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Pre and Probiotics to Postbiotics: A Changing Paradigm

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The relationship between microbiota and human health has long been stated by Hippocrates said, "Death sits in the bowls" in 400 B.C. With recent scientific advance ments, there is a growing understanding of the significance of microbiota in health and disease. The two-way communication between the host and the microbiota involves the production of various metabolites that play crucial roles in host energy metabolism, influence nervous system function and the gut- brain axis, immune maturation and homeostasis, maintenance of mucosal integrity, treatment of metabolic disorders, anti-obesity, cholesterol lowering, antioxidant, anticancer, antiproliferative and anti-inflammatory properties. Postbiotics are inanimate microorganisms or their compounds, including short-chain fatty acids, exopolysaccharides, vitamins, teichoic acids, bacteriocins, enzymes and peptides that provide health benefits to the host. Postbiotics can be stored under normal environmental conditions, have a prolonged shelf life, easy to transport, and handle and overcome the limitations of probiotic use. As a result, postbiotics have immense potential as a safe and effective means of promoting health and well-being.

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Keywords: Postbiotics; microbial metabolites; probiotics; functional foods.

1. INTRODUCTION

In recent years, there has been an growing interest in the field of host-microbiota interactions, particularly concerning human health and disease.The majority of the intestinal microbiota resides in the intestinal lumen, with approximately 10^{11}-10^{12} microorganisms/ gram of intestinal content, potentially outnumbering intestinal cells. Human gut is home to trillions of microbes belonging to over 1000 species of bacteria, with 95% being anaerobic (Afzaal et al., 2022; Liu et al., 2023). The major gut microbial phyla include Firmicutes, Bacteroidetes, Fusobacteria, Actinobacteria, Proteobacteria, and Verrucomicrobia. Bacteroidetes and Firmicutes dominate about 90% of all gut microbiota (Bourebaba et al., 2022; Scarpellini et al., 2022; Xue et al., 2020; Afzaal et al., 2022). The gastrointestinal microbiota (GM) is often referred to as a “metabolic organ” due to its metabolic capacity similar to that of the liver, producing a wide range of bioactive molecules and specialized metabolites that have beneficial effects on the host (Rafique et al., 2023). It is vital organ due to its multidirectional functions with other organs through immunological, endocrine, humoral and metabolic pathways (Afzaal et al., 2022). There are about 23000 genes in the human genome whereas the microbiome encodes over 3 million genes (150 times more genes than the entire human genome) producing thousands of metabolites, which replace many of the functions of the host and consequently influencing the host’s fitness, phenotype, and health (Valdes et al., 2018; Afzaal et al., 2022).

There is a two-way communication between the host and the gut microbiota. Gut microbes interact with by detecting host hormones and peptides, producing a variety of signalling molecules that influence host immune maturation, energy metabolism and mucosal integrity maintenance (Martyniak et al., 2021). They also play a crucial role in the synthesis of essential amino acids, vitamins, breakdown and absorption of undigested food components (Kavita et al., 2024).

Several factors influence the composition of the microbiota including age, sex, host environment, genetics, geography, stress, infant feeding method, birth process, life cycle stages, pharmaceuticals, antibiotic intake, diet and illness. A balanced microbiota is essential for maintaining human health, while dysbiosis can disrupt gut homeostasis and is associated with the onset or exacerbation of certain diseases. This link between dysbiosis and disease development has prompted scientists to find ways to modulate dysbiosis to counteract these pathologies (Peri et al., 2022; Cresci and Bawden, 2015; Afzaal et al., 2022; Aggarwal et al., 2022).

One approach to modifying gut microbiota is through direct fecal microbiota transplantation from a donor to a recipient. Another method involves the ingestion of nutrients that host microorganisms utilize, known as prebiotics (Peri et al., 2022). Prebiotics, such as human milk oligosaccharides, fructo-oligosaccharides, lactulose,and inulin. They have been extensively used in manufacturing of functional foods (Scarpellini et al., 2022; Martyniak et al., 2021). Increasing the diversity and population of intestinal microbiota can be achieved by consuming a variety of fermented foods, whole grains, vegetables, foods rich in polyphenols and other plant-based foods (Ryafique et al., 2023). Replacement of non-healthy, dysregulated microbiota with healthy microbiota is through the administration of probiotics is another way of modulation of gut microbiota. According to the WHO/FAO, probiotics are “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Tomasik and Tomasik, 2020; Martyniak et al., 2021; Scott, et al., 2022; Park et al., 2023; Gurunathan et al., 2024). *Lactobacillus* and *Bifidobacterium* are the most studied and generally recognized as safe (GRAS) probiotic bacteria (Monika et al., 2022) of the colon and they are suitable for amplification in the intestine, without any significant side effects (Moradi et al., 2021). When prebiotics are administered together with probiotics, beneficially affecting host health, they are called as symbiotics (Scarpellini et al., 2022).

Currently, there are two limitations that directly impact the use of probiotics effectively are: Firstly, probiotic therapies must be limited to use food safe, GRAS recognised or have Qualified Presumption of Safety (QPS) by the European Food Safety Authority (EFSA). The second limitation is the challenge of maintaining probiotic viability in the upper gastrointestinal tract, where stomach acids and bile salts may hinder the delivery of an adequate number of viable cells.

