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**Review Article**

# Scope of Paraprobiotics Towards the Development of Functional Food and Nutraceuticals: A Review

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ABSTRACT

Probiotics are the live bacteria that help the host's health. Paraprobiotics, defined as "inactivated microbial cells (non-viable) that confer a health benefit to the consumer," hold the ability to regulate the adaptive and innate immune systems, exhibit anti-inflammatory, antiproliferative and antioxidant properties, and exert antagonistic effects against pathogens. When it comes to developing functional foods and nutraceuticals, paraprobiotics—which include non-viable microbial components or metabolites derived from beneficial bacteria—offer fascinating opportunities. Nutraceuticals and functional foods are becoming more and more popular due to the increased need for preventative health strategies. Beyond just providing a basic diet, many goods have specific health benefits that help prevent disease and enhance overall well-being. Numerous health-promoting benefits of paraprobiotics include immunomodulation, improved gut health, and anti-inflammatory qualities. Paraprobiotic production techniques are always changing, resulting in increased cost and efficacy effectiveness. This review paper delves into the potential of paraprobiotics in shaping the future of functional food and nutraceutical development. By exploring their diverse functionalities, production methods, mechanism of action, and integration into various food matrices, the paper aims to provide a comprehensive understanding of their potential impact.

## Introduction

Over a century has passed since Metchnikoff's initial discovery of probiotics, and their appeal has grown significantly. There has been a significant amount of experimental and clinical data on the health advantages of probiotics during the past few decades, especially in the last five years.[1] The desire for optimal health through diet is greater than ever, which is driving the growth of nutraceuticals and functional foods, which are goods that purport to provide particular health advantages above and above basic sustenance. Of all the tactics used, using microorganisms to power systems has enormous potential. Although probiotics—live microorganisms that offer health benefits—have attracted a lot of attention, there are obstacles to overcome, such as limited food uses and viability issues. Paraprobiotics show up as an intriguing alternative in this search for the best dietary therapies, with promising opportunities for the creation of novel functional foods and nutraceuticals. A broad category of non-viable microbial components derived from probiotics and other helpful bacteria is known as paraprobiotics. This includes acellular materials like exopolysaccharides and spent culture supernatants, as well as cellular components such as cell wall fragments, metabolites, and extracellular vesicles. Since paraprobiotics cannot self-replicate like their living counterparts, there is no need to worry about possible overgrowth or the spread of genes that cause antibiotic resistance. But this seemingly little distinction opens a wealth of benefits.[2] The stability and adaptability of paraprobiotics are what makes them appealing. Their ability to tolerate extreme processing conditions, like high temperatures, acidic environments, and prolonged storage, sets them apart from probiotics and makes them perfect for integration into a broader variety of food

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products. This makes it possible to create fortified drinks, shelf-stable vitamins, and functional yogurts that were previously unattainable with live cultures. Furthermore, paraprobiotics show improved safety profiles, especially for immunocompromised or susceptible individuals that are allergic to particular types of bacteria.[3] But the advantages go much beyond just maintaining stability. A great deal of research indicates that paraprobiotics can nevertheless have health-promoting benefits that are comparable to those of their live counterparts. They display anti-inflammatory and antioxidant qualities, impact the immune system, and affect the composition of the gut flora.[2] Numerous health benefits, including enhanced digestion and intestinal health, immunological support, and cognitive performance, have been associated with them according to studies. Because of their special blend of safety, stability, and functional potential, paraprobiotics are poised to revolutionize the field of functional foods and nutraceuticals. Imagine drinks that are fortified to provide immune support without needing to be refrigerated, or yogurt enhanced with paraprobiotics that continue to have their gut-boosting effects even after baking. These are but a few examples of the opportunities this new profession presents.[3] Scientific evidence has demonstrated that similar to probiotics, molecules present on the cell surface (peptidoglycan, teichoic acid, cell wall polysaccharides, cell surface-associated proteins, etc.) may constitute the first line of interaction between paraprobiotics and the host, thereby mediating the beneficial effects, even though the molecular mechanisms underlying paraprobiotic action still require thorough investigation.[4] Another great advantage is no loss of bioactivity when administered in combination with antibiotics or antifungal agents.[5] Additionally, killed probiotics present a compelling way to get around issues connected to food matrix development. Additionally, as was already mentioned, research on gut microbiota revealed previously unknown bacteria from the gastrointestinal tract that have positive effects on human physiology. Since these next-generation probiotics are frequently strictly anaerobic, producing and maintaining them presents significant challenges, paraprobiotic preparations may help resolve issues with stability during commercialization and safety.Apart from the most researched probiotic genera, *Lactobacillus* and *Bifidobacteria*, which have been granted the generally recognized as safe (GRAS) and qualified presumption of safety (QPS) status for intentional addition to food and feed by the FDA and EFSA, respectively, other probiotic agents and next-generation probiotics, such as *Faecalibacterium prausnitzii* and other members of the Ruminococcaceae, Bacteroides, and *Akkermansia* sp., are emerging. The safety profile of these probiotics needs to be investigated. Additionally, acetic acid bacteria have been shown to have anti-inflammatory and anti-allergic properties in foods (such as fermented milk, kombucha, and nata de coco), while it's unclear if the bacteria's living or dead cells are what cause these advantages.[6-8]

