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REVIEW

Nanobiotic-Enhanced Probiotics for Targeted Gut Delivery: Mechanisms, Therapeutic Applications, and Translational Challenges

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Abstract: The gut microbiota plays a pivotal role in maintaining human health by influencing physiological processes such as digestion, immune regulation, and metabolism. However, disruptions in gut microbial balance, or dysbiosis, are associated with numerous disorders. Probiotics have emerged as potential therapeutic agents, but their efficacy is limited by challenges such as low survival during gastrointestinal transit, poor colonization, and lack of targeted delivery. Nanotechnology has recently provided promising solutions to these limitations by enhancing the stability, viability, and functionality of probiotics. To provide an updated perspective, this article presents a structured narrative review informed by a PRISMA-guided literature search and screening process. Relevant studies published between 2021 and 2025 were identified from PubMed, Scopus, IEEE Xplore, and Google Scholar and were narratively synthesized to examine nanoencapsulation strategies, hybrid nanobiotic systems, smart delivery platforms, therapeutic applications, and translational barriers. Nanoencapsulation techniques, hybrid nanobiotic systems, and smart delivery platforms are at the forefront of probiotic enhancement. These systems improve protection of probiotics against harsh gastric conditions and enable targeted release within specific regions of the gastrointestinal tract, thereby enhancing colonization efficiency and therapeutic potential. Moreover, nanobiotics show promise in modulating gut microbiota composition, strengthening immune responses, and opening new therapeutic avenues for the management of gastrointestinal disorders, metabolic diseases, and immune-related conditions. Despite these advances, challenges related to safety, scalability, and regulatory approval remain significant barriers to clinical translation. This review synthesizes recent progress in nanobiotic-enhanced probiotics, evaluates their therapeutic applications, and discusses key challenges and future directions for precision microbiome therapeutics.

Keywords: nanobiotics, probiotics, nano-encapsulation, gut health, therapeutic applications, immune modulation

Introduction

The microbial community of the gastrointestinal tract (GIT) plays a fundamental role in immune modulation, nutrient metabolism, epithelial barrier integrity, and neuroendocrine signaling through the gut–brain axis.[1] Dysbiosis, or disruption of this microbial equilibrium, has been associated with a broad range of disorders, including inflammatory bowel disease (IBD), obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), allergies, and neuropsychiatric conditions.[2] Landmark initiatives such as MetaHIT and the Human Microbiome Project have significantly advanced understanding of host–microbiome interactions and established gut health as a central focus of modern biomedical research.[3]

Given the central role of dysbiosis in these disorders, there is a clear need for microbiome-directed interventions that can help restore microbial balance, reinforce barrier function, and modulate aberrant immune and metabolic signaling.[4] Probiotics have therefore attracted increasing interest as candidate therapeutic agents because selected strains can suppress pathobionts, support mucosal homeostasis, and contribute beneficial metabolic functions. Against this background, it is important to consider both the therapeutic rationale for probiotic use and the limitations that have constrained their clinical performance.[5,6]

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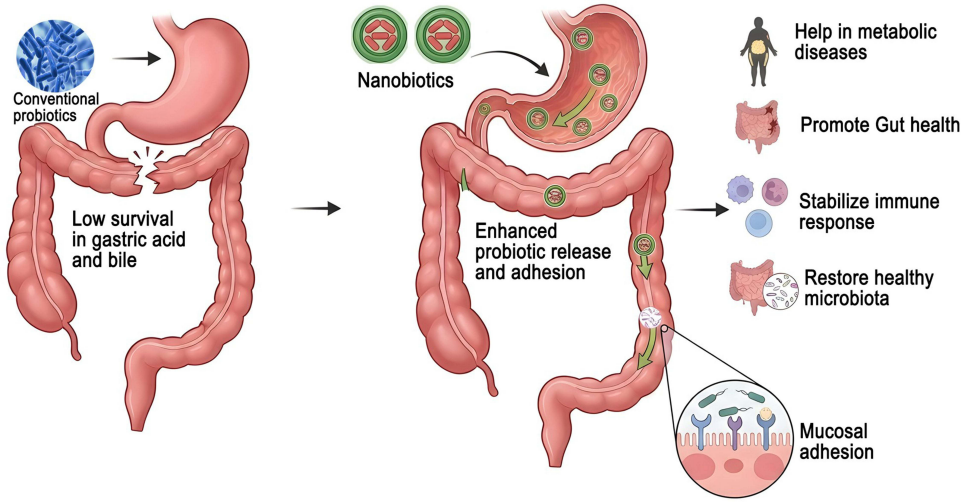
Graphical Abstract



Probiotics, defined by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host", have emerged as promising therapeutic agents.[7] Common probiotic genera such as *Lactobacillus, Bifidobacterium*, and *Bacillus* have been widely investigated for their ability to restore microbial balance, enhance mucosal immunity, inhibit pathogenic colonization, and produce beneficial metabolites. However, the clinical performance of conventional probiotic formulations remains limited by poor stability during storage and insufficient delivery efficiency following oral administration.[8]

Nanotechnology has emerged as a promising strategy to overcome these limitations. By enabling control over particle size, surface properties, encapsulation efficiency, and release behavior, nanoscale delivery systems can improve probiotic stability, retention, and site-specific activity within the intestine.[9] This convergence of microbiology and nanoscience has led to the development of nanobiotic-enhanced probiotics, an emerging class of precision microbiome therapeutics with potential applications in gastrointestinal, metabolic, and immune-related disorders.[10,11]

For example, *Lactobacillus rhamnosus* delivered through chitosan nanoparticle carriers has shown improved mucosal adherence and reduced disease activity compared with free cells in experimental colitis models, illustrating how nanoencapsulation can enhance probiotic stability, localization, and therapeutic function at diseased intestinal sites.[12]

Previous reviews in this area have summarized probiotic encapsulation strategies, nanotechnology-assisted delivery systems, or the broader relationship between probiotics and gut health; however, many have focused mainly on conventional carrier platforms, provided limited comparison among nanocarrier classes, or placed less emphasis on recently emerging systems and translational barriers.[13–15] In contrast, the present review provides an updated synthesis of literature from 2021–2025 with specific emphasis on nanobiotic-enhanced probiotics for targeted gut delivery. Beyond summarizing nanoencapsulation approaches, this review integrates mechanistic discussion, comparative evaluation of major nanocarrier platforms, emerging systems such as exosome-/extracellular-vesicle- and MOF-based carriers, and translational issues including safety, pharmacokinetics, scalability, and regulatory considerations. In this way, the manuscript aims to provide a more focused and current perspective on how nanotechnology is reshaping probiotic delivery for gastrointestinal, metabolic, immune, and gut–brain-axis applications.

Research Methodology

Review Design

This article was conducted as a structured narrative review informed by PRISMA 2020 principles for transparent literature identification, screening, and reporting. The aim of the review was to synthesize recent evidence on nanobiotic-enhanced probiotics for targeted gut delivery, with emphasis on delivery mechanisms, therapeutic applications, and translational challenges. Because the included literature was heterogeneous in study design, model systems, probiotic strains, nanocarrier platforms, and reported outcomes, the evidence was synthesized narratively rather than through formal meta-analysis.

Information Sources and Search Strategy

A literature search was conducted across four major databases: PubMed, Scopus, IEEE Xplore, and Google Scholar. The search covered studies published between January 2021 and December 2025. Search terms combined probiotic-related, nanotechnology-related, and gut-health-related concepts. The search strategy was adapted for each database according to indexing structure and syntax. The exact database-specific search strings are provided in Supplementary Table 1.

Inclusion Criteria

Studies were included if they were published in English between 2021 and 2025 and appeared as peer-reviewed original articles or highly relevant review articles. Eligible studies focused on probiotics, probiotic-derived systems, or probiotic delivery platforms enhanced by nanotechnology, nanoencapsulation, or nanocarrier-based approaches. To be considered relevant for inclusion, studies also had to report findings related to at least one of the following domains: gastrointestinal survival, targeted release, mucoadhesion, colonization-related performance, microbiota modulation, immune regulation, gut barrier protection, or disease-related therapeutic applications.

Exclusion Criteria

Studies were excluded if they focused solely on conventional probiotics without any nanotechnology-enabled delivery component or if they addressed only food formulation, storage stability, or industrial preservation without clear relevance to gastrointestinal delivery or therapeutic application. Editorials, letters, conference abstracts, dissertations, patents, book chapters, and other non-peer-reviewed sources were also excluded. In addition, non-English publications and studies lacking sufficient methodological or outcome detail relevant to the objectives of the present review were not considered for inclusion.

Study Selection and Exclusion Process

A total of 1524 records were initially identified across all databases, including 728 from Google Scholar, 297 from PubMed, 188 from IEEE Xplore, and 311 from Scopus. After duplicate removal (n = 218), 1306 records remained for title and abstract screening. Of these, 742 records were excluded because they did not meet the relevance criteria. The remaining 564 full-text articles were assessed for eligibility. At the full-text stage, 342 articles were excluded because of irrelevant outcomes (n = 132), out-of-scope content (n = 109), or irrelevant study design (n = 101). A final total of 222 studies were included in the narrative synthesis. The study selection workflow is shown in Figure 1.

Screening Procedure and Software

All retrieved references were exported to EndNote for organization and duplicate removal. Duplicate records were first identified electronically and then verified manually. Screening was conducted in two stages: (1) title and abstract screening, and (2) full-text review. Reasons for exclusion at the full-text stage were recorded and categorized to ensure transparency.

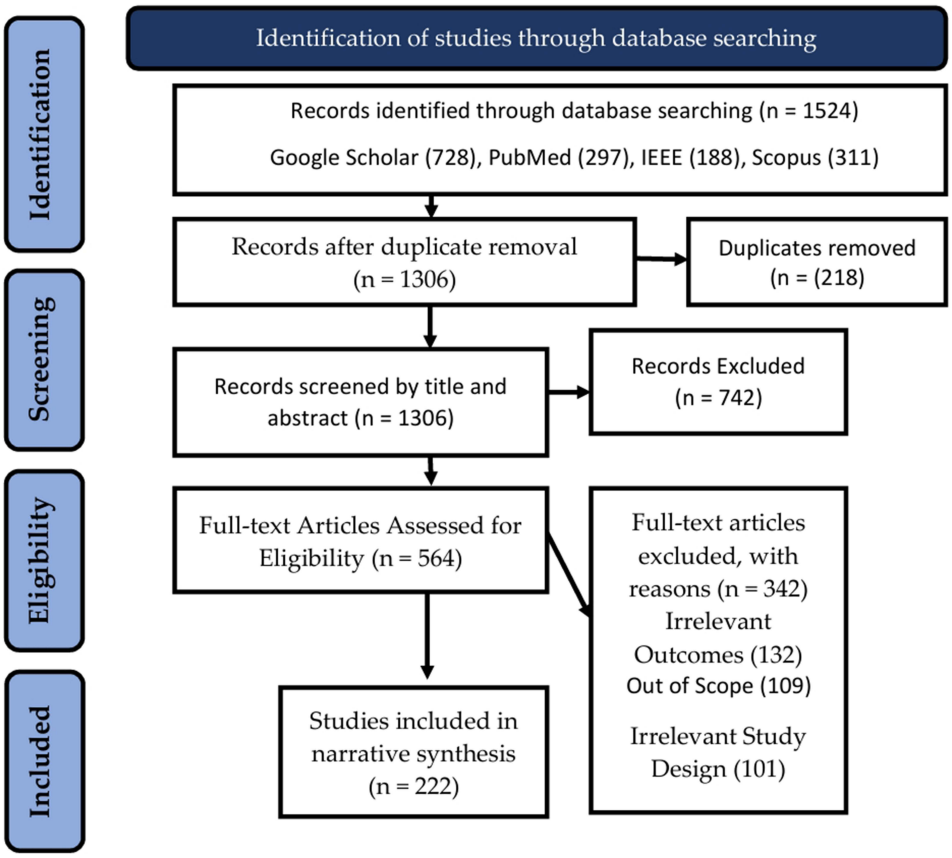


Figure 1 PRISMA-informed flow diagram of literature identification, screening, eligibility assessment, and study inclusion for the present narrative review.

Data Extraction

Data extraction was performed using a structured extraction sheet prepared in Microsoft Excel. The following variables were extracted where available: author and year, study type, biological model, probiotic strain(s), nanocarrier type, encapsulation or coating material, delivery mechanism, disease/application area, survival and release outcomes, colonization or retention-related findings, microbiota-related findings, immune or barrier effects, safety observations, and key translational implications.

Quality Assessment and Risk-of-Bias Appraisal

To improve methodological transparency, formal quality appraisal was conducted for original research articles only, using tools appropriate to study design. Randomized clinical studies were assessed using RoB 2, non-randomized human studies using ROBINS-I, and animal studies using the SYRCLE risk-of-bias tool. In vitro studies were appraised descriptively using predefined methodological domains, including clarity of strain identification, nanocarrier characterization, use of controls, outcome reproducibility, and statistical reporting. Review articles, systematic reviews, meta-analyses, editorials, book chapters, and other non-research sources were not subjected to formal study-level risk-of-bias assessment and were included for contextual synthesis only. Quality appraisal findings were used to guide interpretation of the evidence and are summarized in Supplementary Table 2.

Data Synthesis

Because the included evidence was highly heterogeneous in design and outcome reporting, findings were synthesized narratively rather than through formal meta-analysis. The synthesis was organized by major thematic domains, including probiotic background, nanocarrier systems, delivery mechanisms, microbiota and immune interactions, therapeutic applications, and translational challenges related to safety, scalability, and regulation.

