



The biological activities of postbiotics in gastrointestinal disorders

Amin Abbasi, Aziz Homayouni Rad, Zahra Ghasempour, Sahar Sabahi, Hossein Samadi Kafil, Paniz Hasannezhad, Yalda Rahbar Saadat & Nayyer Shahbazi

To cite this article: Amin Abbasi, Aziz Homayouni Rad, Zahra Ghasempour, Sahar Sabahi, Hossein Samadi Kafil, Paniz Hasannezhad, Yalda Rahbar Saadat & Nayyer Shahbazi (2021): The biological activities of postbiotics in gastrointestinal disorders, Critical Reviews in Food Science and Nutrition, DOI: [10.1080/10408398.2021.1895061](https://doi.org/10.1080/10408398.2021.1895061)

To link to this article: <https://doi.org/10.1080/10408398.2021.1895061>



Published online: 10 Mar 2021.



Submit your article to this journal 



Article views: 161



View related articles 



View Crossmark data 



Citing articles: 1 View citing articles 

REVIEW



The biological activities of postbiotics in gastrointestinal disorders

Amin Abbasi^{a,b} , Aziz Homayouni Rad^b, Zahra Ghasempour^b , Sahar Sabahi^c , Hossein Samadi Kafil^d , Paniz Hasannezhad^e , Yalda Rahbar Saadat^f , and Nayyer Shahbazi^g 

^aStudent Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran; ^bDepartment of Food Science and Technology, Faculty of Nutrition & Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran; ^cDepartment of Nutritional Sciences, School of Paramedical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; ^dDrug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; ^eDepartment of Medical Engineering Science, University College of Rouzbahan, Sari, Iran; ^fNutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; ^gFaculty of Agriculture Engineering, Department of Food Science, Shahrood University of Technology, Shahrood, Iran

ABSTRACT

According to outcomes from clinical studies, an intricate relationship occurs between the beneficial microbiota, gut homeostasis, and the host's health status. Numerous studies have confirmed the health-promoting effects of probiotics, particularly in gastrointestinal diseases. On the other hand, the safety issues regarding the consumption of some probiotics are still a matter of debate, thus to overcome the problems related to the application of live probiotic cells in terms of clinical, technological, and economic aspects, microbial-derived biomolecules (postbiotics) were introducing as a potential alternative agent. Presently scientific literature confirms that the postbiotic components can be used as promising tools for both prevention and treatment strategies in gastrointestinal disorders with less undesirable side-effects, particularly in infants and children. Future head-to-head trials are required to distinguish appropriate strains of parent cells, optimal dosages of postbiotics, and assessment of the cost-effectiveness of postbiotics compared to alternative drugs. This review provides an overview of the concept and safety issues regarding postbiotics, with emphasis on their biological role in the treatment of some important gastrointestinal disorders.

KEYWORDS

Postbiotic; gut microbiota; gastrointestinal disorders; infantile colic; necrotizing enterocolitis; gastrointestinal cancer

Introduction

The gastrointestinal tract (GIT) acts as the main immune organ, comprising approximately 70% of the human body's immune system (Denev et al. 2014). The surface area of the intestine is about 300 to 400 sq. cm, which is covered by masses of living microorganisms. In particular, this surface is colonized by approximately 10^{14} bacteria across over 500 species (Figure 1) (Hsiao et al. 2008). The results of clinical studies demonstrated that issues such as the mother's gut microbiota composition, the type of birth, nurturing manner during infancy, treatment with various antibiotics, low-fiber diet, chronic disorders, and anxiety are important factors that can influence the balance of microbiota in the gut (Moludi et al. 2018; Muñoz-González et al. 2015). In a healthy gut, there is a positive association between commensal bacteria and the host's cells, which leads to the stimulation and development of the gut's immune responses, consequently contributing to the maintenance of homeostasis in the host. The concepts of 'dysbiosis' and 'eubiosis' are used to explain the health and microbial composition of the gut, with the former referring to pathogenic conditions and

the latter describing beneficial microbes or probiotics (Khan et al. 2019; Moludi et al. 2018). In dysbiosis, the presence of pathogenic microbes and their toxic metabolites reduces the population of beneficial microbes and decreases immune function, making the host susceptible to a variety of infectious and noninfectious diseases (Moludi et al. 2018). One of the main approaches for establishing eubiosis is to balance the gut microbiota through the consumption of foods and/or dietary supplements containing probiotics (Abbasi et al. 2021). Probiotics are known as nonpathogenic microorganisms that induce advantageous effects on the host's health when consumed in sufficient amounts (Haghshenas et al. 2016) and contain both bacteria (e.g. *Lactobacillus*, *Bifidobacterium*, and *Bacillus*) and yeast (e.g. *Saccharomyces*, *Kluyveromyces*, *Pichia*, and *Torulaspora*) genera (Rad, Abbasi, Javadi et al. 2020; Saber et al. 2017). Regarding the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus panel the mechanisms of action of probiotic cells can be characterized as strain-dependent (e.g. infrequent and existent in only a few strains of a particular species), species-dependent (e.g. commonly detected among most strains of a probiotic species), for

CONTACT Amin Abbasi  aminabasi.tbz.med.ac@gmail.com  Department of Food Science and Technology, Faculty of Nutrition & Food Sciences, Tabriz University of Medical Sciences, Attar Nishabouri St., Tabriz, Iran; Hossein Samadi Kafil  Kafilhs@tbzmed.ac.ir  Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

This article was originally published with errors, which have now been corrected in the online version. Please see Correction (<http://dx.doi.org/10.1080/10408398.2021.1922741>)

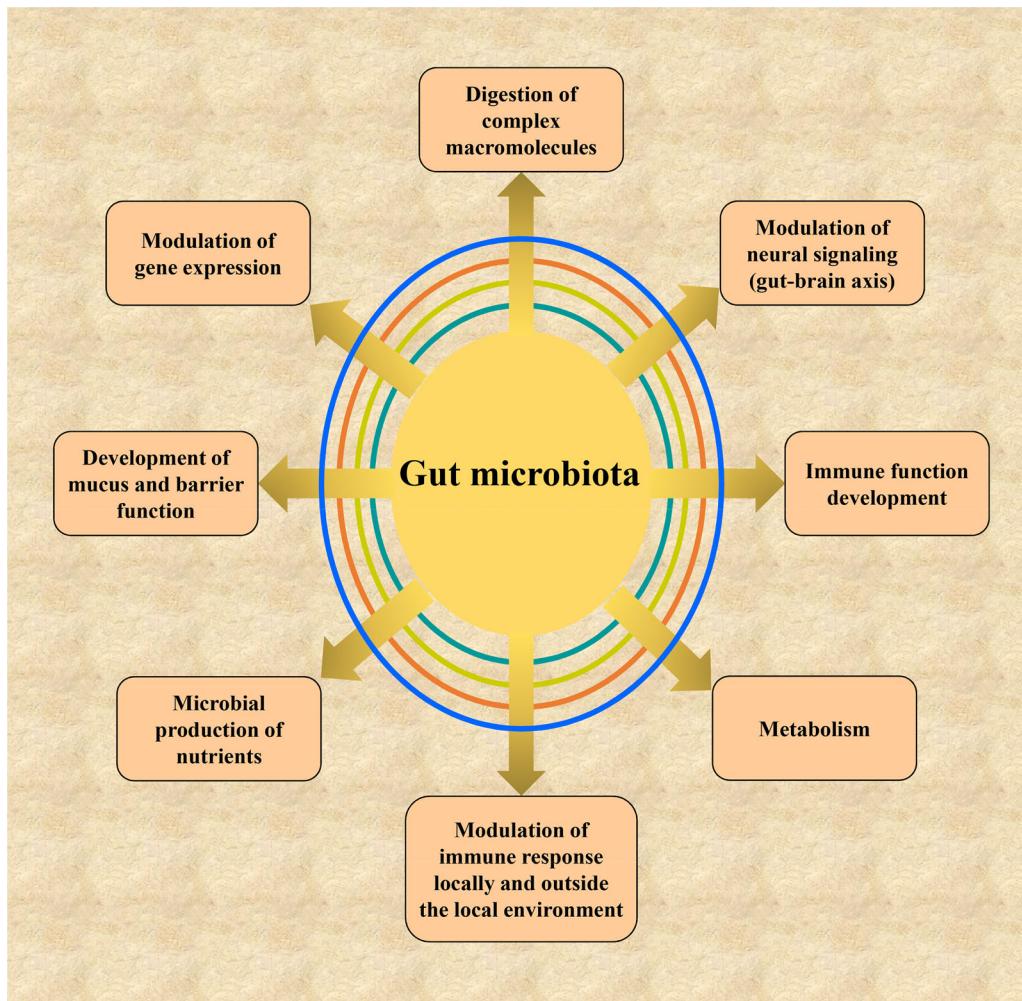


Figure 1. Main functions associated with gut microbiota.

instance, *Lactobacillus paracasei* or *Bifidobacterium infantis*) and some mechanisms of action might be prevalent amid frequently investigated probiotic genera (Cuevas-González, Liceaga, and Aguilar-Toalá 2020). The significant potential of probiotics has been confirmed as therapeutic agents for a diverse group of diseases, mainly intra- and extra-intestinal disorders such as ulcerative colitis, acute infectious diarrhea, Irritable Bowel Syndrome (IBS), antibiotic-associated diarrhea, Necrotizing Enterocolitis (NEC), lactose intolerance, colorectal cancer, and hepatic encephalopathy (Jamalkandi et al. 2020; Karimi et al. 2020; Maia et al. 2019; Mohamadshahi et al. 2014; Vaghef-Mehraban et al. 2017).

Nevertheless the affirmative indications, there are no pieces of evidence from long-term clinical trials with a large statistical sample that the intake of probiotic products stimulates the health status of formerly healthy people (Cohen 2018). The joint FAO/WHO (Joint 2002) guidelines and the outcomes of case report studies have indicated that some probiotic cells (*L. helveticus*, *L. hilgardii*, *L. buchneri*, *Bifidobacterium*, *Streptococcus thermophilus*, and *Bacillus*) applied in various delivery systems (pharmaceuticals and/or foods) may theoretically be related to some undesirable side-effects (e.g. presence of virulence factors, the spread of resistance genes, metabolic disturbances, production of bioactive amines, opportunistic infection), particularly in the

pediatric populations and in patients with underlying diseases (Table 1 and Figure 2) (Appel-da-Silva et al. 2017; Cohen 2018; Doron and Snydman 2015; Gezginc et al. 2013; Ordóñez et al. 2016; Piqué, Berlanga, and Miñana-Galbis 2019; Taylor, Dunstan, and Prescott 2007).

In recent years, to overcome some of the difficulties regarding the use of live probiotic cells in terms of clinical, technological, and economic characteristics, some potential alternative agents such as non-digestible fibers (prebiotics) and/or microbial-derived biomolecules (postbiotics) are employed to balance the composition of the gut microbiome and subsequently to establish eubiosis conditions that in turn, lead to the development of homeostasis (Piqué, Berlanga, and Miñana-Galbis 2019; Rad et al. 2020a). In this regard, there is increasing evidence suggesting that the major health-stimulating effects of gut microbiota may be associated with their non-viable byproducts (postbiotics), which have the potential to mimic the health benefits of live parent cells through similar or dissimilar metabolic pathways (Figure 3) (Guéniche et al. 2009). The term of postbiotics, though they developed newly, have been approved quickly in the field of food science, and also in host health and nutrition, resulting in particular attention for their potential prospective application as nutraceuticals, functional foods, and drugs in the food, biotechnological, and pharmaceutical

Table 1. The possible side-effects associated with the high dietary intake of probiotic products in vulnerable individuals.

Probiotics microorganisms	At-risk individuals	Safety concern	Main side-effect (s)	References
<i>Lactobacillus rhamnosus</i> GG	Patient (17-year-old) with symptoms of ulcerative colitis	Generalized infection	Translocation from the gut lumen to bloodstream	(Vahabnezhad et al. 2013)
<i>Bifidobacterium longum</i>	Patient (74-year-old) with symptoms of polymetastatic prostatic adenocarcinoma	Generalized infection	Translocation from the gut lumen to bloodstream	(Weber et al. 2015)
<i>Lactobacillus</i> sp	–	The spread of antibiotic resistance properties	Transferring vancomycin resistance properties to <i>Enterococcus faecalis</i>	(Devirgiliis, Zinno, and Perozzi 2013)
<i>Lactobacillus paracasei</i>	Patient (77-year-old) with symptoms of prostate cancer	Generalized infection	Infective endocarditis	(Franko et al. 2013)
<i>Lactobacillus lactis</i>	–	Metabolic disorders	Generation of biogenic amines	(Kuley et al. 2012)
<i>Lactobacillus</i> sp	–	The spread of antibiotic resistance properties	Transferring an extensive variety of antibiotic resistance properties (aztreonam, vancomycin, ciprofloxacin, gentamicin, and streptomycin) to <i>Staphylococcus</i> sp	(Tannock et al. 1994; Zheng et al. 2017)
<i>Lactobacillus</i> sp	Immune-competent individual (58-year-old) with mechanical respiration	Generalized infection	Translocation from the gut lumen to bloodstream and sepsis shock	(Kulkarni and Khouri 2014)
<i>Bifidobacterium longum</i> subspecies <i>infantis</i>	Infants and children	Generalized infection	Translocation from the gut lumen to bloodstream	(Bertelli et al. 2015)
<i>Lactobacillus rhamnosus</i>	Patient with respiratory viral infection	Localized infection	Exacerbation the symptoms of pneumonia	(Doern et al. 2014)
<i>Lactobacillus paracasei</i>	Patient (65-year-old) with diabetes mellitus	Localized infection	Translocation from the gut lumen to the bloodstream and pyogenic liver abscess	(Pararajasingam and Uwagwu 2017)
<i>Lactobacillus casei</i>	Patient (60-year-old) with the kidney transplant	Localized infection	Pyogenic abdominal abscess	(Vanichanan et al. 2016)
<i>Lactobacillus acidophilus</i>	Patient (48-year-old) with heart disorders	Generalized infection	Infective endocarditis	(Encarnacion et al. 2016)
<i>Lactobacillus acidophilus</i> LAVRI-A1	Newborns (12 months)	Allergic reaction	Development of atopic sensitization	(Taylor, Dunstan, and Prescott 2007)
<i>Lactobacillus rhamnosus</i> GG	Expectant and lactating mothers (up to 2 years)	Allergic reaction	Development of atopic sensitization and wheezing bronchitis	(Kopp 2008)

industries (Cuevas-González, Liceaga, and Aguilar-Toalá 2020; Homayouni Rad, Samadi Kafil, et al. 2020; Rad, Abbasi, Kafil et al. 2020). The objectives of this manuscript were to provide an overview of the concept and safety issues regarding postbiotics and to assess their biological roles in some important gastrointestinal disorders.

Methods

A literature survey was performed using ISI Web of Knowledge, Google Scholar, PubMed, Medline, and Scopus databases by the composition of search terms: ‘postbiotic’; ‘probiotic’; ‘gastrointestinal disorders’; ‘side-effect’; ‘safety’; ‘immunomodulation’; ‘intestinal barrier’; ‘inflammatory bowel disease’; ‘colitis’; ‘diarrhea’; ‘bloating’; ‘pediatric disorders’; ‘necrotizing enterocolitis’; and ‘gastrointestinal cancer’. Experimental and clinical investigations with regard to the main objectives of the study were enrolled. Papers with unrelated topics and incomplete texts were excluded from the review (Figure 4).

The concept of postbiotics

In recent years, most researchers have employed terms such as ‘biogenic’, ‘cell-free supernatant (CFS)’, ‘abiotic’,

‘metabiotic’, ‘pseudoprobiotic’, ‘ghost probiotic’, and ‘postbiotic’ to describe the non-viable parts of probiotic cells. Among these, the term ‘postbiotic’ is the most used in the literature (Aguilar-Toalá et al. 2018; Barros et al. 2020; de Almada et al. 2016; Homayouni-Rad et al. 2021). The term ‘postbiotic’ is linked with inactivated microbial cells (dead cells), cell fractions (peptidoglycan-derived muropeptides, teichoic acids, endo- and exo-polysaccharides, and cell-surface proteins), or cell metabolites (Short-Chain Fatty Acids (SCFAs), enzymes, bacteriocins, and organic acids) that are made by live probiotic cells through the fermentation process, in response to gut conditions, and/or released after lysis (when exposed to physical and/or chemical cell inactivation conditions) and confer various physiological health benefits to the host when administered in adequate amounts (Figure 5) (Cicenia et al. 2014; Rai, Pandey, and Sahoo 2019).

Classification and safety issues of postbiotics

Given the fact that certain side-effects such as those previously mentioned are possible when probiotic products are administered, it is obligatory to consider safe alternatives such as postbiotic components, which confer selective growth of the gut resident beneficial microorganisms and induce the same physiological health benefits to the host as

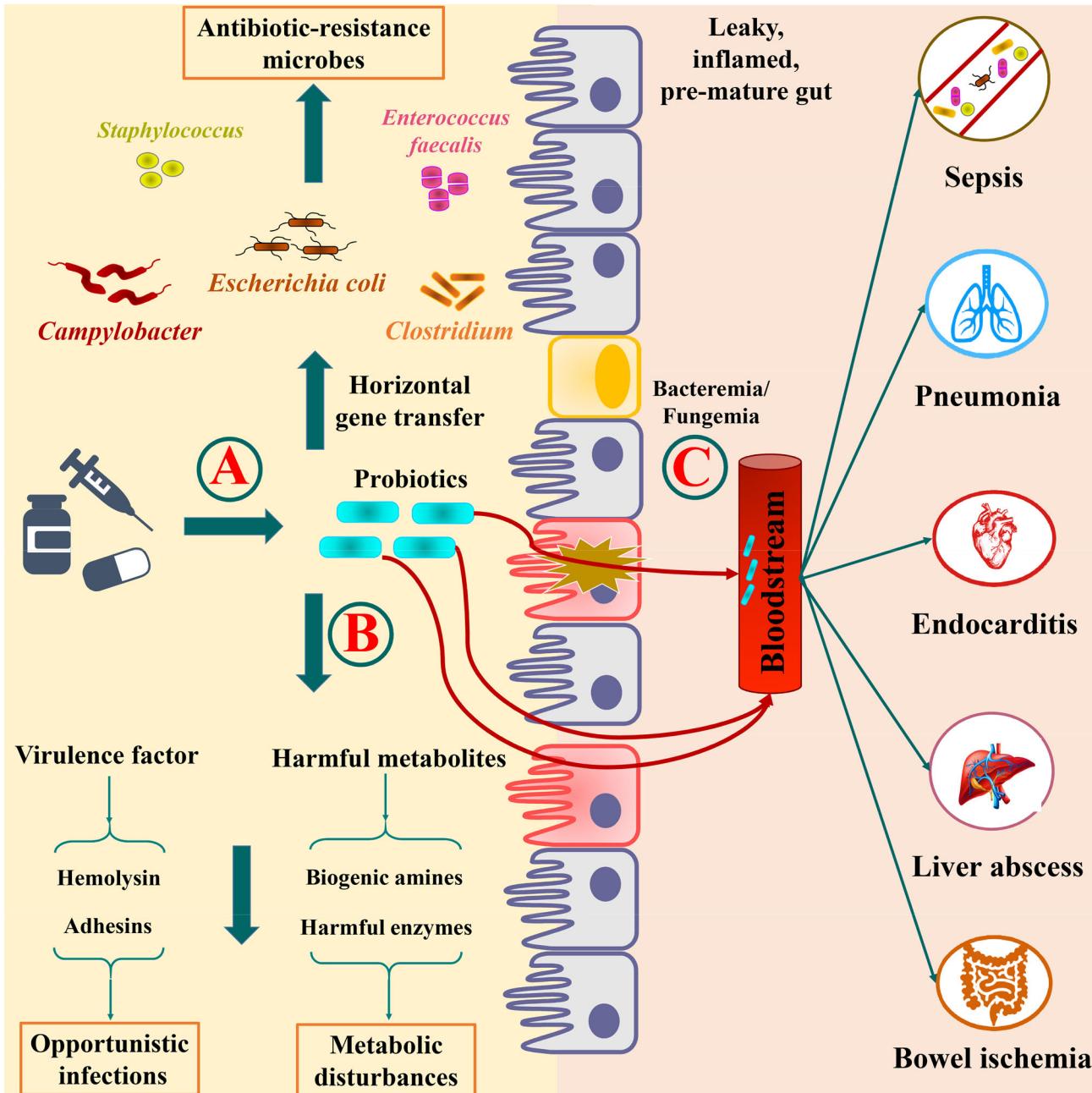


Figure 2. Schematic illustration of the potential risks associated with the (high) dietary intake of some probiotics in the at-risk individuals. (A) Spread (horizontal transfer) of antibiotic resistance genes in the gut microbial populations, which in turn leads to the development of antibiotic-resistant microbes; (B) Presence of virulence factors in probiotic microbial strains and their derived harmful metabolites may be associated with the opportunistic infections and metabolic disturbances; (C) Probiotic translocation from (leaky, inflamed and/or pre-mature) gut lumen to the bloodstream and subsequently into vital organs triggering generalized and localized infections.

live parent cells. Postbiotics can be distinguished either by their fundamental components, i.e., proteins, carbohydrates, lipids, organic acids, vitamins, and certain complex molecules, or by their biological functions (Aguilar-Toalá et al. 2018; Homayouni-Rad et al. 2020).