The journey towards achieving health through diet has given birth to a dynamic pair: function-oriented foods and nutritional pharmaceuticals, or nutraceuticals. This intertwined yet unique path shows a constantly changing terrain, fuelled by scientific progress and consumer needs. To navigate these changes and tap into the potential of paraprobiotics, comprehension of this evolution is key. The 1980s saw the birth of functional foods in Japan, initially tied to improved nutrition and lifespan. Nutraceuticals arrived on stage later, aiming to prevent and handle specific health issues. Both terminologies were somewhat blurry, frequently intersecting in intent and usage.[9] The characteristics of nutraceuticals are shown in Fig. 1. Although interest is on the rise, regulatory entities have had a hard time keeping up. Discerning the line between food and therapeutic products has been a tough task, creating puzzle-like scenarios for both the makers and users. This kickstarted debates and re-evaluations to set straightforward rules for product marking and health statements. The 21$^{st}$ century has witnessed a tidal wave of technical advancements. Methods like gene alteration and various biotechnological techniques have paved the way for nutritionally enhanced foods such as golden rice, which is rich in beta-carotene. Microbiome examinations and DNA tests have enabled tailor-made nutrition plans, providing personalized diet schedules. Today's consumers are seeking speedy, individual-centric solutions and are evolving to become more health-aware. Consequently, the demand for beneficial foods and health supplements offering distinctive benefits like immunity boosters, brain stimulants, and digestive health aids has gone up. Ethical sourcing and sustainability have also grown in importance.[10,11]

## Paraprobiotics Aids

### *Merging the bridge between food and medicine*

Enriching functional foods with paraprobiotics could merge the divide between customary food habits and specific health interventions (Fig. 1). Not like conventional medicines, this food provides a natural, savory, and sustainable alternative to regulate gut microbiota and promote diverse health states. Research indicates their possible role in modulating immune function, promoting gut health, and even enhancing cognitive functions.[12]

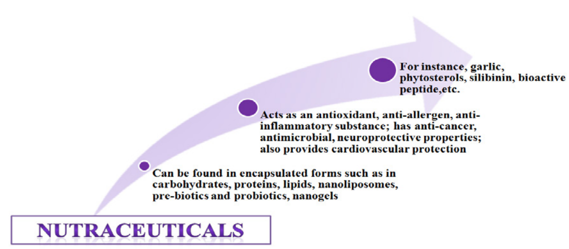


**Fig. 1:** About nutraceuticals

*Enhanced safety and stability*

While the concept of paraprobiotics is closer to that of probiotics, paraprobiotics have emerged as more stable and safety-friendly as opposed to common probiotic strains. These deactivated microorganisms and dead cells stay in the microbiome and keep the structure intact by inhibiting the proliferation of harmful microbes, viruses, and microorganisms. They do so by supplying polysaccharides, proteins, and metabolites. This additional stability that has been gained ensures their use in a much wider range of dairy product formulations, some of which are stable at much higher incubation temperatures, fully overcoming the logistic hurdles that are usually linked with live probiotics.[13]

*Tailored functionality and wider consumer reach*

While utilizing probiotics in the design of dietary supplements and food products manufacturers can introduce these types of probiotics to address specific health problems. Such differentiation is leveled up with an option for the creation of different products that meet different needs, from the ones affected by the immune system to the ones related to cognitive enhancement. Similarly, product development is crucial and the routing of paraprobiotics into commonly known food formats like yogurts, beverages, or bakery products will aid in the acceptability of the consumers and increase the potential outreach of the product.[14]

*Cost-effectiveness and regulatory advantages*

Contrary to conventional therapies, paraprobiotics-based functional foods and nutraceuticals offer a limitations-free approach to health promotion and disease prevention. This budget-friendliness is a major reason behind their popularity among the wider population who might enjoy a less stressful burden on the healthcare system. Furthermore, the regulatory environment on paraprobiotics is usually less rigorous than that of live probiotics which improves the product's development speed and time.[15]

