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Paraprobiotics in the Dairy Industry: Current Research and Future Prospects: A Review

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ABSTRACT

Paraprobiotics, or non-viable microorganisms that have beneficial effects on the host, have gained attention in the dairy industry as a potential alternative to traditional probiotics. Instead, the concept of paraprobiotics shall be put forth in addition to employing probiotics to reap additional benefits. The use of paraprobiotics has become a potential opportunity for diversification of functional foods due to their great versatility when compared to viable probiotic cells. The advantages of paraprobiotics include the possibility of using technologies and formulations with negative impacts on probiotics, the longer shelf life of products and greater convenience during processing, storage and transportation, in addition to being a safer therapeutic approach for immune-compromised individuals. The use of paraprobiotics in dairy industry is potential for these microorganisms to be used as feed additives to improve the health and productivity of dairy cattle.

Key words: Dairy products, Health benefits, Parabiotics, Probiotics.

Probiotic products have gained popularity among consumers looking for healthier, industrialized goods because they are marketed as natural foods that support digestion and health (Roy and Kumar, 2018). Thus, probiotic supplementation is considered a cost-effective, natural and receptive method. In addition to satiating hunger and meeting basic nutritional needs, it also contributes to the expanding niche of functional foods, which represents a highly lucrative market due to its diverse therapeutic applications. Probiotic microorganisms are sold as nutritional supplements in pharmacies or incorporated into food matrices, primarily in fermented dairy products, such as yoghurt and fermented milk, which account for the majority of functional dairy products currently on the market (Dahiya and Nigam, 2022; Trush *et al*., 2020). In 2023, it is anticipated that the global probiotics market will be worth approximately $69.3 billion (Midhun and Arun, 2023). With the food industry being responsible for greater economic value creation.

Probiotics have been consumed by humans since ancient Egypt and the Middle East used fermentation as a method of food preservation. However, health benefits have only been associated with the consumption of fermented dairy products containing lactic acid bacteria since the early 20th century. The concept of probiotics originated from research on the health benefits of bacteria. Probiotics are defined as microorganisms that, when administered in sufficient quantities, confer a health benefit on the human or animal host. Bacteria of the genera *Lactobacillus*, *Bacillus* and *Bifidobacterium* stand out among probiotic microorganisms, as do yeasts of the genus *Saccharomyces* (Crisóstomo-Jiménez *et al*., 2021). According to the current definition of probiotics, microorganisms must remain viable throughout the product's shelf life until ingestion and passage through the gastrointestinal tract in order to provide beneficial effects.

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However, scientific research indicates that non-viable probiotic microorganisms (dead probiotic cells), known as paraprobiotics, can also provide health benefits, indicating that not all probiotic mechanisms and bioactivity are related to the viability of the bacteria (Shripada *et al*., 2020).

This article provides an overview of the concept of paraprobiotics, their production processes, the main advantages of their application in the dairy industry compared to probiotics and their potential effects on consumer health.

Paraprobiotics

Paraprobiotics have also been referred to as inactivated probiotics, non-viable probiotics and ghost probiotics (Zendeboodi *et al*., 2020). They are defined as non-viable microbial cells (intact or broken) or cellular fractions that confer benefits to the consumer when administered in adequate quantities and frequency. Paraprobiotics are microorganisms subjected to inactivation processes, with loss of viability, leading to changes in bacterial cell structures, such as the rupture of DNA filaments and the cell membrane, or changes in their metabolic activity, such as enzymatic inactivation and deactivation of membrane selectivity (Vallejo-Cordoba *et al*., 2020).

Main inactivation methods and production of paraprobiotics

Paraprobiotics, a type of probiotic, can be found in various concentrations within probiotic formulations, ranging from 1×10^5 to 1×10^{14} bacteria per unit dose. Probiotics can be inactivated using a variety of techniques, such as heat treatments, ultraviolet or gamma rays, high pressure, sonication, freeze-drying, chemical reactions and ozonation, which results in the production of paraprobiotics (Shripada *et al*., 2020; Taspinar *et al*., 2022). Other methods, such as pulsed electric field, ohmic heating and supercritical CO_2 drying, among others, may also be used for the production of paraprobiotics (Fig 1). The most prevalent method for obtaining paraprobiotic strains has been heating. Although a variety of inactivation techniques have been employed, the best technique depends on the microorganism and the anticipated clinical benefit because each technique has a different impact on the cellular structural elements, which in turn affects the microorganism's immune modulatory activity (Roy and Kumar, 2018). Therefore, it is important to carefully choose a method that can inactivate the beneficial probiotic effects while also preserving them.

