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# Probiotics in Functional food: A Noble Approach as Biotherapeutic

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## ABSTRACT
The proficiency of probiotics to survive the gastric transit to the low pH value of the stomach characterizes one of the key features linked to their efficacy. During past decades, the beneficial effect of specific strains in several intestinal disorders has been verified by clinical trials. Increasing evidence, including human studies, is also supporting the immunomodulatory and other role attributed by probiotic strains. Postbiotics are functional bioactive compounds, generated in a matrix during fermentation, which may be used to promote health.Postbiotics can include many different constituents including metabolites, short-chain fatty acids (SCFAs), microbial cell fractions, functional proteins, extracellular polysaccharides (EPS), cell lysates, teichoic acid, peptidoglycan-derived muropeptides and pili-type structures. Several current researches indicates that postbiotics can have direct immunomodulatory and clinically relevant effects and evidence can be found for the use of postbiotics in healthy individuals to improve overall health and to relief symptoms in a range of diseases. Postbiotics may contribute to the improvement of host health, even though the exact mechanisms have not been fully clarified. In addition to mechanism of action focused preclinical and in vitro studies, well-designed randomized placebo-controlled intervention studies are needed to demonstrate health effects of postbiotics.
**Keywords:** *probiotics; Functional Food*

## 1. INTRODUCTION

Probiotics are living microorganisms that offer valuable effects to consumers when administered in sufficient amounts (FAO/WHO, 2002). Probiotic cultures are commonly supplemented to milk products because there is less limitation during manufacturing processes (Boza-Mend et al., 2012). Fruit and vegetable juices may use an alternative source of probiotics to consumers because they are categorised healthy products and are frequently consumed, which make probiotics to be beneficial. Prebiotics are non-digestible food constituents that deliver valuable health effects and associated with modulation of human microbiota (FAO/AGNS, 2007). In foods, prebiotic compounds are utilized as substrate and could increase the viability of probiotic cultures during processing and storage. Food packaging is one of the most important aspects which affect the viability of probiotic cultures (Talwalkar & Kailasapathy, 2004). Currently the probiotic area is promoting by both industry and scientists in the multiple disciplines which are crucial for complex research domain. Elie Metchnikoff was the first scientist who recommended the consumption of live cultures of useful microorganisms such as the LAB (Metchnikoff, E 1907). Parker (1974) also describe the impact of probiotics as organisms and substances which contribute to intestinal microbial balance. Today, Europe is the main for consumption of probiotics in the form of dairy-based foods containing mainly lactobacilli or bifidobacteria. Some probiotic products preparations are also based on Enterococcus strains or yeasts such as Saccharomyces boulardii in the form of powders or tablets.

In industrial processing and storage of probiotic products cell viability is major technological challenges. The safety of live microorganisms in case of elderly and immunodeficient individuals should be taken into account. Some drawbacks of viability have heightened the attention toward new and noble products based on non-viable probiotics such as paraprobiotics and postbiotics. Paraprobiotics, defined as non-viable microbial cells that confer a health benefit to the consumer, regulate adaptive and innate immunity, show anti-inflammatory, antiproliferative and antioxidant properties with antagonistic effect against pathogens. Paraprobiotics can also be used in products appropriate for people with weak immunity.

Major activities reported for gut microbiota include metabolic actions that affects the intestinal epithelia, immune structure and function and protect from attack of external microbes (Guarner and Malagelada, 2003). In some cases probiotics was claimed as promoters of the host comfort (Adolfsson et al., 2004). Probiotic is found to be a viable microbial supplement which positively affects the host health by inducing human gut (FAO/WHO, 2002). There are many factors which affect the survival in the gastrointestinal tract as stomach acidity, acid, bile salts and hydrolase activity. Several published reports have recommended a minimum amount between 106-109 CFU/day for potential therapeutic effect (Vasiljevic and Shah, 2008). Probiotics commonly have a suitable growth under anaerobic environment at 370C and can be counted for cfu after 48 to 72 h.The gastrointestinal tract is main microbial active ecosystems which contain majority of bacteria that are critical for the maturation of immune cells. Gut microbiota boosts the functionality and maturation of the immune cells with the help of their metabolites (Hooper et al., 2012).

## 2. Potential bio-therapeutic attribute of probiotics

Based on several recent clinical studies and reports, probiotics have been suggested as an innovative approach for management of several diseases (Majamaa and Isolauri, 1997) (Fig 1). Some alterations in the probiotic response are originated due to several factors which affect the physiological conditions of the host or the quality of the probiotic product. The therapeutic use of probiotics has been found to successful in several cases as lactose intolerance, certain diarrheal diseases, inflammatory bowel disease (IBD) and atopic eczema.