Background: Probiotics and Gut Health

Probiotic Concepts and Mechanisms

The probiotics play a pivotal role in maintaining the balance of the gut microbiota, a community of trillions of microorganisms residing in the human GIT.[16] The gut microbiome influences numerous physiological processes, including digestion, immune system modulation, metabolism, and even neuroendocrine signaling through the gut-brain axis. Maintaining this microbial balance is essential for health, as disruptions in the microbiota, known as dysbiosis, have been implicated in a wide range of health conditions.[17] These include IBD, metabolic syndrome, obesity, T2DM, allergies, and even neuropsychiatric disorders such as depression and anxiety. Given these crucial roles, restoring or maintaining a healthy microbiome has become a central therapeutic strategy, with probiotics emerging as a key tool in promoting gut health (Figure 2).[18,19]

The mechanisms by which probiotics exert their effects on gut health are diverse and multifaceted. One of the primary functions of probiotics is to modulate the gut immune system. The GIT houses a large portion of the body's immune cells, and the gut-associated lymphoid tissue (GALT) plays a central role in immune regulation.[6,20] Probiotics help to enhance local immunity, which is essential for defending against pathogens and maintaining intestinal homeostasis. They achieve this by stimulating the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10). At the same time, they reduce the levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[20,21] This immune modulation helps maintain a balance between immune tolerance and defense, reducing the risk of excessive inflammatory responses that could lead to diseases like IBD and irritable bowel syndrome (IBS).[22]

In addition to immune modulation, probiotics play a critical role in pathogen suppression through several mechanisms. One of the most significant ways they achieve this is through competitive exclusion. In this process, probiotics outcompete harmful pathogens for essential nutrients and colonization sites on the intestinal epithelium.[6,23] This competition prevents pathogens such as *Clostridium difficile, Escherichia coli*, and *Salmonella* from establishing themselves in the gut. Moreover, many probiotics produce antimicrobial peptides which inhibit the growth of harmful

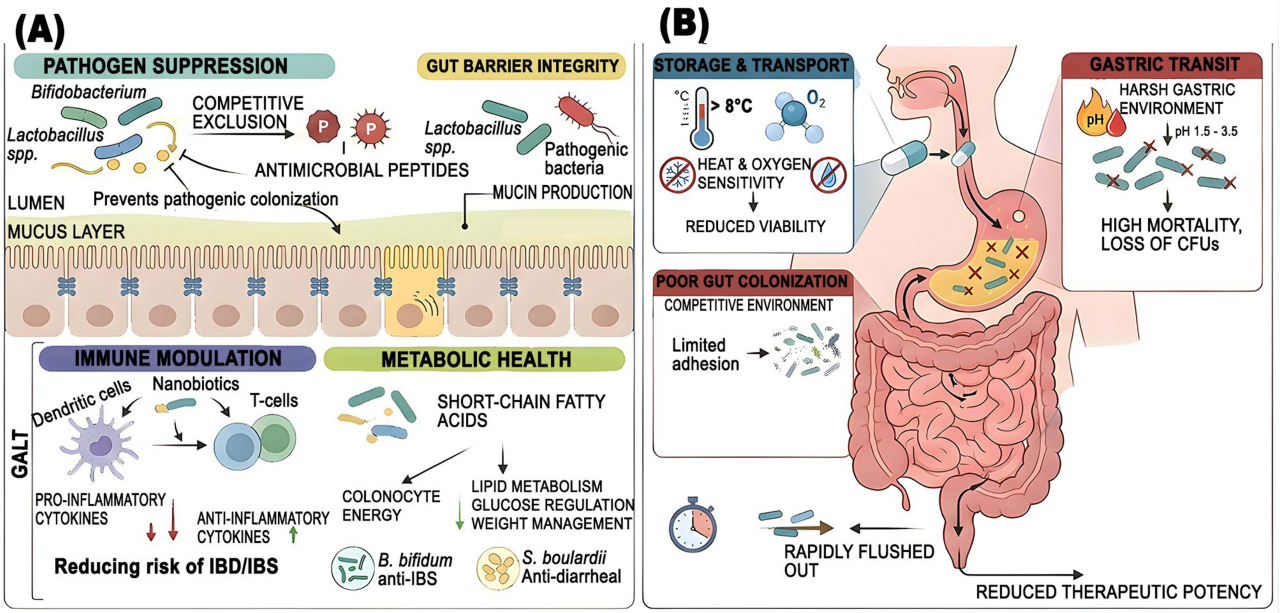


Figure 2 Mechanisms of probiotic action and limitations of conventional oral probiotic delivery. (**A**) Major mechanisms by which probiotics exert beneficial effects in the gastrointestinal tract (GIT), including pathogen suppression through competitive exclusion and antimicrobial peptide production, enhancement of gut barrier integrity through mucin production, immune modulation within gut-associated lymphoid tissue (GALT), and metabolic regulation through the production of short-chain fatty acids (SCFAs). (**B**) Major limitations of conventional oral probiotic delivery, including reduced viability during storage and transport due to heat and oxygen sensitivity, high microbial mortality during gastric transit under acidic conditions (pH 1.5–3.5), poor gut colonization caused by competition with native microbiota, and rapid clearance from the gastrointestinal tract, ultimately resulting in reduced therapeutic potency. Black arrows indicate direction of movement, interaction, or biological effect; downward arrows indicate reduction or loss; red cross marks indicate microbial damage, inhibition, or death; and green downward arrows indicate beneficial reduction in adverse outcomes or metabolic burden.

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microorganisms.[24] For instance, strains of *Lactobacillus* produce lactic acid and hydrogen peroxide, which lower the pH of the gut environment, creating an inhospitable environment for pathogens.[25,26] Probiotics also contribute to gut barrier integrity by enhancing the production of mucins, which form a protective mucus layer over the intestinal epithelium. This further shields the host from pathogen invasion and helps maintain the integrity of the intestinal lining.[27,28]

Beyond immune modulation and pathogen suppression, probiotics contribute to metabolic health, an emerging area of interest in probiotic research. The gut microbiota is known to significantly influence nutrient metabolism, including fat storage, glucose regulation, and cholesterol metabolism.[8,29,30] Probiotics have been shown to enhance glucose metabolism and insulin sensitivity. This is especially beneficial in the management of T2DM. They achieve this by altering the gut microbiome to promote beneficial bacteria that produce short chain fatty acids (SCFAs).[31,32] Among these, butyrate is a primary energy source for colonocytes and has anti-inflammatory effects. Additionally, SCFAs play a role in regulating lipid metabolism and can modulate adiposity, contributing to weight management and the prevention of obesity.[33]

Limitations of Conventional Probiotic Delivery

Although probiotics offer substantial health benefits, their practical application in therapeutic settings faces several significant challenges, particularly in delivery and stability.[6,34] The effectiveness of probiotics depends largely on their ability to survive the harsh gastrointestinal (GI) environment and successfully colonize the gut. However, conventional probiotic formulations often struggle to meet these challenges, resulting in reduced viability and clinical efficacy (Figure 2).[16,35]

The stomach presents one of the most formidable obstacles to probiotic survival. It is characterized by extreme acidity, with pH levels ranging from 1.5 to 3.5, especially after food intake. This acidic environment is designed to break down food and neutralize harmful pathogens, but it also harms the viability of live microorganisms.[36,37] Most probiotic strains, particularly those used in conventional oral formulations, are not acid-resistant, making it difficult for them to survive the journey through the stomach. While some probiotic species, such as *Lactobacillus acidophilus*, have inherent acid tolerance, others are more sensitive to low pH conditions.[35,38] Studies have demonstrated that probiotics can experience significant reductions in colony-forming units (CFUs) upon exposure to gastric acid, resulting in a loss of therapeutic potency. Research on various strains of *Bifidobacterium* and *Lactobacillus* has shown that only a small percentage survives stomach transit when taken orally in their unprotected form. This severely limits their potential for gut colonization and therapeutic impact.[6,39]

Even if probiotics survive against these stressors, their colonization efficiency remains a major challenge. The gut is a highly competitive environment, with an established microbiota that limits the colonization of new bacterial strains.[16,35,40] Probiotics, once reaching the intestines, must adhere to the intestinal mucosa and compete with indigenous bacteria for nutrients and adhesion sites. Many probiotic strains fail to establish a stable population in the gut, especially when not tailored to the host's specific microbiome.[6,25,40] The transient nature of most conventional probiotics means that their effects are often short-lived. The *Lactobacillus* strains commonly used in probiotic formulations often persist in the human gut for only a few days before being flushed out with feces.[7,41] This transient nature reduces their long-term efficacy in terms of sustaining beneficial changes in the gut microbiome, limiting their potential therapeutic effects, particularly for chronic conditions like IBD or IBS.[42,43]

Ultimately, the survival challenges and low colonization efficiency of conventional probiotics affect their clinical efficacy. Inconsistent colonization and viability lead to variable results in clinical trials, making it difficult to determine the true therapeutic potential of probiotics.[44,45] In studies evaluating the efficacy of probiotics for IBS, results have often been inconclusive, with some patients benefiting from probiotic treatment while others show no improvement. This inconsistency has hindered the widespread adoption of probiotics as a mainstream therapeutic intervention.[46,47] Clinical efficacy also depends on the dosage and delivery mechanism of probiotics. Without controlled release or targeted delivery, the therapeutic potential of probiotics is diminished.[6] Some studies have shown that when probiotics are delivered in combination with prebiotics or through advanced delivery systems such as nano-encapsulation, their efficacy is significantly improved. However, these advanced methods are not typically used in conventional probiotic formulations, which often rely on simple oral ingestion of capsules, powders, or yogurt.[13,48–50]

Nanobiotics and Probiotic Enhancement

What are Nanobiotics?

The term *nanobiotics* refers to an emerging interdisciplinary approach that integrates nanotechnology with biological agents to improve their stability, delivery, and therapeutic performance. In the context of probiotics, nanotechnology is used to engineer nanoscale carrier systems that can encapsulate, protect, and transport beneficial microorganisms in a more controlled manner than conventional formulations.[51,52] Unlike traditional encapsulation platforms, which often operate at the micro- to millimeter scale, nanobiotic systems employ carriers with highly tunable physicochemical properties, including particle size, surface charge, permeability, and release behavior. These features allow more precise control over probiotic delivery and functional interaction within the gastrointestinal environment.[53,54]

Nanobiotic platforms may be constructed from polymers, lipids, proteins, or inorganic materials, depending on the intended application. Polymeric nanoparticles based on materials such as alginate, chitosan, and poly(lactic-co-glycolic acid) (PLGA) are widely studied because of their biodegradability, structural versatility, and mucoadhesive potential. Lipid-based systems, including liposomes and nanoemulsions, provide membrane-like environments that can support probiotic encapsulation and facilitate sustained release.[55,56] More broadly, nanobiotic design enables tailoring of carrier architecture to improve retention, site-specific activity, and interaction with mucosal tissues. By combining nanoscale engineering with probiotic functionality, nanobiotics represent a promising extension of probiotic science and a foundation for more precise microbiome-directed therapeutics.[53,57,58]

Rationale for Nanotech in Probiotics

Nanotechnology provides a rational platform for improving probiotic delivery because materials at the nanoscale possess distinctive physicochemical properties, including high surface-area-to-volume ratio, tunable surface chemistry, and controllable interaction with biological environments.[53,54] These features allow probiotic carriers to be engineered with greater precision in terms of encapsulation behavior, surface functionality, and release characteristics than conventional formulations.[6,59] As a result, nanocarrier systems offer a versatile strategy for improving probiotic stability and functional performance within the GIT.[60]

A major advantage of nanocarrier-based systems is the ability to regulate when and where probiotic cells are released. In contrast to conventional formulations, which often provide limited control over delivery, nanomaterials can be designed to respond to physiological triggers such as pH gradients, enzymatic activity, or local intestinal conditions.[58,60] This enables more site-specific probiotic release and can improve retention and activity at the intended intestinal location. In addition, selected nanocarriers may be tailored to exhibit mucoadhesive properties, thereby prolonging residence time at the mucosal surface and enhancing interaction with epithelial tissues.[44]

Nanotechnology also broadens the functional scope of probiotic delivery by enabling co-formulation with complementary agents such as prebiotics, bioactive compounds, or antimicrobial molecules.[53,61] Such integrated delivery strategies may promote synergistic effects after release and enhance the overall therapeutic value of probiotic formulations. Collectively, these features explain why nanotechnology has become an increasingly attractive platform for the development of next-generation probiotic systems.[54,62]

Nanobiotic Delivery Systems

Nanoencapsulation Methods

Nanotechnology has revolutionized the delivery of probiotics, enabling the engineering of nanoencapsulation techniques that enhance stability, viability, and controlled release (Figure 3). These nanoencapsulation methods involve enclosing probiotics within nanosized carriers, which provide physical protection from the harsh environment of the GIT while optimizing their therapeutic potential.[49,63,64] There are several approaches to nanoencapsulation. Each utilizes different materials and mechanisms to ensure probiotics can survive the digestive journey. These approaches help probiotics exert their beneficial effects once they reach their target sites.[49]

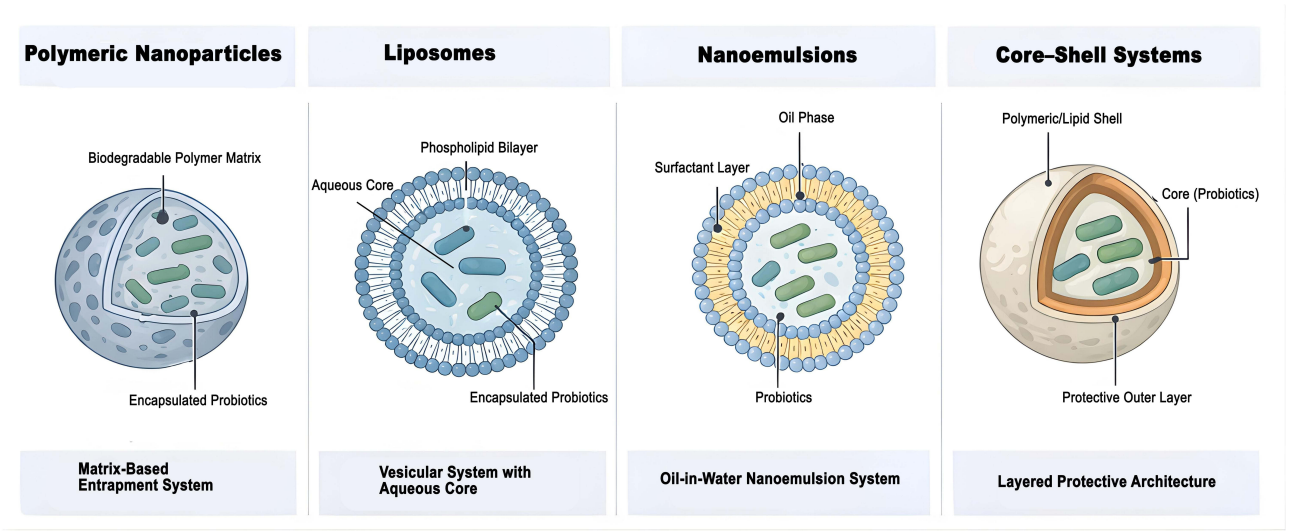

Figure 3 Nanoencapsulation methods used in nanobiotic delivery systems. Polymeric nanoparticles entrap probiotics within biodegradable polymer matrices. Liposomes are phospholipid bilayer vesicles with an aqueous core containing encapsulated probiotics. Nanoemulsions are oil-in-water systems stabilized by a surfactant layer and used to protect probiotic cargo. Core–shell systems consist of a probiotic-containing core surrounded by polymeric or lipid shell layers that provide additional structural protection.