*Synergistic effects with food components*

Incorporating paraprobiotics into functional meals is pretty effective because it is going to pay off by making use of the synergic effects between the paraprobiotic components and the vegetables, fruits, and other bioactive compounds that are naturally present in this kind of food. Thus, in this case, the blending of prebiotics (the fibers that feed the gut bacteria) with paraprobiotics (the makers of molecules that the gut bacteria create) leads to the synergistic action of productive paraprobiotic-prebiotic axis which collectively enhances health outcomes.[11,16] As they have their specific advantages, they are going to play an important role in helping in that mediation and be in charge of making evidence-based dietary solutions regarding health and well-being. The role of paraprobiotics in the human body investigations is relentlessly published to further extend their diverse functions beyond gut health to a range of other activities like immune modulation, inflammation control, and skin health. As it is happening, the companies get a chance to create such exciting options by combining them with next-generation functional foods and nutraceuticals.

## About Paraprobiotics

With the sprouting of the field of paraprobiotics, the horizon presents plenty of opportunity for creative nutraceutical and functional food development with a wide array of health benefits. Despite this, the good manufacturing practice (GMP) principles must be understood for product development and quality control in the manufacturing process. In the following section, we will look into various types of probiotic characterization; some of their possible applications are also discussed.

### By Origin

*Bacterial*

Two strains commonly present are *Lactobacilli* and *Bifidobacteria*. They provide a wide range of functions such as immunomodulation and anti-inflammatory. A few examples are the heat-treated *Lactobacillus plantarum* and *Bifidobacterium animalis lactis* that were used in this study.

*Fungal*

*In-vitro*, some forms of yeasts such as *Saccharomyces boulardii* are capable of making antimicrobial and gut-barrier-constituting effects.

*Algal*

The extracts of microalgae such as *Chlorella* and *Spirulina* have already elucidated implications for diseases such as diabetes, cancer, and cardiovascular diseases through their antioxidants and anti-inflammatory mechanisms of action.[17]

### By Cell Composition

*Whole cells*

Heat, UV, or gamma irradiation inactivation and lyophilization of microbial cells help to preserve important cell wall components, cell internal metabolites that play immunomodulatory and anti-pathogenic roles.[18]

*Cell wall fragments*

Bacterial cell wall components as peptidoglycan and lipoteichoic acid, are known for immune response initiation and for strengthening gut barrier functions.

*Cytoplasmic components*

For instance, components such as DNA, RNA, and proteins at the cellular level play a regulatory role in the microbiota and have anti-inflammatory or antioxidant effects.[19]

## By Mechanism of Action

### *Immunomodulation*

Microscopic probiotic organisms that protect against disease are called paraprobiotics. They activate dendritic cells and macrophages which provide the host with defense against pathogens.[17]

### *Antimicrobial activity*

A specific number of paraprobiotics, even the ones which are active bacteriocin producers or from concurrent access to adhesion sites with pathogenic organisms, are the ones that will cause the colonization of pathogens.

### *Anti-inflammatory activity*

Paraprobiotics help suppress inflammatory pathways and also help promote the production of anti-inflammatory cytokines.

### *Gut barrier modulation*

As these probiotics could positively affect the "tight junctions" integrity, they may improve the intestinal permeability leading to the prevention of a leaky gut syndrome.[18]

## By Application

### *Dietary supplements*

Paraprobiotics can be found in the form of capsules, tablets, or powders and many people use them to support their gut health.

### *Functional foods*

Yogurt, ferments, and fortified dairy products are easy-to-use vessels for the delivery of such nutrients.

### *Topical applications*

Paraprobiotics in ointments and emulsions can not only support skin well-being but can also be beneficial in wound healing.[19]

There are various methods employed for paraprobiotic production from probiotic microorganisms:

- *Thermal treatment*

This typical way of doing it is that probiotic cultures are put under the heat of a controllable temperature for a certain time. The heat inactivates the germs, thus, they are rendered unable to multiply. Nevertheless, the most important thing is to establish the right temperature and time requirements. Thus, this is the key to the conservation of the cell wall components and the other biomolecules, which are the main basis for the health benefits of paraprobiotics.

- *Chemical treatment*

Some substances can act against probiotic bacteria. Some of the harmful substances are acids and formalin. In the same way, this method requires a lot of supervision and validation to make sure that the finished paraprobiotic product is safe and effective. The consumers must be safeguarded by the non-detectable residual substances in the finished product.

- *Enzymatic treatments*

Enzymes are the living catalysts that can be utilized to cohesively break down the cell wall of the probiotic bacteria. Thus, through the given strategy, scientists extract the cell wall components with proven health benefits and use them as paraprobiotics.