2.1 Interactions with the Host Immune System

Probiotic bacteria may interact with host immune cells (Mowat 2003). They stimulate the signalling process of immune system and control the host immune responses of the host (Gill et al. 2001, Foligne et al. 2007). Probiotic microbes should survive in strict environmental conditions of the stomach and GI tract of humans for beneficial health impact. For fulfilment of this condition, probiotics may have ability to survive in gastric juice and bile salt, in upper GT, multiply, colonize, and function in the gut (Wan et al., 2018). Probiotics compete with pathogens for nutrients for growth and proliferation. Therefore, probiotics should support the intestinal barrier by increasing the number of goblet cells which reinforce the mucus layer (De Moreno et al., 2008). Probiotic bacteria encourage health by hindering the growth of pathogenic bacteria by synthesis of some organic acid and some antimicrobial compounds known as bacteriocins (Bermudez et al., 2012).

Habil et al., (2014) established that probiotics differentially regulate human beta 2 defensin mRNA expressions which are guided by inflammatory stimulus and cytokine environment. Antimicrobial peptides are considered as a new class of therapeutics having a selective antimicrobial activity to protect the host. Probiotics modify the arrangement of gut microbes by suppressing the growth of potential pathogenic bacteria in the gut. Probiotics confer protection against pathogen colonization by improving the reaction of the gut-associated immune repertoire (Kim et al., 2015). Maldonado et al., (2011) established the role of cytokine released by probiotics during fermentation on immune cells distant from the intestine. Fermentation process is found to improve the nutritional and nutraceutical status of food through the enrichment of vitamins, proteins, essential amino acids, and essential fatty acids. The long-term intake of fermented food has been showed to exert immunomodulatory effects. The gut immunity is down-regulated by cytokines such as IL-10 (De Moreno et al., 2008).

2.2 Food matrix and probiotic viability

There are many reports which state the there is strong role of food matrices in development of probiotic food and maintain the viability. Several researches now emphases on characterizing specific probiotic strains and interaction of food matrix and the dietary content for efficient probiotic properties (Isolauri, 2007). Yoghurt-like product is now considered the best-known food vehicle for probiotics because, the beneficial effects of probiotic present in the fermented milk are associated with health of the consumers (Vasiljevic and Shah, 2008). The growing request for novel probiotic food products worldwide has encouraged the growth of non-dairy probiotic food, mainly exploring fruit and vegetable juices as a medium for probiotics (Luckow and Delahunty, 2004). The probiotic viability was shown to be strain-dependent. Bialonska et al., 2009 reported that an adding fruit and vegetable functional components suggestively encourage the growth of some claimed probiotic microorganisms as Bifidobacterium breve and Bifidobacterium infantis. Some research report indicates that tomato and beetroot juices showed potential substrates and maintain the probiotic viability (Klewicka et al., 2009). The mixture of carrots, celery and apples also establish as a good matrix for probiotic bacteria (Nicolescu and Buruleanu, 2010). Some reports also specified good prebiotic potential of apple which increases probiotic viability in many functional and probiotic foods. Some key polyphenolic compounds found in fruit and vegetables may also increase the number of probiotic bacteria in gut (Parkar, Stevenson, and Skinner 2008). Dietary fibres are also reported to modulate the intestinal microbiota (Sembries et al., 2003).Some food ingredients i.e apple fiber, oat bran, inulin and unripe banana flour are stated as effective prebiotics which can be used for immobilization of some important probiotic bacteria that promote probiotic viability during storage (Guergoletto et al., 2010). In some reports oligosaccharides of dragon fruit was also establish good prebiotic effect (Wichienchot et al., 2010).

According to the probiotic regulation, probiotics need to be viable form (FAO/WHO 2002).This is the reason why viability play major role in regulatory and biologic aspects. In some cases as fermented food the probiotics are habitually kept in adverse conditions, for example presence of acids. Some study advocated that in case of some available commercial products, the level of viable probiotics does not satisfy the regulatory criteria during storage (Gueimonde et al. 2004).

