



REVIEW ON POSTBIOTICS VERSUS PROBIOTICS : POSSIBLE NEW ALLIES FOR HUMAN HEALTH

1*K. Malleswari

2*Dr. D. Rama Brahma Reddy

3*D. Jaswanthi

*1 K. Malleswari, Department of pharmaceutics, Nalanda institute of pharmaceutical sciences ,Siddharth Nagar, Kantepudi (V), Sattenapalli (M),Guntur(DIST)-522438,AP,India. malleswarikunchala105@gmail.com

*2 Dr. D. Rama Brahma Reddy, Department of phytochemistry, Nalanda institute of pharmaceutical sciences ,Siddharth Nagar, Kantepudi(V), Sattenapalli(M),Guntur (DIST)-522438,AP,India.

malleswarikunchala@gmail.com

*3 D. Jaswanthi Student of B. Pharmacy, Nalanda institute of pharmaceutical sciences, Siddharth Nagar, Kantepudi (v), Sattenapalli(M), Guntur(DIST)-522438,AP, India. malleswarikunchala105@gmail.com

Abstract :

Postbiotics, defined as “preparations of inanimate microorganisms and/or their components that confer a health benefit to the host,” are emerging as a new frontier in nutritional and clinical research. This review aims to summarize the current scientific literature on postbiotics administration, comparing the evidence associated with the use of live or inactivated forms of microorganisms. The administration of a probiotic or postbiotic should not be considered as mutually exclusive, but rather as interdependent approaches, that can be chosen based on the specific microorganism, the target population and its specific needs. In addition, we highlighted the potential of ‘omics approaches as an efficient tool for the screening of microbial strains to identify postbiotic genetic traits. Finally, we discussed the issues that still limit the broad diffusion of postbiotic products on the market. Indeed, we highlighted that there is certainly an urgent need for greater clarity and a specific regulation to encourage research and development in the postbiotic sector

Keywords :

Inactivated microorganisms; Postbiotics; Probiotics; Genomic characterization; Human health; Food technologies; Fermented foods; Food supplement

INTRODUCTION :

The role of nutrition in human health has been known since the time of Hippocrates (400 b.C.), summarized in his famous phrase “Let the food be the medicine and medicine be the food”. In the current era, we are facing

with a sort of renaissance of nutrition, recognizing its importance for the prevention and management of diseases

Among the foods beneficial for human health, fermented foods (FFs) stand out, boasting a long and safe history of use. FFs are defined by the “International Scientific Association on Probiotics and Prebiotics” (ISAPP) as “foods made through desired microbial growth and enzymatic conversions of food components

Unlike probiotics, postbiotics remain effective even when the microorganisms that produced them are no longer alive. These bioactive compounds, including short chain fatty acids (SCFAs), peptides, organic acids, and extracellular polymeric substances (EPSs). The soluble factors are the primary drivers behind many health benefits associated with a healthy gut microbiome

Postbiotics represent the functional compounds that result from the fermentation process carried out by probiotics, often when they consume probiotics. These are not living microorganisms but rather non-living preparations of bacterial components or metabolites that confer a health benefit. The process involves the live bacteria producing these compounds, which are then either secreted into the environment or released upon the breakdown of the microbial cell

These benefits range from preventing cardiovascular Diseases and diabetes, to preventing infections in the gastrointestinal Tract and oral cavity. Probiotics may also improve the immune system, Cognitive function, and facilitate nutrient absorption. Although the positive effects of probiotics in the prevention and treatment of Diseases have been well documented, questions remain about their dosage and long-term safety, especially in patients with underlying medical conditions.

Some mild to moderate side effects, including rash, nausea, Flatulence, abdominal bloating, vomiting, chest pain, constipation, and poor appetite, were observed in children assuming probiotics to treat Diarrhea. Despite the widespread use of probiotics.

