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Review

Dairy propionibacteria as human probiotics: A review of recent evidence

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Abstract – Probiotics have been the subject of intensive research, mainly focusing on bifidobacteria and lactic acid bacteria. However, there is evidence that dairy propionibacteria also display probiotic properties, which as yet have been underestimated. The aim of this paper is to review recent data which report probiotic characteristics of dairy propionibacteria and to distinctly organise them based on the experimental strategy employed: ranked from in vitro evidence to in vivo trials, which is a new approach. In addition to the selection criteria for probiotics in areas such as food safety, technological and digestive stress tolerance, many potential health benefits have been described which include modulation of microbiota and metabolic activity in the gut, modulation of intestinal motility and absorption, impact on intestinal inflammation, modulation of the immune system and potential modulation of risk factors for cancer development. The robust nature of dairy propionibacteria towards technological stresses should allow their future use in various fermented probiotic foods. Among the probiotic properties of dairy propionibacteria described in the literature, some of these properties are different from those reported for bifidobacteria and lactic acid bacteria. However, supplementation with dairy propionibacteria in randomised, placebo-controlled, double-blind human trials has mainly involved mixtures of propionibacteria with probiotic bacteria from other genera. Clinical studies involving the use of dairy propionibacteria alone are lacking. Such studies will allow the specifically observed health benefits to be attributed to dairy propionibacteria. This, in turn, will allow the investigation of the synergistic effects with other probiotic bacteria or beneficial food components.

probiotic / propionibacteria / *Propionibacterium* / short-chain fatty acid

摘要 – 益生性丙酸菌的研究进展。近年来关于双歧杆菌和乳酸菌的益生性得到了广泛的关注、相关的研究报道较多。 尽管乳中的丙酸菌也显示具有益生菌的功能、但并没有引起人们的重视。 本文综述了近年来关于乳源丙酸菌益生功能的研究进展。 论述的内容包括从食品安全性考虑益生菌的选择标准、益生菌的消化极限; 以及益生菌潜在的功能性、如对肠道中微生物菌群和代谢活性的调整作用、促进肠道蠕动和吸收作用、对肠炎的作用、对免疫系统的调节作用以及潜在的对癌症因子抑制作用。 丙酸菌在乳中生产旺盛、因此从技术层面上分析丙酸菌可以用于各种发酵食品。 在关于乳源丙酸菌益生功能性的文献报道中、丙酸菌的一些功能性不同于双歧杆菌和乳酸菌。 然而、在双目失明的人体试验

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中、则是将来源于其他属的丙酸菌与乳源丙酸菌混合使用。 在临床试验中通常用含丙酸菌的乳制品和不含丙酸菌的乳制品同时进行试验、目的是证明乳源丙酸菌对人体健康的作用。 同样方法也可以调查丙酸菌与其他益生菌或食物中其他有益成分的协同作用。

益生性 / 丙酸菌 / 丙酸杆菌属 / 短链脂肪酸

1. INTRODUCTION

Propionibacteria were first described at the end of the 19th century by E. von Freudenreich and S. Orla-Jensen, studying propionic acid fermentation in Emmental cheese, leading to propose the genus *Propionibacterium* [101]. Propionibacteria are firmicutes with a high G + C content, characterised as gram-positive, non-sporing, non-motile pleomorphic rods. They are anaerobic to aerotolerant and generally catalase positive. They grow optimally at 30 °C and are of neutral pH. Cells are hetero-fermentative and metabolise a variety of substrates such as carbohydrates (including glucose, galactose, fructose and lactose), alcohols (glycerol and erythritol) and organic acids (lactate and pyruvate). Propionibacteria present a particular central carbon metabolic pathway, propionic fermentation. This fermentation involves the Wood-Werkmann cycle [147] which produces propionate, acetate, succinate and carbon dioxide. The genus *Propionibacterium* is divided in two groups (Tab. I) based on habitat of origin: classical or dairy propionibacteria (mainly isolated from dairy products such as cheese) and cutaneous propionibacteria (typically found on skin). Recently, a new species, *Propionibacterium acidifaciens*, was isolated from human carious dentine [21]. It was proposed as a member of the cutaneous group because it is closely related to *Propionibacterium australiense*. Dairy propionibacteria are commonly used as starter cultures in the dairy industry. Their main application is the ripening of Swiss-type cheeses, characterised by round “eyes”. In these cheeses, they play an important role in characteristic flavour and opening. Opening is due to the production of carbon dioxide. Flavour is linked to the production by dairy propionibacteria of volatiles, mainly propionate and acetate, and other compounds derived from amino acid and lipid catabolisms [19, 20, 74, 130–132].

