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Current Research in Microbiology

Chapter 1

Applications of Probiotic Bacteria and Dairy Foods in Health

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Abstract

The intestinal microbiota composition has a great impact on physiology and health, since commensal bacteria are crucial to maintain homeostasis and immune regulation of the gut. Consequently, disturbances of this microbiota, a process known as dysbiosis, have severe implications for the host health such as the rise of many gastrointestinal (GI) problems; including inflammatory disorders like the Inflammatory Bowel Diseases (IBD), mucositis, as well as colorectal cancer (CRC). The consumption of probiotics with beneficial effects is a promising tool to help treating such disorders. Indeed, they modulate diverse biological mechanisms involved in GI homeostasis and have been commonly used to reduce such disorders. In this chapter, we present the molecular mechanisms triggered by probiotic bacteria to modulate the gut physiology during gastrointestinal disorder and the importance of the gastrointestinal stresses tolerance as a limiting factors for probiotic application. Moreover, we focus on the emergence of functional probiotic foods, which can act as excellent vehicles, by enhancing stress tolerance and providing a protective matrix towards digestive stresses.

1. Introduction

Bacteria-host cross talk within the gut is a growing field of interest. While significant-knowledge has been achieved by studies of interactions between pathogenic bacteria and the host, much research is required for understanding the impact of commensal bacteria that reside

within the human gastrointestinal tract (GIT) [1]. An increasing number of studies indicate that the intestinal microbiota is essential for host functions, especially immune responses that contributes to gut homeostasis [2-5]. More recently, several studies show correlations between disturbed microbiota composition (dysbiosis) and diseases which involve gastrointestinal inflammation [6-9]. Individuals presenting these inflammatory conditions are colonized by an abnormal microbiota and it has been revealed that the lack of bacteria involved in regulation of the gut immune system might be a key factor in the chronicity of mucosal inflammation [10,11]. Therefore, a novel rationale aiming at the restoration of a healthy microbiota has been glimpsed by researchers to prevent and/or help in treating gastrointestinal diseases. In this context, there has been much encouragement for the use of probiotics and functional foods as therapies for such disorders. In this chapter, we describe the most recent advances of dairy foods and probiotic strains protective effects in animal models of intestinal inflammation and in human clinical trials. Furthermore, the challenges and limitations in regard of stability and safety of these approaches are discussed.

2. Gastrointestinal Tract

2.1. Microbiota

The GIT of mammals is a complex biological system whose main function is the digestion of food. As the GIT is an environment that is very rich in nutrients, particularly the ileum and colon parts, there is a dynamic community of microorganisms, known as intestinal microbiota, which plays a role in the intestinal physiology and immune regulation [12-14].

The community of bacteria found in the GIT contains both indigenous and transient members. The first ones are well adapted to the intestinal environment and thus colonize the lumen. In turn, the transient microorganisms are not able to survive more than a few days. Some transient species are frequently ingested in substantial amounts as they are present in fermented dairy foods such as yogurts, cheeses and fermented milk. However, transiting bacteria also include several of the enteric food-borne pathogens [15,16]. The survival of allochthonous bacteria in the GIT depends on several factors including the ability to tolerate gastric acid, bile salts and pancreatic juice [17].

Many academic and industrial consortiums, such as the MetaHIT (Metagenomics of the Human Intestinal Tract), have attempted to characterize the microbiota associated with the human GIT through genomic sequencing, thus giving a more detailed description of the human intestinal microbiota composition and of its function [18,19]. It is estimated that the intestinal microbiota comprises 500 to 1,000 species of bacteria, exceeding 10 times or more the total number of host cells [7,20,21]. Nowadays, it is known that most species found in mammalian GIT can be classified into four phyla: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria [21-23]. These phyla keep symbiotic relationships with the host, making

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fundamental contributions to the host metabolism while occupying a protected environment rich in nutrients [24,25]. In this context, the intestinal microbiota plays major roles such as nutritional functions, prevention of pathogen colonization, trophic functions on the proliferation and differentiation of the intestinal epithelium, and development and modulation of the host immune system [21,26-9].

Although the microbiome composition varies greatly among individuals, its composition is relatively simple during the first years of life. It has been reported that *Escherichia coli* and streptococci are the most common organisms isolated from the upper GIT shortly after birth [21,30]. These species are responsible for creating a favorable environment, promoting in turn the colonization by anaerobic bacteria, among which *Bifidobacterium* and Bacteroidetes are most prevalent. The *Bifidobacterium* genus plays an important role in the intestines, as these bacteria can down-regulate the expression of key proinflammatory mediators in the gut and inhibit pathogens. Bacteroidetes species have great capability to digest complex sugars, and thus maintain stable symbiotic relationship with the host and central position in the gut microbiome [31-34]. Afterwards, in the course of life, there can be an increase of Firmicutes, especially of the Lactobacillales and Clostridiales Orders. Among these, several members, including remarkably *Faecalibacterium prausnitzii*, are Short Chain Fatty Acid-producers, SCFAs playing an important role on the maturation of regulatory T cells [35]. Although microbiota is stable in older persons, it can be altered in short term duration by dietary intervention [36]. Dietary intake shifts, mainly of dairy foods containing *Lactoccocus* sp or *Propionibacterium* sp and non digestible carbohydrates, may change the composition of the gut microbiota by increasing the number of *Bifidobacterium* sp and *F. prausnitzii,* although these bacteria do not respond in the same way in all human subjects [27,37,38].

In adulthood, the diversity and abundance of bacterial populations vary along the different parts of GIT [13,21,39,40]. In the stomach and duodenum, a small number of microorganisms can be found, while up to 10^3 bacterial cells are present per gram of duodenal content. These bacteria are adhered to the mucosal surface or in transit through the GIT [26,41,42]. Streptococci and lactobacilli are among the most common groups of bacteria found in this part of the intestine [39,43-45]. The bacterial population increases gradually along the jejunum and the ileum, reaching numbers around 10^4-10^7 per gram of small intestinal content. However, it is in the lower GIT (colon) that the highest density of bacteria population is encountered, reaching a number of 10^{11}-10^{12} per gram, making this area one of the most complex microbial ecosystems known to date on Earth [13,45].

