

Postbiotics in Human Health: Mechanisms, Therapeutic Applications, and Future Perspectives

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Abstract:

Postbiotics represent a paradigm shift in microbiome-based therapeutics, offering the functional benefits of probiotics without the challenges associated with live microorganism administration. Defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as "preparations of inanimate microorganisms and/or their components that confer a health benefit on the host," postbiotics encompass a diverse array of bioactive compounds including cell wall components, metabolites, short-chain fatty acids, bacteriocins, and extracellular vesicles. This review synthesizes current evidence on the mechanisms through which postbiotics modulate host physiology, their therapeutic applications across various disease states, and the challenges and opportunities that lie ahead for clinical translation. Emerging evidence supports their efficacy in gastrointestinal disorders, metabolic diseases, immune modulation, and beyond, while their superior stability, safety profile, and standardization potential position them as attractive candidates for next-generation biotherapeutics.

Keywords: Postbiotics, Biotherapeutics, Gut Microbiota

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1. Introduction

The human gut microbiota is a complex and dynamic community of microorganisms that plays a fundamental role in maintaining host health. It is involved in various physiological processes, including digestion, nutrient absorption, metabolism, and immune system regulation. A balanced gut microbiota contributes to intestinal homeostasis, whereas any disturbance in this balance, known as dysbiosis, has been strongly associated with a wide range of diseases such as inflammatory bowel disease (IBD), obesity, type 2 diabetes, and colorectal cancer. In recent

years, there has been increasing interest in modulating the gut microbiota to improve health outcomes and prevent disease progression.

Traditionally, probiotics—defined as live microorganisms that confer health benefits when administered in adequate amounts—have been widely used to restore microbial balance. However, their application is limited by several factors, including reduced viability during storage, sensitivity to environmental conditions, and potential safety concerns in immunocompromised individuals¹. These limitations have led researchers to explore alternative strategies that can provide similar benefits without relying on live microbial cells. In this context, postbiotics have emerged as a promising and safer alternative. According to Salminen *et al.* (2021), postbiotics are defined as preparations of inanimate microorganisms and/or their components that confer a health benefit on the host.

Postbiotics include a wide range of bioactive compounds such as short-chain fatty acids (SCFAs), organic acids, bacteriocins, enzymes, peptides, and cell wall components produced during microbial fermentation. These compounds exert beneficial effects through multiple mechanisms, including antimicrobial activity, enhancement of gut barrier function, and modulation of immune responses. Unlike probiotics, postbiotics are more stable, easier to standardize, and have a longer shelf life, making them highly suitable for therapeutic and industrial applications. Recent studies have demonstrated that postbiotics can effectively mimic or even surpass the functional properties of probiotics, highlighting their potential as next-generation microbiome-based therapeutics².

2.2 Types and Composition of Postbiotics

Postbiotics represent a heterogeneous group of bioactive compounds derived from microbial metabolism or released after cell lysis during fermentation. These include a wide range of substances such as short-chain fatty acids (SCFAs), organic acids, bacteriocins, enzymes, peptides, vitamins, and structural components of microbial cells. Among these, SCFAs—namely acetate, propionate, and butyrate—are the most extensively studied due to their significant role in maintaining gut health and metabolic balance. These metabolites are primarily produced through the fermentation of dietary fibers by lactic acid bacteria and other beneficial gut microbes, and they contribute to host energy metabolism, immune regulation, and intestinal integrity³.

In addition to SCFAs, postbiotics also include antimicrobial compounds such as bacteriocins and organic acids like lactic acid, which play a crucial role in inhibiting pathogenic microorganisms. Bacteriocins are ribosomally synthesized peptides that exhibit targeted antimicrobial activity by disrupting the cell membranes of harmful bacteria. Exopolysaccharides (EPS), another important class of postbiotics, are high-molecular-weight polymers secreted by microorganisms that exhibit antioxidant, immunomodulatory, and anti-inflammatory properties. Furthermore, enzymes and vitamins produced during fermentation contribute to improved digestion and nutritional value, thereby enhancing the overall functional properties of postbiotics⁴.

