that model-guided formulation decisions improve patient outcomes. At present, these approaches should be regarded as research and development tools rather than established methods for prescribing personalised probiotic delivery systems.

6.3. Evidence from Preclinical Studies

Food science and bioengineering studies have demonstrated that encapsulation can improve probiotic survival under simulated gastrointestinal conditions. For instance, pea-protein microencapsulation of *Lacticaseibacillus rhamnosus* preserved viability during simulated digestion [178], while layer-by-layer alginate-chitosan coatings and chitosan-liposome systems have also shown protective effects [179,180]. Other approaches, including the use of yeast cell walls as encapsulating materials, have demonstrated promising storage and

gastrointestinal stability [181]. These findings support the potential of encapsulation to improve formulation performance, but simulated digestion models cannot fully reproduce the complexity of the human gastrointestinal environment.

Co-encapsulation studies have further investigated the combination of probiotics and polyphenols. Examples include a Fu brick tea polysaccharide-based system containing *Lactobacillus kefiranofaciens* and polyphenols [182], and formulations combining anthocyanin-rich extracts with probiotic strains [183,184]. Although these studies suggest potential improvements in microbial viability and bioactive compounds delivery, the extent to which these formulation benefits produce meaningful health effects remains uncertain.

Animal studies have provided additional evidence of biological activity. Synbiotic co-delivery systems and nano-encapsulated multi-strain probiotics have shown beneficial effects in experimental colitis models [185,186]. Other investigations have explored nasal probiotic delivery in murine respiratory infection models [187], as well as probiotic formulations administered alongside antibiotics in pigs [188]. These findings provide preliminary evidence of activity in living biological systems, but differences in animal physiology, microbiome composition, and experimental disease models limit direct extrapolation to human therapeutic efficacy. Moreover, the use of live probiotics with antimicrobial polysaccharides fucoidan in wound-healing studies represents a related delivery approach rather than direct evidence that advanced encapsulation alone improves clinical outcomes [189].

6.4. Human Clinical Studies and Translational Considerations

Human clinical studies are particularly important in determining whether formulation advances provide benefits beyond improved viability or controlled release in laboratory models. Napier et al. conducted a randomised, placebo-controlled trial evaluating a synbiotic containing 24 probiotic strains and a pomegranate-based prebiotic delivered using capsule-in-capsule technology [190]. The intervention was associated with changes in gut microbial diversity, increased Urolithin A synthesis and increased faecal butyrate. These findings provide preliminary human studies that an advanced synbiotic formulation can influence microbiome composition and microbial metabolite production. However, the study was conducted in healthy adults and primarily evaluated microbiome-related and metabolic outcomes. It therefore does not establish clinical efficacy in patients with gastrointestinal or other diseases, nor does it demonstrate that the delivery technology itself was responsible for the observed effects independently of the synbiotic ingredients. Hence, larger studies, including trials in relevant patient populations, are needed to determine whether these changes translate into meaningful clinical benefits.

Clinical trials of probiotic supplementation have also reported potential benefits in other health conditions. For instance, a randomised, double-blind trial in children aged 6 months to 5 years reported reductions in the duration of fever and discomfort associated with viral upper respiratory tract infections following administration of a multi-strain probiotic formulation [191]. Although this finding supports the potential clinical value of specific probiotic interventions, it should not be interpreted as evidence for advanced encapsulation or targeted delivery unless the trial specifically evaluates and compares the relevant delivery technology.

Commercial formulations provide further examples of the application of delivery technologies. Seed DS-01, for instance, uses capsule-in-capsule technology to deliver a multi-strain synbiotic formulation [192], while other products employ specialised approaches to deliver selected microbial strains or prebiotic ingredients [193,194]. However, the commercial availability of these products and evidence from studies of their constituent strains do not, by themselves, establish the clinical superiority of the delivery platform or demonstrate efficacy across different disease. Product-specific, dose-matched clinical trials are required to determine whether the formulation provides additional benefits compared with conventional delivery systems.

In short, advanced formulation and delivery technologies offer promising strategies to improve probiotic stability, gastrointestinal survival, and release characteristics. However, the current evidence is weighted towards formulation studies, simulated digestion models and animal experiments, with more limited evidence demonstrating clinical benefits attributable specifically to the delivery technology. Future research should prioritise direct comparisons between conventional and advanced formulations, clinically relevant endpoints, longer follow-up, manufacturing reproducibility, and cost-effectiveness. Ultimately, the value of these technologies will depend not only on their ability to protect and deliver probiotics, but also on whether they consistently improve patient-relevant outcomes.

7. Clinical Horizons: Emerging Applications in Systemic and Age-Specific Health

The potential applications of probiotics and their derivatives extend beyond gastrointestinal disorders, with increasing interest in their roles in systemic inflammation, metabolic regulation, iron metabolism, and gut-brain communication [195,196]. Microbial metabolites and other postbiotic preparations may influence host physiology through interactions with epithelial barriers, immune pathways, and metabolic signalling. However, the strength of evidence differs considerably across clinical areas. While some applications are supported by human intervention studies, others remain based predominantly on mechanistic investigations and animal models. Accordingly, the following sections

distinguish established clinical observations from emerging hypotheses and preclinical findings.

7.1. Chronic Kidney Disease (CKD): Potential Modulation of Gut-Derived Uremic Toxins and Inflammation

Chronic kidney disease (CKD) is associated with progressive renal impairment, systemic inflammation and oxidative stress [197]. Alterations in gut microbiota composition may contribute to the accumulation of microbiota-derived uremic toxins, including indoxyl sulfate and p-cresyl sulfate, which are implicated in renal and cardiovascular complications [198]. Increased intestinal permeability may further facilitate the translocation of microbial products and promote systemic inflammatory responses [199].

Postbiotics and microbial metabolites have been investigated as potential modulators of pathways involved in gut barrier function and inflammation. Short-chain fatty acids (SCFAs), particularly butyrate and propionate, may support epithelial integrity through effects on tight-junction proteins and inflammatory signalling, including NF-KB-related pathways [196]. Indole-based microbial metabolites can also interact with the aryl hydrocarbon receptor (AhR), which participates in immune regulation and cellular responses to oxidative stress [200]. Other microbial products, including exopolysaccharides from *Bifidobacterium* species, have demonstrated barrier-supporting effects in experimental systems [201]. SCFAs may additionally attenuate lipopolysaccharide-induced epithelial barrier disruption [202]. Lactic acid and bacteriocins have been investigated for their antimicrobial activities [203,204], while microbial cross-feeding involving lactate may contribute to the production of secondary SCFAs [205]. The effects of microbiota-derived products can vary with their source and function. For example, the gut commensal *Ruminococcus gnavus* has been linked to inflammatory conditions, and some strains can produce a pro-inflammatory polysaccharide [206].

Despite these mechanistic findings, the evidence for postbiotic interventions in CKD remains limited. Reports of reduced serum creatinine, improved renal function-related parameters and attenuated renal fibrosis following postbiotic supplementation are from preclinical investigations. Such findings provide a rationale for further research but cannot establish efficacy in patients with CKD. In particular, changes in renal biomarkers in animal models do not necessarily predict improvements in human glomerular filtration, disease progression, or clinical outcomes. The effects may also depend on the specific microbial preparation, metabolite, dose, and stage of renal impairment. Therefore, postbiotics should currently be regarded as investigational candidates rather than established adjunctive

treatments for CKD. Human trials are needed to determine their safety, effects on uremic toxin concentrations, and potential benefits when used alongside standard renal care.

7.2. Iron Deficiency Anemia: Microbial Contributions to Iron and Folate Metabolism

Iron deficiency anaemia (IDA) is a major nutritional and public health concern, particularly among children, women, and individuals with chronic diseases [207]. Although conventional iron supplementation is effective, gastrointestinal adverse effects may compromise adherence. Interest has therefore emerged in the potential contribution of gut microorganisms and their metabolites to iron bioavailability and haematological health.

Certain probiotic strains, including *Lactobacillus plantarum* and *Bifidobacterium bifidum*, may influence non-heme iron availability through organic acid production, which can lower intestinal pH and improve iron solubility [208,209]. Some microorganisms may also produce iron-binding compounds or contribute to the degradation of dietary phytate, which can inhibit mineral absorption. These effects are strain- and substrate-dependent and should not be assumed to occur with all probiotic preparations.

Microbial vitamin production is another potential link between the gut microbiota and haematological health. Folate, or vitamin B9, is required for nucleotide synthesis, cell division, and erythropoiesis [210]. Several gut microorganisms, including selected *Escherichia coli*, *Lactobacillus* and *Bifidobacterium* strains, possess the capacity to synthesise folate [210]. Certain folate-producing strains have consequently been explored in functional food development, including fermented dairy products [211]. However, microbial folate production or increased faecal folate concentrations do not necessarily demonstrate improved systemic folate status or correction of anaemia.

SCFAs have also been proposed to influence iron absorption through changes in intestinal pH and pathways involving hypoxia-inducible factor 2α (HIF-2α), which regulates intestinal iron transport [212]. However, the extent to which these mechanisms contribute to iron status in humans remains to be established. Similarly, altered tryptophan metabolism has been associated with inflammatory states and changes in erythropoiesis [211–213], although these associations do not demonstrate that tryptophan-derived postbiotics can directly correct IDA.

To summarise, microbial modulation of iron solubility, folate availability, and intestinal physiology shows a plausible research direction. However, the current mechanistic evidence should be distinguished from studies on clinical efficacy. Unless supported by adequately controlled human intervention studies, claims that postbiotic-enriched foods improved haemoglobin concentrations, iron stored or treatment adherence should be

interpreted cautiously. Future studies should assess clinically relevant outcomes, including haemoglobin, ferritin, transferrin saturation, and adverse effects, while accounting for dietary iron intake, inflammation, baseline nutritional status, and concurrent iron supplementation. Postbiotic-based interventions should therefore be considered potential complements to establish nutritional and medical management, rather than replacements for iron therapy.

7.3. Psychobiotics and the Gut-Brain Axis: Emerging Evidence for Mental Health Applications

The gut-brain axis comprises bidirectional communication between the gastrointestinal tract and central nervous system through neural, endocrine, immune, and metabolic pathways [214,215]. Alterations in gut microbiota composition have been associated with depression, anxiety, and neurodevelopmental conditions, including autism spectrum disorder [216]. However, microbiome differences observed in these conditions may reflect multiple influences, including diet, medication, lifestyle, and disease-related changes, rather than a direct causal relationship.