Some strains of dairy propionibacteria are also used in probiotic preparations, alone or in combination with lactic acid bacteria and/or bifidobacteria. A probiotic is defined as “a live microorganism which, when administered in adequate amounts, confers a health benefit on the host” [28]. An increasing number of reports on potential probiotic properties of propionibacteria have been published. However, there is far less literature on the probiotic properties of propionibacteria than on the lactobacilli and bifidobacteria. Two book chapters [53, 103] and two earlier reviews [84, 141] have reported on these potentialities. Recent evidence has been described in the literature but never reviewed. Moreover, no one has clearly sorted the probiotic characteristics described according to the level of evidence in the reports (in vitro, ex vivo, in vivo in animal models and in human beings). In addition, clinical studies have mainly reported on the use of dairy propionibacteria in complex bacterial mixtures and rarely with propionibacteria alone. This review provides an update on the probiotic potentialities of dairy propionibacteria and organises the potential health benefits according to the scientific level of the evidence. The paper only covers dairy propionibacteria, and only their probiotic potentialities in the gut. Uses as food preservatives and

Table I. Dairy and cutaneous *Propionibacterium* species.

Dairy (classical) propionibacteria	Cutaneous propionibacteria
P. acidipropionici	*P. acidifaciens*
P. cyclohexanicum	*P. acnes*
P. freudenreichii subsp. *freudenreichii*	*P. australiense*
P. freudenreichii subsp. *shermanii*	*P. avidum*
P. jensenii	*P. granulosum*
P. microaerophilum	*P. propionicum*
P. thoenii	

The species formerly known as *P. inoccuum* and *P. lymphophilum* have been reclassified as *Propioniferax innocua* [150] and *Propionimicrobium lymphophilum* [126], respectively.

animal probiotics are not described here but have been extensively discussed in reports mentioned above. This paper includes six sections reviewing first selection criteria for using propionibacteria as probiotics, then probiotic potentialities of dairy propionibacteria that are suggested distinctly in vitro, ex vivo, in vivo in animal models and in human clinical study. In each section, we will successively evoke the impact of dairy propionibacteria on the gut microbiota (lowering pathogenic microorganisms and favouring beneficial ones), on different aspects of gut mucosa physiology and on the immune system. Finally, the production of others compounds related to propionibacteria and future trends in their further applications are discussed.

2. SELECTION CRITERIA FOR USING PROPIONIBACTERIA AS PROBIOTICS

Selection of bacteria for probiotic application relies on criteria such as safety, technological and digestive stress survival, intestinal cell adhesion and human origin. The two last conditions are controversial and it is now recognised that they are not mandatory, although in some cases they may improve probiotic potential [118]. These selection criteria are summarised in Table II.

The safety of dairy propionibacteria is evidenced by the widespread consumption of Swiss-type cheese. The highest rate of Emmental consumption is found in France, where per capita consumption averages 4 kg·year^{-1}. Propionibacteria are present in Emmental in concentrations close to 10^9 bacteria per gram, and species *Propionibacterium freudenreichii* received the "Generally Recognised As Safe" (GRAS) [90]. This opens the way to other applications such as probiotics, as discussed below. For example, one criterion studied for probiotic use is the absence of antibiotic resistance, because of the risk that any resistance will spread to intestinal microbiota. Dairy propionibacteria have natural resistance to few antibiotics and this resistance does not appear to be encoded by plasmids or other mobile genetic elements [87]. In addition, dairy propionibacteria do not possess any known virulence factors, although some *Propionibacterium thoenii* and *Propionibacterium jensenii* strains have β-haemolytic activity [87]. The European food safety authority has granted "Qualified presumption of safety" (QPS) status to species *P. freudenreichii* [6]. No cytotoxic effect in mouse colonocytes [154] and no effect on the general health of rats [47, 71, 72] or infants [70] have been observed with strains of dairy propionibacteria. No indication of side effects from consuming dairy propionibacteria has been reported

Table II. Selection criteria for using dairy propionibacteria as probiotics.

