



POSTBIOTICS IN PREVENTIVE HEALTHCARE: IMMUNOMODULATORY AND BIOMODULATORY MECHANISMS AND FUTURE TRANSLATIONAL PERSPECTIVES

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Abstract:

Postbiotics are preparations of inanimate microorganisms and/or their components conferring biological activity without microbial viability. Their non-viability offers distinct advantages in safety, stability, shelf life, manufacturing consistency, and formulation flexibility. Strain selection, fermentation, inactivation method, composition, dose, and delivery matrix strongly influence their immunomodulatory and biomodulatory properties. Evidence indicates postbiotics interact with pattern-recognition receptors, regulate cytokine and intracellular signaling, reinforce epithelial-barrier integrity, and modulate metabolism. Consequently, they support immune homeostasis, alleviate inflammation and oxidative stress, inhibit pathogens, and enhance gut function. Strongest evidence exists for barrier protection, immune regulation, antimicrobial activity, and gut modulation. Conversely, applications in cancer prevention, neuroprotection, cardiometabolic health, and ageing remain largely preclinical. Clinical translation is hindered by heterogeneity in preparations, manufacturing, dosage, and analytical methods. Future advancement requires preparation-specific characterization, standardized production, validated biomarkers, and rigorous randomized controlled trials. Advanced technologies like multi-omics and artificial intelligence will optimize formulations, enabling evidence-based preventive applications.

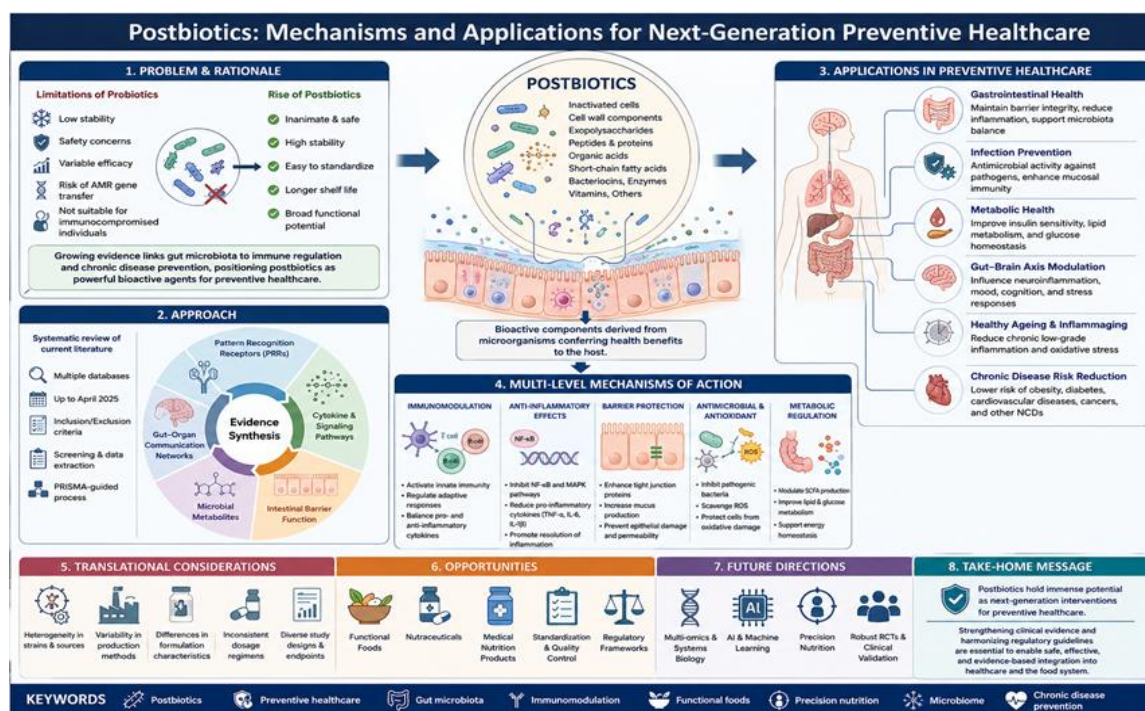
Keywords: Postbiotics; Preventive Healthcare; Immunomodulation; Gut Microbiota; Functional Foods; Disease Prevention.

1. Introduction

The rising burden of obesity, diabetes, cardiovascular disease, cancer, and inflammatory disorders has shifted healthcare toward prevention. Central to this transition is the gut microbiota, given that intestinal microorganisms and their products influence nutrient metabolism, immune development, epithelial-barrier integrity, and resistance to infection. Dysbiosis has been linked to gastrointestinal, metabolic, allergic, and inflammatory

diseases, and as a result, has generated sustained interest in probiotics, prebiotics, and synbiotics. However, the viability of live-microorganism products can be compromised during industrial processing and storage; efficacy is highly strain-dependent, intestinal persistence is inconsistent, and there are concerns regarding the transfer of antimicrobial-resistance determinants and risks to severely immunocompromised individuals.