Functional postbiotic constituents and their biological activities

Cell-wall constituents

Presently, there is increasing evidence suggesting that Cell-Wall Constituents (CWCs) of probiotic cells have beneficial health effects and can be used in the design of a new

delivery system for therapeutic purposes (Desrouillères et al. 2016; Sarkar and Mandal 2016). Among the CWC, peptidoglycan and lipoteichoic acids are the main components with immunomodulatory effects that have been mentioned in most studies (Kim et al. 2017; Lee et al. 2013; Vinogradov et al. 2016). In a model of LPS-stimulated macrophage-like cells, the peptidoglycans derived from various *Lactobacillus* species had a high ability to hinder the release of inflammatory cytokines (Z. Wu et al. 2015). Additionally, in the case of an animal model study, the peptidoglycan derived from *L. rhamnosus* was able to promote innate immune responses in immunocompromised mice (with *Streptococcus* infection) (Kolling et al. 2018). According to the finding of

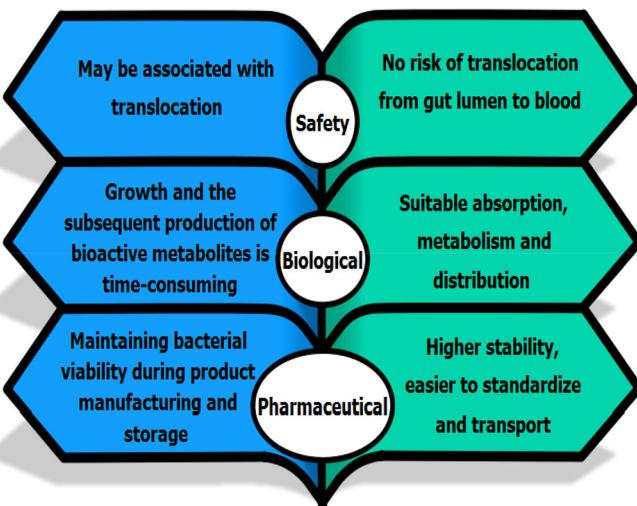


Figure 3. Advantages of postbiotics in terms of safety and biological properties as well as pharmaceutical relative to live probiotics (right column: postbiotics; left column: probiotics).

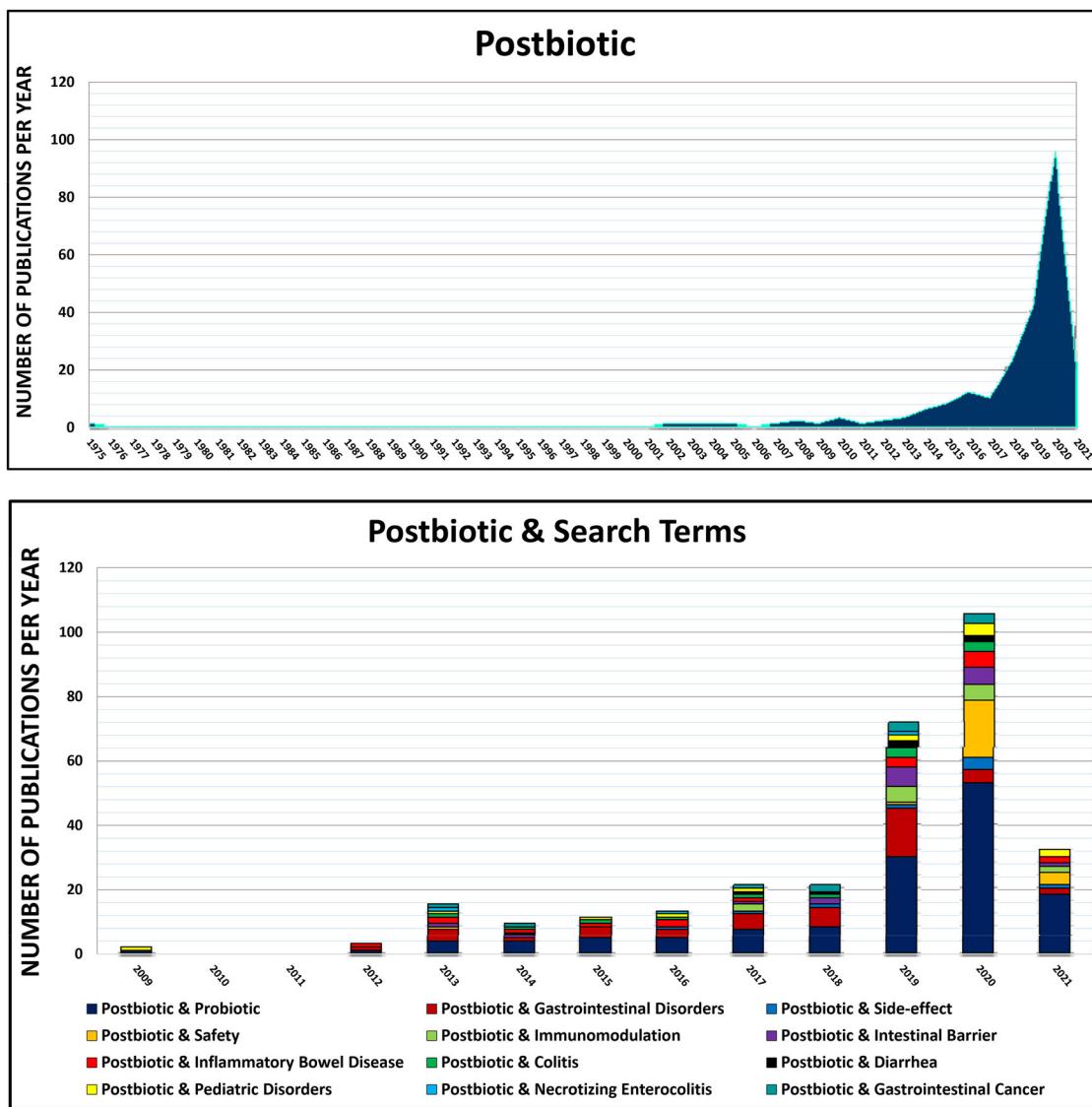


Figure 4. Illustrates the increase in the number of papers reporting research in the field of postbiotic. Comparison between the number of publications; on top the search of postbiotic and its synonyms (non-viable microbial cells, abiotic, metabiotic, ghost probiotics, and paraprobiotic), and below the search of the association between postbiotics and search terms ('probiotic'; 'gastrointestinal disorders'; 'side-effect'; 'safety'; 'immunomodulation'; 'intestinal barrier'; 'inflammatory bowel disease'; 'colitis'; 'diarrhea'; 'pediatric disorders'; 'necrotizing enterocolitis'; and 'gastrointestinal cancer') in PubMed February 2021.

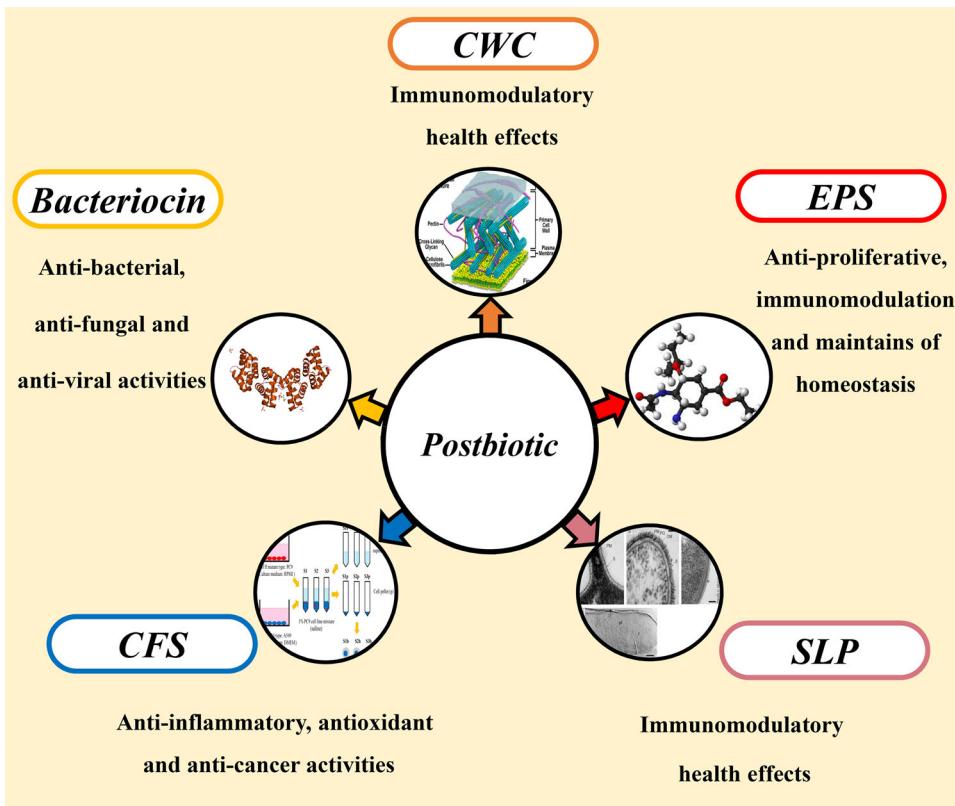


Figure 5. Main postbiotic constituents and their biological activities. Cell-Wall Constituents (CWC), Exopolysaccharides (EPS), Surface-Layer Proteins (SLP), Cell-Free Supernatants (CFS), and bacteriocins are the main postbiotic constituents that have key roles in maintaining the host's homeostasis through their biological activities.

a study performed in porcine intestinal epithelial cell lines, the postbiotics of lipoteichoic acid derived from *L. plantarum* have significant potential in the induction of anti-inflammatory responses (Kim et al. 2017).

Exopolysaccharides

Exopolysaccharides (EPSSs) are extracellular surface carbohydrate polymers, which frequently present in most bacterial cell surfaces (capsular form) and/or are released into the environment around the cell (slime form), and may possess various organic and inorganic components such as phosphate, sulfate, acetylate and acetic acid (Poli, Anzelmo, and Nicolaus 2010; Sutherland 1990). EPS provides an extensive variety of applications in the food and medical practices such as gel formation, thickening agents, emulsification ability, metal biosorption, and cancer therapy (Freitas, Alves, and Reis 2011; Manivasagan and Kim 2014; Suresh Kumar, Mody, and Jha 2007). These substances also have good immunomodulatory and immune-protective functions, including the prevention of bacterial biofilm development and maintenance of intestinal homeostasis (Fanning et al. 2012; Whitfield, Marmont, and Howell 2015). These health-promoting effects of EPS that have been reported in both in vitro and in vivo studies are frequently related to EPS derivatives from various strains including *Lactobacillus*, *Bifidobacterium*, *Bacillus*, and *Leuconostoc* strains (Castro-Bravo et al. 2018; Saadat, Khosrourshahi, and Gargari 2019). The results of studies performed in the cell cultures of immune and epithelial cells confirmed that the EPS derived

from *B. breve* and *Lactobacillus* species carry-out noteworthy immunomodulatory activity by interacting with epithelial cells (Patten et al. 2014). The EPS derived from *B. bifidum* and *B. longum* contribute to the growth of *lactobacilli* and other beneficial anaerobic bacteria, also restraining the growth of pathogenic bacteria such as *Salmonella* spp., *Escherichia coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* (Z. Liu et al. 2017; M.-H. Wu et al. 2010). In a study by Zhang et al. (2017) the potential adsorption capacity of EPS produced via a marine bacterium *Alteromonas* sp. JL2810 was evaluated. They established that the EPS has a significant ability to adsorb investigated heavy metals (Cu^{2+} , Ni^{2+} , and Cr^{6+}), which can be influenced via a medium pH. Moreover, the results from infrared spectrometry analysis indicated that the groups of $\text{C}=\text{O}$, $\text{C}-\text{O}-\text{C}$, and $\text{O}-\text{H}$ were the key functional groups for the adsorption function of EPS with the investigated heavy metals. The authors concluded that the EPS with high adsorption performance can be applied as a novel bio-resource for the removal of heavy metals. On the other hand, some EPSSs contain sugars that can be applied in the food industry as new additives for improving the physicochemical and sensorial properties of products (Aguilar-Toalá et al. 2018; Moghaddas Kia et al. 2018). Overall, EPSSs exert salutary effects through different molecular mechanisms; for instance, EPSSs have the capability of modulating innate and adaptive immune responses, stimulating several types of immune cells (e.g. T, B-lymphocytes, NKs, and macrophages), apoptosis induction, and eliminating free

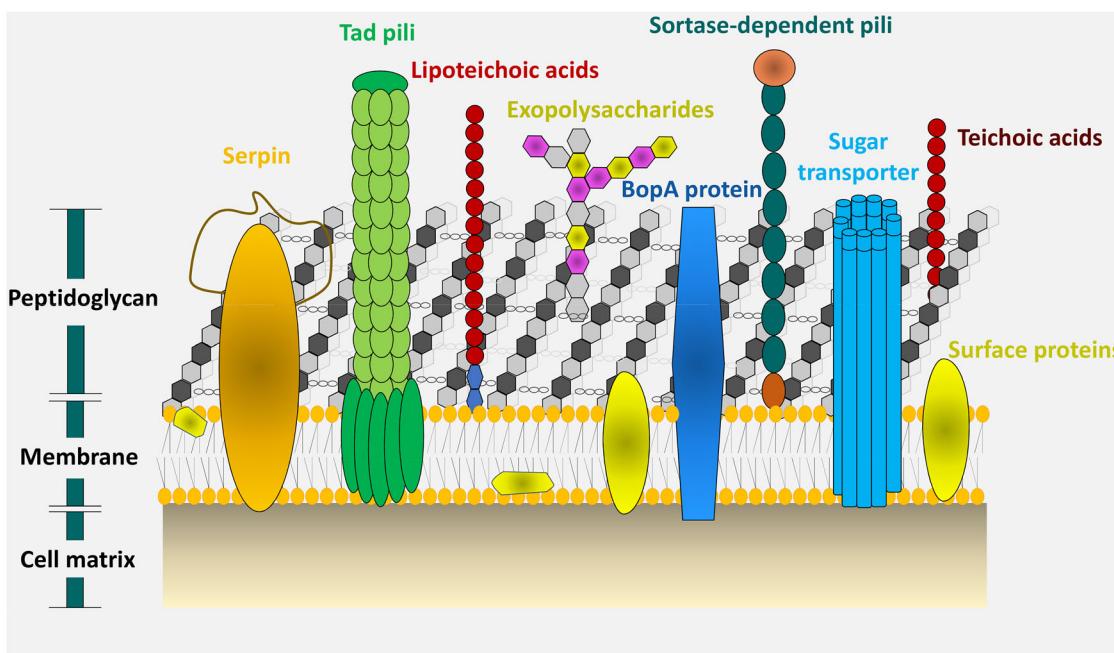


Figure 6. Schematic representation of probiotics' cell-wall constituents.

radicals, though exert anticancer, antioxidant and immunomodulatory effects (Rad et al. 2020b; Rahbar Saadat et al. 2020).

Surface-Layer proteins

The surface of bacterial cells is mainly comprised of a regular layered structure of proteins and glycoproteins called Surface-Layer Proteins (SLPs), which develop a permeable layer and cover the cell surface (Hynönen and Palva 2013). This SLP is frequently found on the cell surface of probiotics, particularly in *Lactobacillus* species. The specific SLP (SLPA) derived from *L. acidophilus* have important health-promoting roles as they bind to immune cells and stimulate immunomodulatory activities (Gareau, Sherman, and Walker 2010; Konstantinov et al. 2008). The SLP derived from *L. helveticus* has a high capacity to interact with epithelial cells and reduce *E. coli* O157: H7 adherence, thereby maintaining epithelial barrier efficiency and improving mucosal homeostasis (Johnson-Henry et al. 2007) (Figure 6).

Cell-free supernatants (CFS)

The Cell Free-Supernatants (CFSs) derived from probiotic cells comprise an extensive range of compounds including hydrogen peroxide, organic acids (butyrate, propionate, and acetate), bacteriocins, reuterin, diacetyl, and other biomolecules (Bianchi et al. 2011; Lukic et al. 2017). A growing body of evidence illustrated diverse health-promoting effects of CFSs' (see Table 3). After the consumption of foods/supplements containing CFS, these substances initially interact with intestinal epithelial cells before interacting with immune cells in the second stage; depending on the origin of the postbiotics (various probiotic cells), such interactions can potentially induce anti-inflammatory and/or antioxidant activity (De Marco et al. 2018). In an in vitro study

conducted on colon epithelial cells, the CFS secreted by *L. rhamnosus* GG were found to have high potency in inhibiting cytokine-induced cell apoptosis; these probiotics have also been introduced as a potential agent for promoting gut homeostasis (Bermudez-Brito et al. 2012; Yan et al. 2007). Besides, CFS derived from probiotics may strongly interfere with the invasion of pathogens. In line with this, Khodaii and colleagues indicated that CSF from *Lactobacilli* and *Bifidobacteria* can inhibit the invasion of Enteroinvasive *E. coli* (EIEC) strain using T84 and Caco-2 colon adenocarcinoma cell lines (Khodaii, Ghaderian, and Natanzai 2017).

Bacteriocins

Bacteriocins are small molecular weight peptides that play an important role in the inhibition of the growth of enteric pathogens (do Carmo et al. 2018; Gareau, Sherman, and Walker 2010). It is essential to note that besides their antibacterial properties, some bacteriocins can exert significant anti-fungal and anti-viral activities (Juturu and Wu 2018). Both in vitro and in vivo studies have confirmed that the bacteriocins derived from Lactic Acid Bacteria (LAB) have considerable activity against the growth and infection of pathogen bacteria such as *Listeria*, *Clostridium*, *Enterococcus*, *Bacillus*, and *Staphylococcus* species (Corr et al. 2007; Juturu and Wu 2018). The bacteriocins can be considered as appropriate ingredients in functional food formulations as they feature various appealing properties such as resistance to temperatures of up to 100 °C, stability in an extensive pH range of 3–10, stability against the action of salts, enzymes, and organic solvents, and stability under refrigerator or freezer conditions (Juturu and Wu 2018; Sarkar and Mandal 2016). The only bacteriocin approved for application in the food industry is nisin, which is derived from *Lactococcus* strains (lantibiotic) and is frequently used as a preservative in food products such as baby foods, canned soups, fishery products, and dairy products (Aguilar-

Table 2. Criteria for the safety evaluation of postbiotics.