Characteristic/effect	Described in vitro	Described ex vivo	Described in animals	Described in humans
Safety	N.D.	No decrease in viability of mouse colonocytes with *P. freudenreichii* and *P. acidipropionici* [154].	No effect on the general health of rats [47, 71, 72].	GRAS and QPS status [87, 90]. Emmental consumption. No effect on the general health in human beings [70, 128].
Digestive stress tolerance and survival in the gut	Constitutive acid and bile tolerance [46, 55, 79, 83, 127, 146, 151]. Efficient adaptive response to acid [54, 56] and bile [78] in *P. freudenreichii*.	N.D.	High propionibacteria survival in rats [47, 72] and mice [107]. 1–5E+10 cfu·day^{-1*} [47]. 2E+0 cfu·day^{-1*} [72]. 1E+09 cfu·day$^{-1*\dagger}$ [107].	*P. freudenreichii* survival in human beings [7, 55, 127]. 5E+10 cfu·day^{-1*} [7]. 5E+09 and 5E+10 cfu·day^{-1*} [55]. 4–8E+10 cfu·day$^{-1\dagger}$ [127].
Gut adhesion	Adhesion of *P. freudenreichii* to immobilised mucus [105, 129, 134]. Adhesion of propionibacteria to cultured human intestinal cells [45, 77, 93]. Increased adhesion of *P. freudenreichii* to immobilised mucus by probiotics combination [12, 104].	Adhesion of propionibacteria to isolated mice intestinal cells [153].	Adhesion of propionibacteria* to mice ileal epithelium [153]. Water with 1E+09 cfu·mL$_{-1}$.	N.D.

N.D.: not determined.
* Propionibacteria alone.
† Propionibacteria in combination with other probiotic bacteria.
Ingested quantities of propionibacteria are given when available.

in any of the human trials reviewed here [7, 25, 26, 40–43, 55, 57–61, 64, 68–70, 89, 94, 96, 97, 103, 116, 119–122, 124, 128, 138, 139].

In addition to their tolerance to technological stresses (cheese making, encapsulation, freeze-drying etc.), dairy propionibacteria present good constitutive survival under digestive stress. In vitro, many studies have described their natural ability to survive low pH conditions and exposure to bile [46, 55, 79, 83, 127, 146, 151]. This tolerance is reinforced by a brief exposure to the same stress at a non-lethal level [54, 56, 78, 80]. Propionibacteria adapted in this way are able to survive pH values as low as two and bile salts' concentrations higher than those reported in the human gut. The probiotic vector is also important for digestive stress tolerance. Propionibacteria in cheese had better tolerance to acid challenge than free cultures [56]. A yoghurt-type fermented milk provided *P. freudenreichii* with a high tolerance towards acid challenge, bile salts challenge and a succession of the two [79]. Survival during gastrointestinal transit has also been reported in vivo in rodents [47, 72, 107] and human beings [7, 55, 127]. A very high level of propionibacteria was detected in faeces but this concentration returned to the initial level a few days (or weeks) after consumption ceased.

Although controversial, another reported criterion for selecting probiotics is the ability to adhere to intestinal cells and/or mucosa. Dairy propionibacteria are able to adhere to immobilised mucus [105, 129, 134] and this adhesion was increased by the presence of other probiotic bacteria [12, 104]. The authors suggest that adhesion to mucus is the result of non-specific interactions, because adhesion to mucus and to bovine serum albumin was similar. Dairy propionibacteria also adhere in vitro to human intestinal epithelial cell lines [45, 77, 93]. Zarate et al. [153] demonstrated the adhesion of propionibacteria ex vivo to isolated mouse intestinal epithelial cells and in vivo by a plate count of the viable propionibacteria adhering to intestinal cells.