Polymeric Nanoparticles

This involves polymeric nanoparticles made from biodegradable, biocompatible polymers (Figure 3). Materials such as chitosan, alginate, pectin, and PLGA are commonly used to form the nanoparticles. These polymers offer several advantages, including their controlled-release capabilities and the ability to protect the encapsulated probiotics from digestive enzymes, stomach acid, and bile salts in the small intestine.[65,66] Chitosan, for example, is a biocompatible polysaccharide that can form stable nanoparticles and exhibit mucoadhesive properties, helping prolong the retention time of probiotics at the intestinal mucosa. Similarly, alginate, a naturally derived polysaccharide, is often used for encapsulating probiotics. It provides an additional benefit of pH-responsive release. This ensures the probiotics are released in the colon's alkaline environment.[67]

Liposomes and Nanoemulsions

Another approach are the use of liposomes and nanoemulsions (Figure 3). Liposomes are phospholipid bilayer vesicles that encapsulate probiotics within an aqueous core, providing a protective barrier against environmental stresses. They are particularly effective at protecting probiotics from stomach acid and improving their bioavailability. Liposomes are also beneficial because they can carry both hydrophilic and lipophilic substances, enabling the co-delivery of probiotics with other beneficial prebiotics or bioactive compounds. Nanoemulsions, which are oil-in-water dispersions, offer similar protective benefits and are especially effective for protecting probiotics from oxidative stress while maintaining their activity. These systems also help improve intestinal adhesion by enhancing interaction with gut epithelial cells, thereby increasing colonization efficiency.[49,63,68]

Core-Shell Coatings

A more advanced nanoencapsulation technique is the core-shell coating method, where probiotics are encapsulated within a central core surrounded by an outer shell of polymeric materials or lipid layers (Figure 3). This design provides an additional layer of protection, ensuring that the probiotics are released in a controlled manner at the desired location. The outer shell can be engineered to respond to specific stimuli, such as changes in pH, enzymatic activity, or temperature, enabling targeted release in regions of the gut that are most beneficial for therapeutic outcomes. The shell can be designed to dissolve or break down in the colon's alkaline environment, releasing the encapsulated probiotics where they are most needed.[49,69]

Emerging Carrier Platforms

Beyond established polymeric and lipid-based systems, recent studies have identified exosome-based and metal-organic framework (MOF)-based platforms as promising next-generation carriers for probiotic delivery. Exosome-based systems, particularly milk-derived exosomes and other extracellular-vesicle-inspired biomimetic coatings, offer high biocompatibility, membrane flexibility, and favorable interaction with the intestinal surface.[70,71] In a recent study, Hao et al[72] developed a milk exosome-based coating system (mExo@DSPE-PEG-PBA) for *Akkermansia muciniphila, Bifidobacterium animalis* subsp. *lactis* BB-12, and *Lactiplantibacillus plantarum* Q7, achieving encapsulation efficiencies of 70.93–90.37% and simulated gastrointestinal survival rates of 80.99–94.53%, while also improving probiotic self-aggregation and adhesion-related behavior. Likewise, extracellular vesicles derived from probiotic microorganisms have shown carrier potential; for example, Mierzejewska et al[73] demonstrated that vesicles from probiotic *Saccharomyces boulardii* could be internalized by human intestinal cell lines and transfer loaded bioactive cargo, supporting their use as biologically active delivery vehicles. MOFs represent another emerging carrier class with highly tunable porosity, large surface area, and potential for protective yet stimulus-responsive encapsulation. FitzGerald et al[74] reported that *L. plantarum* 299v encapsulated within a biocompatible iron(III) fumarate matrix showed improved stability in saline, lysozyme, and pepsin compared with uncoated cells, highlighting the promise of MOFs as protective probiotic carriers. Although these systems remain at an early preclinical stage and require further toxicological and translational validation, they broaden the nanobiotic toolbox beyond conventional nanopolymers and liposomes and better reflect the cutting edge of probiotic carrier design.[53,75]

These nanoencapsulation methods are fundamental in improving the stability, survivability, and targeted release of probiotics, ensuring that therapeutic doses reach the lower GIT, where they can exert their beneficial effects. Advances in nanotechnology continue to enhance the efficiency and precision of these delivery systems, which is critical for improving the clinical efficacy of probiotics.[76]

Mechanisms by Delivery Type

Nanocarrier systems provide significant advantages over conventional probiotic delivery, primarily by enhancing the viability, stability, and bioavailability of probiotics in the GIT. The mechanisms by which nanocarriers protect probiotics are multifaceted and depend on the type of nanocarrier used, but some common features apply across various delivery systems.

pH-Responsive Release

The key mechanisms by which nanocarriers protect probiotics is through pH-responsive release. This is particularly important for ensuring that probiotics are protected from the acidic conditions of the stomach. They must be released at the target site in the colon, where the pH is higher and more favorable for microbial activity.[49] Polymers like chitosan and alginate being used to form nanoparticles that are stable in acidic environments. These polymers break down or become more permeable at neutral or alkaline pH levels. This allows the probiotics to be released gradually and at the right site. This site-specific release maximizes the therapeutic effects of probiotics. It ensures they reach the colon in a viable form, where they can restore gut flora and provide therapeutic benefits such as immune modulation and pathogen suppression.[67,77]

Mucoadhesive Properties

Another critical feature of nanocarriers is their mucoadhesion, which enhances interaction with the gut mucosa. Materials like chitosan and pectin have been shown to adhere to the mucus layer of the intestinal lining. This not only extends the retention time of probiotics at the target site but also facilitates better colonization. This is especially important for prolonged therapeutic effects.[78] It increases the local concentration of probiotics and ensures that the beneficial microbes can interact with the intestinal microbiota more effectively. This contact plays a key role in immune regulation by communicating with the GALT.[20,34,79]

Single-Cell Nanoencapsulation

Single-cell nanoencapsulation, also known as cell-in-shell technology, represents a more advanced form of nanoencapsulation. In this method, individual probiotic cells are encapsulated in ultrathin nanocarriers that act as protective shells. This method offers several advantages, including the protection of probiotics from harsh GIT conditions. The single-cell approach also ensures that each probiotic cell is individually protected. It allows for precision delivery to its target site in the intestine. Furthermore, this technology enables enhanced targeted release. The shell can be designed to disintegrate or release its payload in response to specific triggers, such as pH changes, enzymatic activity, or inflammation markers in the colon. This not only improves the survival and functionality of probiotics but also enhances the therapeutic specificity of probiotic treatments.[69,80]

Beyond simple physical protection, complex nanocarrier systems can modulate probiotic behavior through interfacial and stimulus-responsive mechanisms at the intestinal mucosal surface. Mucoadhesive materials such as chitosan and pectin promote electrostatic and polymer–mucin interactions, thereby increasing residence time within the mucus layer and enhancing contact between viable probiotic cells and the epithelium.[81,82] In parallel, nanoscale dimensions and surface functionalization can improve localization at inflamed or damaged intestinal sites, increasing opportunities for epithelial adhesion and immune crosstalk. Stimuli-responsive systems provide an additional level of control: pH-sensitive or enzyme-responsive matrices remain relatively stable during upper gastrointestinal transit but swell, erode, or dissociate under distal intestinal or colonic conditions, enabling site-specific release of viable cells.[83] Together, these mechanisms help explain why nanobiotic systems may strengthen barrier-associated responses, modulate inflammatory signaling pathways, and enhance probiotic bioactivity beyond the passive survival advantage provided by conventional formulations.[84]

Bioavailability and Targeted Release

One of the primary challenges of conventional probiotic therapies is ensuring that a sufficient number of viable cells reach the lower GIT, where they can provide therapeutic benefits. Nanoencapsulation and targeted delivery systems significantly improve bioavailability. They protect probiotics during their passage through the upper GIT and also facilitate their targeted release.[49,58] Nanocarrier systems improve the fraction of live probiotics that survive this harsh environment by providing physical protection through encapsulation, enabling a larger proportion of viable cells to reach the colon. Additionally, stimuli-responsive nanocarriers release probiotics in response to specific triggers, such as changes in gut pH or enzymatic degradation. This further enhances the effectiveness of the probiotics by ensuring targeted release at the right time and location.[35]

Compared with free probiotics, nanobiotic formulations provide functional advantages at each stage of gastrointestinal transit. In the stomach, unencapsulated probiotic cells are rapidly inactivated by low gastric pH and associated digestive stress, whereas nanoencapsulation provides a protective barrier that preserves cell viability during gastric exposure.[53,57] In the small intestine, free probiotics are further compromised by bile salts and digestive enzymes, which reduce survival and limit subsequent colonization. By contrast, nanocarriers maintain structural integrity during intestinal transit and, in some formulations, enhance mucoadhesion, thereby prolonging residence time at the mucosal surface and improving epithelial interaction and colonization potential.[35] Upon reaching the colon, free probiotics often arrive in reduced numbers and exhibit limited site-specific activity, whereas nanobiotics can undergo pH-triggered or enzyme-triggered release, enabling controlled delivery of viable cells at the target site. This stage-wise protection, retention, and stimulus-responsive release collectively explain why nanobiotics generally achieve greater colonization efficiency, improved restoration of microbial balance, and stronger therapeutic effects than free probiotic formulations (Figure 4).[85]

Functional Interactions with the Gut

Modulation of Microbiota

Nanobiotic-enhanced probiotics have demonstrated a promising capacity to reshape the composition and diversity of the gut microbiome. They do this more effectively than conventional probiotics. This is largely because improved delivery systems increase the number of viable microbes that actually reach the intestine. The gut microbiota is a complex

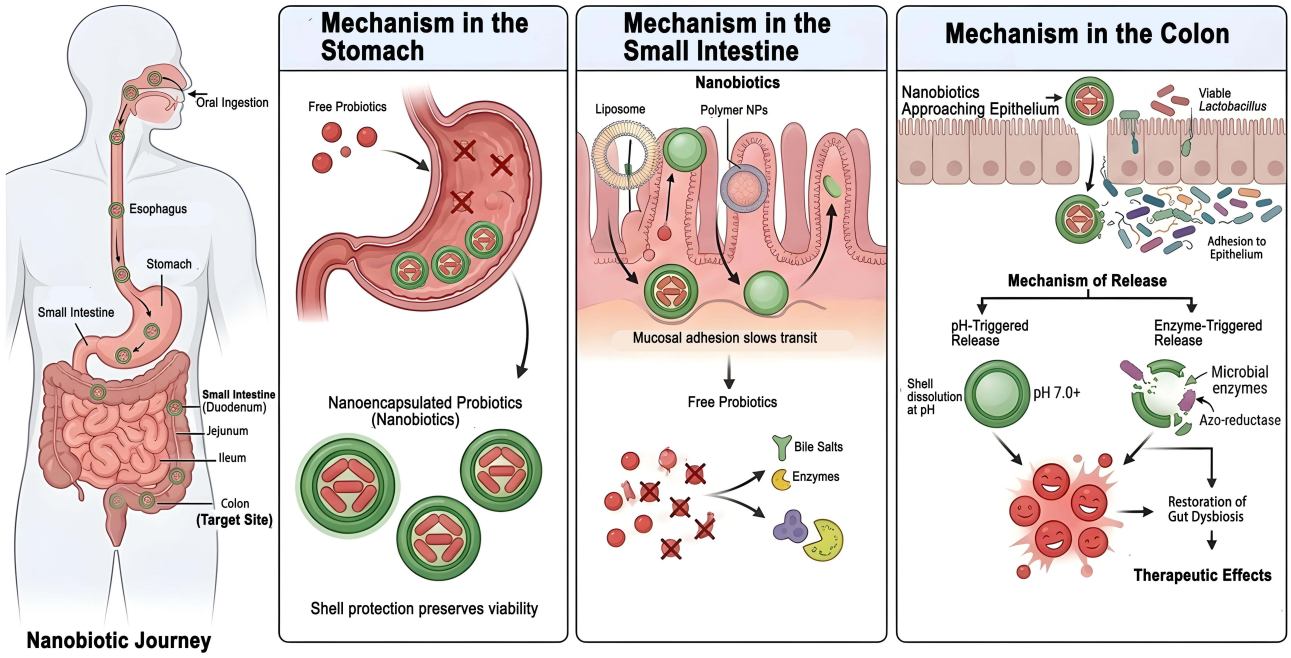

Figure 4 Gastrointestinal transit and targeted colonic release of nanoencapsulated probiotics (nanobiotics). The schematic illustrates the oral journey of nanobiotics through the gastrointestinal tract, from ingestion to colon-targeted release. In the stomach, free probiotics are highly susceptible to degradation under acidic conditions, whereas nanoencapsulated probiotics remain protected by their shell, which preserves viability. In the small intestine, nanobiotics such as liposomes and polymeric nanoparticles can interact with the mucosal surface, thereby slowing transit and enhancing retention, while free probiotics are further compromised by bile salts and digestive enzymes. In the colon, nanobiotics approach and adhere to the epithelium, followed by pH-triggered or enzyme-triggered shell degradation, resulting in localized release of viable probiotics. This targeted colonic delivery supports restoration of gut dysbiosis and contributes to therapeutic effects. Black arrows indicate direction of movement, transit, or biological action; red cross marks indicate microbial damage, loss of viability, or degradation.

microbial ecosystem that plays a central role in metabolic, immune, and neurological functions.[7,53] When this microbial balance is disturbed, a condition known as dysbiosis, it has been linked to a range of diseases. These include inflammatory disorders, metabolic syndrome, and even neurodegenerative processes. Traditional probiotic therapies often fail to induce significant or lasting changes in microbial communities. This is because a large proportion of probiotic cells are inactivated before reaching the colon.[18] However, nanoencapsulation and nanocarrier technologies protect probiotics during gastrointestinal transit. They also promote sustained release in the lower gut. This enhances the probiotics' interactions with the resident microbiota. Research indicates that nano-protected probiotics can increase the abundance of beneficial taxa such as *Bifidobacterium, Lactobacillus*, and *Eubacterium*. At the same time, they reduce the relative abundance of pathogenic genera such as *Enterococcus, Fusobacterium*, and *Pseudomonas*, outcomes that correlate with improved microbial diversity and balance.[54,86] Enhanced microbial diversity is associated with healthier metabolic profiles and greater stability of the gut ecosystem, a factor considered beneficial for long-term host health. These modulatory effects are likely mediated through improved adhesion, colonization, and activity of probiotic strains. These strains would otherwise be lost due to gastric acidity or enzymatic degradation during transit. This highlights the role of nanocarrier technologies in achieving more profound and sustained shifts in microbiome composition.[87]

Immune Modulation

Nanobiotic carriers not only enhance the delivery of probiotics but also modulate their capacity to interact with the host immune system, potentially leading to stronger and more balanced immune responses. The gut mucosa is a major interface between the host immune system and the external environment, densely populated with immune cells that constantly survey microbial signals. Probiotic microorganisms are known to engage with GALT and influence immune signaling pathways. However, their immunomodulatory impact is often limited by suboptimal delivery. By enabling probiotics to survive longer in the intestinal environment and adhere more effectively to the epithelial surface, nanotechnology can amplify their immune interactions. Studies have shown that nanobiotic formulations can reduce

excessive inflammatory signaling, such as through the TLR4/nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway, which is implicated in many chronic inflammatory diseases.[53,80,88] They do this by encouraging the production of anti-inflammatory cytokines and mitigating pro-inflammatory mediators. This shift toward a regulatory immune profile fosters tolerance to commensal microbes while suppressing harmful pathogens, creating an environment that supports immune homeostasis. Furthermore, stimuli-responsive nanocarriers that release probiotics in response to local inflammatory cues may directly engage immune cells in inflamed tissues. This enhances local immunoregulation in conditions such as IBD. By improving the persistence of probiotics at immunologically active sites, nanobiotic strategies enable controlled release in specific intestinal regions. This strengthens the probiotics' ability to modulate innate and adaptive immunity.[89,90]

Gut Barrier Protection

The structural and functional integrity of the intestinal barrier, composed of epithelial cells, mucus layers, and tight junction proteins, is fundamental. It helps prevent the translocation of pathogens and regulates immune responses. Disruption of this barrier, often referred to as "leaky gut", is associated with chronic inflammation and a variety of systemic diseases. Conventional probiotics can support barrier function in some individuals, but their effects are constrained by limited survival through the GIT. Nanobiotic formulations, through enhanced protection and targeted release, increase the number of viable cells that reach the intestine. These cells interact with the mucosal surface, enabling a more robust impact on barrier repair mechanisms.

