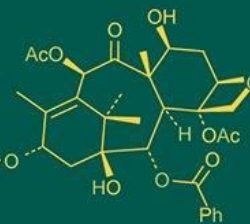
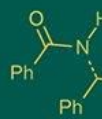
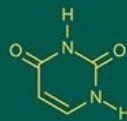
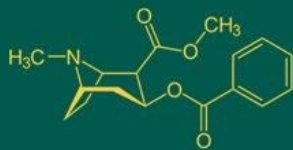


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Postbiotics: A developing notion to application

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Abstract

Postbiotics, encompassing non-viable whole cells, cell fragments, and microbial metabolites produced by probiotic microorganisms, are gaining increasing attention due to their beneficial effects on the host. These compounds include a diverse range of substances such as short-chain fatty acids, teichoic acids, lipoteichoic acids, bacterial lysates, vitamins, plasmalogens, enzymes, and peptides. Their growing interest stems from their capacity to modulate the gut microbiome along with antimicrobial, anti-inflammatory, anti-obesity and immunity boosting properties. Emerging technologies such as electric field, ultrasonication, high pressure, ionizing radiation, pulsed light, magnetic field heating and plasma technology can be explored for the production of postbiotics.

Keywords: Postbiotics, gut microbiome, metabolomics, biocontrol

Introduction

The concept of "biotics" has recently gained public recognition and includes terms such as probiotics, prebiotics, and synbiotics, which have been popular since the 1990s. The Food and Agriculture Organization of the United Nations and the World Health Organization (FAO-WHO) define probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." Prebiotics, meanwhile, are non-digestible food ingredients that positively impact the host. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines prebiotics as "a substrate that is selectively utilized by host microorganisms, conferring a health benefit." Prebiotics, which include dietary fibers, phenolics, phytochemicals, conjugated linoleic acids, polyunsaturated fatty acids, lactulose, inulin, human milk oligosaccharides (HMOs), and various oligosaccharides, can enhance host health by altering the microbiota composition and promoting the growth of beneficial species (Gurunathan S *et al.*, 2023) [14]. Synbiotics, a synergistic combination of prebiotics and probiotics, improve the survival and colonization of live microbes in the gastrointestinal (GI) tract, thereby providing further health benefits (Rasaei N., 2024; Wegh, C.A.M., 2019) [29, 39]. However, the effectiveness of probiotics relies on the viability of the microorganisms, prompting researchers to explore alternatives. This led to the development of postbiotics, which, unlike prebiotics and probiotics, do not contain live microorganisms, resulting in a longer shelf life, greater stability, and numerous health benefits. This review provides a concise overview of the concept of postbiotics, their production methods, classification, and their impact on human and health.

Postbiotics-concept

Postbiotics are low molecular weight soluble compounds derived from live microflora or released after cell lysis. This term encompasses non-viable microbial cells, metabolic byproducts, and their microbial components. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines postbiotics as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (Hill *et al.*, 2014) [15]. ISAPP consensus statement identified five mechanisms through which postbiotics exert their effects: i) modulation of the resident microbiota, ii) enhancement of epithelial barrier functions, iii) modulation of local and systemic immune responses, iv) modulation of systemic metabolic responses, and v) systemic signaling through the nervous system. Postbiotics can have beneficial effects not only in the intestine but also in other organs of humans and animals. Due to their safer profile, postbiotics can be administered anywhere on the host's surface.

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Although postbiotics include metabolites, purified metabolites, and vaccines are excluded from this category. Besides the health benefits discussed here the health benefits attributed to postbiotics include immunomodulatory, antimicrobial, and anticancer effects, as well as the reduction of inflammation, oxidative stress, blood pressure, cholesterol levels, and body weight (Gurunathan *et al.*, 2023) ^[14]. It is believed that the postbiotic content of the body can be enhanced by consuming the foods like buttermilk, cottage cheese, fermented pickles, yogurt, fiber-rich oats, garlic, and flaxseeds. However, overconsumption of postbiotics may have adverse effects on immunocompromised individuals.