2.2. Immune system regulation

Commensal species from the intestinal microbiota are not ignored by the immune system but on the contrary need to be recognized by mammalian cells to deliver tolerogenic sig-

nals and promote intestinal immune homeostasis with an impact on the immune system of the body. Actually, commensal bacteria and their host have co-evolved diverse biological mechanisms making this cross talk possible [46]. For example, pattern recognition receptors (PRRs), especially Toll-like receptors (TLRs), expressed by Intestinal Epithelial Cells (IECs), are able to recognize microbe-associated molecular patterns (MAMP) of the commensal microbiota. In fact, the expression of PRR and their interaction with the microbiota is very important for the healthy development of the host immune system [47-49].

These MAMP are microbial components, such as lipoproteins, nucleic acids (RNA and unmethylated CpG dinucleotides), lipopotheic acids, lipopolysaccharide (LPS), surface proteins such as flagellin and peptidoglycan [7,50-52]. The recognition of a MAMP transduces signals that subsequently activates innate immune responses [50,52].

Species from Lactobacillales order and the Actinobacteria phylum (*Bifidobacterium* sp. and *Propionibacterium* sp.) [30,53] are capable of stimulating luminal secretion of antimicrobial peptides by Paneth cells, mucins by goblet cells and fortifying tight junctions of IECs [54, 55]. Furthermore, commensals are reported to induce signals of immunological tolerance, such as secretion of the TGF-β cytokine that inhibits the NF-κB signaling pathway inside epithelial cells. It has been shown that activation of TLRs by commensal bacteria also promotes the development of CD103 dendritic cells, which are responsible for driving the activation of Treg cells [56-58]. It is known that Treg cells suppress effector T cell responses mainly through the production of IL-10 and TGF-β. The stimulation of these cytokines prevents the recruitment of granulocytes, suppressing the activation of macrophages, neutrophils and endothelial cells. In addition, Treg cells expressing TGF-β and IL-10 drive B cells to undergo antibody class switching to produce IgA antibody, the major humoral defense of mucosal surfaces. Secretory IgA (sIgA) contributes to mucosal homeostasis through a process known as immune exclusion. sIgA is able to bind to opportunistic pathogens avoiding its dissemination throughout the body [59-61].

Although commensal microorganisms show beneficial effects on the host, some microbes of the GIT might present potential risk if case of outgrowth. In this context, potentially pathogenic species, known as pathobionts, composed mainly of Proteobacteria members, such as *Escherichia coli*, and species from the phylum Firmicutes, as *Clostridium difficile* and *Enterococcus faecalis* can elicit a pro-inflammatory immune response after binding to TLR [47, 53,62].

When pathobionts translocate to intestinal epithelium, the host immunity is activated and is usually enough to eliminate the intruder. Nonetheless, the overproduction of pro-inflammatory cytokines, which may occur during dysbiosis, represents a risk once inflammation may also be problematic causing cell disruption and infection to the host. Therefore, to reach intes-

tinal homeostasis, the gut immune system must be able to recognize and eliminate specifically these pathobionts from the GIT [54,63]. Intestinal barrier dysfunction generates an imbalance between immune responses observed for protective and harmful intestinal bacteria and thus contributes to the onset of several inflammatory conditions of the GIT [7,64].

2.3. Inflammatory disorders

The GIT is permanently challenged by antigens from the intestinal microbiota. Under normal conditions, the intestinal mucosa maintains tolerance to commensals, mainly through the action of Treg cells. When the dynamic balance between Treg and activated effector cells is broken, the homeostasis is compromised and this may lead to the development of mucosal inflammation [2]. Besides dysbiosis, multiple factors can influence the proper functioning of the GIT immune system, including individual genetic background, diet, use of drugs and environmental stress. The intersection of these factors generates an exaggerated pro-inflammatory reaction against commensal antigens leading to Inflammatory Bowel Diseases (IBD), a group of chronic inflammatory conditions of the GIT, which primarily includes ulcerative colitis (UC), and Crohn's disease (CD) [21,30]. Clinical symptoms of both diseases are similarly found in patients, such as abdominal pain, diarrhea, rectal bleeding and weight loss [65,66]. Relapse symptoms can last days, weeks, or even months [67]. CD is characteristically discontinuous, with inflamed areas that can be found in all the layers of the intestinal wall, while UC is characterized as a continuous and superficial inflammation limited to the colon [68,69]. The incidence of these diseases varies widely across countries, however, in recent years, it has increased considerably worldwide, being considered a global public health problem. This increase has been associated with the modern lifestyle that includes the ingestion of processed foods usually high in fats and sugar and low in fiber [70-72].

Caesarean delivery and the inappropriate use of antibiotics, especially during childhood, when the microbiota has not yet been established, are factors that can contribute to the development of intestinal inflammation [30,72–74]. Both CD and UC have different immunological aspects when it comes to innate and adaptive immunity [75,76]. Pro-inflammatory cytokines are over expressed in IBD patients; however, the predominant set of cytokines observed in CD patients is the one secreted by Th1 and Th17 cells (IL-12, IL-23, IL-27, IFN-γ) whereas in UC patients a Th2 immune response, characterized by the production of IL-4 and IL-13, appears to be predominant [3,4,74].

Chronic inflammation also plays a role in the pathogenesis in several cancers and it has been shown that there is a direct link between IBD and colorectal cancer (CRC) [77]. Individuals suffering from long-term ulcerative colitis or Crohn's disease have increased risk of developing CRC [78].

Reactive Oxygen Species (ROS), stimulated by proinflammatory response in the intes-

tinal mucosa, play an important role in the development of CRC, as their excessive levels can result in oxidative stress and significant damage to cell structures and macromolecular constituents, such as DNA, RNA, proteins and lipids [79,80]. Large amounts of hydrogen peroxide (H_2O_2) are produced and excreted by human tumor cells, and might participate in tumor invasion and proliferationas well [78,81]. Furthermore, current studies are investigating the role of effector immune responses against intestinal microbiota in modulating the gut microbiota into a carcinogenic profile composition. In fact, a correlation between diet-driven sulfidogenic bacteria and CRC in African Americans has been demonstrated [82,83].

