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Postbiotics: A New Approach from Gut Health to Cancer Therapy

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Abstract

Recent research has increasingly highlighted the potential of postbiotics, non-viable microbial metabolites, and cellular components in enhancing human health, particularly through gut microbiota modulation and cancer therapy. Unlike probiotics, postbiotics offer advantages such as improved stability, safety, and ease of standardization. Their ability to provide therapeutic benefits without the risks associated with live microbes makes them promising candidates for clinical applications, as cancer adjuvants, and functional food applications. These bioactive compounds can enhance treatment outcomes and reduce side effects by exhibiting multiple anti-cancer mechanisms, including the disruption of carcinogenic pathways, enhancement of gut barrier integrity, and reduction of inflammation. Evidence from in vitro and in vivo studies demonstrates their potential against various cancers, including colorectal, breast, gastric, and liver cancers. Despite these promising preclinical results, several challenges hinder their clinical translation, including variability in formulations, lack of standardized production methods, and limited clinical trials to confirm efficacy and safety. This review provides a comprehensive overview of the evolving definitions, classifications, and sources of postbiotics, as well as the mechanisms through which they may influence cancer development and progression, and highlights additional health benefits they confer. Moreover, it underscores the critical need for further research to identify specific bioactive compounds, optimize delivery systems, and establish safety profiles through rigorous clinical investigations. Harnessing postbiotics could revolutionize cancer prevention and treatment strategies, offering safe, effective, and adjunctive therapeutic options that integrate with personalized medicine and functional nutrition.

1. Introduction

Furthermore, the ability of these live microorganisms to survive during storage often decreases. Manufacturers frequently add higher initial amounts to compensate, but this approach does not account for the potential effects of non-viable (dead) microorganisms in the final product (Periti & Mazzei, 1998). In contrast, postbiotics, composed of non-living microorganisms or their metabolites, eliminate these concerns due to their inability to replicate or produce harmful toxins. They also offer superior stability during production and storage, ensuring a consistent shelf life and precise dosing (Sreeja & Prajapati, 2013). Nonetheless, postbiotics are not entirely risk-free, as certain toxic metabolites released by dead bacteria may pose safety concerns, raising the need

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for further research. This combination of safety, stability, and precision makes postbiotics a promising alternative to probiotics for various applications (Wegh et al., 2019). The rapid increase in cancer prevalence has led researchers to explore postbiotics as a potential treatment for cancer. Postbiotics offer a range of health benefits including anti-cancer effects, which are achieved through apoptosis (programmed cell death), slowing the growth of cells (anti-proliferative actions), reducing inflammation (anti-inflammatory actions), and influencing the gut microbiome and immune system (Kim et al., 2021). While the therapeutic potential of postbiotics is increasingly recognized, a focused review of their applications, specifically in cancer, remains essential. This review aims to provide a concise overview of postbiotics, their diverse biological activities, and their potential role in promoting gut health, as well as their therapeutic implications in the prevention and treatment of cancer. It also aims to highlight key mechanisms outlining crucial avenues for future research.

2. Defining Postbiotics

In recent years, various definitions for postbiotics have been proposed; however, these definitions often contain gaps that require further clarification. To create a comprehensive and clear definition of postbiotics, it is essential to consider whether microbial cells or their components should be included, as well as whether the substances they produce can remain effective even without the actual microbial cells. Furthermore, it is important to clarify whether the definition should be limited to substances produced by probiotics and whether postbiotics themselves play a role in health benefits. Tackling these critical points will be essential for enhancing the understanding of postbiotics (Vinderola et al., 2022). Previous studies have employed various definitions of postbiotics over the years, presented in Table 1

Table 1: The Most Significant Definitions of Postbiotics

Definitions of Postbiotics	References
Any substance generated through the metabolic processes of probiotics or any molecule that is released and positively influences the host, either directly or indirectly.	(Tsilingiri & Rescigno, 2013)
Substances known as soluble factors are produced by living bacteria or are released upon the lysis of these bacteria. This category includes enzymes, peptides, teichoic acids, muropeptides derived from peptidoglycan, polysaccharides, cell surface proteins, and organic acids.	(Aguilar-Toalá et al., 2018)
Metabolites produced by microorganisms from food ingredients or microbial constituents, including non-living cells, can support health and well-being when taken in adequate doses.	(Collado Amores et al., 2019)
The metabolites generated by non-living probiotics influence the biological processes of the host organisms.	(Collado et al., 2019)
Inactive bacterial substances or metabolites generated by probiotic microorganisms that exert beneficial effects on the host or the microbiota.	(Johnson et al., 2019)
Bioactive compounds produced during fermentation can promote overall health.	(Wegh et al., 2019)
The development of inert microorganisms and their elements that are beneficial to the host.	(Salminen et al., 2021)

Current definitions of postbiotics do not fully address all relevant questions. According to the International Scientific Association of Probiotics and Prebiotics (ISAPP), Postbiotics are preparations made from inactive microorganisms along with their constituents or solely from those components that offer health benefits to the host (Salminen et al., 2021). In simpler terms, postbiotics consist of whole, non-viable microbial entities or cellular fragments, regardless of whether they include health-promoting metabolites. It is crucial to note that purified metabolites are not classified as postbiotics (Vinderola et al., 2022). However, various physiologically active components derived from microbial cells—such as cell wall fragments,

enzymes, and different metabolites—can enhance the complexity and effectiveness of postbiotic formulations. While these components are not strictly necessary for classification as postbiotics, they illustrate the diverse nature of these preparations. The ISAPP panel has specified that purified metabolites and isolated cellular components do not qualify as postbiotics. Additionally, microbial products such as vitamins, organic acids (e.g., butyric acid), and antibiotics can be collectively categorized as microbe-derived substances when applicable. It is also important to recognize that postbiotics are not confined to the gastrointestinal tract; they can offer beneficial effects in other areas of the body, including the skin, respiratory tract, and vagina (Vinderola, et al., 2022).

