Antioxidant activity of postbiotics 26

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CHAPTER

Antioxidant activity of postbiotics 26

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1. Introduction

There is an interest among consumers toward healthier food choices, driven by a growing awareness of functional foods due to their nutritional value and health effects.

Probiotics are living microorganisms when administered in adequate amounts, confer a health benefit on the host (Holzapfel & Schillinger, 2002). Prebiotics are nondigestible food ingredients that refer to substances that positively impact the host's health by selectively promoting the growth and/or activity of specific bacteria in the colon (Davani-Davari et al., 2019). Symbiotics are a combination of probiotics and prebiotics that can function independently to provide individual health benefits or work together synergistically to offer a unique health benefit (Thorakkattu et al., 2022).

Postbiotic refers specifically to substances that are derived after microorganisms are no longer alive, essentially referring to inanimate, dead, or inactivated components. These are short-chain fatty acids (SCFAs), proteins, enzymes; superoxide dismutase, glutathione peroxidase, and catalase (Izuddin et al., 2020; Kullisaar et al., 2002; Tang et al., 2018) or peptides, and extracellular polysaccharides (Vallejo-Cordoba et al., 2020). However, the specific health-improving properties and bioactivities of postbiotics are very few, antioxidant activities are prominent (Cuevas-Gonzalez, Liceaga et al., 2020; Thorakkattu et al., 2022).

De Oliveira Coelho et al. (2019) revealed that extracellular and intracellular contents of *Leuconostoc mesenteroides*, *Lactobacillus satsumensis*, and *Saccharomyces cerevisiae* exhibited considerable antioxidant activities of 2,2-diphenyl-1-picrylhydrazyl (DPPH). Amaretti et al. (2013) expressed antioxidant activities of seven *Bifidobacterium*, eleven *Lactobacillus*, ten *Streptococcus*, and six *Lactococcus* intracellular postbiotics. According to the results, there were different values for each species (Cuevas-Gonzalez, Liceaga et al., 2020).

Parallelly mentioned that postbiotics have the highest antioxidant activity than the intercellular fraction may be due to the presence of glutathione (Cuevas-Gonzalez, Liceaga et al., 2020).

As a result of this activity, there are a number of applications in various fields, including food, pharmaceuticals, and clinical settings (Fig. 26.1). In comparison to probiotics, postbiotics offer certain advantages, such as shelf life extension and promoting human health (Mayorgas et al., 2021),

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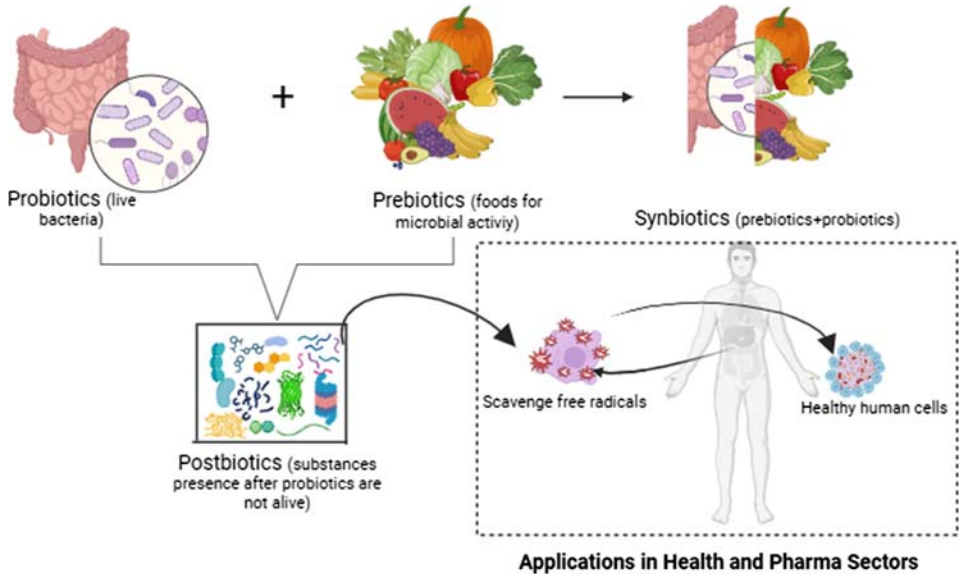

FIGURE 26.1

Postbiotic action in the human body.

inhibiting pathogenic activities, reducing the cholesterol level, controlling obesity, and reducing neurological diseases and glucose homeostasis through their antioxidant action (Kareem et al., 2014).

According to the studies of (Bharti et al., 2017) CFS and lysates from lactic acid bacteria (LAB) (mainly *Lactobacillus* species, *P. acidilactici* and *S. thermophilus*) exhibit a notably stronger anti-oxidative effect compared to whole-cell cultures. This observation implies that postbiotics could potentially manage various disorders linked to free radicals by leveraging both intracellular enzymatic and nonenzymatic antioxidants.

2. Antioxidant properties of postbiotics

2.1 Detailed exploration of the antioxidant activity exhibited by postbiotics

Postbiotics are a metabolic byproducts or chemical substances generated by probiotics during their growth and fermentation (Vinderola et al., 2022). These can include a wide range of compounds such as short-chain fatty acids (SCFAs), which are organic acids with short carbon chains; exopoly-saccharides, which are long chains of carbohydrates produced by probiotics; peptides, which are protein fragments resulting from the breakdown of larger proteins by probiotic enzymes during fermentation.