Other factors such as the use of some medicines can also contribute to the breakdown of this immunological tolerance against commensals commonly observed under normal conditions. It has been described that chemotherapeutic agents, as 5-Fluoracil (5-FU), doxorubicin and irinotecan (CPT-11), widely used in the treatment of advanced solid tumors, may also lead to the development of another inflammatory condition of the GIT, known as mucositis. This painful inflammation of the mucosa can affect all portions of the human GIT and has great medical importance as it arises as an adverse effect of chemotherapy [84,85]. These medicines are effective in cancer treatment because they inhibit cell proliferation. 5-FU, for example, causes cytotoxic effect by inhibiting DNA replication in cells with a high mitotic index such as malignant cells. Moreover, this drug can also be incorporated into RNA molecules interfering with their processing and function. However, as an adverse consequence, the drug also shows an effect in normal cells that presents a higher turnover rate, such as GIT enterocytes [86]. Gastrointestinal mucositis is being regarded as a major risk, occurring in 80% of patients receiving 5-FU [87,88].

Patients with mucositis develop symptoms like odynophagia (pain in swallowing), vomiting, abdominal pain and diarrhea, which make eating difficult. Therefore, weight loss and malnutrition are also reported and quality of patient`s life is Gastrointestinal mucositis is characterized by morphological alterations in the mucosal architecture, as villous atrophy, increased cryptsapoptosis, that expose the mucosa to intestinal pathogens, which are able to translocate across intestinal epithelial cells leading to inflammatory responses [89].

The pathophysiology process of mucositis is very complex and involves the release of endogenous damage-associated molecular pattern (DAMP) molecules and activation ofthe NF-kB pathway, which induces in turn the expression of several genes, including pro-apoptotic enzymes such as caspases, tumor necrosis factor-alpha (TNF-α), IL1-β and IL-6 cytokines, and chemokines involved in the recruitment of neutrophils and eosinophils. Commensal bacteria might have a very important role in promoting many clinical aspects involved in the pathogenesis of mucositis [90-94], as it was demonstrated that germ-free mice are more resistant to mucositis induction [85,95]. Moreover, opportunistic species belonging to the gut microbiota, such as *Entercocccus faecalis, Escherichia* sp and *Clostridium* sp can alter intestinal

permeability during anticancer treatments and promote disruption of the epithelial layer. The translocation of commensals across IEC exacerbates inflammatory responses and amplifies the damage to the intestinal mucosa [92,95].

As alterations of the intestinal microbiota have been implicated in all of these pathologies, the scientific community has been investigating the use of probiotics in order to restore the original gut microbiota, which is responsible for regulating the mucosal immune system.

3. Probiotics

The administration of probiotics for treating gastrointestinal inflammatory disorders have been proposed by many research groups, as they are able to occupy niches that compete with pathogens in the GIT [96-101]. Probiotics are defined as "live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host" [102]. These microorganisms must be safe and present beneficial effects during their transit through the gut. Hence, their ability to resist the stomach and intestine environments are crucial alongwith the capacity of adhesion to intestinal cells, inhibition of pathogens and immunomodulatory effects [103]. Currently, several species of probiotic bacteria are used to prevent or treat a diversity of diseases, including gastrointestinal inflammatory disorders (**Table 1**). Lactobacilli and bifidobacteria, for a long time, were at the front of the stage in the field of this probiotic action. However, outsider bacterial species such as *Lactococcus lactis*, *Streptococcus thermophilus*, *Escherichia coli* and *Propionibacterium freudenreichii* recently revealed promising potential for the treatment of intestinal inflammation as well [104-107]. This is summarized in section 4.

Table 1: Immunomodulatory effects of probiotics in experimental animal model

Probiotic species	Model system	Probiotic effect(s)	Mechanisms involved	Reference(s)
Escherichia coli M17	DSS	Attenuates colitis	Inhibits NF-κB, decreases colonic IL- 12, IL-6, IL1-β and IFN-γ	(FITZPATRICK et al., 2008) (108)
Lactobacillus casei	TLR4 KO and DSS	Attenuates colitis	Reduces proinflammatory cytokines secretion and neutrophil recruitment	(CHUNG et al., 2008) (109)
Faecalibacterium-prausnitzii	TNBS	Attenuates colitis	Increases colonic IL10 and decreases colonic IL12. Tends to correct the dysbiosis associated with TNBS colitis	(SOKOL et al., 2008) (110)
Mix of four *lactobacillus* or four *Bifidobacterium species*	DSS	Attenuates colitis	Reduces colonic proinflammatory cytokines	(NANDA KUMAR et al., 2008) (111)
VSL#3	TNBS	Attenuates colitis	Increases production of IL-10 and Tregs	(DI GIACINTO et al., 2005) (112)

Lactobacillussalivarius Ls33	TNBS	Attenuates colitis	Increases IL-10 production and Tregs	(MACHO FERNANDEZ et al., 2011) (113)
Lactobacillus plantarum DSM 15313, *Lactobacillus fermentum* 35D	DSS	Attenuates colitis	Reduces bacterial translocation	(OSMAN et al., 2008) (114)
Bacteroides fragilis	TNBS	Attenuates colitis	Increases production of IL-10 and Tregs	(ROUND and MAZMANIAN, 2010) *(115)*
Lactobacillus salivarius 433118, *Bifidobacterium infantis*	IL-10 KO	Attenuates colitis	Reduces inflammatory cytokines	(MCCARTHY et al., 2003) (116)
Lactobacillus casei Shirota	DSS	Attenuates colitis	Reduces IL-6 production by lamina propria mononuclear cells	(MATSUMOTO et al., 2005)(117)
Enterococcus faecium CRL 183	1,2 dimethylhydrazine (DMH)	Reduces ACF and adenocarcinomas incidence	Improved the immune response by increasing IL-4, IFN-γ, and TNF-α production	(SIVIEIRI et al., 2008)(118)
Saccharomyces boulardii	C57BL/6J Min/+ (Apc-Min) mice (7 wk old).	Reduces number and diameter of the tumors, the score for low-grade dysplasia, numbers of polyps, and cell proliferation	Inactivation of the EGFR-Mek-Erk pathway signaling. Increase apoptosis	(CHEN et al., 2009)(119)
Lactobacillus acidophilus NCFM	CT-26 cells	Reduces tumor size and the extraintestinal metastatic tissue	Increase apoptosis through increase caspase-9 and caspase-3 and reduces Bcl-2 expression	(CHEN et al., 2012) (88)
Lactobacillus plantarum AdF10 and *Lactobacillus rhamnosus* GG	1,2 dimethylhydrazine (DMH)	Reduces tumor incidence, multiplicity, and size	Reduces COX-2 protein expression	(WALIA et al., 2015) (120)
Lactobacillus salivarius Ren	1,2 dimethylhydrazine (DMH)	Reduces tumor incidence	Reduces Intestinal population of Ruminococcussp and Clostridiales bacteria ↑ Intestinal population of Prevotellasp	(ZHANG et al., 2015) (121)
Dead nanosized *Lactobacillus plantarum*	Azoxymethane/ Dextran Sulfate Sodium-Induced	Reduces tumor incidence; areas of dysplasia, adenocarcinoma, and structural disruption	Reduces Over expression of proinflammatory cytokines and inflammatory genes Increase Apoptosis and cell cycle arrest	(LEE et al., 2015) (122)
Lactobacillus rhamnosus and *Lactobacillus acidophilus*	1,2 dimethylhydrazine (DMH)	Reduces tumor incidence, burden and multiplicity; lipid peroxidation	Reduces GSH, SOD, and GPx activity	(VERMA and SHUKLA 2014) (123)