3. Sources of Postbiotics

Postbiotic molecules represent a diverse array of metabolic byproducts generated by probiotic bacteria during their lifecycle. These include extracellularly produced compounds such as cell-free supernatants and cell wall components, including muropeptides (derived from peptidoglycans), exopolysaccharides (EPSs), and teichoic acids (Malashree, Angadi et al. 2019). Intracellularly produced compounds include organic acids, vitamins, short-chain fatty acids, and diverse bacteriocins (e.g., Acidophilin, Reuterin, and Bifidin) (Malashree et al., 2019). Postbiotics are considered complex molecules due to their varied composition, making it difficult to understand the purposes and uses of this large spectrum of bioactive compounds (Salminen et al., 2021). The complexity of postbiotics is also due to terpenoid-derived compounds (e.g., Genipin, Paeoniflorin, and various Glycosides of Paeonilactone), phenolic-derived substances, flavonoids (e.g., Equol, Desaminotyrosine, Daidzein, Norathyriol, Urolithins and Enterolactone), neurotransmitters, biosurfactants, and various amino acids (Cortés-Martín et al., 2020; Wang et al., 2019). In addition, bacterial structures with unique properties, such as surface structures (e.g., fimbriae, pili, and flagella), play a role in their functional characteristics (Nataraj et al., 2020). Research conducted by Sharma and Shukla (2018) showed the varied functional properties of these compounds, including antimicrobial, immunomodulatory, and antioxidant effects. These properties have a positive influence on metabolic, immunological, and neurological pathways, thereby helping to maintain a balanced microbiota (Sharma et al., 2018). The various modes of action displayed by postbiotics, each dependent on the specific bioactive components, also contribute to their complexity (Aguilar-Toalá et al., 2018).

Fermentation is a vital process for generating postbiotics in the food sector. During fermentation, microbial cells metabolize prebiotics, resulting in the production of multiple bioactive compounds. These compounds can arise from natural metabolic pathways or as responses to specific environmental conditions. Diverse dairy products and fermented foods, including yogurt, kefir, kombucha, and pickled vegetables, naturally contain postbiotics primarily produced by *Lactobacillus* and *Bifidobacterium* species. However, other species such as *Streptococcus, Akkermansia muciniphila, Eubacterium hallii, Faecalibacterium,* and *Saccharomyces boulardii* also contribute to postbiotic production (Bock et al., 2021; Gezginç et al., 2022). Fermentation conditions, including the type of microbe, the composition of the substrate, pH, temperature, and fermentation duration, can greatly affect the type and amount of postbiotics generated (Ji et al., 2023).

Despite this natural production, the concentrations of postbiotics generated through traditional fermentation processes can often be inconsistent and may not achieve levels sufficient to induce a physiological response in vivo (Hosseini et al., 2024; Prajapati et al., 2023). To address these issues, researchers are investigating various production methods that systematically and effectively generate postbiotics. A systematic approach using solid-state fermentation (SSF) with selected strains (*Bacillus amyloliquefaciens J* and *Lactiplantibacillus plantarum SN4*) and substrates (corn flour, soybean meal, etc.) effectively produced bioactive postbiotics (Tong et al., 2023). They found that optimized SSF

conditions significantly enhanced antibacterial activity by 3.62-fold. The extracted postbiotics exhibited broad-spectrum antibacterial activity against *E. coli, Salmonella*, and *S. aureus*, along with strong antioxidant and anti-inflammatory properties, demonstrating optimized SSF as a robust method for generating functional postbiotics. Studies investigating the enhancement of postbiotic applications are vital for advancing their use in the food, pharmaceutical, and nutraceutical industries (Prajapati et al., 2023).

Among the various metabolites produced during fermentation, bacteriocins (antimicrobial peptides synthesized by specific bacteria) have gained notable attention for their potential applications in food preservation and safety (Negash & Tsehai, 2020). Numerous bacteriocins have been identified and characterized for their potential applications across various industries, with their extraction and characterization reliant heavily on the specific microbial strains used and the environmental conditions under which they are cultivated. A well-known example of these bioactive compounds is Nisin, a bacteriocin synthesized by *Lactococcus lactis*, which is commonly employed as a preservative in products such as canned soups, dairy items, and infant formulas. Notably, Nisin requires processing to achieve physiological inactivity before activation (A. Kumar et al., 2024). In addition to bacteriocins, enzymes derived from probiotic strains present viable alternatives for achieving specific health outcomes, further highlighting the multifunctionality of microbial metabolites. For instance, enzymes from *Bifidobacterium pseudocatenulatum a*nd *Bifidobacterium longum*, particularly purified phytases, have demonstrated the ability to enhance myoinositol triphosphate levels while concurrently reducing phytate levels in cereal mixtures. This illustrates the potential of specific bacterial strains to effectively modify the nutritional profiles of food products (Mishra et al., 2024).

Furthermore, another study has established that fermentation techniques can significantly enhance the vitamin content of foods, particularly concerning increasing vitamin B concentrations in cereal grains. While cereal grains are naturally rich in various B vitamins, significant losses can occur during processing steps such as grinding and heat treatment. However, pre-treating these grains with specific strains of lactic acid bacteria before fermentation can enhance the fermentation process and improve their nutritional profile (LeBlanc et al., 2020). The fermentation of cereals by lactic acid bacteria is also linked to enhancements in protein fractions, overall lysine content, soluble dietary fiber, and the bioavailability of essential minerals such as Iron, Calcium, and Zinc. Additionally, the fermentation of wheat has been linked to the production of antioxidant peptides, gamma-aminobutyric acid, and peptides that inhibit angiotensin I-converting enzyme, emphasizing the multifaceted benefits and applications of fermentation in food production and health (Masuda et al., 2012). Another study also explored the production of three significant postbiotic compounds, including conjugated linoleic acid (CLA) and exopolysaccharides (EPSs), using *B. lactis* BB12 in supplemented cheese whey. CLA is known for its anti-carcinogenic, anti-inflammatory, and immune-modulating properties. EPSs play a vital role in promoting gut health, acting as prebiotics, and improving the texture and stability of food products. Optimized fermentation conditions, including temperature, incubation time, and yeast extract concentration, were determined to maximize the co-production of these postbiotics (Amiri et al., 2021).

4. Isolation and Enhancement Techniques

To effectively isolate postbiotics, researchers primarily employ methodologies that focus on extracting bioactive extracellular metabolites from microbial cells, utilizing techniques such as centrifugation and ultrafiltration. After the initial extraction is completed, advanced analytical methods such as gas chromatography, mass spectrometry, and high-performance liquid chromatography are used to examine the composition of postbiotics (Dunand et al., 2019). Metabolomics is another powerful analytical technique that quantifies small molecules within complex biological systems, providing valuable

insights into the interactions and metabolic pathways associated with microbial activity and its resulting byproducts. In controlled laboratory settings, proteolytic cultures often serve as initial cultures during fermentation, where maintaining a neutral pH is essential for optimizing postbiotic release (Birmpa et al., 2013). Additionally, various laboratory techniques can enhance natural fermentation processes to improve nutritional value, extend shelf life, and enhance health benefits in both fermented and non-fermented foods. These methods include high-pressure treatment, heat treatment, gamma and ultraviolet radiation, Tyndallization (a sterilization method), formalin inactivation, thermal processing, ionizing radiation, and sonication (Ananta et al., 2005; Liu et al., 2018). Innovative approaches, such as ohmic heating, supercritical CO2 extraction, pH modulation, pulsed electric fields, and drying, also show promise for the inactivation and generation of postbiotics, facilitating their broader application in health and nutrition (de Almada et al., 2016;Amiri et al., 2021).