Postbiotics provide a non-viable option that can preserve beneficial microbial functions with greater formulation adaptability. A postbiotic is defined as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host," according to the International Scientific Association for Probiotics and Prebiotics (ISAPP). Their biological effects depend on microbial strain, culture conditions, inactivation method, composition, dose, and delivery matrix. The strongest scientific evidence exists for the protection of epithelial barriers, immune regulation, and antimicrobial activity, while proposed effects on cancer prevention, neuroprotection, and longevity remain largely preclinical. This review links preparation-specific properties to molecular targets, strength of evidence, preventive-health outcomes, functional-food applications, and translational needs, while discriminating mechanistic plausibility from clinical efficacy and prioritizing standardization, human validation, regulatory governance, and precision development.



2. Review methodology and evidence synthesis approach

A structured narrative-review approach was adopted to synthesize evidence on the immunomodulatory and biomodulatory mechanisms, preventive-health applications, food-technological relevance, and translational potential of postbiotics. The published literature is heterogeneous, encompassing molecular, *in vitro*, animal, observational, clinical, food-processing, and regulatory studies that are not amenable to quantitative meta-analysis. PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect were searched for peer-reviewed articles published between January 2020 and 27 July 2026. The search terms were combinations of the following: "postbiotic," "paraprobiotic," "inanimate microorganism," "immunomodulation," "inflammation," "intestinal barrier," "gut-organ axis," "preventive healthcare," "functional food," "nutraceutical," "clinical application," "food

processing," "safety," and "standardization." Additional reference lists of pertinent consensus statements and review articles were manually reviewed.

Eligible studies evaluated well-defined preparations of non-living microorganisms and/or their constituents and reported mechanistic, immunological, metabolic, antimicrobial, technological, clinical, or safety outcomes. Excluded studies comprised those on live probiotics, isolated metabolites not associated with an inanimate microbial matrix, conference abstracts, non-peer-reviewed sources, and poorly characterized preparations. Titles and abstracts were screened before full-text assessment. Extracted data parameters included microbial strain, fermentation and inactivation methods, composition, experimental model, dose, duration, molecular targets, outcomes, limitations, and translational relevance. Approximately 50 eligible publications were qualitatively synthesized and grouped as *in vitro*, animal, observational human, or controlled clinical evidence. Methodologically sound, consistent, and preparation-specific controlled human studies were assigned greater interpretive weight.

Table 1: Key distinctions among probiotics, paraprobiotics, and postbiotics

Feature	Probiotics	Paraprobiotics	Postbiotics
Core definition	Live microorganisms that confer a health benefit when administered in adequate amounts	Nonviable intact microbial cells with proposed biological activity	Preparations of inanimate microorganisms and/or their components with a demonstrated health benefit
Viability	Required	Not required	Not required
Principal constituents	Metabolically active cells	Inactivated whole cells and preserved surface structures	Inanimate cells and/or cellular components, with retained metabolites where applicable
Manufacturing priority	Maintenance of viable-cell count	Validated inactivation with structural retention	Controlled production, composition, potency, and batch consistency
Main limitation	Loss of viability and strain-dependent performance	Non-harmonized terminology and limited clinical evidence	Preparation heterogeneity, uncertain dose equivalence, and limited clinical standardization

Note: Under the ISAPP definition, purified microbial metabolites alone are not postbiotics unless retained within a qualifying preparation of inanimate microorganisms and/or their components.

Source: Author-developed synthesis based on Cuevas-González *et al.* (6), Salminen *et al.* (40), and Vinderola *et al.* (44).

3. Postbiotics: definition and classification

Postbiotics represent a paradigm shift in microbiome-based interventions from viable microorganisms to biologically active preparations obtained through controlled inactivation (40, 44). Unlike probiotics, their biological efficacy does not rely upon the survival or intestinal colonization of the organism, conferring superior processing tolerance, extended storage stability, batch-to-batch consistency, and predictable dosage control (42, 44). ISAPP defines a postbiotic as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (40). A qualifying preparation must therefore be comprehensively

characterized and supported by demonstrable evidence of health promotion. Postbiotics strictly exclude purified metabolites, isolated microbial molecules, or inactivated biomass lacking proven efficacy (40, 44). Non-viability significantly reduces cold-chain refrigeration requirements and minimizes risks of systemic translocation, opportunistic bacteremia, unintended colonization, and horizontal transfer of antimicrobial-resistance determinants. These functional attributes render postbiotics highly suitable for integration into foods, beverages, dietary nutraceuticals, and medical nutrition; however, composition, dosage, safety profiles, and therapeutic efficacy must be rigorously validated for each distinct preparation (13, 42).