Psychobiotics are referred broadly to probiotics and other microbiome-targeted interventions that may influence mental health through the gut-brain axis. Their proposed mechanisms include modulation of neurotransmitter-related pathways, stress response, immune signalling, and microbial metabolite production. Microbial metabolites, such as SCFAs and tryptophan-derived compounds, may influence intestinal barrier integrity, neuroimmune signalling, and the hypothalamic-pituitary-adrenal (HPA) axis [217,218]. GABA-related signalling has also attracted interest because of its role in inhibitory neurotransmission, but the presence of neurotransmitter-related metabolites in microbial systems does not establish that they reach the human brain at biologically effective concentrations or produce clinically meaningful psychiatric effects.

Preclinical studies have provided mechanistic support for this field. For example, dietary administration of *Bacillus subtilis* spores was associated with behavioural changes in a mouse model [219]. Such findings are useful for investigating potential gut-brain mechanisms but cannot establish efficacy for human depression or anxiety. Translation is particularly challenging because behavioural outcomes in animal models do not fully capture the complexity of human psychiatric disorders.

Early human investigations provide preliminary evidence for specific psychobiotic interventions. Long-term administration of *Lactobacillus gasseri* CP2305 has been investigated in relation to sleep quality, stress responses, and emotional well-being in adolescents [220]. These findings are relevant to adolescent mental health but should be interpreted in the context of the specific strain, study design, population, and outcome

assessed. Improvements in stress-related or sleep-related measures should not be interpreted automatically as evidence of efficacy for diagnosed psychiatric disorders. In addition, the Malaysian pilot study involving a multistrain probiotic in adults with mild major depressive disorder provides a separate example of early clinical investigation [221]. As this study involved live probiotics and adults, it should not be presented as direct evidence for postbiotic treatment or adolescent efficacy.

The distinction between live psychobiotics and postbiotic interventions is important. Non-viable microbial preparations and isolated metabolites may offer formulation and storage advantages, and may avoid certain risks associated with administering live microorganisms. However, their comparative safety and effectiveness for mental health applications have not been established. Reviews of probiotic interventions in depression and the influence of antidepressant medication on gut microbiota further highlight the need to account for concomitant medication and other confounding factors [222,223]. Psychobiotics therefore represent a promising but still developing area of microbiome research. Future clinical studies should prioritise adequately powered, placebo-controlled trials with validated mental health outcomes, clearly defined microbial preparations, appropriate follow-up and careful assessment of adverse events. For adolescent populations, particular attention should be given to developmental stage, psychiatric diagnosis, psychological and pharmacological co-interventions, and long-term safety. At present, psychobiotics should be regarded as investigational adjunctive approaches rather than substitutes for established psychological or pharmacological treatment.

7.4. Metabolic Syndrome and Youth Obesity: Evaluating Synbiotic and Postbiotic Approaches

Metabolic syndrome comprises interrelated metabolic abnormalities, including central obesity, insulin resistance, dyslipidaemia, and elevated blood pressure. Its increasing prevalence among younger populations has prompted interested in microbiome-targeted interventions as potential complements to lifestyle modification [224]. Synbiotics and postbiotics have been investigated because of their possible effects on intestinal barrier function, energy metabolism, inflammation, and glucose regulation [225,226]. However, evidence from studies of synbiotic formulations should be distinguished from studies specifically supporting postbiotic interventions.

SCFAs, including acetate, propionate and butyrate, are among the microbial metabolites most frequently investigated in metabolic health. They can activate G-protein-coupled receptors, including GPCR41 and GPCR43, and may influence gut hormone secretion, appetite regulation, and energy metabolism [227,228]. SCFAs have also been

implicated in glucose homeostasis, insulin sensitivity, and intestinal gluconeogenesis [229]. However, their effects are context-dependent and may vary according to the metabolite, concentration, route of administration, dietary substrate, and metabolic status of the host. Therefore, mechanistic findings should not be interpreted as evidence that SCFA supplementation consistently improves obesity or metabolic syndrome in humans.

Other microbial products, including exopolysaccharides produced by *Bifidobacterium animalis* and *Lactobacillus paracasei* strains, have demonstrated potential effects on lipid and glucose-related parameters in experimental studies [230,231]. SCFAs may also influence vascular function and blood pressure regulation through receptor-mediated and anti-inflammatory pathways [232]. However, these findings require further clinical validation, particularly because the effects of isolated metabolites may differ from those of complex postbiotic preparations.

The potential application of microbiome-targeted interventions in children and adolescents warrants particular consideration. Younger populations differ from adults in their metabolic development, dietary requirements, and microbiome maturation. Therefore, findings from adult studies cannot automatically be extrapolated to youth obesity or paediatric metabolic syndrome. Future studies should evaluate age-appropriate formulations and clinically relevant outcomes, including body composition, insulin resistance, lipid profiles, and blood pressure. They should also assess whether any metabolic benefits are sustained and whether they provide additional value beyond established dietary and lifestyle interventions. At present, synbiotic and postbiotic strategies remain promising adjunctive research approaches, rather than established treatments for metabolic syndrome.

7.5. Pediatric and Geriatric Populations: Age-Specific Considerations and Evidence Gaps

The microbiome changes substantially throughout the lifespan, making age an important consideration in the development and evaluation of probiotic and postbiotic interventions. However, biological differences between age groups do not, by themselves, establish that a particular intervention is effective or safe in infants, children, or older adults.

7.5.1. Paediatric populations

In early life, the intestinal microbiota undergoes rapid development alongside maturation of the mucosal immune system. Microbial components, including cell-wall fragments and peptidoglycan-derived molecules, may interact with pattern-recognition receptors such as Toll-like receptors and nucleotide-binding oligomerisation domain-containing receptors [233], thereby influencing immune development [234]. These mechanisms

have prompted interest in non-viable microbial preparations as potential approaches to supporting early-life immune responses.

In this context, the scientific studies of immune modulation do not necessarily demonstrate clinical benefits in infants or children. The microbiota of preterm infants, for example, may differ considerably from that of healthy term infants, and early colonisation patterns can be influenced by gestational age, delivery mode, feeding practices, antibiotic exposure, and hospital environment [235]. Findings from general experimental models cannot be directly linked to vulnerable neonatal populations. The use of postbiotics in infants also requires careful consideration of preparation-specific safety, dose, manufacturing consistency, and developmental stage. Further controlled clinical studies are required to establish whether specific postbiotic preparations improve clinically relevant outcomes, such as infection incidence or gastrointestinal health, rather than only altering immune or microbiome-related biomarkers. Moreover, paediatric studies should distinguish neonatal, infant, childhood, and adolescent populations rather than treating them as a single clinical group. A culture-based study in a Malaysian neonatal intensive care unit found that Enterobacteriaceae accounted for 46% of bacterial isolates recovered from early stool samples of preterm infants [236].

7.5.2. Geriatric populations

In geriatric individuals, immunosenescence, altered dietary patterns, medication exposure, and changes in gut microbiota composition may contribute to increased susceptibility to infection, frailty, and chronic inflammatory conditions [237]. SCFAs and polyamines have been investigated for their potential roles in maintaining intestinal barrier integrity and regulating inflammatory responses [196]. The gut-brain axis has also attracted attention in ageing research, including investigations of gut dysbiosis and neuroinflammation in Alzheimer's disease [238].

Despite these mechanistic observations, the evidence provided here does not establish that postbiotic supplementation prevents frailty, cognitive decline, or infection in geriatric individuals. The Malaysian MyAgeWell cohort, which reported variation in salivary C-reactive protein according to participant characteristics, provides contextual information on inflammatory biomarkers in an older population but does not demonstrate the efficacy of a postbiotic intervention [239]. Moreover, although non-viable preparations avoid the administration of live microorganisms, they should not automatically be regarded as risk-free, particularly in older adults with multiple comorbidities or altered immune function. Age-specific clinical investigations should therefore evaluate defined postbiotic preparations in appropriately characterised older populations. Relevant outcomes may include infection

incidence, gastrointestinal function, frailty measures, nutritional status, and inflammatory biomarkers, with adequate follow-up to assess sustained effects and adverse events.

To summarise, postbiotics may offer formulation and stability advantages that warrant investigation across different stages of life. However, their clinical application in paediatric and geriatric care remains insufficiently established. Age-specific efficacy, dose, safety, and clinically meaningful outcomes must be demonstrated before these preparations can be recommended for vulnerable populations.

8. Conclusion

In conclusion, research into microbiome-based interventions has expanded beyond conventional live probiotics to encompass next-generation probiotics (NGPs), engineered live biotherapeutics, synbiotics, postbiotics, paraprobiotics, and proteobiotics. These approaches offer diverse mechanisms for modulating microbial communities, host immunity, metabolism, and epithelial barrier function. Advances in formulation and delivery may further improve product stability, microbial survival, and targeted administration. However, although the field is rich in mechanistic hypotheses and encouraging preclinical findings, a central challenge remains, which is the confirmatory human clinical studies and validations demonstrating reproducible and clinically meaningful benefits remains limited. Thus, promising biological activities should not be equated with established therapeutic efficacy.

Moving these interventions towards clinical validation requires category-specific research priorities. For postbiotics, greater standardisation of microbial preparations, identification, and quantification of active components, and characterisation of dose-response relationships are necessary to ensure reproducible biological activity, safety, and efficacy. For NGPs, including engineered live biotherapeutics, strain-level characterisation, manufacturing consistency, long-term safety assessment, and evaluation of persistence, ecological effects, and potential horizontal gene transfer are essential. Well-designed clinical trials must also establish efficacy for specific indications and patient populations. For proteobiotics, further work is needed to isolate and characterise active peptide components, establish their mechanisms of action, assess stability and bioavailability, and determine whether the promising preclinical anti-virulence effects can be reproduced in human studies. Veterinary applications should not be regarded as evidence of human therapeutic efficacy.

Across these categories, adequately powered, randomised and controlled clinical trials with appropriate comparators, clinically relevant endpoints, and sufficient follow-up are required to establish therapeutic benefit beyond changes in microbiome composition or surrogate biomarkers. Manufacturing reproducibility, regulatory requirements, product-

specific safety, and cost-effectiveness must also be addressed to support clinical implementation. Although microbiome profiling may eventually help identify individuals who are more likely to respond to specific microbiome-based interventions, this remains a hypothesis requiring prospective validation in independent and appropriately characterised patient cohorts. Ultimately, the clinical relevance of these emerging approaches will depend not only on their mechanistic plausibility or technological sophistication, but on the demonstration of consistent, safe, and meaningful benefits in human populations.

Author Contributions: Conceptualization: HSN, JJC and KBL. Formal analysis: AJ, YHL, SMMN and PEK. Investigation: MRFMR, VXYT, ABMHU and KBL. Writing – original draft preparation: SMT, AJ, YHL, SMMN, PEK, MRFMR, VXYT, ABMHU. Writing – review and editing: HSN, JJC, KBL. Validation: SMT. Supervision: KBL. Funding acquisition: HSN, JJC.