The greater shelf life and temperature resilience of postbiotics opens up new possibilities for their use in functional foods and beverages, expanding beyond traditional refrigerated dairy products. Because postbiotics are inanimate compounds, they exhibit far greater tolerance to environmental stressors, including high temperatures and fluctuating moisture levels. This enhanced stability allows for a longer shelf life and enables their incorporation into a wider variety of food products and supplement formats without requiring refrigeration

1. What is known about Postbiotics :

The term postbiotic was derived from ‘post’, meaning ‘after’, and ‘biotic’, relating to or resulting from living organisms, to suggest ‘after life’. The new term means “afterlife” (as opposed to “from life”), and it describes “non-living organisms.” The concept of non-viable microorganisms that positively affect health is not new, and various terms have emerged to characterize these substances. However, “postbiotic” has emerged as the predominant term in recent years. Other terms in this realm include “para probiotics,” “meta biotics,” “tyndallized probiotics,” and “bacterial lysates”. Streamlining the terminology to a singular, precisely defined term would enhance the clarity and coherence within the field, avoiding the need for multiple terms to describe similar concepts.

Before 2021, several definitions of postbiotics had been coined, in some cases contradictory. Therefore, aligning around a common terminology was necessary to facilitate understanding, reduce errors, allow comparison of results and consequently advance scientific research in this field. The ISAPP definition of the term “postbiotic” reported above has raised additional questions. Vinderola, Sanders, et al. (2023c) provided detailed answers to frequently asked questions about the ISAPP postbiotic definition.

One of the most frequent questions is around the term “inanimate”, chosen in the ISAPP consensus definition of postbiotic. Although not a common term in microbiology, this term has been used in the attempt to distinguish “inactive” from “non-viable”, as a postbiotic is undoubtedly “active” in terms of conferring a health benefit. For this reason, the term “inactive” could be misleading. Furthermore, examining the definition provided by the ISAPP consensus, that focus on “inanimate microorganisms and/or their components”, it seems not to consider their metabolites.

The reason for this lies in the etymology of the Latin term post-biotic, that means “after life” . Microbial metabolites, such as vitamins or short-chain fatty acids, are not living beings and therefore cannot have an “after life”. For this reason, preparations consisting only of metabolites have been excluded from the concept of postbiotic. However, metabolites can certainly be part of a postbiotic preparation since preparations with inanimate microbial biomass will inevitably contain some metabolites.

However, the temperature and the length of the treatment influence the nutritional value and the sensory characteristics, so it may not always be the best option for postbiotics intended for use as a food or a food supplement. Non-thermal inactivation treatments are a valid alternative to maintain quality and sensorial properties close to those of their fresh equivalents, while ensuring safety and stability.

Non-thermal inactivation treatments include technologies such as electric field, ultrasound, high pressure, X-rays, etc. Since the inactivation treatment may influence the result, the beneficial effect exerted by the postbiotic must be demonstrated in relation to the pre-established treatment .

However, the maximum concentration of active microorganisms that are acceptable for a fermented formula to be considered as a postbiotic is not specified.

Five mechanisms of action have been proposed for postbiotics:

- i) modulation of the resident microbiota (through lactic acid, short-chain fatty acids (SCFAs), bacteriocins, quorum sensing, cross-feeding, adhesins, etc.);
- ii) enhancement of epithelial barrier functions (through exopolysaccharides (EPS), SCFAs, proteins, etc.);
- iii) modulation of local and systemic immune responses, e.g., through MAMP-PRR (microbe-associated molecular pattern and pattern-recognition receptor) interaction, indole derivatives, keto acids, branched chain fatty acid;
- iv) modulation of systemic metabolic responses (through bile salt hydrolase, succinate, vitamins, SCFAs, etc.);
- v) systemic signaling via the nervous system (through serotonin, dopamine, acetylcholine, γ -aminobutyric acid, etc.) (Salminen et al., 2021).

By definition, postbiotics inherently have advantages over their live counterparts, as reported by Piqué et al. (2019) and listed below:

- No risk of bacterial translocation from the gut lumen to the blood in vulnerable and immunocompromised subjects;
- No chances of acquisition and transfer of antibiotic resistance genes;
- Easier to be standardized, transported, and stored;
- Enhanced and direct interaction of the molecules released by the disrupted microbial cells with the target cells.

The main differences between probiotics and postbiotics are summarized in Fig. 1.