4. Molecular and cellular mechanisms of postbiotic action

Postbiotics encompass preparations of inactivated microorganisms and/or their structural components that confer a demonstrated host health benefit without requiring microbial viability. Because they exhibit superior stability and processing resilience relative to live probiotics, they provide distinct practical advantages. However, their biological activities are fundamentally strain-, composition-, inactivation method-, dose-, and delivery matrix-dependent, necessitating preparation-specific characterization and rigorous clinical substantiation.

Table 2: Mechanistic map of postbiotic bioactivities

Function	Representative constituents	Principal targets	Evidence-based interpretation
Microbial recognition	Peptidoglycan, lipoteichoic acids, surface proteins	TLR2-MyD88-NF- κ B; NOD1/2-RIP2	May calibrate innate immune responses
Immune regulation	Cellular structures, exopolysaccharides, retained metabolites	NF- κ B; MAPK; JAK/STAT	Cytokine effects are preparation- and model-dependent
Barrier support	Retained butyrate, exopolysaccharides, surface proteins	HDAC; AMPK; tight-junction pathways	Consistent mechanistic support; limited standardized clinical validation
Antioxidant activity	Exopolysaccharides, peptides, retained metabolites	Keap1-Nrf2-ARE	Mainly supported by cell and animal studies
Antimicrobial activity	Bacteriocins, organic acids, antimicrobial peptides	Membranes; acidification; quorum sensing	Strong experimental activity but sparse human evidence
Metabolic signalling	Retained SCFAs and other microbial molecules	FFAR2/3; GPR109A; AMPK; HDAC	Plausible systemic effects requiring preparation-specific trials

Note: Constituents and pathways are preparation- and strain-dependent. Isolated metabolites are not independently classified as postbiotics unless retained within a qualifying inanimate microbial preparation.

Abbreviations: AMPK, AMP-activated protein kinase; ARE, antioxidant response element; FFAR, free-fatty-acid receptor; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; NOD, nucleotide-binding oligomerization-domain receptor; TLR, Toll-like receptor.

Source: Author-developed synthesis based on cited investigations.

4.1 Biomodulatory functions of postbiotics

Biomodulation denotes the capacity of a preparation to exert concerted regulatory actions across interconnected physiological networks rather than targeting an isolated pathway. Postbiotics modulate systemic immune

signaling, epithelial barrier integrity, cellular metabolic homeostasis, redox balance, commensal microbial ecology, and gut-organ communication axes (26, 41). These coordinated responses are mediated by inanimate intact cells, cell-wall fragments, surface layer proteins, exopolysaccharides, structural enzymes, bioactive peptides, and matrix-associated fermentation metabolites (16, 44). Specific bioactivities include the molecular tightening of apical junction complexes, upregulation of mucin biosynthesis, metabolic reprogramming, and competitive exclusion of pathogen adhesion and biofilm maturation. Because physiological outcomes depend directly on microbial strain, fermentation media, inactivation kinetics, macromolecular composition, dosage, formulation matrix, and host genetics, biomodulatory claims must remain preparation-specific and substantiated by analytical and functional profiles (46).

4.2 Recognition by pattern recognition receptors

Postbiotics actively engage pattern-recognition receptors expressed along intestinal epithelial surfaces and mucosal immune cells. These receptors identify microbe-associated molecular patterns to prime intracellular cascades controlling host defense, epithelial restitution, inflammatory resolution, and immune tolerance. Inanimate peptidoglycan fragments, lipoteichoic acids, surface-layer proteins, and outer membrane constituents bind extracellular Toll-like receptors (TLRs) or intracellular nucleotide-binding oligomerization domain (NOD) receptors (39, 40). Specifically, TLR2 recognizes surface constituents characteristic of Gram-positive organisms, whereas TLR4 detects Gram-negative outer-membrane lipopolysaccharides. Receptor ligation recruits adaptor proteins such as MyD88, triggering downstream mitogen-activated protein kinases (MAPK) and nuclear factor- κ B (NF- κ B) cascades that orchestrate the expression of cytokines, chemokines, and host antimicrobial peptides (3, 39). The downstream immunological profile is determined by ligand structural preservation, localized concentration, exposure duration, microenvironmental context, and baseline mucosal tone; uncontrolled receptor ligation may exacerbate mucosal inflammation.

