DOI: 10.26599/FSHW.2026.9250967

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Advances in Probiotics Anti-Inflammatory: Mechanisms, Therapeutic Strategies, Industrial Applications and Challenges

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ABSTRACT: Probiotic-derived immunomodulation represents a paradigm shift in managing inflammatory disorders, offering unprecedented opportunities to restore immune homeostasis and combat inflammation-driven pathologies. Despite their therapeutic promise, the clinical translation of probiotics has been hindered by an incomplete mechanistic understanding of their pleiotropic effects. This review systematically delineates the multifaceted anti-inflammatory mechanisms of probiotics, encompassing the reconstruction of gut microbial ecosystems, modulation of immune regulatory circuits, mitigation of oxidative stress, and disruption of pro-inflammatory signaling pathways. Translational advances encompassing gnotobiotic models, randomized controlled trials, and bioengineered probiotics harboring enhanced therapeutic payloads are rigorously evaluated in this review. A systematic examination of industrial applications in nutraceuticals, pharmaceuticals, and functional foods is presented, alongside a critical discussion of persistent translational bottlenecks. Looking forward, we emphasize multi-omics-guided strain discovery, synthetic biology-based engineering of intelligent microbial therapeutics, and optimized translational frameworks to unlock the full potential of microbiota-targeted immunomodulation in precision medicine.

Keywords: Probiotics; Anti-inflammatory mechanisms; Microbiota-based therapeutics; Industrial applications and challenges; Future perspectives

1. Introduction

Inflammation is a fundamental physiological defense mechanism that enables the host to respond to harmful external stimuli. By orchestrating immune responses and promoting tissue repair, inflammation plays a critical role in maintaining internal homeostasis. Accumulating evidence indicates that inflammation is characterized by a cascade of pro-inflammatory cytokine release (e.g., tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6)), the recruitment of immune cells such as neutrophils and macrophages to the site of injury, and alterations in vascular endothelial barrier integrity. [1-2]. However, dysregulated or chronic activation of inflammatory responses can disrupt immune homeostasis and aberrantly activate cell-damaging signaling pathways, leading to tissue damage and organ dysfunction. This pathophysiological shift contributes to the development of various chronic systemic diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis, and atherosclerosis, and is

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Received 19 May 2025
Received in revised from 15 September 2025
Accepted 22 October 2025

increasingly associated with the initiation and progression of multiple malignancies [3-4]. Given its pivotal role in both health and disease, understanding the mechanisms that govern inflammatory processes is essential for developing novel therapeutic strategies that modulate immune responses across a range of clinically significant conditions.

Current clinical strategies for inflammation management primarily rely on three categories of pharmacological agents: (i) nonsteroidal anti-inflammatory drugs [5]; (ii) glucocorticoids [6]; and (iii) biological agents, such as TNF-α inhibitors [7]. While these therapies are effective, they often exhibit limitations such as adverse side effects, long-term toxicity, and immunosuppression. In contrast, probiotic anti-inflammatory (PA) based interventions have garnered growing attention due to their multifaceted mechanisms and favorable safety profiles. Specific probiotic strains have been shown to exert anti-inflammatory effects through multiple pathways, including modulation of gut microbiota composition, enhancement of short-chain fatty acids (SCFAs) production, and regulation of immune signaling pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome [8-9]. Moreover, probiotics are generally well-tolerated and are considered to rarely induce severe adverse reactions in the general population; however, rare cases of bacteremia or fungemia have been reported in immunocompromised individuals. This overall favorable safety profile supports their potential use in the prevention and adjunctive treatment of inflammatory disorders.

As a class of live microorganisms that confer health benefits to the host, probiotics offer unique advantages in the management of inflammation-related diseases. Their therapeutic potential lies primarily in three aspects: (i) multi-target modulation of host immune responses [10-11]; (ii) the ability to maintain or restore gut microbial homeostasis [12-13]; and (iii) a well-established safety profile [14]. These attributes make probiotics a promising strategy for managing inflammation-related diseases and provide valuable insights for developing next-generation anti-inflammatory therapies.

Given these advantageous properties, there has been growing scientific interest in elucidating the mechanisms by which probiotics modulate inflammatory responses. In recent years, there has been increasing scientific interest in elucidating the mechanisms by which probiotics modulate inflammatory responses. Although numerous studies have explored this topic, a comprehensive and systematic review of the anti-inflammatory effects of probiotics remains lacking. This review aims to fill this gap by examining the molecular mechanisms through which probiotics regulate inflammation, summarizing recent advances *in vitro* and *in vivo* studies, highlighting the integration of synthetic biology approaches, evaluating their potential applications in food and pharmaceutical contexts, and discussing current challenges and future research directions. Collectively, this work provides a theoretical framework and translational insights for the development of probiotic-based strategies to prevent and treat inflammatory diseases.

2. Mechanisms and Regulation of Inflammation

Inflammation is increasingly recognized not merely as a host defense mechanism but as a dynamic and context-dependent process intricately involved in tissue homeostasis, repair, and pathology. Upon pathogenic invasion or sterile injury, the host mounts a well-orchestrated inflammatory response aimed at eliminating the trigger and initiating tissue regeneration [15]. As shown in Fig. 1A, tightly regulated inflammation confers protection against microbial threats and facilitates wound healing. Conversely, its dysregulation underlies a wide array of diseases, including autoimmune disorders (e.g., rheumatoid arthritis), metabolic syndromes, atherosclerosis, and systemic complications such as sepsis and multiple organ dysfunction. Chronic, unresolved inflammation can further promote apoptotic and fibrotic processes and even foster a tumor-permissive microenvironment [16].

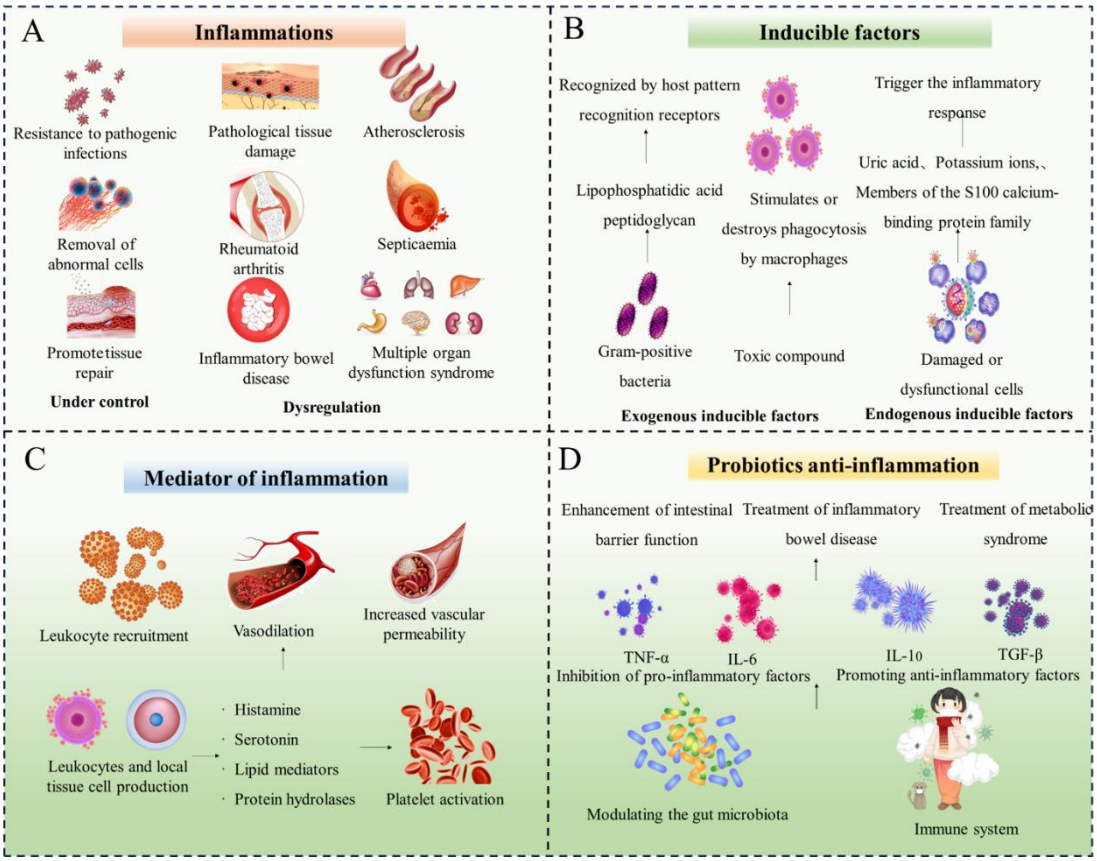

Fig. 1 Mechanisms and Regulation of Inflammation: Pros and cons of inflammation (A); Sources and nature of inflammation (B); Inflammatory mediators (C); Advantages of probiotics (D).