The term "antioxidant properties" describes a substance's capacity to reduce or prevent the negative effects of reactive molecules known as free radicals (Aghebati-Maleki et al., 2022). Free radicals are very reactive molecules that are formed either spontaneously by the body during metabolic processes or as a result of exposure to outside elements like pollution, UV rays, and specific chemicals. Most organisms contain antioxidant defense and repair mechanisms that guard them against oxidative damage, but these mechanisms do not always suffice to avoid all damage (Blazheva et al., 2022).

An antioxidant potential can be expected given the range of substances classified as postbiotics. Exopolysaccharides have an antioxidant effect and provide a number of health advantages. *Leuconostoc mesenteroides*, *Saccharomyces cerevisiae*, and *Liquorilactobacillus satsumensis* all display antioxidant activity that inhibits 2,2-diphenyl-1-picrylhydrazyl (DPPH), both intracellularly and extracellularly (Blazheva et al., 2022). The maximum intracellular and extracellular activity is seen in *L. satsumensis* and *S. cerevisiae*, respectively (Blazheva et al., 2022).

The ability of metal ions to chelate, the antioxidant enzyme system, and the antioxidant metabolites found in postbiotics are some of the factors that affect how different postbiotics differ in their antioxidant properties. In order to avoid inflammation caused by diseases linked to oxidative stress, postbiotics can be administered as a supplement and feed additive (Blazheva et al., 2022).

Lipid or proteinaceous molecules, as well as glutathione, are the major metabolites contributing to the antioxidant activity of the postbiotic fraction with the highest antioxidant activity (Blazheva et al., 2022). An exopolysaccharide derived from *Lactococcus lactis* subsp. *lactis* is a postbiotic that has the ability to raise the levels of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase while decreasing the amounts of lipids in serum. A postbiotic enzyme that is created by analyzing the quality of the meat, such as pH, color, and sensitivity, obtained from the *Lactobacillus plantarum* which is a probiotic strain, has the power to increase the activity of antioxidant enzymes (Aghebati-Maleki et al., 2022). An enzyme derived from *L. plantarum RG14, RG11* produced by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, is a postbiotic that has the ability to increase the antioxidant activity of glutathione peroxidase (GPX) in serum and rumen fluid and GPX1, GPX4, hepatic superoxide dismutase (Aghebati-Maleki et al., 2022). In order to determine the quality of chicken meat, a postbiotic enzyme derived from the *L. plantarum RI11* is created. This postbiotic enzyme has the power to boost the activity of antioxidant enzymes and lower heat stress markers (Aghebati-Maleki et al., 2022).

2.2 Chemical composition of postbiotics contributing to their antioxidant capacity

Postbiotics have a complex chemical composition that varies based on the type of bacteria that made them and the fermentation conditions (Moradi et al., 2021). They include soluble components that were secreted into the medium during bacterial development, such as products or metabolic byproducts. Analyzing the chemical composition of postbiotics can be used to determine if they are effective against pathogenic microbes that affect food safety (Moradi et al., 2021).

Some common components of postbiotics with antioxidant activity include SCFAs, polysaccharides, and enzymes (Hosseini et al., 2022). The fermentation of fiber by gut bacteria results in the production of SCFAs. It has been shown that they have a number of health advantages, including antioxidant activity. In human cells, SCFAs can scavenge free radicals and prevent oxidative stress (Thorakkattu et al., 2022). Long strands of sugar molecules are known as polysaccharides. They can be present in the diet or generated by gut flora (Hino et al., 2012). It has been shown that several polysaccharides, including beta-glucans, have antioxidant properties. For example, beta-glucans can inhibit the production of free radicals by activated macrophages (Hino et al., 2012). Proteins that catalyze chemical processes are known as enzymes. Superoxide dismutase is one of the antioxidant-active enzymes made by gut bacteria (Pryor et al., 2006). For example of antioxidant, superoxide dismutase can scavenge free radicals and inhibit oxidative stress in rat liver cells (Pryor et al., 2006). Some other compounds with antioxidant activity that are found in postbiotics include organic acids, vitamins, peptides, and minerals (Hosseini et al., 2022). The ability of postbiotics to scavenge free radicals and decrease oxidative stress is thought to be the cause of their antioxidant activity. As an example, human colon cells can be protected from oxidative stress by organic acid butyrate, which can scavenge free radicals.

Some analytical techniques used to examine the chemical composition of postbiotics are Gas chromatography (GC), Liquid chromatography (LC), Thin layer chromatography (TLC), Spectrophotometric-based analysis, Nuclear magnetic resonance (NMR) spectroscopy, and Fourier transform infrared (FTIR) spectroscopy (Moradi et al., 2021).

There have not been any negative consequences of postbiotics such as inflammation found in experimental or preclinical investigations. Postbiotics can therefore be a secure substitute for probiotics due to their well-known chemical structures, safe dosage, and prolonged shelf life.

2.3 Mechanisms of action involved in the antioxidant effects of postbiotics

The type of probiotics chosen to extract antioxidant enzymes has the greatest influence on the antioxidant effect of postbiotics (Blazheva et al., 2022; Liu et al., 2022). To extract more antioxidant enzymes, it is therefore important to evaluate the type of probiotics being used. Catalase, superoxide dismutase, and glutathione peroxidases are just a few of the many antioxidant enzymes that probiotic bacteria produce. These enzymes are essential for neutralizing reactive oxygen species (ROS) and preserving cellular redox equilibrium (Aydin et al., 2021).