### *Physical processes*

There are several physical methods to make paraprobiotics. These approaches largely rely on various sources of energy to deactivate the bacterial cells. These approaches largely rely on various sources of energy to deactivate the bacterial cells:

- *Ionizing radiation (IR) and ultraviolet (UV) rays*

They are the main tools that can effectively kill bacteria. Nevertheless, the exact wavelengths and the exposure times must be adjusted to achieve the perfect inactivation of cells while at the same time preserving the good features of the cells.

- *High-pressure processing (HPP)*

This technology applies high hydrostatic pressure to eliminate the microorganisms. The HPP has several benefits, such as the low heat generation and the fact that it can keep the bioactivity of the given molecules.

### *Emerging techniques*

Research is ongoing to explore novel methods for paraprobiotic production. These include:

- *Pulsed electric field (PEF) treatment*

PEF has the cell membrane of bacteria damaged by short, high-voltage electric pulses, hence, bacterial inactivation. This method is useful for the low thermal impact and the possibility of having higher bioactivity retention in the final paraprobiotics.

- *Supercritical CO2 extraction*

Supercritical CO2, which is a state in which carbon dioxide has both liquid and gas qualities, can be employed to isolate specific biomolecules from probiotic cells. This method can be used to get the pure paraprobiotic components without affecting their functionality [Fig.2].

The selection of the right parable manufacturing process is determined by several factors. The factors that are to be considered in the bioengineering process are the target probiotic strain, the bioactives to be retained, and the commercial scalability of the technique. Besides, the structure and the bioactivity of the paraprobiotic product obtained by the procedure of choice should be closely evaluated.

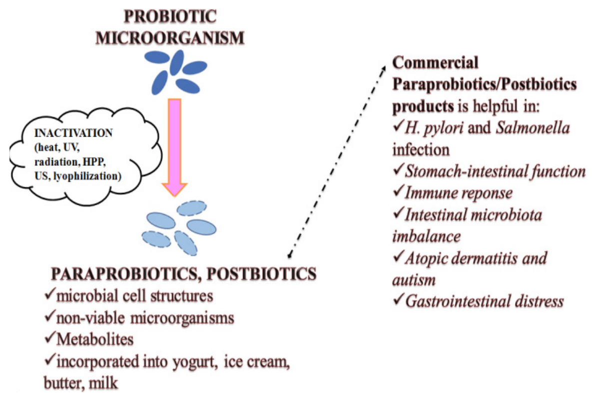


**Fig. 2:** About paraprobiotics

The true potential of paraprobiotics lies in their unique physiological properties, which contribute to a range of health-promoting effects. The strong immunomodulatory action of paraprobiotics impacts both innate and adaptive immune responses. Peptidoglycans and teichoic acids, two components of cell walls, interact with host immune cells to promote the synthesis of cytokines and immunoglobulins, which strengthen the body's defenses against infections.[20] They, therefore, seem like good options for controlling and avoiding allergies, infections, and inflammatory conditions.[21] Probiotics of different kinds can behave like antibiotics, not only eliminating a set of pathogenic germs but also stopping them from colonizing and flourishing. Intrinsically, bacteria have the capability of using several mechanisms such as competition for adhesion sites, the production of bacteriocins, which are antimicrobial peptides, and of course, modification of the composition of the gut microbiota, what appears to be a protective mechanism against pathogenic bacteria is also favorably involved in the establishment of a balanced intestinal microbiota, potentially lowering the risk of suffering an infection of the gastrointestinal tract.[22] Paraprobiotics can suppress the production of an array of pro-inflammatory mediators and cytokines thus leading to anti-inflammatory effects. They could likewise augment and enhance the functionality of antioxidant enzymes and radiate free radicals to regulate oxidative stress. In that case, all those qualities at the same time, might be helpful for the decrease of chronic diseases, caused by oxidative stress, and for the treatment of inflammatory conditions in the intestine, such as irritable bowel syndrome. Research has demonstrated that paraprobiotics improve tight junction integrity and stimulate the synthesis of mucin, which strengthens the gut barrier. By preventing dangerous compounds and pathogenic bacteria from leaving the gut and entering the bloodstream, this improved barrier function supports better immune system function as well as gut health.[23] Despite the gut's important role, probiotics have different physiological effects away from it. The research showed that they would have the potential to affect psychological conditions, cardiovascular well-being, and cognitive performance (Fig. 2). Take the example of paraprobiotics, which have been shown to bring down anxiety and depression symptoms and cholesterol levels, which puts up the possibilities for their use in overall wellness.[22]