Funding: This work was not supported by any funding agency.

Acknowledgements: The authors acknowledge University of Cyberjaya for providing literature search database and facility to complete the review article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hill C, Guarner F, Reid G, *et al*. Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology and Hepatology. 2014;11(8):506. doi:10.1038/nrgastro.2014.66.

2. Tan SM, Widodo RT, Chew YL, *et al*. Probiotic modulation of the skin microbiome: Emerging therapeutic strategies in dermatology. Progress in Microbes and Molecular Biology. 2026;9(1):a0000653. doi:10.36877/pmmb.a0000653.

3. Tay TY, Wong MYZ, Wee AS, *et al*. Clinical Applications of Probiotics in Atopic Dermatitis. Progress in Microbes and Molecular Biology. 2025;8(1):a0000473. doi:10.36877/pmmb.a0000473.

4. Swanson KS, Gibson GR, Hutkins R, *et al*. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nature Reviews Gastroenterology and Hepatology. 2020;17:687. doi:10.1038/s41575-020-0344-2.

5. Salminen S, Collado MC, Endo A, *et al*. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nature Reviews Gastroenterology and Hepatology. 2021;18:649. doi:10.1038/s41575-021-00440-6.

6. Nataraj BH, Ali SA, Behare PV., *et al*. Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. Microbial Cell Factories. 2020;19:168. doi:10.1186/s12934-020-01426-w.

7. Salahi A, Abd El-Ghany WA. Beyond probiotics, uses of their next-generation for poultry and humans: A review. Journal of Animal Physiology and Animal Nutrition. 2024;108(5):1336. doi:10.1111/jpn.13972.

8. Depommier C, Everard A, Druart C, *et al*. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nature Medicine. 2019;25(7):1096. doi:10.1038/s41591-019-0495-2.

9. Puurunen MK, Vockley J, Searle SL, *et al*. Safety and pharmacodynamics of an engineered E. coli Nissle for the treatment of phenylketonuria: a first-in-human phase 1/2a study. Nat Metab. 2021;3(8):1125. doi:10.1038/s42255-021-00430-7.

10. Zmora N, Zilberman-Schapira G, Suez J, *et al*. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. Cell. 2018;174(6). doi:10.1016/j.cell.2018.08.041.

11. Han J, McClements DJ, Liu X, *et al*. Oral delivery of probiotics using single-cell encapsulation. Comprehensive Reviews in Food Science and Food Safety. 2024;23(3):e13322. doi:10.1111/1541-4337.13322.

12. Latif A, Shehzad A, Niazi S, *et al*. Probiotics: mechanism of action, health benefits and their application in food industries. Frontiers in Microbiology. 2023;14:1216674. doi:10.3389/fmicb.2023.1216674.

13. Yeşilyurt N, Yılmaz B, Ağagündüz D, *et al*. Involvement of Probiotics and Postbiotics in the Immune System Modulation. Biologics. 2021;1(2):89. doi:10.3390/biologics1020006.

14. Vinderola G, Druart C, Gosálbez L, *et al*. Postbiotics in the medical field under the perspective of the ISAPP definition: scientific, regulatory, and marketing considerations. Frontiers in Pharmacology. 2023;14:1239745. doi:10.3389/fphar.2023.1239745.

15. Franco W. Postbiotics and parabiotics derived from bacteria and yeast: current trends and future perspectives. CYTA - Journal of Food. 2024;22(1):2425838. doi:10.1080/19476337.2024.2425838.

16. Smolinska S, Popescu FD, Zemelka-Wiacek M. A Review of the Influence of Prebiotics, Probiotics, Synbiotics, and Postbiotics on the Human Gut Microbiome and Intestinal Integrity. Journal of Clinical Medicine. 2025;14(11):3673. doi:10.3390/jcm14113673.

17. Rezaie N, Aghamohammad S, Gholizadeh Khiavi EHA, *et al*. Comparison of novel native probiotics and paraprobiotics in modulating oxidative stress and inflammation in DSS-induced colitis: implications for enhanced therapeutic strategies in high fat diet. BMC Immunology. 2024;25(1):85. doi:10.1186/s12865-024-00678-0.

18. Arora M, Arora M, Bansal P, *et al*. Need and Recommendations for Universal Guidelines on Regulatory Status and Quality Control/Safety of Probiotic Products. Applied Clinical Research, Clinical Trials and Regulatory Affairs. 2019;6(3):231. doi:10.2174/2213476x06666190206120712.

19. Ailioaie LM, Litscher G. Probiotics, photobiomodulation, and disease management: Controversies and challenges. International Journal of Molecular Sciences. 2021;22(9):4942. doi:10.3390/ijms22094942.

20. Spacova I, Binda S, ter Haar JA, *et al*. Comparing technology and regulatory landscape of probiotics as food, dietary supplements and live biotherapeutics. Frontiers in Microbiology. 2023;14:1272754. doi:10.3389/fmicb.2023.1272754.

21. Leeflang J, Wright JA, Worthley DL, *et al*. Evolutionary adaptation of probiotics in the gut: selection pressures, optimization strategies, and regulatory challenges. NPJ Biofilms and Microbiomes. 2025;11(1):96. doi:10.1038/s41522-025-00734-6.

22. Guglielmetti S, Boyte ME, Smith CL, *et al*. Commercial and regulatory frameworks for postbiotics: an industry-oriented scientific perspective for non-viable microbial ingredients conferring beneficial physiological effects. Trends in Food Science and Technology. 2025;163:105130. doi:10.1016/j.tifs.2025.105130.

23. Siciliano RA, Reale A, Mazzeo MF, *et al*. Paraprobiotics: A new perspective for functional foods and nutraceuticals. Nutrients. 2021;13(4):1225. doi:10.3390/nu13041225.

24. Saville SH, Younes JA, Paraskevakos G, *et al*. The prebiotic landscape: history, health and physiological benefits, and regulatory challenges-an IPA perspective part 1. Beneficial Microbes. 2025;16(1):1. doi:10.1163/18762891-bja00056.

25. Ladda B, Jantararussamee C, Pradidarcheep W, *et al*. Anti-Inflammatory and Gut Microbiota Modulating Effects of Probiotic Lactobacillus paracasei MSMC39-1 on Dextran Sulfate Sodium-Induced Colitis in Rats. Nutrients. 2023;15(6):1388. doi:10.3390/nu15061388.

26. Gulnaz A, Lew LC, Park YH, *et al*. Efficacy of Probiotic Strains Lactobacillus sakei Probio65 and Lactobacillus plantarum Probio-093 in Management of Obesity: An In Vitro and In Vivo Analysis. Pharmaceuticals. 2024;17(6):676. doi:10.3390/ph17060676.

27. Lee MC, Cheng TY, Lin PJ, *et al*. Supplementation with Live and Heat-Treated Lacticaseibacillus paracasei NB23 Enhances Endurance and Attenuates Exercise-Induced Fatigue in Mice. Nutrients. 2025;17(15):2568. doi:10.3390/nu17152568.

28. Martyniak A, Medyńska-Przęczek A, Wędrychowicz A, *et al*. Prebiotics, probiotics, synbiotics, paraprobiotics and postbiotic compounds in IBD. Biomolecules. 2021;11(12):1903. doi:10.3390/biom11121903.

29. Saedi S, Derakhshan S, Hasani A, *et al*. Recent Advances in Gut Microbiome Modulation: Effect of Probiotics, Prebiotics, Synbiotics, and Postbiotics in Inflammatory Bowel Disease Prevention and Treatment. Current Microbiology. 2025;82(1):12. doi:10.1007/s00284-024-03997-y.

30. Huang Y, Wang Q, Han X, *et al*. Heat-Inactivated Lactiplantibacillus plantarum FRT4 Alleviates Diet-Induced Obesity via Gut–Liver Axis Reprogramming. Foods. 2025;14(16):2799. doi:10.3390/foods14162799.

31. Cabello-Olmo M, Oneca M, Goñi S, *et al*. Heat-Inactivated Pediococcus acidilactici pA1c®HI Maintains Glycemic Control and Prevents Body Weight Gain in High-Fat-Diet-Fed Mice. International Journal of Molecular Sciences. 2025;26(13):6408. doi:10.3390/ijms26136408.

32. Zhang T, Zhang W, Feng C, *et al*. Stronger gut microbiome modulatory effects by postbiotics than probiotics in a mouse colitis model. NPJ Science of Food. 2022;6(1):53. doi:10.1038/s41538-022-00169-9.

33. Kim JH, Kwak W, Nam Y, *et al*. Effect of postbiotic Lactiplantibacillus plantarum LRCC5314 supplemented in powdered milk on type 2 diabetes in mice. Journal of Dairy Science. 2024;107(8):5301. doi:10.3168/jds.2023-24103.

34. Yavaş A, Akan E. Evaluation of Lacticaseibacillus casei 39 Paraprobiotic in Modulating Inflammatory and Oxidative Pathways in Acetic Acid Induced Ulcerative Colitis. Food Science & Nutrition. 2025;13(7):e70476. doi:10.1002/fsn3.70476.

35. Kang YY, Song HJ, Park SY, *et al*. Comparative Effects of Probiotics and ParaprobioticsDerivedfromLactiplantibacillus plantarum, Latilactobacillus sakei, and Limosilactobacillus reuteri in a DSS-Induced Ulcerative Colitis Mouse Model. Journal of Microbiology and Biotechnology. 2025;35:e2411045. doi:10.4014/jmb.2411.11045.

36. Batista VL, De Jesus LCL, Tavares LM, *et al*. Paraprobiotics and Postbiotics of Lactobacillus delbrueckii CIDCA 133 Mitigate 5-FU-Induced Intestinal Inflammation. Microorganisms. 2022;10(7):1418. doi:10.3390/microorganisms10071418.

37. Alagiakrishnan K, Halverson T. Microbial Therapeutics in Neurocognitive and Psychiatric Disorders. Journal of Clinical Medicine Research. 2021;13(9):439. doi:10.14740/jocmr4575.

38. Abouelela ME, Helmy YA. Next-Generation Probiotics as Novel Therapeutics for Improving Human Health: Current Trends and Future Perspectives. Microorganisms. 2024;12(3):430. doi:10.3390/microorganisms12030430.

39. Fakruddin Md, Shishir MdA, Yousuf Z, *et al*. Next-Generation Probiotics - The Future of Biotherapeutics. Microbial Bioactive. 2022;5(1):156. doi:10.25163/microbbioacts.514309.

40. Gul S, Durante-Mangoni E. Unraveling the Puzzle: Health Benefits of Probiotics—A Comprehensive Review. Journal of Clinical Medicine. 2024;13(5):1436. doi:10.3390/jcm13051436.