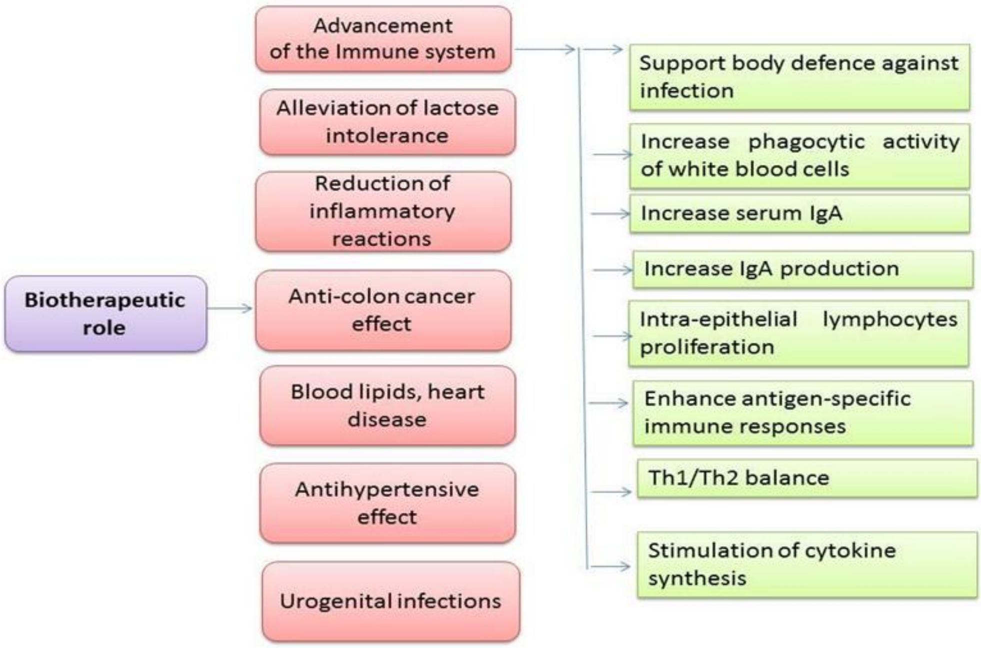


Fig.1. Important biotherapeutic attribute of probiotic bacteria (Naidu et al., 1999; Sanders, M, 2001

## 3. Survival of probiotic microorganisms in the gastrointestinal tract

The survival of ingested microorganisms depends on the inherent resistance of the probiotic, host factors, and vehicle of the probiotic. The effect of the age of a probiotic culture on the growth conditions is very important, but remains unknown. The gastric acid secreted from host was found major defense mechanisms against ingested microbes. Bile salts are also one of significant factor, but the effect of other digestive components such as mucus, pancreatic secretions, and enteric secretions appears to be limited. The gastrointestinal motility categorises the third major defense mechanism of the gut. The equilibrium of the flora and the fate of probiotics are also dependent on microbial interactions which includes competition for substrates or for adhesion sites, and modifications of the environment. Body immune cells and immune system also played an important role in control of the flora. Some studies have evaluated the effect of the matrix on the pharmacokinetics of probiotics. The decline of the pH in the stomach, and the residence time of food in the stomach fluctuate greatly with different meals. As a concern, the pharmacokinetics of acid sensitive probiotics can be intensely influenced by their vehicle. Some reports suggest that showed that the survival of Lactobacillus strain GG differed when this probiotic was ingested in tablets, gelatin capsules, fermented milks, or whey drink (Saxelin et al., 1995). Some authors have proposed to microencapsulate probiotics to enhance their resistance to gastric acidity (Tripathi and Giri, 2014) but the consequences on their survival in vivo and on their effects remain unknown.

## 4. Probiotic and Post biotics: health claims

The postbiotics are the complex mixture of bacterial metabolic products secreted by probiotics such as short chain fatty acids (SCFA), enzymes, secreted proteins, vitamins, amino acids, peptides, organic acids, bio surfactants, etc. Post biotics may increases the potency of active microorganisms or turn them into functional ingredients. Besides that, posbiotics circumvent the technical challenge of colonization efficiency and keeping the microorganisms viable and stable in the product at a high dose. This facilitates delivering the active ingredients at the desired location in the intestine, improves shelf-life, and may simplify packaging and transport (Ouwehand et al., 2000). The current description of both fermented milk and probiotics is focused on viability of the microorganisms. Though, it is not clear whether viable bacteria are essential for all indicated health claims. Many reports and studies concentrated on viable and nonviable probiotic bacteria and their applications such as improved lactose digestion, immune stimulation, antimutagenic activities and anti-hypertensive. Studies concluded that cell components, enzymatic activities or fermentation of products with probiotic bacteria may contribute in many biotherapeutic roles. The demand of probiotic functional foods is increasing speedily due to alertness of consumers for effect of food on health. Many factors involved during processing and storage which affect the viability of probiotic organisms. Therefore, formulation and development of foods with satisfactory amounts of probiotic bacteria at the time of consumption is a major challenge in food industry. Several efforts have been made during the last few decades to increase the viability of probiotics in different food products during their production until the time of consumption (Tripathi and Giri, 2014).