The effectiveness of postbiotics can be influenced by both internal and external factors, as reported in various studies (Rad *et al.*, 2020). Internal factors, such as resident microbiota, enzymes, and food components, can inhibit the function of postbiotic metabolites activity (Rad *et al.*, 2020). Postbiotic dysfunction is mainly associated with proteolytic enzymes (Izuddin *et al.*, 2020) ^[17]. Proteolytic enzymes that interfere with the activity of postbiotic metabolites include chymotrypsin, pepsin etc., (Rad *et al.*, 2020; Izuddin *et al.*, 2020) ^[28, 17]. The optimal pH required for postbiotic activity is between 4 and 9. Among external factors, hydrogen ions can alter postbiotic activity. Foods like pasteurized milk and ground meat, which have an optimal pH, do not interfere with postbiotic function. (Moradi *et al.*, 2020) ^[24]. Temperature variation also affects the antimicrobial activity of postbiotics, (Mirnejad *et al.*, 2013) ^[23]. Therefore, temperature and pH are crucial factors for the production of postbiotics.

Production of postbiotics

The production of postbiotics involves a series of steps. The process begins with the careful selection of specific strains

of microorganisms, often those that are known to produce beneficial metabolites during their life cycle or after cell lysis Aguilar-Toalá *et al.*, 2018, Barros *et al.*, 2020) ^[2, 5]. These strains can be probiotics like *Lactobacillus*, *Bifidobacterium*, or other beneficial microbes. The selected microorganisms are cultivated under controlled fermentation conditions. This step is critical as the growth environment, including factors such as temperature, pH, and nutrient availability, influences the types and quantities of metabolites produced. After fermentation, the microbial biomass and the culture medium are harvested. The culture medium contains the metabolites and other soluble compounds that are released during the growth or after the lysis of the microbial cells (Barros *et al.*, 2020) ^[5]. Postbiotic biomass can be initially separated into cell filtrate and inanimate microorganisms by simple filtration techniques (Vinderola *et al.*, 2022, Barros *et al.*, 2020) ^[38, 5]. The most common method for extracting postbiotics involves separating bioactive extracellular metabolites from the cells that produce them through techniques such as centrifugation, sonication, and ultrafiltration. Effective approaches to inactivate live organisms and produce postbiotics include ohmic heating, supercritical CO₂ treatment, pH adjustments, pulsed electric fields, and drying (Cuevas-González, 2020; de Almada, C.N. 2016) ^[9, 11]. Emerging technologies like electric fields, ultrasonication, high pressure, ionizing radiation, pulsed light, magnetic field heating, and plasma technology offer potential for inactivating microorganisms by preserving overall quality and nutritional value. Metabolomics can also be utilized to quantify postbiotics (Vinderola *et al.*, 2022) ^[38]. Figure 1 Depicts the pathways for the preparation of postbiotic cultures comprising of whole cells or their fragments, with and without metabolites or fermentation products.