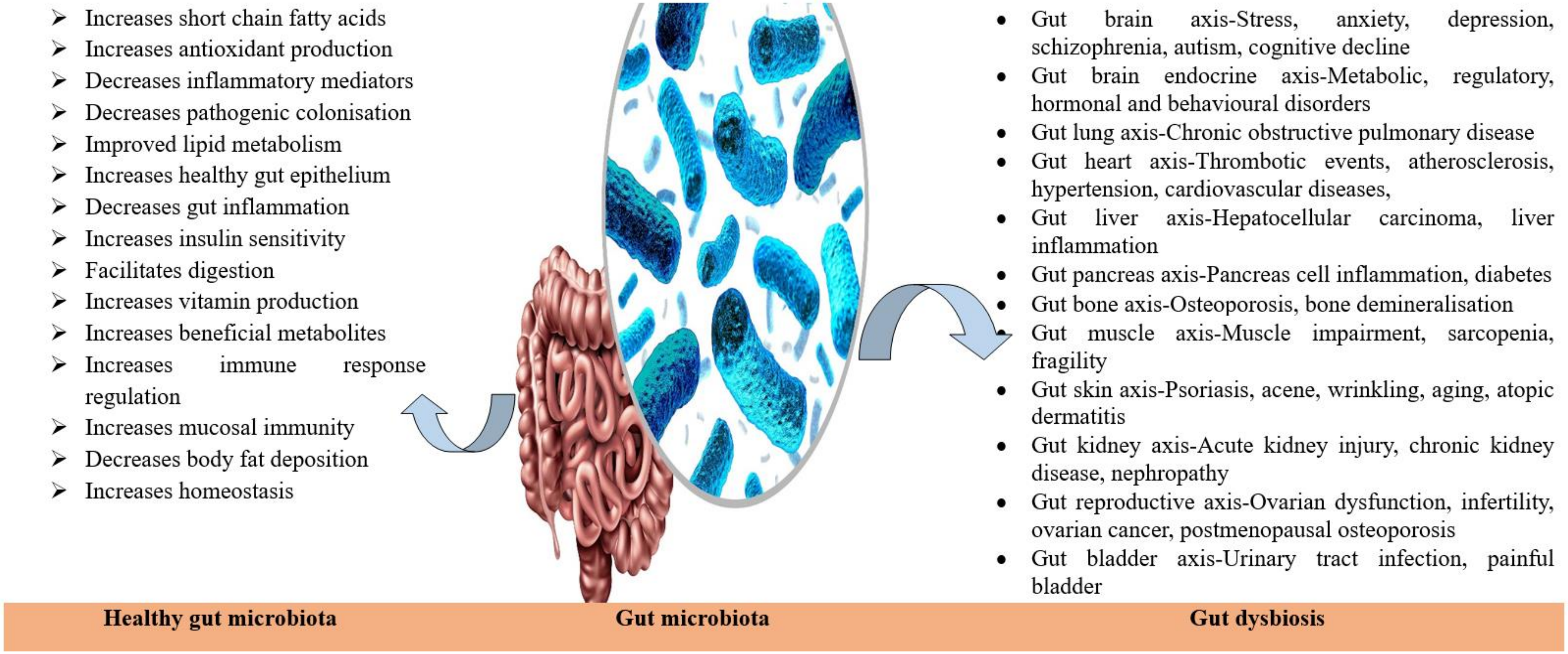

Fig. 1. Gut microbiota

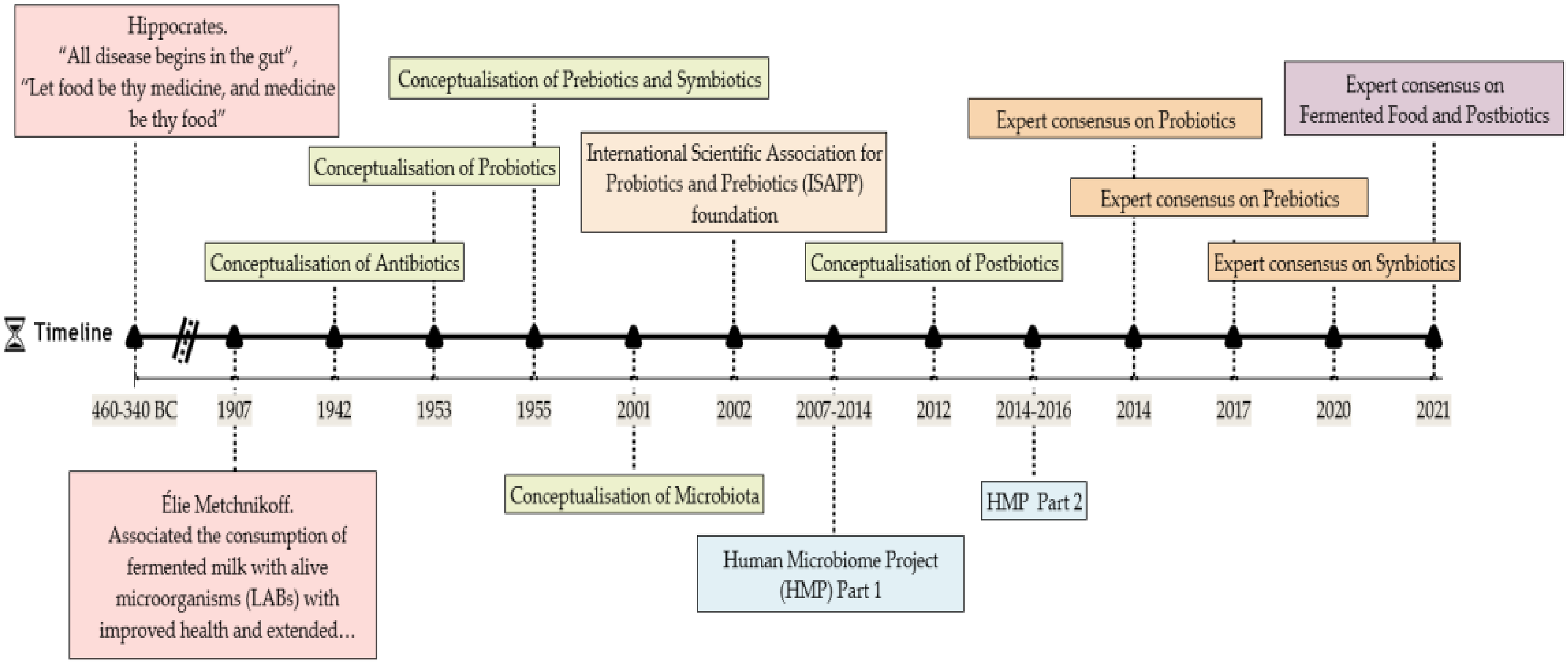

Fig. 2. Timeline illustrating the main historical milestones in microbiology (Cabello-Olmo et al., 2021)

Therefore, oral administration of probiotics may not be successful in colonizing a healthy gut microbiota in long-term studies (Scott et al. 2022).

Despite the potential health benefits of probiotics, limited knowledge exists regarding their safety, effectiveness, dosage and adverse effects when taken in excess (Tomasik and Tomasik, 2020; Peri et al., 2022), particularly in immunosuppressd individuals, those with compromised gastrointestinal flora, abnormal mucosal barriers and individuals experiencing stress (Zhao et al., 2024). During production, maintaining stability and viability is crucial, as the presence of antibiotic resistance genes in probiotics could be transmitted through horizontal gene transfer, leading to unpredictable strain specific behaviours (Peri et al., 2022; Scarpellini et al., 2022).

The translocation of probiotics from the gut lumen to the bloodstream and vital organs could potentially trigger systemic infections (Rad et al., 2021; Zhao et al., 2024). However, emerging evidence suggests that the health benefits of probiotics may be attributed to the metabolites they produce rather than solely the presence of live microbes in the host. Some studies have indicated that specific cell constituents of microbes are associated with health benefits (Scott et al., 2022). As a result, attention has shifted towards postbiotics as an alternative clinical approach to microbiota modulation (Peri et al., 2022; Scarpellini et al., 2022).

2. CONCEPT OF POSTBIOTICS

Over 2000 years ago, Hippocrates stated that “all disease begins in the gut”.Today, it was found that pathogenesis of many inflammatory and auto immune disorders was associated with intestinal microbiota. In the early 1900s, Elie Metchnikoff, a Russian microbiologist working with Louis Pasteur at the Pasteur Institute in Paris, initiated studies on intestinal microbiota and is knownas the “Founding Father of Probiotics”. The Human Genome Project marked the beginning of modern microbiome science, with significant advancement in postbiotics development (Gurunathan et al., 2024).