At the molecular level, inflammation is orchestrated through a cascade of organized signaling modules comprising inducers, receptors, mediators, and effectors. As illustrated in Fig. 1B, inducers are broadly categorized as exogenous (e.g., microbial Pathogen-associated Molecular Patterns (PAMPs) like lipoteichoic acid) or endogenous (e.g., DAMPs such as uric acid and S100 proteins), depending on their origin [17]. These signals are sensed by pattern recognition receptors, including Toll-like receptors (TLRs) and inflammasome components such as NLRP3, which initiate downstream signaling cascades [18-19]. Despite advances, the sensing pathways for certain inducers, particularly non-microbial allergens and xenobiotics, remain incompletely elucidated. Following signal initiation, a diverse repertoire of inflammatory mediators is secreted, mainly by innate immune cells and tissue-resident effectors [20]. As shown in Fig. 1C, these include

classical mediators (e.g., histamine, lipid-derived prostaglandins) and proteolytic enzymes that modulate vasodilation, vascular permeability, and leukocyte trafficking [21-22]. Beyond their immediate effects, these mediators also shape the resolution or progression of inflammation through crosstalk with metabolic, epigenetic, and neuroimmune pathways [21].

The molecular mechanisms described above collectively determine the phenotypic manifestation and clinical outcome of inflammatory responses, which are broadly classified as acute or chronic based on their duration and resolution profile. Inflammatory responses are generally classified as acute or chronic, depending on their kinetics and resolution dynamics [3]. Acute inflammation is typically rapid, transient, and self-limiting, whereas chronic inflammation arises from unresolved acute responses or sustained noninfectious stimuli [23]. In particular, metabolic inflammation—characterized by pro-inflammatory cytokine secretion from adipose tissue macrophages and adipocytes—disrupts insulin signaling and promotes a feed-forward loop of metabolic dysfunction [3]. Recent insights have also highlighted the role of trained immunity and macrophage polarization in sustaining chronic inflammation independent of pathogen persistence. Given the central role of inflammation in disease, various anti-inflammatory interventions have been developed. These include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, and biologics (e.g., anti-TNF-α), as well as emerging small-molecule inhibitors targeting inflammasomes and kinases [24]. As shown in Fig. 1D, probiotics have gained attention as a next-generation strategy capable of modulating immune responses via the gut microbiota. They suppress pro-inflammatory cytokines (e.g., TNF-α, IL-6), induce anti-inflammatory mediators (e.g., IL-10), and reinforce epithelial barrier integrity, offering promising therapeutic avenues for IBD, metabolic syndrome, and beyond [25].

3. Anti-Inflammatory Mechanisms of Probiotics

Probiotics primarily colonize the gastrointestinal tract, with smaller populations at other mucosal surfaces [26]. Emerging as promising biotherapeutics for inflammation-associated disorders, their anti-inflammatory effects are not parallel but operate through a cohesive causal hierarchy. This framework involves (i) microbiota-dependent ecological modulation as an upstream influence, which sets the stage for (ii) direct host immunoregulation as the core mechanistic interface, ultimately manifesting in (iii) downstream oxidative stress resolution as a critical physiological outcome (Table 1).

Table 1. Anti-Inflammatory Mechanisms of Probiotics

Probiotic type	Experimental model	Dose	Main findings	References
Bacillus subtilis BS3	Mouse, oxidative stress model	0.2 mL/only / day (10^8 CFU/mL)	Alleviates hepatic histopathological damage and attenuates colonic inflammatory cell infiltration. Regulates Keap1/Nrf2 signaling pathway and attenuates oxidative damage. Change the structure of intestinal flora, increase the abundance of intestinal flora and reduce harmful bacteria.	[4]
Bacillus subtilis BS7	Mouse, oxidative stress model	0.2 mL/only / day (10^8 CFU/mL)	Alleviates hepatic histopathological damage and attenuates colonic inflammatory cell infiltration. Regulates Keap1/Nrf2 signaling pathway and attenuates oxidative damage. Change the structure of intestinal flora, increase the abundance of intestinal flora and reduce harmful bacteria.	[4]
Lactobacillus plantarum OLL2712	Mice，BALB/c Mice，DO11.10 transgenic	4 mg/0.2 mL/ day	Six-day administration significantly upregulated IL-10 mRNA expression in dendritic cells isolated from the mesenteric lymph nodes.A single dose significantly increased IL-10 mRNA expression in dendritic cells from Peyer's patches 12 hours post-administration.The study demonstrates that heat-killed L. plantarum OLL2712 can modulate immune responses by specifically inducing the anti-inflammatory cytokine IL-10 in intestinal DCs.	[27]
Clostridium butyricum	Rat, osteoarthritis model	100 mg/kg/ day	Reduced OARSI score, cartilage degeneration score, and synovial tissue inflammation score; reduced IL-1β, TNF-α levels; increased weight-bearing capacity	[28]
Clostridium butyricum	Rat, osteoarthritis model	10^8 or 10^{10} CFU / only / day	Reduced OARSI score; reduced levels of TIMP1, TIMP3, MMP2, MMP3, MMP9, and MMP13; reduced levels of COX-2, LTB4, IFN-γ, and IL-6; increased weight-bearing capacity	[28]
Lactobacillus suis R0052	C57BL/6 mouse, oxidative stress model	200 μL/ only / day（2×10^9 CFU）	*Lactobacillus* abundance was significantly reduced; reversing the reduction in *Lactobacillus* abundance, probiotics reduced IFN-γ and TNF-α levels in the hippocampus and exerted anti-inflammatory effects.	[29]
Lactobacillus plantarum R1012	C57BL/6 mouse, oxidative stress model	200 μL/ only / day（2×10^9 CFU）	*Lactobacillus* abundance was significantly reduced; reversing the reduction in *Lactobacillus* abundance, probiotics reduced IFN-γ and TNF-α levels in the hippocampus and exerted anti-inflammatory effects.	[29]
Bifidobacterium longum R0175	C57BL/6 mouse, oxidative stress model	200 μL/ only / day（2×10^9 CFU）	*Lactobacillus* abundance was significantly reduced; reversing the reduction in Lactobacillus abundance, probiotics reduced IFN-γ and TNF-α levels in the hippocampus and exerted anti-inflammatory effects.	[29]
Bifidobacterium shortum CCFM683	Male C57BL/6J, Colorectal cancer model	10^9 CFU / only / day	Activation of PPAR-γ receptor, inhibition of NF-κB signaling pathway, reduction of production of pro-inflammatory cytokines TNF-α and IL-1β, and increase of anti-inflammatory cytokine IL-10, resulting in attenuation of inflammatory response.	[30]
Bifidobacterium pseudostreptococcus MY40C	C57BL/6J, Colorectal cancer model	10^9 CFU / only / day	Activation of PPAR-γ receptor, inhibition of NF-κB signaling pathway, reduction of production of pro-inflammatory cytokines TNF-α and IL-1β, and increase of anti-inflammatory cytokine IL-10, resulting in attenuation of inflammatory response.	[30]
Lactobacillus plantarum ZJ316	C57BL/6 J SPF mice, intestinal inflammation model	1×10^9 CFU/only / day，400 μ L / day	Significantly attenuated intestinal tissue damage and inflammatory cells and lowered pathological scores in mice; reduced the expression of pro-inflammatory cytokines IL-8, IL-6, and TNF-α; inhibited the IkBa/NF-κB signaling pathway and reduced p65 phosphorylation and IκBα degradation in HT-29 cells, thereby reducing inflammatory responses	[31]
Lactobacillus fermentum 016	C57BL/6J mouse, ulcerative colitis model	1.0×10^9 CFU/only / day，100 μL / day	Significantly reduced DSS-induced weight loss, diarrhea, and rectal bleeding in mice; decreased the levels of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and IFN-γ, increased the levels of anti-inflammatory cytokines IL-4 and IL-10, and alleviated intestinal inflammation.	[32]