Category	Safety factors	Methodology approach	References
Postbiotics' parent cells	Identification of safe strain	Emerging molecular (DNA-based) technologies including high throughput sequencing and genetic-based apparatuses	(Fijan 2014; Galimberti et al. 2015)
	Toxicological features	<i>In vitro</i> and <i>in vivo</i> investigations for assessing the generation of biogenic amines, harmful enzymes, and hemolytic activity	(Kim et al. 2018)
	Target individuals	Infants and children, immunocompromised, allergic, expectant mothers, and vulnerable patients with symptoms of acute and/or chronic infectious diseases	(Sanders et al. 2010)
Postbiotic components	Functionality	Functional evaluation through the experimental, animal, and/or human investigations including randomized controlled trials	(Papadimitriou et al. 2015)
	Toxicological features	<i>In vitro</i> and <i>in vivo</i> investigations on the presence of biogenic amines, harmful enzymes, and hemolytic activity; long-term and high-dosage effects	(Chuah et al. 2019)
	Formulation and labeling characteristics of the final product	Identity, purity, strength, composition, doses information, the possible presence of biological and/or non-biological contaminants, and health-promoting claims (general and specific)	(Aguilar-Toalá et al. 2018; Sanders et al. 2013)

Toalá et al. 2018). Bifidocins and acidocin are other types of bacteriocins derived from *bifidobacteria*; these bacteriocins have an extensive variety of antimicrobial activity versus both Gram-negative and Gram-positive microbes (bacteria and some yeasts) through the mechanism of cell lysis, particularly in fermented food products (Bali, Panesar, and Bera 2016; G. Liu et al. 2015).

Safety issues of postbiotics

With regard to the safety issues, many clinical trials have been carried out through which the appropriate absorption, metabolism, and distribution of postbiotics has been confirmed; these biomolecules can also prompt signaling to various organs in the host (Peng et al. 2020; Shenderov 2013; Tomaszik and Tomaszik 2020). Regarding the safety issue of postbiotics, some possible adverse effects of postbiotics are reported in a systematic review of seven Randomized Controlled Trials (RCTs) with 1740 children, which assessed the role of postbiotics in inhibiting and treating common infectious diseases among children younger than 5 years. Among investigations only three of the included RCTs evaluated the adverse effects of postbiotics, some of the described secondary effects include; a higher rate of abdominal distention, severe dehydration, and vomiting in the group of individuals that received inactivated *L. acidophilus* LB plus micronutrients. The remaining RCTs did not report probable side effects. The authors concluded that there are a few investigations that have reported potential side effects of postbiotics administration (Malagón-Rojas et al. 2020). The postbiotics with unique features such as known chemical structures, safety profiles, more shelf-life, and stability in both market and digestive system conditions can be safe alternatives to live probiotic cells, applied in the pharmaceutical and food industries, for offering health benefits, inhibiting illnesses and achieving therapeutic targets (Table 2) (Rad et al. 2020a; Shigwedha et al. 2014).

However, the maintenance of the physiological properties and stability of postbiotic metabolites during the preparation process and in delivery systems (pharmaceuticals/foods), as well as the related safety factors, merit further investigation.

Biological activities of postbiotics in gastrointestinal disorders: Experimental and clinical pieces of evidence

In recent years, a noteworthy number of scientific reports have been published in confirmation of the health effects related to the intake of postbiotic foods and/or supplements (Burta et al. 2018; Taverniti and Guglielmetti 2011; Vandenplas et al. 2017). Due to their appealing characteristics (non-toxic; safe; extended shelf-life; stability), postbiotics can be used in delivery systems (pharmaceuticals and/or functional foods) for preventive and/or therapeutic purposes (Figure 7 and Table 3).

The role of postbiotics in the growth inhibition of pathogenic germs

The capability of postbiotics to safeguard the host's health against serious infections induced by pathogens is fulfilled through various mechanisms such as inhibition of pathogenic adhesion, invasion, biofilm formation, and improvement of immune responses in the gut environment (Decuyper & Dierick 2003). In an *in vitro* study performed on cell culture of mice intestinal epithelial cells, it was demonstrated that the postbiotics derived from *L. plantarum* can reduce the adherence and invasion of *Salmonella* sp in epithelial cells (Ishikawa et al. 2010; Moradi, Mardani, and Tajik 2019). The postbiotics derived from *Leuconostoc mesenteroides* inhibited the invasion and infection of *Listeria monocytogenes*, in both *in vitro* and *in vivo* models, and can be exploited to promote the host's immune system efficacy against infections induced by *Listeria monocytogenes* (Nakamura et al. 2012).

The bioactive metabolites produced by probiotics can prevent periodontal pathogenic bacteria. In this context, research conducted by Rossoni et al. indicated that the supernatants of different strains of *Lactobacillus* can inhibit *Streptococcus mutans*, thus improve dental caries (Rossoni et al. 2018). The results of various studies confirm that in addition to LAB, the postbiotics of *Bifidobacterium* also have biological effects on the improvement of oral health status. In this regard, the postbiotics derived from *Bifidobacterium*

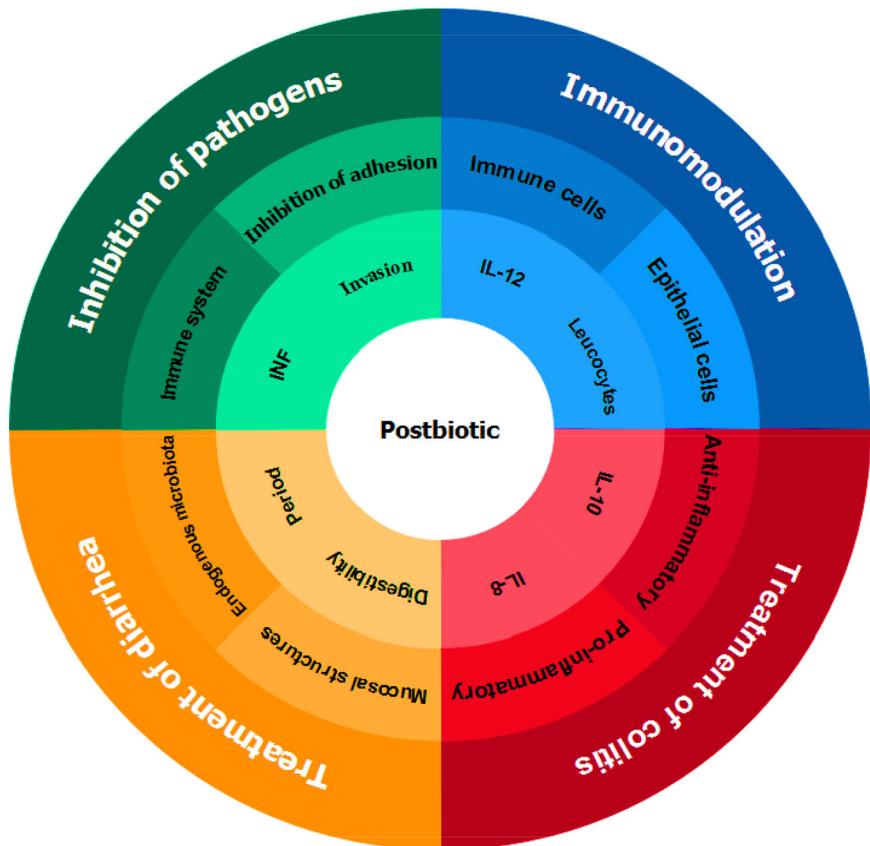


Figure 7. Main mechanisms of postbiotics regarding their biological role in the inhibition of pathogens, immunomodulation, treatment of colitis, and diarrhea. Inhibition of pathogens: in the *first step*, the postbiotics reduce the adherence of pathogens and promote the host's immune system; in the *second step*, they exert anti-bacterial and anti-viral activities through reducing the invasion of pathogens and producing INF. Immunomodulation: in the *first step*, postbiotics interact with immune and epithelial cells to activate innate immunity; in the *second step*, they stimulate the secretion of IL-12 and improve immune system functioning through increasing the phagocytic activity of leucocytes. Treatment of colitis: in the *first step*, postbiotics exert significant anti-inflammatory activities; in the *second step*, they regulate the inflammatory responses in gut epithelial cells through stimulating the production of IL-10 as an anti-inflammatory cytokine and inhibiting the production of IL-8 as a pro-inflammatory cytokine. Treatment of diarrhea: in the *first step*, probiotics alter the mucosal structure by increasing the villi size and fortifying the endogenous beneficial microbiota; in the *second step*, they reduce the symptoms of diarrhea through improving digestibility and reducing the duration of the disease.

BB12 can prevent the development of biofilms induced by *Streptococcus mutans* in dental cavities to a significant extent (Schwendicke et al. 2014). Furthermore, Lim et al. demonstrated that the CFS derived from probiotic *Weissella cibaria* strain CMU exerts an inhibitory role against oral pathogens (e.g. *Porphyromonas gingivalis* and *Prevotella intermedia*). Their findings illustrated that the CFS's inhibitory role depends on acidic pH, production of hydroxyl radicals, specific proteins, fatty acid (e.g. oleic acid), and organic acids such as lactic acid, acetic acid, and citric acid (Lim et al. 2018). In a randomized double-blind, placebo-controlled study performed on 100 children, it has been shown that the bacteriocins, dextranase, and urease enzymes produced by the probiotic *Streptococcus salivarius* strain M18, led to reduction of dental caries and offer oral health benefits (Burton et al. 2013).

Additionally, some postbiotics derived from LAB can provide effective protection against infections induced by certain viruses. *Lactobacillus* species possess antibacterial (Di Cerbo et al. 2016) and anti-viral properties (Sunmola et al. 2019) (inhibition of Gastric Corona, HIV, and Rotavirus *in vitro* along with a noticeable diminution in viral load *in vivo* (Hasan et al. 2020; Ismail 2017)), by producing an extensive variety of metabolites (biomolecules/postbiotics)

such as plantaricin, lactic acid, acetic acid, and gamma-aminobutyric acid (Albarracin et al. 2017), plays a significant role in the treatment of gastrointestinal disorders. In this regard, according to the appealing results of an *in vivo* study, the postbiotics derived from *L. gasseri* TMC0356 can act significantly against infections induced by the H1N1 flu virus via promoting local and systemic immune responses (Kawase et al. 2012). Further, Anwar et al. (2020), investigated the potential antiviral effect of some postbiotics derived from *Lactobacillus plantarum* (Plantaricin BN, Plantaricin JLA-9, Plantaricin W, Plantaricin D) by a computational target to block the residual binding protein (RBP) on spike proteins (S), and Angiotensin-Converting Enzyme 2 (ACE2) receptor proteins along with RNA-dependent RNA polymerase (RdRp). The results demonstrated that Plantaricin W, D, and JLA-9 were capable to block the residues (THR556, ALA558) surrounding the deep groove catalytic site (VAL557) of RdRp making them more therapeutically active for SARS coronavirus (COVID-19). Moreover, molecular dynamics investigations further reinforce the stability of the complexes of plantaricin w and SARS-CoV-2 RdRp enzyme, RBD of spike protein, and human ACE2 receptor. Hence, this study offers multi-way possibilities either by interacting of S protein with ACE2

Table 3. Main biological activities of postbiotics in gastrointestinal disorders.

Biological activities in gastrointestinal disorders			
Species	Postbiotics	Benefits	References
<i>Lactobacillus acidophilus</i> LB	Indeterminate	Treatment of diarrhea in patients with irritable bowel syndrome	(Tarrerias et al. 2011)
The mixture of <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Lactococcus</i> , and <i>Streptococcus thermophilus</i>	Intracellular content	Antioxidant activity <i>in vitro</i>	(Amaretti et al. 2013)
<i>Lactobacillus plantarum</i> b240	Heat-killed cells	Protection against <i>Salmonella</i> infection and translocation	(Ishikawa et al. 2010)
<i>Lactobacillus johnsonii</i> BB12	Heat-killed cells Heat inactivated cells	Inhibition of the colonization of <i>Helicobacter pylori</i> Interference with <i>Streptococcus mutans</i> biofilm formation	(Aiba et al. 2017) (Schwendicke et al. 2014)
<i>Lactobacillus casei</i> GG <i>Lactobacillus fermentum</i> BGHV110	Heat-inactivated cells Bioactive bacterial lysate	Treatment of diarrhea induced by rotavirus Activation of PINK1-dependent autophagy in HepG2 cells and alleviation of hepatotoxicity induced by acetaminophen	(Kaila et al. 1995) (Dinić et al. 2017)
<i>Faecalibacterium prausnitzii</i> A2-165	Cell-free supernatant, and extracellular vesicles	Up-regulation of anti-inflammatory cytokines (IL-10, TGF- β 2, and IL-1Ra) and down-regulation of some of the important pro-inflammatory cytokines such as IL-6, TNF- α , and TNF- β	(Jafari et al. 2019)
<i>Bacillus pumilus</i> SES <i>Lactobacillus plantarum</i> RG11, RG14, RI11, UL4, TL1, RS5	Indeterminate Cell-free supernatant	Inhibition of the colonization of pathogenic bacteria Antimicrobial activity <i>in vitro</i>	(Wang et al. 2019) (Kareem et al. 2014)
<i>Lactobacillus casei</i> ATCC 393	Cell-free supernatant, heat-killed sonicated, and live cells	Anti-proliferative activity in murine CT26 and human HT29 colon cancer cell lines	(Tiptiri-Kourpeti et al. 2016)
<i>Bifidobacterium</i> sp	Cell-free supernatant	Producing bacteriocins against pathogenic bacteria and yeasts	(Bali, Panesar, and Bera 2016)
<i>Lactobacillus casei</i> ATCC334	Cell-free supernatant, and Ferrichrome	Induction of apoptosis by the activation of c-jun N-terminal kinase	(Konishi et al. 2016)
<i>Lactobacillus rhamnosus</i> SHA111, SHA12, and SHA13	Cell-free supernatant	Induction of apoptosis by up-regulation of BAD, BAX, Caspase-3, Caspase-8, Caspase-9, and down-regulation of BCL-2 genes	(Rajoka et al. 2019)
<i>Lactobacillus rhamnosus</i> MD 14	Cell-free supernatant	Anti-genotoxic and cytotoxic potential against Caco-2 and HT-29 Human Colon Cancer Cells	(Sharma, Chandel, and Shukla 2020)
<i>Clostridium butyricum</i> sp	Short-chain fatty acids	Suppresses the Wnt/ β -catenin signaling pathway and modulate the gut microbiota composition	(Chen et al. 2020)
<i>Lactobacillus acidophilus</i> GG <i>Lactobacillus plantarum</i> I-UL4	Indeterminate Bacteriocin	Prevention of necrotizing enterocolitis Prevention of the colonization of <i>Aeromonas hydrophila</i> in fish	(Underwood 2019) (Foo et al. 2019)
<i>Lactobacillus brevis</i> SBC8803 <i>L. paracasei</i>	Polyphosphates Exopolysaccharides	Enhancement of the epithelial barrier and homeostasis Induction of apoptosis through down-regulation of the anti-apoptotic genes, and up-regulation of pro-apoptotic genes	(Segawa et al. 2011) (Rahbar Saadat et al. 2020)
<i>Pediococcus acidilactici</i> NCDC 252	Exopolysaccharides	Anti-oxidant and anti-cancer activity on human colon cancer cell line (HCT116)	(Kumar et al. 2020)

receptor proteins or blocking RBD on S proteins, or hindering RdRp to counter any effect of COVID-19 by postbiotic molecules paving a way that can be valuable in the treatment of COVID-19 until some better therapeutic option will be available (Anwar et al. 2020). In another study, it was reported that the postbiotics of *L. plantarum* L-137 also inhibited H1N1 flu virus infection through stimulating innate immune responses and producing Interferons (INF). Therefore, the soluble postbiotics derived from *L. plantarum* L-137, *L. gasseri* TMC0356, and *L. plantarum* 06CC2 can be applied as potential anti-viral agents in pharmaceutical products for the treatment of viral infections (Maeda et al. 2009; Takeda et al. 2011).

The role of postbiotics in immunomodulation

A body of evidence confirms that there is a complex relationship between beneficial gut microbes (e.g. probiotics), immune system function, and the host's health (Sun, Wang, and Jiang 2010). In recent years, scientific reports have demonstrated that a large part of the immunomodulatory effects of probiotics is related to

their derived postbiotics (de Almada et al. 2016). The postbiotics derived from LAB can interact swiftly with epithelial and immune cells to activate innate immunity, which provides an instantaneous defense to the host (Parkin and Cohen 2001; Taverniti and Guglielmetti 2011). In this regard, the finding of an *in vitro* study showed that both the live probiotics and derived postbiotics of *L. gasseri* TMC0356 can exert admissible immunomodulatory effects, but the postbiotics interestingly induced a further increase in the secretion of IL-12 compared with the live probiotics (Miyazawa et al. 2011). The special chemical structure of the cell-wall of postbiotics derived from *L. rhamnosus* HN001 leads to an increase in the phagocytic activity of leucocytes, which in turn improves immune system function (Gill and Rutherford 2001). It is noteworthy that the postbiotics derived from different strains of LAB induce an extensive range of immunomodulatory effects. The parent microbial strain, preparation method, and the maintenance of optimal dosage of postbiotics in a delivery system are the main factors that influence the immunomodulatory activity of postbiotics (Table 4) (Chuang et al. 2007; C. C. Ou et al. 2011).

Table 4. In vitro and in vivo immunomodulatory activities of postbiotics.

Immunomodulatory activities			
Species	Postbiotics	Benefits	References
<i>Bifidobacterium bifidum</i> BGN4	Cell-free extracts, purified cell-walls, and supernatants	Immunomodulatory activity in RAW 264.7 cells	(Lee et al. 2002)
<i>Faecalibacterium prausnitzii</i> A2-165	Cytosolic fraction	Immunomodulatory activity in Caco-2 cells	(Sokol et al. 2008)
A mixture of <i>Bifidobacterium</i> sp., <i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Lactobacillus gasseri</i> , and <i>Lactobacillus helveticus</i>	Cytoplasmic extract and cell-wall components	Immunomodulatory activity in RAW 264.7 macrophage cell line	(Tejada-Simon and Pestka 1999)
<i>Bacillus coagulans</i>	Cell-wall components	Immunomodulation and anti-inflammatory effect on human polymorphonuclear cells Production of IgA	(Jensen et al. 2010)
<i>Bifidobacterium breve</i> C50 and <i>Streptococcus thermophilus</i> 065	Heat inactivated cells	Production of IgA	(Campeotto et al. 2011)
<i>Bifidobacterium breve</i> M 16-V	Live and heat-killed cells	Suppression of pro-inflammatory cytokine production	(Sugahara et al. 2017)
<i>Lactobacillus acidophilus</i> A2, <i>L. gasseri</i> A5	Heat-killed cells	Modulation of the immune response <i>in vitro</i>	(Chuang et al. 2007)
<i>Lactobacillus plantarum</i> 06CC2	Heat-killed cells	Reduced influenza symptoms due to the immunomodulatory effect	(Takeda et al. 2011)
<i>Lactobacillus johnsonii</i> La1, <i>Lactobacillus acidophilus</i> La10	Lipoteichoic acids	Immunomodulatory activity in human HT29 cells	(Vidal, Donnet-Hughes, and Granato 2002)
<i>Lactobacillus plantarum</i> K8	Lipoteichoic acids	Immunomodulatory activity in human monocyte THP-1 cells	(Kim et al. 2011)
<i>Lactobacillus rhamnosus</i> OLL2838	Live and heat-killed cells	Barrier protective activity	(Miyauchi, Morita, and Tanabe 2009)
<i>Lactobacillus paracasei</i> MCC1849	Heat-killed cells	Induction of IgA production, up-regulation of IL-12p40, IL-10, IL-21, STAT4, and Bcl-6 gene expression	(Arai et al. 2018)
<i>Lactobacillus acidophilus</i> LB	Heat-killed cells	Reduced cellular permeability in intestinal Caco-2/TG7 cells	(Liévin-Le Moal, Sarrazin-Davila, and Servin 2007)
<i>Lactobacillus plantarum</i> L-137	Heat-killed cells	Enhancement of <i>in vitro</i> and <i>in vivo</i> immunomodulatory activity	(Fujiki et al. 2012)
<i>Lactobacillus reuteri</i> CRL1098	Cell-free supernatant	Anti-inflammatory activity	(De Marco et al. 2018)
<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , and <i>Lactobacillus reuteri</i>	Cell-free supernatant	Reducing PGE-2 and IL-8 expression	(De Marco et al. 2018)
<i>Enterococcus faecium</i> and <i>Lactococcus lactis</i>	Cell-free supernatant	Cytoprotective and anti-inflammatory properties	(Dowdell et al. 2020)
The mixture of <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus fermentum</i> , and <i>Enterococcus faecium</i>	Cell-free supernatant	Enhancement of <i>in vitro</i> and <i>in vivo</i> immunomodulatory activity	(Chen et al. 2013)
<i>Lactobacillus rhamnosus</i> KL37	Exopolysaccharides	Regulation of T cell-dependent immune responses in different inflammatory diseases	(Nowak et al. 2020)
<i>Lactobacillus Casei</i> DG	Indeterminate	Reduction of the inflammatory mucosal response in an <i>ex-vivo</i> organ culture model of post-infectious irritable bowel syndrome	(Compare et al. 2017)
<i>Lactobacillus rhamnosus</i> GG	Surface layer proteins	Anti-inflammatory properties through reduction of inflammatory cytokines (TNF- α and IL-6)	(Qi et al. 2020)

IgA, Immunoglobulin A; IL, interleukin; PGE2, Prostaglandin E2; TNF- α , tumor necrosis factor- α .