The term “postbiotics” is derived from the Greek words“post”, meaning after, and “bios”, meaning life (Rafique et al., 2023; Vinderola et al., 2022; Park et al., 2023).The term postbiotics refers to all metabolic bioactive components produced by bacteria during fermentation or microbial metabolism , which have beneficial effects on both microbes and humans (Tomasik and Tomasik, 2020; Wegh et al., 2019). In 2021, TheInternational Scientific Association of Probiotics and Prebiotics (ISAPP) proposed a consensus definition of postbiotics as the “preparation of inanimate microorganisms and/or their components that confer a health benefit on the host” (Scott et al., 2022; Vinderola et al., 2022; Kvakova et al.,2022; Zhao et al., 2024; Cabello-Olmo et al., 2021; Park et al., 2023; Gurunathan et al., 2024). Paraprobiotics, ghost probiotics, inactivated probiotics, non-viable microbial cells, biogenic, supernatant, pseudobiotic, abiotic, metabolic, and postbiotic, with postbiotics being the most commonly used term. In some studies, cell wall components of probiotics are categorized as paraprobiotics (Rad et al., 2021; Teame et al., 2020; Teame et al., 2020; Vinderola et al., 2022; Zhao et al., 2024; Park et al., 2023; Aghebati-Maleki et al., 2022). The different postbiotic particles incorporate metabolic byproducts of live probiotic microorganisms.

Postbiotics are classified into intra and extracellular compounds (Malashree et al., 2019). Postbiotics can include cell supernatant, nutrients, natural acids, bacterial lysates with cell surface proteins, bacterial enzymes and peptides, metabolites produced by bacteria such as short-chain unsaturated fats, emitted proteins/peptides, bacteriocins, synapses, teichoic acids, cell wall fragments, peptidoglycan-derived neuropeptides, exopolysaccharides, polysaccharides, released biosurfactants, amino acids, flavonoids , and lower organic acids like lactic acid (Tomasik andTomasik, 2020; Monika et al., 2022; Scott et al., 2022; Mishra et al., 2024; Liang and Xing, 2023; Rad et al., 2021; Patel et al., 2020; Fesseha et al., 2022; Kim et al., 2021; Mantziari et al., 2020; Kvakova et al., 2022; Gurunathan et al., 2024).

VEnzymes and vitamins produced by gut microbes are more consumer- friendly than synthetic ones and can help counter gut dysbiosis by directly modifying the gut microbiota (Mishra et al., 2024). The ISAPP stated postbiotic action by five mechanisms such as modulation of the resident microbiota; enhancement of epithelial barrier functions; modulation of local and systemic immune responses; modulation of systemic metabolic responses; and systemic signalling via the nervous system (Salminen et al., 2021).