Cells and tissues are at risk of oxidative stress and damage from ROS such as superoxide anion, hydrogen peroxide, and hydroxyl radicals. Postbiotics that have antioxidant substances that actively scavenge these ROS reduce oxidative stress (Blazheva et al., 2022). For an example, hydrogen peroxide is broken down into oxygen and water by the catalase enzyme, which is naturally present in bacteria and other organisms. Since catalase is a byproduct produced by probiotic bacteria, it is considered as a postbiotic. Catalase is a type of enzyme known as a Reductase Oxidase (Chang et al., 2021). Thus, by inhibiting active oxygen species, it functions as an antioxidant and defends the cell from oxidative stress (Chang et al., 2021). Catalase functions best at a pH between 4 and 11. Consequently, it is important to take the pH of the diet into account while applying these enzymes as postbiotics with antioxidant characteristics.

Also, metal chelating capabilities can be seen in some postbiotic substances. Chelation of metals is an important procedure by which postbiotics produce antioxidant properties (Chang et al., 2021). Chelation is the process by which some compounds in postbiotics bind metal ions, notably transition metals like iron and copper. Postbiotics can reduce these metals' capacity to produce damaging ROS by chelating them, hence lowering oxidative stress (Aydin et al., 2021).

Superoxide dismutase is another antioxidant enzyme that can catalyze and facilitate the radical degradation of superoxide into molecules of regular oxygen or hydrogen peroxide. With its antioxidant action, this enzyme defends tissues from the effects of oxidative stress and is a vital component of the antioxidant system in living things (Chang et al., 2021). Probiotics have this superoxide dismutase enzyme, which is a sort of postbiotic that can be utilized as an antioxidant agent, just like other types of organism. Superoxide has a variety of functions in maintaining healthy cells, including defending the cytoplasm of cells, defending mitochondria from damage caused by free radicals, and helping to build immunity to inflammatory disorders (Aydin et al., 2021).

Glutathione, which is another antioxidant enzyme, possesses peroxidase activity, which protects organisms from oxidative damage. Another important characteristic of glutathione peroxidase is that it converts peroxides to alcohol and prevents the production of free radicals (Chang et al., 2021). Numerous isoenzymes of glutathione peroxidase are produced by several genes. These isoenzymes have various substrate characteristics and can be found at various locations throughout the cell (Aghebati-Maleki et al., 2022).

Through these actions, antioxidant-active postbiotics can provide protection against a variety of chronic diseases, including cancer, heart disease, and neurological diseases. Also, the balance of gut bacteria can be improved with the aid of postbiotics, which is essential for gut health. A healthy gut microbiome is essential for many aspects of health, including immunity, metabolism, and mental health. Postbiotics can help to enhance immune function because they can help to activate immune cells and promote the production of antibodies. Additionally, postbiotics are effective in reducing inflammation, a chronic condition associated with a number of illnesses including heart disease, cancer, and arthritis. Furthermore, postbiotics may enhance cognitive performance by protecting against neurodegenerative disorders and reducing brain inflammation.

3. Role of postbiotics in health promotion

3.1 Impact of postbiotics on oxidative stress and its relevance to human health

Oxidative stress plays a pivotal role in the pathogenesis of various diseases, including cancer, liver cirrhosis, and fatty liver disease, by damaging cellular components and promoting inflammation. Understanding and managing oxidative stress is essential for preventing and treating these conditions (Vasanthakumari et al., 2015). Antioxidant activity has a beneficial impact on microbiota balance and the host's metabolic and signaling pathways. Consequently, postbiotics can affect various physiological, immunological, neuro-hormonal, regulatory, and metabolic responses. While the provided sources do not directly address the specific impact of postbiotics on oxidative stress, they collectively provide a foundation for understanding the potential health benefits of postbiotics. They have ability to modulate inflammation and support a healthy gut microbiome indirectly suggests a potential role in mitigating oxidative stress. Although more research is needed to fully understand their mechanisms and applications, several mechanisms of action and some findings suggest that postbiotics may indirectly influence oxidative stress and supporting overall health (Cancer et al., 2021; Shenderov, 2013).

The most currently available classes of postbiotics are peptidoglycans-derived muropeptides, exopolysaccharide (EPS), teichoic acids, and surface protruding molecules like fimbriae, pili, or flagella that constitute cell wall components, secreted proteins/peptides, bacteriocins such as acidophilin, reuterin, and bifidin, cell-free supernatant, organic acids such as lactic acid and acetic acid, vitamins, SCFAs like butyric acid and propionate, neurotransmitters, biosurfactants, etc. (Gupta & Garg, 2009; Matsuguchi et al., 2003; Nataraj et al., 2020). These diverse postbiotics play crucial roles in influencing metabolic processes and promoting health. They have gained attention as potential therapeutic agents for various conditions, as they can modulate the gut microbiota and have beneficial effects on human health.

Cell-free supernatants (CFS) are liquid extracts from LAB and yeasts, containing diverse biomolecules like organic acids, carbon dioxide, and bacteriocins-like compounds (Amaretti et al., 2013; Antonina et al., 2019; Saide & Gilliland, 2005; Siedler et al., 2019). They are rich in active compounds and have the potential to promote health equilibrium. Studies emphasize their antioxidative capabilities: *Bifidobacterium longum* and *Lactobacillus acidophilus* CFS effectively combat free radicals and inhibit linoleic acid peroxidation, indicating significant antioxidant potential. *Saccharomyces boulardii*, containing a mix of antioxidants, shows promise in managing redox imbalance and mitochondrial dysfunction, potentially benefiting overall health, especially in gut-related contexts. Lipid peroxidation pathways, alongside free radical chain reactions, are crucial in cellular damage and aging-related degenerative diseases (Lin & Chang, 2000). Cell-free extracts display enhanced antioxidant activity compared to whole cell cultures, attributed to their mix of intracellular antioxidants, both enzymatic and nonenzymatic.