For functional food development, the stability and survivability of paraprobiotics in food matrices is a very crucial need. However, a critical challenge lies in ensuring their stability and survivability throughout the food production chain, storage, and within the human gastrointestinal tract. Several factors in food matrices can significantly impact paraprobiotic viability, potentially hampering their intended health effects. High temperatures, acidic or alkaline pH, and oxygen exposure are only a few of the stresses that paraprobiotics can encounter during the food processing process. Because of their inherent ability to act as a buffer and their need for cold storage, dairy products provide a suitable environment. But for better survival, acidic goods like drinks or fermented foods require the use of encapsulation techniques or the selection of acid-resistant strains.[23] One major problem in thermal processing is the need for protective matrices like liposomes or microgels, or strains resistant to heat.[24] Depending upon the type of food ingredient, their effects may be beneficial or negative only. Preservatives, as well as certain spices, can undo what paraprobiotics can do. Vitamin C or E can improve paraprobiotics' survival.[25] Moreover, the interaction of paraprobiotics with the already coexisting indigenous bacterial species in the food matrix may disrupt their viability.[26] Paraprobiotics must be shielded from harsh stomach conditions to be successfully delivered to the colon, which is their intended destination. Paraprobiotics are protected from stomach acidity by encapsulation in different biopolymers such as alginate or chitosan, which then release the probiotics into the more hospitable intestinal environment.[27] Prebiotic-based delivery systems increase survival and functionality by giving paraprobiotics an easily accessible supply of nutrients.[28] The inherent stability and stress resistance are among the factors that make paraprobiotics strains to be genetically unique. Keeping viability means picking the strains that particularly fit the food matrix here and the conditions of the production process. Also in the same vein, knowledge of the mechanisms of action of paraprobiotics that tolerate and survive stress is very instrumental in designing therapies to enhance their survival.[29]

## Mechanism of Action

Besides living probiotic bacteria, paraprobiotics such as inactivated microbial cells, their components, and metabolites have several other advantages, such as ensuring storage, overcoming the problems related to regulations, and viability while the biota of the host is still affected in many manners. As further studies reveal their mechanisms of action, interaction with the gut microbiome thrives a rather confusing scenario. The paraprobiotics manage and sculpt the intra-gut microbiota through different techniques. These species possibly slow the growth or the colonization of bad strains of bacteria that are competing with them for vital nutrients and energy sources.[13] The viability of paraprobiotics like *Lactobacilli* with inactivation and bacteriocins, which target and destroy pathogens, simply multiply these competitive merits.[30] Furthermore, it also has the ability to obstruct prebiotics, making the growth of beneficial bacteria act through genetic enhancements, for instance, increasing the production of SCFAs and serving as easy-to-use sources of power.[11] This approach in turn guides and develops a healthy array of beneficial microorganisms, which is one of the key factors for maintaining the good condition of the gut and the prevention of diseases.

## Interaction with Host Microbiota

Paraprobiotics orchestrate a multifaceted performance within the gut, influencing composition like a skilled conductor. Firstly, it helps in competitive advantage because the cell wall is a structural barrier that functions as a nutritional fiber that both protects the microorganisms from competitors with low chances and creates a safe space for the ones that can be of benefit.[31] Secondly, it offers antimicrobial properties as bacteriocins are the particular munitions of the antimicrobial defense system. These advances are aimed at specific diseases and leave the order of the microbial world intact.[30] Also, they assist in the increase and supply of SFCAs that energize the friendly bacteria to live happily among each other, thus making the community vibrant.[32]

Paraprobiotics also engage in influencing its response for optimal health. They help in cellular activation. They administer the pieces of their cell casings with waves of both arms, talking to the immune cells utilizing PRRs to form a cytokine melody that drives away the invaders.[33] Paraprobiotics help in subsiding inflammation. They work as a go-between; they increase the first mediator and have a suppressive influence on pro-inflammatory signals to calm the gut fires.[5] They can generate mucin and provide tight junctions thus solidifying the barrier that protects against those harmful invaders.[6]

Paraprobiotics also known as metabolic maestros, influence gut processes. They are known as the powerhouse of short-chain fatty acids. Without them, the fermentation would easily get spoilt, which then would harm SCFA production. SCFA, on the other hand, are microbial metabolites that carry out important functions in the gut and colonocyte (colon cells) environments.[7] This community of microbiota is responsible for intricate actions such as aiding the production of bile acids, which are considered to have anti-inflammatory and anti-cancer effects.[8] They also enhance nutrient absorption. They support digestion and vitamin and mineral absorption, making sure that the fishes are nourished as well as possible.[9]