5. Categorization of Postbiotics

The categorization of postbiotics is based on factors such as the type of microorganism, their unique physical, chemical, structural, and functional characteristics, as well as their biological effects (Fig 1). This classification highlights the complexity and diversity of postbiotics while underscoring their potential roles in various biological processes and applications in health promotion and disease management. Consequently, the investigation of postbiotics presents a wide array of therapeutic opportunities, positioning them as valuable resources in modern health and nutrition science. This understanding provides a clear context for examining the specific implications and applications of various postbiotic compounds in promoting human health (Malashree et al., 2019).

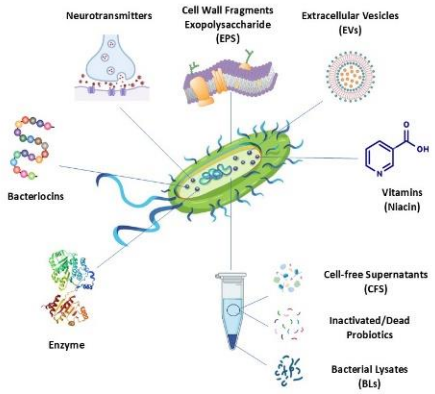

Figure 1: Classification of Postbiotics

Note. This figure was created using publicly available icons from various online sources, as mentioned in the acknowledgment section.

5.1.Cell-free Supernatants (CFS)

CFS are liquid extracts containing a variety of metabolites produced during microbial growth, along with residual nutrients from the growth medium that are not consumed. These supernatants are produced during the fermentation of microorganisms and exhibit a range of beneficial properties, such as anti-inflammatory, antioxidant, and antitumor activities. CFS is increasingly utilized in therapeutic contexts, particularly for the treatment of diarrhea (Wang et al., 2019). When derived from lactic acid bacteria (LAB), CFS demonstrates notable antibacterial effects, primarily attributed to the presence of organic acids, bioactive peptides, and fatty acids. Importantly, lactic and acetic acids are crucial for facilitating the antibacterial actions of cell-free supernatants (CFS) derived from lactic acid bacteria (LAB) (Mgomi et al., 2023). Research has

shown that CFS obtained from *Lactobacillus brevis* and *Lactobacillus casei* exhibit significant potential in breast cancer treatment. They induce apoptosis in cancer cells, inhibit metastasis, and modulate immune responses while sparing healthy cells. These postbiotics can complement conventional therapies, enhancing efficacy and reducing side effects. Their bioactive compounds also inspire the development of targeted therapies, making them a promising tool in cancer research (Dameshghian et al., 2024).

Moreover, strains of *Lactobacillus* and *Bifidobacterium* have been shown to inhibit the growth of *V. cholera*, further emphasizing their capacity as effective antibacterial agents (Derakhshan-Sefidi et al., 2024). Another study also highlights the potential of CFS postbiotics from *Lactiplantibacillus plantarum* and *Bifidobacterium* species in promoting mutual growth, enhancing probiotic stability, and serving as safe alternatives to live probiotics. These strain-specific effects support the development of functional foods to improve gut health, offering a stable and risk-free option for probiotic applications (Altieri et al., 2024). Given that CFS is produced by non-pathogenic bacterial strains, they present a promising alternative to traditional antimicrobial agents and are generally recognized as safe for human consumption. Nonetheless, it is essential to proceed with caution, as CFS may contain biogenic amines and D-lactic acid, which can have adverse effects (Lee et al., 2023). Thus, the broad spectrum of health benefits associated with cell-free supernatants positions them as a valuable area of study.

5.2. Inactivated and Dead Probiotics

Inactivated and dead probiotics, along with postbiotics (commonly known as bioactive compounds made by probiotic bacteria), have garnered attention for their potential health benefits, particularly in gut health and immune function. Various methodologies can be employed to produce these postbiotics, including gamma and ultraviolet radiation, sonication, and chemical treatments. While heat treatment remains the most widely used approach for generating inactivated or dead probiotic organisms (Karbowiak et al., 2022), it is important to note that alternative methods may be preferred based on the specific characteristics required for the postbiotic or in accordance with regulatory standards. The application of heat significantly alters the cellular structure and biological functions of probiotics, effectively eradicating viable cells while preserving key bioactive compounds. This process not only facilitates the release of metabolites, cell wall constituents, and other active substances but also enhances the bioavailability and bioactivity of the resulting postbiotics. Notably, heat treatment has been shown to improve the solubility of specific polysaccharides and proteins, promoting their interaction with intestinal epithelial cells. Such interactions are crucial for maintaining gut health and reinforcing immune responses (Chen et al., 2024).

Recent research on eight different strains of *Lactobacillus reuteri* has demonstrated that both viable and heat-inactivated forms of these bacteria can adhere to Caco-2 cell cultures, a critical characteristic that helps prevent the colonization of harmful pathogens like *E. coli, Salmonella typhi, Listeria monocytogenes,* and *Enterococcus faecalis* (Singh et al., 2017). Furthermore, evidence indicates that heat-inactivated probiotics can still trigger positive immune responses, such as stimulating secretory IgA production and enhancing the integrity of tight junctions in epithelial cells, thereby supporting gut barrier function (Qin et al., 2022). Additionally, heat treatment can lead to the production of bioactive peptides and various metabolites with intrinsic antimicrobial properties (Chai et al., 2020). This underscores the potential of heat-treated probiotics as vital components in therapeutic strategies aimed at combating gastrointestinal pathogens.

5.3. Cell Wall Fragments

Approximately 60% of the total mass of the cell wall in gram-positive bacteria consists of teichoic and lipoteichoic acids (Nguyen et al., 2020). Lipoteichoic acid (LTA) is a significant postbiotic used in wound care and skin health and is found in various wound care products. Its

immunomodulatory properties help regulate inflammation and promote its resolution, facilitating faster and more effective tissue regeneration. LTA also exhibits antimicrobial activity, reducing the risk of infection and enhancing the skin's protective barrier (Wang et al., 2024). Studies indicate that the structure of lipoteichoic acids varies between different strains of *Lactobacillus plantarum*. This structural diversity leads to distinct responses in immune cells, underscoring the complex and strain-specific effects of this postbiotic (Jung et al., 2022).