At the epithelial level, nanoencapsulation may enhance the ability of probiotic cells to remain in close contact with the mucus layer and intestinal surface, thereby increasing the likelihood of adhesion-mediated signaling. Rather than acting solely through improved survival, these systems can prolong mucosal residence, promote interaction with epithelial receptors, and facilitate localized modulation of barrier-associated pathways.[91] Such interactions may stimulate mucin production by goblet cells, reinforce tight junction assembly, and reduce epithelial permeability, while also limiting the translocation of luminal antigens and inflammatory microbial products into the submucosa. In this way, nanobiotic formulations may strengthen barrier integrity not only by improving probiotic delivery, but also by amplifying functional communication between probiotic cells and the intestinal epithelium.[92]

For example, Wang et al[93] encapsulated *Lactobacillus plantarum* P-8 in gelatin/gum Arabic microcapsules, first confirmed improved survival under simulated gastric and intestinal conditions, and then administered the formulation to DSS-induced colitis mice for 21 days. Compared with free probiotic cells, the microcapsules more effectively reduced disease activity and histopathologic injury while increasing colonic MUC-2, ZO-1, and occludin expression, indicating stronger restoration of both the mucus layer and tight-junction barrier.[94] Similarly, Alkushi et al[94] evaluated orally delivered multi-strain-probiotic-loaded nanoparticles in a DSS-induced colitis model and found that nanoparticle delivery suppressed inflammatory and oxidative injury more effectively than free probiotics, while also producing more prominent upregulation of barrier-associated genes, including MUC-2, MUC-5, ZO-1, occludin, and claudin-1. In another pre-clinical study, Zhang et al[95] developed sulfhydryl-modified double-layered multinucleated microcapsules containing *Bifidobacterium adolescentis* FS2-3 and *Bacillus subtilis* SN15-2; in vitro digestion and adhesion assays showed improved probiotic survival and mucus interaction, and in an *Escherichia coli* O157:H7 murine enteritis model the formulation increased intestinal probiotic retention, alleviated inflammation, and repaired microbiota disruption. Collectively, these studies suggest that nano-protected probiotic systems can enhance barrier repair not only by improving survival during gastrointestinal transit, but also by increasing mucosal retention, reinforcing mucus-associated defenses, and restoring tight-junction integrity.

Collectively, these effects contribute to reduced intestinal permeability. These effects not only reduce inflammation by limiting the passage of microbial products into the submucosa but also support the regeneration of epithelial cells and the maintenance of gut homeostasis. Certain advanced nanoencapsulation techniques have been linked with improved barrier enhancement outcomes in models of gut injury. In necrotizing enterocolitis models, formulations that protect probiotic cells until they reach the damaged intestinal region have been associated with intensified barrier repair. These formulations also help downregulate inflammatory signals. This illustrates the therapeutic potential of nanobiotic systems in clinical settings. In these settings, barrier disruption is central to disease progression.[96,97]

Therapeutic Applications

This section shows where nanobiotic-enhanced probiotics have a real-world impact and clinical potential. Each subsection includes specific applications, mechanisms, and evidence from recent studies (Table 1). To maintain focus on nanobiotic-enhanced probiotics for targeted gut delivery, each subsection briefly distinguishes established evidence on conventional probiotics from findings specific to nanoencapsulation or nanobiotic delivery platforms, and then identifies areas that remain preliminary or translational.

Inflammatory Bowel Diseases and IBS

Nanobiotic-enhanced probiotics are increasingly being investigated as adjuncts or alternatives to conventional therapies for ulcerative colitis (UC), Crohn's disease (CD), and IBS. These disorders are linked, to varying degrees, with immune dysregulation, epithelial barrier dysfunction, and microbiome imbalance, while current pharmacological therapies often remain limited by suboptimal targeting and systemic adverse effects. Nanotechnology-based delivery systems may improve the therapeutic performance of probiotics by enabling colon-directed delivery, prolonged mucosal retention, and stronger local immunomodulatory effects at sites of intestinal injury or inflammation.[53,105] Recent studies indicate that nanocarrier-based probiotic formulations can enhance mucosal interaction, regulate inflammatory signaling, and reduce disease severity more effectively than free probiotics in preclinical intestinal disease models.[13,49,54]

Among intestinal disorders, UC has been one of the most intensively studied targets for nanobiotic probiotic delivery because its localized colonic pathology is well suited to colon-directed release and mucosal-retention strategies. In experimental UC models, nano-coated probiotics have been shown to reduce key inflammatory mediators such as IL-6 and TNF-α more effectively than non-encapsulated formulations.[106] Encapsulation within biocompatible materials such as chitosan or alginate has also been associated with improved mucosal adherence and prolonged retention at inflamed colonic sites, thereby enhancing modulation of the local immune microenvironment. For example, *Lactobacillus rhamnosus* delivered through chitosan nanoparticle carriers improved disease activity scores in chemically induced colitis models compared with free cells, supporting the therapeutic potential of nanocarrier-assisted probiotic delivery in UC.[13,69,107]

Although CD has been studied less extensively than UC in the context of nanobiotic probiotics, emerging preclinical evidence suggests beneficial effects of nano-delivery strategies in experimental models. Nanoencapsulated probiotics have been reported to modulate immune pathways involved in tissue injury and inflammation while also supporting gut barrier integrity, which is frequently compromised in CD.[108] In particular, nano-protected probiotic cells have been associated with increased tight junction protein expression and reduced epithelial permeability, both of which are important for limiting the translocation of luminal antigens and sustaining mucosal homeostasis.[109,110] While human clinical evidence remains limited, these findings suggest that nanobiotic delivery may enhance the functional effects of probiotics in CD.

IBS, although distinct from classical IBD, is increasingly linked to low-grade inflammation, visceral hypersensitivity, altered motility, and microbiota disruption. Nanocarrier-based probiotic systems may improve therapeutic effects in IBS by enabling more localized delivery and sustained probiotic activity within the intestine.[111] Small cohort studies using nano-protected probiotic formulations have reported improved symptom control and better quality-of-life outcomes compared with standard probiotic preparations.[54,60] Although large-scale clinical evidence is still lacking, these early findings support the potential of nanobiotics as a more effective probiotic strategy in IBS management.

Collectively, current evidence suggests that nanobiotic probiotic systems may offer therapeutic advantages across UC, CD, and IBS by improving mucosal retention, reinforcing barrier integrity, and enhancing local immunoregulatory effects.[88] However, most supporting data remain preclinical, and further well-designed clinical studies are needed to confirm their translational value.

Gastrointestinal Infections

Gastrointestinal infections caused by bacterial, parasitic, and viral agents remain a major global health challenge and contribute substantially to morbidity and mortality (Figure 5). Conventional antimicrobial therapies are increasingly limited by antimicrobial resistance, treatment-associated side effects, and disruption of the native gut microbiota. In this context, nanobiotic-enhanced

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Table 1 Summary of Recent Studies with Outcomes

Study	Evidence level	Probiotic Strain	Nanocarrier	Model/Context	Key Outcome	Reference
***E. coli* Nissle**	In vivo	Nanoarmor (Fe^{3+}-tannic acid) coating	Rat antibiotic-associated diarrhea model	Protected against antibiotic disruption; improved colonization and reduced diarrhea	Reduced AAD symptoms; more resilient probiotic activity	[98]
***L. rhamnosus* GG**	In vitro	Layer-by-layer, tannic acid + casein coating	Simulated GI conditions	Enhanced survival and reactive oxygen species (ROS) scavenging; improved epithelial cell protection	Improved survival in the GIT simulation	[99]
Chitosan-based probiotic encapsulation	In vitro	*L. acidophilus* and others	Polymeric nanoparticles	In vitro GI simulation	Increased viability vs. free cells through gastric stress	[100]
Nanocoated *L. casei* and probiotic blend	In vivo	Nanoarmor ($Fe[3]^{+}$-tannic acid)	Antibiotic pressure model	$Fe[3]^{+}$-TA nanoarmor preserved CFUs and strain diversity under antibiotics	Higher compound viability vs. non-armored probiotic	[98]
Probiotic nano-encapsulation reviews	In vitro	Various *Lactobacillus*/*Bifidobacterium*	Nanomaterials (polymeric, lipid)	Encapsulation studies and analyses	Nanocarriers improve survival, targeted release potential	[101]
Nano-enhanced delivery	In vitro	General probiotic encapsulation	Nanoemulsions/nanogels	Delivery optimization context	Higher survival rates through acid tolerance; controlled release mechanisms explored	[60]
Nano-coated probiotics for food matrices	In vitro	Probiotic cultures	Nano-encapsulation systems	Food application modeling	Higher probiotic viability in food delivery systems	[49]
Probiotic nano-encapsulation strategies	In vivo	Multiple probiotics	Polymer/lipid-based nanocarriers	Simulated GIT and food stability context	Improved probiotic survival and bioavailability	[102]
Hybrid nano-probiotic systems	In vitro	*Lacticaseibacillus spp.* (review)	Advanced nanocomposites	Encapsulation survival and ROS protection studies	Show improved ROS neutralization and viability	[103]
Emerging encapsulation	In vivo	Synbiotic nano systems	Chitosan + prebiotic coatings	Animal absorption/nutrient studies	Promoted gut villi growth, immune indicators	[104]

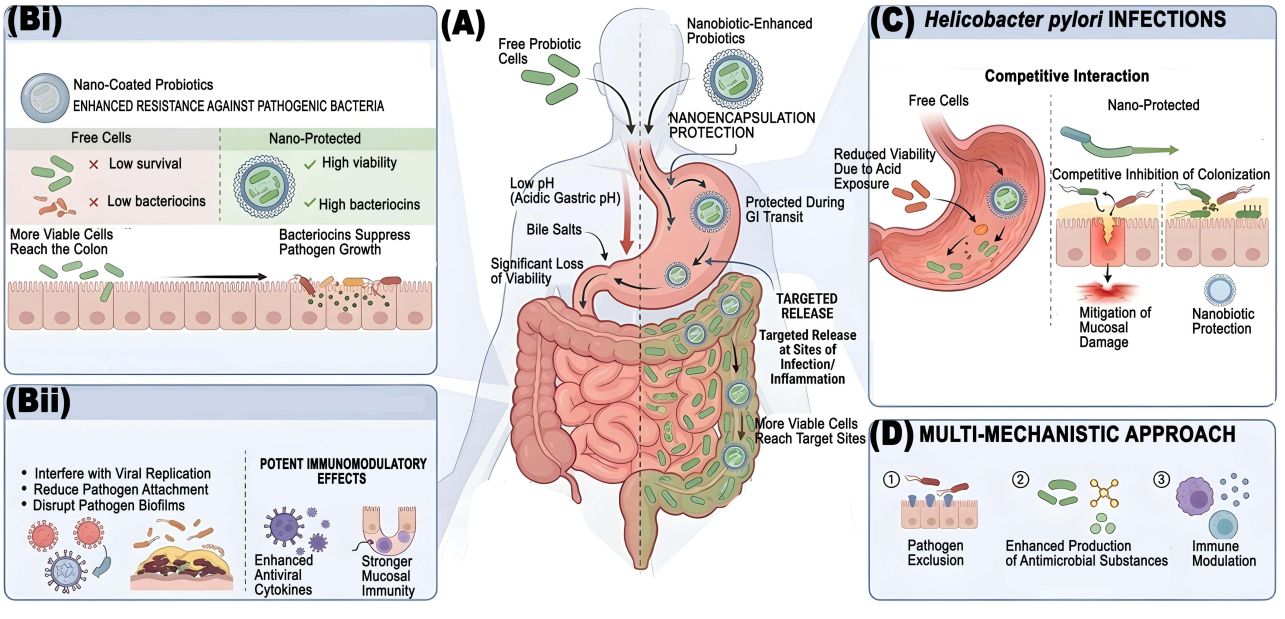

Figure 5 Therapeutic applications and multi-mechanistic efficacy of nanobiotic-enhanced probiotics in gastrointestinal infections. (**A**) Comparison of free probiotic cells and nanobiotic-enhanced probiotics during gastrointestinal transit. Nanoencapsulation protects probiotic cells against acidic gastric conditions and bile salts, thereby reducing viability loss and enabling targeted release at sites of infection or inflammation, with a greater proportion of viable cells reaching target sites in the lower gastrointestinal tract. (**Bi–Bii**) Applications in bacterial, viral, and fungal gastrointestinal infections. In bacterial gastroenteritis, nano-coated probiotics improve viability, enhance bacteriocin-associated activity, and increase the proportion of viable cells reaching the colon, thereby suppressing pathogen growth. In viral and fungal gut infections, nanobiotic formulations interfere with viral replication, reduce pathogen attachment, disrupt pathogen biofilms, and promote immunomodulatory responses, including enhanced antiviral cytokine production and stronger mucosal immunity. (**C**) Application in Helicobacter pylori infections. Nanocarrier protection improves probiotic persistence under acidic gastric conditions, facilitating competitive inhibition of colonization, mitigation of mucosal damage, and overall nanobiotic protection. (**D**) Summary of the major shared therapeutic mechanisms, including pathogen exclusion, enhanced production of antimicrobial substances, and immune modulation. Black arrows indicate direction of transit, release, or biological action; red cross marks indicate reduced viability or microbial damage; green check marks indicate improved probiotic performance or protection.

probiotics are emerging as promising adjunctive strategies for infection control because they can improve localized probiotic activity, strengthen pathogen suppression, and support restoration of microbial balance at infected mucosal sites.[112,113]

Bacterial gastroenteritis caused by pathogens such as *E. coli, Salmonella enterica*, and *C. difficile* is characterized by intestinal inflammation, diarrhea, abdominal pain, and, in severe cases, systemic complications. Multiple studies have shown that nano-coated probiotics exhibit stronger antibacterial activity than their free-cell counterparts. In addition to improving probiotic persistence at the intestinal mucosa, nanobiotic systems can enhance competitive exclusion of pathogens and increase the production or functional activity of antimicrobial substances such as bacteriocins.[114] In one recent study, probiotics encapsulated in nano-chitosan matrices showed substantially greater antibacterial activity against gastrointestinal pathogens than non-encapsulated formulations, indicating that nanoencapsulation can amplify probiotic antimicrobial performance.[115,116] These effects may contribute not only to direct pathogen inhibition but also to restoration of a healthier microbial ecosystem, thereby reducing the likelihood of recurrent infection.