Weizmannia coagulans BC99	Adult, chronic constipation model	1g / only / day	Increase the level of anti-inflammatory factors IL-4 and IL-10, and decrease the level of pro-inflammatory factors IL-6 and IFN-γ, which can effectively reduce inflammation in constipated patients and improve intestinal health.	[33]
Lactiplantibacillus plantarum FRT4	Chicken, high-fat dietary model	Low dose group:10^9 CFU/kg/only / day Medium Dose Group: 10^{10} CFU/kg/only / day; High Dose Group: 10^{11} CFU/kg/only / day	Down-regulate the levels of pro-inflammatory factors TNF-α, IL-1β, IL-8 and NLRP3, and up-regulate the levels of anti-inflammatory factors IL-4 and IL-10, to reduce oxidative damage and inflammation; regulate the mRNA expression of the factors related to the FoxO/TLR-4/NF-κB signaling pathway, to improve the antioxidant and inflammatory status of the body.	[34]
Lactiplantibacillus plantarum S58	C57BL/6 mouse, colitis model	1×10^{10} CFU/kg only / day	Reduces neuronal damage, microglial hyperactivation and neuroinflammation in the hippocampus, and down-regulates levels of the pro-inflammatory factors TNF-α and IL-6. Decreases the relative abundance of harmful bacteria (e.g., Clostridium spp., Streptococcus spp., Rhombus spp.) and increases the relative abundance of beneficial bacteria (e.g., Bifidobacterium spp.). Down-regulates pro-inflammatory factors, up-regulates anti-inflammatory factors and Reg3γ expression, enhances intestinal barrier function, and reduces serum LPS levels.	[35]
Bacteroides plebeius	Male C57BL/6JN, colon cancer model	10^7 CFU/only / day	Inhibits the development of colitis-associated colon cancer in SPF mice. Alters the structure of intestinal flora. Promotes the production of beneficial metabolites in germ-free mice, with anti-inflammatory and anti-cancer effects. Regulates gene expression in the colon tissue of SPF mice.	[36]
Bacillus pumilus LV149	Male C57BL/6 mice, colitis model	Low dose group:1×10^8 CFU /only / day; High dose group: 1×10^9 CFU/ only / day	Reduces levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and affects intestinal repair effects through the JAK-STAT signaling pathway.	[37]
Lactobacillus plantarum HGD228	Male C57BL/6 mice, colitis model	10^9 CFU / only / day	Inhibiting NF-κB pathway, reduce the level of pro-inflammatory cytokines such as TNF-α and IL-1β, and increases the level of anti-inflammatory cytokines such as IL-10. Increase the activities of antioxidant enzymes such as SOD, GSH-PX and CAT, and reduce the level of MDA. Increase the concentration of butyric acid and propionic acid, inhibit pro-inflammatory cytokines and strengthen the intestinal mucosal barrier.	[38]
Lacticaseibacillus paracasei K56	C57BL/6J mice, high-fat diet model.	No specific dose concentration mentioned	Enhances antioxidant capacity and reduces liver damage. Regulates colon immunity, reduces inflammation and improves intestinal permeability. Change the structure of intestinal flora and increase beneficial bacteria.	[39]
Lacticaseibacillus rhamnosus	Swiss line albino mice, contact dermatitis model	No specific dose concentration mentioned	Skin inflammation was reduced and skin pathology was improved in mice.	[40]
Lactobacillus reuteri TISTR 2736	Male Sprague Dawley rats, high-fat diet model	2×10^8 CFU only / day	Inhibits oxidative stress and enhances antioxidant enzyme activity. Reduces inflammation and lowers liver inflammatory factor levels.	[41]
Bifidobacterium longum BAA2573	C57BL/6J mice，**Dextran sulfate sodium (DSS)-induced colitis**	10^9 CFU /only / day	Pretreatment significantly alleviated DSS-induced colitis symptoms, including reducing weight loss, disease activity index scores, and colon shortening. Helped restore the integrity of the intestinal mucosal barrier. Rectified the DSS-induced gut microbiota dysbiosis, notably by increasing the abundance of beneficial bacteria like *Akkermansia* and *Lactobacillus*. Suppressed the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6).	[42]

3.1 Upstream Ecological Modulation: Restoring Gut Microbial Homeostasis

IBD is a multifactorial chronic disorder characterized by persistent intestinal inflammation and altered gut microbiota. Current pharmacological therapies often yield suboptimal outcomes and adverse effects [12,43,44]. In IBD, microbial dysbiosis is characterized by the loss of beneficial taxa such as *Bifidobacteria* and *Lactobacillus*, alongside an expansion of proinflammatory bacteria including *Enterobacteriaceae* and *Clostridium* [45,46] (Fig. 2A).

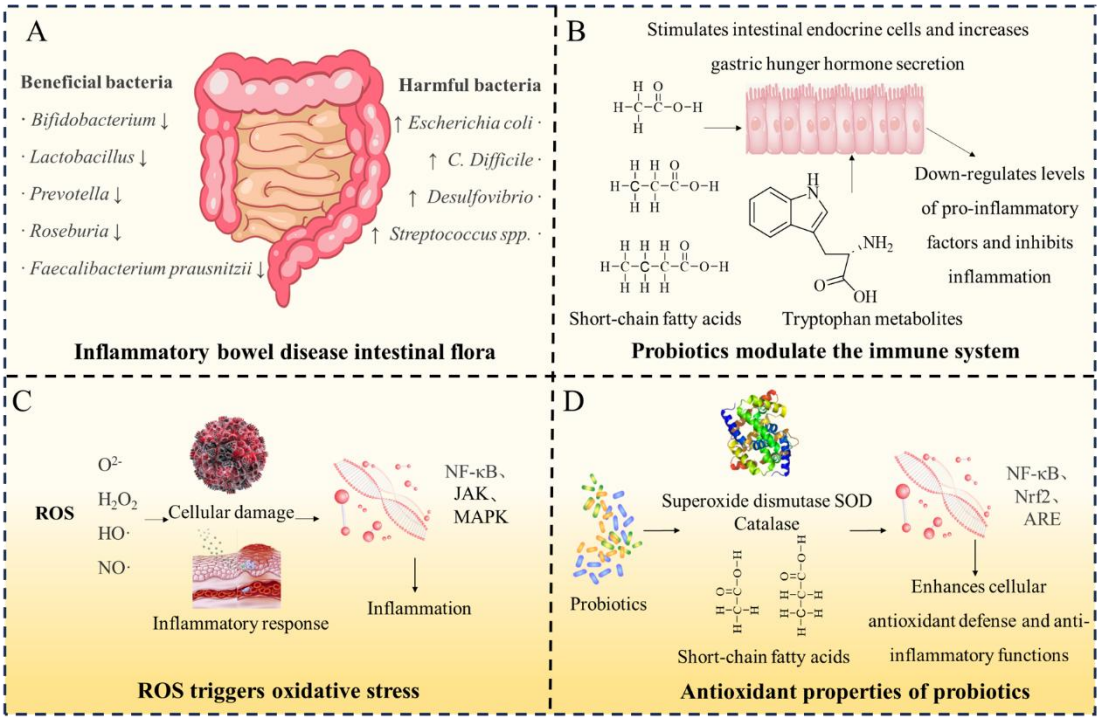

Figure 2. Probiotics anti-inflammation mechanisms: Regulation of intestinal flora (A); Modulation of the immune system (B); Reactive oxygen species (ROS) Modulation by Probiotics (C); Antioxidant properties of probiotics (D).