41. Martín R, Langella P. Emerging health concepts in the probiotics field: Streamlining the definitions. Frontiers in Microbiology. 2019;10:1047. doi:10.3389/fmicb.2019.01047.

42. Zhang H, Duan Y, Cai F, *et al*. Next-Generation Probiotics: Microflora Intervention to Human Diseases. BioMed Research International. 2022;2022:5633403. doi:10.1155/2022/5633403.

43. Arora M, Baldi A. Regulatory categories of probiotics across the globe: A review representing existing and recommended categorization. Indian Journal of Medical Microbiology. 2015;33:S2. doi:10.4103/0255-0857.150868.

44. Loo KY, Thong JYH, Tan LTH, *et al*. A Current Overview of Next-Generation Probiotics and Their Prospects in Health and Disease Management. Progress in Microbes and Molecular Biology. 2024;7(1):a0000457. doi:10.36877/pmmb.a0000457.

45. Fontana L, Bermudez-Brito M, Plaza-Diaz J, *et al*. Sources, isolation, characterisation and evaluation of probiotics. British Journal of Nutrition. 2013;109 Suppl 2:S35. doi:10.1017/S0007114512004011.

46. Derrien M, Vaughan EE, Plugge CM, *et al*. Akkermansia municiphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. International Journal of Systematic and Evolutionary Microbiology. 2004;54(5):1469. doi:10.1099/ijs.0.02873-0 PubMed PMID: 15388697.

47. Zhang T, Li Q, Cheng L, *et al*. Akkermansia muciniphila is a promising probiotic. Microbial Biotechnology. 2019;12(6):1109. doi:10.1111/1751-7915.13410.

48. Effendi RMRA, Anshory M, Kalim H, *et al*. Akkermansia muciniphila and Faecalibacterium prausnitzii in Immune-Related Diseases. Microorganisms. 2022;10(12):2382. doi:10.3390/microorganisms10122382.

49. Lukovac S, Belzer C, Pellis L, *et al*. Differential modulation by Akkermansia muciniphila and faecalibacterium prausnitzii of host peripheral lipid metabolism and histone acetylation in mouse gut organoids. MBio. 2014;5(4):e01438. doi:10.1128/mBio.01438-14.

50. Xie L, Lu J, Han H, *et al*. Mechanism and application of Akkermansia muciniphila in inflammatory diseases. Frontiers in Cellular and Infection Microbiology. 2026;16:1819005. doi:10.3389/fcimb.2026.1819005.

51. Ottman N, Geerlings SY, Aalvink S, *et al*. Action and function of Akkermansia muciniphila in microbiome ecology, health and disease. Best Practice and Research: Clinical Gastroenterology. 2017;31(6):637. doi:10.1016/j.bpg.2017.10.001.

52. Martín R, Miquel S, Benevides L, *et al*. Functional characterization of novel Faecalibacterium prausnitzii strains isolated from healthy volunteers: A step forward in the use of F. prausnitzii as a next-generation probiotic. Frontiers in Microbiology. 2017;8:1226. doi:10.3389/fmicb.2017.01226.

53. Chen J, Vitetta L. The role of butyrate in attenuating pathobiont-induced hyperinflammation. Immune Network. 2020;20(2):e15. doi:10.4110/in.2020.20.e15.

54. Lopez-Siles M, Duncan SH, Garcia-Gil LJ, *et al*. Faecalibacterium prausnitzii: From microbiology to diagnostics and prognostics. The ISME Journal. 2017;11(4):841. doi:10.1038/ismej.2016.176.

55. Ma J, Lyu Y, Liu X, *et al*. Engineered probiotics. Microbial Cell Factories. 2022;21:72. doi:10.1186/s12934-022-01799-0.

56. O'Toole PW, Marchesi JR, Hill C. Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. Nature Microbiology. 2017;2:17057. doi:10.1038/nmicrobiol.2017.57.

57. Zhang M, Eshraghian EA, Jammal O Al, *et al*. CRISPR technology: The engine that drives cancer therapy. Biomedicine and Pharmacotherapy. 2021;133:111007. doi:10.1016/j.biopha.2020.111007.

58. Yadav R, Kumar V, Baweja M, *et al*. Gene editing and genetic engineering approaches for advanced probiotics: A Review. Critical Reviews in Food Science and Nutrition. 2018;58(10):1735. doi: 10.1080/10408398.2016.1274877.

59. Yadav M, Shukla P. Efficient engineered probiotics using synthetic biology approaches: A review. Biotechnology and Applied Biochemistry. 2020;67(1):22. doi:10.1002/bab.1822.

60. Tang X, Lowder LG, Zhang T, *et al*. A CRISPR-Cpf1 system for efficient genome editing and transcriptional repression in plants. Nature Plants. 2017;3:17018. doi:10.1038/nplants.2017.18.

61. Puchta H. Applying CRISPR/Cas for genome engineering in plants: the best is yet to come. Current Opinion in Plant Biology. 2017;36:1. doi:10.1016/j.pbi.2016.11.011.

62. Mekler V, Kuznedelov K, Severinov K. Quantification of the affinities of CRISPR–Cas9 nucleases for cognate protospacer adjacent motif (PAM) sequences. Journal of Biological Chemistry. 2020;295(19):6509. doi:10.1074/jbc.RA119.012239.

63. McGinn J, Marraffini LA. Molecular mechanisms of CRISPR–Cas spacer acquisition. Nature Reviews Microbiology. 2019;17(1):7. doi:10.1038/s41579-018-0071-7.

64. Tarrant I, Finlay BB. The potential of live biotherapeutic products in allergic disease: current findings and future directions. Frontiers in Microbiomes. 2024;3:1418633. doi:10.3389/frmbi.2024.1418633.

65. Cordaillat-Simmons M, Rouanet A, Pot B. Live biotherapeutic products: the importance of a defined regulatory framework. Experimental and Molecular Medicine. 2020;52(9):1397. doi:10.1038/s12276-020-0437-6.

66. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. Nature Biomedical Engineering. 2021;5(9):951. doi:10.1038/s41551-021-00698-w.

67. Heavey MK, Durmusoglu D, Crook N, *et al*. Discovery and delivery strategies for engineered live biotherapeutic products. 2021;40(3):354. doi: 10.1016/j.tibtech.2021.08.002.

68. Mimee M, Citorik RJ, Lu TK. Microbiome therapeutics — Advances and challenges. Advanced Drug Delivery Reviews. 2016;105(Pt A):44. doi:10.1016/j.addr.2016.04.032.

69. Tseng CH, Wong S, Yu J, *et al*. Development of live biotherapeutic products: a position statement of Asia-Pacific Microbiota Consortium. Gut. 2025;74(5):706. doi:10.1136/gutjnl-2024-334501.

70. Ang WS, Law JWF, Letchumanan V, *et al*. A Keystone Gut Bacterium Christensenella minuta—A Potential Biotherapeutic Agent for Obesity and Associated Metabolic Diseases. Foods. 2023;12(13):2485. doi:10.3390/foods12132485.

71. Paquet JC, Claus SP, Cordaillat-Simmons M, *et al*. Entering First-in-Human Clinical Study With a Single-Strain Live Biotherapeutic Product: Input and Feedback Gained From the EMA and the FDA. Frontiers in Medicine. 2021;8:716266. doi:10.3389/fmed.2021.716266.

72. Puurunen MK, Vockley J, Searle SL, *et al*. Safety and pharmacodynamics of an engineered E. coli Nissle for the treatment of phenylketonuria: a first-in-human phase 1/2a study. Nature Metabolism. 2021;3(8):1125. doi:10.1038/s42255-021-00430-7.

73. Isabella VM, Ha BN, Castillo MJ, *et al*. Development of a synthetic live bacterial therapeutic for the human metabolic disease phenylketonuria. Nature Biotechnology. 2018;36(9):857. doi:10.1038/nbt.4222.

74. Nataraj BH, Ali SA, Behare PV, *et al*. Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. Microbial Cell Factories. 2020;19(1):168. doi:10.1186/s12934-020-01426-w.

75. Rezaie N, Aghamohammad S, Khiavi EHAG, *et al*. The Analysis and Comparison of Anti-Inflammatory and Antioxidant Characteristics of Postbiotic and Paraprobiotic Derived From Novel Native Probiotic Cocktail in DSS-Induced Colitic Mice. Food Science and Nutrition. 2025;13(2):e70034. doi:10.1002/fsn3.70034.

76. Yu B, Wang KY, Wang NR, *et al*. Effect of probiotics and paraprobiotics on patients with sleep disorders and sub-healthy sleep conditions: a meta-analysis of randomized controlled trials. Frontiers in Neurology. 2024;15:1477533. doi:10.3389/fneur.2024.1477533.

77. Russo E, Giudici F, Fiorindi C, *et al*. Immunomodulating Activity and Therapeutic Effects of Short Chain Fatty Acids and Tryptophan Post-biotics in Inflammatory Bowel Disease. Frontiers in Immunology. 2019;10:2754. doi:10.3389/fimmu.2019.02754.

78. Ozma MA, Abbasi A, Akrami S, *et al*. Postbiotics as the key mediators of the gut microbiota-host interactions. Infezioni in Medicina. 2022;30(2):180. doi:10.53854/liim-3002-3.

79. Gill PA, van Zelm MC, Muir JG, *et al*. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. Alimentary Pharmacology and Therapeutics. 2018;48(1):15. doi:10.1111/apt.14689.

80. Hamer HM, Jonkers DMAE, Vanhoutvin SALW, *et al*. Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. Clinical Nutrition. 2010;29(6):738. doi:10.1016/j.clnu.2010.04.002.

81. Langfeld LQ, Du K, Bereswill S, *et al*. A review of the antimicrobial and immune-modulatory properties of the gut microbiota-derived short chain fatty acid propionate - What is new? European Journal of Microbiology and Immunology. 2021;11(2):50. doi:10.1556/1886.2021.00005.

82. Tang R, Li L. Modulation of Short-Chain Fatty Acids as Potential Therapy Method for Type 2 Diabetes Mellitus. Canadian Journal of Infectious Diseases and Medical Microbiology. 2021;2021:6632266. doi:10.1155/2021/6632266.

83. Li M, van Esch BCAM, Henricks PAJ, *et al*. The anti-inflammatory effects of short chain fatty acids on lipopolysaccharide- or tumor necrosis factor α-stimulated endothelial cells via activation of

GPR41/43 and inhibition of HDACs. Frontiers in Pharmacology. 2018;9:533. doi:10.3389/fphar.2018.00533.

84. Chambers ES, Morrison DJ, Frost G. Control of appetite and energy intake by SCFA: What are the potential underlying mechanisms? Proceedings of the Nutrition Society. 2015;74(3):328. doi:10.1017/S0029665114001657.