The role of postbiotics in the maintenance of intestinal barrier

The epithelial barrier is characterized as a primary defense line of the intestine and comprises a mucous layer, an adhesive layer of gut cells, and antimicrobial peptides that prevent epithelial harm induced by pathogenic bacteria and their toxins as well as foreign antigens and other harmful substances (Bermudez-Brito et al. 2012; Piqué, Berlanga, and Miñana-Galbis 2019). The results of the related studies confirm that the consumption of beneficial microbes (in the

matrix of food/supplements) can be an appropriate strategy for maintaining the intestinal barrier (Martín et al. 2019). In this regard, there is a noteworthy association between probiotics/postbiotics and intestinal barrier function; the key mechanisms include repairing mucosal disruption induced by an extensive variety of pathological agents and inhibiting cytokine-induced epithelial impairments (Hou et al. 2018; Mujagic et al. 2017). A large part of the maintenance of the intestinal barrier by probiotics may depend on their special cell structures rather than their metabolism. In this regard, an animal model study revealed that the CWSs derived from

S. boulardii have a significant ability to protect the gut barrier by preserving intestinal permeability while decreasing microbial translocation (Generoso et al. 2011). Additionally, the presence of a wide range of the postbiotic components of *L. bulgaricus*, *S. thermophilus*, and *L. acidophilus* (1×10^9 cells/mL) in functional yogurt was shown to effectively inhibit gut barrier damage induced by various antigens via triggering Nitric Oxide (NO) synthesis through the activation of pro-inflammatory cytokines (Zeng et al. 2016).

The role of postbiotics in the treatment of colitis

Colitis is a chronic inflammatory disorder that affects the usual function of the intestine (X. Xiao et al. 2015; B. Zheng et al. 2014). Some postbiotics are derived from *Lactobacilli* and *Bifidobacteria* strains to exert positive health effects in the host via the prevention of the progression of colitis (Wasilewska, Zlotkowska, and Wroblewska 2019). In an in vitro study performed on the cell samples of patients with colitis disorder, it was demonstrated that the postbiotics derived from *B. bifidum* and *B. breve* have noteworthy anti-inflammatory effects on peripheral blood mononuclear cells. In this regard, the administration of postbiotics stimulated the generation of IL-10 (an anti-inflammatory cytokine that has a key role in regulating inflammatory responses) in peripheral blood mononuclear cells and prevented the production of IL-8 (a cytokine connected with inflammation) in intestinal epithelial cells (de Almada et al. 2016; Yan and Polk 2010). Colibiogen® is a commercial postbiotic product derived from *E. coli* and mainly comprises fatty acids, peptides, amino acids, and polysaccharides. In a murine model, regulated consumption of Colibiogen led to the improvement of colitis and general health status. The use of postbiotic components with health-promoting effects as commercial products, therefore, comprises a novel field in the treatment of colitis (Aguilar-Toalá et al. 2018).

The role of postbiotics in the treatment of diarrhea

Diarrhea is a well-known malady of the gastrointestinal system, which is frequently caused by microbial and viral infections; conventional cancer therapies such as radiotherapy can also lead to radiation-induced diarrhea in radio-oncology patients (Linn, Thu, and Win 2019). The body of clinical studies demonstrates that probiotics and their derived postbiotics unceasingly play important roles in reducing the symptoms of diarrhea (Lai et al. 2019; S.-D. Xiao et al. 2003). Some scientific reports have demonstrated that there is a positive association between the consumption of postbiotic supplements derived from *L. plantarum* and the reduction of diarrhea incidence. The possible mechanism for this phenomenon is through changes in mucosal structure (increased villi size and digestibility) and an augmented population of beneficial gut microbiota (Loh et al. 2014). The regular consumption of postbiotic capsules (from *L. acidophilus* LB) comprising around five billion non-viable cells in patients with chronic diarrhea leads to a decrease in the period of the disease and improves in fecal constancy, abdominal discomfort, bloating, and the perception of

imperfect evacuation (S. D. Xiao et al. 2002). In a clinical trial on patients undergoing diarrhea treatment (oral rehydration solution), the addition of a powder of postbiotics derived from *L. acidophilus* LB to the oral rehydration solution significantly reduced the period of the disease down to one day (Liévin-Le Moal, Sarrazin-Davila, and Servin 2007). Consequently, postbiotics can be introduced as promising tools for treating diarrhea without causing any serious side-effects.

The role of postbiotics in the treatment of bloating

Bloating is known as a very common gut disorder of all ages, which is reported about 16 to 31% of society (Barbosa and Vieira-Coelho 2020). Functional Bloating (FB) is distinguished in individuals with revolving indications of bloating who do not meet the clinical criteria of IBS or other gastrointestinal disorders (Jiang et al. 2008). Even though the meticulous pathophysiology of bloating is not fully determined to date. Several parameters are recognized to be involved and their relative involvement differs between persons. Some of the main possible mechanisms include; increasing intestinal gas generation, food intolerance, abdominal (small intestinal) distension as a result of the accumulation of luminal fluid, visceral hypersensitivity, abdominal diaphragmatic muscle dysfunction, constipation, changing the composition of gut microbiota, and Small Intestinal Bacterial Overgrowth (SIBO) (Foley et al. 2014; Iovino et al. 2014; Seo, Kim, and Oh 2013). SIBO is a prevalent gut dysbiosis that can be triggered by various factors such as excessive use of certain drugs (e.g. proton pump inhibitors), long-term reduction of gastric secretion that creates appropriate conditions for the growth and development of various microbial species (mainly Gram-negative, strict anaerobes, and *Enterococci*), and active *Helicobacter pylori* infection that can modify the balance and composition of gut microbiota, and in turn, leads to the presence of SIBO (Enko and Kriegshäuser 2017; Konrad et al. 2018). Recent double-blind, multicenter, RCTs performed by Burta et al. (2018), evaluated the safety and efficacy of a medical device (APT036) containing the intestinal mucosal bio-protector xyloglucan plus inactivated *L. reuteri* and *B. brevis*, and simethicone as a comparator in treating FB in adult patients. In this study the important result measure was safety and the efficacy was measured at each visit (on days 2, 10, 20) via individual-reported symptom severity (Likert scale) and abdominal circumference measurement. Besides, a hydrogen breath test was accomplished at baseline and end of treatment (on day 20). They established that study subjects have a great tolerance for both APT036 and simethicone and no side-effects were reported with either treatment strategy. The oral administration of APT036 for 20 successive days, created higher FB symptoms relief, mainly with abdominal distension and flatulence in comparison with simethicone. It is noteworthy that, the baseline hydrogen breath test established the attendance of SIBO in all investigated subjects, while at the end of treatment a significant reduction in mean hydrogen gas production was observed that it's was

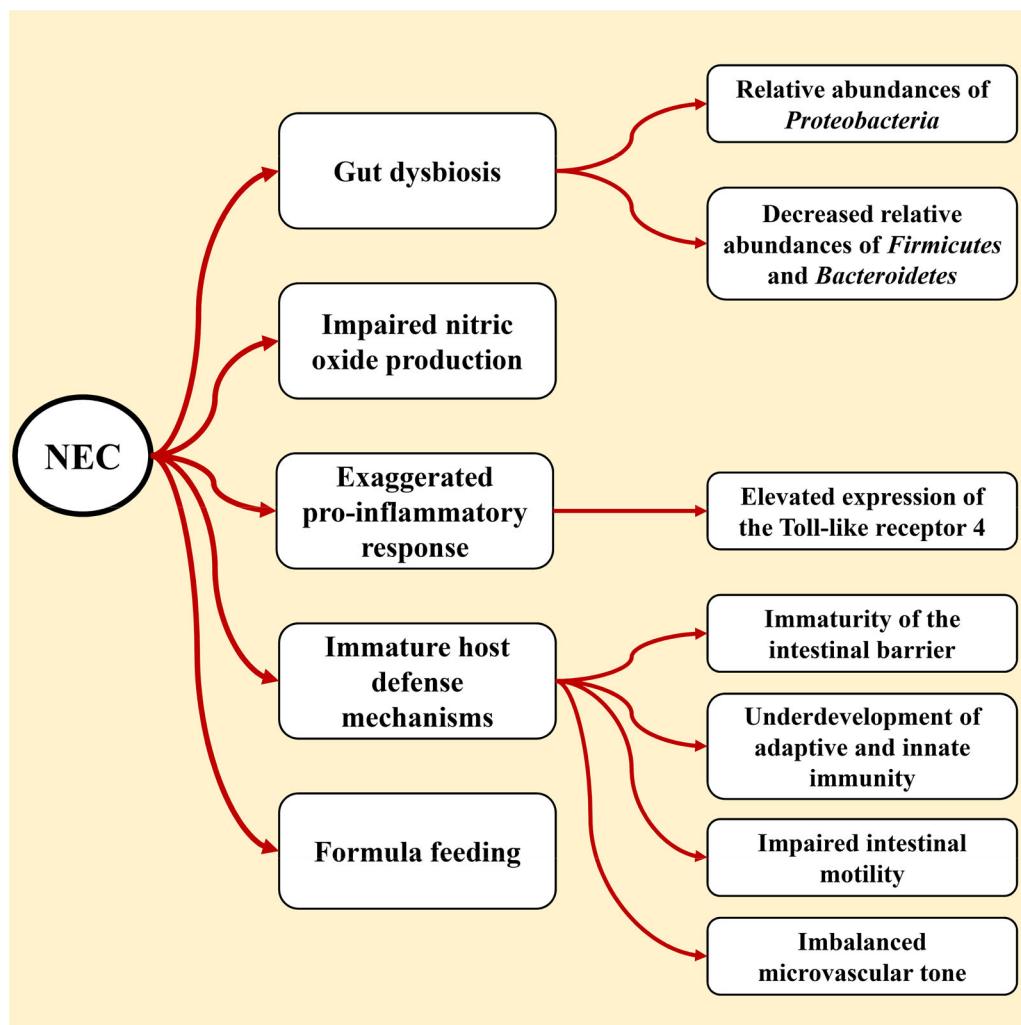


Figure 8. Main factors involved in NEC development.

below the threshold for a diagnosis of SIBO in both treatment strategies.

The role of postbiotics in the management of pediatric disorders

The mammalian gut is one of the densest microbial communities known, such that the number of microbial cells more than the number of eukaryotic cells constituting its host (Al Nabhan et al. 2019). This intestinal microbial community is contributing to the digestion of foodstuffs and the generation of vital constituents (e.g. secondary bile acids and various postbiotic components such as vitamins, and SCFAs), and possess a key function in direct and host-mediated defense versus the invasion of pathogenic germs (Homayouni-Rad et al. 2021; Sonnenburg and Bäckhed 2016). Nowadays, novel sequencing techniques provide the opportunity to precisely study the intestinal microbiota and the features of gut dysbiosis, in more detail, particularly in pediatric subjects (Piqué, Berlanga, and Miñana-Galbis 2019). According to the results of recent studies, the evolutionary status (mature/immature) of the intestinal mucosa, the composition and balance of gut microbiota, and also the balance between gut eubiosis and dysbiosis conditions in

infants, are the main factors that directly associated with both health promotion and development of relevant severe diseases (e.g. sepsis, necrotizing enterocolitis, and infantile colic) (Daelemans et al. 2018; Graspeuntner et al. 2019; Hoang et al. 2018).

At birth, microorganisms colonize entire body surfaces and strongly take part in the development of the immune system. In neonates, the gut microbiota is first formed via the nutrients and immunological (mother-derived immunoglobulin A (IgA)) constituents of milk and afterward alters upon the ingestion of solid food during weaning, creates a new stage in the growth and development of gut microbiota that determined via a huge increase in bacterial numbers, and progress unto a composition that is related to adult persons (Subramanian et al. 2014). Al Nabhan et al. (2019), in a mouse model, investigated the functionality (reactivity) of the gut immune system during the first weeks after birth and into adulthood. They established that at the weaning phase the gut microbiota stimulates a drastic immune response as a "weaning reaction" that is planned in time. Prevention of this immune response (weaning reaction) in turn, leads to pathological imprinting and increased susceptibility to chronic diseases such as allergic inflammation, colitis, and cancer later in life.

From the perspective of “therapeutic microbiology”, a probiotic strategy can signify an alternative therapy for enteric disorders. In this regard, among different probiotic strains of *Lactobacillus* and *Bifidobacterium* genera, the species of *B. breve* as dominant species colonized in the intestine of breast-fed infants and isolated from human milk, due to its biological functions (antimicrobial and immunomodulatory effects) and safe profiles (without transferring of resistance properties and cytotoxicity) are broadly used for the prevention and/or treatment of pediatric pathologies (Bozzi Cionci et al. 2018). On the other hand, one of the most important issues regarding neonates is the colonization of commensal gut bacteria that can be affected and altered by adding the exogenous probiotic strains to an infant's intestine ecosystem, (Campeotto et al. 2011) therefore, supporting the use of safe alternative agents such as prebiotic and postbiotic components, for example in neonates for the management of infantile colic or in enteral nutrition (Daelemans et al. 2018; Vandenplas et al. 2017). In this regard, Martinelli et al. (2017), in an open RCT, investigated the efficacy of a standardized extract of *Matricaria chamomilla*, *Melissa officinalis*, inactivated *L. acidophilus* HA122 and simethicone as a comparator in treating infantile colic. They established that the administration of *Matricaria chamomilla* and *Melissa officinalis* extracts in combination with inactivated *L. acidophilus* HA122 (at 2×10^9 CFU/2 mL dosage) significantly decreased the mean daily crying time in comparison with simethicone in children aged between two weeks and four months old. Besides, Vandenplas et al. (2017), in a pilot study evaluated the efficacy and safety of a medical device (APT198K) containing gut mucosal protector xyloglucan plus inactivated *L. reuteri* SGL01 and *B. breve* SGB01 (at 10^{10} CFU/g dosage) and a lactase dietary supplement as a comparator in treating 46 infants (three to 16 weeks old) with symptoms of infantile colic. The results demonstrated a meaningful reduction in the mean duration of crying episodes, which in turn create an opportunity for the combined application of xyloglucan and postbiotic components in the prevention and/or treatment of infantile colic with any undesirable side-effects, though further RCTs with larger statistical samples is needed.

The role of postbiotics in the prevention and treatment of necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is the most common and serious intestinal disorder that characteristically occurs in the second to the third week of life in the intestine of premature, formula-fed infants with a mortality rate of 30% (Papillon, Short, and Ford 2020). NEC is characterized by the invasion of pathogenic microbes, mucosal injury, local infection, inflammation, and full-thickness necrosis that can eventually create noticeable damages in the intestinal cell walls. The common symptoms of NEC may include bloating, decreased physical activity, decreased appetite, vomiting of bile, and presence of blood in the stool (N. M. Lee 2020). Furthermore, the economic load of NEC is very high accounting for up to one billion dollars in developed

countries annually such as the United States (Hodzic, Bolock, and Good 2017). A body of evidence confirms that NEC is a multifactorial disease and various factors which directly associated with the development of severe inflammation and intestinal injury have a key role in the establishment and development of NEC, particularly in infants and children, although the precise pathophysiology has not been completely explained (Figure 8) (Mosca, Gianni, and Rescigno 2019). The effectiveness of conventional therapies for NEC is inadequate to supportive care at diagnosis, therefore researchers have focused on the characterization of novel preventive strategies for NEC. In this regard, the administration of probiotics and their biological by-products (postbiotics) has been suggested as an effective strategy in diminishing the risk of expanding NEC in at-risk preterm infants (Patel and Underwood 2018). Taking into account the main risk factors illustrated in figure 8, postbiotics modulate the composition of gut microbiota, improve intestinal barrier integrity, immune system function, promote the NEC treatment effectiveness, and reduces its side-effects in patients due to possessing anti-oxidant, antimicrobial, immunomodulatory, and anti-inflammatory properties (Homayouni-Rad et al. 2021; Mosca, Gianni, and Rescigno 2019; Rad et al. 2020a). Notwithstanding considerable development, more studies are necessary to fully understand how postbiotics can be used as an effective therapy to either prevent or treat NEC in preterm infants.

The role of postbiotics in the prevention and treatment of gastrointestinal cancer

Cancer is one of the most common gastrointestinal disorders and recognized as multi-factorial diseases that overgrowth (irregular and/or uncontrolled) of cells is the typical properties (Siegel, Miller, and Jemal 2020). In positive cases of cancer, patients treated commonly with immunotherapy, radiotherapy, surgery, or chemotherapy mainly with 5-fluorouracil, and in some cases, these conventional therapies may be associated with adverse effects such as systemic toxicity, resistance to chemotherapy, and recurrence of cancer (Hosseiniyan, Haddad-Mashadrizeh, and Dolatabadi 2018; Yu et al. 2020). In this regard, a growing body of epidemiological evidence confirms the positive effects of gut beneficial microbes and their metabolites/byproducts (postbiotics) on the colon, liver, bladder, breast, and gastric cancers (Chuah et al. 2019). The anticancer activity of postbiotic components is primarily associated with their ability to connect with host immune cells via different G Protein-Coupled Receptors (GPRs), which in turn, leads to the activation of several signaling pathways, increase the innate immune system response, and reduction of inflammation (as an effective factor in tumor development) (Francescone, Hou, and Grivennikov 2014; Venegas et al. 2019). Several studies established the potential function of postbiotics in the prevention and treatment of cancer, mainly in gastrointestinal cancer cases (Gao et al. 2019; Schwartz, Rebeck, and Dantas 2019). The unique characteristic of postbiotic components is

their capability to differentiate between normal and tumor cells, which promotes the proliferation of normal cells but inhibits angiogenesis and stimulates apoptosis responses in cancerous cells (Davis and Milner 2009). In this context, butyrate-as histone deacetylase (HDAC) inhibitors (a new class of anti-cancer agents) exert opposing effects on normal and cancerous colonocytes. In normal colonocytes it functions as an oxidative energy source, however, it can inhibit the growth of cancerous colonocytes as a result of accumulation in the nucleus and functions as an HDAC inhibitor due to the Warburg effect and ineffective metabolization (Donohoe et al. 2012; Hamer et al. 2008). Besides, the outcomes from clinical investigations have established that the gut beneficial microbes and their derived postbiotics can be valuable tools in the promotion of cancer treatments effectiveness (Ou et al. 2013; Wang et al. 2014) through reducing the abdominal pain, vomiting, severity of diarrhea, stomatitis, atrophy, vascular damage, neural damage, skin erythema, and bowel toxicity compared to individuals who received a placebo (Österlund et al. 2007). Therefore postbiotics due to their positive role, in regulating cell cycle, stimulating differentiation, and up-regulating the pro-apoptotic pathways, have received much scientific attention and are considered as a novel approach for adjuvant therapy in individuals with cancer (Kurata et al. 2019; Rad, Aghebati-Maleki et al. 2020; Sharma and Shukla 2016). Moreover, further preclinical and clinical investigations are needed to design suitable carriers, delivery approaches, and evaluate the biological fate of postbiotics after oral administration, as well as investigate the precise mechanisms of cell-death responses in vivo conditions (Abbasi et al. 2020).