Structural components of microbial cells, such as peptidoglycan, lipoteichoic acids, and surface-layer proteins, also form an integral part of postbiotics. These components interact with host immune receptors, such as pattern recognition receptors (PRRs), to modulate immune responses and maintain homeostasis. The composition of postbiotics may vary depending on the microbial strain, fermentation conditions, and substrate used, leading to differences in their biological activity. This complex and diverse composition enables postbiotics to exert multiple synergistic effects, making them highly promising for therapeutic, pharmaceutical, and functional food applications⁵.

2.3 Mechanisms of Action of Postbiotics

2.3.1 Antimicrobial Activity

Postbiotics exhibit strong antimicrobial activity through the production of organic acids, bacteriocins, and other inhibitory compounds. Organic acids reduce environmental pH, thereby inhibiting the growth of pathogenic microorganisms, while bacteriocins disrupt bacterial cell membranes, leading to cell death. Additionally, postbiotics interfere with microbial metabolism and biofilm formation, further enhancing their antimicrobial efficacy⁶. Furthermore, postbiotics can inhibit quorum sensing in pathogenic bacteria, preventing virulence expression and colonization. Certain metabolites also induce oxidative stress within microbial cells, causing cellular damage. These combined mechanisms contribute to broad-spectrum antimicrobial activity, making postbiotics effective against both antibiotic-sensitive and resistant strains.

2.3.2 Enhancement of Intestinal Barrier Function

Postbiotics play a significant role in maintaining gut barrier integrity. They enhance the expression of tight junction proteins such as occludin and claudins, which prevent the translocation of harmful substances across the intestinal epithelium. Furthermore, postbiotics stimulate mucin production, strengthening the mucosal barrier and protecting against gastrointestinal disorders⁷. Additionally, they promote epithelial cell regeneration and repair, aiding in the maintenance of intestinal lining integrity. Postbiotics also modulate signaling pathways involved in barrier function, such as the AMP-activated protein kinase (AMPK) pathway. These effects collectively reduce intestinal permeability and help prevent inflammation associated with “leaky gut” conditions.

2.3.3 Immunomodulatory Effects

Postbiotics modulate the immune system by influencing both innate and adaptive immune responses. They regulate cytokine production, including interleukins and tumor necrosis factor-alpha, thereby maintaining immune balance. Postbiotics also affect T-cell differentiation and activation, promoting anti-inflammatory responses while suppressing excessive inflammation⁸. Additionally, postbiotics can enhance the activity of macrophages and dendritic cells, improving pathogen recognition and clearance. They interact with pattern recognition receptors

such as Toll-like receptors (TLRs), triggering immune signaling pathways. These interactions help in maintaining immune homeostasis and preventing chronic inflammatory conditions⁹.

2.3.4 Anti-inflammatory and Antioxidant Effects

Postbiotics exhibit significant anti-inflammatory and antioxidant properties. They reduce oxidative stress by scavenging free radicals and enhancing antioxidant enzyme activity. Additionally, postbiotics inhibit inflammatory signaling pathways and regulate gene expression through mechanisms such as histone deacetylase (HDAC) inhibition. These effects are particularly important in preventing chronic diseases¹⁰. Furthermore, postbiotics can downregulate pro-inflammatory mediators such as NF- κ B, thereby reducing inflammation at the molecular level. They also enhance the activity of endogenous antioxidant systems, including superoxide dismutase and catalase¹¹. These combined actions help protect cells from oxidative damage and maintain cellular homeostasis.