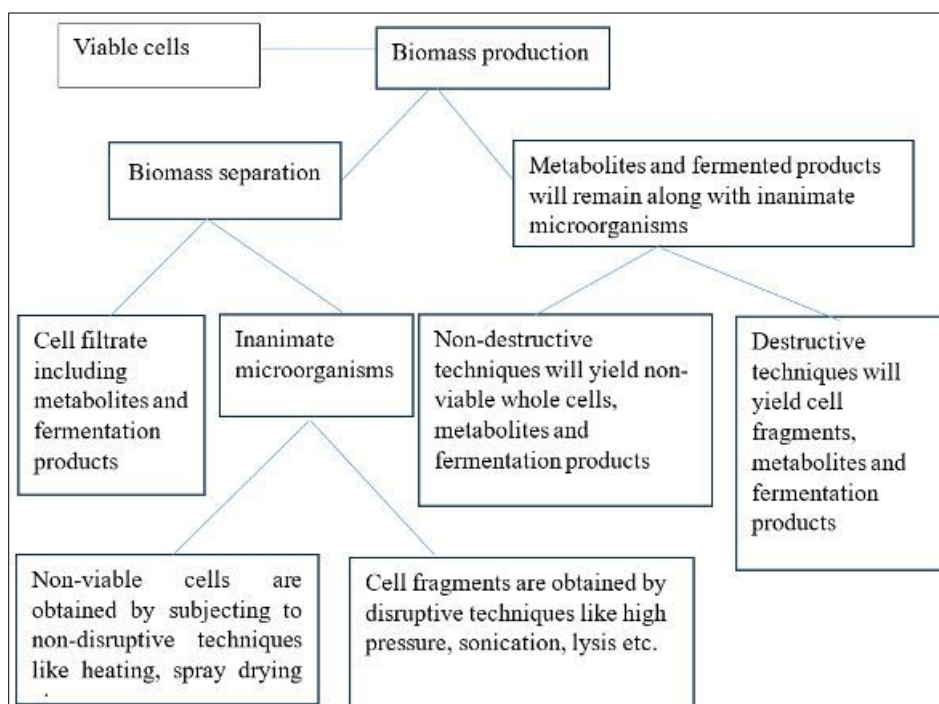


Fig 1: Production of postbiotics (after da Silva Vale A *et al.*, 2023, Vinderola *et al.*, 2022) ^[10, 38]

Classification of postbiotics

Postbiotics is an umbrella term that includes a wide range of components such as inanimate microorganisms, cell wall

fragments, cell-free supernatants, and metabolites. It includes fermentation products like muropeptides derived from peptidoglycans, exopolysaccharides (EPSs), teichoic

acids, surface molecules that protrude out (e.g., fimbriae, pili, or flagella), secreted proteins/peptides, bacteriocins (such as acidophilin, reuterin, and bifidin), organic acids, bioactive peptides, biosurfactants and neurotransmitters. Postbiotics can be classified based on their composition and origin. The main categories include:

- 1. Metabolites:** These are small molecules produced by microbes during fermentation or metabolism. Short-chain fatty acids (SCFAs) are one such metabolite. Three most common metal ions that makeup SCFAs, during microbial fermentation include propionate (C3), acetate (C2), and butyrate (C4). The proportion of acetate, propionate and butyrate in the colon and feces is 60:20:20 (Prajapati *et al.*, 2023; Thorakkattu P., 2022) [27, 36]. Short chain fatty acids will maintain the mucosal barrier in the intestine and acts as signaling molecule. It has the ability to improve insulin homeostasis, and glucose and lipid metabolism. They will also assist the growth of probiotic bacteria in gut. Other metabolites include vitamins, amino acids, exopolysaccharides, organic acids and peptides. Most widely discussed antimicrobial peptide include bacteriocins. Soltani *et al.* in 2021 emphasize the therapeutic potential of bacteriocins as next-generation antimicrobials for combating drug-resistant pathogenic organisms, noting their targeted broad-spectrum inhibitory effects against bacterial growth.
- 2. Cell Wall Components:** Microbial cell wall components, such as peptidoglycans, teichoic acids (TA), and lipopolysaccharides, are known for their immune-modulating effects. Teichoic acid glycopolymers are essential components of Gram-positive bacterial cell walls, playing roles in immune response and antimicrobial resistance. Both TA and lipoteichoic acids (LTA) display various bioactivities, including anticancer, immunomodulatory, and antioxidant properties. LTA can activate the immune system by interacting with toll-like receptors (TLRs) and shows potential for therapeutic or preventive use in

managing metabolic syndrome and diabetes-related disorders. (Żółkiewicz *et al.*, 2020) [43].

- 3. Cell-free Supernatants:** These are liquids obtained after removing live bacteria from fermented products, containing various bioactive compounds with low or high molecular weights, such as organic acids, diacetylene, carbon dioxide, and bacteriocin-like substances that will help to maintain homeostasis in the body (Kapustian, V *et al.*; 2018; Siedler, S. *et al.*; 2019) [18, 31]. After incubating the liquid culture, the microbes are centrifuged and removed. The resulting mixture thus obtained is filtered to ensure sterility. Supernatants of different organisms exhibit different activities. Some exhibit anti-oxidant and anti-inflammatory effect on intestinal epithelial cells, macrophages and neutrophils by reducing the secretion of the pro-inflammatory tumour necrosis factor. Many of the cell-free supernatants can reduce oxidative stress *in vivo* and provide direct anti-tumour activity (Amaretti *et al.*, 2013) [3].
- 4. Enzymes and Proteins:** Enzymes such as lactase or antimicrobial proteins produced by microorganisms can contribute to health benefits. Enzymes are categorized into six main groups: transferases, isomerases, hydrolases, oxidoreductases, lyases, and ligases.
- 5. Microbial Lysates:** Inactivated or dead microbial cells that release their internal components, which can positively affect the host's health. Characteristics such as oxygen scavenging ability, and modifying host physiology, are retained by nonviable cells. Studies proved that both live and heat-killed cells of *Lactobacillus reuteri* adhered to Caco-2 cell cultures and prevented enteropathogens from adhering to them (Singh, T.P *et al.*, 2017) [32].