85. Corrêa-Oliveira R, Fachi JL, Vieira A, *et al*. Regulation of immune cell function by short-chain fatty acids. Clinical and Translational Immunology. 2016;5(4):e73. doi:10.1038/cti.2016.17.

86. Pandey M, Bhati A, Priya K, *et al*. Precision Postbiotics and Mental Health: the Management of Post-COVID-19 Complications. Probiotics and Antimicrobial Proteins. 2022;14:426. doi:10.1007/s12602-021-09875-4.

87. Jastrząb R, Graczyk D, Siedlecki P. Molecular and cellular mechanisms influenced by postbiotics. International Journal of Molecular Sciences. 2021;22(24):13475. doi:10.3390/ijms222413475.

88. Kazemi A, Soltani S, Nasri F, *et al*. The effect of probiotics, parabiotics, synbiotics, fermented foods and other microbial forms on immunoglobulin production: a systematic review and meta-analysis of clinical trials. International Journal of Food Sciences and Nutrition. 2021;72(5):632. doi:10.1080/09637486.2020.1857710.

89. Guo J, Zhao Y, Guo W, *et al*. Effects of Lactobacillus paracei JY062 Postbiotic on Intestinal Barrier, Immunity, and Gut Microbiota. Nutrients. 2025;17(7):1272. doi:10.3390/nu17071272.

90. Ding W, Cheng Y, Liu X, *et al*. Harnessing the human gut microbiota: an emerging frontier in combatting multidrug-resistant bacteria. Frontiers in Immunology. 2025;16:1563450. doi:10.3389/fimmu.2025.1563450.

91. Talbi C, Elmarrakchy S, Youssfi M, *et al*. Bacterial Exopolysaccharides: From Production to Functional Features. Progress in Microbes and Molecular Biology. 2023;6(1):a0000384. doi:10.36877/pmmb.a0000384.

92. Banakar M, Pourhajibagher M, Etemad-Moghadam S, *et al*. Antimicrobial Effects of Postbiotic Mediators Derived from Lactobacillus rhamnosus GG and Lactobacillus reuteri on Streptococcus mutans. Frontiers in Bioscience - Landmark. 2023;28(5):88. doi:10.31083/j.fbl2805088.

93. Butrungrod W, Chaiyasut C, Makhamrueang N, *et al*. Postbiotic Metabolite Derived from Lactiplantibacillus plantarum PD18 Maintains the Integrity of Cell Barriers and Affects Biomarkers Associated with Periodontal Disease. Antibiotics. 2024;13(11):1054. doi:10.3390/antibiotics13111054.

94. Thye AYK, Kumari Y, Chan KG, *et al*. In Vitro Antagonistic Activity of Probiotic Strains against Antibiotic-Resistant Klebsiella pneumoniae isolated from Preterm Infant Stools. Progress in Microbes and Molecular Biology. 2025;8(1):a0000477. doi:10.36877/pmmb.a0000477.

95. Chong KJ, Feng H, Letchumanan V, et al. Tackling Microbial Resistance and Emerging Pathogens with Next-Generation Antibiotics. Progress in Microbes and Molecular Biology. 2024;7(1):a0000447. doi:10.36877/pmmb.a0000447.

96. Zhao Z, Wu J, Sun Z, *et al*. Postbiotics Derived from L. paracasei ET-22 Inhibit the Formation of S. mutans Biofilms and Bioactive Substances: An Analysis. Molecules. 2023;28(3):1236. doi:10.3390/molecules28031236.

97. Jung JI, Baek SM, Nguyen TH, *et al*. Effects of probiotic culture supernatant on cariogenic biofilm formation and rankl-induced osteoclastogenesis in raw 264.7 macrophages. Molecules. 2021;26(3):733. doi:10.3390/molecules26030733.

98. Aghebati-Maleki L, Hasannezhad P, Abbasi A, *et al*. Antibacterial, antiviral, antioxidant, and anticancer activities of postbiotics: A review of mechanisms and therapeutic perspectives. Biointerface Research in Applied Chemistry. 2022;12(2):2629. doi:10.33263/BRIAC122.26292645.

99. Chang HM, Foo HL, Loh TC, *et al*. Comparative Studies of Inhibitory and Antioxidant Activities, and Organic Acids Compositions of Postbiotics Produced by Probiotic Lactiplantibacillus plantarum Strains Isolated From Malaysian Foods. Frontiers in Veterinary Science. 2021;7:602280. doi:10.3389/fvets.2020.602280.

100. Chen J, Zhang L, Jiao Y, *et al*. Lacticaseibacillus paracasei L21 and Its Postbiotics Ameliorate Ulcerative Colitis Through Gut Microbiota Modulation, Intestinal Barrier Restoration, and HIF1α/AhR-IL-22 Axis Activation: Combined In Vitro and In Vivo Evidence. Nutrients. 2025;17(15):2537. doi:10.3390/nu17152537.

101. Li HY, Zhou DD, Gan RY, *et al*. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: A narrative review. Nutrients. 2021;13(9):3211. doi:10.3390/nu13093211.

102. Rodríguez-Pastén A, Pérez-Hernández N, Añorve-Morga J, *et al*. The Activity of Prebiotics and Probiotics in Hepatogastrointestinal Disorders and Diseases Associated with Metabolic Syndrome. International Journal of Molecular Sciences. 2022;23(13):7229. doi:10.3390/ijms23137229.

103. Park M, Joung M, Park JH, *et al*. Role of Postbiotics in Diet-Induced Metabolic Disorders. Nutrients. 2022;14(18):3701. doi:10.3390/nu14183701.

104. Sim AAXH, Cheam JY, Law JWF, *et al*. The Ameliorative Role of Probiotics in 5-fluorouracil Induced Intestinal Mucositis. Progress in Microbes and Molecular Biology. 2023;6(1):a0000339. doi:10.36877/pmmb.a0000339.

105. Shinkai S, Toba M, Saito T, *et al*. Immunoprotective effects of oral intake of heat-killed Lactobacillus pentosus strain b240 in elderly adults: A randomised, double-blind, placebo-controlled trial. British Journal of Nutrition. 2013;109(10):1856. doi:10.1017/S0007114512003753.

106. Akatsu H. Exploring the effect of probiotics, prebiotics, and postbiotics in strengthening immune activity in the elderly. Vaccines. 2021;9(2):136. doi:10.3390/vaccines9020136.

107. Homayouni Rad A, Pourjafar H, Mirzakhani E. A comprehensive review of the application of probiotics and postbiotics in oral health. Frontiers in Cellular and Infection Microbiology. 2023;13:1120995. doi:10.3389/fcimb.2023.1120995.

108. Hong Q, Ren Y, Tang X, *et al*. Impact of Live Ligilactobacillus salivarius CCFM1332 and Its Postbiotics on Porphyromonas gingivalis Colonization, Alveolar Bone Resorption and Inflammation in a Rat Model of Periodontitis. Microorganisms. 2025;13(7):1701. doi:10.3390/microorganisms13071701.

109. Twetman S, Belstrøm D. Effect of Synbiotic and Postbiotic Supplements on Dental Caries and Periodontal Diseases—A Comprehensive Review. International Journal of Environmental Research and Public Health. 2025;22:72. doi:10.3390/ijerph22010072.

110. Basir L, Moghimipour E, Saadatzadeh A, *et al*. Effect of postbiotic-toothpaste on salivary levels of IgA in 6- to 12-year-old children: Study protocol for a randomized triple-blind placebo-controlled trial. Frontiers in Pediatrics. 2022;10:1042973. doi:10.3389/fped.2022.1042973.

111. Butera A, Gallo S, Pascadopoli M, *et al*. Home Oral Care of Periodontal Patients Using Antimicrobial Gel with Postbiotics, Lactoferrin, and Aloe Barbadensis Leaf Juice Powder vs. Conventional Chlorhexidine Gel: A Split-Mouth Randomized Clinical Trial. Antibiotics. 2022;11(1):118. doi:10.3390/antibiotics11010118.

112. Guo S, Ma T, Kwok LY, *et al*. Effects of postbiotics on chronic diarrhea in young adults: a randomized, double-blind, placebo-controlled crossover trial assessing clinical symptoms, gut microbiota, and metabolite profiles. Gut Microbes. 2024;16(1):2395092. doi:10.1080/19490976.2024.2395092.

113. Mosca A, Abreu Y Abreu AT, Gwee KA, *et al*. The clinical evidence for postbiotics as microbial therapeutics. Gut Microbes. 2022;14(1):2117508. doi:10.1080/19490976.2022.2117508.

114. Halimi MM, Wu YS, Lee MF, et al. Blastocystis sp.: A Hidden Player in Gut Health and Disease. Progress in Microbes and Molecular Biology. 2025;8(1):a0000471. doi:10.36877/pmmb.a0000471.

115. Jin Y, Wu J, Huang K, *et al*. Heat-Killed Saccharomyces boulardii Alleviates Dextran Sulfate Sodium-Induced Ulcerative Colitis by Restoring the Intestinal Barrier, Reducing Inflammation, and Modulating the Gut Microbiota. Nutrients. 2024;16(5):702. doi:10.3390/nu16050702.

116. Tan LTH, Law JWF, Chua KO, *et al*. Phylogenomics, antimicrobial resistance, and mobile genetic elements in clinical Clostridioides difficile isolates from Hong Kong, China. Progress in Microbes and Molecular Biology. 2026;9(1):a0000651. doi:10.36877/pmmb.a0000651.

117. Ong IJ, Loo KY, Law LNS, *et al*. Exploring the impact of Helicobacter pylori and potential gut microbiome modulation. Progress in Microbes and Molecular Biology. 2023;6(1):a0000273. doi:10.36877/pmmb.a0000273.

118. Basir L, Moghimipour E, Saadatzadeh A, *et al*. Effect of postbiotic-toothpaste on salivary levels of IgA in 6- to 12-year-old children: Study protocol for a randomized triple-blind placebo-controlled trial. Frontiers in Pediatrics. 2022;10:1042973. doi:10.3389/fped.2022.1042973.

119. Linh NV, Khang LT, Permpoonpattana P, *et al*. Postbiotics and Paraprobiotics as Next-Generation Gut Microbiome Modulators in Sustainable Aquaculture Health. Antibiotics. 2026;15(9):887. doi:10.1080/19490976.2022.2117508.

120. Kim YS, Choi SC. The Long and Winding Road to the Best Clinical Research and Personalized Therapy with Probiotics: Do Not Forget Host Physiology. Journal of Neurogastroenterology and Motility. Korean Society of Neurogastroenterology and Motility. 2023;29(2):129. doi:10.5056/jnm23034.

121. Ma L, Tu H, Chen T. Postbiotics in Human Health: A Narrative Review. Nutrients. 2023;15(2):291. doi:10.3390/nu15020291.