Several studies demonstrate that probiotics can restore microbial balance. For instance, the engineered strain BL@B-SA50 (*Bifidobacterium longum* expressing artificial enzymes) was shown to improve colitis symptoms in murine models by enriching anti-inflammatory taxa such as *Lachnospiraceae*, *Muribaculaceae*, and *Lactobacillaceae* and reducing enteric pathogens like *Shigella* and *Escherichia* [47]. Similarly, the engineered variant of *Escherichia coli* Nissle 1917 expressing catalase and superoxide dismutase [ECN-pE(C/A)] promoted the growth of butyrate-producing genera such as *Roseburia* and *Odoribacter* [13]. Butyrate, a key SCFA, is known to enhance epithelial energy metabolism and suppress NF-κB-mediated inflammatory signaling. Although engineered strains provide proof of concept, further investigation into native and clinically used probiotic species is essential for translational relevance.

It is important to critically acknowledge the substantial gap between such sophisticated experimental tools and the native, clinically applied probiotic strains. While engineered systems enable precise manipulation and hypothesis testing, their clinical translation faces challenges, including regulatory hurdles, scalability issues, and differences in efficacy and safety profiles compared to conventional probiotics.

Therefore, further investigation is essential not only to advance the design of engineered probiotics but also to bridge these findings with the behavior and mechanisms of native, clinically used probiotic species, ultimately enhancing their translational relevance.

3.2 Core Mechanistic Interface: Direct Immunoregulatory Signaling

Building upon ecological changes, probiotics exert their most definitive anti-inflammatory effects through direct molecular interactions with the host immune system (Fig. 2B). This core mechanism encompasses direct host interactions, metabolite signaling, and the targeted approaches of engineered probiotics.

First, specific probiotics directly engage host pattern-recognition receptors. Certain *Bifidobacterium* strains, for example, activate TLR2 on dendritic cells, triggering anti-inflammatory IL-10 production and promoting immune tolerance [49,50].

Second, probiotic-derived microbial metabolites exert immunoregulation through sophisticated molecular mechanisms, with SCFAs acting as pivotal mediators. Their anti-inflammatory effects are largely attributed to two primary mechanisms: epigenetic regulation via histone deacetylase (HDAC) inhibition and cell signaling through G-protein-coupled receptors (GPR43/GPR109a). The SCFA butyrate, for example, as an HDAC inhibitor, promotes regulatory T cell (Treg) differentiation, while GPCR activation broadly suppresses NF-κB-driven inflammation [51,52]. Additionally, SCFAs and tryptophan-derived indole compounds participate in a gut-endocrine-immune axis by stimulating ghrelin secretion. This axis ultimately attenuates the JAK/STAT3 pathway to inhibit IL-6 expression [10,11]. Complementing these direct immunomodulatory pathways, probiotics enhance the physical epithelial barrier by upregulating key tight junction proteins (occludin, claudins, ZO-1), thereby limiting the paracellular transit of cytokines and other inflammatory agents [48].

Finally, engineered probiotics exemplify the precision of this direct signaling layer. A synthetic yeast strain secreting the ATP-degrading enzyme apyrase reduces extracellular ATP (eATP), a known activator of the P2X7 receptor-inflammasome axis. By dampening this pathway, the strain rebalances Treg responses and alleviates colitis [43,51]. Through these multifaceted direct signals, probiotics precisely orchestrate immunoregulatory networks.

3.3 Downstream Physiological Resolution: Modulation of Oxidative Stress

The immunoregulatory actions of probiotics converge on the resolution of oxidative stress, a key downstream effector of inflammation. While ROS function as signaling molecules at physiological levels, their excess causes oxidative damage and perpetuates inflammatory cascades by activating pro-inflammatory pathways like NF-κB, JAK/STAT, and MAPK [53]. NF-κB, in particular, serves as a critical node, driving the transcription of cytokines such as TNF-α, IL-6, and IL-1β [54].

Probiotics mitigate this oxidative burden as a consequence of their immunomodulatory and direct antioxidant activities. Strains of *Lactobacillus* and *Bifidobacterium* secrete antioxidant enzymes (e.g.,

superoxide dismutase, catalase) and metabolites that collectively suppress the NF-κB pathway and its downstream mediators [55] (Fig. 2D).

Furthermore, crosstalk between probiotic signals and host redox systems is crucial. *Lactiplantibacillus plantarum* ZJ316, for example, activates the Nrf2/ARE pathway, upregulating defense enzymes like glutathione peroxidase and heme oxygenase-1. This enhances the host's endogenous antioxidant capacity while simultaneously dampening inflammation [56]. Intriguingly, a transient, Nrf2-mediated ROS elevation may act as a hormetic signal to prime cellular defenses, increasing resilience to subsequent oxidative insults [57].

Finally, the upstream ecological modulation described in section 3.1 contributes to this downstream outcome. By suppressing ROS-producing pathogens and promoting antioxidant-producing commensals, probiotics create a gut environment that systemically mitigates oxidative stress and inflammation [57].

4. Models and Methods for Evaluating the Anti-Inflammatory Effects of Probiotics

Probiotics have emerged as promising agents in the modulation of inflammation, representing a rapidly evolving research frontier. With increasing interest in deciphering their multifaceted mechanisms of action, an expanding body of preclinical and clinical evidence is paving the way for their potential application in immune-related disease management. Current research advances can be systematically organized into four key domains: cellular studies, animal models, clinical trials, and the development of next-generation engineered probiotics.

4.1 Cellular studies

In recent years, significant progress has been made in understanding the molecular mechanisms underlying the anti-inflammatory effects of probiotics, particularly in the modulation of immune responses and gut barrier function. As illustrated in Fig. 3A, probiotics exert anti-inflammatory effects through a variety of mechanisms, including the regulation of immune cell functions and the inhibition of key inflammatory signaling pathways [57,59].To dissect these mechanisms, a range of in vitro models are employed, including macrophage cell lines (e.g., RAW 264.7, THP-1), intestinal epithelial cells (e.g., Caco-2, HT-29), and more complex systems like intestinal organoids. These mechanisms act synergistically, enhancing the overall anti-inflammatory effect by not only modulating immune responses but also reinforcing gut barrier integrity, thus preventing pathogen translocation and immune overactivation. In vitro cellular experiments offer distinct advantages, such as precise control over experimental conditions and high reproducibility, which are crucial for dissecting dose-response relationships and molecular interactions between probiotics and host cells in ways not possible in more complex animal models. These experiments are particularly valuable for investigating cellular signal transduction and dose-response dynamics. Critical experimental parameters, such as the physiological state of probiotics (live, heat-inactivated, or bacterial-conditioned medium), multiplicity of infection (MOI), and co-culture duration, are key to interpreting outcomes.