4.3 Modulation of cytokine response

Cytokine networks coordinate tissue inflammation, barrier tolerance, and wound healing. Defined postbiotic preparations stimulate regulatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor- β (TGF- β), while downregulating pro-inflammatory mediators including tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and circulating chemokines (3, 39). Cellular fragments and associated metabolites also steer macrophage polarization toward resolving M2 phenotypes, direct dendritic-cell maturation, support regulatory T-cell (Treg) differentiation, and modulate mucosal lymphocyte proliferation. Although these mechanisms promote mucosal tolerance and repair, their quantitative effects vary according to preparation characteristics, dosage regimens, and host disease phenotypes. Preclinical findings from cell cultures, zebrafish (*Danio rerio*), and rodent models cannot serve as direct surrogates for clinical efficacy (34). Demonstrating genuine immunomodulatory efficacy requires human intervention trials employing standardized preparations, validated systemic biomarkers, defined kinetics, and rigorous statistical power (46).

4.4 Improvement of the integrity of the intestinal barrier

The intestinal epithelial barrier facilitates selective nutrient absorption while excluding luminal pathogens, dietary antigens, and microbial toxins. This functional interface comprises intestinal epithelial cells, apical tight junction networks, a protective mucus layer, secreted antimicrobial peptides, secretory immunoglobulin A (sIgA), and underlying immune subsets. Barrier failure triggers pathological hyperpermeability, microbial translocation, and systemic inflammation (20, 33). Postbiotics support barrier restoration via coordinated structural, metabolic,

and immunoregulatory mechanisms. Inanimate-matrix short-chain fatty acids (SCFAs)—predominantly butyrate, acetate, and propionate—serve as critical substrates for epithelial homeostasis. Butyrate fuels colonocyte metabolism and upregulates tight junction proteins, including occludin, claudin isoforms, and zonula occludens-1 (ZO-1), through AMP-activated protein kinase (AMPK) activation and histone deacetylase (HDAC) inhibition (16, 26). Concurrently, preparation exopolysaccharides, surface peptides, and cell-wall polymers stimulate goblet-cell mucin secretion and induce enterocyte antimicrobial peptide production, highlighting the need for quantitative permeability biomarkers in human trials.

4.5 Control of anti-inflammatory signalling

Chronic inflammatory signaling drives the progression of metabolic disorders, enteropathies, cardiovascular diseases, neurodegenerative pathologies, and epithelial malignancies. The NF- κ B transcription factor regulates downstream pro-inflammatory cytokines, chemokines, endothelial adhesion molecules, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). Postbiotic preparations can suppress excessive NF- κ B transactivation through receptor-mediated, metabolic, and epigenetic mechanisms (3, 39). Retained SCFAs inhibit class I/II HDACs, altering histone acetylation to repress pro-inflammatory gene expression and promote tolerogenic programs. Simultaneously, exopolysaccharides, peptides, and peptidoglycans modulate extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK phosphorylation; select fractions induce the Keap1-Nrf2-antioxidant response element pathway, upregulating protective enzymes such as superoxide dismutase and heme oxygenase-1 (10, 16). Complete pathway suppression is detrimental given the role of acute inflammation in pathogen clearance and wound healing. Preparation-specific clinical studies must calibrate dosing to restore homeostasis without inducing immunosuppression.