Conclusion

In a healthy gut, there is a constructive association between commensal microbiota and eukaryotic cells that leads to the promotion and progression of gut immune responses, thereby contributing to the maintenance of the eubiosis status in the host. One of the approaches to gain eubiosis is balancing the gut microbiota through the consumption of foods and dietary supplements containing probiotic/postbiotic ingredients. On the other hand, notwithstanding the confirmed health-promoting benefits of live probiotic cells, there are no pieces of evidence from long-term clinical trials that the intake of probiotic products promotes the health status of formerly healthy individuals. Besides, the outcomes of case report studies and the joint FAO/WHO guidelines have established that some probiotic cells (*L. buchneri*, *L. helveticus*, *L. hilgardii*, *Bifidobacterium*, *Bacillus*, and *S. thermophilus*) applied in pharmaceutical and food products may theoretically be associated with some undesirable side-effects, particularly in the pediatrics and also in patients with underlying diseases (Appel-da-Silva et al. 2017; Cohen 2018; Malagón-Rojas et al. 2020; Piqué, Berlanga, and Miñana-Galbis 2019). Currently, to overcome the problems related to the application of the live form of probiotics in terms of clinical, technological, and economic aspects, microbial-

derived biomolecules (postbiotics) were introduced as a potential alternative agent. A body of clinical evidence confirms that there is a complex relationship between the gut beneficial microbiota, their derived postbiotics, and the host's health status. Overall, these points suggest that postbiotic components may have superiority in terms of safety relative to their parent live cells, particularly important in infants and pediatrics, thus can be applied in delivery systems (pharmaceutical and/or functional foods) for inducing positive health effects without any serious undesirable side-effects. Currently, scientific literature approves that postbiotics can be applied as promising tools for both prevention and treatment strategies in gastrointestinal disorders. Future head-to-head trials are necessary to distinguish appropriate strains of parent cells, active compounds, biological function, optimal dosages, and administration frequency of postbiotics, including the assessment of the cost-effectiveness of postbiotics compared to alternative drugs.

Acknowledgements

The research protocol was approved & supported by the Student Research Committee, Tabriz University of Medical Sciences (grant number: 66361).

Author contributions

A.A and H.S.K created and executed the literature search, provided input on the literature tables, and wrote the manuscript. Z.Gh, S.S, P.H, Y.R.S, and N.Sh contributed significantly to the improvement of the manuscript. All authors read, made critical revisions to, and approved the final manuscript.

Declaration of interest

The authors declare that they have no conflicts of interest.

Abbreviations:

ISAPP	International Scientific Association for Probiotics and Prebiotics
IBS	Irritable Bowel Syndrome
FAO	Food and Agriculture Organization
WHO	World Health Organization
SCFAs	Short-Chain Fatty Acids
CWC	Cell-Wall Constituents
EPS	Exopolysaccharides
SLP	Surface-Layer Proteins
CFS	Cell-Free Supernatants
LAB	Lactic Acid Bacteria
COVID-19	coronavirus disease 2019
RCTs	Randomized Controlled Trials
INF	Interferons
NO	Nitric Oxide
FB	Functional Bloating
SIBO	Small Intestinal Bacterial Overgrowth
IgA	Immunoglobulin A
NEC	Necrotizing Enterocolitis
GIT	Gastrointestinal Tract
GPRs	G Protein-Coupled Receptors
EIEC	Enteroinvasive <i>E. coli</i>
EVs	Extracellular Vesicles.

ORCID

- Amin Abbasi  <http://orcid.org/0000-0001-5957-0540>
 Zahra Ghasempour  <http://orcid.org/0000-0002-9928-6808>
 Sahar Sabahi  <http://orcid.org/0000-0001-6064-1924>
 Hossein Samadi Kafil  <http://orcid.org/0000-0001-6026-8795>
 Paniz Hasannezhad  <http://orcid.org/0000-0001-6129-5736>
 Yalda Rahbar Saadat  <http://orcid.org/0000-0002-3295-404X>
 Nayyer Shahbazi  <http://orcid.org/0000-0003-2609-7712>

References

- Abbasi, A., A. Aghebati-Maleki, M. Yousefi, and L. Aghebati-Maleki. 2021. Probiotic intervention as a potential therapeutic for managing gestational disorders and improving pregnancy outcomes. *Journal of Reproductive Immunology* 143:103244. doi: [10.1016/j.jri.2020.103244](https://doi.org/10.1016/j.jri.2020.103244).
- Abbasi, A., N. Hajipour, P. Hasannezhad, A. Baghbanzadeh, and L. Aghebati-Maleki. 2020. Potential in vivo delivery routes of postbiotics. *Critical Reviews in Food Science and Nutrition* :1–39. doi: [10.1080/10408398.2020.1865260](https://doi.org/10.1080/10408398.2020.1865260).
- Aguilar-Toalá, J., R. García-Varela, H. García, V. Mata-Haro, A. González-Córdoba, B. Vallejo-Cordoba, and A. Hernández-Mendoza. 2018. Postbiotics: An evolving term within the functional foods field. *Trends in Food Science & Technology* 75:105–14. doi: [10.1016/j.tifs.2018.03.009](https://doi.org/10.1016/j.tifs.2018.03.009).
- Aiba, Y., H. Ishikawa, M. Tokunaga, and Y. Komatsu. 2017. Anti-Helicobacter pylori activity of non-living, heat-killed form of lactobacilli including Lactobacillus johnsonii No.1088. *FEMS Microbiology Letters* 364 (11):1–5. doi: [10.1093/femsle/fnx102](https://doi.org/10.1093/femsle/fnx102).
- Al Nabhani, Z., S. Dulauroy, R. Marques, C. Cousu, S. Al Bouenny, F. Déjardin, T. Sparwasser, M. Bérard, N. Cerf-Bensussan, and G. Eberl. 2019. A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. *Immunity* 50 (5):1276–88. e1275. doi: [10.1016/j.immuni.2019.02.014](https://doi.org/10.1016/j.immuni.2019.02.014).
- Albarracin, L., H. Kobayashi, H. Iida, N. Sato, T. Nochi, H. Aso, S. Salva, S. Alvarez, H. Kitazawa, and J. Villena. 2017. Transcriptomic analysis of the innate antiviral immune response in porcine intestinal epithelial cells: Influence of immunobiotic Lactobacilli. *Frontiers in Immunology* 8:57. doi: [10.3389/fimmu.2017.00057](https://doi.org/10.3389/fimmu.2017.00057).
- Amaretti, A., M. di Nunzio, A. Pompei, S. Raimondi, M. Rossi, and A. Bordoni. 2013. Antioxidant properties of potentially probiotic bacteria: In vitro and in vivo activities. *Applied Microbiology and Biotechnology* 97 (2):809–17. doi: [10.1007/s00253-012-4241-7](https://doi.org/10.1007/s00253-012-4241-7).
- Anwar, F., H. N. Altayb, F. A. Al-Abbas, A. L. Al-Malki, M. A. Kamal, and V. Kumar. 2020. Antiviral effects of probiotic metabolites on COVID-19. *Journal of Biomolecular Structure and Dynamics* 9:1–10. doi: [10.1080/07391102.2020.1775123](https://doi.org/10.1080/07391102.2020.1775123). PMC: 32475223.
- Appel-da-Silva, M. C., G. A. Narvaez, L. R. Perez, L. Drehmer, and J. Lewgoy. 2017. Saccharomyces cerevisiae var. boulardii fungemia following probiotic treatment. *Medical Mycology Case Reports* 18:15–7. doi: [10.1016/j.mmcr.2017.07.007](https://doi.org/10.1016/j.mmcr.2017.07.007).
- Arai, S., N. Iwabuchi, S. Takahashi, J-z Xiao, F. Abe, and S. Hachimura. 2018. Orally administered heat-killed Lactobacillus paracasei MCC1849 enhances antigen-specific IgA secretion and induces follicular helper T cells in mice. *PloS One* 13 (6):e0199018. doi: [10.1371/journal.pone.0199018](https://doi.org/10.1371/journal.pone.0199018).
- Bali, V., P. S. Panesar, and M. B. Bera. 2016. Trends in utilization of agro-industrial byproducts for production of bacteriocins and their biopreservative applications. *Critical Reviews in Biotechnology* 36 (2): 204–14. doi: [10.3109/07388551.2014.947916](https://doi.org/10.3109/07388551.2014.947916).
- Barbosa, R. S., and M. A. Vieira-Coelho. 2020. Probiotics and prebiotics: Focus on psychiatric disorders—a systematic review. *Nutrition Reviews* 78 (6):437–50. doi: [10.1093/nutrit/nuz080](https://doi.org/10.1093/nutrit/nuz080).
- Barros, C. P., J. T. Guimarães, E. A. Esmerino, M. C. K. Duarte, M. C. Silva, R. Silva, B. M. Ferreira, A. S. San’Ana, M. Q. Freitas, and A. G. Cruz. 2020. Paraprobiotics and postbiotics: Concepts and potential applications in dairy products. *Current Opinion in Food Science* 32:1–8. doi: [10.1016/j.cofs.2019.12.003](https://doi.org/10.1016/j.cofs.2019.12.003).
- Bermudez-Brito, M., J. Plaza-Díaz, S. Muñoz-Quezada, C. Gómez-Llorente, and A. Gil. 2012. Probiotic mechanisms of action. *Annals of Nutrition & Metabolism* 61 (2):160–74. doi: [10.1159/000342079](https://doi.org/10.1159/000342079).
- Bertelli, C., T. Pillonel, A. Torregrossa, G. Prod’hom, C. J. Fischer, G. Greub, and E. Giannoni. 2015. Bifidobacterium longum bacteremia in preterm infants receiving probiotics. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 60 (6):924–7. doi: [10.1093/cid/ciu946](https://doi.org/10.1093/cid/ciu946).
- Bianchi, F., M. Dall’Asta, D. Del Rio, A. Mangia, M. Musci, and F. Scazzina. 2011. Development of a headspace solid-phase microextraction gas chromatography-mass spectrometric method for the determination of short-chain fatty acids from intestinal fermentation. *Food Chemistry* 129 (1):200–5. doi: [10.1016/j.foodchem.2011.04.022](https://doi.org/10.1016/j.foodchem.2011.04.022).
- Bozzi Cionci, N., L. Baffoni, F. Gaggia, and D. Di Gioia. 2018. Therapeutic microbiology: The Role of Bifidobacterium breve as food supplement for the prevention/treatment of paediatric diseases. *Nutrients* 10 (11):1723. doi: [10.3390/nu10111723](https://doi.org/10.3390/nu10111723).
- Burta, O., C. Iacobescu, R. B. Mateescu, T. Nicolaie, N. Tiuca, and C. S. Pop. 2018. Efficacy and safety of APT036 versus simethicone in the treatment of functional bloating: A multicentre, randomised, double-blind, parallel group, clinical study. *Translational Gastroenterology and Hepatology* 3:72. doi: [10.21037/tgh.2018.09.11](https://doi.org/10.21037/tgh.2018.09.11).
- Burton, J. P., B. K. Drummond, C. N. Chilcott, J. R. Tagg, W. M. Thomson, J. D. Hale, and P. A. Wescombe. 2013. Influence of the probiotic Streptococcus salivarius strain M18 on indices of dental health in children: A randomized double-blind, placebo-controlled trial. *Journal of Medical Microbiology* 62 (Pt 6):875–884. doi: [10.1099/jmm.0.056663-0](https://doi.org/10.1099/jmm.0.056663-0).
- Campeotto, F., A. Suau, N. Kapel, F. Magne, V. Viallon, L. Ferraris, A.-J. Waligora-Dupriet, P. Soulaines, B. Leroux, N. Kalach, et al. 2011. A fermented formula in pre-term infants: Clinical tolerance, gut microbiota, down-regulation of faecal calprotectin and up-regulation of faecal secretory IgA. *The British Journal of Nutrition* 105 (12):1843–1851. doi: [10.1017/S0007114510005702](https://doi.org/10.1017/S0007114510005702).
- Campeotto, F., A. Suau, N. Kapel, F. Magne, V. Viallon, L. Ferraris, A.-J. Waligora-Dupriet, P. Soulaines, B. Leroux, N. Kalach, et al. 2011. A fermented formula in pre-term infants: Clinical tolerance, gut microbiota, down-regulation of faecal calprotectin and up-regulation of faecal secretory IgA. *The British Journal of Nutrition* 105 (12):1843–1851. doi: [10.1017/S0007114510005702](https://doi.org/10.1017/S0007114510005702).
- Castro-Bravo, N., J. M. Wells, A. Margolles, and P. Ruas-Madiedo. 2018. Interactions of Surface Exopolysaccharides From Bifidobacterium and Lactobacillus Within the Intestinal Environment. *Frontiers in Microbiology* 9:2426. doi: [10.3389/fmicb.2018.02426](https://doi.org/10.3389/fmicb.2018.02426). PMC: 30364185.
- Chen, D., D. Jin, S. Huang, J. Wu, M. Xu, T. Liu, W. Dong, X. Liu, S. Wang, W. Zhong, et al. 2020. Clostridium butyricum, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. *Cancer Letters* 469: 456–467. doi: [10.1016/j.canlet.2019.11.019](https://doi.org/10.1016/j.canlet.2019.11.019).
- Chen, C.-Y., H.-Y. Tsen, C.-L. Lin, C.-K. Lin, L.-T. Chuang, C.-S. Chen, and Y.-C. Chiang. 2013. Enhancement of the immune response against *Salmonella* infection of mice by heat-killed multi-species combinations of lactic acid bacteria. *Journal of Medical Microbiology* 62 (Pt 11):1657–1664. doi: [10.1099/jmm.0.061010-0](https://doi.org/10.1099/jmm.0.061010-0).
- Chuah, L.-O., H. L. Foo, T. C. Loh, N. B. M. Alitheen, S. K. Yeap, N. E. A. Mutalib, R. A. Rahim, and K. Yusoff. 2019. Postbiotic metabolites produced by Lactobacillus plantarum strains exert selective cytotoxicity effects on cancer cells. *BMC Complementary and Alternative Medicine* 19 (1):114. doi: [10.1186/s12906-019-2528-2](https://doi.org/10.1186/s12906-019-2528-2).
- Chuang, L., K.-G. Wu, C. Pai, P.-S. Hsieh, J.-J. Tsai, J.-H. Yen, and M.-Y. Lin. 2007. Heat-killed cells of lactobacilli skew the immune response toward T helper 1 polarization in mouse splenocytes and dendritic cell-treated T cells. *Journal of Agricultural and Food Chemistry* 55 (26):11080–11086. doi: [10.1021/jf071786o](https://doi.org/10.1021/jf071786o).
- Cicenia, A., A. Scirocco, M. Carabotti, L. Pallotta, M. Marignani, and C. Severi. 2014. Postbiotic activities of lactobacilli-derived factors. *Journal of Clinical Gastroenterology* 48 (Supplement 1):S18–S22. doi: [10.1097/MCG.0000000000000231](https://doi.org/10.1097/MCG.0000000000000231).