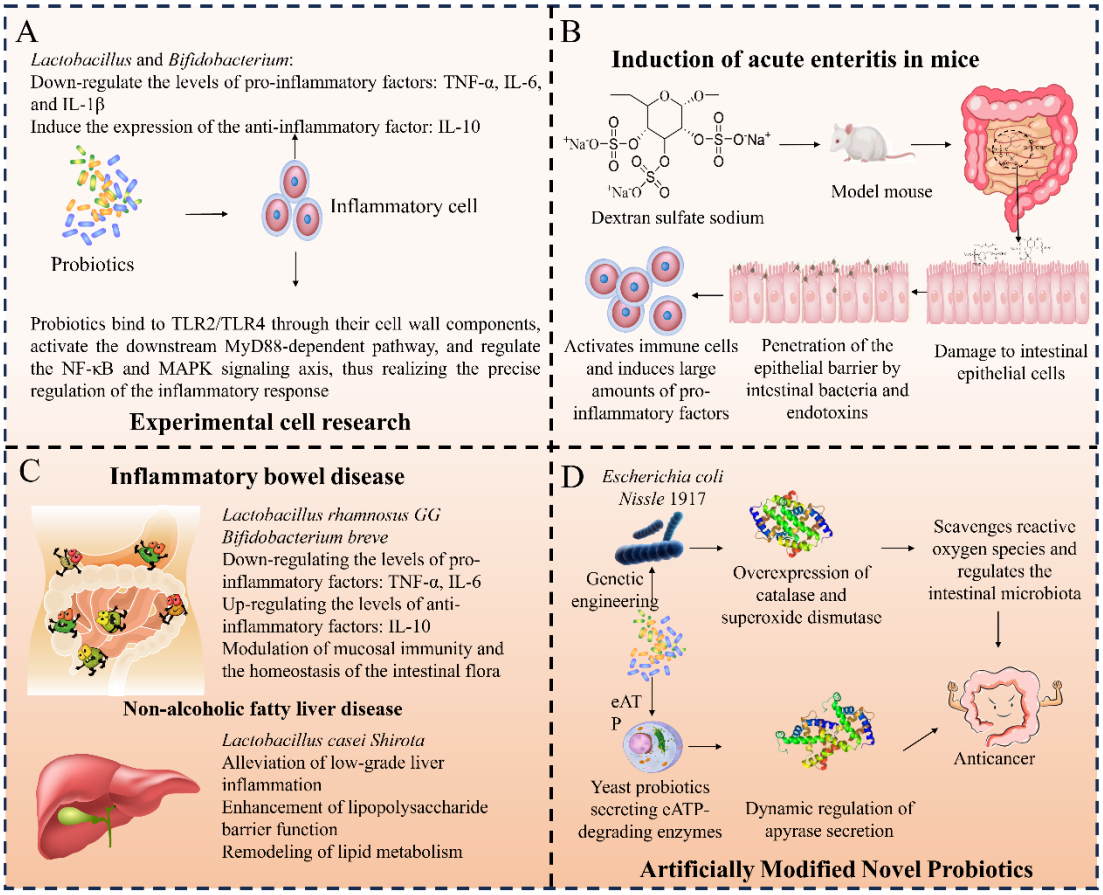

Fig. 3. Anti-inflammatory Properties of Probiotics: Cell models (A), Animal models (B), Human clinical trials (C); Artificially modified novel probiotics (D)

Numerous studies have demonstrated that probiotics can regulate various immune cells to mitigate inflammatory responses. Representative strains, such as *Lactobacillus rhamnosus* GG and *Bifidobacterium longum* BB536, have been shown to effectively downregulate pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, in macrophages. For instance, co-culture of LPS-stimulated RAW 264.7 macrophages with live *Lactobacillus rhamnosus* GG (MOI 1:20) for 24 hours resulted in a significant reduction in the secretion of TNF-α and IL-6, while simultaneously inducing the expression of the anti-inflammatory cytokine IL-10 [60]. Further investigations have revealed that probiotics interact with TLR2/TLR4 through their cell wall components (e.g., lipoteichoic acid and peptidoglycan), activating MyD88-dependent pathways and modulating the NF-κB and MAPK signaling axes, thereby enabling precise control of the inflammatory response [61,62]. Additionally, probiotics can influence dendritic cell maturation and antigen-presenting functions, promote the differentiation of regulatory T cells, and enhance immune tolerance in the host [63].A study using bone marrow-derived dendritic cells (BMDCs) showed that exposure to *Pediococcus pentosaceus* KF159 for 24 hours promoted a tolerogenic phenotype, characterized by increased TGF-β production and enhanced capacity to drive Treg cell differentiation.

Furthermore, probiotics can indirectly alleviate inflammation by maintaining the integrity of the intestinal barrier. For example, *Lactobacillus plantarum* LP3 upregulates the expression of tight junction proteins (such as ZO-1, occludin, and claudin-1) in Caco-2 cell monolayers, an effect observed after 24 hours of co-culture and leading to a significant increase in Transepithelial Electrical Resistance (TEER),

strengthening intercellular connections between intestinal epithelial cells and reducing the translocation of pathogens and endotoxins [50]. Probiotic metabolites, particularly SCFAs, not only provide energy to intestinal epithelial cells but also activate receptors like GPR41/43, promoting cell proliferation and mucus secretion, which further reinforces barrier function [64]. Treatment of dendritic cells with butyrate (1.0 mM) for 24 hours has been shown to enhance tolerogenic function by promoting anti-inflammatory cytokine IL-10 production and increasing the expression of the immunoregulatory enzyme IDO via HDAC inhibition [64].

The synergistic effects between the antioxidant and anti-inflammatory properties of probiotics are particularly noteworthy. Certain strains secrete antioxidant enzymes like SOD and catalase, which reduce ROS accumulation, preventing ROS-mediated NF-κB activation and NLRP3 inflammasome formation. In a model of H_2O_2-induced oxidative stress in intestinal epithelial Caco-2 cells, the conditioned medium from *Lactobacillus fermentum* ME-3 (containing antioxidative metabolites) significantly reduced intracellular ROS levels and suppressed the subsequent activation of the NF-κB pathway [65]. In addition, probiotics can activate the Nrf2/ARE signaling pathway, promoting the expression of downstream antioxidant enzymes like glutathione peroxidase and heme oxygenase-1, enhancing the cellular antioxidant defense system, and alleviating oxidative stress-related inflammatory responses [56]. For example, *Lactiplantibacillus plantarum* ZJ316 was demonstrated to activate the Nrf2 pathway in IPEC-J2 cells within 24 hours of treatment, culminating in increased expression of heme oxygenase-1 (HO-1) and conferring protection against oxidative stress-induced damage. While cellular experiments provide a strong theoretical foundation for understanding the anti-inflammatory mechanisms of probiotics, their limitations in simulating the complexity of the human gut microbiome, dynamic probiotic colonization, and full dose-response effects highlight the need for more advanced models to better replicate these physiological conditions.

4.2 Animal models

Animal models offer indispensable insights into the anti-inflammatory mechanisms of probiotics. Among them, the dextran sulfate sodium (DSS)-induced colitis model in mice is one of the most widely employed to evaluate therapeutic efficacy. As illustrated in Fig. 3B, DSS compromises the intestinal epithelial barrier, promoting the translocation of bacterial components such as lipopolysaccharides into the submucosa, thereby activating local immune responses and triggering the production of proinflammatory cytokines, including TNF-α and IL-6 [66].

Using this model, numerous studies have confirmed the anti-inflammatory potential of probiotic interventions. For instance, Zhao et al. [67] reported that *Lactobacillus* supplementation significantly suppressed NF-κB signaling-related gene expression, leading to reduced colonic inflammation. In parallel, Patel et al. [68] demonstrated that *Bifidobacterium* strains increased SCFAs levels, stimulated enteroendocrine hormone secretion (e.g., ghrelin), and downregulated IL-6 expression. Furthermore, postbiotics—defined as bioactive metabolites derived from probiotic metabolism—have shown the capacity to attenuate oxidative stress, inhibit NF-κB signaling, alleviate DSS-induced colitis, and enhance epithelial barrier repair [69].

Of particular note, Wu et al. [70] introduced genetically modified probiotic strains engineered to express antioxidant enzymes such as SOD and catalase. These engineered probiotics significantly reduced intestinal ROS, downregulated both NF-κB and MAPK signaling pathways, and mitigated mucosal inflammation. Collectively, these findings offer strong preclinical evidence supporting the utility of probiotics as a therapeutic approach for inflammatory diseases.

4.3 Clinical trials

While preclinical findings are encouraging, human clinical trials remain the gold standard for evaluating the real-world efficacy of probiotic interventions. As summarized in Fig. 3C, a growing number of randomized, double-blind, placebo-controlled trials have been conducted to assess the impact of probiotics on chronic inflammatory conditions such as IBD, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and cutaneous inflammation.

In IBD patients, several strains — including *Lactobacillus* and *Bifidobacterium* species have demonstrated significant reductions in disease activity indices and inflammatory cytokines [71-72]. For example, a meta-analysis of 12 RCTs showed that probiotic supplementation significantly reduced CRP levels and TNF-α compared to placebo groups [71]. Similarly, in individuals with NAFLD, probiotic administration has improved hepatic biomarkers and attenuated liver inflammation, potentially by modulating gut barrier integrity and reprogramming lipid metabolism [73-74]. Notably, a recent trial reported a mean reduction in ALT levels by 22.6 U/L and an 18.3% decrease in hepatic fat fraction (MRI-PDFF) after 12 weeks of probiotic intervention [73].

With the advent of high-throughput multi-omics platforms—including metagenomics, transcriptomics, and metabolomics—researchers are now uncovering system-wide interactions between probiotics and host physiology. For example, Ma et al. [8] employed an integrative omics approach to demonstrate that specific probiotics influence bile acid metabolism, SCFAs production, and host immune modulation, providing mechanistic insight beyond traditional markers.