Helicobacter pylori infection is a major cause of peptic ulcer disease and is strongly associated with chronic gastritis and gastric cancer (Figure 5). Although standard multidrug regimens remain the mainstay of treatment, they may induce side effects and further promote antimicrobial resistance. Conventional probiotic adjuncts have been explored to reduce antibiotic-associated disturbances and improve gastric microbial balance, but their effects on eradication outcomes remain inconsistent. In the context of this review, the more relevant question is whether nanobiotic delivery systems can improve probiotic persistence and local activity at the gastric mucosal surface. As illustrated in Figure 5, nano-protected formulations, including liposomal probiotic systems, may enhance survival under acidic gastric conditions, strengthen competitive interactions with *H. pylori*, and help mitigate mucosal damage more effectively than unprotected probiotics.[117,118] However, direct evidence for nanoprobiotic strategies against *H. pylori* remains limited, and most current claims should still be regarded as translational rather than clinically established, particularly with respect to eradication efficacy and long-term outcomes.[119]

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Evidence for nanobiotic-enhanced probiotics in viral and fungal gut infections remains limited and largely preclinical. At present, the main mechanistic rationale is that nanocarrier-assisted delivery may enhance probiotic viability, local mucosal persistence, and interference with pathogen attachment or biofilm formation.[23,25,120] Some studies also suggest that nanoencapsulation may strengthen probiotic-mediated immunomodulatory effects, including antiviral cytokine responses and mucosal immune support. However, these observations remain preliminary, and controlled human data are still insufficient to define the therapeutic role of nanobiotic probiotics in viral or fungal gastrointestinal infections.[86]

Metabolic Health

Metabolic disorders are increasingly linked to gut dysbiosis and systemic inflammation, underscoring the central role of the gut microbiome in host metabolic regulation. Evidence from conventional probiotics suggests some benefit in modulating metabolic risk factors through effects on microbial composition and low-grade inflammation, but these outcomes have generally been modest and inconsistent, partly because of poor gastrointestinal survival and limited site-specific delivery.[121,122] Within the scope of this review, however, the more relevant question is whether nanobiotic-enhanced probiotics can improve these effects by increasing probiotic viability, protecting cells during gastrointestinal transit, and enabling more targeted delivery to distal intestinal sites where host–microbiome metabolic interactions are most relevant. By improving survival and localization, nanocarrier systems may enhance downstream effects on systemic inflammation, short-chain fatty acid production, and bile acid and lipid metabolism.[53,54,60]

Lifestyle-related factors also shape the metabolic efficacy of probiotic and nanobiotic interventions by influencing both gut microbial ecology and colonization potential. Diet is a major determinant of microbiome composition: short-term dietary changes can rapidly alter community structure, whereas fiber-rich, plant-diverse diets generally support greater microbial diversity and short-chain-fatty-acid-producing taxa, while Western-style high-fat, high-sugar, low-fiber diets are associated with dysbiosis, enrichment of bile-tolerant organisms, barrier dysfunction, and low-grade inflammation.[123] Likewise, antibiotic exposure can markedly reduce microbial richness and diversity, disrupt colonization resistance, and alter the ecological niche into which administered probiotics are introduced. Exercise habits are also relevant, as regular physical activity is generally associated with greater microbial diversity and enrichment of metabolically favorable taxa, whereas sedentary lifestyles are linked to less favorable microbiome profiles.[124] These variables are directly relevant to probiotic persistence, because probiotic engraftment is highly individualized and depends in part on baseline host and microbiome features. Accordingly, although nanobiotic formulations may improve survival and site-specific delivery, their colonization efficiency and metabolic impact are still likely to be conditioned by diet quality, antibiotic exposure, exercise habits, and the pre-existing gut microbiome.[53] In this context, healthy dietary and lifestyle patterns may provide a more permissive ecological environment for sustained probiotic activity, whereas unhealthy diets, recurrent antibiotic exposure, and adverse lifestyle habits may blunt the benefits even when delivery is improved by nanoencapsulation.

Obesity is often characterized by alterations in gut microbial communities that influence energy harvest, fat storage, and hormonal regulation. In experimental models, nanotechnology-based probiotic delivery has shown promise in modulating these metabolic processes more effectively than conventional probiotic formulations. Nanoencapsulation improves the stability and gut delivery of probiotics, enabling a higher proportion of viable cells to reach the colon, where they interact with resident microbiota and host tissues. Studies using nanocarrier-encapsulated probiotic strains have reported reduced weight gain and adiposity in treated animals. This is likely linked to shifts in bile acid metabolism. It may also involve changes in microbial communities that regulate energy balance.[125,126] These findings align with broader evidence that modifying gut microbiota composition can support improvements in metabolic health. This includes increasing beneficial bacteria such as *A. muciniphila*, which is known to influence diet-induced obesity and metabolic endotoxemia.[127]

T2DM is characterized by chronic low-grade inflammation, insulin resistance, and metabolic dysregulation, processes in which the gut microbiota contributes. Probiotics have been shown in clinical and preclinical studies to improve insulin sensitivity and modulate glucose metabolism, though the magnitude of these effects varies widely.[31] Nanobiotic delivery systems further enhance probiotic efficacy by ensuring that higher concentrations of live microbial cells reach the distal gut. There, they can interact with enteroendocrine cells and modulate the release of metabolic hormones. These hormones regulate glucose homeostasis and appetite. Improved probiotic colonization via nanocarriers has been associated with

more robust metabolic signaling in experimental settings. By enhancing the delivery and persistence of probiotics in the colon, nanobiotic systems have the potential to lower fasting glucose levels. They can also improve insulin responsiveness and reduce inflammatory mediators associated with metabolic disease.[53,128]

NAFLD represents a hepatic manifestation of systemic metabolic dysfunction and is strongly associated with obesity, insulin resistance, and dysregulated microbiota. Standard probiotic interventions have demonstrated favorable effects on liver enzymes and other metabolic markers in both human and animal studies. This suggests that altering gut microbial composition can have positive effects on liver health.[129] In preclinical models, nanobiotic formulations designed for improved probiotic stability and targeted colon delivery have been shown to modulate the gut–liver axis. These formulations reduce hepatic fat accumulation and improve liver histology more effectively than conventional probiotics. By enhancing probiotic colonization and activity, nanocarriers support reductions in hepatic inflammatory signals. They also enhance barrier function, preventing the translocation of endotoxins that drive liver inflammation. Nanocarriers may improve serum liver enzyme profiles, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Although clinical data on nanobiotic probiotics in NAFLD remain limited, these early preclinical findings suggest that targeted probiotic delivery could become an important adjunctive strategy in treating or managing NAFLD and its progression.[130,131]

Gut–Brain Axis and Neurobehavioral Health

The gut–brain axis is a complex communication network linking the GIT and its microbiota with the central nervous system through neural, endocrine, and immune pathways (Figure 6). Through these interconnected pathways, gut microbes can influence brain function and behavior by modulating neurotransmitters, immune signaling, the hypothalamic–pituitary–adrenal (HPA) axis, and related metabolic processes.[19] In conventional probiotic research, neurobehavioral benefits have been reported, but these effects have often remained limited and inconsistent, partly because poor gastrointestinal survival and insufficient site-specific delivery reduce functional activity in vivo. In the context of this review, the more relevant question is whether nanobiotic-enhanced probiotics can overcome these limitations through improved viability, protected gastrointestinal transit, and stronger interaction with host neural and immune signaling

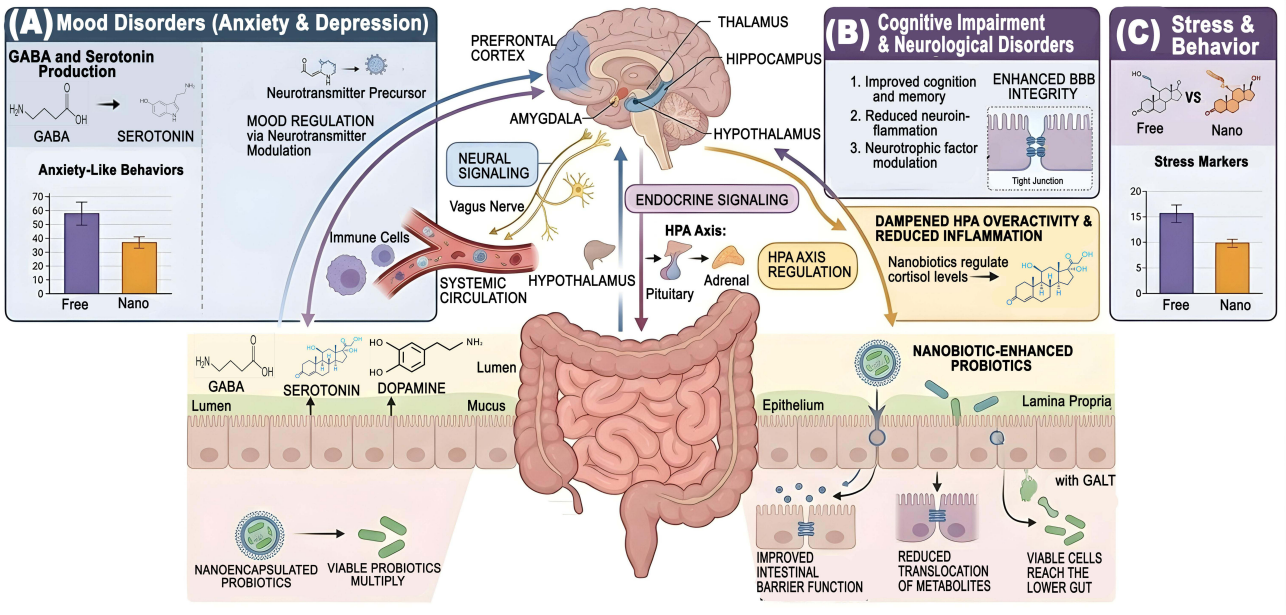

Figure 6 Modulation of the gut–brain axis and neurobehavioral health via nanobiotic-enhanced probiotics. This schematic illustrates bidirectional communication between the gastrointestinal tract (GIT) and the central nervous system mediated by nanobiotic-enhanced probiotics. (**A**) Nanocarrier delivery improves probiotic viability and enhances microbial production of neuroactive metabolites, including γ-aminobutyric acid (GABA), serotonin, and dopamine, which contribute to modulation of mood-related behaviors such as anxiety and depression. (**B** and **C**) Nanobiotic formulations improve cognitive function and stress resilience by reducing neuroinflammation, strengthening blood–brain barrier (BBB) integrity, and regulating hypothalamic–pituitary–adrenal (HPA) axis activity, resulting in decreased circulating stress markers such as cortisol. Central and lower sections show improved intestinal colonization and barrier integrity enable enhanced signaling through neural (vagus nerve), endocrine, immune, and metabolic pathways, collectively supporting gut–brain axis regulation and neurobehavioral health.

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pathways. Current evidence suggests that nanoencapsulation and targeted delivery systems may enhance probiotic persistence and thereby strengthen gut–brain-axis-related effects more effectively than unprotected formulations.[132,133]

Mood disorders like anxiety have strong associations with gut microbiota composition and gut–brain communication. Certain gut microbes can produce or influence the metabolism of neuroactive compounds. These include gamma-aminobutyric acid (GABA), serotonin, and dopamine, which are critical mediators of mood regulation. Bacterial species such as *Bifidobacterium* and *Lactobacillus* can modulate GABA and other neurotransmitters. These neurotransmitters influence the activity of inhibitory and excitatory neural circuits. These effects have been observed in both rodent and preliminary human studies. Nanobiotic approaches can enhance the survival and targeted release of probiotic strains capable of these functions. This increases the likelihood that sufficient numbers of viable microbes reach the lower gut. There, they produce neurotransmitter precursors and metabolites that interact with the gut–brain axis. In animal models, probiotics delivered with protective nanocarriers have demonstrated greater reductions in anxiety-like behaviors. They also show more pronounced modulation of stress markers compared with non-nano formulations. This may be due to improved microbial persistence, enhanced metabolic activity, and stronger interactions with neural and immune signaling pathways.[134,135]

Emerging evidence suggests that probiotic interventions can influence cognitive function and neuroinflammation, processes intimately linked to gut–brain axis signaling. Studies have shown that probiotics such as *Bifidobacterium longum* and other beneficial microbes may improve memory and learning outcomes in animal models. They do so by reducing systemic and neural inflammation, enhancing blood–brain barrier integrity, and modulating neurotrophic factor production. Nanobiotic delivery systems can improve the effectiveness of these interventions.[136,137] They achieve this by increasing probiotic survival through the GIT and promoting sustained interaction with the enteroendocrine and neural pathways that influence cognition. By enhancing probiotic viability and colonization, nanocarrier approaches amplify the probiotic's ability to influence gut-derived signals transmitted through the vagus nerve and systemic circulation. This may potentially lead to improved outcomes in models of cognitive impairment. Although clinical evidence remains limited and largely exploratory, these findings support the potential role of nanobiotic probiotics in managing neurological complications. These complications stem from gut–brain axis dysfunction.[6,138]

The link between gut microbiota and stress responses is partially mediated by interactions with the HPA axis, which governs the body's central stress response. Dysbiosis can lead to heightened HPA activation. This leads to increased release of stress hormones, such as cortisol, and to subsequent behavioral effects.