### *Immunomodulatory effects*

Paraprobiotics can interact with the host immune system through various mechanisms, including- direct interaction with immune cells happens when natural killer cells, dendritic cells, macrophages, and other immune cells are stimulated by paraprobiotic components such as cell wall fragments (peptidoglycans, lipoteichoic acids). Pro-inflammatory cytokines (TNF-α, IL-1β) and chemokines are produced because of this activation, which triggers the immune response and draws additional immune cells to the infection site.[34] Also, modulation of gut microbiota in which it works by modifying the composition of the gut microbiota, paraprobiotics have the potential to indirectly affect the immune system. While preventing the growth of harmful bacteria, they can encourage the growth of helpful bacteria. As a result, the gut microbiota becomes balanced, which is important for controlling immune responses and averting inflammatory diseases.[35] Improvement of barrier function by upregulating the expression of tight junction proteins and the generation of mucus, paraprobiotics can fortify the intestinal barrier. By preventing dangerous microorganisms and their poisons from moving into the systemic circulation, this strengthened barrier shields the host against immunological assaults.[36]

Paraprobiotics have been demonstrated to exert various immunomodulatory effects, such as possessing anti-inflammatory traits. Paraprobiotics can boost the synthesis of signals with anti-inflammatory activity, for example, IL-4, IL-10, IL-13 while all the same inhibit the production of their pro-inflammatory counterparts like cytokines and chemokines. It does this by addressing the intensity of the exaggerated inflammatory response characteristic of long-term inflammatory disorders like allergies and inflammatory bowel disease (IBD).[37] Providing enhanced immune response is also an important immunomodulatory effect. Interstreaming the immune system, paraprobiotics can enable the body to resist infections. These compounds can stimulate natural killer cells, thereby enhancing their cytotoxic activity, and activation of antigen-presenting cells boosting the production of antibodies, which leads to an augmented size of the immune system of the host.[5] Paraprobiotics turned out to be very helpful for allergy treatment: they can contain the immune system overreacting to allergens and thus prevent allergies. In this way, they can block the development of the Th2-type allergy response and lead to immunological tolerance, which may dramatically decrease the symptoms of asthma or allergic rhinitis.[6]

Specific examples include:

- *Lipoteichoic acid (LTA) from Lactobacillus casei*

One of the main benefits of low-level laser therapy has been shown to modulate macrophages and dendritic cells which, in turn, helps in the production of cytokines and chemokines that can activate the immune response.[7]

- *Heat-killed lactobacillus plantarum*

The article according to,[8] has revealed that after the heat-killed *L. plantarum* bacteria the macrophage phagocytosis increases and antibody production rises which could be considered as the improvement of the immune system.

- *Bifidobacterium bifidum cell wall fragments*

Scientific research has confirmed the possibility that the particles probably block the production of the type of cytokines that cause inflammation and pose an impact on the composition of the microbiota in the gut, which could help cure inflammatory bowel disease.[9]

## Application in Functional Food and Nutraceuticals

Since the viability of probiotics in food is an important consideration, certain food matrices are better suited for the delivery of probiotics than others. The food carrier also influences the capacity of the bacteria to cling to intestinal epithelial cells, their immunomodulatory qualities, and their tolerance to severe gastrointestinal conditions (acidity, bile, and different enzymes). Dairy products, such as yogurt and other fermented milk, cheese, and frozen fermented dairy treats, constitute a suitable and marketable carrier of probiotic bacteria to customers since milk and milk fat's buffering ability ensures bacterial survival through processing and storage.[38,39] When it comes to dietary goods, yogurt is very effective at delivering probiotics. However, ice cream, which is high in milk fat, can also help improve microbial survivability and acid tolerance.[40]

### *Incorporation in dairy products*

Paraprobiotics can be used in dairy products instead of live probiotics. Because of their unique benefits, paraprobiotics become more advantageous compared to live probiotics. They not only maintain the stability of their functions under conditions that include several processing steps, pasteurizing, fermenting, and storage but also do not of their function through those processes. Stability is another crucial advantage of long-chain triglycerides considers. It is the reason why the delivery of advantageous components is not disrupted during a longer shelf-life of the product. This provides more flexibility in product formulation.[41]

The paraprobiotics do not need to assist in meeting the environmental requirements of keeping bacterial cultures active in the food products which simplifies the whole process and lowers the manufacturing costs. It also solves the issue of contamination that could occur while handling live probiotic cultures and processing food products.[42,43]

Paraprobiotics have a flavorless, texture-less, or odorless profile to them, which is important because, even though they must remain inactive, they will still need to be placed into dairy products without a change to the taste, texture, and smell so that they blend in seamlessly, especially those who are sensitive to certain probiotic product's taste or texture profiles.[44,45] Probiotics, which are live bacteria, differ from paraprobiotics in terms of safety – the latter are safe to eat in any case including weakened immune people. The delivery of live probiotics via the intestinal tract could be an issue in immuno-compromised patients.[46]

Paraprobiotics can be incorporated into various dairy products using different approaches:

- *Direct addition*

After being obtained in a purified form, the paraprobiotics can be directly added to a product at the end of the production process to maintain stability during storage. This method is suitable for products such as yogurt, cheese, and fermented milk beverages.[45]