By counting the number of cells that can multiply and form visible colonies, using the proper culture media and ignoring the existence of non-cultivable paraprobiotic cells following inactivation treatment, the traditional plate counting technique has been used as a standard method to evaluate the viability of bacterial cells (Bernardeau and Cretenet, 2019). In contrast, flow cytometry, which provides detailed information about the structural characteristics and metabolic activities in real-time measurements, can evaluate the viability of bacteria beyond their reproductive capacity (Zendeboodi *et al*., 2020). Considering the level of damage caused to the paraprobiotic strains, such data is crucial for evaluating the most effective inactivation techniques.

Impact of probiotics on children's health

Probiotics have been found to be safe for healthy individuals and have demonstrated therapeutic benefits in high-risk populations. However, the mechanisms by which probiotics improve gut microbiota, immune function, inflammation and intestinal epithelial cell retention is not fully understood. According to FAO/WHO guidelines on probiotic evaluation, probiotics may cause four types of side effects in patients with chronic medical conditions: excessive immune system stimulation in susceptible individuals, systemic infections, harmful metabolic effects and translocation of probiotic bacteria across the intestinal barrier (Byakika *et al*., 2019). This is particularly concerning in vulnerable populations, such as those with weakened immune systems or gut dysbiosis, as the deliberate administration of microorganisms (*i.e.* probiotics) must be carefully evaluated.

Studies have found that probiotic strains such as *Lactobacillus*, *Pediococcus*, *Leuconostoc*, *Bifidobacterium* and *Enterococcus* have been found in the infection sites of sepsis, indicating their ability to translocate (Cosme *et al*., 2022). However, *Lactobacillus bacteremia* can indicate severe underlying disease and certain probiotic strains have been linked to sepsis in certain populations (Kothari *et al*., 2019). For example, *Lactobacillus rhamnosus* GG has been linked to sepsis in children and compromised gut mucosa has been found to allow probiotic strains to enter the bloodstream in some cases. Additionally, studies have linked sepsis in low-birth weight infants to the probiotic strain NISSLE 1917 of *Escherichia coli* and aspiration pneumonia in a Down syndrome child to *L. rhamnosus. Clostridium spp.* strains have also been linked to infant botulism and necrotizing enterocolitis in infants (Bhardwaj *et al*., 2016).

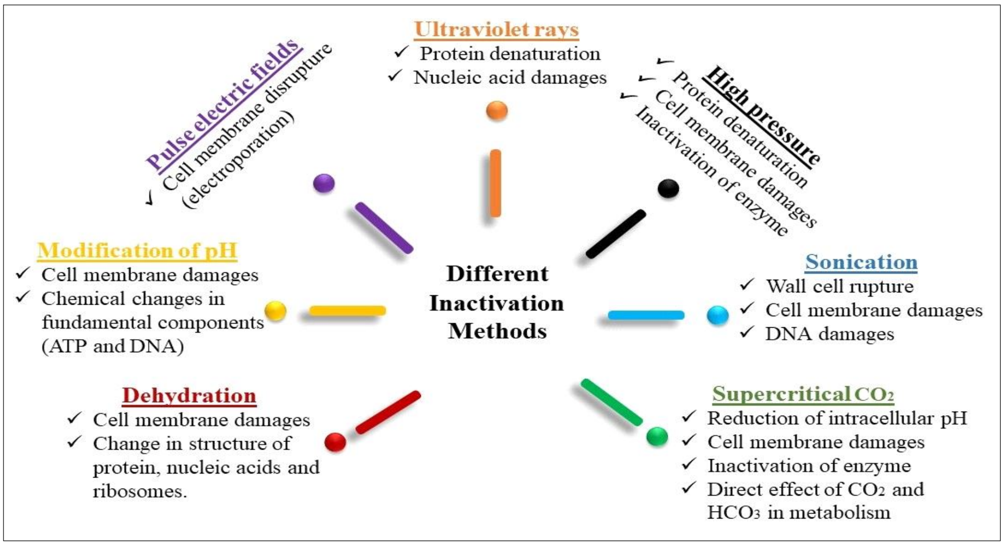

Fig 1: Inactivation methods of microorganisms.