Lactobacillus casei BL23	1,2 dimethylhydrazine (DMH)	Reduces colorectal cancer	Regulates Treg and Th17 T-cell populations	(LENOIR et al., 2016) (124)
Pediococcus pentosaceus GS4	Azoxymethane	Attenuates colon cancer	Triggered apoptosis in colonocytes	(DUBEY et al., 2016) (125)

3.1. Bacteria for the treatment of gastrointestinal disorders

Many strains of bacteria are known to exert anti-inflammatory effects through the modulation of factors that are involved in maintaining intestinal homeostasis in humans and other animals [97,101]. In this context, bacterial effectors of distinct nature have been implicated in probiotic effects. These include metabolites, peptidoglycan, surface proteins, lipoproteins and lipoteichoic acids, lipopolysaccharides, flagelin and CpG motifs in DNA. Some of these molecules, such as anti-microbial peptides and prebiotic metabolites may interact directly with other species of bacteria that colonize the gut, modulating their growth. Others bacterial factors, called MAMP, bind to PRRs of eukaryotic cells and stimulate different patterns of gene expression in the host involved in innate immunity activation and differentiation of antigen-specific immunity [53,126]. The mechanism of action of these bacteria can be classified in three main categories: alteration of gut microbiome composition, stimulation of epithelial barrier function; and induction of the immune responses [127].

Recent advances in genomic sequencing technologies have provided the scientific community with tools to explore the human microbiome and how different treatments affect its global composition and function. Several studies have shown that probiotics can increase or decrease the abundance and diversity in gut microbial species composition. The secretion of antimicrobial compounds acts by directly inhibiting the growth of pathogens. In addition, probiotic strains may also reduce the impact of pathogens through a mechanism known as competitive exclusion, in which they occupy binding sites at the mucosal surface [97,128,129].

Epithelial barrier function enhancement is a well-established mechanism of probiotic bacteria in the protection of the host against invasive harmful bacteria. Numerous studies have shown that probiotics have the potential to modulate many of the processes involved in mucosal barrier formation and are able to upregulate expression of defensins, mucins or proteins associated with tight junctions such as claudins and occludins [130-132]. This effect is therefore considered as one of most important for the prevention and treatment of IBD and mucositis, as it might avoid translocation of opportunistic pathogens to systemic circulation [84,101].

Probiotics can affect the host heath by modulating inflammatory signaling pathways. Several probiotics are reported to inhibit the NF-kB activation and thus to influence downstream cytokine secretion [133]. Recent studies demonstrated that the anti-inflammatory effects of some bacteria involve inhibition of IkB degradation by targeting the different steps involved

in this process which are phosphorylation, ubiquitination or proteasome degradation[134]. Some Lactobacilli have shown inhibitory activity of TNF-alpha induced secretion of IL-8 [135]. Other well established immunological mechanism of probiotics is the stimulation of immunological tolerance to GIT microbiota through the increase in IL-10 secretion. For instance, Santos and collaborators (2014) showed that the probiotic effect of *L. delbrueckii* strain CNRZ327 was related to an expansion of Treg cells and an increase of total IgA in Dextran sulfate sodium (DSS)-induced colitis in mice. Recently, it was reported that a *Lactococcus-lactiss* sp. lactis NCDO2118 strain prevented DSS-induced colitis in mice and the protective effect was related to increased IL-10 levels in the colon and to the induction of Treg cells in the mesenteric lymph nodes [99].

Most studies focused on the beneficial effects autochthonous Lactobacilli (**Table 1**). However, recent studies have demonstrated that some allochthonous strains have anti-inflammatory properties. Ballal and colleagues (2015) found that *L. lactis* I-1631 prevents colitis in T-bet−/− Rag2−/− mice. Two additional studies have shown that, among the *L. lactis* species, NCDO2118 subsp. *lactis* or FC subsp. *cremoris* are anti-inflammatory when inoculated in inflamed mice receiving the chemical agent DSS [99,136]. Moreover, *L. lactis* NZ9000 by itself was able to prevent histological damage and reduce neutrophil and eosinophil infiltration in mice injected with 5-FU. Another allochthonous species with anti-inflammatory effects in IBD models is *Propionibacterium freudenreichii,* used extensively as a ripening starter of Emmental cheese [104,137,138].

3.2. Challenges and limitations to select probiotic bacteria

For probiotic bacteria selection, the robustness of a bacterium against different abiotic and biotic stresses is crucial, and may constitute a limiting factor for its application as probiotic. Firstly, to prepare probiotic ingredients, a plethora of stresses are applied, thus the bacterial tolerance is a prerequisite for reaching a high survival rate in the product. In the traditional cheese products, the manipulation of bacterial population could be limited by other factors. However, for the probiotic powders, great efforts were made to maintain a high viable bacterial population during freeze-drying or spray drying, such as usage of encapsulation methods. Gastrointestinal stresses also constitute the main bottleneck of probiotic efficacy.

A probiotic microorganism must be able to tolerate digestive stresses and to adhere to intestinal epithelium, for a long persistence in the host and for an enhanced beneficial effect. Gastric acid and bile salts are defense mechanisms encountered during intestinal transit whereas pancreatic secretions can also exert some antimicrobial activity via the digestive enzymes. The existing microbiota may also interfere with the probiotic effect by competition for adhesion or nutrients. The investigation of molecular basis of the adaptive response to stresses and identification of the pivotal genes involved provided pertinent tools for probiotic screening.