2.3.5 Metabolic Regulation

Postbiotics influence metabolic processes by improving insulin sensitivity, regulating lipid metabolism, and enhancing energy homeostasis. Short-chain fatty acids, particularly butyrate, play a crucial role in regulating glucose metabolism and reducing inflammation. Postbiotics also stimulate the secretion of gut hormones such as GLP-1, which are involved in appetite regulation and metabolic control¹². Additionally, postbiotics can modulate hepatic lipid synthesis and reduce fat accumulation in tissues. They also influence key metabolic signaling pathways such as AMP-activated protein kinase (AMPK), promoting energy balance. These effects collectively contribute to the prevention and management of metabolic disorders such as obesity and type 2 diabetes.

2.3.6 Gut–Brain Axis Modulation

Emerging evidence suggests that postbiotics influence the gut–brain axis. SCFAs regulate neurotransmitter production and modulate neuroinflammatory pathways. Postbiotics also affect brain-derived neurotrophic factor (BDNF), which is essential for neuronal health and cognitive function. These findings indicate potential applications in neurological and psychiatric disorders¹³. Additionally, postbiotics can influence the production of neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA). They also help regulate the hypothalamic–pituitary–adrenal (HPA) axis, which is involved in stress responses. These interactions contribute to improved mental health and may help in managing conditions such as anxiety and depression.

2.4 Therapeutic Applications of Postbiotics

2.4.1 Gastrointestinal Disorders

Postbiotics are widely studied for their role in managing gastrointestinal disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and infectious diarrhoea.

They improve gut barrier function, restore microbial balance, and reduce inflammation, thereby alleviating symptom¹⁴. Additionally, postbiotics help inhibit the growth of pathogenic microorganisms, contributing to improved gut health. They also enhance mucosal immunity, providing protection against recurrent gastrointestinal infections. Furthermore, postbiotics may aid in faster recovery of the intestinal lining following infection or inflammation.

2.4.2 Immune and Inflammatory Disorders

Postbiotics play a critical role in modulating immune responses and reducing inflammation. They have been shown to be effective in managing autoimmune diseases, allergies, and atopic dermatitis. By regulating cytokine production and immune cell activity, postbiotics help maintain immune homeostasis¹⁵. Additionally, postbiotics can suppress pro-inflammatory cytokines while enhancing anti-inflammatory mediators such as IL-10. They also influence the balance of regulatory T cells, which are essential for controlling immune tolerance. These effects contribute to the prevention and management of chronic inflammatory and immune-mediated disorders.

2.4.3 Cancer Prevention and Therapy

Postbiotics exhibit promising anticancer properties through mechanisms such as induction of apoptosis, inhibition of cell proliferation, and regulation of gene expression. SCFAs, particularly butyrate, act as histone deacetylase inhibitors, leading to epigenetic modifications that suppress tumor growth. These effects are particularly relevant in colorectal cancer¹⁶. Additionally, postbiotics can induce cell cycle arrest at different phases, thereby preventing uncontrolled cell division. They also enhance the production of reactive oxygen species in cancer cells, leading to programmed cell death. Postbiotics may modulate signaling pathways such as Wnt/ β -catenin and PI3K/Akt, which are involved in tumor progression. Furthermore, they can improve the efficacy of conventional cancer therapies when used as adjunct agents.

2.4.4 Metabolic Disorders

Postbiotics have shown potential in the management of metabolic disorders, including obesity, type 2 diabetes, and dyslipidemia. They improve insulin sensitivity, reduce lipid accumulation, and regulate metabolic pathways. Clinical studies have demonstrated improvements in metabolic markers following postbiotic supplementation¹⁷. Additionally, postbiotics help reduce systemic inflammation associated with metabolic dysfunction. They also modulate gut microbiota composition, contributing to improved metabolic health. Furthermore, postbiotics can influence appetite regulation by affecting gut hormone secretion. These combined effects support long-term metabolic balance and disease prevention.

2.4.5 Antimicrobial and Food Applications

Postbiotics are increasingly used in food preservation and safety due to their antimicrobial properties. They act as natural preservatives by inhibiting spoilage microorganisms and pathogens. Additionally, postbiotics are being explored as alternatives to antibiotics, reducing

the risk of antimicrobial resistance¹⁸. Furthermore, they can extend the shelf life of food products without compromising nutritional quality. Postbiotics are also being incorporated into functional foods to enhance their health benefits. These applications highlight their importance in both food technology and public health.