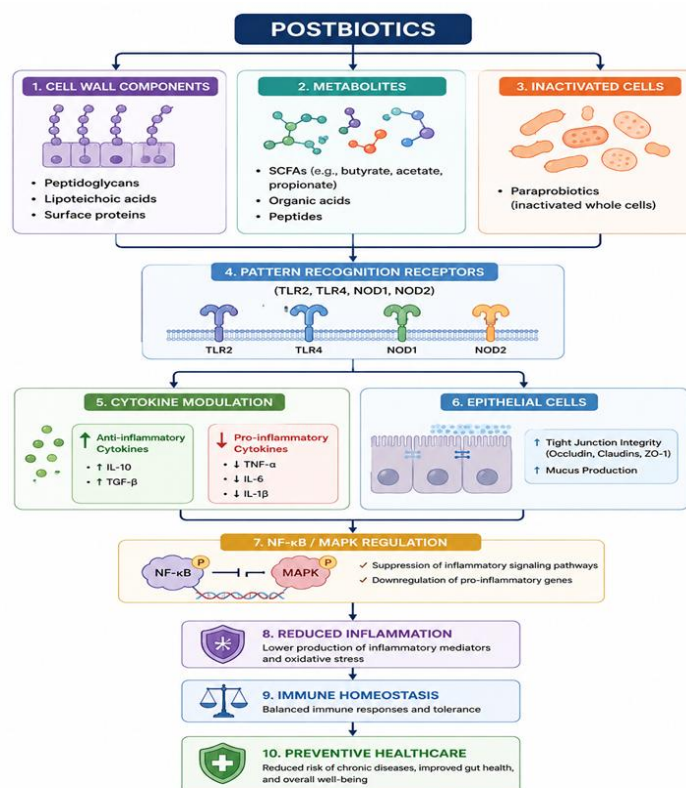


Figure 1: Immunomodulatory mechanisms of postbiotics

5. Health outcomes related to disease prevention

Beyond the gut lumen, postbiotic preparations exert systemic effects across interconnected immunomodulatory, antimicrobial, anti-inflammatory, metabolic, and barrier-protective networks. However, scientific evidence across clinical indications remains variable. Molecular and clinical investigations offer the strongest support for barrier maintenance, mucosal immune regulation, and antimicrobial inhibition, whereas applications in cancer prevention, neuroprotection, cardiometabolic management, and healthy ageing remain largely supported by preclinical observations (12, 15, 25, 49). Interpreting these outcomes requires accounting for microbial strain, fermentation parameters, inactivation kinetics, macromolecular stability, dosing schedules, delivery matrices, and endpoint metrics. Establishing credible preventive indications demands preparation-specific characterization that delineates theoretical plausibility from verified clinical outcomes.

5.1 Gut microbiome health

The gastrointestinal tract represents the direct site of host-postbiotic interactions. The primary clinical benefit conferred by postbiotics is the stabilization of the intestinal epithelial lining, which restricts the translocation of luminal pathogens, enterotoxins, and pro-inflammatory bacterial fragments into mesenteric circulation (26, 49). Matrix-associated SCFAs, notably butyrate, supply primary energy to colonocytes and upregulate occludin, claudins, and zonula occludens-1, preserving selective paracellular barrier function (41). Accompanying structural polymers stimulate mucin synthesis and defensin secretion, recalibrate cytokine networks, and competitively displace enteric pathogens, supporting clinical management in dysbiosis and inflammatory bowel diseases (20, 33). Isolated, chemically synthesized SCFAs do not meet the consensus criteria for postbiotics unless embedded within an inanimate microbial preparation (40). Heterogeneity in bacterial strains, inactivation protocols, and clinical outcome metrics continues to limit generalized recommendations, highlighting the need for standardized multicenter trials measuring gut permeability.

5.2 Antibiofilm activity and inhibited infection

Escalating rates of antimicrobial resistance demand non-antibiotic prophylactic and therapeutic strategies to augment existing infection control measures. Inanimate microbial preparations contain bacteriocins, organic acids, antimicrobial peptides, biosurfactants, and exopolysaccharides capable of suppressing pathogenic bacteria and fungi (2, 42). Identified antimicrobial mechanisms include cell-membrane destabilization, targeted luminal acidification, competitive nutrient sequestration, quorum-sensing interference, and transcriptional downregulation of virulence factors. Furthermore, specific postbiotic fractions prevent initial microbial adhesion and disrupt the extracellular polymeric substance matrix of established microbial biofilms (11, 18). Because biofilms confer substantial tolerance to host immune clearance and conventional antibiotics across oral, enteral, medical-device, and food-processing environments, their disruption is of clinical relevance. However, *in vitro* clearance cannot be directly extrapolated to clinical therapeutic efficacy. Postbiotic formulations must be evaluated as complementary adjuncts within rigorous clinical trials comparing efficacy against standard-of-care antimicrobial regimens.

5.3 Opportunities for cancer prevention

Intestinal dysbiosis, chronic mucosal barrier breakdown, unmitigated oxidative stress, and persistent low-grade inflammation represent recognized drivers of carcinogenesis. Consequently, postbiotic fractions have been

examined for their capacities to modulate pro-inflammatory signaling, bolster endogenous antioxidant mechanisms, improve immune surveillance, suppress aberrant cell proliferation, and activate apoptotic cascades (14, 25). Retained butyrate exhibits antineoplastic properties via the inhibition of HDACs, inducing chromatin remodelling that promotes differentiation and selective apoptosis in transformed cells. However, free, chemically synthesized butyrate constitutes an isolated microbial metabolite rather than a postbiotic (40, 44). Although defined inanimate bacterial fractions demonstrate anti-proliferative and pro-apoptotic activities across cultured malignant lines and rodent xenograft models, these findings do not equate to clinical cancer chemoprevention in humans. Broad preventive claims remain premature until reproducible formulations are validated in long-term human cohort trials evaluating intermediate neoplastic biomarkers and clinical safety.

5.4 The gut–brain axis and metabolic health

Metabolic syndrome, obesity, and type 2 diabetes mellitus are characterized by dysregulated energy balance, impaired glucose disposal, systemic lipid abnormalities, compromised gut barrier integrity, and metabolic endotoxemia. Postbiotic preparations retain active biomolecules and SCFAs that engage systemic metabolic targets via G-protein-coupled receptors and intracellular kinase pathways (12, 24). Specifically, SCFAs activate GPR41 (FFAR3) and GPR43 (FFAR2) on enteroendocrine cells to stimulate glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) release, enhancing peripheral insulin sensitivity and regulating adipocyte lipolysis (23). Because active component concentrations and systemic bioavailability differ across preparations, generalized claims across products are invalid. Postbiotics also influence gut–brain bidirectional communication via vagal afferent pathways, neuroendocrine loops, and systemic neuroimmune networks; microbial metabolites and cell-wall components influence central neurotransmission, microglial activation, stress reactivity, and blood–brain barrier stability (35). While early metabolic intervention studies report encouraging results, structural heterogeneity across tested formulations requires long-term, dose-ranging human clinical trials paired with deep microbiome profiling to identify responder phenotypes.