Exopolysaccharides (EPSs) produced by diverse LAB strains like *Lactobacillus, Leuconostoc, Weissella*, etc., possess varied chemical properties and potential health benefits. LAB-derived EPSs, such as those from *Lactobacillus acidophilus and Pediococcus acidilactici* NCDC 252, exhibit notable antioxidative effects. Studies show EPS from *L. acidophilus* demonstrated strong antioxidative activity on colon cancer cells in vitro, with increased efficacy at higher concentrations (Rahbar et al., 2019). Similarly, in vivo experiments with EPS from *P. acidilactici* NCDC 252 revealed significant antioxidant potential and inhibited colon cancer cells, hinting at therapeutic promise as both an antioxidant and anticancer agent (Kumar et al., 2020). These findings propose the potential use of LAB-derived EPSs in various applications, including as natural antioxidants to combat oxidative stress and potentially replace synthetic antioxidants in different industries.

Probiotics, notably LAB, produce vital antioxidant enzymes like catalase, glutathione peroxidase, NADH-oxidase, and superoxide dismutase. These enzymes play a crucial role in neutralizing harmful free radicals, combating oxidative stress, and preventing cellular damage caused by reactive oxygen species (Zolkiewicz et al., 2020; Strandén & Garrick, 2009). Strains of *Lactococcus, S. thermophilus*, and *Lactobacillus* contain superoxide dismutase and catalase, effectively reducing oxidative stress by preventing free radical accumulation. Specific strains like *L. fermentum* E−3 and E−18 express high levels of glutathione peroxidase and manganese-superoxide dismutase, showcasing significant antioxidant activity crucial for averting lipid peroxidation and eliminating hydrogen peroxide (Kullisaar et al., 2002).

Vitamins are heat-sensitive organic compounds with significant roles in various biological processes within organisms. Several B-complex vitamins serve as specific coenzymes in vital metabolic reactions. In contrast, vitamin K, the only fat-soluble vitamin to function as a coenzyme, plays a unique role in preventing microvascular and cardiovascular disorders (Giacco & Brownlee, 2010; Nataraj et al., 2020; Saide & Gilliland, 2005).

Folate plays a crucial role in reducing oxidative stress, enhancing endothelial function, and preventing cell death by lowering homocysteine levels (Hou et al., 2018; Wald et al., 2006). Its treatment influences antioxidant mechanisms, reducing superoxide radicals, enhancing BH4 availability, and potentially being produced by select probiotic strains, contributing to its positive effects, especially noted in diabetic rats (Ahire et al., 2013; Mutavdzin et al., 2019; Stanhewicz & Kenney, 2017).

Certain probiotics like *L. reuteri, L. sanfranciscensis*, and others have been found to produce vitamin B12, offering potential for industrial production. Vitamin B12 is crucial for blood cell formation, nervous system health, and combating oxidative stress by scavenging ROS and supporting glutathione conservation (Pearl et al., 2012; Hunt et al., 2014; Karamshetty et al., 2016). Its deficiencies are linked to oxidative stress-related diseases like type 2 diabetes mellitus. Vitamin B12 also helps regulate inflammation and homocysteine levels, essential in mitigating oxidative stress caused by advanced glycation end products. While probiotics' production of vitamins shows promise for metabolic health, more research is needed to understand their full impact (Birch et al., 2009; Tyagi et al., 2005; Vogel et al., 2011)

3.2 Exploration of postbiotics as natural alternatives to synthetic antioxidants in health promotion

They are considered natural alternatives to synthetic antioxidants and have shown promise in health promotion. Postbiotics hold promise as therapeutic agents due to their ability to influence health-related biomolecules positively. Reactive Organic Species (ROS) accumulation can have detrimental effects on cellular function, leading to various health issues such as, conducing to irreversible malfunctions including diabetes and its complications, microvascular and cardiovascular affections, but organisms utilize natural antioxidants like vitamin C and E to combat this oxidative stress (Giacco & Brownlee, 2010; Saide & Gilliland, 2005). These antioxidants help quench ROS and protect cells from oxidative damage, thereby playing a crucial role in maintaining cellular health and preventing the onset of various diseases.

4. Applications of postbiotics in the pharmaceutical industry

The pharmaceutical industry has shown a significant interest in postbiotics, a category of nonviable microbial products or metabolic byproducts, owing to their promising therapeutic potential (Cuevas-Gonzalez, Liceaga et al., 2020). The International Scientific Association for Probiotics and Prebiotics defines postbiotics as "a preparation of inanimate microorganisms and/or their components that confer a health benefit on the host" (Wegh et al., 2019). In recent years, researchers have established a link between the microbiome and immunological support, as well as overall health, leading to increased interest in gut health (Rafique et al., 2023). Additionally, postbiotics have antiinflammatory effects and the ability to enhance the gut barrier function, making them potential treatments for gastrointestinal disorders and inflammatory conditions (Plaza-Díaz et al., 2017). Although the exact mechanisms are not yet fully understood, in vitro research has shown that postbiotics have antibacterial, antiproliferative, and antioxidant activities, in addition to antiinflammatory and immunomodulatory activities (Mayorgas et al., 2021). These attributes, coupled with the safety and stability of postbiotics compared with live probiotics, position them as an exciting and innovative avenue for pharmaceutical exploration (Bourebaba et al., 2022).