Direct preclinical evidence for stress reduction by nanocarrier-assisted probiotics is still emerging, but several studies support this concept. In a recent nanomaterial-assisted study, Eldeeb et al[139] engineered *E. coli* Nissle 1917 with Fe3_33O4_44 nanoparticles and a protective poly-norepinephrine coating to improve oral viability and enable alternating-magnetic-field-triggered GABA release. In a restraint-stress mouse model, oral administration of this engineered probiotic significantly reduced anxiety-like behavior, and the effect was associated with reduced neuronal activation in the nucleus of the solitary tract and locus coeruleus as well as modulation of gut microbial homeostasis, supporting a vagus nerve-dependent gut–brain mechanism. Conventional preclinical psychobiotic studies also provide mechanistic support for this broader concept.[140] For example, Gao et al[141] administered *Lactobacillus helveticus* WHH1889 to chronic unpredictable mild stress (CUMS) mice for five weeks and found improvement in depressive- and anxiety-like behaviors together with reduced serum corticosterone, restoration of hippocampal 5-HT/5-HTP levels, and partial normalization of gut microbiota composition. Similarly, Tian et al[142] showed that *Bifidobacterium breve* CCFM1025 reversed chronic stress-induced depressive and anxiety-like behaviors in mice, attenuated HPA-axis hyperactivity and inflammation, increased brain-derived neurotrophic factor expression, and restored stress-related gut microbial and metabolite abnormalities. Collectively, these findings suggest that nanocarrier-assisted probiotic strategies may reduce chronic stress-related behavioral and biochemical abnormalities, but they also highlight that direct evidence for nanoencapsulated psychobiotics remains more limited than for conventional probiotic stress models and requires further validation.[143]

By dampening HPA axis overactivity and decreasing inflammatory mediators, nanobiotic probiotics may contribute to more resilient stress responses. They may also help stabilize behavioral outcomes in experimental models.[144,145]

Immune Disorders & Autoimmunity

Modulating the immune system through probiotic interactions has important implications that extend beyond gastrointestinal disease. This includes allergic disorders, autoimmune conditions, and even the potential to act as vaccine adjuvants. Conventional probiotics influence systemic immunity by interacting with the GALT. They modulate cytokine profiles and balance T helper cell responses. However, their clinical effects in immune disorders have been variable, often due to limited survival and delivery challenges. Nanotechnology-based delivery systems can overcome these constraints. They protect probiotic cells throughout gastrointestinal transit and enhance their functional interactions with host immune cells. This may lead to better immune regulation, reduced inflammation, and improved therapeutic outcomes in immune-related conditions.[20,101]

In allergic conditions, the immune response is typically skewed toward a T-helper 2 (Th2)- dominant phenotype, with increased production of IgE and pro-inflammatory cytokines that drive hypersensitivity reactions. Conventional probiotics have been shown to help modulate immune responses by influencing T-helper 1 (Th1)/Th2 balance and enhancing mucosal tolerance. However, their effectiveness is often limited by poor survival in the gastrointestinal environment. Nanobiotic-enhanced delivery have shifted the immune balance toward a more regulatory phenotype.[146,147] This increases anti-inflammatory cytokine production while attenuating Th2-driven responses and IgE-mediated inflammation in allergic disorders. Although direct clinical evidence on nano-formulated probiotics in allergy is still emerging, mechanistic research suggests that enhancing probiotic viability and targeted release in the gut can strengthen mucosal immune regulation. It may also decrease allergic inflammation more effectively than unprotected probiotics. This points to potential benefits in conditions like allergic rhinitis, food allergies and atopic dermatitis.[148,149]

In autoimmune conditions, in which the immune system aberrantly attacks host tissues, modulating immune tolerance is a key therapeutic target. Studies on probiotics have shown that microbial modification of the gut microbiota can influence immune cell function. It can also increase regulatory T cell responses and reduce systemic inflammation in animal models of autoimmune disease. These include conditions like arthritis and lupus. This suggests a protective or modulatory role of probiotics in autoimmune pathology.[150] Nanobiotic formulations may amplify these immunomodulatory effects by ensuring that more live probiotic cells survive to interact with immune tissues. They also enhance the delivery of probiotics to immune regulatory sites. Preclinical evidence suggests that more consistent probiotic survival and colonization can support improvements in autoimmune markers and immune regulation. This has been observed in models of diseases such as rheumatoid arthritis and systemic lupus erythematosus. However, controlled clinical data remain limited.[10,60]

Beyond direct modulation of allergic and autoimmune responses, nanobiotic-enhanced probiotics are also being explored as oral vaccine adjuvants that can improve mucosal immune responses. The rationale is that probiotics, when co-administered with vaccine antigens and delivered via nanocarriers, may help stimulate both innate and adaptive immune pathways at mucosal sites. This could lead to stronger and more durable immune protection. While this area of research is still in its infancy, emerging studies indicate that co-delivery of probiotics with antigens using nanotechnology-based systems can enhance mucosal IgA production and T cell responses. This offers potential advantages for vaccines targeting respiratory, enteric, or systemic pathogens.[151,152]

Cancer Prevention & Supportive Care

Probiotics have been increasingly studied not only for general gut health but also for their potential anti-tumor properties and supportive roles in cancer prevention and care. Research on traditional probiotics suggests that their ability to modulate the enhance immune responses, gut microbiota, and produce metabolites with anticancer effects could help reduce cancer risk. It may also improve outcomes, particularly for cancers of the GIT such as colorectal cancer (CRC). Nanobiotic-enhanced probiotics, by improving survival through the digestive system, may enable targeted release in the colon. This could further amplify anticancer and supportive benefits compared with conventional probiotic formulations.[153]

CRC is the most studied cancer types in relation to probiotics, largely due to its strong links with gut dysbiosis, inflammation, and microbial metabolites. Traditional probiotics have been shown in in vitro and animal models to exert pro-apoptotic effects and antiproliferative on colon cancer cells. These effects are often mediated by mechanisms that

modulate gene expression and induce programmed cell death. Probiotic metabolites, such as SCFAs, especially butyrate, have been shown to act as histone deacetylase (HDAC) inhibitors. This leads to increased apoptosis and inhibition of tumor cell proliferation, a phenomenon known as the "butyrate paradox" in colon cancer biology.[154,155] Nanoformulations designed to enhance probiotic retention and viability in the colon have the potential to increase the local concentration of these beneficial microbes and their metabolites at sites of tumorigenesis, enhancing anti-inflammatory effects and reducing tumor development in preclinical CRC models. Strategies such as nanoencapsulation and mucoadhesive coatings are being explored to maximize the delivery of therapeutic probiotics to the colonic epithelium, a key site for early colorectal tumor formation. While direct clinical evidence for nanobiotic probiotics in human cancer prevention is limited, the mechanistic rationale and preclinical data support continued investigation into how enhanced probiotic delivery might reduce CRC risk through microbiota modulation, immune stimulation, and direct effects on epithelial cell signaling.[156,157]

Beyond cancer prevention, nanobiotic probiotics, have demonstrated potential in supporting patients undergoing chemotherapy by minimizing its side effects. Chemotherapy can cause intestinal mucositis, a painful inflammation of the gut mucosa that impairs nutrient absorption, leads to diarrhea, and often necessitates dose reductions or treatment interruptions. Traditional probiotic supplementation has been shown in animal studies to attenuate chemotherapy-induced intestinal mucositis.[158,159] This is likely due to inhibiting excessive apoptosis of intestinal epithelial cells, promoting cell proliferation, and preserving the gut barrier. Nanobiotic probiotics, thanks to improved delivery and survival enabled by nanoencapsulation, enhance these protective effects. Enhanced probiotics delivered via nanocarriers could reduce inflammation, support gut mucosal repair, and stabilize the microbiota during chemotherapy. This lower the severity of mucositis and improve treatment adherence and outcomes. Although human clinical trials specifically using nanobiotic formulations in this context are not yet available, the existing evidence supporting probiotic therapy for chemotherapy-induced mucosal injury provides a strong foundation. This foundation supports future research into nanotechnology-enhanced approaches in supportive cancer care.[53,128]

Pediatric and Geriatric Applications

Age-related differences in gut microbiota composition and host physiology make targeted probiotic interventions particularly relevant in both pediatric and elderly populations. In infants and children, the gut microbiome is still developing and is highly sensitive to disruption by infection, antibiotic exposure, and feeding practices, with potential short- and long-term consequences for immune and metabolic health. In contrast, older adults often exhibit reduced microbial diversity, diminished production of beneficial metabolites, and increased susceptibility to inflammation and infection.[160,161] These age-associated alterations highlight the need for delivery systems that can improve probiotic stability, retention, and functional activity in vulnerable populations. Nanobiotic platforms may help address these challenges more effectively than conventional formulations.[160,162]

In pediatric settings, probiotics have been investigated for prevention and management of infantile colic, diarrhea, and antibiotic-associated dysbiosis. Meta-analyses and clinical guidelines indicate that selected strains can reduce the incidence or severity of some of these conditions, although efficacy remains strain- and condition-dependent. For example, *Limosilactobacillus reuteri* has been reported to reduce crying time in infants with colic compared with placebo, supporting its relevance in early-life gut modulation.[163,164] Nanobiotic formulations may further improve pediatric probiotic performance by promoting more consistent delivery and intestinal activity, which could be particularly useful in immature or unstable microbial ecosystems. Although direct clinical evidence for nanobiotic probiotics in children remains limited, early preclinical findings suggest potential benefits in reducing dysbiosis-related gut symptoms more effectively than conventional formulations.[53,80]

Older adults represent another population in which microbiota-targeted interventions may be beneficial. Aging is associated with chronic low-grade inflammation, reduced immune responsiveness, and increased susceptibility to gastrointestinal disturbances such as diarrhea, constipation, and infection. Probiotic supplementation in older individuals has been associated with shifts toward more beneficial microbial profiles, reduced inflammation, and support of gut barrier function, although outcomes remain variable across strains and dosing strategies.[165] Nanobiotic-enhanced delivery may strengthen these effects by improving probiotic persistence and functional interaction with the aged intestinal environment.[166,167] This may help support nutrient utilization, reduce dysbiosis-related symptoms, and improve resilience against age-related

gastrointestinal dysfunction. However, direct clinical studies evaluating nanobiotic probiotics specifically in elderly populations remain scarce, and further translational work is needed to define their clinical utility (Table 2).[53]

Safety, Translational, and Regulatory Challenges

Although nanobiotic-enhanced probiotics hold considerable promise, the transition from concept to clinical application and commercialization is fraught with complex challenges. These stem from safety concerns related to nanomaterials, regulatory ambiguity, manufacturing and scalability limitations, and consumer perceptions. Addressing these issues is critical if nanobiotic technologies are to fulfill their potential as effective, safe, and socially acceptable therapeutics for gut health and systemic diseases.

The introduction of nanomaterials into food and therapeutic products raises valid safety concerns. These concerns must be rigorously evaluated, especially when live microorganisms are involved. Unlike traditional probiotic supplements, nanobiotic systems employ engineered nanoparticles to protect and deliver microbial cells. These materials can interact with biological tissues and the gut environment in unpredictable ways.[180] There is ongoing scientific debate about the potential toxicity of nanomaterials, including risks of oxidative stress, inflammation, and unintended immune activation. Some studies have shown that certain inorganic nanoparticles can penetrate epithelial barriers. They can accumulate in tissues or interfere with cellular signaling pathways. This raises concerns about long-term exposure within

Table 2 Mechanisms of Action in Nanobiotic Probiotic Therapy

Mechanism	Therapeutic Application	Key Benefits	References
Competitive Exclusion	IBD, IBS, Gut Infections	Nanobiotics block pathogen adhesion sites, reducing pathogen colonization and promoting the growth of beneficial microbiota.	[168]
Antimicrobial Peptide Production	Cancer, GIT Infections	Increased antimicrobial activity through probiotic production of bacteriocins inhibits pathogen growth in the gut.	[169]
Modulation of Pro-inflammatory Cytokines	Obesity, Metabolic Health	Reduced TNF-α, IL-6, and IL-1β levels, shifting immune response to a more regulatory phenotype.	[170]
Strengthening of Gut Barrier Function	Chemotherapy Support, IBD, IBS	Enhanced mucin secretion, tight junction integrity, and epithelial cell regeneration to restore barrier function.	[171]
SCFAs Production	Obesity, T2DM, IBD	Nanobiotic probiotics increase SCFAs production, which supports insulin sensitivity and gut health.	[172]
Regulation of Neurotransmitters	Mood Disorders, Cognitive Health	The production of neuroactive compounds such as GABA and serotonin influences mood regulation via the gut–brain axis.	[173]
Vagus Nerve Activation	Mood Disorders, Stress Management	Stimulation of vagus nerve signaling, influencing neuroimmune interactions and stress response.	[174]
Immune Modulation via T-cells and Regulatory Responses	Autoimmunity, Allergies	Promotion of regulatory T-cell (Treg) responses, reduction of Th2 dominance, and modulation of IgE response.	[175]
Mucosal Immune System Activation	Vaccines, Immune Health	Mucosal IgA production and increased immune responses at epithelial surfaces, supporting vaccine adjuvancy.	[176]
Gut–Liver Axis Modulation	NAFLD	Nanobiotics modulate gut-derived signals to reduce hepatic fat accumulation and improve liver function.	[177]
Oxidative Stress Reduction	Inflammatory Diseases, Aging	Reduced oxidative stress through ROS scavenging, improving immune responses, and reducing inflammation.	[178]
Tight Junction Preservation	IBD, IBS	Preservation of tight junction proteins and intestinal permeability prevents microbial translocation.	[179]

the gut or beyond. Many nanocarrier materials used in probiotic delivery, such as chitosan, alginate, or lipids, are considered biocompatible and generally recognized as safe (GRAS).[181] However, the impact of chronic exposure, potential effects on host microbiota ecology, and interactions with gut immunity warrant extensive in vivo and clinical evaluation. Long-term studies are largely lacking. The gut microbiome itself plays a central role in metabolic and immune homeostasis. Any perturbations caused by nanostructured materials must be understood before widespread clinical use. The complexity of the ecosystem and interindividual variability further complicate safety assessments, as responses to nanobiotic formulations may differ across age groups, genetics, and health statuses.[1,124]

Pharmacokinetics, Biodistribution, and Clearance of Nanobiotic Systems

An important translational consideration for nanobiotic systems is their pharmacokinetic behavior after oral administration, including intestinal uptake, systemic distribution, clearance, and excretion. For most gut-targeted nanobiotic formulations, therapeutic activity is intended to remain primarily local within the GIT, and systemic absorption may therefore be limited.[182] Nevertheless, a fraction of orally administered nanocarriers may cross the intestinal barrier and enter systemic circulation, where their biodistribution becomes relevant for both efficacy and safety. In such cases, hepatic uptake and renal handling are key determinants of nanocarrier fate, while fecal excretion remains an important route of elimination for non-absorbed material or carriers cleared through the hepatobiliary pathway.[183]