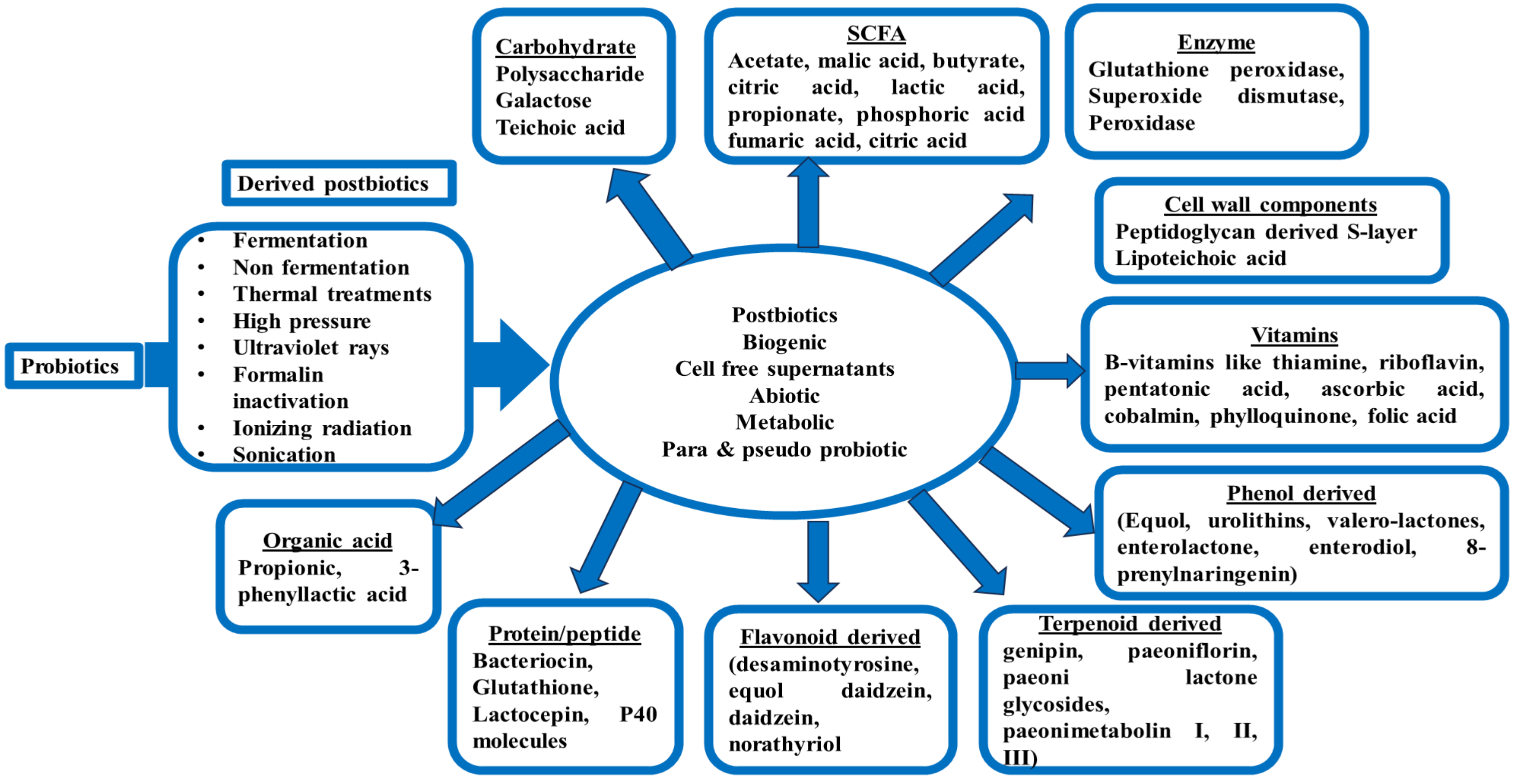

Fig. 3. Main postbiotics generated by microbiota in colon and cecum

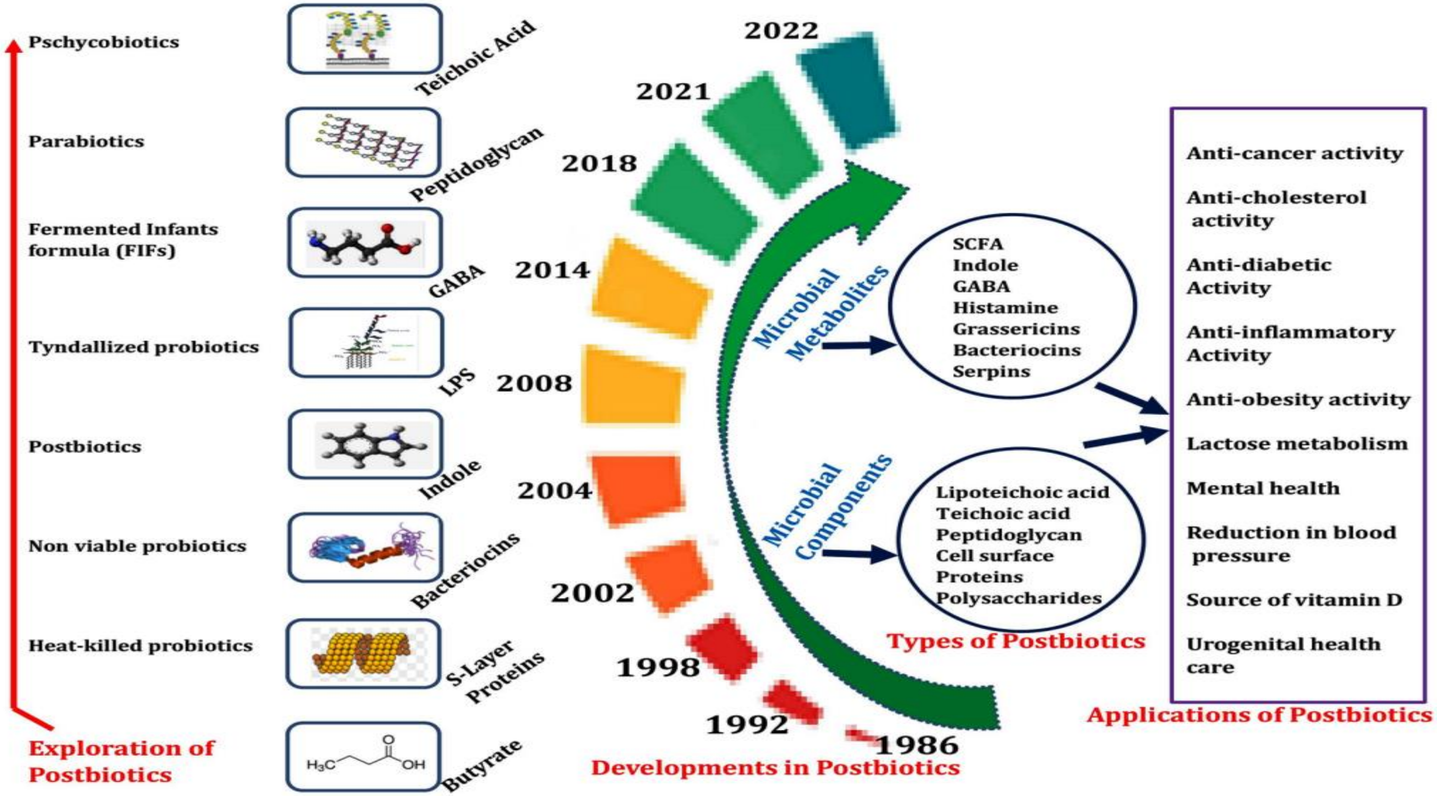

Fig. 4. Developments and applications of postbiotics (Babu et al., 2023)

Postbiotics can exert antioxidant, immunomodulatory, anti-inflammatory, anti-obesogenic, anticancer, antitumor, antiproliferative, antibiofilm, anti-adhesion, antihypertensive, hypocholesterolaemic, hepatoprotective, cardioprotective, anti-atherosclerotic, and anti-ulcerative effects (Cabello-Olmo et al., 2021).

Postbiotics are naturally found in fermented foods such as tempeh, yogurt, kefir, kimchi, sauerkraut, and certain pickles, as well as in the human body. The production of postbiotics depends on the type of microorganism, strain and metabolic products (Martyniak et al., 2021). Foods like buttermilk, fermented pickles, yogurt, cottage cheese and high-fiber foods like oats, flaxseed and garlic can increase postbiotics in the gut (Aggarwal et al., 2022).

Various internal and external factors can affect the activity of postbiotics. Interactions between resident microbiota, food compounds and enzymes with postbiotics can inhibit their metabolic functions. External factors like pH of the food can also alter the antimicrobial activity of postbiotics, with the optimal pH for postbiotic activity being between 4-9. Studies have shown that pasteurized milk and ground meat have an optimal pH, causing no disturbance in postbiotic production (Aggarwal et al., 2022).

Postbiotics have unique characteristics such as safety, stability, non-toxicity, definitive chemical structure, easy transportability, low-cost maintenance, and are considered safe substitutes for certain populations, providing health benefits similar to probiotic cells (Pirhadi et al., 2021; Rad et al., 2021; Mishra et al., 2024; Cabello-Olmo et al., 2021; Mishra et al., 