4.1 Postbiotics and paraprobiotics

The several postbiotic molecules such as cell-free supernatant, vitamins, organic acids, short- phenolic-derived postbiotics are metabolic by- chain fatty acids, secreted proteins, short peptides, amino acids, bacteriocins, neurotransmitters, secreted bio surfactants, flavonoids and derivative, terpenoids derived, products of live probiotic bacteria (Cortés-Martín et al., 2020, Cavallari et al., 2017, Wang et al., 2019). Whereas, the paraprobiotics constitutes inactivated or non-viable microbial cells of probiotics as intact or ruptured forms containing cell components of probiotic cells upon lysis such as teichoic acids, peptidoglycan-derived muropeptides, surface protruding molecules (pili, fimbriae, flagella), polysaccharides like exopolysaccharides, cell surface-associated proteins, cell wall-bound biosurfactants, teichoic acids, etc. (Shenderov 2013, Singhal et al., 2018). Various postbiotic molecules have drawn attention due to their known chemical structure, long storage stability, and the ability to trigger the various mechanisms in controlling inflammation, adhesion of pathogens to GIT, obesity, hypertension, coronary artery diseases (CVD), cancer, and oxidative stress (Fig. 2).

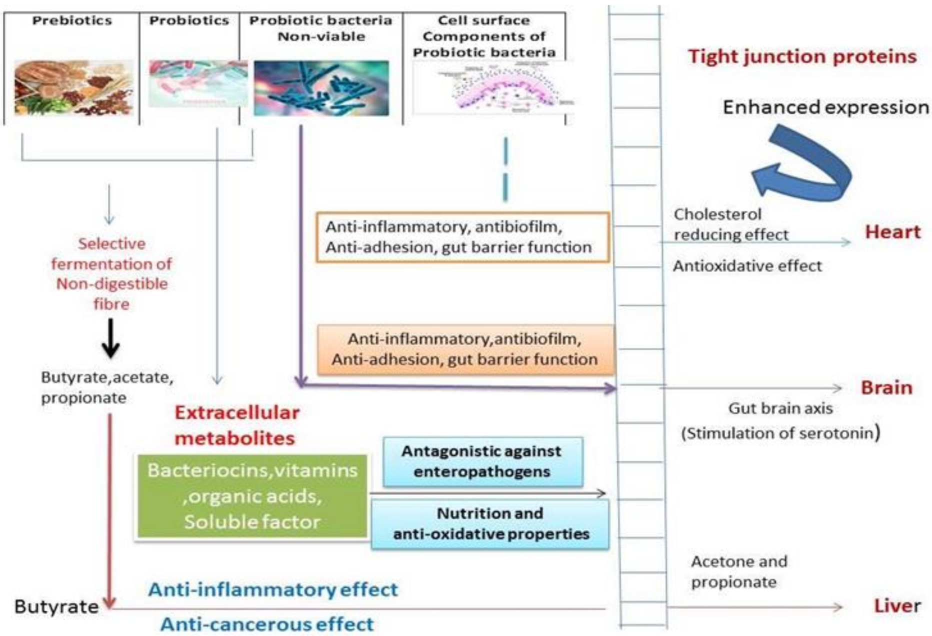


Fig 2: Health benefits of postbiotic molecules

## 5. Non-viable probiotics

The non-viable probiotics are dead cells or inactivated probiotics. The inactivation of live bacteria can be accomplished by many methods viz. heat treatment process, use of chemicals (e.g., formalin), ultraviolet or gamma irradiation, and using sonication method., Heat treatment is most common method for inactivation (Taverniti and Guglielmetti, 2011). Different inactivation methods effect on different cellular structural components which are identical for all biological activities (Deshpande et al., 2018). Heat treatments based on complete killing of bacteria in the suspension (Fig. 3). The probiotic cell inactivation can also be completed by tyndallization and cell freezing process.