Each type of postbiotic offers distinct health benefits, such as modulating the immune system, improving gut health, or exhibiting antimicrobial properties. Table 1. Shows a classification of postbiotics.

Table 1: Classification of postbiotics (Zhong *et al.*, 2022; Park *et al.*, 2023) [42, 26]

Category	Description	Example
Metabolites	Small molecules produced by microbes during fermentation or metabolism.	Short-chain fatty acids (SCFAs), vitamins, amino acids, peptides, exopolysaccharides.
Cell Wall Components	Components of microbial cell walls with immune-modulating and antimicrobial properties	Peptidoglycan derived muropeptides, teichoic acids (TA), lipopolysaccharides (LPS), Surface layer protein, dimethyl acetyl derived plasmalogen, Polysaccharides, cell surface proteins
Cell-free Supernatants	Liquids containing bioactive compounds after removing live bacteria from fermented products.	Organic acids, bacteriocins
Enzymes and Proteins	Microbial enzymes and proteins that contribute to health benefits.	Lactase, antimicrobial proteins, exopolysaccharides

Effect of postbiotics on human health

Postbiotics as anti-inflammatory agents

Inflammation is considered as the first response of an organism towards infection or inflammatory disorders such as inflammatory bowel disease, atherosclerosis, chronic inflammation etc. Postbiotics influence inflammatory pathways by modulating the transcription of pro-inflammatory genes and the expression of related proteins. Their effect on the inflammatory response, however, varies based on factors like their source, bacterial species and strains, the use of cell-free supernatant (CFS), and heat-killed bacteria (HKB). Evidence shows that postbiotics can produce both anti-inflammatory and immunostimulatory

effects, reflecting the diverse structures and compositions found in different postbiotic formulations. (De Marco *et al.*, 2018; Uchinaka *et al.*, 2018) [12, 37]. *Bifidobacterium longum*, when used as a whole-cell postbiotic, has demonstrated several barrier-protection properties, including antioxidation, anti-inflammation, and the inhibition of bacterial colonization (Ma *et al.*, 2023) [21]. Similarly, certain whole-cell postbiotic products derived from *Lactobacillus* species have shown anti-inflammatory effects, such as the downregulation of IL-6 and TNF- α and the upregulation of IL-10, along with antioxidative properties like free radical scavenging, in both *in vitro* and *in vivo* animal models (Behzadi *et al.*, 2022) [6]. Products from certain Gram-

positive bacteria can activate signaling pathways, such as TLR2, leading to anti-inflammatory states and enhancing transepithelial resistance against bacterial invasion. Short-chain fatty acids (SCFAs) are particularly effective in reducing inflammation and inhibiting malignant cell growth, making them therapeutically valuable in treating inflammatory bowel disease (IBD) and colorectal cancer. Additionally, postbiotic metabolites, including amino acids, bacteriocins, SCFAs, peptide glycan-derived muropeptides, and vitamins, contribute to promoting and enhancing anti-inflammatory functions in the human gut (Ma *et al.*, 2023) [21].