2024). Postbiotics are deemed safer than probiotics and therefore, it has great potential value in the field of food (Ruan and Serventi, 2022). However, there is currently no specific regulatory framework for postbiotic preparations for human application and safety assessments. Characterization of postbiotic products can help develop standardized concentrations for postbiotic therapies and expand research efforts (Scott et al., 2022). Research is currently focussing on the isolating and characterizing of postbiotics for potential therapeutic use. Postbiotics like Nyaditumresea, Cytoflora and Lacteol have been approved for use as immunomodulators, supplements and infection control agents (Mishra et al., 2024). Lactobacillus is the most studied bacteria among the various Lactic acid bacteria for the production of postbiotics (Aggarwal et al., 2022; Barros et al., 2020).

There is no interaction between the postbiotics metabolites and food. Therefore, there is no chance of undesirable changes in the sensory quality and no risk of acquiring antibiotic resistance genes. Hence, postbiotics are used as a safe alternative in immune suppressive individuals and for newborns. Postbiotics can act locally and systematically on other organs through communication axes like the gut-brain axis, gut-liver axis and gut-lung axis (Nataraj et al., 2020).

ISAPP Criteria for the preparation of Postbiotics are:

1. Molecular characterization of the progenitor microbes by sequencing their genes.
2. Detailed description of the inactivation methods and the matrix.
3. Confirmation that inactivation has occurred.
4. Evidence of health benefits in the host from a controlled, high-quality trial.
5. Detailed description of the composition of the postbiotic preparation.
6. Assessment of safety of the postbiotic preparation in the target host for the intended use (Babu et al., 2023).