4.1 Use of postbiotics as natural antioxidants in pharmaceutical formulations

Ensuring the stability and efficacy of drugs is of utmost importance in the pharmaceutical industry. To safeguard pharmaceutical formulations against oxidative degradation, it is crucial to include antioxidants, as underscored by (Gabric et al., 2022), thereby preventing the deterioration of active pharmaceutical ingredients (APIs) and maintaining their efficacy throughout storage and use. Traditionally, synthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) have been employed (Abubakr et al., 2012; Arai et al., 2018). However, concerns about their safety and potential adverse effects have led researchers to explore natural alternatives, like postbiotics(Rafique et al., 2023). Postbiotics have emerged as promising natural antioxidants (Chang et al., 2021). Postbiotics have shown the ability to scavenge-free radicals effectively and reduce oxidative stress in pharmaceutical formulations by the activities of the compounds such as metabolites, cell-free supernatants, and extracellular polymeric substances (Abubakr et al., 2012; Plaza-Díaz et al., 2017).

4.2 Advantages of postbiotics over synthetic antioxidants

Postbiotics hold great promise as natural antioxidants in pharmaceutical formulations. Although there have been numerous studies on the advantages of postbiotic production, the subsequent health benefits are well-documented. Examples of postbiotics include vitamin B12, vitamin K, and folate, as well as various amino acids, which are produced by gut bacteria. Additionally, lipopolysaccharides, enzymes, SCFAs, bacterium lysates, and cell-free supernatants are also postbiotics (Mayorgas et al., 2021). Unlike synthetic antioxidants, postbiotics are derived from natural sources and are generally considered safe and well-tolerated. Furthermore, they are eco-friendly and have a multifaceted role in promoting gut health and enhancing overall well-being, making them an attractive option in pharmaceutical applications (Arai et al., 2018; Plaza-Díaz et al., 2017).

Postbiotics have shown great promise in addressing digestive issues and enhancing immune function. According to the research, postbiotic supplementation may help alleviate symptoms of irritable bowel syndrome (IBS) and inflammatory bowel disease, as well as prevent respiratory tract infections.

4.3 Potential therapeutic applications of postbiotics

Beyond their critical in pharmaceutical formulations, postbiotics show potential for the prevention and treatment of various diseases (Plaza-Díaz et al., 2017).

Plaza-Diaz et al. (2019) and Plaza-Diaz et al. (2017) highlight the various ways in which postbiotics can address a range of diseases, including inflammatory bowel disease, diabetes, and allergy. For instance, Eindor-Abarbanel et al. (2021) conducted research indicating that postbiotics can effectively modulate gut microbiota and reduce inflammation, making them a potential therapeutic option for managing.

Postbiotics have also shown promising results in regulating blood glucose levels and improving insulin sensitivity, suggesting their potential as adjunct therapies in the comprehensive management of diabetes (Cabello-olmo et al., 2021).

Additionally, studies on allergy reveal the immune-modulating properties of postbiotics, suggesting their potential in alleviating allergic conditions. They have been mainly associated with immunomodulatory activities by playing a role in maintaining the integrity of the intestinal mucosal barrier and antagonizing pathogens with antimicrobial compounds by stimulating the natural and adaptive immune system, but the immunomodulation response still appears to be strain dependent

(Yesilyurt et al., 2021). This highlights the diverse and promising applications of postbiotics in addressing various health challenges.

Simultaneously, the expanding research on postbiotics underscores their potential in preventing and treating diseases such as IBD, diabetes, and allergy, offering a holistic perspective on their therapeutic applications.

4.4 Research advancements and clinical trials involving postbiotics in the pharmaceutical sector

The advances in research on postbiotics in the pharmaceutical sector have garnered significant attention due to their potential as innovative therapeutic agents. Postbiotics, defined as the bioactive compounds produced by probiotic microorganisms, offer a unique avenue for pharmaceutical exploration owing to their diverse biological activities.

Recent research has focused on understanding the mechanisms and applications of postbiotics in the context of pharmaceutical interventions. For example, studies have highlighted the immunomodulatory properties of postbiotics, underscoring their potential in addressing inflammatory conditions (Taverniti & Guglielmetti, 2011). Additionally, advancements in characterizing specific postbiotic compounds, such as SCFAs and peptides, have opened doors to targeted pharmaceutical applications (Salminen et al., 2021).

Clinical trials have also been initiated to assess the efficacy of postbiotics in various medical conditions. Plaza-Díaz et al. (2017) conducted a randomized controlled trial exploring the use of postbiotics in individuals with IBS, demonstrating positive outcomes in symptom management. Such trials contribute valuable insights into the practical applications of postbiotics in real-world pharmaceutical settings.

Mosca et al. (2022) are investigating the potential of postbiotics in preventing respiratory infections in a pediatric population. This trial reflects the pharmaceutical interest in leveraging postbiotics to enhance immune function and combat infectious diseases.

The outcomes of these trials provide a foundation for the development of postbiotic-based pharmaceutical interventions. The multifaceted benefits of postbiotics, including their stability and safety profile, position them as attractive candidates for incorporation into pharmaceutical products (Derrien & van Hylckama Vlieg, 2015).