Teichoic is also notable for its immunogenic properties and is capable of eliciting robust immune responses (John et al., 2025). The role of teichoic acids extends beyond mere structural elements; they are integral to understanding the pathophysiology of bacterial infections and the mechanisms underlying antibiotic resistance. Their involvement is critical, as these acids facilitate various interactions between bacteria and host systems, thus contributing to bacterial adaptability in the face of therapeutic challenges. Significantly, research conducted by Lebeer et al. (2012) emphasizes that the presence of teichoic and lipoteichoic acids is noteworthy because they exhibit various bioactive properties (e.g., anti-cancer, immunomodulatory, and antioxidant effects), pointing to their potential for innovative therapeutic applications.

5.4. Exopolysaccharides (EPS)

Exopolysaccharides (EPS) are biopolymers produced by microorganisms within their growth stages (Nicolescu et al., 2023), with a wide variety of structures (linear to highly branched forms) and monosaccharide composition. Several species of lactic acid bacteria, including *Lactobacillus fermentum*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Pediococcus pentosaceus*, *Lactobacillus delbrueckii* and different species of *Leuconostoc*, are well-known for their capacity to produce EPS (Zhang et al., 2023). The synthesis of extracellular polymeric substances is significantly influenced by the specific strain of microorganisms and is affected by various environmental factors, including the composition of the culture medium, the developmental stage of microbial cells, and conditions such as pH and temperature (Prasad & Purohit, 2023).

In the dairy sector, the exopolysaccharides produced by specific strains of starter cultures offer significant benefits by enhancing the rheological properties of fermented products. They improve hydration and moisture retention, which significantly enhances the overall quality and texture of these products (Liu et al., 2023; Wang et al., 2023). In addition to their functional applications in food science, EPS synthesized by lactic acid bacteria exhibit a wide range of beneficial bio-functional properties. These include antioxidant activities that help neutralize free radicals, as well as the capacity to lower cholesterol levels through binding with free cholesterol. Furthermore, EPS displays immunomodulatory effects, contributes to anti-aging benefits, and plays a vital role in modulating the gut microbiota. Additional bioactivities include anti-toxic properties, inhibition of biofilm formation, and potential antitumor activities, as demonstrated in preclinical studies (Di et al., 2017; Wang et al., 2020; Xu et al., 2019).

5.5. Enzymes

Enzymes, as specialized proteins, play an essential role in accelerating biochemical reactions within living organisms. Enzymes present in postbiotics are key contributors to their bioactivity and potential applications. These enzymes, derived from microbial metabolic activities, include proteases, amylases, cellulases, and lipases. They facilitate the degradation of complex substrates and enhance the production of beneficial compounds. Enzyme-containing postbiotics can also be considered as natural preservatives in food systems. Their ability to produce antimicrobial peptides that inhibit pathogenic microorganisms makes them effective in extending shelf life and improving the nutritional value of food products (Rao et al., 2023).

Enzymatic postbiotics also exhibit significant antioxidant properties, helping to reduce oxidative stress and promote overall health. Two strains of *Lactobacillus fermentum* have been identified to produce notable quantities of glutathione peroxidase (GPx), an enzyme renowned for its potent antioxidant properties in laboratory settings. In therapeutic applications, these enzymes have been shown to support gut health by improving nutrient digestion and absorption, maintaining the intestinal barrier, and modulating immune responses (Ghiasi et al., 2023). In addition to their antioxidant effects, postbiotics can also influence immune system function. By improving gut barrier function and modulating systemic immune responses, they may help prevent harmful bacteria and toxins from entering the bloodstream, which can contribute to systemic inflammation (Arroyo et al., 2023).

Furthermore, certain postbiotics may have direct effects on tumor cells, such as inducing apoptosis (programmed cell death) or inhibiting cell proliferation. These tumor-suppressing effects, in combination with their antioxidant properties, suggest that postbiotics could be a valuable tool in cancer prevention and therapy, offering a natural approach that could complement traditional cancer treatments (Izuddin et al., 2020). Another key aspect of postbiotics is their ability to upregulate hepatic antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT). These enzymes play crucial roles in neutralizing reactive oxygen species (ROS), which are highly reactive molecules that can cause oxidative stress and damage to cellular components, including DNA. Oxidative stress is a key factor in the development and progression of cancer, and by enhancing the activity of these antioxidant enzymes, postbiotics may help reduce the oxidative damage that can lead to cancer (Izuddin et al., 2020).

5.6. Bacteriocins

Bacteriocins, a subset of antimicrobial peptides produced by both Gram-positive and Gram-negative bacteria, are known for their diverse antimicrobial properties (Darbandi et al., 2022). These peptides inhibit the proliferation of closely related bacterial species, thereby contributing to microbial competition and ecological balance. There are four primary categories for classifying bacteriocins, determined by their characteristics, structure, and mechanism of action. The first class, known as Lantibiotics, is usually generated by lactic acid bacteria. Notable examples include Nisin and Lacticin 3147, which are produced by *Lactococcus lactis*, as well as Epidermin, produced by *Staphylococcus epidermidis*. Class 2 are post-translationally modified peptides (PTMs), which undergo significant modifications after translation. PTMs include bacteriocins like Acidocin B (produced by *Lactobacillus acidophilus*) and Pediocin PA-1 (produced by *Pediococcus acidilactici*). Class 3 are non-modified peptides (NMPs), which are relatively small and heat-stable, such as Brevicin (produced by *Brevibacterium*) and Subtilin (produced by *Bacillus subtilis*). The heat stability, attributed to secondary structures such as α-helices and β-sheets (Cotter et al., 2013), prevents NMPs from denaturing and aggregating, allowing them to remain active and functional during high-temperature processes like pasteurization or boiling, making them valuable for food preservation and therapeutic applications (Yang et al., 2014). The final class is Protein-bacteriocins, which are composed of larger, more complex proteins that can interact with multiple targets, including Micacin and Subtilosin (produced by *Bacillus subtilis*) (Alvarez-Sieiro et al., 2016; Field et al., 2018; Zimina et al., 2020).