3. SOURCES AND PRODUCTION OF POSTBIOTICS

Postbiotics can be produced through natural or laboratory methods (Park et al., 2023). Various techniques are employed for isolating and purifying of postbiotics from probiotic species. Fermentation is a key method for producing postbiotics, where microbial cells utilize prebiotics to generate range of postbiotics with diverse biological properties, enriching of food with beneficial substances. In addition to natural production, laboratory techniques can enhance the nutritional profile, shelf life, and health-promoting properties of a variety of foods (Rafique et al., 2023; Park et al., 2023).

Isolating postbiotic metabolites involves cell disruption techniques such as enzymatic, thermal, solvent extraction, radiation, ohmic heating, high pressure processing, sonification, pulse electric field and drying. For the production of cell component postbiotics, microbial cells should be exposed to factors without destroying the cell structure. Remaining extraction and purification steps include centrifugation, dialysis, lyophilization and column purification (Teame et al., 2020; Malashree et al., 2019). Formalin and thermal treatment are popular techniques for producing of postbiotics with beneficial health-promoting qualities during the generation of postbiotics (Rafique et al., 2023). Magnetic resonance spectroscopy (NMR) and chromatographic techniques are used for identification and characterisation of postbiotics (Malashree et al., 2019). The most ideal method for detecting postbiotics in complex biological systems is metabolomics (Rafique et al., 2023). Presently, these inactivation methods are useful only for the bench scale production of postbiotics. Therefore, further research is required to develop innovative techniques for the commercial scale postbiotic production that maintain functional benefits while being cost- and time-effective (Park et al., 2023).

Numerous probiotics, including genera such as *Lactobacillus, Bifidobacterium, Streptococcus, Bacillus,* and *Faecalibacterium* , are known to produce postbiotics (Park et al., 2023; Gurunathan et al., 2024). The Lactobacillus genus comprises approximately 60 species. Lactic acid bacteria produce a wide variety of metabolites like short chain fatty acids, fructooligosaccharides, exopolysaccharides, conjugated linoleic acids, bacteriocins, and selenoproteins, which have demonstrated promising health benefits (Zhao et al., 2024). *Lactococcus lactis*, a commonly studied species, exhibits postbiotic characteristics in vitro by stimulating immune cells to produce cytokines, which are beneficial for overall health. Postbiotics minimize the requirement for exposure to live microbes, which is crucial for kids with developing immune systems and leaky intestinal barriers (Park et al., 2023).

4. CLASSIFICATION AND FUNCTIONAL ROLE OF POSTBIOTICS

Exopolysaccharides (EPS): During growth, exopolysaccharides are produced by the microorganisms to the outside of the cells act as virulence factors for pathogens. In addition, EPS have antioxidant, anti-infective and anticancer effects (Ying et al., 2023). Peptidoglycan, a complex component of the cell wall in both gram-negative and gram-positive bacteria shows anticancer, antiproliferative, and immunomodulatory effects, and also inhibits proinflammatory cytokines (Silva et al., 2020; Park et al., 2022). Exopolysaccharides protect intestinal epithelial cells from pathogenic microbes by forming protective biofilms. They have immunomodulatory, anti-inflammatory, anti-tumor, anti-mutagenicity, antioxidant, antibacterial, and antiviral effects (Szydłowska and Sionek, 2023). They interact with macrophages, dendritic cells and modulate the immune response by enhancing the proliferation of T and NK lymphocytes (Zółkiewicz et al., 2020; Chen et al., 2024). Exopolysaccharides from Lactobacilli and Bifidobacteria play an important role in inhibiting pathogenic bacteria such as *E. coli* and *Citrobacter rodentium* (Mantziari et al., 2020).

Lipoteichoic and teichoic acids are essential components of cell wall of the gram-positive bacteria possessing immunomodulatory, antioxidant and anticancer properties. Lipoteichoic acid releases anti-infectious peptides like cathelicidin and defensin promotes non-specific anti-inflammatory response (Szydłowska and Sionek, 2023). Teichoic acids have antioxidant, anticancer and immunomodulatory capabilities (Jose and Elena, 2020). Exopolysaccharides inhibit cholesterol absorption and regulate lipid metabolism (Zółkiewicz et al., 2020; Prajapati et al., 2023). Exopolysaccharides from *Lactobacillus kefiranofaciens* , known as kefiran, delayed the development of atherosclerosis in a rabbit model (Zółkiewicz et al., 2020). Wang et al (2014) reported that exopolysaccharides (EPS) derived from *Lactobacillus spp* exhibited significant antiproliferative activities against colonic carcinoma cells. Peptides present in the form of peptidoglycan, an important component of the bacterial cell wall, reduced insulin resistance and adipose tissue inflammation in an obese mouse model (Wu et al., 2023). Exopolysaccharides derived from *Lactococcus lactis* showed antioxidant activity by increasing antioxidant enzymes like catalase, glutathione peroxidase, and superoxide dismutase activities and lowering lipid peroxidation levels in serum and liver of mice (Thorakkattuet al., 2022). Exopolysaccharides produced by lactic acid bacteria, particularly *Lacticaseibacillus rhamnosus*, enhance the physicochemical and sensory properties of milk products (Gurunathan et al., 2024). Currently, EPS are used as emulsifying, stabilizing, and water-binding agents in the food industry (Thorakkattuet al., 2022).