5. Gut microbiota modulation by postbiotics

5.1 Influence of postbiotics on the gut microbiota composition and diversity

The human gut is a habitat for a diverse microbial community, comprising over 1000 species of bacteria, crucial for individual health. This microbiota's diversity is influenced by dietary choices and host health, establishing a complex interplay with the host's well-being (Rinninella et al., 2019). Studies have delved into nonliving microbial components, termed postbiotics, which encompass inactivated microbial cells, their structural parts, and metabolites. These bioactive substances, produced by the gut microbiota, exert various effects such as inhibiting pathogen growth, supporting intestinal mucosal health, and shaping the gut microbial community (Ozma et al., 2022).

Postbiotics, arising from anaerobic fermentation processes within the gastrointestinal tract involving indigestible and digestible materials, interact with host cells via specific receptors. This interaction stimulates immune function and enhances the human microbiome's composition and functionality, promising therapeutic potential for maintaining gut microbial balance and overall health (Bron et al., 2012; Canani et al., 2017).

Fermentation products, notably organic acids, hinder pathogenic organisms' growth while serving as substrates for certain gut bacteria that produce SCFAs, including acetate, propionate, and butyrate. SCFAs, key products of gut microbial activity and potential postbiotics, promote colonic absorption and colonocyte proliferation (Abbasi et al., 2021; Homayouni Rad et al., 2021; Rad et al., 2021). Bacteria such as *Blautia hydrogenotrophica, Clostridium, Streptococcus* spp., and *Bacteroides* spp. contribute to the synthesis of acetate and propionate (Louis et al., 2014).

Micronutrient cross-feeding, exemplified by B-group vitamins produced by certain gut microbes, plays a crucial role in maintaining microbial populations. The exchange of these vitamins among microbes and the host influences intestinal bacteria populations (Rodionov et al., 2019).

Extracellular polysaccharides (EPS), a form of postbiotic, potentially modulate gut microbiota composition and activity. Certain EPS polymers serve as fermentable substrates for commensal gut bacteria, influencing compound production patterns and interactions among gut flora (Castro-Bravo et al., 2018). *Bifidobacterium* strains utilize EPS for fermentation, altering compound production, and gut flora interactions. *Lactobacillus acidophilus*, associated with higher B12 and folate serum levels, showcases similar attributes (Homayouni Rad et al., 2021).

Furthermore, postbiotics like bacteriocins and organic acids contribute to suppressing harmful microorganisms. Bacteriocins, ribosomally produced antimicrobial peptides, exhibit bacteriostatic or bactericidal characteristics. Products derived from certain *L. plantarum* strains and LAB, such as nisin from *Lactococcus lactis*, demonstrate capabilities in inhibiting pathogens within the host microbiome (Favaro et al., 2015; Heilbronner et al., 2021; Kareem et al., 2014). These multifaceted postbiotics derived from gut microbial activities collectively contribute significantly to gut health maintenance and modulation.

5.2 Role of a balanced gut microbiota in maintaining redox homeostasis and reducing oxidative stress

Redox homeostasis, governing electron transfer balance in cells and organisms, is vital for energy production and biomolecule synthesis. Oxidative stress, an imbalance favoring increased oxidation due to excess ROS and Reactive Nitrogen Species (RNS), leads to cellular damage and disease (Luca et al., 2019).

In depression, oxidative stress linked to gut microbiota involves altered cytokines (IL-1, IL-6, TNF-α) and reduced antiinflammatory cytokines, highlighting the gut–brain axis's role (Luca et al., 2019). Gut microbes, primarily anaerobic, engage in redox reactions through metabolic processes, contributing to oxidative stress modulation (Hu et al., 2019).

The gut microbiota's fermentation of dietary fibers produces SCFAs like acetate, propionate, and butyrate. SCFAs exhibit antiinflammatory properties, regulating redox balance by curbing ROS generation in response to inflammation SCFAs also mitigate telomere shortening, DNA damage, and boost antioxidant glutathione production, influencing COX-2 activity (Hamer et al., 2009).

Moreover, gut microbes indirectly shield against oxidative stress. Butyrate, a notable SCFA, fortifies the gut barrier, preventing prooxidative substance leakage and systemic inflammation (Hamer et al., 2009). Conversely, dysbiosis induced by pathogens like *Salmonella*, *E. Coli,* producing hydrogen sulfide (H2S) impedes mitochondrial function and COX activity, exacerbating oxidative stress (Beaumont et al., 2016).

6. Applications of postbiotics in the food industry

In this regard, mounting evidence points to the possibility that the gut microbiota's primary health-stimulating effects may be related to their nonviable byproducts (postbiotics), which have the potential to mimic the health benefits of live parent cells through analogous or dissimilar metabolic pathways (Abbasi et al., 2022). The term "postbiotics," though recently developed, has gained rapid acceptance in the fields of food science, host health, and nutrition. This has drawn attention to their potential future use as nutraceuticals, functional foods, and drugs in the food, biotechnology, and pharmaceutical industries.

According to the researchers, there are possibilities for using these antioxidant activities of probiotics in food production and food technologies to generate safe and healthy food items. They can be the biopreservation action in food packaging, functional activities, and health benefits in food products due to the availability of bioactive compounds.

6.1 Functional food production

Postbiotics exhibit a range of health-enhancing traits such as immunomodulation, antiinflammatory effects, cholesterol reduction, antiproliferative properties, antihypertensive action, and antiobesity potential through their antioxidant activities. The application of postbiotics within the food industry is on the rise, driven by their distinctive biological characteristics (Hosseini et al., 2022).