A study also found that infant *Lactobacillus acidophilus* supplementation did not reduce the risk of atopic dermatitis and increased allergen sensitization. Therefore, it is important to carefully evaluate the use of probiotics in vulnerable populations and monitor for potential side effects (Kothari *et al*., 2019).

Probiotics v/s paraprobiotics

To ensure that bacterial cultures can survive the production process on a wide scale and that the amount consumed will have the desired health effects, a probiotic product must be developed according to precise specifications. However, the vitality of probiotic cells can be altered by a variety of circumstances, including food matrix components, technological processing and long-term storage.

Dairy matrices are good for carrying probiotic bacteria due to their high buffering capacity and the beneficial effect of their components (fat globules, casein micelles and lactose), which protects the passage through gastrointestinal transit (Lillo-Pérez *et al*., 2021). However, various precautions must be taken to minimise cell viability loss and maintain probiotic benefits during processing. Due to the poor proteolytic activity of probiotic bacteria on casein, these strategies include the incorporation of nitrogen sources into the milk matrix (Rashidinejad *et al*., 2022). They also include selecting probiotic strains compatible with the starter culture to avoid competition between cultures, decreasing acidification kinetics and product quality and limiting probiotic exposure to low pH values for a short period of time to induce tolerance to acid pH and avoid acid stress (Kothari *et al*., 2019). Furthermore, packaging materials and procedures that reduce oxidative damage during storage should be used.

In contrast, because paraprobiotic microorganisms are more stable for large-scale industrial production, their inclusion in dairy products can provide several technological advantages over probiotics. Once it is composed of dead probiotic cells, there is little or no interaction with other food matrix components, ingredients, or additives, which has a direct impact on the product's shelf life and sensory characteristics. Other benefits include increased convenience and ease of handling during processing, as well as a reduction in the possibility of microbiological contamination after processing because they can be introduced before to pasteurisation, preserving the milk's metabolic activity. It also saves money on storage and transportation because they remain stable over a wide temperature range and do not require a cold chain, such as instant milk powder and newborn formulae.

This provides a significant economic advantage to food businesses. Paraprobiotics can also be used as functional components in heterogeneous (non-dairy) food matrices, which are thought to be stressful substrates for probiotic survival, contributing to the diversification of the functional food niche.

Paraprobiotics as a therapeutic option

Several clinical trials in humans and animals have proven the health benefits of paraprobiotics in the prophylaxis and treatment of various disorders, such as viral and bacterial infections, atopic dermatitis, colitis, respiratory and metabolic diseases, inhibition of pathogens, cancer, prevention of dental caries, modulation of the intestinal microbiota and the immune system, maintenance of intestinal integrity, maintenance of desirable mood, improvement in physical fitness, among others (Kothari *et al*., 2019).

However, most of these trials are related to the direct consumption of paraprobiotics in the form of suspension or lyophilised powder (Barros *et al*., 2020). Although there is an increasing demand for studies about the application of paraprobiotics in food, they are still rare (Table 1). In addition, paraprobiotics are safer alternatives for individuals with weakened immune systems (for example, elderly and premature newborns) when compared to the administration of live bacteria, which can offer risks of developing opportunistic infections, increased inflammatory responses to allergens or vaccines, acquisition of virulent genes or antibiotic resistance by horizontal transfer and microbial translocation. These findings may also contribute to facilitating the approval of the use of paraprobiotics as an ingredient or food supplement by the regulatory as a health promotion strategy (Barros *et al*., 2020; Kothari *et al*., 2019). Table 2 shows examples of approved paraprobiotie products that are commercially available as supplements including Pylopass, Lacteol and Nyaditum resae, which have proven to be effective in preventing and treating *H. pilori* infection, acute diarrhea and development of active tuberculosis, respectively.