- *Encapsulation*

Encapsulation technologies avoiding loss of the active compounds to harsh environmental conditions during processing and storage could be used to protect paraprobiotics in addition to the effects obtained by their intrinsic natural properties thereby improving overall stability and controlled release in the gut.[46]

- *Incorporation through fermentation substrates*

In the dairy fermentation process, certain strains of lactic acid bacteria can naturally generate paraprobiotic components. This method takes advantage of current fermentation techniques to incorporate paraprobiotics into the final product, eliminating the need for additional production steps or the addition of exogenous substances.[45]

Studies suggest that paraprobiotics incorporated into dairy products may offer various health benefits. First and foremost, it makes the gut health game strong. Paraprobiotics can change the microbiome in the gut. They help beneficial bacteria to grow and prevent harmful ones from growing. This can result in better digestion, less inflammation, and a stronger immune system.[47] Paraprobiotics stimulate the immune system by turning on immune cells and creating molecules that control the immune system. This can strengthen the body's defenses against infections and allergies.[48] Some probiotics act as antioxidants by neutralizing harmful substances called free radicals. This can potentially help protect cells from damage and reduce the risk of developing chronic diseases.[49]

### *Fortification of beverages*

Fortification of beverages with paraprobiotics offers an attractive strategy for developing functional food and nutraceutical products. Overcoming the current obstacles with persistence and continuous research and development activities could give rise to innovative, effective products that help fulfill the requirement of ever-increasing demands of scientists, health professionals, and consumers for rationalized health solutions offered in convenient forms.

Drinks have various benefits when it comes to serving as paraprobiotic carriers, such as, including paraprobiotics in beverages makes it convenient to consume them regularly, promoting their consistent use.[5] Paraprobiotics can be added to various beverages, such as teas, dairy alternatives, and juices, without significantly altering their flavor or consistency, making them palatable for a range of preferences. Hence, providing palatability.[6] Different paraprobiotic strains can be combined or blended with other beneficial substances in beverages to target specific health outcomes, allowing for personalized and versatile wellness solutions.[7]

Some beverages sold in stores already contain added paraprobiotics. Examples include:

- *Yogurt drinks*

Probiotic yogurt drinks are widely consumed, containing both living, active cultures, and paraprobiotic strains that have been heat-treated to increase their shelf life.[21]

- *Kombucha*

Kombucha, a fermented tea drink, is often claimed to have gut health benefits because it contains beneficial yeasts and bacteria, known as paraprobiotics.[40]

- *Fruit juices and dairy alternatives*

More and more versions of popular drinks are being enriched with nutrients and vitamins, targeted at customers who want more than just a beverage but also health advantages.[24]

### *Utilization in dietary supplements*

Paraprobiotics, which are non-living microbial cells, provide a valuable opportunity for use in dietary supplements. They present certain advantages compared to live microbes, including the ability to address challenges related to stability and shelf-life. Live probiotics can lose their effectiveness during processing, and storage, and in harsh conditions, reducing their benefits in the final product. In contrast, paraprobiotics are more stable because they are inactivated, which means they can handle the heat and other processing techniques without losing their functionality. They also have a longer shelf life without needing to be refrigerated, making them easier to store and transport.[43] It also raises certain safety concerns. Using live probiotics in at-risk groups like those with weak immune systems (immunocompromised), babies, and older adults can be risky. This is because the probiotics might accidentally move to other body parts and cause harm. Non-living paraprobiotics, on the other hand, are safer because they cannot grow in the gut or cause infections.[44] It also may be difficult to apply to specific products. When it's not possible to keep probiotics alive in certain foods and drinks, such as fruit juices or those that need to be heated during production, paraprobiotics provide a good substitute. Paraprobiotics are made up of useful bacterial components, so they can be added to food and drinks without having to worry about the live cultures dying off.[43] These could be some challenges that can occur. But, it also poses severe benefits. Modulating gut microbiome as it contains elements like cell parts, waste products, and active molecules that affect the intestinal immune system. They encourage the growth of beneficial bacteria and suppress the growth of harmful ones.[45] Studies indicate that paraprobiotics have the potential to provide similar health benefits to probiotics, such as:paraprobiotics, have been found to activate the body's natural defenses, which improve the body's ability to combat infections and reduce inflammation.[44] They have the potential to reduce inflammation hence, they could be beneficial for people experiencing chronic conditions characterized by inflammation.[45] Some paraprobiotics protect against oxidative stress and associated diseases.[45] Paraprobiotics can fight against harmful microorganisms by preventing them from growing and limiting their presence in the gut. This promotes the health of the digestive system and reduces the risk of infections.[46]