Therefore, the incorporation of postbiotics into functional foods and dietary supplements to enhance functional activities through antioxidant properties is a trend nowadays. These activities can be carried out by different *Lactobacillus* and *Bifidobacterium* strains. The cell free-supernatants (CFSs) of probiotics contain a wide variety of substances, including hydrogen peroxide, organic acids (butyrate, propionate, and acetate), bacteriocins, reuterin, diacetyl, and other biomolecules (Bianchi et al., 2011). As food supplements, they can first interact with intestinal epithelial cells and next immune cells. These interactions potentially induce antioxidant activity that is very important to a variety of health-promoting effects of CFSs' (De Marco et al., 2018). Therefore, these CFS can be used as food supplements to enhance human health.

According to the fermented goat's milk that contains *Lactobacillus fermentus,* it demonstrated antioxidative impacts in the human body, resistance to lipoprotein oxidation, reduced levels of oxidized LDL, and peroxidized lipoproteins (Verruck et al., 2019).

Most of the activities in different compounds and their direct and indirect pathways for these antioxidant activities are less understood (Sharma & Shukla, 2016). Further, intracellular postbiotics and their intercellular contents of different *Lactobacillus* strains protect erythrocytes from oxidative damage (Cuevas-Gonzalez, Aguilar-Toala et al., 2020). Exopolysaccharides derived from *Lactococcus lactis* subsp. lactis also contribute to this protective effect.

6.2 Shelf life extension and food preservation

There are potential uses of postbiotics in food preservation and extending shelf life through their antioxidant effects.

Postbiotic products offer enhanced convenience compared to probiotics, attributed to industrial benefits. They exhibit stability across broad pH, and temperature ranges and show minimal interaction with matrices. When considering CFSs consist of hydrogen peroxide, organic acids (butyrate, propionate, and acetate), bacteriocins, and other biomolecules (Bianchi et al., 2011). Among them are bacteriocins; small molecular weight peptides that can inhibit the pathogenic growth of food pathogens including *Clostridium, Staphylococcus, Listeria,* and *Enterococcus* (do Carmo et al., 2018; Gareau et al., 2010). Nicin is the only bacteriocin that can be applied in the food industry to preserve baby food products, dairy products, canned soups, and fishery products. Some postbiotics facilitate to preservation of foods mostly beverages, including dairy products, artisanal fresh orange, chicha beverages, and fermented beverages. Notably, this CFS exerted an inhibitory influence on the production of aflatoxin B1 and ochratoxin A. In the context of treating wheat grains, the application of CFS led to the complete inhibition of *Aspergillus* species in grains due to the oxidative stress (Nataraj et al., 2020). Antioxidant enzymes produced by *Lactococcus lactis* subsp. lactis (e.g., catalase, superoxide dismutase, and glutathione peroxidase activities) are good applications to decrease the lipid peroxidation of oils and keep their quality (Cuevas-Gonzalez, Liceaga et al., 2020).

These preservation actions are due to advantageous attributes of postbiotics including specific chemical configurations and safe sourcing (Hosseini et al., 2022).

6.3 Food packaging

Postbiotics play a significant role in preventing food spoilage within the food industry. These bioactive compounds are byproducts generated by probiotic bacteria and offer numerous health benefits. Of paramount importance are their nontoxicity and safety, coupled with their capacity to inhibit the growth of microorganisms responsible for food spoilage. The pivotal attributes of postbiotics for application in the food industry revolve around their potential to curb spoilage-causing microbes.

Moreover, postbiotics have found application in active food packaging, particularly through the integration of bacteriocins produced by LAB into antimicrobial films. For instance, an active film composed of alginate and collagen was infused with *L. lactis* ATCC 11454, which produces nisin. This incorporation resulted in robust inhibition against *Listeria monocytogenes, Staphylococcus aureus,* and *E. Coli* through the antioxidant action (Ma et al., 2020).

Research into postbiotics' utilization within the food sector has unveiled potential challenges stemming from their interaction with various elements within the food matrix. This underscores the potential interference of postbiotic function. To circumvent this, incorporating postbiotics into food packaging emerges as a potentially more efficacious approach. The distinctive characteristics of postbiotics have propelled them into the spotlight within the food industry, offering a novel avenue for innovation in food packaging strategies (Hosseini et al., 2022).

These findings collectively underscore the potential of incorporating postbiotics as an innovative strategy to mitigate the degradation of food product quality.

6.4 Safety issues of postbiotics

To determine the safety issues of postbiotics, a number of studies have been carried out with many clinical trials by determining the metabolism, absorption, and distribution of postbiotics (Shenderov, 2013; Tomasik, 2018). Only very few investigations reported the potential side effects of postbiotics, including vomiting and abdominal (Malagón-Rojas et al., 2020).

Most investigations reported that unique features of postbiotics; chemical structures, safety profiles, and stability in the human body and market level are safe to live probiotics and applications of the food and pharmaceutical industries (Rad et al., 2020). But, to maintain these features during food and pharmaceutical productions and preparations, further studies are required.

7. Challenges of using postbiotics as antioxidant compounds

Various studies have highlighted the antioxidant properties of postbiotics derived from diverse food fermentations. These postbiotics show potential applications in functional foods, supplements, and pharmaceuticals for addressing noncommunicable diseases associated with oxidative stress (Rafique et al., 2023; Zolkiewicz et al., 2020). However, ensuring the stability and shelf life of postbiotic products containing antioxidants presents challenges due to the sensitivity of both antioxidants and microbial metabolites to environmental factors such as temperature, humidity, and light (Nataraj et al., 2020).