The in vivo fate of nanobiotic systems is strongly influenced by physicochemical characteristics such as particle size, surface charge, composition, degradability, and coating properties. Smaller or more degradable carriers may be cleared more readily through renal filtration, whereas larger or less degradable systems are more likely to undergo hepatic sequestration, prolonged tissue retention, or biliary excretion.[184] Circulation time may also vary depending on the extent of intestinal absorption and interactions with biological barriers or phagocytic clearance systems. However, direct pharmacokinetic data for probiotic-specific nanobiotic formulations remain limited, and most current understanding is extrapolated from broader oral nanoparticle studies rather than dedicated nanoprobiotic ADME investigations. This remains an important translational gap, because biodistribution, renal and hepatic clearance, and excretion profiles will ultimately influence biosafety evaluation, dose optimization, and clinical applicability.[53,128]

Nanobiotic probiotics challenge existing translational and regulatory pathways because they combine two layers of development complexity within a single platform: the biological complexity of live microorganisms and the physicochemical complexity of nanoscale carriers.[53] Recent peer-reviewed literature on microbiome therapeutics indicates that the field has begun to move beyond proof-of-concept, as illustrated by the approval of Rebyota in 2022 and VOWST in 2023 for recurrent *C. difficile* infection.[185] These real-world examples demonstrate that microbiota-based therapeutics can reach clinical practice when product composition, manufacturing controls, safety evaluation, and efficacy are sufficiently standardized. At the same time, published reviews emphasize that such products require substantially greater control than conventional probiotics, including compositional standardization, current good manufacturing practice, and structured clinical safety assessment.[8] For nanobiotic probiotics, the translational burden is likely to be even greater, because developers must demonstrate not only strain identity, potency, viability, and microbial consistency, but also reproducible nanocarrier properties such as particle size distribution, surface chemistry, encapsulation efficiency, coating stability, and batch-to-batch uniformity. Recent analyses further highlight that the lack of harmonized analytical methods for live biotherapeutic products, together with unresolved standards for potency testing and complex microbial characterization, remains a major obstacle to regulatory maturation.[53,58]

Recently published studies further shows that the regulatory framework remains fragmented and strongly dependent on intended use. If a microbiome-based product is marketed for general digestive or nutritional support, it may fall under food or supplement regulation, whereas products intended to prevent, treat, or mitigate disease are more likely to enter biologic or medicinal-product pathways.[186,187] European reviews specifically note that microbiome-based therapies may fall under multiple legislative categories, creating uncertainty in how safety, efficacy, and quality should be evaluated across products with overlapping microbiological and therapeutic functions. Parallel reviews of nanotechnology-enabled health products indicate that nano-enabled formulations face additional regulatory ambiguity because nanotechnology-specific requirements are still distributed across broader pharmaceutical, food, and device frameworks rather than governed by a single dedicated pathway.[146] In practical terms, this means that future nanobiotic probiotics will likely require early regulatory agreement on product classification, validated methods for both microbial and nanomaterial characterization, GMP-compatible scale-up

strategies, and long-term surveillance for unintended microbiome perturbation, host immune effects, and chronic exposure to carrier materials. These issues indicate that translational success in this field depends not only on therapeutic efficacy, but also on whether nanobiotic systems can be manufactured reproducibly and evaluated within a regulatory pathway capable of addressing both live biological agents and engineered nanoscale materials.[53,188]

Even if safety and regulatory challenges are addressed, consumer acceptance of nanobiotic-enhanced probiotics may pose a barrier to adoption. The use of nano-engineered materials in products intended for ingestion, particularly those containing live microorganisms, may raise public concerns. These concerns are influenced by perceptions of "unnatural" technology and uncertainty about long-term safety. Surveys of consumer attitudes toward nanotechnology in food and medicine reveal mixed responses, with acceptance often hinging on perceived benefits versus risks, trust in regulatory oversight, and understanding of the underlying science.[53,189] Clear communication is therefore essential, including transparent labeling, education on the mechanisms and benefits, and informed consent in clinical contexts where nanobiotic probiotics are used therapeutically. Misinformation or lack of public understanding could undermine confidence and slow the translation of nanobiotic innovations into widespread clinical and consumer use.[190]

Comparative Analysis of Recent Findings

As research into nanobiotic-enhanced probiotics expands, an emerging body of literature has begun to quantitatively and qualitatively compare traditional probiotic systems with nano-enhanced delivery platforms. This comparative analysis highlights clear trends in improved efficacy and survivability in preclinical and in vitro models. It summarizes what meta-analyses suggest about overall effects. The analysis also identifies key gaps and contradictions that must be addressed before widespread clinical translation can occur.

Trends in Efficacy

Recent comparative studies establish a definitive efficacy paradigm shift. These studies demonstrate that nano-enhanced probiotic systems substantially outperform traditional free-cell formulations. This is observed across three critical metrics: targeted delivery, gastrointestinal survivability, and downstream in vivo health effects.[191]

Superior Survivability Under Physiological Stress

The primary limitation of conventional probiotic administration is the rapid loss of bacterial viability when exposed to the hostile conditions of the upper gastrointestinal GIT. Recent in vitro simulated digestion models have quantified this discrepancy. A study evaluating the electrospun nanoencapsulation of *Lactobacillus* and *Bifidobacterium* strains within biopolymer matrices demonstrated that free probiotic cells suffered a severe 10-log (CFU/mL) reduction within 120 minutes of exposure to simulated gastric and intestinal fluids. In stark contrast, the nano-encapsulated counterparts exhibited only a 3-log reduction, preserving 81–100% of the initial bacterial population.[57] Similarly, encapsulation utilizing solid lipid nanoparticles (SLNs) has been shown to maintain viability above the therapeutic threshold of 8.0 log CFU/g. This is achieved under severe acidic stress (pH 2.0) and bile salt exposure. In contrast, free cells routinely plummet below 3.5 log CFU/mL.[192] Furthermore, nanoencapsulation provides significant thermal stability, shielding probiotics from heat stress generated during industrial processing and extended shelf-storage, a feat unattainable by free cells.[13]

Enhanced Delivery and Colonization

Beyond passive protection, nanobiotics exhibit superior delivery and colonization capabilities. The physicochemical properties of nanomaterials, specifically their size, high surface-area-to-volume ratio, and tunable zeta potential, enable deep penetration into the intestinal mucosal layer. These properties enhance their ability to interact with and deliver therapeutic agents effectively.[86] Chitosan-based and water chestnut starch-based nanocapsules possess inherent mucoadhesive properties that significantly slow intestinal transit times.[13] This prolonged retention facilitates a controlled, sustained release of viable bacteria directly at the colonic epithelium. It dramatically increases the successful colonization rates compared to free probiotics. Free probiotics are rapidly flushed through the GIT.[53]

Augmented in vivo Health Effects

The physical superiority of nanobiotic delivery directly translates into enhanced therapeutic outcomes in vivo. Comparative animal models indicate that nano-enhanced probiotics exert more profound immunomodulatory and metabolic effects than equal doses of free bacteria.[41] Nano-encapsulated multi-strain probiotics have been linked to significantly accelerated restoration of intestinal villi morphology and enhanced nutrient absorption in dysbiotic models. Furthermore, nanobiotics drive a more robust local immune response. They upregulate the expression of critical cytokines. Nanobiotics also enhance epithelial barrier integrity by increasing tight junction protein expression. This is more effective than unencapsulated controls.[193] Consequently, nanobiotics are currently demonstrating elevated clinical potential for modulating complex conditions. These conditions include IBD, CRC, and systemic metabolic syndromes like obesity and diabetes. Nanobiotics achieve this by successfully shifting the host microbiome toward an eubiotic state.[41]

Comparative Performance of Major Nanocarrier Classes

Although nanocarrier-mediated delivery consistently improves probiotic performance relative to free cells, the magnitude and mechanism of benefit differ across carrier classes. A recent meta-analysis confirmed an overall survival advantage for nanoparticle-encapsulated probiotics under simulated gastrointestinal conditions, with odds ratios of 2.79 at 0 min and 2.41 at 120 min relative to free cells.[194] Polymeric systems, particularly chitosan–alginate-based carriers, currently show the most consistent evidence for acid and bile protection; for example, chitosan–alginate nanoparticles limited simulated gastric losses of *Bacillus coagulans* and *Enterococcus faecium* to 0.86 and 0.27 log CFU, respectively, with similarly low losses in simulated intestinal fluid.[195] Core–shell platforms appear especially advantageous when colon-targeted retention is prioritized. In vivo, polysaccharide-based core–shell formulations prolonged intestinal persistence and yielded higher cecal counts than free probiotics, indicating improved colonization-related performance. By contrast, liposomes offer excellent biocompatibility and high encapsulation efficiency, but their physicochemical instability remains a relevant limitation for long-term storage and translational robustness.[196] Emerging platforms such as milk-exosome-based coatings and MOF-based shells are promising but remain less validated: exosome-based systems have shown simulated gastrointestinal survival rates of 80.99–94.53% together with improved adhesion-related behavior, whereas MOF-based carriers have mainly demonstrated enhanced protection against saline, lysozyme, and pepsin stress, with limited colonization data to date.[72] Taken together, current evidence suggests that polymeric and core–shell systems are presently the most mature platforms for combining gastrointestinal protection with colon-directed retention, whereas exosome- and MOF-based systems remain promising but early-stage alternatives.

To facilitate a clearer cross-platform comparison, Table 3 summarizes the major nanocarrier classes currently used for probiotic delivery with emphasis on gastrointestinal survival, colonization- or retention-related performance, principal advantages, and current limitations. This structured comparison helps distinguish carrier systems supported by relatively mature evidence from those that remain promising but are still in an early preclinical stage.

Meta-Analysis and Effect Size

Quantitative evaluations through recent systematic reviews and meta-analyses provide robust statistical validation for the improved performance of probiotics when delivered via nanocarriers.[194] A landmark meta-analysis assessing the biological effects of nanocarrier-mediated probiotic delivery utilized random-effects models to aggregate survival data across various simulated gastrointestinal conditions. The study reported a highly favorable, statistically significant effect size for encapsulation. Specifically, upon initial exposure to simulated gastric stress (0 min), nano-encapsulated probiotics demonstrated an Odds Ratio (OR) of 2.79 (95% CI: 2.79–2.80) for survival compared to free-state counterparts. This protective advantage remained significant throughout the digestion timeline, maintaining an OR of 2.41 at 120 minutes of exposure to harsh simulated intestinal fluids.[194]

Similarly, comprehensive meta-analytical reviews focus on specific microbial strains, such as *Lactobacillus* species and yeast-based probiotics. These reviews confirm that micro- and nano-encapsulation techniques consistently yield a 1–2 log CFU/g increase in survival rate. This is compared to unencapsulated controls post-gastrointestinal transit.[205] These statistical models provide definitive proof that the physical shielding of nanocarriers directly translates to higher viable cell delivery to the colon.

Table 3 Comparative Evaluation of Representative Nanocarrier Classes for Probiotic Delivery

Nanocarrier Class	Representative System	Survival Assessment	Colonization/Retention-related Assessment	Editorial Interpretation	References
Polymeric nanoparticles	Chitosan–alginate nanoparticles encapsulating *Bacillus coagulans* and *Enterococcus faecium.*	After 120 min of simulated gastric exposure, viable counts decreased by only 0.86 log CFU for *B. coagulans* and 0.27 log CFU for *E. faecium*; in simulated intestinal fluid, reductions were 1.03 and 0.17 log CFU, respectively.	Direct colonization efficiency was not measured in this study.	Best-supported class for gastrointestinal protection and viability preservation.	[37,197,198]
Liposome-based /hybrid lipid nanocarriers	Layer-by-layer coated probiotics with chitosan and liposomes.	The coated probiotics showed improved survival in simulated gastrointestinal conditions and better protection against hostile gut factors than free cells.	The formulation showed enhanced adhesion to colonic mucus; coating shedding in the colon coincided with probiotic proliferation, and in vivo efficacy improved in DSS colitis mice.	Strong option when mucosal adhesion and multifunctional delivery are desired, but more formulation complexity than polymer-only systems.	[199,200]
Core–shell systems	Shell–core microbeads and coaxial starch/alginate–pectin core–shell system	In shell–core microbeads, probiotic reduction during simulated digestion was <1.5 log CFU/g; in the coaxial core–shell system, 83.1% of encapsulated bacteria remained viable after 2 h in simulated gastric fluid versus 0% survival for free cells.	These systems are designed for colon-targeted release; however, direct colonization efficiency is still rarely quantified.	Strong for protected transit + site-specific release, but you should describe this as retention/targeted delivery, not overclaim exact colonization efficiency.	[201,202]
Exosome-based carriers	Milk exosome-based coating system	Reported encapsulation efficiencies of 70.93–90.37% and simulated gastrointestinal survival rates of 80.99–94.53%.	The system also improved self-aggregation and adhesion-related behavior, supporting better intestinal interaction potential.	Highly promising biomimetic platform, but still early-stage.	[72,203]
MOF-based carriers	Iron(III) fumarate MOF matrix encapsulating *Lactiplantibacillus plantarum* 299v	Encapsulated cells showed improved stability in saline, lysozyme, and pepsin compared with uncoated cells.	Direct colonization or long-term gut retention data were not established.	Interesting emerging class with protective and controlled-release potential, but biologically the least validated of the platforms listed here.	[74,204]

Limitations and the Lack of Standardized Outcomes

Despite these promising statistical confirmations, meta-analyses simultaneously expose a critical vulnerability in current research: the severe limitation of standardized outcomes.[206] High degrees of statistical heterogeneity ($I^2 > 75\%$) are frequently observed across aggregated studies. The extreme diversity in experimental designs primarily drives this variance.[41] Researchers utilize vastly different encapsulating materials. These include solid lipid nanoparticles versus ternary biopolymer hydrogels like alginate-chitosan. They also use distinct encapsulation methods, such as electrospraying vs. emulsion. Additionally, researchers work with variable baseline probiotic strains that have inherent differences in acid/bile tolerance.[207,208]

Furthermore, the lack of universally adopted in vitro digestion protocols means that primary studies often evaluate varying concentrations of bile salts, enzymes, and pH levels.[41] This methodological inconsistency makes it exceedingly difficult to perform direct comparisons of effect sizes across different nano-formulations. Consequently, while meta-analyses unequivocally confirm that nanocarriers improve probiotic efficacy, the field requires urgent methodological standardization. This is necessary to translate these heterogeneous effect sizes into universally accepted clinical dosing guidelines.[206]

Gaps and Contradictions

Despite the profound efficacy demonstrated in controlled laboratory environments, the progression of nanobiotic formulations from bench to bedside is currently hindered by significant translational gaps. There are also contradictory findings within the recent literature.[54]

The Preclinical vs. Clinical Translational Discrepancy

The most glaring contradiction exists between the overwhelming success of nanobiotics in preclinical animal models and the stark lack of predictive consistency in human clinical trials.[53] In murine and poultry models, orally administered nano-encapsulated probiotics consistently demonstrate near-perfect colonic targeting. They also show massive reductions in pathogen shedding and precise modulation of inflammatory markers.[209,210] However, extrapolating these localized effects to human subjects is fraught with physiological hurdles.