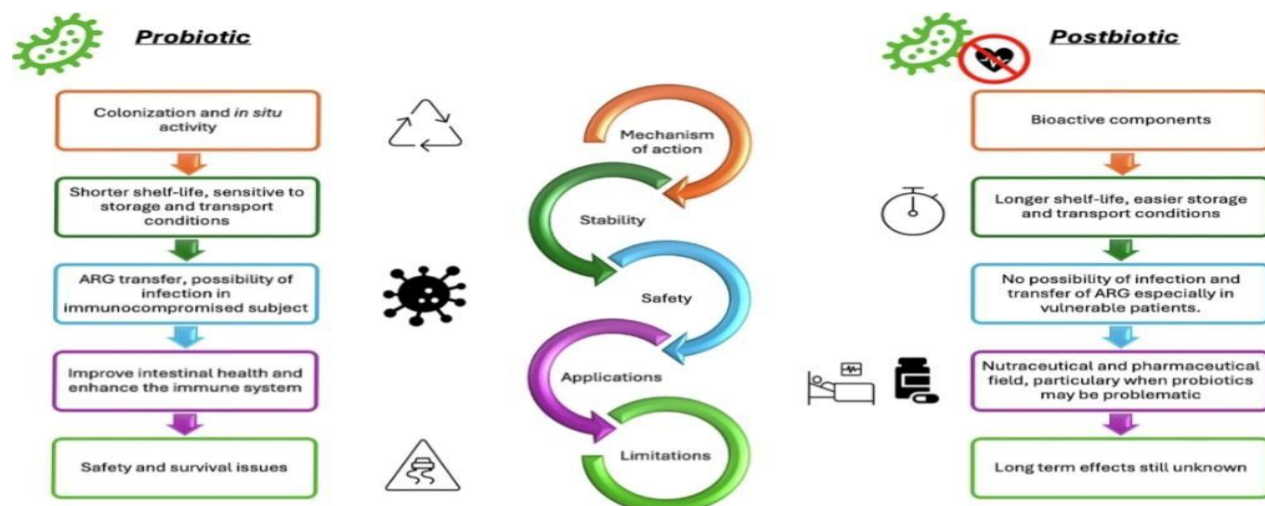


Fig. 1. Comparison between probiotics and postbiotics. The discriminating factors between probiotics and postbiotics concern the mechanism of action, stability, safety, application and limitations, apparently demonstrating a potential advantage of postbiotics over their live counterparts. ARG,

2. Post treatments in humans :

Recent years have seen significant challenges in drug development. High failure rates during preclinical and clinical trials, often due to the lack of efficacy or safety concerns, lead to wasted resources and prolonged development times. The long and complex development process, combined with stringent regulatory hurdles, further increases costs and delays, with the average cost of developing a new drug estimated as > \$2.8 billion. While existing drugs offer numerous benefits, they also have limitations.

Side effects can impact patients' quality of life and adherence to treatment. Additionally, individual variations in genetics and disease can affect the efficacy. Some drugs have narrow therapeutic windows, making precise dosing critical to avoid adverse effects or suboptimal outcomes. Antibiotics are traditionally used to treat and prevent infections. Appropriate use of antibiotics saves millions of lives by providing the ability to specifically kill infecting microorganisms with minimal side effects on host cells.

However, despite their long history of controlling bacterial pathogens, reckless and inappropriate use of antibiotics may negatively alter gut eubiosis, reducing microbial diversity. In addition, the uncontrolled and widespread use of antibiotics also contributes to the spread of antibiotic-resistant strains, posing a significant threat to public health and lowering the effectiveness of the treatment.

The limitations of conventional medicine in treating human diseases necessitate and the development of innovative approaches. Research on postbiotics represents an opportunity not only to elucidate their mechanisms of action in detail, but also to develop novel therapeutic strategies for improving health.

Some human studies have shown that postbiotic treatment can modulate the composition and activity of the human microbiome, indirectly influencing human health. While there is a large literature focused on the therapeutic use of viable beneficial bacteria in clinical trials, the study of postbiotics has been relatively neglected. However, scientific evidence of their beneficial health effects is steadily accumulating, although their precise composition and underlying mechanisms remain under investigation.