Nevertheless, current clinical trials often suffer from limitations such as small cohort sizes, short intervention periods, and inter-individual microbiota variability. Future research should prioritize large-scale, multi-center, longitudinal studies that incorporate personalized nutrition strategies and artificial intelligence-driven data analytics. Such integrative approaches may facilitate the development of precision probiotic therapies tailored to specific inflammatory phenotypes, offering innovative avenues for chronic disease prevention and management.

4.4 Artificially Engineered Novel Probiotics

With the rapid development of advanced biotechnologies such as gene editing and synthetic biology, the engineerability and functional controllability of probiotics have been greatly enhanced, positioning them at the forefront of contemporary microbiological research. In the context of anti-inflammatory therapy, artificially engineered probiotics exhibit distinct advantages over natural strains, including improved target

specificity, regulatory precision, and enhanced resilience under complex environmental conditions (Fig. 3D).

Gene-editing tools offer robust platforms for functionally optimizing probiotics. For example, *Escherichia coli Nissle* 1917, genetically modified to overexpress catalase and SOD, has demonstrated the ability to scavenge ROS while simultaneously reshaping the intestinal microbiota, thereby mitigating gut inflammation. In parallel, directed evolution strategies have enabled the development of probiotics with novel sensing and regulatory capabilities. A representative example involves the engineering of a yeast strain expressing the human P2Y2 G-protein-coupled receptor, capable of sensing eATP, a key inflammatory signal in IBD. This strain was further equipped with a synthetic gene circuit to dynamically control the expression of apyrase, an eATP-degrading enzyme, thereby achieving a stimulus-responsive anti-inflammatory effect [13,75].

Despite these promising advances, several challenges must be addressed before clinical translation. Key concerns include the colonization efficiency and genetic stability of engineered strains within the host, as well as their potential unintended effects on the native microbiota [76]. Moreover, long-term safety assessments and regulatory frameworks for engineered probiotics remain underdeveloped.

Nonetheless, the versatility and programmable nature of synthetic probiotics provide a compelling framework for next-generation anti-inflammatory therapeutics. With ongoing interdisciplinary integration and rigorous clinical validation, artificially engineered probiotics are expected to contribute substantially to the precision treatment of inflammation-related diseases.

5. Applications of Anti-Inflammatory Probiotics: Innovations in Food, Nutrition, and Pharmaceutical Technology Frontiers

Anti-inflammatory probiotics, often referred to as immunobiotics (a term used to describe probiotic strains with defined immunomodulatory functions), are a subset of probiotic strains that confer health benefits by modulating immune responses and attenuating inflammation through defined molecular pathways. These probiotics act via multiple mechanisms, including reshaping gut microbiota composition, enhancing epithelial barrier function, downregulating pro-inflammatory cytokines, and reducing oxidative stress. Recent advances in biotechnology have refined strain selection, genomic characterization, and delivery technologies, supporting their increasing applications in the food, nutraceutical, and pharmaceutical sectors. As shown in Table 2, this section examines the translational potential of anti-inflammatory probiotics, with a focus on functional food products and emerging pharmaceutical applications.

Table 2. Application Potential of Anti-Inflammatory Probiotics

Probiotics Types	Applications and Functions	References
Bacillus subtilis, especially BS3 strain	Applications: Functional food; Dietary supplements. Functions: Oxidative stress relief; Gut microbiota regulation; Antioxidant and anti-inflammatory effects.	[4]
Artificial enzyme-modified *Bifidobacterium longum* (BL@B-SA50)	Applications: Functional food; Dietary supplements. Functions: IBD treatment; Microbiota regulation; Barrier restoration.	[26]
Lactobacillus helveticus R0052、*Lactobacillus plantarum* R1012、*Bifidobacterium longum* R0175	Applications: Functional food; Dietary supplements. Functions: Gut microbiota modulation; Cytokine inflammatory suppression.	[28]
Lactiplantibacillus plantarum ZJ316	Applications: Functional food. Functions: Intestinal inflammation prevention; Gut microbiota regulation; Intestinal barrier enhancement.	[30]
Lactobacillus fermentum 016	Applications: Functional food. Functions: Ulcerative colitis treatment; Antioxidant and anti-inflammatory effects; Gut microbiota modulation; Intestinal health protection.	[31]
Weizmannia coagulans BC99	Applications: Functional food; Dietary supplements. Functions: Constipation relief; Intestinal motility regulation; Inflammation and neurotransmitter modulation; Lipid metabolism improvement.	[32]
Lactiplantibacillus plantarum FRT4	Applications: Functional food; Dietary supplements Functions: Antioxidant enhancement; Inflammation regulation; Gut microbiota modulation; Reproductive performance improvement.	[33]
Lactobacillus plantarum S58 (LP. S58)	Applications: Functional food; Dietary supplements. Functions: Colitis-associated cancer prevention; Microbiota-derived metabolites; Anti-inflammatory and antitumor effects.	[34]
Bacteroides plebeius	Applications: Functional food; Dietary supplements. Functions: Obesity intervention; Metabolic regulation; Gut microbiota modulation.	[35]
Bacillus pumilus LV149	Applications: Functional food. Functions: Ulcerative colitis amelioration; Gut microbiota modulation; Intestinal barrier repair; Anti-inflammatory effects.	[36]
Lactobacillus plantarum GD228	Applications: Functional food; Dietary supplements. Functions: Anti-inflammatory; Antioxidant enhancement; Gut microbiota regulation.	[37]

Lactobacillus paracasei K56 viable bacteria (VLP)	Applications: Functional food. Functions: Obesity intervention; Metabolic regulation; Gut microbiota modulation; Anti-inflammatory and antioxidant effects.	[38]
Lacticaseibacillus rhamnosus	Applications: Functional food; Dietary supplements. Functions: Inflammation reduction; Intestinal microbiota modulation.	[39]
Lactobacillus reuteri TISTR 2736	Applications: Functional food. Functions: Type 2 diabetes adjunct therapy; Antioxidant and anti-inflammatory effects; Anti-inflammatory; Glucose homeostasis improvement; Liver function support.	[40]
Engineered Saccharomyces cerevisiae (expressing human P2Y2 purinergic receptor and secreting apyrase)	Applications: Functional food; Dietary supplements. Functions: IBD treatment; Anti-fibrotic effects; Gut dysbiosis correction; Inflammation-driven disease management.	[42]
Bifidobacterium bifidum *L*actobacillus *casei* *Lactobacillus acidophilus* *Lactobacillus reuteri* *Streptococcus thermophilus*	Applications: Functional food. Functions: Immune homeostasis modulation; Autoimmune disease prevention.	[73]
Lactobacillus acidophilus *Lactobacillus plantarum* *Lactobacillus casei* *Lactobacillus rhamnosus* *Bifidobacterium bifidum* *Streptococcus thermophilus*	Applications: Dietary supplements; Functional food. Functions: IBD management; Inflammatory signaling regulation; Adjunct therapy.	[74]
Lactobacillus fermentum GR-3	Applications: Functional food; Dietary supplements. Functions: Colorectal cancer prevention; Gut microbiota modulation; Anti-tumorigenic effects.	[75]
Escherichia coli Nissle 1917 (EcN)	Applications: Functional food; Dietary supplements. Functions: IBD therapy; Mucosal barrier repair; Immune homeostasis restoration.	[76]
Bacillus amyloliquefaciens	Applications: Functional food; Dietary supplements. Functions: Ulcerative colitis therapy; Anti-inflammatory and antioxidant effects; Gut microbiota modulation; Tissue repair promotion.	[77]
Akkermansia muciniphila	Applications: Functional food; Dietary supplements. Functions: Ulcerative colitis treatment; Intestinal barrier repair; Anti-inflammatory effects.	[78]

5.1 Applications in Functional Foods and Dietary Supplements

As illustrated in Fig. 4, anti-inflammatory probiotics have been incorporated into a variety of functional food platforms, such as fermented dairy products, plant-based beverages, and dietary supplements. Historically, probiotics were valued primarily for their contributions to flavor and texture. However, accumulating evidence now underscores their potential for immune modulation and inflammation control.