Lactic acid bacteria (LAB) are essential in the food production industry due to their functions in food processing and fermentation, particularly as natural bio-preservatives that enhance the safety and shelf-life of food products (Raj et al., 2022). The antimicrobial compounds produced by LAB are widely utilized to preserve various foods, including cheese, meat, and vegetables. Nisin, a class I bacteriocin produced by *Lactococcus* species, is employed as a biopreservative in food and has applications in biomedical fields. Nisin is highly effective in inhibiting the growth of bacterial strains resistant to antibiotics, such as methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococci*, and

Clostridium difficile. This mechanism highlights the potential of LAB and their bacteriocins as natural preservatives, as well as their relevance in addressing challenges related to microbial resistance and food safety (Zapaśnik et al., 2022).

5.7.Vitamins

The realm of vitamins is complex and multifaceted, playing a pivotal role in various physiological processes within the human body. As essential nutrients, vitamins facilitate a range of biological activities, including DNA replication, repair, and methylation, which are critical for maintaining cellular integrity and overall health. Riboflavin, for instance, serves as a crucial hydrogen carrier in redox reactions, while vitamin K functions as a key cofactor for gamma carboxylase, a vital enzyme involved in blood clotting. Furthermore, lactic acid bacteria and *Bifidobacterium* species possess the capacity to synthesize essential vitamins, including folate, riboflavin, cobalamin, pyridoxine, thiamine, niacin, and nicotinic acid, which are vital for a diverse array of metabolic processes (Batta et al., 2024; LeBlanc et al., 2013).

Fermented foods (yogurt, cheese, and fermented milk) are significant sources of various vitamins that promote digestive and general health. The gut microbiome also plays a vital role in producing several vitamins (B12, B2, B6, B9, and K), which are essential for energy metabolism, gene regulation, and immune response modulation within the intestinal environment (Pham et al., 2021). Cobalamin, or vitamin B12, is an essential water-soluble vitamin critical for hematopoiesis, red blood cell production, and neuronal function; it is primarily derived from animal-based foods (Malik et al., 2023). The complex relationship between the consumption of fermented foods and the production of B vitamins by gut microbiota highlights the significance of maintaining a balanced and diverse diet for achieving optimal health. Notably, certain B vitamins have been associated with anti-tumorigenic effects, particularly against pro-monocytic lymphoma cells, highlighting their significance in maintaining digestive health and influencing cancer biology (Contestabile et al., 2020; Heilfort et al., 2022).

Lactic acid bacteria also play a significant role in synthesizing essential vitamins, particularly B-group vitamins and vitamin K, which depend on their metabolic pathways and can be influenced by genetic factors and environmental conditions (LeBlanc et al., 2011). *Lactobacillus plantarum* and *Bifidobacterium longum* are capable of synthesizing folate, a crucial vitamin for DNA synthesis and cell division, the pterin and para-aminobenzoic acid (PABA) pathways. The efficiency of folate production varies with fermentation conditions, such as pH and nutrient availability. This makes LAB valuable for increasing folate in fermented foods such as yogurt and kefir (Sybesma et al., 2003). Riboflavin is also synthesized by LAB, such as *Lactobacillus fermentum*. The biosynthesis pathway involves the conversion of GTP into riboflavin through a series of enzymatic reactions. Certain LAB strains overproduce riboflavin due to mutations in related regulatory genes that normally suppress biosynthesis when riboflavin levels are sufficient. This overproduction is beneficial for food fortification, as riboflavin-enriched fermented products can help prevent deficiencies in populations with limited dietary intake (Burgess et al., 2006).

Vitamin B12 is mainly produced by *Propionibacterium freudenreichii* and some *Lactobacillus reuteri*. Most LAB cannot synthesize bioactive B12 for humans but produce pseudocobalamin, which is functionally inactive. However, *Propionibacterium freudenreichii*, commonly used in dairy fermentation, produces bioactive B12 under anaerobic conditions, making it a valuable candidate for B12 fortification in vegan and vegetarian foods (Martens et al., 2002). Another study has also identified specific probiotic strains, including *Lactobacillus sanfranciscensis*, *Lactobacillus reuteri*, *Lactobacillus rossiae*, and *Lactobacillus fermentum*, which possess the genetic ability to synthesize vitamin B12 (LeBlanc et al., 2015). Furthermore, LAB strains like *Lactococcus lactis* and *Bifidobacterium infantis* in the gut also

produce vitamin K2 (menaquinone). They create different forms of menaquinone (like MK-7 and MK-9) from other substances, which are essential for blood clotting and bone health. Since fermented foods and gut bacteria are key sources of vitamin K2 for humans, the menaquinone produced by LAB is crucial for maintaining adequate vitamin K levels (Bentley & Meganathan, 1982). These findings suggest that using probiotics could be a practical alternative for producing vital vitamins industrially, thereby reducing reliance on animal-derived sources.

5.8. Neurotransmitters

Gut microbiota, including *Bifidobacterium* genus, *Lactobacillus plantarum*, *Lactobacillus brevis*, and *Bacillus subtilis*, synthesize neurotransmitters like Serotonin, Dopamine, Norepinephrine, Catecholamines, and Acetylcholine. These biochemical mediators are essential for brain function, as they significantly impact the gut-brain axis and modulate the signaling pathways of enteric nerves (Ortega et al., 2022). Tryptophan, an amino acid, is particularly notable because it is converted to serotonin, a key neurotransmitter involved in mood regulation. Conversely, gamma-aminobutyric acid (GABA) serves as an inhibitory neurotransmitter, and its dysregulation is linked to anxiety and depression (Ortega et al., 2022). Furthermore, acetylcholine and catecholamines are crucial for various central nervous system functions, including emotional regulation, memory consolidation, learning mechanisms, and motor control (Teleanu et al., 2022). The interaction between these neurotransmitters and the gut microbiota highlights the pivotal role of gut health in supporting mental well-being and cognitive performance. Research by Patterson and Turnbaugh (2014) suggests that modulation of the microbiome might help alleviate mental health challenges, such as depression, indicating that these neurotransmitters could possess antidepressant properties.

5.9.Extracellular Vesicles (EVs)

Extracellular vesicles (exosomes) are lipid bilayer-enclosed spherical particles that play a crucial role in mediating intercellular communication among bacteria. These vesicles facilitate the exchange of a variety of biomolecules (glycolipids, polysaccharides, proteins, DNA, RNA, enzymes, and toxins), thereby promoting horizontal gene transfer and modulating bacterial behavior (Yoon et al., 2014). Studies have shown that the biomolecular cargo of these vesicles plays essential roles in regulating gut barrier function, influencing signaling pathways, and maintaining intestinal homeostasis. Furthermore, EVs are involved in lipid metabolism and facilitate interactions between the gut and the central nervous system. Their functions extend to bacterial survival, competition, pathogenesis, immunomodulation, and the ability to rapidly penetrate the mucosal barrier. This capacity may play a role in reducing the risk of sepsis by enhancing the efficient removal of pathogens from the gut lumen (Liang et al., 2022).