- Cohen, P. A. 2018. Probiotic safety-no guarantees. *JAMA Internal Medicine* 178 (12):1577–1578. doi: [10.1001/jamainternmed.2018.5403](https://doi.org/10.1001/jamainternmed.2018.5403).
- Compare, D., A. Rocco, P. Coccoli, D. Angrisani, C. Sgamato, B. Iovine, U. Salvatore, and G. Nardone. 2017. Lactobacillus casei DG and its postbiotic reduce the inflammatory mucosal response: An ex-vivo organ culture model of post-infectious irritable bowel syndrome. *BMC Gastroenterology* 17 (1):53. doi: [10.1186/s12876-017-0605-x](https://doi.org/10.1186/s12876-017-0605-x).
- Corr, S. C., Y. Li, C. U. Riedel, P. W. O'Toole, C. Hill, and C. G. Gahan. 2007. Bacteriocin production as a mechanism for the antiinfective activity of *Lactobacillus salivarius* UCC118. *Proceedings of the National Academy of Sciences* 104 (18):7617–7621. doi: [10.1073/pnas.0700440104](https://doi.org/10.1073/pnas.0700440104).
- Cuevas-González, P., A. Liceaga, and J. Aguilar-Toalá. 2020. Postbiotics and Paraprobiotics: From concepts to applications. *Food Research International* 136:109502. doi: [10.1016/j.foodres.2020.109502](https://doi.org/10.1016/j.foodres.2020.109502).
- Daelemans, S., L. Peeters, B. Hauser, and Y. Vandenplas. 2018. Recent advances in understanding and managing infantile colic. *F1000Research* 7:1426. doi: [10.12688/f1000research.149401](https://doi.org/10.12688/f1000research.149401).
- Davis, C. D., and J. A. Milner. 2009. Gastrointestinal microflora, food components and colon cancer prevention. *Journal of Nutritional Biochemistry* 20 (10):743–752. doi: [10.1016/j.jnutbio.2009.06.001](https://doi.org/10.1016/j.jnutbio.2009.06.001).
- de Almada, C. N., C. N. Almada, R. C. Martinez, and A. S. Sant'Ana. 2016. Paraprobiotics: Evidences on their ability to modify biological responses, inactivation methods and perspectives on their application in foods. *Trends in Food Science & Technology* 58:96–114. doi: [10.1016/j.tifs.2016.09.011](https://doi.org/10.1016/j.tifs.2016.09.011).
- De Marco, S., M. Sichetti, D. Muradyan, M. Piccioni, G. Traina, R. Pagiotti, and D. Pietrella. (2018). Probiotic cell-free supernatants exhibited anti-inflammatory and antioxidant activity on human gut epithelial cells and macrophages stimulated with LPS. *Evidence-Based Complementary and Alternative Medicine* 2018:1–12. doi: [10.1155/2018/1756308](https://doi.org/10.1155/2018/1756308).
- Decuyper, J. A., and N. A. Dierick. 2003. The combined use of triacylglycerols containing medium-chain fatty acids and exogenous lipolytic enzymes as an alternative to in-feed antibiotics in piglets: Concept, possibilities and limitations. An overview. *Nutrition Research Reviews* 16 (2):193–210. doi: [10.1079/NRR2003369](https://doi.org/10.1079/NRR2003369).
- Denev, P., M. Kratchanova, M. Ciz, A. Lojek, O. Vasicek, P. Nedelcheva, D. Blazheva, R. Toshkova, E. Gardeva, L. Yossifova, et al. 2014. Biological activities of selected polyphenol-rich fruits related to immunity and gastrointestinal health. *Food Chemistry* 157: 37–44. doi: [10.1016/j.foodchem.2014.02.022](https://doi.org/10.1016/j.foodchem.2014.02.022).
- Desrouillères, K., M. Millette, M. Jamshidian, B. Maherani, O. Fortin, and M. Lacroix. 2016. Cancer preventive effect of a specific probiotic fermented milk components and cell walls extracted from a biomass containing *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 on male F344 rats treated with 1,2-dimethylhydrazine. *Journal of Functional Foods* 26:373–384. doi: [10.1016/j.jff.2016.08.005](https://doi.org/10.1016/j.jff.2016.08.005).
- Devirgiliis, C., P. Zinno, and G. Perozzi. 2013. Update on antibiotic resistance in foodborne *Lactobacillus* and *Lactococcus* species. *Frontiers in Microbiology* 4:301. doi: [10.3389/fmicb.2013.00301](https://doi.org/10.3389/fmicb.2013.00301).
- Di Cerbo, A., B. Palmieri, M. Aponte, J. C. Morales-Medina, and T. Iannitti. 2016. Mechanisms and therapeutic effectiveness of lactobacilli. *Journal of Clinical Pathology* 69 (3):187–203. doi: [10.1136/jclinpath-2015-202976](https://doi.org/10.1136/jclinpath-2015-202976).
- Dinić, M., J. Lukić, J. Djokić, M. Milenović, I. Strahinić, N. Golić, and J. Begović. 2017. Lactobacillus fermentum postbiotic-induced autophagy as potential approach for treatment of acetaminophen hepatotoxicity. *Frontiers in Microbiology* 8:594. doi: [10.3389/fmicb.2017.00594](https://doi.org/10.3389/fmicb.2017.00594).
- do Carmo, M. S., C. Itapary dos Santos, M. C. Araújo, J. A. Girón, E. S. Fernandes, and V. Monteiro-Neto. 2018. Probiotics, mechanisms of action, and clinical perspectives for diarrhea management in children. *Food & Function* 9 (10):5074–5095. doi: [10.1039/c8fo00376a](https://doi.org/10.1039/c8fo00376a).
- Doern, C. D., S. T. Nguyen, F. Afolabi, and C.-A D. Burnham. 2014. Probiotic-associated aspiration pneumonia due to *Lactobacillus rhamnosus*. *Journal of Clinical Microbiology* 52 (8):3124–3126. doi: [10.1128/JCM.01065-14](https://doi.org/10.1128/JCM.01065-14).
- Donohoe, D. R., L. B. Collins, A. Wali, R. Bigler, W. Sun, and S. J. Bultman. 2012. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. *Molecular Cell* 48 (4):612–626. doi: [10.1016/j.molcel.2012.08.033](https://doi.org/10.1016/j.molcel.2012.08.033).
- Doron, S., and D. R. Snydman. 2015. Risk and safety of probiotics. *Clinical Infectious Diseases* 60 (suppl_2):S129–S134. doi: [10.1093/cid/civ085](https://doi.org/10.1093/cid/civ085).
- Dowdell, P., S. Chankhamhaengdecha, W. Panbangred, T. Janvilisri, and A. Aroonnuual. 2020. Probiotic activity of *Enterococcus faecium* and *Lactococcus lactis* isolated from Thai fermented sausages and their protective effect against *Clostridium difficile*. *Probiotics and Antimicrobial Proteins* 12 (2):641–648. doi: [10.1007/s12602-019-09536-7](https://doi.org/10.1007/s12602-019-09536-7).
- Encarnacion, C. O., A. M. Loranger, A. Bharatkumar, and G. H. Almassi. 2016. Bacterial endocarditis caused by *Lactobacillus acidophilus* leading to rupture of sinus of Valsalva aneurysm. *Texas Heart Institute Journal* 43 (2):161–164. doi: [10.14503/THIJ-15-5121](https://doi.org/10.14503/THIJ-15-5121).
- Enko, D., and G. Kriegshäuser. 2017. Functional 13C-urea and glucose hydrogen/methane breath tests reveal significant association of small intestinal bacterial overgrowth in individuals with active *Helicobacter pylori* infection. *Clinical Biochemistry* 50 (1–2):46–49. doi: [10.1016/j.clinbiochem.2016.08.017](https://doi.org/10.1016/j.clinbiochem.2016.08.017).
- Fanning, S., L. J. Hall, M. Cronin, A. Zomer, J. MacSharry, D. Goulding, M. O'Connell Motherway, F. Shanahan, K. Nally, G. Dougan, et al. 2012. Bifidobacterial surface-exopolysaccharide facilitates commensal-host interaction through immune modulation and pathogen protection. *Proceedings of the National Academy of Sciences* 109 (6):2108–2113. doi: [10.1073/pnas.1115621109](https://doi.org/10.1073/pnas.1115621109).
- Fijan, S. 2014. Microorganisms with claimed probiotic properties: An overview of recent literature. *International Journal of Environmental Research and Public Health* 11 (5):4745–4767. doi: [10.3390/ijerph110504745](https://doi.org/10.3390/ijerph110504745).
- Foley, A., R. Burgell, J. S. Barrett, and P. R. Gibson. 2014. Management strategies for abdominal bloating and distension. *Gastroenterology & Hepatology* 10 (9):561–571.
- Foo, H. L., T. C. Loh, N. E. A. Mutalib, and R. A. Rahim. 2019. Chapter 21 the Myth and therapeutic potentials of postbiotics. In *Microbiome and metabolome in diagnosis, therapy, and other strategic applications*, ed. J. Faintuch and S. Faintuch, 201–211. Cambridge: Academic Press. doi: [10.1016/b978-0-12-815249-2-00021-x](https://doi.org/10.1016/b978-0-12-815249-2-00021-x).
- Francesconi, R., V. Hou, and S. I. Grivennikov. 2014. Microbiome, inflammation and cancer. *The Cancer Journal* 20 (3):181–189. doi: [10.1097/PPO.0000000000000048](https://doi.org/10.1097/PPO.0000000000000048).
- Franko, B., M. Vaillant, C. Recule, E. Vautrin, J. Brion, and P. Pavese. 2013. *Lactobacillus paracasei* endocarditis in a consumer of probiotics. *Médecine et Maladies Infectieuses* 43 (4):171–173. doi: [10.1016/j.medmal.2013.01.007](https://doi.org/10.1016/j.medmal.2013.01.007).
- Freitas, F., V. D. Alves, and M. A. Reis. 2011. Advances in bacterial exopolysaccharides: From production to biotechnological applications. *Trends in Biotechnology* 29 (8):388–398. doi: [10.1016/j.tibtech.2011.03.008](https://doi.org/10.1016/j.tibtech.2011.03.008).
- Fujiki, T., Y. Hirose, Y. Yamamoto, and S. Murosaki. 2012. Enhanced immunomodulatory activity and stability in simulated digestive juices of *Lactobacillus plantarum* L-137 by heat treatment. *Bioscience, Biotechnology, and Biochemistry* 76 (5):918–922. doi: [10.1271/bbb.110919](https://doi.org/10.1271/bbb.110919).
- Galimberti, A., A. Bruno, V. Mezzasalma, F. De Mattia, I. Bruni, and M. Labra. 2015. Emerging DNA-based technologies to characterize food ecosystems. *Food Research International* 69:424–433. doi: [10.1016/j.foodres.2015.01.017](https://doi.org/10.1016/j.foodres.2015.01.017).
- Gao, J., Y. Li, Y. Wan, T. Hu, L. Liu, S. Yang, Z. Gong, Q. Zeng, Y. Wei, W. Yang, et al. 2019. A novel postbiotic from *Lactobacillus rhamnosus* GG with a beneficial effect on intestinal barrier function. *Frontiers in Microbiology* 10:477. doi: [10.3389/fmicb.2019.00477](https://doi.org/10.3389/fmicb.2019.00477).
- Gareau, M. G., P. M. Sherman, and W. A. Walker. 2010. Probiotics and the gut microbiota in intestinal health and disease. *Nature*

- Reviews Gastroenterology & Hepatology* 7 (9):503–514. doi: [10.1038/nrgastro.2010.117](https://doi.org/10.1038/nrgastro.2010.117).
- Generoso, S. V., M. L. Viana, R. G. Santos, R. M. Arantes, F. S. Martins, J. R. Nicoli, J. A. Machado, M. I. T. Correia, and V. N. Cardoso. 2011. Protection against increased intestinal permeability and bacterial translocation induced by intestinal obstruction in mice treated with viable and heat-killed *Saccharomyces boulardii*. *European Journal of Nutrition* 50 (4):261–269. doi: [10.1007/s00394-010-0134-7](https://doi.org/10.1007/s00394-010-0134-7).
- Gezginc, Y., I. Akyol, E. Kuley, and F. Özogul. 2013. Biogenic amines formation in *Streptococcus thermophilus* isolated from home-made natural yogurt. *Food Chemistry* 138 (1):655–662. doi: [10.1016/j.foodchem.2012.10.138](https://doi.org/10.1016/j.foodchem.2012.10.138).
- Gill, H., and K. Rutherford. 2001. Viability and dose-response studies on the effects of the immunoenhancing lactic acid bacterium *Lactobacillus rhamnosus* in mice. *British Journal of Nutrition* 86 (2): 285–289. doi: [10.1079/BJN2001402](https://doi.org/10.1079/BJN2001402).
- Graspeuntner, S., S. Waschina, S. Künzel, N. Twisselmann, T. K. Rausch, K. Cloppenborg-Schmidt, J. Zimmermann, D. Viemann, E. Herting, W. Göpel, et al. 2019. Gut dysbiosis with Bacilli dominance and accumulation of fermentation products precedes late-onset sepsis in preterm infants. *Clinical Infectious Diseases* 69 (2):268–277. doi: [10.1093/cid/ciy882](https://doi.org/10.1093/cid/ciy882).
- Guéniche, A., P. Bastien, J. M. Ovigne, M. Kermici, G. Courchay, V. Chevalier, L. Breton, and I. Castiel-Higounenc. 2009. Bifidobacterium longum lysate, a new ingredient for reactive skin. *Experimental Dermatology* 19 (8):e1–e8. doi: [10.1111/j.1600-0625.2009.00932.x](https://doi.org/10.1111/j.1600-0625.2009.00932.x).
- Haghshenas, B., M. Haghshenas, Y. Nami, A. Y. Khosrourshahi, N. Abdullah, A. Barzegari, R. Rosli, and M. S. Hejazi. 2016. Probiotic assessment of *Lactobacillus plantarum* 15HN and *Enterococcus mundtii* 50H isolated from traditional dairies microbiota. *Advanced Pharmaceutical Bulletin* 6 (1):37–47. doi: [10.15171/apb.2016.007](https://doi.org/10.15171/apb.2016.007).
- Hamer, H. M., D. Jonkers, K. Venema, S. Vanhoutvin, F. Troost, and R. J. Brummer. 2008. Review article: The role of butyrate on colonic function. *Alimentary Pharmacology & Therapeutics* 27 (2):104–119. doi: [10.1111/j.1365-2036.2007.03562.x](https://doi.org/10.1111/j.1365-2036.2007.03562.x).
- Hasan, A., B. A. Paray, A. Hussain, F. A. Qadir, F. Attar, F. M. Aziz, M. Sharifi, H. Derakhshankhah, B. Rasti, M. Mehrabi, et al. 2020. A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin. *Journal of Biomolecular Structure & Dynamics*. 1–9. doi: [10.1080/07391102.2020.1754293](https://doi.org/10.1080/07391102.2020.1754293). PMC: 32274964.
- Hoang, T. K., B. He, T. Wang, D. Q. Tran, J. M. Rhoads, and Y. Liu. 2018. Protective effect of *Lactobacillus reuteri* DSM 17938 against experimental necrotizing enterocolitis is mediated by Toll-like receptor 2. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 315 (2):G231–G240. doi: [10.1152/ajpgi.00084.2017](https://doi.org/10.1152/ajpgi.00084.2017).
- Hodzic, Z., A. M. Bolock, and M. Good. 2017. The role of mucosal immunity in the pathogenesis of necrotizing enterocolitis. *Frontiers in Pediatrics* 5:40. doi: [10.3389/fped.2017.00040](https://doi.org/10.3389/fped.2017.00040).
- Homayouni-Rad, A., L. Aghebati Maleki, H. Samadi Kafil, and A. Abbasi. 2021. Postbiotics: A novel strategy in food allergy treatment. *Critical Reviews in Food Science and Nutrition* 61 (3):492–499. doi: [10.1080/10408398.2020.1738333](https://doi.org/10.1080/10408398.2020.1738333).
- Homayouni-Rad, A., H. Fathi-Zavoshti, N. Douroud, N. Shahbazi, and A. Abbasi. 2020. Evaluating the Role of Postbiotics as a New Generation of Probiotics in Health and Diseases. *Journal of Ardabil University of Medical Sciences* 19 (4):381–399. doi: [10.29252/jarums.19.4.381](https://doi.org/10.29252/jarums.19.4.381).
- Homayouni-Rad, A., H. Samadi Kafil, H. Fathi Zavoshti, N. Shahbazi, and A. Abbasi. 2020. Therapeutically Effects of Functional Postbiotic Foods. *Clinical Excellence* 10 (2):33–52.
- Hosseiniyan, S.-A., A. Haddad-Mashadrizeh, and S. Dolatabadi. 2018. Simulation and Stability Assessment of Anti-EpCAM Immunotoxin for Cancer Therapy. *Advanced Pharmaceutical Bulletin* 8 (3): 447–455. doi: [10.15171/apb.2018.052](https://doi.org/10.15171/apb.2018.052).
- Hou, Q., L. Ye, H. Liu, L. Huang, Q. Yang, J. Turner, and Q. Yu. 2018. *Lactobacillus* accelerates ISCs regeneration to protect the integrity of intestinal mucosa through activation of STAT3 signaling pathway induced by LPLs secretion of IL-22. *Cell Death and Differentiation* 25 (9):1657–1670. doi: [10.1038/s41418-018-0070-2](https://doi.org/10.1038/s41418-018-0070-2).
- Hsiao, W. W. L., C. Metz, D. P. Singh, and J. Roth. 2008. The microbes of the intestine: An introduction to their metabolic and signaling capabilities. *Endocrinology and Metabolism Clinics of North America* 37 (4):857–871. doi: [10.1016/j.ecl.2008.08.006](https://doi.org/10.1016/j.ecl.2008.08.006).
- Hynönen, U., and A. Palva. 2013. *Lactobacillus* surface layer proteins: Structure, function and applications. *Applied Microbiology and Biotechnology* 97 (12):5225–5243. doi: [10.1007/s00253-013-4962-2](https://doi.org/10.1007/s00253-013-4962-2).
- Iovino, P., C. Bucci, F. Tremolaterra, A. Santonicola, and G. Chiarioni. 2014. Bloating and functional gastro-intestinal disorders: Where are we and where are we going? *World Journal of Gastroenterology* 20 (39):14407–14419. doi: [10.3748/wjg.v20.i39.14407](https://doi.org/10.3748/wjg.v20.i39.14407).
- Ishikawa, H., E. Kutsukake, T. Fukui, I. Sato, T. Shirai, T. Kurihara, N. Okada, H. Danbara, M. Toba, N. Kohda, et al. 2010. Oral administration of heat-killed *Lactobacillus plantarum* strain b240 protected mice against *Salmonella enterica* Serovar Typhimurium. *Bioscience, Biotechnology, and Biochemistry* 74 (7):1338–1342. doi: [10.1271/bbb.90871](https://doi.org/10.1271/bbb.90871).
- Ismail, B. 2017. The use of probiotics as vaccine vectors to prevent viral infections. In *New insights on antiviral probiotics*, 47–60. Cham: Springer International Publishing. doi: [10.1007/978-3-319-49688-7-2](https://doi.org/10.1007/978-3-319-49688-7-2).
- Jafari, B., R. A. K. Nejad, F. Vaziri, and S. D. Siadat. 2019. Evaluation of the effects of extracellular vesicles derived from *Faecalibacterium prausnitzii* on lung cancer cell line. *Biologia* 74 (7):889–898. doi: [10.2478/s11756-019-00229-8](https://doi.org/10.2478/s11756-019-00229-8).
- Jamalkandi, S. A., A. Ahmadi, I. Ahrari, J. Salimian, M. Karimi, and M. Ghanei. 2020. Oral and nasal probiotic administration for the prevention and alleviation of allergic diseases, asthma and chronic obstructive pulmonary disease. *Nutrition Research Reviews*. 1–16. doi: [10.1017/S0954422420000116](https://doi.org/10.1017/S0954422420000116). PMC: 32281536.
- Jensen, G. S., K. F. Benson, S. G. Carter, and J. R. Endres. 2010. GanedenBC30™ cell wall and metabolites: Anti-inflammatory and immune modulating effects in vitro. *BMC Immunology* 11 (1):15. doi: [10.1186/1471-2172-11-15](https://doi.org/10.1186/1471-2172-11-15).
- Jiang, X., G. Locke, R. Choung, A. Zinsmeister, C. Schleck, and N. J. Talley. 2008. Prevalence and risk factors for abdominal bloating and visible distention: A population-based study. *Gut* 57 (6):756–763. doi: [10.1136/gut.2007.142810](https://doi.org/10.1136/gut.2007.142810).
- Johnson-Henry, K. C., K. E. Hagen, M. Gordonpour, T. A. Tompkins, and P. M. Sherman. 2007. Surface-layer protein extracts from *Lactobacillus helveticus* inhibit enterohaemorrhagic *Escherichia coli* O157:H7 adhesion to epithelial cells. *Cellular Microbiology* 9 (2): 356–367. doi: [10.1111/j.1462-5822.2006.00791.x](https://doi.org/10.1111/j.1462-5822.2006.00791.x).
- Joint, F. A. O. 2002. WHO working group report on drafting guidelines for the evaluation of probiotics in food. London, 30.
- Juturu, V., and J. C. Wu. 2018. Microbial production of bacteriocins: Latest research development and applications. *Biotechnology Advances* 36 (8):2187–2200. doi: [10.1016/j.biotechadv.2018.10.007](https://doi.org/10.1016/j.biotechadv.2018.10.007).
- Kaila, M., E. Isolauri, M. Saxelin, H. Arvilommi, and T. Vesikari. 1995. Viable versus inactivated *lactobacillus* strain GG in acute rotavirus diarrhoea. *Archives of Disease in Childhood* 72 (1):51–53. doi: [10.1136/adc.72.1.51](https://doi.org/10.1136/adc.72.1.51).
- Kareem, K. Y., F. Hooi Ling, L. Teck Chwen, O. May Foong, and S. Anjas Asmara. 2014. Inhibitory activity of postbiotic produced by strains of *Lactobacillus plantarum* using reconstituted media supplemented with inulin. *Gut Pathogens* 6 (1):23. doi: [10.1186/1757-4749-6-23](https://doi.org/10.1186/1757-4749-6-23).
- Karimi, N., V. Jabbari, A. Nazemi, K. Ganbarov, N. Karimi, A. Tanomand, S. Karimi, A. Abbasi, B. Yousefi, and E. Khodadadi. 2020. Thymol, cardamom and *Lactobacillus plantarum* nanoparticles as a functional candy with high protection against *Streptococcus mutans* and tooth decay. *Microbial Pathogenesis* 148:104481.
- Kawase, M., F. He, K. Miyazawa, A. Kubota, K. Yoda, and M. Hiramatsu. 2012. Orally administered heat-killed *Lactobacillus* gasseri TMC0356 can upregulate cell-mediated immunity in senescence-accelerated mice. *FEMS Microbiology Letters* 326 (2):125–130. doi: [10.1111/j.1574-6968.2011.02440.x](https://doi.org/10.1111/j.1574-6968.2011.02440.x).