It is reported that non-viable cells also conserved their properties to provide beneficial effects on the host at the intestinal level in vivo condition, thus there is greater utility in the development of safer preparations with more optimal pharmaceutical properties (Thakur et al., 2016, Caimari et al., 2017). (Fig.3). It was also found that heat-killed probiotics show anti-adhesion ability against various entero-pathogens in several experimental models (Singh et al., 2017). Several heat-killed probiotics strains of Lactobacillus have confirmed the anti-inflammatory and anti-oxidative effects in many experimental models (Jang et al., 2018, Chung et al., 2019). In some cases it was found that probiotic heat-killed preparation had a significant influence over serotonin secretion in the gut (gut-brain axis) (Hara et al., 2018). Some studies established that oral administration of heat-killed preparations of L. brevis SBC8803 to rats increased the ratio of acyl to des-acyl (inactive) ghrelin in blood (Saito et al., 2019). These outcomes recommend that both live bacteria and their heat-killed cells have potential to modify host physiology. There are several evidence which show similar mode of action of heat-killed probiotics and viable cells (Hsieh et al., 2016, Caimari et al., 2017, Sugahara et al., 2017). (Fig.3).

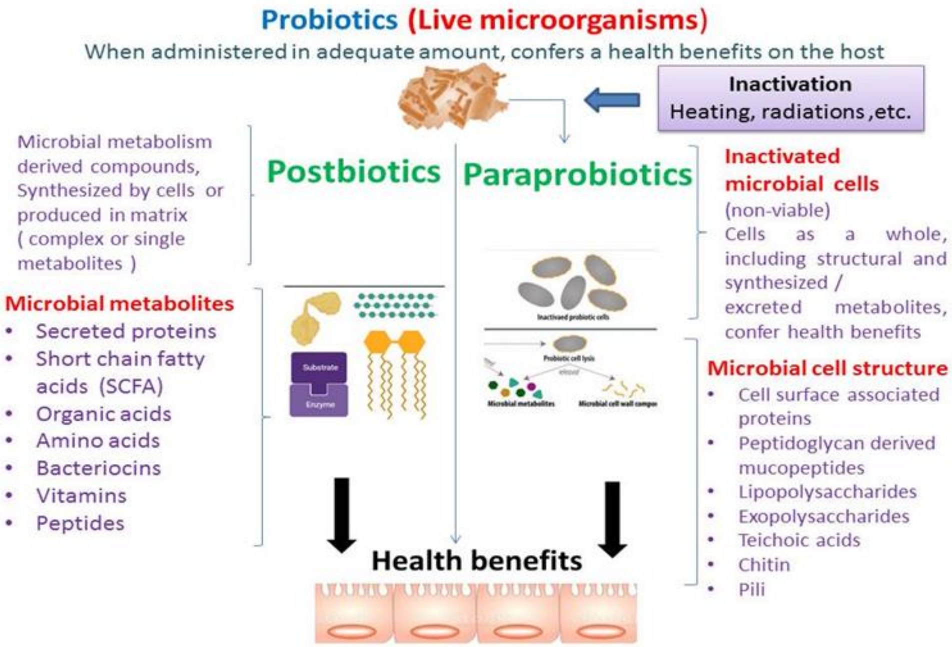


Fig. 3: Health effects of postbiotics and paraprobiotics

## 6. Conclusions

Preserving the efficacy of probiotic bacteria shows top tasks that need to be addressed during the development of functional food products. Several factors have been claimed to be responsible for reducing the viability of probiotics including matrix acidity, level of oxygen in products, occurrence of other bacteria and effects of metabolites produced by other competing bacteria. Several approaches are assumed to improve and sustain microbial cell viability such as; strain selection, immobilization skills, synbiotics development etc. Among them, cell immobilization in various carriers, including composite carrier matrix systems has recently attracted interest targeting to protect probiotics from different types of environmental stress. Effectively deliver the probiotics in the large intestine, cells must survive during food processing and storage, and survive with stress conditions in gastrointestinal tract. Awareness on the pharmacokinetics of probiotics is increasing due to advancements of in vitro models and tools for consistent identification of probiotics.

Paraprobiotics represent an important opportunity for the development of innovative functional foods suitable for people with weak immunity. These products have higher stability and can be stored without the cold chain, thereby facilitating industrial handling and wide commercialization. Probiotic cell inactivation may be attained by physical or chemical methods, which may alter cell structure and function, making bacteria lose their ability to grow and reproduce while preserving the beneficial effects exhibited by their viable counterparts. Thus, a further challenge is the use of appropriate methodologies to evaluate their biological activity and to identify the components responsible for the health effect. Their application must then necessarily go through the development of an approach able to correlate the biological response with the physical state and vitality of the microbial strain and to allow quality control of these products and regulatory interventions.

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