2.4.6 Skin and Systemic Health

Recent studies suggest that postbiotics contribute to skin health by improving barrier function and reducing inflammation. They also influence systemic health through the gut–skin axis, highlighting their potential in dermatological applications¹⁹. Additionally, postbiotics can enhance skin hydration and promote repair of damaged skin tissues. They may help in managing conditions such as acne, eczema, and psoriasis by modulating inflammatory responses. Furthermore, their antioxidant properties protect skin cells from oxidative stress and environmental damage²⁰.

2.5 Advantages of Postbiotics over Probiotics

Postbiotics offer several advantages compared to probiotics. They are non-viable, eliminating the risk of infection in immunocompromised individuals. They exhibit greater stability and longer shelf life, making them suitable for storage and transportation. Additionally, postbiotics allow for easier standardization and controlled dosing. These features make them highly suitable for pharmaceutical and functional food applications²¹. Furthermore, postbiotics are less sensitive to environmental conditions such as temperature and pH, ensuring consistent efficacy. They do not require strict storage conditions, unlike live probiotics. Postbiotics also reduce the risk of horizontal gene transfer of antibiotic resistance. These advantages make them more reliable and safer for large-scale industrial applications²².

2.6 Limitations and Challenges

Despite their promising potential, postbiotics face several challenges. There is a lack of standardized production methods, leading to variability in composition and efficacy. Limited clinical trials in humans restrict their widespread application. Furthermore, optimal dosage, long-term safety, and regulatory guidelines remain unclear. Addressing these challenges is essential for the successful translation of postbiotics into clinical practice²³. Additionally, variations in microbial strains and fermentation conditions can result in inconsistent postbiotic profiles. The complexity of postbiotic mixtures makes it difficult to identify specific bioactive compounds responsible for their effects. There is also limited understanding of their mechanisms of action at the molecular level²⁴. Overcoming these limitations will require advanced analytical techniques and well-designed clinical studies.

2.7 Future Perspectives

Future research on postbiotics should focus on identifying specific bioactive compounds responsible for therapeutic effects. Advanced techniques such as metabolomics and proteomics can aid in understanding their mechanisms of action. Large-scale clinical trials are necessary

to validate their efficacy and safety. Additionally, the development of targeted postbiotic formulations and personalized therapeutic approaches represents a promising direction for future research. Furthermore, integration of multi-omics approaches will help in elucidating host–microbe interactions at a deeper level²⁵. The exploration of postbiotics in combination with probiotics or prebiotics (synbiotics) may enhance their therapeutic efficacy. Advances in biotechnology and fermentation processes can improve large-scale production and consistency. There is also growing interest in incorporating postbiotics into functional foods and nutraceuticals. These developments will pave the way for their application in precision medicine and next-generation therapeutics.

2.8 Conclusion

Postbiotics represent a significant advancement in microbiome-based therapeutics. Their ability to modulate immune responses, enhance gut barrier function, and provide antimicrobial and metabolic benefits makes them a promising alternative to probiotics. While current evidence supports their potential, further research is required to fully establish their clinical applications and ensure their safe and effective use. Moreover, their stability, safety profile, and ease of standardization provide a clear advantage for large-scale industrial and pharmaceutical applications. Continued research focusing on molecular mechanisms and clinical validation will strengthen their role in disease prevention and treatment. The integration of postbiotics into functional foods and therapeutic formulations is expected to expand their application in healthcare.

In conclusion, postbiotics hold immense potential as next-generation bioactive agents, bridging the gap between microbiome science and clinical practice. Their multifaceted mechanisms and wide-ranging therapeutic applications highlight their importance in improving human health. With ongoing advancements in research and technology, postbiotics are poised to become a key component in future medical and nutritional strategies.

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