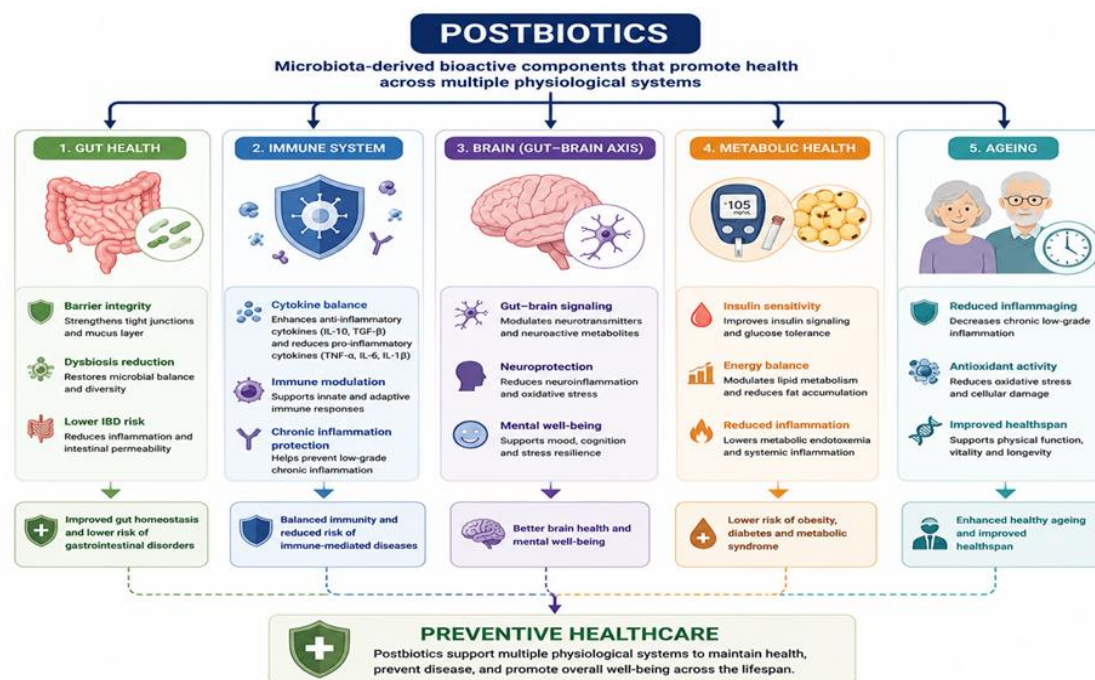
5.5 Healthy ageing

Biological senescence is characterized by declining physiological reserve, immune senescence, barrier degradation, and chronic systemic inflammation ("inflammageing"). Age-related gut microbiota dysbiosis exacerbates mucosal permeability, immune hyperactivation, oxidative damage, and susceptibility to age-associated pathologies (15). Because postbiotics lack viable microorganisms, they eliminate risks of systemic bacteremia and unintended opportunistic colonization in immunocompromised, frail, or elderly individuals while offering storage stability (16, 49). Inanimate microbial components downregulate inflammatory cytokines, promote tight junction repair, and support endogenous antioxidant enzymes. Nonetheless, non-viability does not eliminate safety concerns; every preparation must be evaluated for pro-inflammatory cell components, trace endotoxins, allergens, and unintended active constituent concentrations (13). The therapeutic premise of postbiotics in extending healthspan remains largely based on animal and *in vitro* models. Extended clinical trials assessing muscle grip strength, functional frailty scores, cognitive scores, inflammatory biomarkers, and biological ageing indices are required before postbiotics can be recommended for routine geriatric care.

Table 3: Reporting framework for postbiotic food formulations

Domain	Minimum information required
Biological identity	Microbial species and strain; provenance; relevant genomic or phenotypic characteristics
Production	Culture substrate; fermentation conditions; harvest stage; downstream processing
Inactivation	Method, intensity, and validated confirmation of absence of viable cells
Composition	Cell number or biomass equivalent; structural markers; retained metabolites; potency marker
Food matrix	Product category; incorporation level; interactions with matrix components; sensory effects
Processing stability	Thermal, pH, oxygen, pressure, or shear exposure and retained activity
Storage stability	Packaging, temperature, duration, compositional stability, and potency at end of shelf life
Biological evaluation	Dose, comparator, experimental model, primary outcome, and adverse-event assessment

Source: Adapted from Mafe *et al.* (27).