Table 1: Parabiotics application in food.

Parabiotic-food	Production treatment	Health benefits	Reference
Lactobacillus gasseri CP2305 isotonic beverage	Heated	Help athletes recuperate from stress, anxiety and depression	(Cooke *et al*., 2022)
Lactobacillus amylovorus CP1563 dairy beverage	Heated	Influenced the gut microbial ecosystem and decreased abdominal body fat in pre-obese healthy people	(Palade *et al*., 2022)
Lactobacillus gasseri CP2305 fermented milk	Heated at 95°C	Impact on the environment and regulate of the gastrointestinal tract	(Sawada *et al*., 2022)
	Heated at 95°C for 30s	Relief of stress-related symptoms, helping those with physical and mental conditions to improve their health	(Del Toro-Barbosa *et al*., 2020)

Treatment of diarrhea

Probiotics have been found to be beneficial in treating diarrhea. One such probiotic is Lacteol Fort, which has been shown to improve symptoms such as stool consistency, abdominal pain and bloating. Studies have also demonstrated its effectiveness in treating both viral and bacterial diarrhea in children, reducing the duration of the illness and improving stool consistency (de Almada *et al*., 2016). Furthermore, it has been found to alleviate symptoms of Irritable Bowel Syndrome (IBS) in patients with diarrhea, by decreasing pain, swelling and improving quality of life. The mechanism behind this is thought to be *L. acidophilus* LB's ability to line the colonic mucous membrane and protect it from the adhesion and invasion of harmful microorganisms (Taverniti and Guglielmetti, 2011). Nishida *et al.* (2017) also suggested that fermented milk containing heat-inactivated *L. gasseri* CP2305 can effectively regulate intestinal function and improve defecation and stool characteristics in patients with constipation (Sawada *et al*., 2016).

Modulation of inflammation

Inflammation is a complex immune response that occurs when the body is facing infection, exposure to toxins, or cell damage (de Almada *et al*., 2016). Probiotics have been found to have potential in reducing inflammation, particularly the probiotic and paraprobiotic strain *Lactobacillus rhamnosus* GG. Studies have shown that it can reduce pro-inflammatory mediators and increase anti-inflammatory mediators in rats. Paraprobiotic form of LGG has also been found to be effective in modulating inflammation (Li *et al*., 2009).

Inhibition of the growth of cancer

Colon and gastric cancer can be prevented through screening, surveillance and chemoprevention. Probiotics have been shown to have chemopreventive properties and have been used in this way (Rafter, 2003). Two specific probiotics, *L. paracasei* IMPC2.1 and *L. rhamnosus* GG, when suspended in certain media, have been shown to have anti-proliferative and pro-apoptotic effects on gastric and colorectal cancer cell lines. Different fractions of probiotics, such as whole cells, heat-inactivated cells, cell walls, peptidioglycan and cytoplasmic fractions, have also been shown to have anti-proliferative effects against human cancer cell lines. However, it is not yet known which heat-stable component of the bacteria is most effective in inhibiting cancer cell proliferation (de Almada *et al*., 2016; Orlando *et al*., 2012).

Treatment of atopic dermatitis

Atopic dermatitis (AD) is a chronic skin condition characterized by itching eczema and repeated flare-ups. The condition is caused by a breakdown or damage to the skin barrier, leading to increased production of pro-inflammatory cytokines and activation of the immune system (de Almada *et al*., 2016). Studies have shown that probiotics, specifically *L. sakei*, may be effective in treating AD by reducing skin inflammation and lesions, decreasing frequency of itching and lowering levels of immunoglobulin E and chemocins. Additionally, paraprobiotic *L. paracasei* K71 has been shown to reduce symptoms of AD in adult patients (de Almada *et al*., 2016; Karki *et al*., 2012).