Furthermore, although certain postbiotics have demonstrated antioxidant *properties* in vitro, their bioavailability and effectiveness within the complex human body are not well understood. While controlled laboratory settings may reveal promising antioxidant activity, translating these findings to real-world clinical applications poses significant obstacles. Factors like digestion, absorption, and metabolism in the intricate gastrointestinal environment can profoundly affect the availability of these compounds to exert antioxidant effects in vivo (Moradi et al., 2020). Additionally, individual variations among human hosts and the diversity of gut microbiota further complicate predicting postbiotic performance within the body. To harness the potential of postbiotics as effective antioxidants, extensive research is needed to bridge the gap between in vitro results and practical benefits for human health (Moradi et al., 2020).

Concerns about the ethical and environmental implications of postbiotic production, especially when derived from live microbial cultures in large-scale fermentation processes, also arise. The production of postbiotics necessitates inactivated microorganisms, achievable through various technological strategies that may alter cell structures or physiological functions (Sharma et al., 2023). It is crucial to emphasize that the inactivation method used should preserve the beneficial effects provided by the viable form. Safety concerns must also be addressed, as some postbiotics may have unintended side effects or interactions with other compounds. Regulatory hurdles may further complicate the maintenance of postbiotics with antioxidant activity, given their ambiguous classification between food, dietary supplements, and pharmaceuticals. Clear guidelines from regulatory agencies are essential for their development and marketing, and comprehensive research is required to understand these interactions fully (Salminen et al., 2021).

8. Potential areas for further research and future perspectives

While existing literature has highlighted the antioxidant properties of postbiotics derived from various food fermentations, there is ambiguity in distinguishing between probiotics and postbiotics in certain experiments. The observed outcomes may be due to a synergistic effect, necessitating a more focused effort in future research to clearly delineate the antioxidant effects of postbiotics, as opposed to prebiotics or probiotics. Additionally, the identification and characterization of novel postbiotics emerge as promising avenues for further exploration. Given the complex nature of these molecules, sophisticated analytical approaches are required, and the choice of instrumental techniques should align with the study goals and the type of characterization pursued (Aguilar-Toalá et al., 2018, 2020).

Moreover, the effectiveness of postbiotics may be influenced by factors such as the microorganism strain or metabolic product, daily dosage, and duration. To adequately assess their efficacy and demonstrate potential health effects, high-quality preclinical and clinical studies are essential, taking into account the mentioned factors (Deshpande et al., 2018; Faintuch & Faintuch, 2019). The study of postbiotics and their antioxidant properties involves intricate interactions between microbial metabolites and the host, requiring comprehensive research to fully understand these interactions. Although the potential beneficial effects of postbiotics in managing inflammatory, obesity, type 2 diabetes, and oxidative stress-associated disorders are evident (Lou et al., 2023), further in-depth investigations are warranted to elucidate the signaling pathways governing these effects.

Additionally, exploring the integration of postbiotics into pharmaceutical formulations to enhance drug efficacy and reduce side effects presents an avenue for future research (Lou et al., 2023). Emphasis should be placed on developing uniform and rigorously defined culture procedures to eliminate potential variability in postbiotics production, as uncontrolled environmental factors can alter metabolism and introduce unexpected transient variability. Well-designed randomized placebo-controlled human/clinical intervention trials, along with metabolomics studies, are crucial to support health claims associated with postbiotics supplementation (Aguilar-Toala et al., 2018; Moradi et al., 2020).

In conclusion, the antioxidant activity of postbiotics in the health and pharmaceutical industry holds promising opportunities for disease prevention, health promotion, and therapeutic interventions. However, addressing challenges related to stability, dosage, regulation, bioavailability, research complexity, and ethical considerations is imperative to fully harness the potential of these innovative products. As science and technology advance, postbiotics with antioxidant properties have the potential to revolutionize healthcare and wellness practices.

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Postbiotics

Edited by Dhanasekaran Dharumadurai and Prakash M. Halami

Postbiotics: Health and Industry provides a detailed overview on the fundamentals, biological and therapeutic properties, safety, and application of postbiotics in health and industry.

This book is organized into five sections providing a comprehensive discussion of postbiotics. This book begins with coverage on the fundamentals of postbiotics which includes insights on probiotic microorganisms, postbiotics and host–microbe interaction, analysis, and characterization of postbiotics. The book goes on to delve into the different types of postbiotics and their mechanisms. The remaining portion of this book explores the various health, pharmaceutical, and industrial applications of postbiotics.

Key Features

- Provides an overview on the separation, characterization, and identification of postbiotics from probiotic microbes
- Includes classes of postbiotics and their mechanisms of action
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About the Editors

Dr. Dhanasekaran Dharumadurai is a Professor in the Department of Microbiology, Principal Investigator in National Repository for Microalgae and Cyanobacteria—Freshwater (NRMC-F) at Bharathidasan University in Tiruchirappalli, India. His research experience is in the fields of actinobacteriology and mycology. His current research focuses on probiotic microorganisms and postbiotics and microbiome profiling in plant and animal system. He has been awarded an UGC-Raman Post-Doctoral Fellowship and has worked in the Department of Molecular, Cellular, and Biomedical Sciences at the University of New Hampshire in Durham, USA. He studied the genome properties of probiotic bacteria by whole genome, metagenome sequencing, and formulated probiotic feed supplements for dairy cow. He edited 17 books with international publishers and served as a reviewer, guest editor, and on the editorial boards of national and international journals.

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