3.2.1. Acid stress

The probiotic resistance to acid stress is a desired characteristic of selected strains, as low pH is widely encountered both during technological processing and during gastric digestion. The bacterial adaptive responses to acid challenge have been investigated and some of the molecular mechanisms involved were elucidated, such as induction of proton ATP-dependent pumps F_1F_0-ATPase. The function of this transmembrane protein complexis the extrusion of protons from the cell cytoplasm, resulting in a Proton Motive Force (PMF), and avoiding acid-stress induced drop in intracellular pH [139]. Mutations leading to a reduction of membrane-bound ATPase activity were observed in some strains of *Lactococcus lactis* subsp. *lactis* and *Lactobacillus helveticus*, where they cause growth inhibition under acid conditions [140,141]. Gram-positive bacteria, such as *Lactococcus lactis* [142] and *Lactobacillus brevis* [143], possess a second mechanism for an adaptive response to acid stress, involving the enzyme glutamate decarboxylase (GAD). The GAD system imports glutamate into the cell prior to its decarboxylation, which consumes protons, participating in intracellular pH homeostasis, followed by the efflux of the resulting γ-aminobutyrate (GABA), thanks to a GAD/GABA antiporter. Another mechanism involved in pH homeostasis is the proton-consuming malolactic fermentation (MLF). This metabolic pathway leads to the conversion of the dicarboxylic malic acid to the monocarboxylic lactic acid. The latter is excreted via a lactate-malate antiporter, resulting in intracellular alkanization. Such mechanism was observed within several bacteria like *Lactobacillus sakei* [144], *Lactobacillus plantarum* [145], and *Lactococcus lactis* [146]. Finally, other acid-adaptive mechanisms induced in lactic acid bacteria includethe citrate-lactate antiporter (CitP), the arginine deiminase (ADI) system and some heat shock [147-149].

3.2.2. Bile salts

Conjugated bile salts are synthesized by the liver with the amino acids glycine or taurine, those amphipathic molecules act like biological detergents with strong antimicrobial activity cause can emulsify biological membrane lipids [150,151]. These compounds may enter into the bacterial cytoplasm by flip-flop mechanism and cause oxidative stress which leads to DNA damage [152-154]. In fact, there are different remarkable mechanisms leading to bile salts tolerance; those molecular actors can also provide bacteria a cross protection towards other stress types. Some probiotic bacteria hold the ability to hydrolyze bile salts by bile salt hydrolases (BSHs) which enhances their survival in the digestive tract [155]. Alternative mechanisms exist such as bile-efflux systems, which are multidrug transporters that mediate the active extrusion of bile salts from the bacterial cytoplasm [156]. Regarding *Lactobacillus acidophilus* particularly, an eight-gene operon encoding for, a two-component regulatory system, a transporter belonging to the major facilitator super family, an oxido reductase, and four hypothetical proteins, has been implicated in bile salts removal [157].

3.2.3. Heat stress

Heat stress is another type of ordeal that is commonly suffered during technological processes, either during food fermentation (cheese cooking-step) or during drying, which may impose high temperatures (>60°C) or low temperatures, depending on the chosen technology. The response to heat stress involves a set of proteins called Heat Shock Proteins (HSP), which include chaperones and proteases. They are essential for overcoming protein denaturation, maintaining cell homeostasis in response to variations of temperature, which can affect membrane fluidity and compromise cellular integrity and basic cell processes [158,159]. Among those crucial proteins, DnaK and GroEL, are two HPSs that have a critical role in cellular processes by maintaining DNA replication process, preventing mutagenesis and preventing protein denaturation [158,160]. Otherwise, low temperatures are frequently used to prevent spoilage during frozen and freeze-dried storing process. Such a cold stress leads to induction of specific proteins called cold shock proteins (CSPs). Their role consists in maintaining transcription and translation processes under cold stress adaptation [159].

3.3. Protective matrix and vectorization

Although the adaptive response to various stresses is a quite important feature to screen tolerant or sensitive probiotic strains, vehicle matrix can confer a protection for an efficient delivery of probiotic bacteria to the GIT. Probiotics are commonly consumed under the form of dried powder, in capsules or tablets. Recently, various studies focused on "2-in-1"starter bacteria: microorganisms widely used in food fermentation and which exert beneficial effects. There is a huge variety of fermentative microorganisms known for their probiotic properties like *S. thermophilus, L. delbrueckii* ssp. *bulgaricus, L. lactis,* and other strains used for specific fermented foods [161]. The growth in such stressful medium as dairy fermented foods selects bacteria with a high robustness to GIT stresses there by promoting long-term survival during storage in industrial process.

3.3.1. Encapsulation by biopolymers

Encapsulation is a standard process used to produce protected dried probiotic ingredients. Encapsulation may confer a protection against industrial stresses during the drying process, and allow a controlled release in the GIT [162,163]. Depending on the type of drying technology (capsule spray-drying, emulsification, extrusion, co-extrusion, or spray-coating), different particles sizes may be obtained and interfere in the encapsulation yield. Moreover, semi-permeable and biocompatible matrices including food-grade biopolymers like alginate, pectin and cellulose acetate phthalate are used for preventing oxidative reaction, masking flavor and odor changes. The encapsulation essentially provides a protection for bacteria and a specific addressing of active probiotic compounds to specifics sites [164,165]. Among polymers used for encapsulation; alginate, a polysaccharide composed of β-D-mannuronic and

αL-guluronic acids, is widely used, because of its simplicity, biocompatibility, low cost, and non-toxicity. Recently, the encapsulation by alginate was shown to confer enhanced viability upon storage and simulated gastrointestinal digestion for *Lactococcus lactis* subsp. *cremoris* LM0230, *Lactobacillus casei* NCDC 298, *Bifidobacterium longum* and other probiotics [166-168].

3.3.2. Encapsulation by milk proteins

The utilization of milk proteins for probiotic encapsulation is a high quality choice due to their biocompatibility, structural and physico-chemical properties [169]. Milk proteins are categorized in two types: caseins and whey proteins. Caseins are a complex aggregate of phosphoproteins and are extremely heat-stable proteins, present in colloidal form known as caseins micelles in fresh milk [170]. Whey proteins are a group of globular proteins, α-lactalbumin, ß-lactooglobulin, immunoglobulins, and serum albumin and also various other minor proteins [171]. Milk proteins clotting followed by spray-drying appears as new innovative methodology to encapsulate probiotic bacteria to enhance survival in GIT [172]. Heidebach *et al.* in 2009 demonstrated new methodologies based on a transglutaminase-catalyzed gelation of casein suspensions and spray drying to encapsulate *Lactobacillus paracei s*sp. *paracasei* F19 and *Bifidobacterium lactis* Bb12. It was shown to enhance robustness instressing conditions [173,174].