## Challenges and Opportunities

While paraprobiotics bring a thrilling possibility to the table for functional foods and nutraceuticals, navigating through regulations can be a mixed bag of difficulties and advantages. In contrast to living probiotics, the rules surrounding paraprobiotics could be less strict, paving the way for faster product creation and a quicker path to the market. Yet, it's key to show safe usage and prove health benefits for customer trust and regulatory approval. It sets the stage for scientists to create strong research trials. This will reinforce the health advantages of paraprobiotics with hard science.[2] Paraprobiotics present a new world for health foods and nutraceuticals, yet we need to dig deeper into their safety. Unlike probiotics, which are living bugs, paraprobiotics are usually seen as safer. But it's key that they're free from any live cells and possible toxins from dead microbes. Knowing how paraprobiotics boost our health is important, too. It helps scientists use them better and aim for the health benefits we want. Rules for paraprobiotics are still changing, so we need more studies to set solid safety checks for these new additions.[50] Paraprobiotics are very promising for improved health foods and supplements. They don't change during storage or travel, unlike live probiotics. So, they can reach more places and there's no need to keep them cold. This makes moving them easier and cuts down expenses.[51] We now need to focus on refining how we make paraprobiotics so they work well in foods. We also need more detailed health studies. These will prove that paraprobiotics improve health when added to certain foods and supplements. By doing this, paraprobiotics could transform healthy foods. They might become a popular, easy, and effective choice for people wanting to stay healthy.[52]

## Case Studies and Success Stories

The research on paraprobiotics is new but already has interesting applications. They're being added to popular products like healthy foods and nutritional supplements. A standout example is heat-treated *L. gasseri* CP2305. It's found in sports drinks. Even though it's inactive, this paraprobiotic strain aids young athletes in recuperating from exhaustion and lowering stress-induced anxiety and depression. This underscores paraprobiotics' potential to offer health advantages not just limited to live bacteria.[53] Most probiotics are found in dairy food. Yogurt and cheese, for instance, contain lots of them. That's because they provide a safe environment that protects these helpful bacteria. Their other names? Probiotic bacteria. But these helpful bacteria aren't just for dairy. Scientists are thinking about adding them to other foods and drinks. However, there's more work to do. Have you heard of *L. gasseri* CP2305? Well, it shows that we can use these helpful bacteria in other ways. Investigating the use of paraprobiotics in many types of healthy foods and wellness products can lead to new options. These may address certain health issues. This field of study can bring amazing prospects for dietary strategies. The goal? Boost health and happiness.[54]

Right now, there is a big demand for functional food and nutraceuticals. Why? More people around the world care about staying healthy and finding easy ways to feel better. They're not just looking for basic nutrition anymore. They want food and supplements that boost health. This is where paraprobiotics come in. They are a perfect fit for this trend.[55] Paraprobiotics offer several advantages over traditional probiotics, making them an attractive option for both manufacturers and consumers. Unlike live bacteria in probiotics, paraprobiotics are inactivated microbial cells. This translates to greater stability during processing, storage, and transportation, allowing for a wider range of food applications and eliminating the need for cold storage. This is a significant advantage for manufacturers, reducing production costs and expanding distribution possibilities.[56-58] For users, paraprobiotics hold the promise of achieving the same health benefits as probiotics, including immune modulation, anti-inflammatory, and gastrointestinal effects improved health, without the worries associated with live bacteria.[59-61] However, consumer acceptance of paraprobiotics will depend on several factors. Education will be important. Users may need to be informed about the potential health benefits of paraprobiotics and how they differ from probiotics. Furthermore, clear labeling and strong scientific evidence supporting the efficacy of paraprobiotics will be important to build trust and encourage consumer adoption.[62,63]

## Conclusion

A significant opportunity to create novel functional meals that are appropriate for those with compromised immune systems is presented by paraprobiotics. Additionally, these items have higher stability and do not require a cold chain for storage, which makes them easier for industrial handling and widespread commercialization. On the other hand, the scientific community needs to put in a lot of work on certain elements and define others. Probiotic cell inactivation can be accomplished using chemical or physical means that modify the structure and function of the cells. This results in the loss of the bacteria's capacity to proliferate and expand while either maintaining or losing the advantageous properties displayed by their living counterparts. Consequently, another problem lies in applying suitable approaches to assess their biological activity and pinpoint the constituents accountable for the health impact. Furthermore, like probiotics, there are certain difficulties with using food as a delivery system for paraprobiotics. Easy production—that is, quick, controllable, and reasonably priced inactivation techniques—good solubility in food, and little interaction with food ingredients are further factors that should be considered for the practical use of paraprobiotics in food. To apply them, an approach that can link the microbial strain's physical state and vitality with the biological response must be developed. This will enable regulatory interventions (also known as "health claims") and quality control of the products.

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