3. Clinical Trails comparing probiotics & postbiotics

In this section, we screened current literature for clinical trials comparing the same microbial strain administered either as a probiotic or a postbiotic to the similar target population. The comparison may come from the same or different studies. The initial literature search was carried out using Scopus and different combinations of the

keywords: “postbiotics”, “human clinical trial”, “heat-killed bacteria”, “human subject”, “probiotics”, “postbiotics”, “live bacteria”, “heat-killed bacteria”. We excluded trials on animals and *in vitro studies*, articles not in English and reviews. In addition, we only included a study in Table 2

if both the live and the inactivated strain was tested, or if we could find this comparison on similar target populations in two different studies.

Table 2. Clinical trials comparing probiotic & postbiotic administration to the similar target population

Target population	Probiotic	Postbiotic	Main finding
IBS -D patients	Bifidobacterium longum CECT 7347	Heat treated B. longum CECT 7347	Both significantly reduced IBS symptom severity compared with placebo
Adults with allergic rhinitis	Live B. longum CECT 7347	Heat-treated B. longum CECT 7347	Postbiotic supplementation significantly reduced the combined symptom and medication score after 8 weeks.
Patients with previous colorectal cancer	Live L. paracasei SD1 + L. rhamnosus SD11	Heat-killed forms of the same strains	Both groups showed reductions in several pro-inflammatory cytokines; the trial included postbiotic, probiotic and placebo groups.

4. Omic's approach to identify postbiotics

Although postbiotic mechanisms of action are mostly unknown, recent advances in the field of “ OMICS ” approaches may facilitate the screening of multiple strains to highlight the presence of potentially relevant traits. In order to design a novel probiotic or postbiotic, a series of efforts are necessary to understand its functionality, as well as safety. Thus, a new approach, called probiogenomics .

which includes the application of high-throughput techniques such as genomics, transcriptomics, proteomics and metabolomics, which provide a valuable resource for the prediction of strain functionality and the rational selection of new, uncharacterized strains . Data obtained from ‘omics approaches allow an in-depth characterization of physiology, functionality and mechanisms of action of the microorganisms.

Besides this, genomic screening is also important for determining the absence of unwanted traits, such as antibiotic-resistance genes or virulence factors. The postbiotics market is one of the fastest growing sectors in the food industry, most likely due to the increasing scientific evidence supporting the positive role in consumer health. This encourages and accelerates the search for new microorganisms that can be used as potential postbiotics. However, there are gaps in the validation procedures that need to be addressed. It is important to note that although the multi-omics approach can provide many advantages to the actual investigations, there are also some challenges in the downstream analysis, especially the correct functional interpretation of the generated data . Moreover, genetic screening may support the identification of genes involved in functional activities of interest, as well as the absence of undesirable traits, allowing also to identify those characteristics of a strain that are independent of their vital state.

Vitamins production by progenitor strains, subsequently found within postbiotic preparations, is another interesting feature. Vitamins are micronutrients essential for the metabolism of all living organisms. Indeed, even in highly industrialized countries, vitamin deficiencies, due to malnutrition or unbalanced diets are still very common. LAB have been shown to produce several vitamins, such as B and K. Therefore, the use of vitamin-

producing microorganisms represents a natural, cheap and more sustainable alternative to the use of chemically synthesized pseudo vitamins, for the production of fortified foods .

This approach allowed to identify 19 strains belonging to the species *Limosilactobacillus fermentum*, *L. plantarum*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, and *Limosilactobacillus mucosae* having the complete biosynthetic pathway, highlighting that the presence of riboflavin biosynthesis genes is strain-specific and the power of a comparative genome approach to screen a high number of potentially producing strains, thus reducing those to be tested in time-consuming, *_in vitro_* analyses .