The therapeutic potential of EVs has been demonstrated in various studies. For instance, outer membrane vesicles produced by *Pseudomonas aeruginosa* showed antibacterial and antibiofilm activities against *Streptococcus mutans* (Gurunathan, Thangaraj et al., 2023), while extracellular nanovesicles derived from *Bacillus licheniformis* displayed potential to inhibit growth in breast and lung cancer cells. (Gurunathan, Ajmani et al., 2023). These findings suggest that EVs may serve as promising novel therapeutic agents, preventing and treating different diseases, particularly those related to gut health and metabolic disorders (M.A. Kumar et al., 2024).

5.10. Bacterial Lysates (BLs)

Bacterial Lysates (BLs) are generated through the degradation of Gram-positive and Gram-negative bacteria through various chemical or physical processes, with Gram-positive species typically yielding higher concentrations of cell wall components. The resulting lysates can be broadly categorized into three main types: whole-cell lysates containing the complete cellular

complement, cell wall-enriched fractions abundant in immunostimulatory peptidoglycans and teichoic acids, and filtered soluble fractions primarily composed of proteins and metabolites. This structural diversity underlies their wide-ranging biological activities, particularly in modulating immune responses and in the context of the gut-lung axis, which highlights the connections between immune responses in the gastrointestinal tract and the respiratory system (Żółkiewicz et al., 2020). When lyophilized bacterial lysates are administered orally, they reach the Peyer's patches in the small intestine, where they stimulate dendritic cells, activating T and B lymphocytes, thereby enhancing the innate immune response and inducing the rate of immunoglobulin A (IgA) production as mature lymphocytes migrate toward the mucosal membranes of the respiratory tract (Fesseha, 2022). Secretory immunoglobulin A (SIgA) plays a crucial role in immune defense by preventing pathogen adhesion, neutralizing viruses and toxins, and modulating immune responses without inducing excessive inflammation. In the respiratory system, SIgA serves as the first line of defense against inhaled pathogens such as influenza viruses, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis* (Woof & Mestecky, 2015).

Another research study suggests that the multimodal immunomodulatory effects of bacterial lysates may offer novel therapeutic opportunities in oncology by harnessing the body's natural defense mechanisms against malignant cells (Żółkiewicz et al., 2020). They function as potent immune system activators, stimulating antigen-presenting cells such as dendritic cells and macrophages to initiate robust antitumor immune responses. The immunogenic components within lysates, particularly peptidoglycans and lipopolysaccharides promote the production of pro-inflammatory cytokines and type I interferons, creating a tumor-hostile microenvironment while simultaneously enhancing the cytotoxic activity of natural killer cells and CD8+ T lymphocytes. Lysates can also induce apoptotic pathways in malignant cells and restrict the tumor's blood supply. All these multifaceted mechanisms position bacterial lysates as promising candidates for cancer immunotherapy (Górska et al., 2019). Moreover, bacterial lysates have shown efficacy in reducing recurrent upper respiratory tract infections in pediatric populations (Scarpellini et al., 2021).

A 2018 comprehensive meta-analysis of 53 randomized controlled trials, involving nearly 4,800 children, demonstrated that a commercially available bacterial lysate preparation (Broncho-Vaxom) significantly reduced the frequency of respiratory infections compared to control groups. This systematic review, which searched multiple databases up to January 2017, also indicated benefits in the duration of infections, associated symptoms, and immunological parameters. However, the authors noted the overall level of evidence was low, underscoring the need for further high-quality, large-scale trials to confirm these findings and fully establish the potential of bacterial lysates as a therapeutic intervention for recurrent respiratory illnesses in children (Yin, Xu et al. 2018). Additionally, the intake of heat-inactivated *Lactobacillus paracasei* has been associated with symptom relief in conditions like dry eye syndrome, which can result from prolonged exposure to blue light emitted by LED screens (Morita et al., 2018). This suggests that bacterial lysates may have broader implications for immune health and disease management beyond respiratory health.

6. Postbiotics and Cancer

Cancer continues to be a major cause of death globally, with its incidence continuing to rise due to an aging population and lifestyle factors (Mahmood & Srivastava, 2022). Cancer is defined by uncontrolled cell proliferation and the potential for metastasis, consisting of over 100 different types and classified into six major groups based on tissue types: carcinoma, lymphoma, sarcoma, myeloma, leukemia, and mixed types. Among these, breast, lung, colon, prostate, and stomach cancer are the most prevalent (Sriharikrishnaa et al., 2023). Treatment approaches are complex and typically involve surgery, chemotherapy, immunotherapy, and radiation therapy. However,

these conventional treatments often cause significant side effects that can diminish patients' quality of life (Kaur, Bhardwaj et al., 2023). Recently, there has been increasing interest in the potential role of probiotics and postbiotics as adjuncts in cancer therapy. Emerging evidence suggests that these microbial-derived products may enhance the effectiveness of chemotherapy and reduce adverse effects (Lu et al., 2021). As research progresses, understanding the mechanisms by which postbiotics exert anti-cancer effects is crucial for developing innovative and more tolerable therapeutic strategies.

In vitro and in vivo studies on postbiotics highlight their significant anti-cancer properties through various mechanisms (Fig 2). These mechanisms include the modulation of the immune responses, reduction of genetic mutations, and enhancement of programmed cell death (apoptosis) in cancer cells (Kim et al., 2010; Song et al., 2023; Sudaarsan & Ghosh, 2024). Postbiotics also enhance the immune response, thereby strengthening the body's defenses against cancer and improving overall anti-cancer efficacy. They can promote gut health by improving intestinal barrier function and fostering beneficial gut bacteria, key factors in preventing gastrointestinal cancers (Zhou et al., 2024). Another study further reveals that postbiotics can reduce tumor growth and metastasis by inhibiting carcinogenic signaling pathways (Mishra et al., 2024). Moreover, the antioxidant capabilities help neutralize free radicals, protecting cells from oxidative stress and preventing DNA damage (Thorakkattu et al., 2022). They can also prevent new blood vessel formation and exhibit selective cytotoxicity against cancer cells (Nowak et al., 2022; Ou et al., 2013). Postbiotics can also produce antimicrobial peptides that are effective against harmful bacteria. Maintaining a healthy balance of gut microbiota is essential for overall health, and an imbalance can contribute to cancer risk. By producing antimicrobial substances, postbiotics help prevent the overgrowth of pathogenic bacteria, thereby supporting gut health and potentially reducing cancer risk (Sivan et al., 2015). An overview of the effects of postbiotics is presented in Table 2**:** Mechanisms that Contribute to the Efficacy of Postbiotics Against Various Types of Cancer, Summarized in Table 3