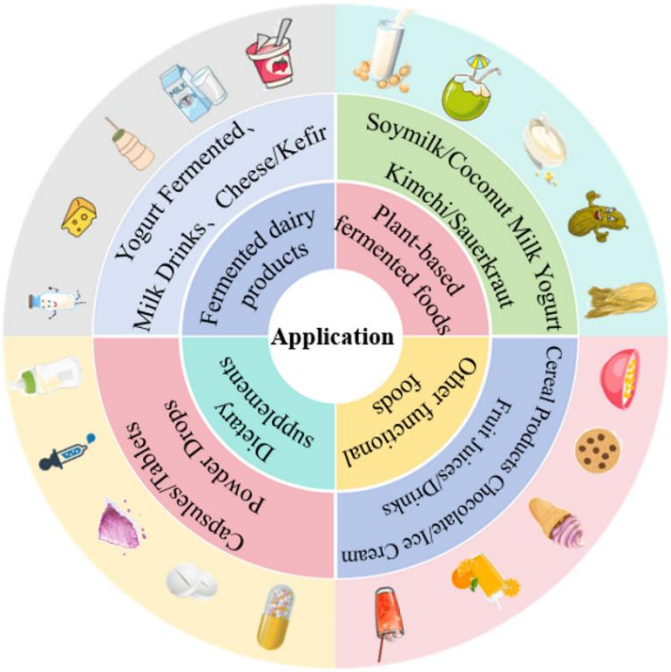

Fig. 4. Probiotics in foods and dietary supplements

A representative example is the traditional Chinese fermented beverage “Jiangshui”, from which *Lactobacillus* GR-3 was isolated. This strain exhibits potent antioxidant properties and supports gut microbial equilibrium—two essential anti-inflammatory mechanisms [79]. In a randomized clinical study, GR-3-enriched yogurt significantly reduced serum uric acid levels in patients with hyperuricemia, highlighting its therapeutic promise. While the exact mechanisms remain to be fully elucidated, we hypothesize that strain GR-3 may modulate the gut-kidney axis through the production of bioactive metabolites (e.g., SCFAs or purine-degrading enzymes), which could influence systemic uric acid homeostasis and exert renal anti-inflammatory effects. Nonetheless, the precise cellular and molecular mechanisms warrant further elucidation.

Despite such a promise, probiotics in food matrices face several technological barriers. The gastrointestinal tract presents a hostile environment, with acidic pH, bile salts, and digestive enzymes significantly impairing probiotic viability [83]. Various encapsulation technologies have been employed to address this, ranging from microcapsules to nanocarriers. For example, Alkushi et al. [81] designed a chitosan-alginate nanoparticle system encapsulating *Bacillus subtilis* for IBD intervention. This formulation significantly downregulated pro-inflammatory cytokines in murine models, outperforming unprotected

strains. However, long-term safety assessments and human trials are still needed to validate efficacy and safety profiles.

5.2 Applications in the Pharmaceutical Field

In contrast to food-grade applications, pharmaceutical-grade probiotics must meet stricter regulatory standards, including validated therapeutic efficacy, standardized formulations, and safety documentation. Current formulations include lyophilized powders, capsules, and oral suspensions. Nevertheless, probiotic viability remains a concern due to gastrointestinal degradation.

To overcome this, advanced encapsulation technologies have been adopted (Fig. 5). For instance, multilayered chitosan-alginate microcapsules protect *Bacillus subtilis* and ensure controlled release in the gut [81]. Moreover, genetically engineered *Escherichia coli* with electrostatically assembled multilayer membranes demonstrate improved environmental resilience and targeted mucosal delivery [13].

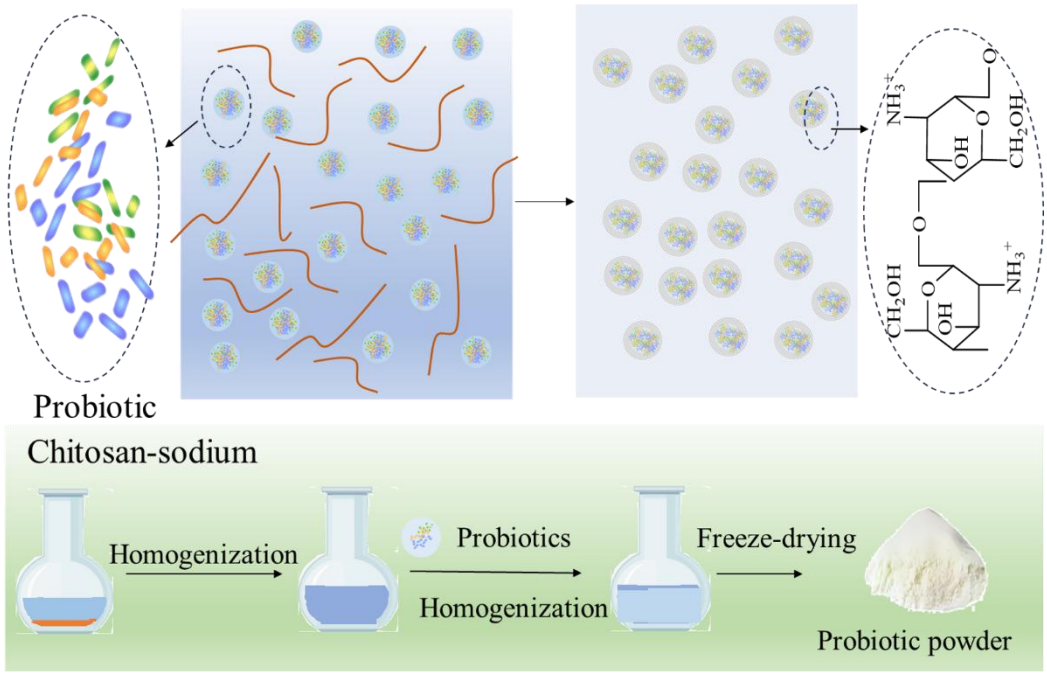

Fig. 5. Probiotic encapsulation

Pharmaceutical probiotics offer distinct advantages over conventional anti-inflammatory drugs such as corticosteroids and antibiotics, which often present systemic side effects and fail to address root causes [12]. In contrast, probiotics restore microbial homeostasis and scavenge ROS, thereby reducing inflammation at its origin with minimal adverse reactions [84]. Beyond IBD, probiotics show potential in managing metabolic diseases, such as type 2 diabetes and NAFLD, primarily through reinforcement of intestinal barrier integrity and modulation of systemic immunity [61].

Despite their potential, only a limited number of probiotic-based pharmaceuticals have progressed to late-stage clinical trials or achieved regulatory approval. Further efforts are needed to standardize probiotic pharmacokinetics, establish dose-response relationships, and develop regulatory frameworks for live biotherapeutics.

6. Critical Challenges in Probiotic Therapy and Translational Applications

Research on anti-inflammatory probiotics has opened up new avenues for preventing and treating inflammation-related diseases. As shown in Fig. 6, while this field holds considerable promise, several pressing challenges remain that necessitate the exploration of new research directions.

6.1 Limited Availability and Functional Characterization of Anti-Inflammatory Strains

To date, only a small subset of probiotic strains has exhibited reproducible anti-inflammatory properties in preclinical studies. This limited availability is further constrained by the rigorous screening and validation processes required before clinical or commercial application. A major contributing factor is the current limitation of microbial identification and characterization techniques. For instance, meta-analyses are frequently employed to extract generalizable trends from studies investigating probiotic efficacy. However, this approach may obscure strain-specific effects and lead to the inclusion of non-relevant taxa, thereby reducing the accuracy and translational relevance of the findings [85].

Moreover, while 16S rRNA gene sequencing remains a widely used method for taxonomic identification, its resolution is often insufficient for detecting low-abundance but potentially critical strains [86]. Compounding this issue is the narrow repertoire of known probiotic species with proven anti-inflammatory activity, as many microbial candidates either lack such properties or remain unexplored.

Addressing this challenge requires methodological innovation. The integration of high-resolution approaches, such as whole-genome shotgun metagenomics, with conventional 16S rRNA profiling could enhance both taxonomic precision and functional annotation. Additionally, the application of synthetic biology and gene-editing technologies holds great promise for engineering novel strains with optimized anti-inflammatory functions, thereby expanding the pool of therapeutically relevant probiotics.