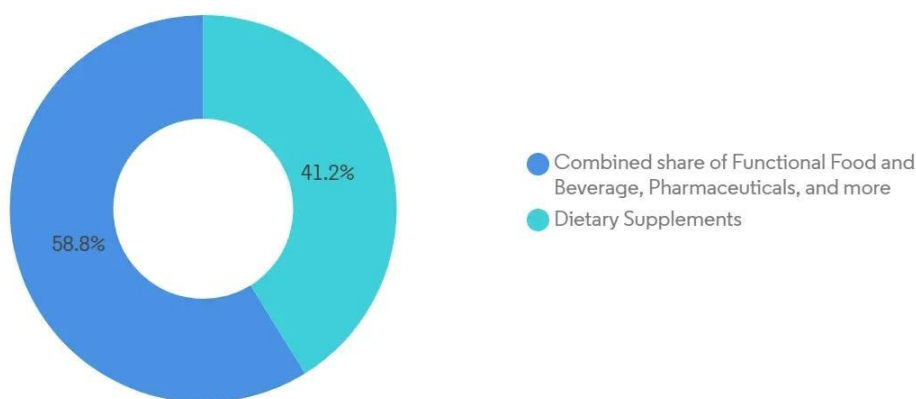
5. Postbiotics to market : commercial and industrial aspects

Government authorities around the world are exploring the regulation of the postbiotic category, but there are no official published guidelines or regulations for postbiotics as food/dietary supplements or foods to date. The current situation for postbiotics globally varies and here are some examples: in Thailand several dietary supplements containing heat-killed bacteria have been authorized by the Thai FDA, whereas the Chinese government has no official position, but industry and associations are working on quantification standards. . Japan has no regulations specific to postbiotics but postbiotic ingredients have been used in foods and are possible under the current regulatory framework for food (FFC, Food with Functional Claim) provided they meet the requirements.

In Europe, the use of the term ‘postbiotic’ is not regulated; postbiotic ingredients have to follow the regulations in place for foods and food supplements, or medicinal products, depending on their intended use. No regulations for postbiotic foods or food supplements currently exist in Brazil or Argentina. In Australia, the Therapeutic Goods Administration (TGA) has allowed the inclusion of some postbiotic ingredients (inactivated microorganisms) in Listable Medicines.

The postbiotics market is experiencing significant growth, driven by increasing consumer awareness and the demand for functional foods and supplements. The market is segmented by type , from , application and geography with North America leading in market share and asia -pacific showing fastest expansion

Postbiotics Market: Market Share by By Application, 2024



Source: Mordor Intelligence



FIG 2. Postbiotics market share in 2024

6. The link between traditional fermented foods and postbiotics

Traditional fermented foods represent significant natural sources of postbiotics, owing to the complex microbial fermentation processes involved in their production. For instance, kimchi is a Korean fermented vegetable product that contains a variety of bioactive metabolites synthesized by lactic acid bacteria (LAB), including organic acids, bacteriocins, and functional peptides. Similarly, tempeh, a fermented soybean product from Indonesia, is rich in bioactive compounds generated by *Rhizopus* species, many of which exhibit antioxidant and anti-inflammatory effects.

Yogurt, produced through the fermentation of milk by *Lactobacillus delbrueckii* subsp. *Bulgaricus* and *Streptococcus thermophilus*, contains postbiotic substances such as β -galactosidase, SCFAs, and peptides with physiological relevance. Quantitative data on representative postbiotic compounds across traditional fermented foods are provided. These foods not only provide nutrition but also act as delivery vehicles for stable postbiotic compounds, enhancing their health-promoting potential. In addition to widely studied fermented foods such as tempeh and sauerkraut, traditional products like African *ogi* (fermented cereal gruel) and Japanese *natto* (fermented soybeans) have also demonstrated postbiotic potential, particularly in their content of bioactive peptides, *natto* kinase, and organic acids.

Moreover, food industry by-products such as cheese whey and fruit pomace are emerging as sustainable reservoirs for postbiotic extraction due to their rich microbial fermentation substrates. Certain herbs traditionally incorporated into fermented dishes, for instance, *Polygonum minus* (PM), used in Southeast Asian *laksa*, not only enhance flavor but also exhibit antimicrobial activity and support postbiotic formation through synergistic fermentation effects. These underexplored sources broaden the cultural and ecological diversity of postbiotic research.

7. Postbiotic in food technologies:

Postbiotics are gaining attention in food technologies for their potential to enhance food safety and quality. They are derived from inanimate microorganisms and/or their components, providing health benefits without the presence of viable cells. Postbiotics offer several advantages over traditional probiotics,

Postbiotics derived from the metabolic processes of microorganisms, could be used as food additives of natural origin and improve the functional, nutritional and sensory aspects of various foods.