- Khan, N., L. Mendonca, A. Dhariwal, G. Fontes, D. Menzies, J. Xia, M. Divangahi, and I. L. King. 2019. Intestinal dysbiosis compromises alveolar macrophage immunity to *Mycobacterium tuberculosis*. *Mucosal Immunology* 12 (3):772–783. doi: [10.1038/s41385-019-0147-3](https://doi.org/10.1038/s41385-019-0147-3).
- Khodaii, Z., S. M. H. Ghaderian, and M. M. Natanzi. 2017. Probiotic bacteria and their supernatants protect enterocyte cell lines from enteroinvasive *Escherichia coli* (EIEC) invasion. *International Journal of Molecular and Cellular Medicine* 6 (3):183–189. doi: [10.22088/acadpub.BUMS.6.3.183](https://doi.org/10.22088/acadpub.BUMS.6.3.183).
- Kim, K. W., S.-S. Kang, S.-J. Woo, O.-J. Park, K. B. Ahn, K.-D. Song, H.-K. Lee, C.-H. Yun, and S. H. Han. 2017. Lipoteichoic acid of probiotic *Lactobacillus plantarum* attenuates poly I:C-Induced IL-8 Production in Porcine Intestinal Epithelial Cells. *Frontiers in Microbiology* 8:1827. doi: [10.3389/fmicb.2017.01827](https://doi.org/10.3389/fmicb.2017.01827).
- Kim, M. J., S. Ku, S. Y. Kim, H. H. Lee, H. Jin, S. Kang, R. Li, T. V. Johnston, M. S. Park, and G. E. Ji. 2018. Safety Evaluations of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI. *International Journal of Molecular Sciences* 19 (5):1422. doi: [10.3390/ijms19051422](https://doi.org/10.3390/ijms19051422).
- Kim, H. G., S. Y. Lee, N. R. Kim, H. Y. Lee, M. Y. Ko, B. J. Jung, C. M. Kim, J. M. Lee, J. H. Park, S. H. Han, et al. 2011. *Lactobacillus plantarum* lipoteichoic acid down-regulated *Shigella flexneri* peptidoglycan-induced inflammation. *Molecular Immunology* 48 (4):382–391. doi: [10.1016/j.molimm.2010.07.011](https://doi.org/10.1016/j.molimm.2010.07.011).
- Kolling, Y., S. Salva, J. Villena, and S. Alvarez. 2018. Are the immunomodulatory properties of *Lactobacillus rhamnosus* CRL1505 peptidoglycan common for all *Lactobacilli* during respiratory infection in malnourished mice? *PLoS One* 13 (3):e0194034. doi: [10.1371/journal.pone.0194034](https://doi.org/10.1371/journal.pone.0194034).
- Konishi, H., M. Fujiya, H. Tanaka, N. Ueno, K. Moriuchi, J. Sasajima, K. Ikuta, H. Akutsu, H. Tanabe, and Y. Kohgo. 2016. Probiotic-derived ferrichrome inhibits colon cancer progression via JNK-mediated apoptosis. *Nature Communications* 7 (1):1–12. doi: [10.1038/ncomms12365](https://doi.org/10.1038/ncomms12365).
- Konrad, P., J. Chojnicki, A. Gąsiorowska, C. Rudnicki, A. Kaczka, and C. Chojnicki. 2018. Therapeutic efficacy of amoxicillin and rifaximin in patients with small intestinal bacterial overgrowth and *Helicobacter pylori* infection. *Przeglad Gastroenterologiczny* 13 (3): 213.
- Konstantinov, S. R., H. Smidt, W. M. de Vos, S. C. M. Bruijns, S. K. Singh, F. Valence, D. Molle, S. Lortal, E. Altermann, T. R. Klaenhammer, et al. 2008. S layer protein A of *Lactobacillus acidophilus* NCFM regulates immature dendritic cell and T cell functions. *Proceedings of the National Academy of Sciences of the United States of America* 105 (49):19474–19479. doi: [10.1073/pnas.0810305105](https://doi.org/10.1073/pnas.0810305105).
- Kopp, M. 2008. Probiotika in der Prävention und Therapie von Atopien. *Monatsschrift Kinderheilkunde* 156 (11):1084–1092. doi: [10.1007/s00112-008-1832-6](https://doi.org/10.1007/s00112-008-1832-6).
- Kuley, E., E. Balıkci, İ. Özogul, S. Gökdogan, and F. Özogul. 2012. Stimulation of cadaverine production by foodborne pathogens in the presence of *Lactobacillus*, *Lactococcus*, and *Streptococcus* spp. *Journal of Food Science* 77 (12):M650–M658. doi: [10.1111/j.1750-3841.2012.02825.x](https://doi.org/10.1111/j.1750-3841.2012.02825.x).
- Kulkarni, H. S., and C. C. Khoury. 2014. Sepsis associated with *Lactobacillus* bacteremia in a patient with ischemic colitis. *Indian Journal of Critical Care Medicine: Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine* 18 (9):606.
- Kumar, R., P. Bansal, J. Singh, and S. Dhanda. 2020. Purification, partial structural characterization and health benefits of exopolysaccharides from potential probiotic *Pediococcus acidilactici* NCDC 252. *Process Biochemistry* 99:79–86. doi: [10.1016/j.procbio.2020.08.028](https://doi.org/10.1016/j.procbio.2020.08.028).
- Kurata, N., N. Tokashiki, K. Fukushima, T. Misao, N. Hasuoka, K. Kitagawa, M. Mashimo, J. W. Regan, T. Murayama, and H. Fujino. 2019. Short chain fatty acid butyrate uptake reduces expressions of prostanoïd EP4 receptors and their mediation of cyclooxygenase-2 induction in HCA-7 human colon cancer cells. *European Journal of Pharmacology* 853:308–315. doi: [10.1016/j.ejphar.2019.04.014](https://doi.org/10.1016/j.ejphar.2019.04.014).
- Lai, H.-H., C.-H. Chiu, M.-S. Kong, C.-J. Chang, and C.-C. Chen. 2019. Probiotic *Lactobacillus casei*: Effective for Managing Childhood Diarrhea by Altering Gut Microbiota and Attenuating Fecal Inflammatory Markers. *Nutrients* 11 (5):1150. doi: [10.3390/nut11051150](https://doi.org/10.3390/nut11051150).
- Lee, N. M. 2020. Epidermal growth factor as a reliable marker of necrotizing enterocolitis in preterm neonates. *Clinical and Experimental Pediatrics* 63 (2):1–2.
- Lee, I.-C., S. Tomita, M. Kleerebezem, and P. A. Bron. 2013. The quest for probiotic effector molecules—unraveling strain specificity at the molecular level. *Pharmacological Research* 69 (1):61–74. doi: [10.1016/j.phrs.2012.09.010](https://doi.org/10.1016/j.phrs.2012.09.010).
- Lee, M. J., Z. L. Zang, E. Y. Choi, H. K. Shin, and G. E. Ji. 2002. Cytoskeleton reorganization and cytokine production of macrophages by *Bifidobacterial* cells and cell-free extracts. *Journal of Microbiology and Biotechnology* 12:398–405.
- Liévin-Le Moal, V., L. E. Sarrazin-Davila, and A. L. Servin. 2007. An experimental study and a randomized, double-blind, placebo-controlled clinical trial to evaluate the antisecretory activity of *Lactobacillus acidophilus* strain LB against nonrotavirus diarrhea. *Pediatrics* 120 (4):e795–e803. doi: [10.1542/peds.2006-2930](https://doi.org/10.1542/peds.2006-2930).
- Lim, H.-S., J.-E. Yeu, S.-P. Hong, and M.-S. Kang. 2018. Characterization of antibacterial cell-free supernatant from oral care probiotic *Weissella cibaria*. *Molecules* 23 (8):1984. doi: [10.3390/molecules23081984](https://doi.org/10.3390/molecules23081984).
- Linn, Y. H., K. K. Thu, and N. H. H. Win. 2019. Effect of probiotics for the prevention of acute radiation-induced diarrhoea among cervical cancer patients: A randomized double-blind placebo-controlled study. *Probiotics and Antimicrobial Proteins* 11 (2):638–647. doi: [10.1007/s12602-018-9408-9](https://doi.org/10.1007/s12602-018-9408-9).
- Liu, G., L. Ren, Z. Song, C. Wang, and B. Sun. 2015. Purification and characteristics of bifidocin A, a novel bacteriocin produced by *Bifidobacterium* animals BB04 from centenarians' intestine. *Food Control* 50:889–895. doi: [10.1016/j.foodcont.2014.10.049](https://doi.org/10.1016/j.foodcont.2014.10.049).
- Liu, Z., Z. Zhang, L. Qiu, F. Zhang, X. Xu, H. Wei, and X. Tao. 2017. Characterization and bioactivities of the exopolysaccharide from a probiotic strain of *Lactobacillus plantarum* WLPL04. *Journal of Dairy Science* 100 (9):6895–6905. doi: [10.3168/jds.2016-11944](https://doi.org/10.3168/jds.2016-11944).
- Loh, T., D. Choe, H. Foo, A. Sazili, and M. Bejo. 2014. Effects of feeding different postbiotic metabolite combinations produced by *Lactobacillus plantarum* strains on egg quality and production performance, faecal parameters and plasma cholesterol in laying hens. *BMC Veterinary Research* 10 (1):149. doi: [10.1186/1746-6148-10-149](https://doi.org/10.1186/1746-6148-10-149).
- Lukic, J., V. Chen, I. Strahinic, J. Begovic, H. Lev-Tov, S. C. Davis, M. Tomic-Canic, and I. Pastar. 2017. Probiotics or pro-healers: The role of beneficial bacteria in tissue repair. *Wound Repair and Regeneration : Official Publication of the Wound Healing Society [and] the European Tissue Repair Society* 25 (6):912–922. doi: [10.1111/wrr.12607](https://doi.org/10.1111/wrr.12607).
- Maeda, N., R. Nakamura, Y. Hirose, S. Muroski, Y. Yamamoto, T. Kase, and Y. Yoshikai. 2009. Oral administration of heat-killed *Lactobacillus plantarum* L-137 enhances protection against influenza virus infection by stimulation of type I interferon production in mice. *International Immunopharmacology* 9 (9):1122–1125. doi: [10.1016/j.intimp.2009.04.015](https://doi.org/10.1016/j.intimp.2009.04.015).
- Maia, L. P., Y. L. D. A. S. Levi, R. L. do Prado, C. d S. Santinoni, and J. A. Marsican. 2019. Effects of probiotic therapy on serum inflammatory markers: A systematic review and meta-analysis. *Journal of Functional Foods* 54:466–478. doi: [10.1016/j.jff.2019.01.051](https://doi.org/10.1016/j.jff.2019.01.051).
- Malagón-Rojas, J. N., A. Mantzari, S. Salminen, and H. Szajewska. 2020. Postbiotics for preventing and treating common infectious diseases in children: A systematic review. *Nutrients* 12 (2):389. doi: [10.3390/nu12020389](https://doi.org/10.3390/nu12020389).
- Manivasagan, P., and S.-K. Kim. 2014. Extracellular polysaccharides produced by marine bacteria. *Advances in Food and Nutrition Research* 72:79–94. doi: [10.1016/B978-0-12-800269-8.00005-1](https://doi.org/10.1016/B978-0-12-800269-8.00005-1). PMC: 25081078.
- Martín, R., C. Chamignon, N. Mhedbi-Hajri, F. Chain, M. Derrien, U. Escrivano-Vázquez, P. Garault, A. Cotillard, H. P. Pham, C. Chervaux, et al. 2019. The potential probiotic *Lactobacillus*

- rhamnosus CNCM I-3690 strain protects the intestinal barrier by stimulating both mucus production and cytoprotective response. *Scientific Reports* 9 (1):5398. doi: [10.1038/s41598-019-41738-5](https://doi.org/10.1038/s41598-019-41738-5).
- Martinelli, M., D. Ummarino, F. P. Giugliano, E. Sciorio, C. Tortora, D. Buzzese, D. De Giovanni, I. Rutigliano, S. Valenti, C. Romano, et al. 2017. Efficacy of a standardized extract of Matricariae chamomilla L., Melissa officinalis L. and tyndallized Lactobacillus acidophilus (HA 122) in infantile colic: An open randomized controlled trial. *Neurogastroenterology & Motility* 29 (12):e13145. doi: [10.1111/nmo.13145](https://doi.org/10.1111/nmo.13145).
- Miyuchi, E., H. Morita, and S. Tanabe. 2009. *Lactobacillus rhamnosus* alleviates intestinal barrier dysfunction in part by increasing expression of zonula occludens-1 and myosin light-chain kinase in vivo. *Journal of Dairy Science* 92 (6):2400–2408. doi: [10.3168/jds.2008-1698](https://doi.org/10.3168/jds.2008-1698).
- Miyazawa, K., F. He, M. Kawase, A. Kubota, K. Yoda, and M. Hiramatsu. 2011. Enhancement of immunoregulatory effects of *Lactobacillus gasseri* TMC0356 by heat treatment and culture medium. *Letters in Applied Microbiology* 53 (2):210–216. doi: [10.1111/j.1472-765X.2011.03093.x](https://doi.org/10.1111/j.1472-765X.2011.03093.x).
- Moghaddas Kia, E., Z. Ghasempour, S. Ghanbari, R. Pirmohammadi, and A. Ehsani. 2018. Development of probiotic yogurt by incorporation of milk protein concentrate (MPC) and microencapsulated *Lactobacillus paracasei* in gellan-caseinate mixture. *British Food Journal* 120 (7):1516–1528. doi: [10.1108/BFJ-12-2017-0668](https://doi.org/10.1108/BFJ-12-2017-0668).
- Mohamadshahi, M., M. Veissi, F. Haidari, H. Shahbazian, G.-A. Kaydani, and F. Mohammadi. 2014. Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes. *BioImpacts: BI* 4 (2):83.
- Moludi, J., M. Alizadeh, N. Lotfi Yagin, Y. Pasdar, S. M. Nachvak, H. Abdollahzad, and A. Sadeghpour Tabaei. 2018. New insights on atherosclerosis: A cross-talk between endocannabinoid systems with gut microbiota. *Journal of Cardiovascular and Thoracic Research* 10 (3): 129–137. doi: [10.15171/jcvtr.2018.21](https://doi.org/10.15171/jcvtr.2018.21).
- Moradi, M., K. Mardani, and H. Tajik. 2019. Characterization and application of postbiotics of *Lactobacillus* spp. on *Listeria monocytogenes* in vitro and in food models. *LWT* 111:457–464. doi: [10.1016/j.lwt.2019.05.072](https://doi.org/10.1016/j.lwt.2019.05.072).
- Mosca, F., M. L. Gianni, and M. Rescigno. 2019. Can postbiotics represent a new strategy for NEC? In *Probiotics and child gastrointestinal health: Advances in microbiology, infectious diseases and public health*. Vol. 10, 37–45. Cham: Springer International Publishing. doi: [10.1007/978-3-030-20584-2_4](https://doi.org/10.1007/978-3-030-20584-2_4).
- Mujagic, Z., P. de Vos, M. V. Boekschen, C. Govers, H.-J. H. M. Pieters, N. J. W. de Wit, P. A. Bron, A. A. M. Masclee, and F. J. Troost. 2017. The effects of *Lactobacillus plantarum* on small intestinal barrier function and mucosal gene transcription; a randomized double-blind placebo controlled trial. *Scientific Reports* 7 (1):40128. doi: [10.1038/srep40128](https://doi.org/10.1038/srep40128).
- Muñoz-González, C., C. Cueva, M. Ángeles Pozo-Bayón, and M. Victoria Moreno-Arribas. 2015. Ability of human oral microbiota to produce wine odorant aglycones from odourless grape glycosidic aroma precursors. *Food Chemistry* 187:112–119. doi: [10.1016/j.foodchem.2015.04.068](https://doi.org/10.1016/j.foodchem.2015.04.068).
- Nakamura, S., T. Kuda, C. An, T. Kanno, H. Takahashi, and B. Kimura. 2012. Inhibitory effects of *Leuconostoc mesenteroides* 1RM3 isolated from narezushi, a fermented fish with rice, on *Listeria monocytogenes* infection to Caco-2 cells and A/J mice. *Anaerobe* 18 (1):19–24. doi: [10.1016/j.anaerobe.2011.11.006](https://doi.org/10.1016/j.anaerobe.2011.11.006).
- Nowak, B., M. Śrótkę, M. Ciszek-Lenda, A. Skalkowska, A. Gamian, S. Górska, and J. Marcinkiewicz. 2020. Exopolysaccharide from *Lactobacillus rhamnosus* KL37 inhibits T cell-dependent immune response in mice. *Archivum Immunologiae et Therapiae Experimentalis* 68 (3):1–11. doi: [10.1007/s00005-020-00581-7](https://doi.org/10.1007/s00005-020-00581-7).
- Ordóñez, J. L., A. M. Troncoso, M. D. C. García-Parrilla, and R. M. Callejón. 2016. Recent trends in the determination of biogenic amines in fermented beverages—A review. *Analytica Chimica Acta* 939:10–25. doi: [10.1016/j.aca.2016.07.045](https://doi.org/10.1016/j.aca.2016.07.045).
- Österlund, P., T. Ruotsalainen, R. Korpela, M. Saxelin, A. Ollus, P. Valta, M. Kouri, I. Elomaa, and H. Joensuu. 2007. *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: A randomised study. *British Journal of Cancer* 97 (8): 1028–1034. doi: [10.1038/sj.bjc.6603990](https://doi.org/10.1038/sj.bjc.6603990).
- Ou, J., F. Carbonero, E. G. Zoetendal, J. P. DeLany, M. Wang, K. Newton, H. R. Gaskins, and S. J. D. O'Keefe. 2013. Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans. *The American Journal of Clinical Nutrition* 98 (1):111–120. doi: [10.3945/ajcn.112.056689](https://doi.org/10.3945/ajcn.112.056689).
- Ou, C. C., S. L. Lin, J. J. Tsai, and M. Y. Lin. 2011. Heat-killed lactic acid bacteria enhance immunomodulatory potential by skewing the immune response toward Th1 polarization. *Journal of Food Science* 76 (5):M260–M267. doi: [10.1111/j.1750-3841.2011.02161.x](https://doi.org/10.1111/j.1750-3841.2011.02161.x).
- Papadimitriou, K., G. Zoumpopoulou, B. Foligné, V. Alexandraki, M. Kazou, B. Pot, and E. Tsakalidou. 2015. Discovering probiotic microorganisms: In vitro, in vivo, genetic and omics approaches. *Frontiers in Microbiology* 6:58. doi: [10.3389/fmicb.2015.00058](https://doi.org/10.3389/fmicb.2015.00058).
- Papillon, S. C., S. S. Short, and H. R. Ford. 2020. Necrotizing enterocolitis. In *Pediatric surgery: General principles and newborn surgery*, 963–971. Berlin: Springer International Publishing. doi: [10.1007/978-3-662-43588-5_70](https://doi.org/10.1007/978-3-662-43588-5_70).
- Pararajasingam, A., and J. Ugwu. 2017. *Lactobacillus*: The not so friendly bacteria. *Case Reports* 2017:bcr-2016.
- Parkin, J., and B. Cohen. 2001. An overview of the immune system. *The Lancet* 357 (9270):1777–1789. doi: [10.1016/S0140-6736\(00\)04904-7](https://doi.org/10.1016/S0140-6736(00)04904-7).
- Patel, R. M., and M. A. Underwood. 2018. Probiotics and necrotizing enterocolitis. *Seminars in Pediatric Surgery* 27 (1): 39–46. doi: [10.1053/j.sempedsurg.2017.11.008](https://doi.org/10.1053/j.sempedsurg.2017.11.008).
- Patten, D. A., S. Leivers, M. J. Chadha, M. Maqsood, P. N. Humphreys, A. P. Laws, and A. Collett. 2014. The structure and immunomodulatory activity on intestinal epithelial cells of the EPSs isolated from *Lactobacillus helveticus* sp. Rosyjski and *Lactobacillus acidophilus* sp. 5e2. *Carbohydrate Research* 384:119–127. doi: [10.1016/j.carres.2013.12.008](https://doi.org/10.1016/j.carres.2013.12.008).
- Peng, M., Z. Tabashsum, M. Anderson, A. Truong, A. K. Houser, J. Padilla, A. Akmel, J. Bhatti, S. O. Rahaman, and D. Biswas. 2020. Effectiveness of probiotics, prebiotics, and prebiotic-like components in common functional foods. *Comprehensive Reviews in Food Science and Food Safety* 19 (4):1908–1933. doi: [10.1111/1541-4337.12565](https://doi.org/10.1111/1541-4337.12565).
- Piqué, N., M. Berlanga, and D. Miñana-Galbis. 2019. Health benefits of heat-killed (Tyndallized) probiotics: An overview. *International Journal of Molecular Sciences* 20 (10):2534. doi: [10.3390/ijms20102534](https://doi.org/10.3390/ijms20102534).
- Poli, A., G. Anzelmo, and B. Nicolaus. 2010. Bacterial exopolysaccharides from extreme marine habitats: Production, characterization and biological activities. *Marine Drugs* 8 (6):1779–1802. doi: [10.3390/md8061779](https://doi.org/10.3390/md8061779).
- Qi, S., Y. Cui, J. Liu, X. Luo, and H. Wang. 2020. *Lactobacillus rhamnosus* GG components, SLP, gDNA and CpG, exert protective effects on mouse macrophages upon lipopolysaccharide challenge. *Letters in Applied Microbiology* 70 (2):118–127. doi: [10.1111/lam.13255](https://doi.org/10.1111/lam.13255).
- Rad, A., A. Abbasi, A. Javadi, H. Pourjafar, M. Javadi, and M. Khaleghi. 2020. Comparing the microbial quality of traditional and industrial yogurts. *Biointerface Research in Applied Chemistry* 10 (4):6020–6025.
- Rad, A., A. Abbasi, H. Kafil, and K. Ganbarov. 2020. Potential pharmaceutical and food applications of postbiotics: A review. *Current Pharmaceutical Biotechnology* 21 (15):1576–1587. doi: [10.2174/1389201021666200516154833](https://doi.org/10.2174/1389201021666200516154833).
- Rad, A. H., L. Aghebati-Maleki, H. S. Kafil, and A. Abbasi. 2020. Molecular mechanisms of postbiotics in colorectal cancer prevention and treatment. *Critical Reviews in Food Science and Nutrition* 15: 1–17. doi: [10.1080/10408398.2020.1765310](https://doi.org/10.1080/10408398.2020.1765310).
- Rad, A. H., L. A. Maleki, H. S. Kafil, H. F. Zavoshti, and A. Abbasi. 2020a. Postbiotics as novel health-promoting ingredients in functional foods. *Health Promotion Perspectives* 10 (1):3–4. doi: [10.15171/hpp.2020.02](https://doi.org/10.15171/hpp.2020.02).
- Rad, A. H., L. A. Maleki, H. S. Kafil, H. F. Zavoshti, and A. Abbasi. 2020b. *Postbiotics as promising tools for cancer adjuvant therapy*.