Postbiotics as immunomodulators

Postbiotics are widely recognized for their ability to modulate the immune system, including both innate and adaptive responses, while also maintaining intestinal mucosal barrier integrity and countering potential pathogens (Yeşilyurt N *et al.*, 2021; De Marco, S *et al.*, 2018) [41, 12]. Their anti-inflammatory properties help regulate acute inflammatory responses and prevent gut disruption by activating pathways related to specific immune responses. Several bioactive components in postbiotics contribute to these effects. For example, bacterial peptidoglycan (PGN) and lipopolysaccharide (LPS) can stimulate the immune system in a receptor-dependent manner. Similarly, the surface layer (S-layer) of lactobacilli, formed by the self-assembly of glycoprotein subunits, is known to enhance host immune responses. Other microbial metabolites, such as histamine and branched-chain fatty acids, also play a role in stimulating the immune system. Postbiotics offer additional protective benefits against pathogens. Pure teichoic acids isolated from *Lactobacillus* strains can inhibit biofilm formation by oral and enteric pathogens, including *Streptococcus mutans*, *Staphylococcus aureus*, and *Enterococcus faecalis*. Biosurfactants from *Lactobacillus gasseri* have demonstrated antibiofilm activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Furthermore, organic acids and intracellular components like pyrrole derivatives have been found to exhibit oxidative inhibitory activity. *In vitro* studies have highlighted the antioxidant properties of intracellular contents and cellular fractions from strains such as *Lactobacillus casei* and *Bacillus coagulans* (Ma *et al.*, 2023) [21]. Studies also show that postbiotics from *Lactobacillus* species support immune function by protecting the intestinal barrier and promoting pathogen aggregation through antagonistic activity (Teame *et al.*, 2020) [35]. Interestingly, the immunomodulatory effects of postbiotics produced by inactivating probiotics are often stronger than those of live probiotics. For instance, heat shock proteins (Hsp) generated during the heating process have been found to enhance immunomodulatory activity (De Almada, C.N. *et al.*, 2016) [11].

Postbiotics against obesity

Consumption of biotics is said to have favourable effect on anthropometric indices of obesity in the normal population. Major cell wall components that play a crucial role as anti-obese factors include muramyl dipeptidase, lipoteichoic acids, exopolysaccharides and S layer proteins. Studies proved that supplementing with muramyl dipeptide, an excellent postbiotic, will assist in lowering adipose inflammation and glucose intolerance in obese mice (Cavallari, *et al.*, 2017) [8]. Another important cell wall

component of microorganism is surface layer protein (SLP). SLP generally attach to the host intestinal wall (Nataraj *et al.*, 2020, Fagan, *et al.*, 2014) [25, 13]. SLPs act against obesity and metabolic disturbances by improving systemic inflammation, insulin resistance and adipogenesis (Kim *et al.*, 2021) [20]. A recent report demonstrated the fat-reducing effects of lipoteichoic acid (LTA) from *Bifidobacterium animalis* subsp. *lactis* BPL1 using the nematode *Caenorhabditis elegans* as a pre-clinical model. Lipoteichoic acid is a novel lipid modulator which has the ability to reduce fat through insulin-like signalling pathway. Study also suggests that lipoteichoic acid may have potent preventive and therapeutic application in metabolic syndrome and diabetes related diseases. (Balaguer, *et al.*, 2022) [4]. Short chain fatty acids like acetate, propionate, butyrate etc are said to have reduction in cholesterol level, inhibiting weight gain and promoting beige adipogenesis (Lu, *et al.*, 2016, Weitkunat *et al.*, 2017) [19, 40].

Postbiotics as cosmetic

Postbiotics are applied either by incorporating them into topical formulations, such as creams, or by encapsulating them for oral administration (Catic, T *et al.*, 2022; Inoue, Y *et al.*, 2014) [7, 16]. Research has shown that cold creams containing postbiotic components from *Lactobacillus fermentum* ATCC9338, *Lactobacillus reuteri* ATCC 23272, and *Bacillus subtilis* can accelerate wound healing (da Silva Vale *et al.*, 2023) [10]. Additionally, postbiotics have been found to enhance UV protection and delay the aging process of skin cells. Oral intake of heat-killed cells from the *Lactococcus lactis* strain H61 has been shown to improve skin properties, such as reducing dehydration caused by seasonal changes and enhancing skin elasticity on the inner forearms.

Conclusion

Postbiotics represent a promising frontier in microbiome research and therapeutic interventions. They support gut health and immune function to potentially mitigate various diseases. They also play important roles in weight management, skin care and mental health. Through further research, innovation, and collaboration across scientific disciplines, we can unlock the full potential of postbiotics to revolutionize healthcare and enhance the quality of life for individuals worldwide.

Conflict of Interest

None declared.

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