The human GIT presents a vastly different anatomical landscape compared to laboratory animals. Crucial differences in gastric emptying rates and localized pH fluctuations create variability. Human fasting stomach pH can drop to 1.5, whereas murine stomachs often maintain a less severe pH of 3.0–4.0. Additionally, the basal composition of the indigenous gut microbiome contributes to this variability. These factors create immense variability in the degradation kinetics of nanocarriers.[211] Consequently, the sustained-release profiles meticulously optimized in silico or in murine models often result in premature probiotic release. Alternatively, they may cause incomplete matrix degradation when introduced to the human GIT.[53] As highlighted in recent critical reviews, this discrepancy leads to unpredictable colonization rates and suboptimal therapeutic outcomes in human subjects, directly contradicting the uniform 8 to 9 log CFU/g survival rates observed in preclinical data.[53,54]

Contradictions in Nanomaterial Biocompatibility and Toxicity

A secondary, heavily debated contradiction concerns the long-term safety profile of the nanomaterials used for encapsulation.[212] Current in vitro assays predominantly promote biopolymers (eg, low-molecular-weight chitosan, sodium alginate) and advanced synthetic hydrogels as highly biocompatible.[191] However, longitudinal in vivo data present a more complicated and sometimes contradictory narrative.

While short-term studies report no acute toxicity, emerging pharmacokinetic research indicates that chronic administration of certain nanoscale vehicles may lead to unintended bioaccumulation within the intestinal crypts or the reticuloendothelial system (RES).[213] Furthermore, an inherent therapeutic paradox exists. While the primary goal of the nanocarrier is to deliver probiotics to restore eubiosis, some studies suggest that prolonged accumulation of specific degradation products may inadvertently cause problems. This is particularly true for synthetic polymers. These degradation products might alter the mucus layer's viscosity, disrupt native commensal populations, or induce low-grade localized inflammatory responses.[86] This contradiction, where the delivery vehicle potentially antagonizes the immunomodulatory aim of the probiotic, remains largely unresolved. It is primarily due to a severe lack of standardized, multi-year human toxicological evaluations.[212]

Manufacturing Scalability and Process-Induced Viability Gaps

Finally, there is a pronounced operational gap between laboratory-scale encapsulation efficiency and industrial scalability. Literature frequently reports exceptional encapsulation efficiencies exceeding 95% utilizing precise, low-stress methodologies such as layer-by-layer single-cell nanocoating, electrospinning, or microfluidics.[57,191] However, transitioning these delicate procedures to commercial production exposes the fragile bacterial payload to severe mechanical shear stress. It also subjects the payload to extreme pressures and unfavorable thermal conditions during processes like high-shear extrusion or industrial lyophilization.[206]

The literature reveals a harsh operational contradiction. Nano-formulations that achieve near-perfect viability in benchtop simulated digestion protocols often suffer massive, multi-log viability losses. These losses occur during actual industrial processing and during extended shelf storage.[191,206] Additionally, critical gaps exist regarding multi-strain encapsulations. Industrial matrices often inadvertently favor the survival and release kinetics of one specific strain over another. For example, *Lactobacillus* survives industrial heat better than *Bifidobacterium*. This fundamentally alters the intended symbiotic ratio before the product even reaches the consumer's colon.[206] Overcoming these process-induced damages without compromising the structural integrity of the "nano-armor" represents a critical, yet unmet, milestone for the clinical viability of nanobiotic therapeutics (Table 4).[54,206]

Table 4 Comparative Analysis of Traditional vs. Nano-Enhanced Probiotic Systems

Analytical Domain	Traditional Probiotics	Nano-Enhanced Probiotics (Nanobiotics)	Key Statistical & Literature Findings	Identified Gaps, Contradictions & Limitations
GI Survivability (Acid & Bile Stress)	Rapid degradation under gastric acid (pH ~1.5–3.5) and bile salts	High structural integrity; physical shielding of the bacterial core via polymers/lipids	Free cells drop to <3.5 log CFU/mL; Nanobiotics maintain >8.0 log CFU/g viability	Survivability varies drastically based on the specific encapsulating material (eg, solid lipid nanoparticles vs. hydrogels)
Release Kinetics & Targeting	Uncontrolled, immediate burst release in the upper GIT	Stimuli-responsive (pH, redox, or enzyme-triggered) delayed release	Nanocarriers prevent release until colon pH (7.0–8.0) or specific bacterial enzymes degrade the matrix	Human GIT pH fluctuates wildly depending on diet and fasting state, causing premature or incomplete release in vivo
Colonization & Mucoadhesion	Rapid GI transit time; poor adhesion to the colonic epithelium	Nanomaterials (eg, chitosan) exhibit high mucoadhesion and tissue penetration	Prolonged mucosal retention allows higher localized CFU counts and deep crypt colonization	Over-adhesion of certain synthetic polymers may artificially increase local mucus viscosity, altering natural peristalsis
Thermal Tolerance & Shelf-Life	Highly sensitive to heat; heavily reliant on cold-chain logistics	"Nano-armor" insulates against thermal shock during processing and storage	Ternary hydrogels preserve 6.58 log CFU/mL even after exposure to 70 °C, increasing room-temperature shelf life	Matrix hydration over long-term storage can eventually lead to premature swelling and loss of payload viability
Physiological & Immunomodulatory Effects	Generalized gut health support; requires high continuous dosing	Targeted localized effects; precise modulation of inflammatory cytokines	Nanobiotics significantly upregulate mucosal healing markers faster than free cell equivalents	Unclear if the immunomodulatory effects are purely from the probiotic, or if the nanocarrier degradation products are actively altering immune signaling
Multi-Strain Co-Delivery (Symbiotic Ratio)	Strains with lower acid tolerance die off, altering the ingested ratio	Co-encapsulation ensures multiple strains arrive at the target site simultaneously	Encapsulation preserves strict synergistic ratios (eg, 1:1 *Lactobacillus* to *Bifidobacterium*) through the upper GIT	Different strains possess varying sizes and surface charges, making uniform encapsulation of diverse multi-strain consortia highly difficult
Meta-Analytical Effect Sizes	Serves as the baseline control (OR = 1.0)	Demonstrates highly favorable standard mean differences and OR	Meta-analyses report an OR of ~2.79 favoring nanocarriers for survival under initial gastric stress	Exceptionally high statistical heterogeneity (I^2 > 75%) plagues meta-analyses due to a severe lack of standardized in vitro digestion protocols

(*Continued*)

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Table 4 (Continued).

Analytical Domain	Traditional Probiotics	Nano-Enhanced Probiotics (Nanobiotics)	Key Statistical & Literature Findings	Identified Gaps, Contradictions & Limitations
Clinical Translation (Animal vs. Human)	Established historical baseline in human clinical trials	Near-perfect targeting and disease mitigation in murine and poultry in vivo models	Preclinical models show 8–9 log CFU/g colonic delivery and massive pathogen shedding reduction	Major gap: Profound anatomical differences (transit times, basal microbiome) between mice and humans result in unpredictable clinical outcomes
Material Biocompatibility & Toxicity	GRAS status established	Short-term assays (<30 days) show high biocompatibility for natural polymers.	Chronic in vivo models report no acute hepatic or renal toxicity from the degradation of the natural biopolymer.	Major contradiction: Long-term chronic exposure to certain synthetic nanoparticles may cause localized crypt inflammation or RES bioaccumulation
Manufacturing Scalability & Cost	Easily manufactured via standard, low-cost industrial lyophilization	Achieves >95% encapsulation efficiency using low-stress benchtop methods	Microfluidics and electrospinning yield perfect lab-scale nanobiotics	Major gap: High-shear industrial extrusion and thermal stress during commercial scale-up cause severe structural damage to the nanocarrier
Regulatory Landscape	Regulated loosely as dietary supplements or functional foods	Straddles the line between dietary supplement, biomaterial, and targeted drug	Requires rigorous pharmacokinetic and toxicological profiling to satisfy FDA nanomedicine guidelines	Lack of specific regulatory frameworks for "living nano-therapeutics" severely delays commercialization and inflates R&D costs

Future Directions and Research Needs

As nanobiotic probiotics transition from concept to clinical relevance, research is rapidly evolving toward smarter, more personalized, and clinically translatable systems. While early results demonstrate enhanced viability and targeted delivery, the next decade of innovation must focus on advanced nanocarrier designs, integration with individualized microbiome insights, and robust human clinical validation.[10] Addressing these areas will be key to unlocking the full therapeutic potential of nanobiotic probiotics in medicine.

Emerging Nanocarrier Technologies

Next-generation nanocarrier platforms are advancing beyond basic protective encapsulation toward "smart" and stimuli-responsive systems that can dynamically interact with specific physiological cues in the GIT. These smart carriers are engineered to respond to changes in pH, enzymatic activity, redox conditions, or inflammatory markers, enabling on-demand release of probiotic cells when and where they are most needed.[214,215] The platforms are being developed that release their cargo only upon encountering the alkaline environment of the distal intestine or specific enzymatic triggers. These platforms aim to maximize probiotic efficacy at target sites while reducing unnecessary activation upstream. Other sophisticated triggers, explored in drug delivery research, could theoretically be adapted for probiotic release. These include ultrasound-responsive hydrogels or electro-responsive polymer systems. This approach could achieve spatial and temporal precision in complex disease settings.[216]

Hybrid platforms that integrate functional nanocarriers with bioactive scaffolds or sensing elements offer additional opportunities to condition probiotic release based on real-time gut conditions. These multifunctional designs could detect inflammatory biomarkers and precisely secrete probiotics in response, thereby improving relevance for chronic inflammatory diseases such as IBD.[217] Continued research into precision targeting strategies is important. This includes nanocarriers that can sense and react to local microenvironments. Such research represents a frontier in nanobiotic delivery. It should be prioritized in the coming years.[54,194]

Personalized Probiotic Therapy

One of the most promising directions for nanobiotic probiotics is personalized therapy, in which formulations are tailored to an individual's unique gut microbiome profile, genetics, and disease context. The gut microbiota differs significantly across individuals, influenced by diet, genetics, age, environment, and health status, and emerging research in precision microbiome interventions highlights the need to move beyond "one-size-fits-all" approaches.[8,218] Integrating microbiome profiling technologies (such as metagenomic sequencing and metabolomic analyses) with nanobiotic design could enable formulations that are optimized for specific microbial compositions or functional deficiencies in a given patient. Like, if a person's microbiome shows depletion of specific beneficial taxa, nanobiotic probiotics could be engineered to release strains or prebiotic co-factors. These strains or cofactors would most likely restore the ability to produce key metabolites, such as SCFAs.[219] Realizing truly personalized probiotic therapy also requires development of diagnostics and biomarkers that reliably predict response to specific probiotic interventions and can be tracked longitudinally. Coupling these diagnostics with customizable nanocarrier platforms could allow clinicians to deliver strain-specific, dose-optimized probiotic treatments. These treatments would adapt to changes in an individual's gut ecosystem. This approach moves nanobiotic probiotics closer to the goals of precision medicine.[220]

Clinical Translation

Despite compelling preclinical results, there remains a critical need for well-designed human clinical trials to validate the safety, efficacy, and long-term benefits of nanobiotic probiotics. Much of the current evidence comes from in vitro studies and animal models, which, although informative, cannot fully capture the complexity of human physiology.[41] They also fail to account for microbiome variability and disease progression. Meta-analyses of nanoparticle-encapsulated probiotics demonstrate improved viability under controlled conditions, but standardized clinical outcomes for human health benefits remain limited.[60,194] Future clinical research should prioritize randomized, controlled trials across diverse patient populations and disease states. These trials should assess not only surrogate outcomes, such as probiotic survival and colonization, but also patient-relevant endpoints.[221] These endpoints include symptom improvement, quality of life, inflammatory biomarkers, and disease progression. Trials should also evaluate long-term safety, including effects of repeated or chronic exposure to nanocarriers, interactions with the host microbiota, and potential off-target effects.[222]

Conclusion

Nanobiotic approaches represent a transformative strategy for enhancing the therapeutic efficacy of probiotics. By leveraging nanotechnology, these systems address longstanding limitations of traditional probiotics, such as poor survival rates, limited colonization, and inconsistent therapeutic outcomes. Nanoencapsulation protects probiotic cells from harsh gastrointestinal conditions, improving their viability and ensuring targeted delivery to specific gut regions, particularly those with the highest levels of inflammation or infection. This enhanced delivery allows probiotics to exert more powerful effects, not only on gut health but also on systemic conditions related to the gut–brain axis, immune modulation, and metabolic health. Nanobiotic probiotics show significant promise in treating gastrointestinal disorders such as IBD, IBS, and CRC, as well as supporting patients undergoing chemotherapy.

Furthermore, immune disorders and metabolic diseases, including obesity, diabetes, and NAFLD, stand to benefit from the advanced delivery capabilities and precision targeting offered by these technologies. By enhancing microbial survival and functional performance, nanobiotics may reshape the therapeutic landscape for these complex diseases, offering more effective, sustainable interventions compared to conventional probiotics. Despite these advancements, continued research is essential to optimize nanocarrier designs, improve scalability, and assess long-term safety. Clinical trials are particularly important to translate the promising preclinical results into real-world therapies, ensuring that these innovative delivery systems are both safe and effective across diverse populations. Regulatory frameworks need to evolve alongside these advancements to provide clear guidelines for clinical application, enabling nanobiotics to fulfill their potential in personalized medicine. In conclusion, nanobiotics offer an exciting future for probiotic therapy, but achieving their full potential requires collaboration between researchers, clinicians, and regulators, along with a commitment to rigorous clinical testing to ensure these therapies can be safely and effectively integrated into mainstream healthcare.

Data Sharing Statement

All data related to the manuscript is available in the manuscript.

Bioethics Approval and Consent

This is a review article so, no approval and consent required.

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Disclosure

The author declares no conflict of interest.

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