3.3.3. Dairy Fermented foods

The emergence of functional foods concept such as fermented products is a promising research area. Indeed, the dairy fermented foods constitute an important part of our daily diet [175], as well as our main microbial daily intake. The dairy product matrix may increase tolerance of bacteria towards digestive stresses and adhesion to cells, depending on its biochemical composition, its physical microstructure and the existing microbial ecosystem, which affects directly the viable bacterial amount reaching the gut. Beyond the protection effect of the vehicle matrix, fermentation allows improvement of food nutritional value through the microbial release of a high amount of essential nutrient for consumers [176], including vitamins.

Probiotic bacteria convert different molecules, producing valuable nutrients like conjugated fatty acid, B-galactosidase enzyme, beneficial dairy peptide, which can enhance their probiotic functionality [24,25]. Indeed, *L. casei* BL23 incubated in milk reduced significantly the symptoms of a dextran sulfate sodium (DSS) - induced colitis in a murine model, compared to the same strain provided in phosphate buffered saline [178,179]. Yogurt enhances the therapeutic value of some probiotic bacteria, however the low pH of yogurt decreases viable population [177,180,181]. To contend this problem, a combination of encapsulated probiotic bacteria was used to increase survival in yogurt. For example, *L. paracasei* subsp. *paracasei* E6 were encapsulated using whey proteins and gum arabic, before being added to the yogurt

matrix after fermentation. This bacterium exhibited greater viability, compared to cells without encapsulation, upon exposure of the probiotic yogurt to simulated gastric juice [182,183].

Cheese matrix favors probiotic beneficial effects by providing a favorable environment with relatively high fat content, enhancing probiotic survival in transit through the GIT, especially towards lethal conditions of the stomach [184]. Özer and colleagues showed increased viability of *Bifidobacterium bifidum* BB-12 and of *Lactobacillus acidophilus* LA-5, when these bacteria were microencapsulated in white-brined cheese, compared to same strains without encapsulation protection [185]. Other strains have been used to produce experimental probiotic cheese, including *Lactobacillus casei* and *Lactobacillus acidophilus* in Crescenza cheese. They exhibited improved viability, during the refrigerated storage, after a cheese manufacture using High-pressure homogenization (HPH) as an alternative to traditional thermal treatment [186]. The potential probiotic *P. freudenreichii*, alone or in combination with *Lactobacillus delbrueckii*, was investigated with respect to the prevention of UC. The experimental fermented cheeses exhibited promising anti-inflammatory properties in mice with colitis [187,188]. Moreover, inclusion within a cheese enhanced *P. freudenreichii* tolerance towards digestive stresses and thus its probiotic properties [105].

4. *Propionibacterium Freudenreichii* for Treating Gastrointestinal Disorders

During the last two decades, an outsider, that had until then been ignored, was considered for probiotic applications. The propionibacterium *P. freudenreichii,* until then used almost exclusively to confer aroma to pressed cheeses, joined the main probiotic actors on the stage of probiotic research and development. *P. freudenreichii* indeed recently revealed unexpected immunomodulatory effects. This evidenced for the first time a "two-in-one" property of an ill-known ripening starter, with both technological and probiotic abilities.

4.1. General aspects of *P. freudenreichii*

4.1.1. Taxonomy

P. freudenreichii is a dairy propionibacterium, which belongs to Actinobacteria, characterized as gram-positivewith a high G+C content, non- sporing, anaerobic to aerotolerant, non-motile pleomorphic rods [189,190]. Actinobacteria comprise bacterial species with a mycelium-like aspect, found in various environments, including animal hosts and soil [189,190]. The genus *Propionibacterium* comprises both cutaneous species, which may act as opportunistic pathogens, and dairy species, which have no reported adverse effects up to date [191]. The typical dairy species isolated from milk are: *P. freudenreichii, P. acidipropionici, P. jensenii* and *P. thoenii;* they are clearly distinct from cutaneous species. Dairy propionibacteria were firstly described by E. von Freudenreich and S. Orla-Jensen at the end of 19th century, since their presence in Emmental cheese was associated with propionic fermentation [192]. Dairy

propionibacteria, specifically *P. freudenreichii*, possess a long history of safe use in food, particularly by Swiss-type cheese. *P. freudenreichii* received the "Generally Recognized As Safe" (GRAS) status [193]. The European food safety authority has granted "Qualified presumption of safety" (QPS) status to two species: *P. freudenreichii* and *P. acidipropionici* [194]. The sequencing of *P. freudenreichii* genome revealed the genetic basis of the great adaptation ability to various environments [195]. They moreover display a peculiar fermentative metabolism, which relies on propionic fermentation, may use various carbon and energy sources, and release in the extracellular medium various beneficial metabolites [190,195].

4.2. *P. freudenreichii* technological applications

4.2.1. Swiss-type cheese manufacturing

The major use of *P. freudenreichii* strains is as ripening culture in Swiss-type cheeses manufacturing. They play an important role in characteristic flavor of cheeses such as Emmental cheese [189]. *P. freudenreichii* produces several flavor compounds via different substrates catabolism. lactate and aspartate fermentations generate short fatty acids accumulation, mainly propionic and acetic acids, and to a lesser extent valeric and isovaleric acids. These short fatty acids are considered as principal flavor compounds in Emmental. *P. freudenreichii* also possesses a strain-dependent lipolysis activity, which produces free fatty acids that are important molecules for cheese flavor. The amino acids catabolism by *P. freudenreichii* produces two branched-chain flavor compounds: 2-methylbutanoic acid and isovaleric acid [190]. In Emmental cheeses, *P. freudenreichii* reaches a high population density, with counts depending in ripening period. The *P. freudenreichii* robustness permit a high tolerance to different stresses during cheese manufacturing process, such as high and low temperature, acidification, osmotic stress induced by NaCl [190,196]. In addition, *P. freudenreichii* can also be found in low amount in various cheeses, in addition to Emmental cheese [189].