- Advanced Pharmaceutical Bulletin* 11 (1):1–5. doi: 10.34172/apb.2021.007.
- Rahbar Saadat, Y., B. Pourghassem Gargari, A. Shahabi, Y. Nami, and A. Yari Khosroushahi. 2020. Prophylactic role of Lactobacillus Paracasei exopolysaccharides on colon cancer cells through apoptosis not ferroptosis. *Pharmaceutical Sciences*. doi: 10.34172/PS.2020.39. [Online ahead of print].
- Rai, A. K., A. Pandey, and D. Sahoo. 2019. Biotechnological potential of yeasts in functional food industry. *Trends in Food Science & Technology* 83:129–137. doi: 10.1016/j.tifs.2018.11.016.
- Rajoka, M. S. R., H. Zhao, H. M. Mehwish, N. Li, Y. Lu, Z. Lian, D. Shao, M. Jin, Q. Li, L. Zhao, et al. 2019. Anti-tumor potential of cell free culture supernatant of Lactobacillus rhamnosus strains isolated from human breast milk. *Food Research International* 123:286–297. doi: 10.1016/j.foodres.2019.05.002.
- Rossoni, R. D., M. dos Santos Velloso, P. P. de Barros, J. A. de Alvarenga, J. D. dos Santos, A. C. C. dos Santos Prado, F. de Camargo Ribeiro, A. L. Anbinder, and J. C. Junqueira. 2018. Inhibitory effect of probiotic Lactobacillus supernatants from the oral cavity on Streptococcus mutans biofilms. *Microbial Pathogenesis* 123:361–367. doi: 10.1016/j.micpath.2018.07.032.
- Saadat, Y. R., A. Y. Khosroushahi, and B. P. Gargari. 2019. A comprehensive review of anticancer, immunomodulatory and health beneficial effects of the lactic acid bacteria exopolysaccharides. *Carbohydrate Polymers* 217:79–89.
- Saber, A., B. Alipour, Z. Faghfoori, and A. Yari Khosroushahi. 2017. Cellular and molecular effects of yeast probiotics on cancer. *Critical Reviews in Microbiology* 43 (1):96–115. doi: 10.1080/1040841X.2016.1179622.
- Sanders, M. E., L. M. A. Akkermans, D. Haller, C. Hammerman, J. Heimbach, G. Hörmannsperger, G. Huys, D. D. Levy, F. Lutgendorff, D. Mack, et al. 2010. Safety assessment of probiotics for human use. *Gut Microbes* 1 (3):164–185. doi: 10.4161/gmic.1.3.12127.
- Sanders, M. E., F. Guarner, R. Guerrant, P. R. Holt, E. M. Quigley, R. B. Sartor, P. M. Sherman, and E. A. Mayer. 2013. An update on the use and investigation of probiotics in health and disease. *Gut* 62 (5):787–796. doi: 10.1136/gutjnl-2012-302504.
- Sarkar, A., and S. Mandal. 2016. Bifidobacteria-Insight into clinical outcomes and mechanisms of its probiotic action. *Microbiological Research* 192:159–171. doi: 10.1016/j.micres.2016.07.001.
- Schwartz, D. J., O. N. Rebeck, and G. Dantas. 2019. Complex interactions between the microbiome and cancer immune therapy. *Critical Reviews in Clinical Laboratory Sciences* 56 (8):567–585. doi: 10.1080/10408363.2019.1660303.
- Schwendicke, F., K. Horb, S. Kneist, C. Dörfer, and S. Paris. 2014. Effects of heat-inactivated Bifidobacterium BB12 on cariogenicity of Streptococcus mutans in vitro. *Archives of Oral Biology* 59 (12): 1384–1390. doi: 10.1016/j.archoralbio.2014.08.012.
- Segawa, S., M. Fujiya, H. Konishi, N. Ueno, N. Kobayashi, T. Shigyo, and Y. Kohgo. 2011. Probiotic-derived polyphosphate enhances the epithelial barrier function and maintains intestinal homeostasis through integrin-p38 MAPK pathway. *PloS One* 6 (8):e23278. doi: 10.1371/journal.pone.0023278.
- Seo, A. Y., N. Kim, and D. H. Oh. 2013. Abdominal bloating: Pathophysiology and treatment. *Journal of Neurogastroenterology and Motility* 19 (4):433–453. doi: 10.5056/jnm.2013.19.4.433.
- Sharma, M., D. Chandel, and G. Shukla. 2020. Antigenotoxicity and cytotoxic potentials of metabiotics extracted from isolated probiotic, Lactobacillus rhamnosus MD 14 on Caco-2 and HT-29 human colon cancer cells. *Nutrition and Cancer* 72 (1):110–119. doi: 10.1080/01635581.2019.1615514.
- Sharma, M., and G. Shukla. 2016. Metabiotics: One step ahead of probiotics; an insight into mechanisms involved in anticancerous effect in colorectal cancer. *Frontiers in Microbiology* 7:1940. doi: 10.3389/fmicb.2016.01940.
- Shenderov, B. A. 2013. Metabiotics: Novel idea or natural development of probiotic conception. *Microbial Ecology in Health and Disease* 24 (1):20399.
- Shigwedha, N., L. Sichel, L. Jia, and L. Zhang. 2014. Probiotical Cell Fragments (PCFs) as “Novel Nutraceutical Ingredients. *Journal of Biosciences and Medicines* 2 (3):43–55. doi: 10.4236/jbm.2014.23007.
- Siegel, R. L., K. D. Miller, and A. Jemal. 2020. Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians* 70 (1):7–30. doi: 10.3322/caac.21590.
- Sokol, H., B. Pigneur, L. Watterlot, O. Lakhdari, L. G. Bermúdez-Humarán, J. J. Gratadoux, S. Blugeon, C. Bridonneau, J. P. Furet, G. Corthier, et al. 2008. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proceedings of the National Academy of Sciences of the United States of America* 105 (43):16731–16736. J. https://f1000.com/1135879. doi: 10.1073/pnas.0804812105.
- Sonnenburg, J. L., and F. Bäckhed. 2016. Diet-microbiota interactions as moderators of human metabolism. *Nature* 535 (7610):56–64. doi: 10.1038/nature18846.
- Subramanian, S., S. Huq, T. Yatsunenko, R. Haque, M. Mahfuz, M. A. Alam, A. Benezra, J. DeStefano, M. F. Meier, B. D. Muegge, et al. 2014. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature* 510 (7505):417–421. doi: 10.1038/nature13421.
- Sugahara, H., R. Yao, T. Odamaki, and J. Z. Xiao. 2017. Differences between live and heat-killed bifidobacteria in the regulation of immune function and the intestinal environment. *Beneficial Microbes* 8 (3):463–472. doi: 10.3920/BM2016.0158.
- Sun, P., J. Wang, and Y. Jiang. 2010. Effects of Enterococcus faecium (SF68) on immune function in mice. *Food Chemistry* 123 (1):63–68. doi: 10.1016/j.foodchem.2010.03.128.
- Sunnmola, A. A., O. O. Ogbole, T. O. Faleye, A. Adetoye, J. A. Adeniji, and F. A. Ayeni. 2019. Antiviral potentials of Lactobacillus plantarum, Lactobacillus amylovorus, and Enterococcus hirae against selected Enterovirus. *Folia Microbiologica* 64 (2):257–264. doi: 10.1007/s12223-018-0648-6.
- Suresh Kumar, A., K. Mody, and B. Jha. 2007. Bacterial exopolysaccharides—a perception. *Journal of Basic Microbiology* 47 (2):103–117. doi: 10.1002/jobm.200610203.
- Sutherland, I. W. 1990. *Biotechnology of microbial exopolysaccharides*. Vol. 9. Cambridge: Cambridge University Press.
- Takeda, S., M. Takeshita, Y. Kikuchi, B. Dashnyam, S. Kawahara, H. Yoshida, W. Watanabe, M. Muguruma, and M. Kurokawa. 2011. Efficacy of oral administration of heat-killed probiotics from Mongolian dairy products against influenza infection in mice: Alleviation of influenza infection by its immunomodulatory activity through intestinal immunity. *International Immunopharmacology* 11 (12):1976–1983. doi: 10.1016/j.intimp.2011.08.007.
- Tannock, G. W., J. B. Luchansky, L. Miller, H. Connell, S. Thode-Andersen, A. A. Mercer, and T. R. Klaenhammer. 1994. Molecular characterization of a plasmid-borne (pGT633) erythromycin resistance determinant (ermGT) from Lactobacillus reuteri 100-63. *Plasmid* 31 (1):60–71. doi: 10.1006/plas.1994.1007.
- Tarrerias, A. L., V. Costil, F. Vicari, J. C. Létard, P. Adenis-Lamarre, A. Aisène, D. Batistelli, G. Bonnau, S. Carpentier, P. Dalbiès, et al. 2011. The effect of inactivated Lactobacillus LB fermented culture medium on symptom severity: observational investigation in 297 patients with diarrhea-predominant irritable bowel syndrome. *Digestive Diseases* 29 (6):588–591. doi: 10.1159/000332987.
- Taverniti, V., and S. Guglielmetti. 2011. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: Proposal of paraprobiotic concept). *Genes & Nutrition* 6 (3): 261–274. doi: 10.1007/s12263-011-0218-x.
- Taylor, A. L., J. A. Dunstan, and S. L. Prescott. 2007. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: A randomized controlled trial. *Journal of Allergy and Clinical Immunology* 119 (1):184–191. doi: 10.1016/j.jaci.2006.08.036.
- Tejada-Simon, M. V., and J. J. Pestka. 1999. Proinflammatory cytokine and nitric oxide induction in murine macrophages by cell wall and cytoplasmic extracts of lactic acid bacteria. *Journal of Food Protection* 62 (12):1435–1444. doi: 10.4315/0362-028x-62.12.1435.

- Tiptiri-Kourpeti, A., K. Spyridopoulou, V. Santarmaki, G. Aindelis, E. Tompoulidou, E. E. Lamprianidou, G. Saxami, P. Ypsilantis, E. S. Lampri, C. Simopoulos, et al. 2016. Lactobacillus casei exerts anti-proliferative effects accompanied by apoptotic cell death and up-regulation of TRAIL in colon carcinoma cells. *PloS One* 11 (2): e0147960. doi: [10.1371/journal.pone.0147960](https://doi.org/10.1371/journal.pone.0147960).
- Tomasik, P., and P. Tomasik. 2020. Probiotics, non-dairy prebiotics and postbiotics in nutrition. *Applied Sciences* 10 (4):1470. doi: [10.3390/app10041470](https://doi.org/10.3390/app10041470).
- Underwood, M. A. 2019. Probiotics and the prevention of necrotizing enterocolitis. *Journal of Pediatric Surgery* 54 (3):405–412. doi: [10.1016/j.jpedsurg.2018.08.055](https://doi.org/10.1016/j.jpedsurg.2018.08.055).
- Vaghef-Mehrabany, E., L. Vaghef-Mehrabany, M. Asghari-Jafarabadi, A. Homayouni-Rad, K. Issazadeh, and B. Alipour. 2017. Effects of probiotic supplementation on lipid profile of women with rheumatoid arthritis: A randomized placebo-controlled clinical trial. *Health Promotion Perspectives* 7 (2):95–101. doi: [10.15171/hpp.2017.17](https://doi.org/10.15171/hpp.2017.17).
- Vahabnezhad, E., A. B. Mochon, L. J. Wozniak, and D. A. Ziring. 2013. Lactobacillus bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. *Journal of Clinical Gastroenterology* 47 (5):437–439. doi: [10.1097/MCG.0b013e318279abf0](https://doi.org/10.1097/MCG.0b013e318279abf0).
- Vandenplas, Y., A. Bacarea, M. Marusteri, V. Bacarea, M. Constantin, and M. Manolache. 2017. Efficacy and safety of APT198K for the treatment of infantile colic: A pilot study. *Journal of Comparative Effectiveness Research* 6 (2):137–144. doi: [10.2217/cer-2016-0059](https://doi.org/10.2217/cer-2016-0059).
- Vanichanan, J., V. Chávez, A. Wanger, A. M. De Golovine, and K. J. Vigil. 2016. Carbapenem-resistant Lactobacillus intra-abdominal infection in a renal transplant recipient with a history of probiotic consumption. *Infection* 44 (6):793–796. doi: [10.1007/s15010-016-0903-1](https://doi.org/10.1007/s15010-016-0903-1).
- Venegas, D. P., K. Marjorie, G. Landskron, M. J. González, R. Quera, G. Dijkstra, H. J. Harmsen, K. N. Faber, and M. A. Hermoso. 2019. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Frontiers in Immunology* 10:277. doi: [10.3389/fimmu.2019.00277](https://doi.org/10.3389/fimmu.2019.00277).
- Vidal, K., A. Donnet-Hughes, and D. Granato. 2002. Lipoteichoic acids from Lactobacillus johnsonii strain La1 and Lactobacillus acidophilus strain La10 antagonize the responsiveness of human intestinal epithelial HT29 cells to lipopolysaccharide and gram-negative bacteria. *Infection and Immunity* 70 (4):2057–2064. doi: [10.1128/IAI.70.4.2057-2064.2002](https://doi.org/10.1128/IAI.70.4.2057-2064.2002).
- Vinogradov, E., I. Sadovskaya, T. Grard, and M.-P. Chapot-Chartier. 2016. Structural studies of the rhamnose-rich cell wall polysaccharide of Lactobacillus casei BL23. *Carbohydrate Research* 435:156–161. doi: [10.1016/j.carres.2016.10.002](https://doi.org/10.1016/j.carres.2016.10.002).
- Wang, C., J. Chuprom, Y. Wang, and L. Fu. 2020. Beneficial bacteria for aquaculture: Nutrition, bacteriostasis and immunoregulation. *Journal of Applied Microbiology* 128 (1):28–40. doi: [10.1111/jam.14383](https://doi.org/10.1111/jam.14383).
- Wang, K., W. Li, X. Rui, X. Chen, M. Jiang, and M. Dong. 2014. Characterization of a novel exopolysaccharide with antitumor activity from Lactobacillus plantarum 70810. *International Journal of Biological Macromolecules* 63:133–139. doi: [10.1016/j.ijbiomac.2013.10.036](https://doi.org/10.1016/j.ijbiomac.2013.10.036).
- Wasilewska, E., D. Zlotkowska, and B. Wroblewska. 2019. Yogurt starter cultures of Streptococcus thermophilus and Lactobacillus bulgaricus ameliorate symptoms and modulate the immune response in a mouse model of dextran sulfate sodium-induced colitis. *Journal of Dairy Science* 102 (1):37–53. doi: [10.3168/jds.2018-14520](https://doi.org/10.3168/jds.2018-14520).
- Weber, E., Q. Reynaud, F. Suy, A. Gagneux-Brunon, A. Carricajo, A. Guillot, and E. Botelho-Nevers. 2015. Bifidobacterium species bacteremia: Risk factors in adults and infants. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America* 61 (3):482–484. doi: [10.1093/cid/civ347](https://doi.org/10.1093/cid/civ347).
- Whitfield, G. B., L. S. Marmont, and P. L. Howell. 2015. Enzymatic modifications of exopolysaccharides enhance bacterial persistence. *Frontiers in Microbiology* 6:471. doi: [10.3389/fmicb.2015.00471](https://doi.org/10.3389/fmicb.2015.00471).
- Wu, Z., D. Pan, Y. Guo, Y. Sun, and X. Zeng. 2015. Peptidoglycan diversity and anti-inflammatory capacity in Lactobacillus strains. *Carbohydrate Polymers* 128:130–137. doi: [10.1016/j.carbpol.2015.04.026](https://doi.org/10.1016/j.carbpol.2015.04.026).
- Wu, M.-H., T.-M. Pan, Y.-J. Wu, S.-J. Chang, M.-S. Chang, and C.-Y. Hu. 2010. Exopolysaccharide activities from probiotic bifidobacterium: Immunomodulatory effects (on J774A.1 macrophages) and antimicrobial properties. *Int J Food Microbiol* 144 (1):104–110. doi: [10.1016/j.ijfoodmicro.2010.09.003](https://doi.org/10.1016/j.ijfoodmicro.2010.09.003).
- Xiao, S.-D., Z. De Zhang, H. Lu, S. H. Jiang, H. Y. Liu, G. S. Wang, G. M. Xu, Z. B. Zhang, G. J. Lin, and G. L. Wang. 2003. Multicenter, randomized, controlled trial of heat-killed Lactobacillus acidophilus LB in patients with chronic diarrhea. *Advances in Therapy* 20 (5):253–260. doi: [10.1007/BF02849854](https://doi.org/10.1007/BF02849854).
- Xiao, X., J. Kim, Q. Sun, D. Kim, C.-S. Park, T.-S. Lu, and Y. Park. 2015. Preventive effects of cranberry products on experimental colitis induced by dextran sulphate sodium in mice. *Food Chemistry* 167:438–446. doi: [10.1016/j.foodchem.2014.07.006](https://doi.org/10.1016/j.foodchem.2014.07.006).
- Xiao, S. D., D. Z. Zhang, H. Lu, S. H. Jiang, H. Y. Liu, G. S. Wang, G. M. Xu, Z. B. Zhang, G. J. Lin, and G. L. Wang. 2002. Multicenter randomized controlled trial of heat-killed Lactobacillus acidophilus LB in patients with chronic diarrhea. *Chinese Journal of Digestive Diseases* 3 (4):167–171. doi: [10.1046/j.1443-9573.2002.00095.x](https://doi.org/10.1046/j.1443-9573.2002.00095.x).
- Yan, F., H. Cao, T. L. Cover, R. Whitehead, M. K. Washington, and D. B. Polk. 2007. Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. *Gastroenterology* 132 (2):562–575. doi: [10.1053/j.gastro.2006.11.022](https://doi.org/10.1053/j.gastro.2006.11.022).
- Yan, F., and D. B. Polk. 2010. Disruption of NF- κ B signalling by ancient microbial molecules: Novel therapies of the future? *Gut* 59 (4):421–426. doi: [10.1136/gut.2009.179614](https://doi.org/10.1136/gut.2009.179614).
- Yu, B., Z. Wang, L. Almutairi, S. Huang, and M.-H. Kim. 2020. Harnessing iron-oxide nanoparticles towards the improved bactericidal activity of macrophage against *Staphylococcus aureus*. *Nanomedicine: Nanotechnology, Biology and Medicine* 24:102158. doi: [10.1016/j.nano.2020.102158](https://doi.org/10.1016/j.nano.2020.102158).
- Zeng, J., J. Jiang, W. Zhu, and Y. Chu. 2016. Heat-killed yogurt-containing lactic acid bacteria prevent cytokine-induced barrier disruption in human intestinal Caco-2 cells. *Annals of Microbiology* 66 (1): 171–178. doi: [10.1007/s13213-015-1093-2](https://doi.org/10.1007/s13213-015-1093-2).
- Zhang, Z., R. Cai, W. Zhang, Y. Fu, and N. Jiao. 2017. A novel exopolysaccharide with metal adsorption capacity produced by a marine bacterium *Alteromonas* sp. *Marine Drugs* 15 (6):175. doi: [10.3390/md15060175](https://doi.org/10.3390/md15060175).
- Zheng, B., J. van Bergenhenegouwen, S. Overbeek, H. J. van de Kant, J. Garssen, G. Folkerts, P. Vos, M. E. Morgan, and A. D. Kraneveld. 2014. Bifidobacterium breve attenuates murine dextran sodium sulfate-induced colitis and increases regulatory T cell responses. *Plos One* 9 (5):e95441. doi: [10.1371/journal.pone.0095441](https://doi.org/10.1371/journal.pone.0095441).
- Zheng, M., R. Zhang, X. Tian, X. Zhou, X. Pan, and A. Wong. 2017. Assessing the risk of probiotic dietary supplements in the context of antibiotic resistance. *Frontiers in Microbiology* 8:908. doi: [10.3389/fmicb.2017.00908](https://doi.org/10.3389/fmicb.2017.00908).