6.1. Colorectal Cancer

Postbiotics, particularly the short-chain fatty acid butyrate produced by gut bacteria, show significant promise in the management of colorectal cancer. Research consistently demonstrates that butyrate inhibits the growth of colorectal cancer cells by promoting programmed cell death (apoptosis) and halting their division cycle (cell cycle arrest) (Woof & Mestecky, 2015; Song et al., 2023). Beyond these direct effects on cancer cells, butyrate also contributes to an anti-inflammatory environment by increasing the production of anti-inflammatory signaling molecules, which can help prevent cancer progression (Rafter, 2003; Martens et al., 2002). Chronic inflammation is a significant risk factor for colorectal cancer, and postbiotics like butyrate can mitigate this risk by modulating the body's immune response (Martens et al., 2002). Furthermore, specific postbiotics derived from *Lactobacillus rhamnosus GG* and *Lactobacillus casei* have also shown anti-cancer effects in the context of colorectal cancer (Escamilla et al., 2012). Clinical observations in patients with colorectal cancer who received postbiotic supplements have indicated benefits such as reduced tumor size and improved immune responses (Rad et al. 2021). Also, catalase derived from a genetically modified strain of *Lactococcus lactis* has demonstrated promising protective effects against chemically induced colon cancer in murine models (de Moreno de Leblanc, LeBlanc et al. 2008).

6.2. Cervical Cancer

Research on cervical cancer indicates that cell-free supernatants (CFS) derived from human breast milk, specifically those containing *Lactobacillus casei* and *Lactobacillus paracasei*, demonstrate anti-cancer properties against cervical cancer cell lines (Rajoka, Zhao et al. 2018).

6.3. Breast Cancer

Propionate, another short-chain fatty acid derived from postbiotic fermentation, has shown the potential to inhibit the growth of breast cancer cells. Studies have demonstrated that propionate can induce apoptosis and inhibit cell proliferation in breast cancer cell lines (Dameshghian et al., 2024).

6.4. Liver Cancer

Liver cancer cells have also shown responsiveness to postbiotic compounds like propionate. Research indicates that propionate can affect liver cancer cell behavior, inhibit the proliferation of liver cancer cells, and induce apoptosis, thereby reducing tumor growth (Bindels et al., 2012).

6.5. Gastric Cancer

Postbiotics derived from *Lactobacillus* species have shown potential in addressing gastric cancer. These postbiotics can inhibit the growth of *Helicobacter pylori*, a bacterium known to increase the risk of gastric cancer (Ohland & MacNaughton, 2010). Furthermore, they can induce apoptosis in gastric cancer cells (Cimini, D'ambrosio et al. 2022). Research also suggests that postbiotics from *Lactobacillus* and *Bifidobacterium* species can generally reduce the multiplication of cancer cells, particularly in the gastrointestinal tract (Liang & Xing, 2023).

6.6. Mechanisms of Cancer Inhibition

Research indicates that postbiotics can inhibit cancer cell invasion by reducing the activity and expression of matrix metalloproteinase-9 (MMP-9), a key enzyme involved in the degradation of the extracellular matrix, ranging from 26% to 39%. They can also enhance the integrity of epithelial barriers by increasing the levels of the tight junction protein ZO-1, with reported increases between 34% and 70%. This strengthening of the epithelial barrier helps to limit the spread of cancer cells. The anti-invasive effects are primarily attributed to macromolecular bioactive components within the postbiotics, specifically fractions larger than 30 kDa, likely comprising proteins or polysaccharides. In contrast, smaller molecules below 3 kDa do not demonstrate this activity (Escamilla et al., 2012). These findings suggest that postbiotics could complement cancer therapies. Further research should identify the specific bioactive compounds and optimize delivery methods for clinical use.

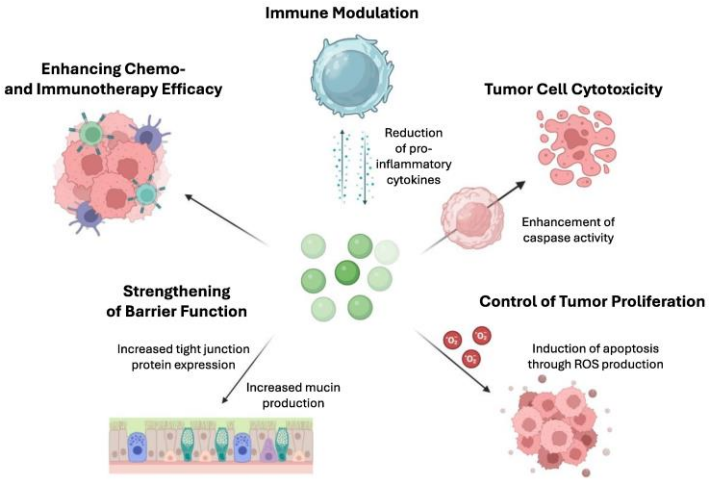

Figure 1: *Mechanisms Involved in the Effectiveness of Postbiotics in Cancer Therapy (Balendra et al., 2024)*

Table 2: *Summary of the Effects of Postbiotics*

Mechanism	Effect of Postbiotics
Cancer Cell Apoptosis Induction	Postbiotics are recognized for their ability to hinder the growth and proliferation of cancer cells by altering apoptosis-related signaling via death receptor and mitochondrial pathways. HeLa cells demonstrate both intrinsic and extrinsic apoptosis when exposed to postbiotics (Asoudeh-Fard et al., 2024).
Preventing Cancer Cell Cycle Progression	Cell cycle arrest induced by postbiotics results in suppressed growth by modulating cell division. Antiproliferative effects have been noted against different cancer cell lines through mechanisms that involve cell wall components, peptidoglycans, cytoplasmic extracts, and supernatants (Mishra et al., 2024).
Autophagic Induction in Cancer Cells	Autophagy, which maintains intracellular homeostasis, is promoted by postbiotics and is associated with tumor growth inhibition in cancer cells (Zhong et al., 2024).
Immune Response Modulation	The balance between tumor microenvironment and immune responses, influenced by postbiotics, plays a crucial role in carcinogenesis and is essential for therapeutic interventions and prevention, affecting neutrophils, macrophages, and anti-inflammatory cytokines (Żółkiewicz et al., 2020).
Enhanced Cellular Connection and Gut Barrier Proteins	The mucus layer maintains homeostasis while intestinal epithelial cells protect the gut. Postbiotics enhance tight junction integrity between epithelial cells, with SCFA, particularly butyrate, contributing to colorectal cancer prevention and treatment (Song et al., 2023).
Inhibition of Bacterial Pathogen Growth	Diets enriched with heat-killed bacteria support beneficial microbial growth, while acidic conditions in the gut hinder pathogenic bacteria. Postbiotics may reduce cancer risk by modifying gut microbiota composition, diversity, and richness (Sivan et al., 2015).