4.2.2. Anti-microbial & Nutraceutical molecules production

P. freudenreichii is a well-known vitamin B_{12} producer, actually, the only B_{12} producingbacteria with the GRAS status [190,197]. Vitamin B_{12} is an essential vitamin, required for maintaining healthy nerve cells, DNA synthesis and energy, and for other important functions. Vitamin B_{12} is synthesized industrially by chemical synthesis, which is too difficult and expensive. Many efforts were made to enhance the productivity of vitamin B_{12}, by using genetic engineering and by optimizing fermentation conditions. In addition, *Propionibacterium* spp strains, have preservatives properties and are widely employed to extend foods shelf-life by inhibiting undesirable microorganisms growth. A commercial product is available under MicrogardTM name, which is composed of skim milk fermented by *P. freudenreichii* subsp *shermanii* [190,192,197]. The short chain fatty acids propionate and acetate, as well as other organic acids such as succinate, are the main anti-microbial molecules produced by dairy pro-

pionibacteria. However, *P. acidipropionici* species were shown to be the best producer of propionic acid, through glycerol fermentation without acetic acid production [197]. Different bacteriocins that are produced by both dairy and cutaneous propionibacteria, have been reported and characterized [190,192,197]. However, further studies are required to assess their possible use as food biopreservatives or bacteriocin producer probiotics to inhibit intestinal pathogens, as dairy propionibacteria bacteriocins are not still recognized as GRAS by the FDA.

4.3. Probiotic application

Recent data suggest the probiotic potential application of dairy propionibacteria, mainly *P. freudenreichii*, for human and animal, as this species presents all characteristics for probiotic application [192]. Indeed, it shows a high tolerance to digestive stresses, which is one of the main factors limiting the use of microorganisms as live probiotic agent [192]. Propionibacteria species have a slow growth rate, so their adherence to intestinal epithelium is crucial for their persistence in the gut and for exerting their beneficial effects [190,192]. Some studies demonstrated the dairy propionibacteria ability to adhere to intestinal cells, however all those studies are *in vitro* experiments, and the adhesion presented a lot of variations according to adhesion model used, species types, and vehicle or growing medium [192]. *In vivo* studies, in humans and mammalians, suggest that this adhesion ability allows only a transient colonization, since fecal propionibacteria population in human volunteer's decreases after ceasing the ingestion of propionibacteria [198,199]. *P. freudenreichii* produces several beneficial metabolites, allows specific changes, as microbiota and intestinal immunity modulations [192]. Some strains of dairy propionibacteria are already used in probiotic preparations, alone or in combination with lactic acid bacteria and/or bifidobacteria [192]. Recently, the spray-drying was shown as a better alternative method to dry probiotic bacteria, since energy costs are lower and the process is sustainable [200,201]. *P. freudenreichii* was shown to tolerate stresses undergone during different technological stresses, which will lead to the development of several fermented ingredients to exert probiotic potential of dairy propionibacteria for improving animal and human health.

4.3.1. Molecular mechanisms of *P. freudenreichii* beneficial effects

Regarding *P. freudenreichii*, animal studies and clinical trials indicate its ability to modulate gut immunity and microbiota, specifically in the context of UC. *P. freudenreichii* was shown to prevent trinitrobenzene sulfonic acid (TNBS) induced colitis in conventional mice, alone or associated with other probiotic bacteria [202,203]. Immunomodulation by *P. freudenreichii* was further evidenced in pigs, by decreasing plasma haptoglobulin and proinflammatory cytokines (IL-8 and TNF-α) in gut mucosa, after lipopolysaccharides (LPS) stimulation *ex vivo* [198]. Recently, a probiotic mixture containing both *Lactobacillus rhamnosus* and *P. freudenreichii* was tested in humanized mice (colonized with human microbiota) consuming

a high-fat diet [204]. It tended to down-regulate both intestinal and systemic pro-inflammatory changes induced by the diet. A commercial preparation of bifidogenic growth stimulator (BGS), which is produced by *P. freudenreichii* ET-3, led to an improvement in the clinical activity scores of UC patients [205,206]. In the same study, patients also showed a decrease in the endoscopic index and an improvement in serum hemoglobin and albumin concentrations. Although, no clinical evidences on propionibacteria consumption within CRC patients exist, when tested in healthy men, this probiotic mixture reduced fecal α-glucosidase, which is associated with carcinogenesis [207,208]. Studies strongly suggest that those anti-inflammatory and potential anti-cancerous effects are related with the molecular factors of *P. freudenreichii* such as metabolites, S-layer proteins, short fatty acids, and 1, 4-dihydroxy-2-naphtoic acid [209–211].

4.3.1.1. S-layers proteins

S-layer proteins (Slps) constitute a surface-exposed proteinaceous lattice, non-covalently anchored to the cell wall via Surface Layer Homology (SLH) domains. This structure is present in many Gram-positive bacteria other than propionibacteria [212,213]. *P. freudenreichii* strains have seven genes encoding Slps proteins, exhibiting a wide variety of sequences between species but also within the same species [195]. S-layer proteins play various functions: adhesion, virulence factors, transport of molecules, masking of receptors to phages, and protection against environmental stresses [212,213]. The stimulation of Peripheral Blood Mononuclear Cells (PBMC) with *P. freudenreichii* Slps proteins mixture leads to the release of regulatory IL-10, in a dose-dependent manner. When applied in conjunction with a proinflammatory stimulus such as *Lactococcus lactis* MG1363 or *Escherichia coli* EPS, *P. freudenreichii* Slps considerably reduce the induction of the proinflammatory cytokines IL-12, IFN-γ and TNF-α [214]. The presence of a capsule of exopolysaccharides in several strains of *P. freudenreichii* blocks the immunostimulation of PBMCs, but the deletion of this EPS capsule by genetic mutation restores the immunomodulatory properties inthe mutant [215,216]. This indicates a key role of surface proteins as PAMPs in this probiotic/host cross-talk. A further molecular study specified that the immunomodulatory properties do not result from the presence of one single Slp protein but rather from a combination of several surface layer protein species [217].