**Figure 2: Organ-specific preventive effects of postbiotics**

6. Future outlook and functional food applications

Expanding scientific focus on microbiome-targeted nutrition has accelerated the formulation of postbiotic ingredients across functional foods, functional beverages, and clinical nutraceuticals. Postbiotics demonstrate enhanced thermal resilience, prolonged ambient storage stability, dose uniformness, and formulation flexibility compared to live probiotics (40, 42). Their technological integration into diverse matrices is supported by demonstrated immunomodulatory, mucosal-protective, antimicrobial, antioxidant, and metabolic activities.

However, industrial formulation must follow evidence-based principles, wherein the final, finished commercial formulation serves as the primary unit of scientific, safety, and regulatory evaluation.

6.1 Applications in dairy and functional food

Fermented dairy foods have served as the traditional delivery vehicle for probiotic and postbiotic concepts. In products such as cultured buttermilk, yogurt, kefir, aged cheeses, and fermented whey beverages, pasteurization yields matrices containing inactivated cells, lysed cellular envelopes, and fermentation metabolites (8, 21). However, the unintentional presence of lysed biomass does not qualify a food matrix as a postbiotic; the matrix must deliver a defined preparation of inanimate microorganisms and/or their cellular structures with demonstrated clinical efficacy (40, 44). While postbiotics withstand severe processing operations, factors including thermal cycling, spray drying, extreme pH shifts, water activity, and food matrix constituents can alter molecular conformation and reduce biological potency (48). Promising applications extend to infant nutrition formulations, plant-based dairy alternatives, baked goods, functional confectioneries, and medical feeding solutions, all of which require rigorous validation of stability, bioactivity, sensory profiles, and consumer acceptability (5, 36).

6.2 Applications in nutraceuticals

Postbiotic ingredients can be formulated into dry delivery formats including gelatin capsules, tablets, sachets, powders, and shelf-stable suspensions, enabling precise dosing, standardized batch-to-batch consistency, and stable room-temperature logistics (46, 49). Target clinical indications include immune support, barrier maintenance, oxidative stress reduction, pathogen inhibition, and metabolic regulation. Non-viability mitigates the risks of systemic infection, unintended bacterial translocation, and antibiotic-resistance gene transfer in vulnerable patient cohorts (30). However, absence of viability does not guarantee commercial safety. Functional claims must be substantiated directly through clinical evaluation of the finalized product formulation, as safety and efficacy data established for parent live cultures or isolated cellular extracts cannot be transferred to derivative postbiotic preparations (13).

6.3 Standardization and safety

Translating postbiotics into validated clinical products requires reproducible manufacturing protocols and preparation-specific safety appraisals. Structural composition, functional potency, and host biological interactions are directly governed by starting strain lineage, fermentation substrates, culture kinetics, biomass harvest stage, inactivation methodology, downstream purification, storage conditions, and the food delivery matrix (4, 40, 44, 45). Manufacturing standards must enforce strict quality control to verify taxonomic authenticity, confirm total microbial inactivation, quantify active chemical markers, and rule out chemical contaminants or microbiological endotoxins. Standard optical density or whole-cell enumeration methods are insufficient for preparations where fragmented cell envelopes or bound metabolites confer primary biological activity (46). Cross-study reproducibility requires validated reference standards and standardized analytical protocols. Finally, regulatory review frameworks should remain proportional to the targeted commercial claims, delivery vehicles, and consumer safety margins (13).

6.4 Individualized healthcare and precision nutrition

Individual clinical responses to postbiotic interventions vary according to baseline gut microbiome diversity, host genomics, dietary patterns, metabolic state, pharmacological regimens, age, lifestyle habits, and existing disease states (12, 28). Precision nutrition frameworks aim to characterize this inter-individual variance to tailor specific

postbiotic combinations to defined biological responder profiles. Multi-omics platforms—such as deep shotgun metagenomics, high-resolution metabolomics, host transcriptomics, and proteomics—enable the mapping of microbial biosynthetic shifts, localized metabolite signatures, host epithelial responses, and clinical efficacy biomarkers (4, 32). Concurrently, artificial intelligence and machine-learning models can process multi-omic datasets to guide strain selection, optimize fermentation parameters, predict synergistic matrix interactions, and identify patient populations most likely to benefit. However, computational models cannot substitute for empirical biological validation and randomized controlled clinical trials; advancing "precision postbiotics" requires rigorous prospective human trial validation.