Table 3: In Vitro and In Vivo Evidence of the Anti-cancer Effects of Postbiotics

Postbiotic Used	Type of Study	Bacterial Source	Type of Cancer	Metabolic Pathway	Antitumor Activity	Reference
Extracellular vesicles, Cell-free supernatant	In-vitro	*Lactobacillus spp. (Lactobacillus crispatus)*	Gastric cancer	Modulation of immune response, Apoptosis induction	Inhibits proliferation of gastric cancer cell lines, Inhibit the growth of *Helicobacter pylori*	(Fakharian et al., 2024)
Short-chain fatty acids (SCFAs)	In-vivo	*Bifidobacterium spp Lactobacillus spp.*	Colorectal cancer	Histone deacetylase inhibition, Apoptosis induction	Reduces tumor growth in animal models	(Rad et al., 2020), (Song et al., 2023)
Propionate (SCFAs)	In-vitro	*Lactobacillus plantarum*	Breast cancer	Immune modulation, Apoptosis induction, Growth inhibition	Suppresses breast cancer cell proliferation	(Dameshghian et al., 2024)
Extracellular nanovesicles	In-vitro	*Bacillus licheniformis*	Breast cancer	Reduction of inflammation, Apoptosis induction, Growth inhibition	Suppresses breast cancer cell proliferation	(Gurunathan, Ajmani, et al., 2023)
Butyrate (SCFAs)	In-vitro	Various probiotic strains	Liver cancer	Apoptosis induction, Growth inhibition	Inhibit the proliferation of liver cancer cells	(Panebianco et al., 2022)
Cell-free supernatants	In vitro	*Lactobacillus* spp.	Cervical cancer	Apoptosis induction, Growth inhibition	Inhibit the proliferation of HeLa cells	(Asoudeh-Fard et al., 2024)

7. Advantages and Disadvantages of Postbiotics in Cancer Therapy

Postbiotics are a relatively new concept in the realm of health and nutrition, particularly regarding their potential impact on cancer prevention and treatment (Alvarez-Sieiro et al., 2016). A significant advantage of postbiotics is their stability and safety. As non-viable entities, they tend to be more stable than live probiotics and have a favorable safety profile, making them ideal for prolonged use (Salminen et al., 2021). Moreover, they complement traditional cancer treatments such as chemotherapy and radiotherapy. By improving gut health and reducing side effects associated with these treatments (Iida et al., 2013), postbiotics could enhance overall effectiveness and hold promise as adjuvant therapies (Rad et al., 2020).

However, there are significant challenges and limitations associated with their use. A significant obstacle is the lack of extensive clinical evidence supporting the efficacy of postbiotics in cancer treatment (Abbasi, Saadat et al., 2022). For example, most studies have been conducted in animal models or laboratory settings, and more rigorous clinical trials are necessary to confirm their effectiveness and safety in human patients (Zheng et al., 2020). Furthermore, variability in the composition of postbiotics can lead to inconsistencies in the effectiveness of different postbiotic preparations. Without standardized production methods, the results obtained from postbiotic supplements may vary, affecting their reliability as a cancer treatment option (Aguilar-Toalá et al., 2018). Although postbiotics are generally safe, some individuals might experience side effects such as gastrointestinal discomfort or allergic reactions (Ma et al., 2023). There is also a lack of long-term safety data, which raises concerns about potential adverse effects with prolonged use. Therefore, careful monitoring and further research are required to ensure their safety (Patel & DuPont, 2015). Additionally, the optimal dosage and administration methods for postbiotics are not well-defined. Without established guidelines, determining the correct amount and frequency of postbiotic use can be challenging. This uncertainty makes it difficult to standardize treatments and assess their overall effectiveness (O'Callaghan & Van Sinderen, 2016). The effects of postbiotics on the existing gut microbiota are not fully understood as well. While they can help maintain gut health, there is a potential risk that they might disrupt the balance of gut bacteria. Such disruptions could have unintended consequences, potentially affecting digestive health and overall well-being (Ma et al., 2023; Ohland & MacNaughton, 2010). Postbiotics face regulatory and quality control challenges as they are relatively new in the field of health supplements and therapeutics. Ensuring consistent quality and efficacy across different products can be difficult, which may affect their acceptance and widespread use. Effective regulation and quality assurance are essential to ensure that postbiotic products meet safety and efficacy standards (Salminen et al., 2021). Addressing these challenges is essential for enhancing the clinical use of postbiotics in cancer therapy and maximizing their therapeutic potential. Further clinical trials are needed to confirm initial findings, evaluate long-term benefits, and identify potential side effects. Future research should focus on determining the most effective postbiotic compounds and their optimal dosages, as well as exploring their interactions with conventional cancer therapies for integrative treatment approaches (Kim et al., 2021).

8. Conclusion

In conclusion, the evolving field of postbiotics presents exciting opportunities for enhancing health and potentially revolutionizing dietary and therapeutic interventions. Postbiotics, as non-viable microbial metabolites, offer a distinct avenue for promoting well-being without the complexities associated with live probiotics. The health benefits of postbiotics, particularly in areas such as gut health, immune modulation, and even cancer therapy, have been highlighted in this paper. However, the ongoing discourse surrounding the precise definitions, classifications, and mechanisms of action of postbiotics emphasizes the need for further investigation. Continued exploration will not only

clarify existing uncertainties but also pave the way for innovative applications in food production, pharmaceuticals, and nutraceuticals. Ultimately, understanding and harnessing the power of postbiotics may lead to enhanced nutritional strategies and therapeutic approaches that effectively address both current and future health challenges.

Conflict of interest

The authors have no conflict of Interest.

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Figure 1 was created using icons obtained from various online sources, including

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Authors' Contributions

P.S Contributed to conceptualization, supervision, writing the original draft, review, and editing. S.A and P.G contributed to writing the original draft and review. S.S, S.I, H.R, A.S and Z.R contributed to writing the original draft.

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