Paraprobiotics have been shown to exert anti-inflammatory and immunomodulatory effects in animal models of AD. For example, heat-killed *Lactobacillus fermentum* RC-14 has been found to reduce the severity of AD and improve skin barrier function in a mouse model of AD. The mechanisms by which probiotics and paraprobiotics may modify the biological responses associated with effects by modulating the gut-skin axis, which is a bidirectional communication pathway between the gut and the skin. Probiotics and paraprobiotics influence the gut microbiota composition and activity, leading to the production of metabolites that can affect skin function and inflammation. They may also modulate the immune system and reduce the activation of immune cells that contribute to the inflammation and skin damage in AD. These findings suggest that probiotics and paraprobiotics may be able to modify the biological responses associated with AD.

Perspectives and challenges for food applications of paraprobiotics

Paraprobiotics are microorganisms that are similar to probiotics but do not have the same beneficial properties. Paraprobiotics can be found in food products and supplements and they can cause negative effects if consumed in large quantities. Therefore, it is important to inactivate them in a controlled manner to produce safe and effective paraprobiotics. The use of paraprobiotics in food applications have been studied as a means to extend the shelf-life of food products, improve their safety and quality and as a source of natural food preservatives.

One of the key challenges in using paraprobiotics in food applications are to ensure their safety and efficacy. This requires a thorough characterization of the microorganisms, as well as testing their safety and efficacy in animal models and clinical trials. It is also important to

Table 2: Commercial parabiotic product.

Parabiotic	Product	Effect
L.reuteri DSMZ17648	Pylopass	Effective in control of H. pylori infection
Mycobecterium manresensis	Nyaditum resae	Effective in reducing the risk of developing active tuberculosis, As a supplement food
L.acidophilus LB	Lacteol	Effective in treatment of diarrhea

ensure that the methods used to inactivate the microorganisms do not negatively impact the quality and safety of the food products.

Another challenge is to ensure the stability and shelf-life of food products containing paraprobiotics. Additionally, it is important to consider the potential interactions between the microorganisms and other ingredients in the food product. Despite these challenges, the use of paraprobiotics in food applications have the potential to provide a range of benefits. For example, they can be used as natural preservatives to extend the shelf-life of food products, without the use of synthetic chemicals (Moradi *et al*., 2020; Zendeboodi *et al*., 2020). They can also improve the safety and quality of food products by reducing the growth of harmful microorganisms. Additionally, they can be used as a source of functional ingredients, such as enzymes and vitamins, that can enhance the nutritional value of food products.

FUTURE PERSPECTIVES

The future perspectives of paraprobiotics are promising. With the increasing interest in the human microbiome and its role in health and disease, more research is needed to fully understand the potential of these trends and to develop safe and effective therapies. Microbiome-based therapies are an emerging area of research and development and it is expected that these will become increasingly important in the future. The use of paraprobiotics as an adjunct or alternative to traditional therapies has the potential to improve health outcomes and reduce healthcare costs. However, more research is needed to understand the long-term safety and efficacy of these therapies.

The field of paraprobiotics is rapidly evolving and new trends are emerging. Current trends include the use of synbiotics, postbiotics, psychobiotics, microbiota-based therapies and microbiota-directed therapies. These trends are based on the understanding that the human microbiome plays a crucial role in maintaining health and preventing disease. Further research is needed to fully understand the potential of these trends and to develop safe and effective therapies. It is important to consult with a healthcare professional before adding paraprobiotics to your diet, especially if you have a pre-existing medical condition or are pregnant or breastfeeding.

CONCLUSION

In summary, the field of paraprobiotics is rapidly evolving and new trends are emerging. Due to their greater versatility than viable probiotic cells, the use of paraprobiotics has become a potential avenue for the diversification of functional foods. In addition to being a safer therapeutic approach for immune-compromised individuals, the benefits of paraprobiotics include the ability to use technologies and formulations that have negative effects on probiotics, the longer shelf life of products and greater convenience during processing, storage and transport. However, studies on the addition of paraprobiotics to dairy matrices are still uncommon, as the vast majority of research to date has been limited to direct consumption. Therefore, additional research is required to investigate the application of paraprobiotics in foods using the appropriate protocols in order to assess the impact of use and the product's stability throughout its shelf life.

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