These properties of dairy propionibacteria − safety, gastrointestinal transit survival and adherence to intestinal cells and mucosa − offer good prospects for their use as human probiotics. Table III summarises promising properties further described below.

3. PROBIOTIC POTENTIALITIES OF DAIRY PROPIONIBACTERIA SUGGESTED IN VITRO

As regards modulation of gut microbiota, some authors have described a reduction in pathogen adhesion to immobilised mucus in the presence of *P. freudenreichii* subsp. *shermanii* JS, alone or in combination with other probiotic bacteria [11, 13–15, 95]. Collado et al. [15] showed that *P. freudenreichii* subsp. *shermanii* JS is able to aggregate with pathogenic bacteria. Myllyluoma et al. [95] described inhibition of *Helicobacter pylori* adhesion to a human intestinal epithelial cell line by *P. freudenreichii* subsp. *shermanii* JS alone. The authors observed the same inhibition with a combination with other probiotic bacteria. This combination also inhibited *H. pylori*-induced cell membrane leakage [95]. A major advantage of dairy propionibacteria for microbiota modulation is their ability to enhance the growth of bifidobacteria [62, 93, 116, 146]. Two bifidogenic compounds have been already identified in vitro: 1,4-dihydroxy-2-naphthoic acid (DHNA) [51] and 2-amino-3-carboxy-1, 4-naphthoquinone (ACNQ) [61, 92]. DHNA is a precursor of menaquinone (vitamin K2) biosynthesis in bacteria. Some DHNA is released from propionibacteria during growth [31]. ACNQ stimulated the growth of bifidobacteria at an extremely low concentration (0.5 nM) and enhanced the activity of NADH peroxidase and

Table III. Useful characteristics for probiotic applications and beneficial effects reported for dairy propionibacteria.

Characteristic/ effect	Described in vitro	Described ex vivo	Described in animals	Described in humans
Gut microbiota	1) Identification of bifidogenic compounds (DHNA and ACNQ) in *P. freudenreichii* [51, 61, 62, 67, 92, 116, 146].	N.D.	1) Modulation of mice microbiota by *P. acidipropionici*[*] [108]. Water with 1E+08 cfu·mL^{-1}.	1) Enhancement of bifidobacteria by *P. freudenreichii*[*] [7, 43, 61, 116, 121]. 5E+10 cfu·day^{-1} [7, 116].
	2) Coaggregation with pathogen strains by *P. freudenreichii* [15].		2) Reduction in the level of coliforms and increase in the level of bifidobacteria and lactobacilli in rat faecal microbiota by *P. freudenreichii*[†] [119, 120].	2) Modulation of intestinal microbiota in children by *P. freudenreichii*[†] [119, 120, 124]. 1E+10 cfu·day^{-1} [119].
	3) Reduction in pathogens adhesion to immobilised mucus by *P. freudenreichii* [11, 13, 14, 137].		3) Decrease in tissue colonisation and increase in time survival to *S. typhimurium* in mice by *P. acidipropionici*[*] [4]. 1.2E+09 cfu·day^{-1}.	3) Increase in bifidobacteria and decrease in bacteroides in human beings receiving DHNA [89, 122].
	4) Reduction in *H. pylori* adhesion on intestinal cells by *P. freudenreichii* [95].		4) Increase in bifidobacteria in mice receiving DHNA [99].	4) Improvement of the tolerance to the treatment of *H. pylori* infection by *P. freudenreichii*[†] [94, 97]. 5–9E+10 cfu·day^{-1} [97].
	5) Inhibition of *H. pylori*-induced cell membrane leakage in Caco-2 cells by *P. freudenreichii* [95].		5) DHNA recovery of loss of *Lactobacillus* and *Enterobacteriaceae* by DSS-induced colitis in mice [100].	5) Beneficial effect on gastric mucosa in *H. pylori* infected patients by *P. freudenreichii*[†] [96]. 2.5E+09 cfu·day^{-1}. 6) Decreased prevalence in oral *Candida* in elderly by *P. freudenreichii*[†] [40]. 5E+08 cfu·day^{-1}.