6.5 Future prospects and gaps in research

The current body of postbiotic literature remains dominated by *in vitro* cell models and rodent trials, with an ongoing shortage of adequately powered human clinical studies (2, 28). Positive preclinical responses cannot be directly equated with clinical efficacy, as clinical outcomes depend on dosage, matrix delivery, and individual human host physiology. Future clinical designs must employ fully standardized preparations, matched placebos, predefined clinical endpoints, validated mechanistic biomarkers, and extended monitoring windows in representative demographic cohorts. Clinical trial registrations should transparently document subject dietary backgrounds, concurrent medications, baseline microbiota, and production parameters (13). Research priorities encompass determining clear dose–response thresholds, evaluating long-term toxicological safety, mapping cellular uptake mechanics, assessing industrial matrix interactions, and establishing harmonized regulatory standards. Commercial translation must remain grounded in scientific evidence, restricting commercial health claims strictly to the specific preparation, dosage, target population, and clinical endpoint validated by clinical research.

Table 4: Challenges and future opportunities in postbiotic research and applications

Challenges	Future opportunities
Non-standardized production methods	Development and validation of harmonized manufacturing protocols
Variability in postbiotic composition	Multi-omics characterization and compositional fingerprinting
Limited large-scale clinical evidence	Well-designed, adequately powered human intervention trials
Incomplete mechanistic understanding	Identification of strain- and preparation-specific bioactivities
Absence of harmonized regulations	Establishment of internationally coordinated regulatory frameworks
Uncertainty regarding optimal dosage	Dose-response evaluation and long-term safety assessment
Limited personalization strategies	Precision-nutrition and microbiome-guided interventions
Restricted commercial translation	Development of scalable functional foods, nutraceuticals, and medical-nutrition products

Source: Adapted from Kaya *et al.* (21).

7. Limitations of the current evidence

Despite promising preliminary evidence, the clinical translation of postbiotic preparations remains constrained by marked variability in microbial strains, culture media, fermentation kinetics, inactivation methods, compositional profiles, and analytical quantification standards (2, 46, 49). This methodological heterogeneity impedes inter-study comparisons and undermines scientific reproducibility. A substantial majority of mechanistic claims continue to rely upon *in vitro* monoculture platforms and animal models, while published human randomized controlled trials remain scarce, small, short, and disparate in their choice of endpoints (28, 49). Furthermore, physiological mechanisms established under controlled laboratory conditions cannot be generalized across diverse patient populations because host responses are modulated by host genetics, dietary variations, age, systemic comorbidities, pharmacological therapies, and baseline microbial architecture (12, 28). Compounding these biological limitations is the lack of harmonized manufacturing standards, validated potency assays, analytical reference standards, and internationally aligned regulatory guidelines (13, 45, 46). Establishing reliable preventive and clinical recommendations will require multicenter randomized trials using characterized preparations, valid control arms, dose–response profiling, validated biomarkers, and standardized adverse-event reporting. Until such clinical verification is attained, functional and therapeutic claims must remain restricted to the specific preparation, dosage, and patient cohort evaluated.

8. Conclusion

Postbiotics represent a promising evolution in microbiome-targeted therapeutic and nutritional strategies by delivering biological activity without the viability constraints inherent to living microorganisms. In comparison to conventional probiotics, non-viable preparations provide superior formulation resilience, extended shelf-life stability, batch-to-batch consistency, and simplified industrial handling (40, 42). However, these technological and biological characteristics are preparation-specific and cannot be generalized across all inanimate microbial products. Postbiotics exert biomodulatory effects through pattern-recognition receptor activation, cytokine signaling modulation, apical tight-junction reinforcement, pathogen exclusion, and the release of active fermentation components that coordinate host metabolic and gut–organ axes (3, 26, 39, 41). These mechanisms provide biological plausibility for applications in mucosal health, systemic immune homeostasis, metabolic management, pathogen defense, neuroprotection, and healthy ageing. Nevertheless, robust evidence remains largely concentrated within gastrointestinal barrier protection, mucosal immune regulation, and localized antimicrobial action, whereas applications in systemic oncology, neurodegenerative disease, metabolic syndrome, and longevity remain in early preclinical stages (12, 15, 25, 49).

The inherent stability of postbiotic preparations supports their incorporation into functional food formulations, dietary supplements, and clinical medical foods (13, 27, 42). Successful clinical translation depends on transparent compositional characterization, verified production consistency, demonstrated toxicological safety, and rigorous human clinical trials conducted with finished commercial formulations. Future progress will benefit from integrating high-throughput multi-omics profiling, computational machine learning, and precision nutrition models to identify specific responder populations (4, 32). While postbiotics hold substantial promise for preventive healthcare, their clinical adoption requires preparation-specific substantiation, harmonized regulatory standards, and claims limited strictly to demonstrated benefits. Adhering to this evidence-based framework will determine whether preclinical promise can be translated into safe, standardized, and clinically meaningful preventive interventions.

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