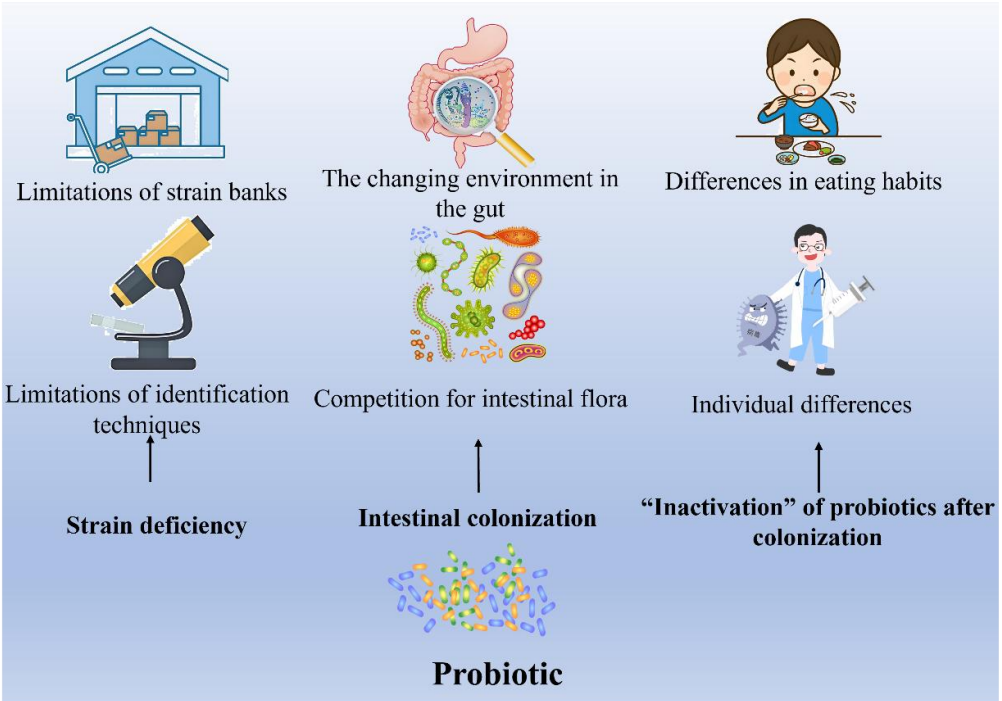

Fig. 6: Current challenges with probiotics

6.2 Barriers to Gut Colonization and Ecological Integration

The therapeutic efficacy of probiotics depends not only on their ingestion but also on their successful colonization within the gastrointestinal tract, where they must adhere to mucosal surfaces, proliferate, and exert immunomodulatory effects. However, the gut ecosystem is highly complex and dynamically regulated, posing substantial barriers to stable colonization. Native microbial communities occupy established ecological niches, creating competitive exclusion for exogenous strains [87]. In addition, environmental fluctuations within the gut, such as pH shifts, peristaltic motion, and temperature changes, can further hinder the survival and growth of introduced probiotics, particularly those that are physiologically sensitive [88]. Strain-specific differences in adhesion capability, driven by surface adhesion factors and cell wall structures, also critically influence colonization efficiency [89].

Several emerging strategies may help overcome these colonization hurdles. Genetic engineering can enhance the adhesive and stress-resilient features of probiotic strains [13]. Specifically, acid-resistant promoters can be used to drive the expression of protective molecules (e.g., molecular chaperones, stress proteins) in probiotics, mitigating gastric acid and bile salt damage [90,91,92]. Concurrently, prebiotics can be used to modulate the intestinal environment, creating favorable conditions for colonization [90]. Additionally, microencapsulation technologies (e.g., alginate-chitosan coatings) provide a physical barrier against harsh gastric pH, enhancing probiotic viability until reaching the intestinal tract [93]. Innovative delivery systems such as magnetic nanoparticle carriers have demonstrated efficacy in directing probiotic accumulation at target sites. For example, Chen et al. [91] developed a nanomaterial system composed of magnetic iron clusters and mannose-conjugated polysaccharides, which, under an external magnetic field, facilitated targeted colonization and significantly alleviated colitis in murine models. This system also incorporated a pH-responsive polymer layer to prevent premature probiotic release in the stomach, ensuring optimal delivery to the colon [94].

6.3 Functional Inactivation Following Colonization

Even when colonization is successfully achieved, probiotics may not necessarily exert their intended anti-inflammatory effects on the host. This functional inactivation is partly attributable to the disconnect between experimental models and the physiological complexity of the human gut. Most mechanistic studies are conducted in vitro or in animal models, which fail to replicate the full spectrum of host-microbe interactions in humans [92]. Furthermore, inter-individual variability is a fundamental determinant of probiotic efficacy, stemming from a complex interplay of host genetics (e.g., polymorphisms in immune-related genes such as TLRs and NOD2), baseline gut microbiota composition, diet (e.g., habitual fiber intake), immune status, and metabolic phenotypes [93,94]. This heterogeneity necessitates a shift from universal probiotic applications toward personalized strategies.

The personalized nature of probiotic efficacy cannot be overstated. For instance, the same strain of *Lactobacillus* may exhibit robust anti-inflammatory effects in individuals with a specific enterotype but fail in others (e.g., Bacteroides dominant) due to differential microbial cross-feeding networks [95]. Similarly,

host immune status, such as variations in mucosal IgA secretion or inflammatory cytokine profiles, can dramatically alter probiotic-immune crosstalk, rendering generalized outcomes unpredictable [96]. To address this issue, future studies should focus on elucidating how environmental and host-specific factors influence probiotic function post-colonization. Priority should be given to multi-omics approaches (metagenomics, metabolomics, transcriptomics) integrated with machine learning to identify biomarkers predictive of probiotic response [97]. Experimental models that more accurately simulate the human gut microenvironment are urgently needed. This includes leveraging humanized gnotobiotic mice, gut-on-a-chip systems incorporating patient-derived cells, and ex vivo organoid cultures to capture inter-individual differences [98]. In parallel, the synergistic use of prebiotics should be systematically explored. Understanding how different types and ratios of prebiotics affect probiotic metabolism, resilience, and adaptability may enable the development of personalized formulations that maintain probiotic efficacy across diverse host conditions. For example, prebiotics like fructooligosaccharides may selectively enhance probiotic persistence in individuals with low baseline *Bifidobacterium* abundance [99]. Ultimately, clinical trials must adopt stratified recruitment based on host genetics, microbiota composition, and immune parameters to validate personalized probiotic regimens [100].

7. Conclusion and Future Perspectives

This review synthesizes the mechanistic basis of inflammation and the anti-inflammatory pathways modulated by probiotics, highlighting recent advances from reductionist *in vitro* models, complex *in vivo* studies, and innovative synthetic biology approaches. Despite promising applications in functional foods and pharmaceuticals, the field faces significant translational challenges, including strain-specificity, context-dependent efficacy, and inter-individual variability, as critically analyzed in Section 6. To overcome these hurdles and realize a transformative vision for the field, we propose the following ambitious, actionable research agenda: First, the establishment of a standardized, high-throughput functional screening cascade is urgently needed. This system should integrate human cell-based organoid models, immune cell co-cultures, and validated murine colitis models, complemented by AI-driven analysis of host-microbe interaction datasets to prioritize lead strains with robust anti-inflammatory effects. Second, expanding the functional strain repertoire must move beyond conventional genera. We advocate for a systematic exploration of Next-Generation Probiotics (NGPs), such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, and engineered live biotherapeutics with targeted immunomodulatory circuits. Third, bridging the clinical translation gap necessitates rigorous precision nutrition trials that stratify participants based on enterotype, immune status, and genetic polymorphisms to develop individualized intervention strategies. Converging advances in multi-omics, synthetic biology, and machine learning will be instrumental in deconvoluting the complex dialogue between probiotics and the host immune system. By systematically addressing the specific challenges outlined, this concerted effort will not only provide a solid theoretical foundation but also deliver a definitive technical and clinical roadmap for launching next-generation, personalized microbiota-based anti-inflammatory therapies. We foresee an era where engineered and

naturally selected probiotics will precisely recalibrate host immune homeostasis, ultimately revolutionizing the management of chronic inflammatory diseases.

Declaration of competing interest

All authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (22378146) and the Fundamental Research Funds for the Central Universities (2023ZYGXZR037)

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