122. Vinderola G, Sanders ME, Salminen S, *et al*. Postbiotics: The concept and their use in healthy populations. Frontiers in Nutrition. 2022;9:1002213. doi:10.3389/fnut.2022.1002213.

123. Zhao X, Liu S, Li S, *et al*. Unlocking the power of postbiotics: A revolutionary approach to nutrition for humans and animals. Cell Metabolism. 2024;36(4):725. doi:10.1016/j.cmet.2024.03.004.

124. Kumar A, Green KM, Rawat M. A Comprehensive Overview of Postbiotics with a Special Focus on Discovery Techniques and Clinical Applications. Foods. 2024;13(18):2937. doi:10.3390/foods13182937.

125. Cunha N, Santos-Sodré S de JL, Teixeira-Costa BE, *et al*. New Trends in the Development of Products with Probiotics, Prebiotics, Symbiotics, Paraprobiotics and Postbiotics. Brazilian Archives of Biology and Technology. 2025;68:e25240323. doi:10.1590/1678-4324-2025240323.

126. Vinderola G, Sanders ME, Salminen S. The Concept of Postbiotics. Foods. 2022;11(8):1077. doi:10.3390/foods11081077.

127. Sionek B, Gantner M. Probiotics and Paraprobiotics—New Proposal for Functional Food. Applied Sciences. 2025;15(1):366. doi:10.3390/app15010366.

128. Kerksick CM, Moon JM, Jäger R. It's Dead! Can Postbiotics Really Help Performance and Recovery? A Systematic Review. Nutrients. 2024;16(5):720. doi:10.3390/nu16050720.

129. Wang C. Bioactive Peptides in Probiotic Fermented Foods: Structure-Activity Relationships and Cardiometabolic Protective Effects. Physiological research. 2026;75(4):625. doi:10.33549/physiolres.935776.

130. Salman MK, Abuqwider J, Mauriello G. Anti-Quorum Sensing Activity of Probiotics: The Mechanism and Role in Food and Gut Health. Microorganisms. 2023;11(3):793. doi:10.3390/microorganisms11030793.

131. Khan I, Bai Y, Zha L, *et al*. Mechanism of the Gut Microbiota Colonization Resistance and Enteric Pathogen Infection. Frontiers in Cellular and Infection Microbiology. 2021;11:716299. doi:10.3389/fcimb.2021.716299.

132. Zeinhom M, Tellez AM, Delcenserie V, *et al*. Yogurt containing bioactive molecules produced by Lactobacillus acidophilus la-5 exerts a protective effect against enterohemorrhagic Escherichia coli in mice. Journal of Food Protection. 2012;75(10):1796. doi:10.4315/0362-028X.JFP-11-508.

133. Adnan M, Siddiqui AJ, Noumi E, *et al*. Biosurfactant derived from probiotic Lactobacillus acidophilus exhibits broad-spectrum antibiofilm activity and inhibits the quorum sensing-regulated virulence. Biomolecules and Biomedicine. 2023;23(6):1051. doi:10.17305/bb.2023.9324.

134. Kuai YH, Law JWF, Ong YS, *et al*. Role of SarA in Staphylococcus aureus: A Virulence Target For Therapeutic Strategies. Progress in Microbes and Molecular Biology. 2024;7(1):a0000444. doi:10.36877/pmmb.a0000444.

135. Pusparajah P, Law JWF, Chan KG, *et al*. Whole-Genome Sequence of Streptomyces pluripotens strain MUM 16J, a Potential Resource of Glycopeptide Antibiotic and Biocontrol Agent against Biofilm-forming Bacteria. Progress in Microbes and Molecular Biology. 2023;6(1):a0000330. doi:10.36877/pmmb.a0000330.

136. Loo KY, Tan LTH, Chua KO, *et al*. Complete Whole-Genome Sequence of Streptomyces sp. MUM 178J, a Potential Anti-Vibrio Agent. Progress in Microbes and Molecular Biology. 2024;7(1):a0000399. doi:10.36877/pmmb.a0000399.

137. Tarsillo B, Priefer R. Proteobiotics as a new antimicrobial therapy. Microbial Pathogenesis. 2020;142:10409. doi:10.1016/j.micpath.2020.104093.

138. Zhou P, Chen C, Patil S, *et al*. Unveiling the therapeutic symphony of probiotics, prebiotics, and postbiotics in gut-immune harmony. Frontiers in Nutrition. 2024;11:1355542. doi:10.3389/fnut.2024.1355542.

139. Rocchetti MT, Russo P, De Simone N, *et al*. Immunomodulatory Activity on Human Macrophages by Cell-Free Supernatants to Explore the Probiotic and Postbiotic Potential of Lactiplantibacillus plantarum Strains of Plant Origin. Probiotics and Antimicrobial Proteins. 2024;16(3):911. doi:10.1007/s12602-023-10084-4.

140. Zain A, Rubab M, Awad WA, *et al*. The Role of Postbiotics in Poultry Health and Performance: A Review on Existing Knowledge and Further Research Needs. International Journal of Molecular Sciences. 2026;27(18):8132. doi:10.3390/ijms27188132.

141. Rahaman MM, Wangchuk P, Sarker S. Therapeutic Potential Targeting Gut Microbiota Modulation With Emphasis on Lactobacillus spp. in Common Metabolic Disorders: A Systematic Review. Scientifica. 2025;2025(1):3367875. doi:10.1155/sci5/3367875.

142. Mârza SM, Munteanu C, Papuc I, *et al*. The Role of Probiotics in Enhancing Animal Health: Mechanisms, Benefits, and Applications in Livestock and Companion Animals. Animals. 2025;15(20):2986. doi:10.3390/ani15202986.

143. Ouwehand AC, Ten Bruggencate SJM, Schonewille AJ, *et al*. Lactobacillus acidophilus supplementation in human subjects and their resistance to enterotoxigenic Escherichia coli infection. British Journal of Nutrition. 2014;111(3):465. doi:10.1017/S0007114513002547.

144. Atuahene D, Zuniga-Chaves I, Martello E, *et al*. The Canine Gut Health: The Impact of a New Feed Supplement on Microbiota Composition. Animals. 2024;14(8):1189. doi:10.3390/ani14081189.

145. Goh JXH, Tan LTH, Law JWF, *et al*. Streptomyces sp. MUM 195J: A Promising Probiotic for Controlling Vibrio parahaemolyticus Infection in Aquaculture. Progress in Microbes and Molecular Biology. 2024;7(1):a0000443. doi:10.36877/pmmb.a0000443.

146. Goh JXH, Tan LTH, Law JWF, et al. Probiotics: Comprehensive Exploration of the Growth Promotion Mechanisms in Shrimps. Progress in Microbes and Molecular Biology. 2023;6(1):a0000324. doi:10.36877/pmmb.a0000324.

147. Govender M, Choonara YE, van Vuuren S, *et al*. A Dual-Biotic System for the Concurrent Delivery of Antibiotics and Probiotics: In Vitro, Ex Vivo, In Vivo and In Silico Evaluation and Correlation. Pharmaceutical Research. 2016;33(12):3057. doi:10.1007/s11095-016-2030-1.

148. Vivek K, Mishra S, Pradhan RC, *et al*. A comprehensive review on microencapsulation of probiotics: technology, carriers and current trends. Applied Food Research. 2023;3(1):100248. doi:10.1016/j.afres.2022.100248.

149. Pupa P, Apiwatsiri P, Sirichokchatchawan W, *et al*. The efficacy of three double-microencapsulation methods for preservation of probiotic bacteria. Scientific Reports. 2021;11(1):13753. doi:10.1038/s41598-021-93263-z.

150. Agriopoulou S, Smaoui S, Chaari M, *et al*. Encapsulation of Probiotics within Double/Multiple Layer Beads/Carriers: A Concise Review. Molecules. 2024;29(11):2431. doi:10.3390/molecules29112431.

151. Cui C, Li M, He X, *et al*. In vitro digestion and fecal fermentation of encapsulated starch constructed via layer-by-layer coating of calcium alginate. Food Hydrocolloids. 2024;148:109441. doi:10.1016/j.foodhyd.2023.109441.

152. Anselmo AC, McHugh KJ, Webster J, *et al*. Layer-by-Layer Encapsulation of Probiotics for Delivery to the Microbiome. Advanced Materials. 2016;28(43):9486. doi:10.1002/adma.201603270.

153. Sbehat M, Altamimi M, Sabbah M, *et al*. Layer-by-Layer Coating of Single-Cell Lacticaseibacillus rhamnosus to Increase Viability Under Simulated Gastrointestinal Conditions and Use in Film Formation. Frontiers in Microbiology. 2022;13:838416. doi:10.3389/fmicb.2022.838416.

154. Yu H, Liu W, Li D, *et al*. Targeting delivery system for Lactobacillus plantarum based on functionalized electrospun nanofibers. Polymers (Basel). 2020;12(7):1. doi:10.3390/polym12071565.

155. Shi J, Li SF, Feng K, *et al*. Improving the Viability of Probiotics under Harsh Conditions by the Formation of Biofilm on Electrospun Nanofiber Mat. Foods. 2022;11(9):1203. doi:10.3390/foods11091203.

156. Teleanu RI, Moldoveanu ET, Niculescu AG, *et al*. Liposomal and Lipid-Based Drug Delivery Systems: Bridging Gut Microbiota and Pediatric Disorder Treatments. Pharmaceutics. 2025;17(6):707. doi:10.3390/pharmaceutics17060707.

157. Liu J, Sun Z, Liu S, *et al*. Liposome-mediated encapsulation of probiotics: current status, challenges and future directions. Critical Reviews in Food Science and Nutrition. 2025;65(31):7792. doi:10.1080/10408398.2025.2480169.

158. Wang D, Wang W, Wang P, *et al*. Research progress of colon-targeted oral hydrogel system based on natural polysaccharides. International Journal of Pharmaceutics. 2023;643:123222. doi:10.1016/j.ijpharm.2023.123222.

159. Barberio D. Navigating regulatory and analytical challenges in live biotherapeutic product development and manufacturing. Frontiers in Microbiomes. 2024;3:1441290. doi:10.3389/frmbi.2024.1441290.

160. Yang S, Wei S, Wu Y, *et al*. Encapsulation techniques, action mechanisms, and evaluation models of probiotics: Recent advances and future prospects. Food Frontiers. 2024;5(3):1212. doi:10.1002/fft2.374.

161. Taha MW, Fenwick DJC, Marrs ECL, *et al*. Assessing Bacterial Viability and Label Accuracy in Human and Poultry Probiotics Sold in the United Kingdom. Microorganisms. 2025;13(8):1933. doi:10.3390/microorganisms13081933.