5. NEUROTRANSMITTERS

Gut bacteria like *Bifidobacterium, Bacillus subtilis, Lactobacillus plantarum* and *Lactobacillus brevi*s produce neurotransmitters like catecholamines, norepinephrine, dopamine and acetylcholamine, which plays vital role in brain function by modulating nerve signalling through the gut-brain axis. Acetylcholine and catecholamines are involved in emotions, motor control, memory and learning processes,while serotonin is known for its mood-elevating effects (Patterson et al., 2014). Gamma amino butyric acid (GABA) acts as an inhibitory neurotransmitter, promoting relaxation, modulating sleep disorders and decrease anxiety. These metabolites play a crucial role as antidepressants and psychiatric related disorders management (Patterson et al., 2014). GABA can also stimulate insulin production, enhance glucose tolerance and insulin sensitivity, and have anti-inflammatory and immunomodulatory effects, making it beneficial for managing diabetes (Cabello-Olmo et al., 2021).

Bacteriocins: Bacteriocins are ribosomally-synthesized, heat-stable antimicrobial proteins or peptides produced by the gut microbiota (Wu et al., 2023; Prajapati et al., 2023). They exhibit bacteriostatic or bactericidal effects that inhibit the activity of pathogenic microorganisms such as *Listeria monocytogenes, Clostridium perfringens, Salmonella enterica,* and *Escherichia coli* (Mantziari et al., 2020). The antimicrobial activity of bacteriocins is directly linked to their impact on the structure and function of bacterial peptides, as well as their ability to inhibit spore and pore formation on the cell membrane of pathogens (Rad et al., 2021; Mishra et al., 2024). Bacteriocins have the potential to suppress or eliminate drug-resistant organisms by disrupting bacterial cell membranes and causing the leakage of internal components (Lou et al., 2023). They are considered the next generation of antimicrobials and show promise for use in food preservation. Nisin, the first bacteriocins approved for commercial use as a food preservative by the European Food Safety Authority (EFSA), the Food and Drug Administrative (FDA), and Health Canada, is currently used in over 80 countries as a food additive. Other bacteriocins include subtilosin, lactococcin G&Q, enterocin, lactocyclicin, bovicin, plantaricin, and lacticin (Gurunathan et al., 2024).

Short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate are produced in the large intestine by the microbiota during the fermentation of non-digestible polysaccharides (Wu et al., 2023; Chudzik et al., 2021; Babu et al., 2023). These are the most studied postbiotics and the molar ratio of acetate: propionate: butyrate is approximately 60:20:20 (Vrzácková, et al., 2021; Park et al., 2022). SCFA s have a direct or indirect influence on brain function (Chudzik et al., 2021). They are absorbed by colonocytes and influence intestinal mucosal immunity, barrier integrity and function. SCFA promote indirect signalling to the brain via systemic or vagal pathways by stimulating the production of gut hormones such as glucagon-like peptide 1 (GLP1) and peptide YY (PYY) as well as neurotransmitters like serotonin and γ-aminobutyric acid (GABA) (Silva et al., 2020). SCFAs also regulate liver mitochondrial function, insulin secretion and increase whole-body energy homeostasis by entering the systemic circulation and reaching other tissues (Silva et al., 2020; Psichas et al., 2015; Larraufie et al., 2018). SCFAs, including formic acid and propionic acid, act against the activity of pathogenic bacteria by interfering with the cytoplasmic membrane structure, nutrient transport and macromolecular synthesis. They also possess antibacterial and antifungal properties (Mantziari et al., 2020). SCFAs facilitate the growth of beneficial bacteria by creating a more acidic intestinal environment (Park et al., 2022).

Propionic acid is the main source of gluconeogenesis and prevents long-term weight gain. Acetic acid has antioxidant properties and helps manage hunger and weight in the central nervous system (Park et al., 2022). Propionate regulates hepatic gluconeogenesis, carbohydrate metabolism, and inhibits cholesterol synthesis (Liu et al., 2023). Butyrate is the essential SCFA and the primary source of energy for colonocytes. It also possesses anticancer and anti-inflammatory properties through the inhibition of proinflammatory cytokines (Afzaal et al., 2022; Szydłowska and Sionek, 2023; Vrzácková, et al., 2021). SCFAs have the ability to cross the blood brain barrier and can reach the central nervous system, regulating the immune response (Szydłowska and Sionek, 2023). Butyrate salt participates in intestinal cell nutrient metabolism, promotes epithelial regeneration, increases the expression of immune suppressive cytokines and downregulates pro-inflammatory genes (Liu et al., 2023). SCFAs influence blood pressure in humans through various mechanisms. Butyric acid diminishes angiotensin

II-induced hypertension in mice (Park et al., 2022).

Compared to butyric and propionic acid, acetic acid is less abundant but possesses anti-inflammatory and analgesic properties. It may help manage hunger and weight in the central nervous system, suggesting it may help prevent cardiovascular disease (Park et al., 2022). Acetate acts as a lipogenic substrate and propionate inhibits lipogenesis by down regulating fatty acid synthase in the liver. Therefore, the acetate/propionate ratio is thought to be significant for de novo lipogenesis (Babu et al., 2023). SCFAs may play a key role in regulating inflammatory diseases by controlling the movement and activity of immune cells to sites of inflammation, allowing the number of pathogens to decrease quickly (Lou et al., 2023). SCFAs promote mucous production in the colorectal region and provide protection of the intestinal barrier through their anti-inflammatory effects. Insufficient availability of SCFAs is linked to many diseases including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), obesity, metabolic syndrome, type 2 diabetes, cancer, and autoimmune diseases, disrupting homeostasis and causing functional disorders (Babu et al., 2023). Autoimmune disorders like rheumatoid arthritis are often associated with intestinal barrier dysfunction. Hence, the restoration of the intestinal barrier has shown potential in reducing the onset of arthritis (Ying et al., 2023).