Postbiotics may be added before thermal processing without compromising their functionality and they are generally stable at high temperatures and within a wide range of pH values, being suitable for the addition into different food matrices without loss of

Conclusion :

In this review, we highlighted the versatility and the possible applications of the emerging class of postbiotics, although many challenges remain to be addressed. The studies available in the scientific literature speculate that postbiotics have multiple beneficial properties on human health, such as anti-inflammatory, antihypertensive, immunomodulatory, hypocholesterolemic, antitumor, antiproliferative and antioxidant activity. However, although several clinical trials suggested that postbiotics can be an effective approach to different types of health conditions

In addition, we highlighted that only few studies compared the same strains in both the live and inactivated forms (pro- and postbiotic) on the same target population, therefore it is difficult to speculate on the possibility that a microorganism may have the same health effect both as pro- and postbiotic.

Finally, there is certainly an urgent need for greater clarity in the terminology and a specific regulation that should include clear indications on the label, on the benefits and how to use the term postbiotics, ensuring uniform production and quality standards for postbiotic products, simplifying authorization procedures, thus reducing the costs and time needed to place these products on the market.

References :

1. Salminen, S., Collado, M.C., Endo, A., et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nature Reviews Gastroenterology & Hepatology*. 18(9): 649–667, 2021.
2. Aguilar-Toalá, J.E., Arioli, S., Behare, P., et al. Postbiotics—when simplification fails to clarify. *Nature Reviews Gastroenterology & Hepatology*. 18(11): 825–826, 2021.
3. Aguilar-Toalá, J.E., Garcia-Varela, R., Garcia, H.S., et al. Postbiotics: An evolving term within the functional foods field. *Trends in Food Science & Technology*. 75: 105–114, 2018.
4. Collado, M.C., Vinderola, G., Salminen, S. Postbiotics: Facts and open questions. A position paper on the need for a consensus definition. *Beneficial Microbes*. 10(7): 711–719, 2019.
5. Tsilingiri, K., Rescigno, M. Postbiotics: What else? *Beneficial Microbes*. 4(1): 101–107, 2013.
6. Taverniti, V., Guglielmetti, S. The immunomodulatory properties of probiotic microorganisms beyond their viability. *Genes & Nutrition*. 6(3): 261–274, 2011.
7. Hernández-Granados, M.J., Franco-Robles, E. Postbiotics in human health: Possible new functional ingredients? *Food Research International*. 137: 109660, 2020.
8. Cuevas-González, P.F., Liceaga, A.M., Aguilar-Toalá, J.E. Postbiotics and para probiotics: From concepts to applications. *Food Research International*. 136: 109502, 2020.
9. Patel, R.M., Denning, P.W. Therapeutic use of prebiotics, probiotics and postbiotics to prevent necrotizing enterocolitis. *Clinics in Perinatology*. 40(1): 11–25, 2013.
10. Mantziari, A., Salminen, S., Szajewska, H., Malagon-Rojas, J.N. Postbiotics against pathogens commonly involved in pediatric infectious diseases. *Microorganisms*. 8(10): 1510, 2020.
11. Calvanese, C.M., Villani, F., Ercolini, D., De Filippis, F. Postbiotics versus probiotics: Possible new allies for human health. *Food Research International*. 217: 116869, 2025.
12. Ghadiri Harat, S., Pourjafar, H. Health Benefits and Safety of Postbiotics Derived from Different Probiotic Species. *Current Nutrition & Food Science*. 31(2): 116–127, 2025.
13. Mokashe, N.U., Talkal, R., Tokdar, P. Postbiotics: Definitions, Manufacturing, Analytical Characterization, and Clinical Evidence for Human and Animal Health. *Current Microbiology*. 83(5): Article 278, 2026.
14. Hill, C., Guarner, F., Reid, G., et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of probiotics. *Nature Reviews Gastroenterology & Hepatology*. 11(8): 506–514, 2014.
15. Sanders, M.E., Merenstein, D.J., Reid, G., et al. Probiotics and prebiotics in intestinal health and disease. *Gut*. 68(11): 211–222, 2019.