162. Yoha KS, Nida S, Dutta S, *et al*. Targeted Delivery of Probiotics: Perspectives on Research and Commercialization. Probiotics and Antimicrobial Proteins. 2022;14(1):15. doi:10.1007/s12602-021-09791-7.

163. Vinarov Z, Abdallah M, Agundez JAG, *et al*. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: An UNGAP review. European Journal of Pharmaceutical Sciences. 2021;162:105812. doi:10.1016/j.ejps.2021.105812.

164. Xu C, Guo J, Chang B, *et al*. Design of probiotic delivery systems and their therapeutic effects on targeted tissues. Journal of Controlled Release. 2024;375:20. doi:10.1016/j.jconrel.2024.08.037.

165. Ji C, Li D, Liang Y, *et al*. Co-encapsulation of probiotics with functional components: design strategies, synergistic mechanisms, biomedical applications, and challenges for industrialization. Journal of Materials Chemistry B. 2025;13 (41):13122. doi:10.1039/d5tb01747e.

166. Ramírez-Damián M, Garfias-Noguez C, Bermúdez-Humarán LG, *et al*. Synbiotic Microencapsulation of Lactobacillus Strains from Mexican Fermented Beverages for Enhanced Probiotic Functionality. Molecules. 2025;30(5):1185. doi:10.3390/molecules30051185.

167. Witika BA, Makoni PA, Matafwali SK, *et al*. Enhancement of biological and pharmacological properties of an encapsulated polyphenol: Curcumin. Molecules. 2021;26(14):4244. doi:10.3390/molecules26144244.

168. Ma J, Tan Z, Wu M, *et al*. Co-encapsulation of probiotic Lactiplantibacillus plantarum and polyphenol within novel polyvinyl alcohol/fucoidan electrospun nanofibers with improved viability and antioxidation. International Journal of Biological Macromolecules. 2024;282:136907. doi:10.1016/j.ijbiomac.2024.136907.

169. Savedboworn W, Teawsomboonkit K, Surichay S, *et al*. Impact of protectants on the storage stability of freeze-dried probiotic Lactobacillus plantarum. Food Science and Biotechnology. 2019;28(3):795. doi:10.1007/s10068-018-0523-x.

170. Fuhren J, Rösch C, ten Napel M, *et al*. Synbiotic matchmaking in Lactobacillus plantarum: Substrate screening and gene-trait matching to characterize strain-specific carbohydrate utilization. Applied and Environmental Microbiology. 2020;86(18):e01081. doi:10.1128/AEM.01081-20.

171. Zhang L, Lou Y, Schutyser M. 3D printing of cereal-based food structures containing probiotics. Food Structure. 2018;18:14. doi:10.1016/j.foostr.2018.10.002.

172. Truong-Le QA, Lee SO, Ubeyitogullari A. Encapsulation of Bifidobacterium bifidum into a pH-sensitive alginate-pectin gel system using 3D food printing: Enhanced viability and targeted release. International Journal of Biological Macromolecules. 2025;318:145134. doi:10.1016/j.ijbiomac.2025.145134.

173. Westfall S, Carracci F, Estill M, *et al*. Optimization of probiotic therapeutics using machine learning in an artificial human gastrointestinal tract. Scientific Reports. 2021;11(1):1067. doi:10.1038/s41598-020-79947-y.

174. Ang WS, Law JWF, Kumari Y, *et al*. Unleashing the Power of Artificial Intelligence-Driven Drug Discovery in Streptomyces. Progress in Microbes and Molecular Biology. 2024;7(1):a0000453. doi:10.36877/pmmb.a0000453.

175. Gkouskou K, Vlastos I, Karkalousos P, *et al*. The “virtual Digital Twins” Concept in Precision Nutrition. Advances in Nutrition. 2020;11(6):1405. doi:10.1093/advances/nmaa089.

176. Burade N, Sharma G, Sunitha S, *et al*. Digital-Twin Modelling of the Gut Microbiome to Guide Personalized Probiotic-Drug Combinations. In: International Conference on Sustainable Innovation with Artificial Intelligence and Machine Learning 2025 (ICSIAIML 2025). 2025;476. doi:10.2991/978-94-6463-948-3_34.

177. Zhang Y, Zhou K, Chen X, *et al*. A temporal-aware machine learning framework enables microbial community dynamics prediction with personalized precision. Microbiome. 2025;13(1):261. doi:10.1186/s40168-025-02269-6.

178. Saiz-Gonzalo G, Arroyo-Moreno S, McSweeney S, *et al*. Pea protein microencapsulation improves probiotic survival during gastrointestinal digestion. International Journal of Food Science and Technology. 2025;60(2):vvaf154. doi:10.1093/ijfood/vvaf154.

179. Han M, Yang S, Song J, *et al*. Layer-by-layer coated probiotics with chitosan and liposomes demonstrate improved stability and antioxidant properties in vitro. International Journal of Biological Macromolecules. 2024;258:128826. doi:10.1016/j.ijbiomac.2023.128826.

180. Cook MT, Tzortzis G, Khutoryanskiy V V., *et al*. Layer-by-layer coating of alginate matrices with chitosan-alginate for the improved survival and targeted delivery of probiotic bacteria after oral administration. Journal of Materials Chemistry B. 2013;1(1):52. doi:10.1039/c2tb00126h.

181. Ismail AS, Sreedharan DK, Ng ZJ, *et al*. Microencapsulation of Lactobacillus cells utilizing the β-glucan-rich cell wall of Saccharomyces cerevisiae for enhanced stability and efficacy. International Journal of Biological Macromolecules. 2025;311:143971. doi:10.1016/j.ijbiomac.2025.143971.

182. Sun R, Lv Z, Wang Y, *et al*. Different polysaccharide-enhanced probiotic and polyphenol dual-functional factor co-encapsulated microcapsules demonstrate acute colitis alleviation efficacy and food fortification. Carbohydrate Polymers. 2024;345:122572. doi:10.1016/j.carbpol.2024.122572.

183. Mohamed DA, Mabrok HB, El-Sayed HS, *et al*. Cardio-Protective Effects of Microencapsulated Probiotic and Synbiotic Supplements on a Myocardial Infarction Model Through the Gut–Heart Axis. Applied Microbiology. 2025;5(3):72. doi:10.3390/applmicrobiol5030072.

184. Bolea CA, Cotârleț M, Enachi E, *et al*. Co-microencapsulated black rice anthocyanins and lactic acid bacteria: Evidence on powders profile and in vitro digestion. Molecules. 2021;26(9):2579. doi:10.3390/molecules26092579.

185. Ma W, Lian L, Guo L, *et al*. A synbiotic combination of mixed probiotics and oligofructose restores intestinal microbiota disturbance in DSS-induced colitis in mice. Frontiers in Microbiology. 2025;16:1593065. doi:10.3389/fmicb.2025.1582155.

186. Alkushi AG, Elazab ST, Abdelfattah-Hassan A, *et al*. Multi-Strain-Probiotic-Loaded Nanoparticles Reduced Colon Inflammation and Orchestrated the Expressions of Tight Junction, NLRP3 Inflammasome and Caspase-1 Genes in DSS-Induced Colitis Model. Pharmaceutics. 2022;14(6):1183. doi:10.3390/pharmaceutics14061183.

187. He J, Tian W, Feng P, *et al*. Nasal delivery of Lacticaseibacillus rhamnosus GG modulates respiratory immune responses and attenuates Mycoplasma pneumoniae pneumonia in a murine model. Microbiology Spectrum. 2026;14(1):e0077125. doi:10.1128/spectrum.00771-25.

188. Govender M, Choonara YE, van Vuuren S, *et al*. A Dual-Biotic System for the Concurrent Delivery of Antibiotics and Probiotics: In Vitro, Ex Vivo, In Vivo and In Silico Evaluation and Correlation. Pharmaceutical Research. 2016;33(12):3057. doi:10.1007/s11095-016-2030-1.

189. Mei L, Zhang D, Shao H, *et al*. Injectable and Self-Healing Probiotics-Loaded Hydrogel for Promoting Superbacteria-Infected Wound Healing. ACS Applied Materials & Interfaces. 2022;14(18):20538. doi:10.1021/acsami.1c23713.

190. Napier BA, Allegretti JR, Feuerstadt P, *et al*. Multi-Species Synbiotic Supplementation Enhances Gut Microbial Diversity, Increases Urolithin A and Butyrate Production, and Reduces Inflammation in

Healthy Adults: A Randomized, Placebo-Controlled Trial. Nutrients. 2025;17(17):2734. doi:10.3390/nu17172734.

191. Andrade-Platas D, Martinez-Figueroa MG, Rodriguez-Palmero M, *et al*. A probiotic containing L. plantarum and P. acidilactici strains for treating upper respiratory infection in children aged 6 months to 5 years: a randomized, double-blind trial. European Journal of Pediatrics. 2025;184(12):795. doi:10.1007/s00431-025-06587-7.

192. Allegretti JR, Kassam Z, Kelly CR, *et al*. A Randomized, Placebo-Controlled Trial Evaluating Multi-Species Synbiotic Supplementation for Bloating, Gas, and Abdominal Discomfort. Nutrients. 2026;18(2):255. doi:10.3390/nu18020255.

193. Chakkalakal M, Nadora D, Gahoonia N, *et al*. Prospective Randomized Double-Blind Placebo-Controlled Study of Oral Pomegranate Extract on Skin Wrinkles, Biophysical Features, and the Gut-Skin Axis. Journal of Clinical Medicine. 2022;11(22):6724. doi:10.3390/jcm11226724.

194. Iemoli E, Trabattoni D, Parisotto S, *et al*. Probiotics Reduce Gut Microbial Translocation and Improve Adult Atopic Dermatitis. Journal of Clinical Gastroenterology. 2012;46 Suppl:S33. doi: 10.1097/MCG.0b013e31826a8468.

195. Belkaid Y, Harrison OJ. Homeostatic Immunity and the Microbiota. Immunity. 2017;46(4):562. doi:10.1016/j.immuni.2017.04.008.

196. Asefa Z, Belay A, Welelaw E, *et al*. Postbiotics and their biotherapeutic potential for chronic disease and their feature perspective: a review. Frontiers in Microbiomes. 2025;4:1489339. doi:10.3389/FRMBI.2025.1489339/FULL.

197. Kalantar-Zadeh K, Jafar TH, Nitsch D, *et al*. Chronic kidney disease. The Lancet. 2021;398(10302):786. doi:10.1016/S0140-6736(21)00519-5.

198. Koppe L, Mafra D, Fouque D. Probiotics and chronic kidney disease. Kidney International. 2015;88(5):958. doi:10.1038/KI.2015.255.