Bacterial lysates (BL): Chemical or mechanical degradation of Gram-positive and negative bacteria results in the production of bacterial lysates. Bacterial lysates have been sold on the market for decades as an immune product for respiratory infections. Bacterial lysates recognize and resist pathogenic bacterial infections and stimulates the bacterial infections (Liu et al., 2023).

Cell-free supernatants: Cell-free supernatant contains metabolites produced by the microbes. Supernatants of different microbes possess different activities. Supernatants of *Lactobacillus acidophilus* and *Lactobacillus casei* have anti-inflammatory and antioxidant effects on intestinal epithelial cells, macrophages, and neutrophils by increasing the secretion of the anti-inflammatory cytokine interleukin 10 (IL-10) (Fesseha et al., 2022). Supernatants from *Bifidobacterium shorteri* can reduce the release of various inflammatory mediators in dendritic cells and thus safeguarding the immune system against pathogenic bacteria (Ying et al., 2023).

Vitamins: The gut microbiota produces essential vitamins like thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, biotin, folate, cobalamin and menaquinone, which are crucial for DNA replication, RBC formation, immune function, and enzymatic processes (Nicholson et al., 2012; Forster et al., 2017; Liu et al., 2023). Folate produced by the microbiota has an important role in methylation, DNA synthesis, repair, and acts as an antioxidant (Zółkiewicz et al., 2020). Niacin induces anti-inflammatory properties in macrophages and dendritic cells and supress colonic inflammation (Puccetti et al., 2020). Vitamin K synthesized by gut microbiota plays an important role in blood clotting and bone health (Prajapati et al., 2023). Various microorganisms such as *Viridans Streptococci, B. subtilis natto, L. lactis, L. reuteri, Pichia pastoris*, and *Flavobacterium sp*. produce vitamin K2 (Ying et al., 2023). Cobalamin, exclusively synthesized by anaerobic bacteria, is not produced by animals, plants, or fungi (Park et al., 2022). Vitamin B12 is produced by *Propionibacterium feldsponenum, Salmonella*, and *Lactobacillus roehlis* (Ying et al., 2023).

Enzymes: Various physiological, metabolic and regulations functions were performed by the enzymes produced by the microorganisms. At industrial level, enzymes were produced from different fungal and bacterial strains. Enzymes such as peroxide dismutase (SOD), NADH-oxidase, glutathione peroxidase (GPx), and catalase act as antioxidants. In vitro studies found highest glutathione peroxidase in two strains of *L. fermentum* (Rafique et al., 2023). The genus Bacillus produces proteolytic enzymes with high stability against adverse conditions such as temperature, pH, organic solvents, oxidizing compounds, and detergenst. Additionally, enzyme catalase from genetically modified *Lactobacillus lactis* has shown inhibitory properties against chemically induced colon cancer in mice (Thorakkattu et al., 2022).

Organic acids: Organic acid-based postbiotics have antimicrobial properties. Citric acid, acetic acid, and tartaric acid are the most important acids produced by probiotic bacteria have strong antibacterial effects. Lowering intracellular pH and reducing membrane integrity are the main mechanisms responsible for the antibacterial mechanism of organic acids (Aghebati-Maleki et al., 2022). Lactic acid and acetic acid have very strong antibacterial activities and so, they can be used in the food sector for biopreservation (Rad et al., 2021).

Secondary bile acids: In the liver, cholesterol combines with taurine or glycine to form primary bile acids which are stored in the gall bladder and released into the duodenum to aid in the emulsification of dietary fats. While most primary bile acids are reabsorbed in the intestine, a small percentage is degraded by anaerobic bacteria in the gut, leading to production of secondary bile acids. These secondary bile acids are primarily excreted in feces, with a small portion entering circulation. These active metabolites possess bioregulatory activity and act as signalling molecules in the human body and plays regulating role in the host metabolism (Chen et al., 2024).

6. CHALLENGES OF POSTBIOTICS

The field of postbiotics faces several challenges that must be addressed. The definition and scope of postbiotics need further refinement and expansion as most postbiotic compounds are still in the experimental stage. Scientific evidence is lacking to prove the efficacy of postbiotics against various pathological conditions,and metabolic signalling pathways are not well understood. Though animal models demonstrated the efficacy of postbiotics, FDA regulatory approval of postbiotics requires human trials. It is crucial to establish recommended intake, toxicity and dosage of postbiotic products based on scientific evidence. Additionally, the shelf life and viability of these products need to be tested in both *in vitro* and *in vivo*.

7. CONCLUSION

Postbiotics are considered superior to pre and probiotics due to ease of preparation, mass production, purity, precise action, targeted responses and long shelf life. When comparison to pre and probiotics, postbiotics are not very common and available. But in the recent years, there is an increase interest in the utilisation of postbiotics as functional bioactive compounds, may contribute to improvement of host health. Hence, researchers are focusing to utilise postbiotics to modulate nutrition, health and disease. They can best use as an alternative to probiotics in premature neonates, children's, immunosuppressive individuals and as therapeutic agent for the treatment of diseases. They can also be used in the food preservation, food packaging, functional food and food supplements. As postbiotics are inanimate microorganisms, they cannot colonise the host buy modify the function and composition of gut microbiota. Regulation of the term postbiotics is still in the infancy stage. Hance, postbiotics are like next generation therapeutic agents for various health disorders.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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