4.3.1.2. Short-chain fatty acids

P. freudenreichii, among other dairy propionibacteria species, produces mainly acetate and propionate as SCFAs in ratio 2:1 by anaerobic fermentation of carbohydrates or organic acids [190]. Propionate and acetate were identified as responsible for the anti-cancerous effect of dairy propionibacteria in colorectal and gastric cancerous cells. The pro-apoptotic effect, confirmed in an animal model of carcinogenesis, was studied and the molecular mechanism

was determined [218–221]. SCFAs activate firstly the apoptotic intrinsic pathway, by acting on the mitochondria adenine nucleotide translator (ANT) pore. The ANT activation leads to mitochondria depolarization and permeabilisation; and then leakage of cytochrome C and caspase activation. Furthermore, as demonstrated by Cousin *et al.* (2016), SCFAs could act on the extrinsic apoptotic pathway by enhancing the cytotoxicity of the TNF-Related Apoptosis-Inducing Ligand (TRAIL) cytokine treatment in HT-29 cells [222] and by inducing expression of the corresponding R2/DR5 receptor, a TNF receptor super family member that mediates apoptosis by activating the extrinsic apoptotic death pathway. A combination lead to a modulation of genes expression involved in apoptosis, decreasing FLIPL and XIAP expression, which are two apoptosis inhibitors, regulating extrinsic and intrinsic cell death pathways respectively. SCFAs was demonstrated to have a Histone Deacetylase (HDACs) inhibitory activity in HT29 cells, which cause cell cycle arrest and p21 expression [222]. HDACs inhibition seems to be induced in part by SCFAs activated G-protein-coupled receptors, which are known to modulate gut immune system [223]. Finally, SCFAs treatments increased of NOD-like receptors and cytokine-cytokine receptors interaction gene expression, known to play a role in immune response [222]. Finally, *P. freudenreichii* consumption by humans increase SCFAs in feces, suggesting the possibility to modulate gut SCFAs concentrations for preventing CRC occurrence.

4.3.1.3. DHNA

Dairy probionibacteria, including *P. freudenereichii*, produce a vitamin K_2 (or menaquinone) biosynthesis intermediate, called 1,4-dihydroxy-2-naphtoic acid (DHNA) [224-226]. It is considered as bifidogenic component and modulates animal and human microbiota, in healthy and disease context. DHNA was shown to be able to stimulate *in vitro* and *in vivo* bifidobacteria growth. Indeed, the consumption of dried cultures of the *P. freudenreichii* ET-3 strain leads to an increased population of bifidobacteria within the human gut microbiota in healthy human volunteers [227,228]. Similar results were observed using a cell-free culture supernatant of *P. freudenreichii*, which was called bifidogenic growth stimulator (BGS) [229]. In addition, DHNA treatment was shown to restore Lactobacillus and Enterobacteriacea flora in dextran sulfate sodium (DSS)-induced-colitis in mice [230]. It induces also the expression of anti-microbial C-type lectin Reg III protein family, which certainly affects the microbiota [231]. DHNA is an anti-inflammatory metabolite which prevents inflammation in different murine colitis models [230–232]. It decreased the lymphocytes infiltration in tissues by reducing cell adhesion molecules expression (MAdCAM-1 or VCAM-1), in a mice colitis model [230,232]. Those adhesion molecules are highly expressed In IBD patients, which exacerbate the inflammation by increasing immune cells infiltration in tissues. DHNA acts via the aryl hydrocarbon receptor (AhR) activation, a transcriptional factor involved in inflammation [231]. AhR activation was shown to be involved in the inhibition of secretion of proinflammatory

cytokines. Indeed, the inhibition of proinflammatory cytokine IL6 in LPS-stimulated macrophages was related to AhR activation by DHNA [231].

5. Discussion

The Scientific community along with some enterprises have been through a technological race to sequence and characterize the genome of GIT commensal bacteria, the so-called gut microbiota. This approach is crucial to understand the interactions and associations within this high complexity biological system and with the host. The human intestinal microbiota composition is not only considered in the healthy state, but also in the context of disease, in order to understand the dysregulation of the cross talk mechanisms that are involved. Such dysregulation, especially when immune system is affected, lead to IBD, cancer or other inflammatory disorders, such as mucositis [7,18,19,46,64]. It is clear that the use of probiotics with anti-inflammatory or immunomodulatory properties, may change the microbiota composition, enhance epithelial barrier function and dampen immune responses by modulating inflammatory signaling pathways. Based on this rationale, several research groups aimed at treating gastrointestinal inflammatory disorders [103,127]. Due to adverse conditions of the GIT environment, it is important that probiotics be screened, in order to select tolerant strains to avoid massive bacterial death and loss of probiotic efficacy, while favoring robustness against digestive stresses, adherence to intestinal epithelium and long persistence in the host.

In this context, protection of probiotics could optimize fitness of sensitive strains or even improve tolerant strains, and consequently increase their beneficial effects in the GIT. Technological processes like microencapsulation, using biocompatible materials, or a combination of several processes that are used to make functional foods, have indeed been shown to enhance probiotic bacteria activity [182,233-235]. Currently, wide varieties of probiotics are available within commercial dairy products including fresh milk, yogurt and cheese. Interestingly, these commercial products may improve probiotics by converting biomolecules into dairy metabolites which can help in probiotic effect such as conjugated fatty acid, β-galactosidase enzyme, etc. [161,236,237]. For instance, fermented milk with *L. casei* BL23 showed a significant reduction of the clinical state of colitis in mice, suggesting that it is safe and efficient to use dairy fermented foods with probiotic strains in animal models [178]. In addition, this might be the initial step for their clinical use. Therefore, the search for new studies in different models of diseases should be encouraged [178,179].

Recent studies have pointed out the emergence of the potential probiotic application for *P.freudenreichii,* and other dairy propionibacteria, used extensively for Emmental cheese ripening, in the treatment of different gastrointestinal inflammatory diseases such as mucositis, colitis and in CRC using a rat model. In addition, ongoing studies investigate the benefit of designer fermented dairy products in the context of clinical trials (NCT02488954)

[104,105,187,188,238–240]. Finally, exploration of probiotic aptitudes in robust, traditional and easy-to-implement fermentation starter bacteria is a promising area of research.

6. Conclusion

The potential of different probiotic bacteria strains in treating GIT disorders, in animal models and in clinical trials, strongly suggests that they open avenues for the development of novel clinical biotherapies. We believe that the use of functional dairy foods is a useful way for enhancing immunological effects, as they provide additional beneficial properties and serve as excellent protection matrices for probiotic bacteria. In this context, exploring the potential of the variety of lactic acid and propionic acid bacteria selected by centuries of traditional fermentation worldwide, will allow identification of yet unknown superbugs.

7. Reference

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