199. Favero C, Giordano L, Mihaila SM, *et al*. Postbiotics and Kidney Disease. Toxins. 2022;14(9):623. doi:10.3390/TOXINS14090623/S1.

200. Meena KK, Joshi M, Gupta L, *et al*. Comprehensive insights into postbiotics: Bridging the gap to real-world application. Food Nutrition. 2025;1(2):100024. doi:10.1016/J.FNUTR.2025.100024.

201. Schiavi E, Gleinser M, Molloy E, *et al*. The Surface-Associated Exopolysaccharide of Bifidobacterium longum 35624 Plays an Essential Role in Dampening Host Proinflammatory Responses and Repressing Local TH17 Responses. Applied and Environmental Microbiology. 2016;82(24):7185. doi:10.1128/AEM.02238-16.

202. Feng Y, Wang Y, Wang P, *et al*. Short-Chain Fatty Acids Manifest Stimulative and Protective Effects on Intestinal Barrier Function Through the Inhibition of NLRP3 Inflammasome and Autophagy. Cellular Physiology and Biochemistry. 2018;49(1):190. doi:10.1159/000492853.

203. Corr SC, Li Y, Riedel CU, *et al*. Bacteriocin production as a mechanism for the antiinfective activity of Lactobacillus salivarius UCC118. Proceedings of the National Academy of Sciences. 2007;104(18):7617. doi:10.1073/PNAS.0700440104.

204. Sun Z, Harris HMB, McCann A, *et al*. Expanding the biotechnology potential of lactobacilli through comparative genomics of 213 strains and associated genera. Nature Communications. 2015;6(1):1. doi:10.1038/NCOMMS9322;TECHMETA.

205. Laverde Gomez JA, Mukhopadhya I, Duncan SH, *et al*. Formate cross-feeding and cooperative metabolic interactions revealed by transcriptomics in co-cultures of acetogenic and amylolytic human colonic bacteria. Environmental Microbiology. 2019;21(1):259. doi:10.1111/1462-2920.14454.

206. Kandasamy S, Letchumanan V, Hong KW, et al. The Role of Human Gut Microbe Ruminococcus gnavus in Inflammatory Diseases. Progress in Microbes and Molecular Biology. 2023;6(1):a0000396. doi:10.36877/pmmb.a0000396.

207. Suprapti E, Hadju V, Ibrahim E, *et al*. Anemia: etiology, pathophysiology, impact, and prevention: a review. Iranian journal of public health. 2025;54(3):509. doi: 10.18502/ijph.v54i3.18244.

208. Sazawal S, Dhingra U, Hiremath G, *et al*. Effects of Bifidobacterium lactis HN019 and prebiotic oligosaccharide added to milk on iron status, anemia, and growth among children 1 to 4 years old. Journal of Pediatric Gastroenterology and Nutrition. 2010;51(3):341. doi:10.1097/MPG.0B013E3181D98E45.

209. Scholz-Ahrens KE, Ade P, Marten B, *et al*. Prebiotics, Probiotics, and Synbiotics Affect Mineral Absorption, Bone Mineral Content, and Bone Structure. The Journal of Nutrition. 2007;137(3):838S. doi:10.1093/JN/137.3.838S.

210. Zakrzewska Z, Zawartka A, Schab M, *et al*. Prebiotics, Probiotics, and Postbiotics in the Prevention and Treatment of Anemia. Microorganisms. 2022;10(7):1330. doi:10.3390/MICROORGANISMS10071330.

211. Pompei A, Cordisco L, Amaretti A, *et al*. Folate Production by Bifidobacteria as a Potential Probiotic Property. Applied and Environmental Microbiology. 2007;73(1):179. doi:10.1128/AEM.01763-06.

212. Das NK, Schwartz AJ, Barthel G, *et al*. Microbial Metabolite Signaling Is Required for Systemic Iron Homeostasis. Cell Metabolism. 2020;31(1):115. doi:10.1016/j.cmet.2019.10.005.

213. Eleftheriadis T, Pissas G, Antoniadi G, *et al*. Kynurenine, by activating aryl hydrocarbon receptor, decreases erythropoietin and increases hepcidin production in HepG2 cells: A new mechanism for anemia of inflammation. Experimental Hematology. 2016;44(1):60. doi:10.1016/j.exphem.2015.08.010.

214. Mayer EA. Gut feelings: The emerging biology of gut-"brain communication. Nature Reviews Neuroscience. 2011;12(8):453. doi:10.1038/NRN3071;SUBJMETA.

215. Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterology & Motility. 2011;23(3):187. doi:10.1111/J.1365-2982.2010.01664.X.

216. El Mazouri S, Aanniz T, Bouyahya A, *et al*. Gut Microbiota in Autism Spectrum Disorder: A Systematic Review. Progress in Microbes and Molecular Biology. 2024;7(1):a0000442. doi:10.36877/pmmb.a0000442.

217. Calvani R, Picca A, Lo Monaco MR, *et al*. Of microbes and minds: A narrative review on the second brain aging. Frontiers in Medicine. 2018;5:53. doi:10.3389/FMED.2018.00053/FULL.

218. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nature Neuroscience. 2017;20(2):145. doi:10.1038/NN.4476;TECHMETA.

219. Morozova M, Alekseev A, Saeidi A, *et al*. Normalization of Deviant Behavior in Muc2+/+ Mice through Dietary Incorporation of Bacillus subtilis Spores. Progress in Microbes and Molecular Biology. 2023;6(1):a0000386. doi:10.36877/pmmb.a0000386.

220. Nishida K, Sawada D, Kuwano Y, *et al*. Health benefits of lactobacillus gasseri cp2305 tablets in young adults exposed to chronic stress: A randomized, double-blind, placebo-controlled study. Nutrients. 2019;11(8):1859. doi:10.3390/nu11081859.

221. Johnson D, Chua KO, Selvadurai J, *et al*. Pilot Trial of Probiotics in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Approach. Progress in Microbes and Molecular Biology. 2025;8(1):a0000462. doi:10.36877/pmmb.a0000462.

222. Lee LH. Probiotics in Depression Management: Efficacy, Mechanisms and Future Directions. Progress in Microbes and Molecular Biology. 2025;8(1):a0000459. doi:10.36877/pmmb.a0000459.

223. Tang EK, Loo KY, Thye AYK, *et al*. The Impact of Antidepressants on Gut Microbiome and Depression Management. Progress in Microbes and Molecular Biology. 2024;7(1):a0000446. doi:10.36877/pmmb.a0000446.

224. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obesity Reviews. 2015;16(1):1. doi:10.1111/OBR.12229.

225. Shin HS, Park SY, Lee DK, *et al*. Hypocholesterolemic effect of sonication-killed Bifidobacterium longum isolated from healthy adult Koreans in high cholesterol fed rats. Archives of Pharmacal Research. 2010;33(9):1425. doi:10.1007/s12272-010-0917-7.

226. Vallianou N, Stratigou T, Christodoulatos GS, *et al*. Probiotics, Prebiotics, Synbiotics, Postbiotics, and Obesity: Current Evidence, Controversies, and Perspectives. Current Obesity Reports. 2020;9(3):179. doi:10.1007/s13679-020-00379-w.

227. Yao Y, Yan L, Chen H, *et al*. Cyclocarya paliurus polysaccharides alleviate type 2 diabetic symptoms by modulating gut microbiota and short-chain fatty acids. Phytomedicine. 2020;77:153268. doi:10.1016/J.PHYMED.2020.153268.

228. Zhang S, Zhao J, Xie F, *et al*. Dietary fiber-derived short-chain fatty acids: A potential therapeutic target to alleviate obesity-related nonalcoholic fatty liver disease. Obesity Reviews. 2021;22(11):e13316. doi:10.1111/OBR.13316.

229. He L. Alterations of Gut Microbiota by Overnutrition Impact Gluconeogenic Gene Expression and Insulin Signaling. International Journal of Molecular Sciences. 2021;22(4):2121. doi:10.3390/IJMS22042121.

230. Salazar N, Neyrinck AM, Bindels LB, *et al*. Functional effects of EPS-producing bifidobacterium administration on energy metabolic alterations of diet-induced obese mice. Frontiers in Microbiology. 2019;10:1809. doi:10.3389/fmicb.2019.01809.

231. Bhat B, Bajaj BK. Hypocholesterolemic potential and bioactivity spectrum of an exopolysaccharide from a probiotic isolate Lactobacillus paracasei M7. Bioactive Carbohydrates and Dietary Fibre. 2019;19:100191. doi:10.1016/J.BCDF.2019.100191.

232. Muralitharan RR, Marques FZ. Diet-related gut microbial metabolites and sensing in hypertension. Journal of Human Hypertension. 2021;35(2):162. doi:10.1038/s41371-020-0388-3.

233. Ozma MA, Abbasi A, Akrami S, *et al*. Postbiotics as the key mediators of the gut microbiota-host interactions. Infezioni in Medicina. 2022;30(2):180. doi:10.53854/LIIM-3002-3.

234. Liuu S, Nepelska M, Pfister H, *et al*. Identification of a muropeptide precursor transporter from gut microbiota and its role in preventing intestinal inflammation. The Proceedings of the National Academy of Sciences of the United States of America. 2023;120(52):e2306863120. doi:10.1073/PNAS.2306863120.

235. Chen X, Shi Y. Determinants of microbial colonization in the premature gut. Molecular Medicine. 2023;29(1):90. doi:10.1186/s10020-023-00689-4.

236. Thye AYK, Kumari Y, Chan KG, et al. Early colonization by Enterobacteriaceae in the developing gut microbiota of preterm infants: A culture-based insight. Progress in Microbes and Molecular Biology. 2026;9(1):a0000479. doi:10.36877/pmmb.a0000479.

237. Goyani P, Christodoulou R, Vassiliou E. Immunosenescence: Aging and Immune System Decline. Vaccines. 2024;12(12):1314. doi:10.3390/VACCINES12121314.

238. Jazuli I, Jazeel A, Selvaratnam L, *et al*. Navigating the Role and Approach of Gut Microbiota in Addressing Alzheimer's Disease Pathogenesis. Progress in Microbes and Molecular Biology. 2024;7(1):a0000454. doi:10.36877/pmmb.a0000454.

239. Lim WG, Lim WL, Lau TP, *et al*. Association Between Salivary C-Reactive Protein Levels and Covariates in an Older Adult Population in Malaysia – A Cross-Sectional Study of The MyAgeWell Cohort. Progress in Microbes and Molecular Biology. 2025;8(1):a0000461. doi:10.36877/pmmb.a0000461

Author(s) shall retain the copyright of their work and grant the Journal/Publisher right for the first publication with the work simultaneously licensed under:

Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0). This license allows for the copying, distribution and transmission of the work, provided the correct attribution of the original creator is stated. Adaptation and remixing are also permitted.