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Table III. Continued.

Characteristic/ effect	Described in vitro	Described ex vivo	Described in animals	Described in humans
Beneficial metabolic activities in the gut	β-galactosidase activity enhanced in the presence of bile by *P. acidipropionici* [151, 152].	N.D.	1) Increase in β-galactosidase activity and propionic acid in mice caecum by *P. acidipropionici*[*] [107]. 1E+09 cfu·day^{-1}. 2) Propionic acid fermentation of *P. freudenreichii*[*] in rats [72]. 2E+10 cfu·day^{-1}.	1) Modulation of SCFA in human faeces by *P. freudenreichii*[*] [55]. 5E+09 and 5E+10 cfu·day^{-1}. 2) Propionic acid fermentation of *P. freudenreichii* in human[*] [42]. 1E+11 cfu·day^{-1}.
Modulation of intestinal motility and absorption	1) Cholesterol uptake by *P. freudenreichii* [125].	1) Enhanced iron absorption from the rat colon in the presence of *P. freudenreichii* [8].	1) Decrease in serum cholesterol, in mice fed with a lipid rich diet, by *P. acidipropionici*[*] [106]. Water with 1E+08 cfu·mL^{-1}.	1) Constipation alleviation by *P. freudenreichii*[*] [43]. 2) Modulation of digestive motility by propionibacteria[*] [7]. 5E+10 cfu·day^{-1}. 3) Increase in defecation frequency in elderly by *P. freudenreichii*[*†] [102, 122].
Potential modulation of risk factors for cancer development	1) Binding of carcinogenic toxins [22, 23, 35–37, 39, 76, 98, 154].	Binding of carcinogenic toxins [24, 34, 35, 154].	1) Decrease in β-glucuronidase activity in mice caecum* [108]. Water with 1E+08 cfu·mL^{-1}.	1) Reduction in the faecal level of azoreductase activity in elderly subjects by *P. freudenreichii*[†] [102].

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Table III. Continued.

Characteristic/ effect	Described in vitro	Described ex vivo	Described in animals	Described in humans
Potential modulation of risk factors for cancer development	2) Binding of heavy metals [37, 50].		2) Increase in apoptosis in rats treated with DMH by *P. freudenreichii** [71]. 2E+10 cfu·day^{-1}.	2) Decrease in β-glucosidase and urease by *P. freudenreichii*† [41]. 2E+10 cfu·day^{-1}.
	3) Antimutagenic properties [140–143].			3) Decrease in β-glucuronidase activity by *P. freudenreichii*† [59]. 2E+09 cfu·day^{-1}.
	4) Induction of apoptosis [52, 73].			4) Reduction in the faecal level of aflatoxin B1 by *P. freudenreichii*† [25].
	5) Induction of NKG2D ligand expression on cancer cells by *P. freudenreichii* and *P. acidipropionici* [5].			5) Reduction of colon exposure to aflatoxin B1 by *P. freudenreichii*† [26]. 2–5E+10 cfu·day^{-1}.
Healing on intestinal inflammation	N.D.	N.D.	1) Healing by *P. freudenreichii** and *P. acidipropionici** of TNBS-induced colitis in rats [88, 135].	1) Improvement of the clinical activity index scores in active ulcerative colitis patients receiving DHNA [89, 128].
			2) Attenuation of DSS-induced colitis in mice by DHNA [100].	2) Alleviation of the symptoms of irritable bowel syndrome by *P. freudenreichii*† [57, 58, 60]. 1–2E+09 cfu·day^{-1}.
Immunomodulation	1) Inhibition of *H. pylori*-induced IL-8 and PGE_2 released in Caco-2 cells by *P. freudenreichii* [95].	N.D.	1) Stimulation of mice phagocytosis by *P. acidipropionici** [91, 106]. Water with 1E+08 cfu·mL^{-1} [106].	1) Decrease in serum levels of CRP by *P. freudenreichii** [64]. 3.3E+10 cfu·day^{-1}.

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Table III. Continued.

Characteristic/ effect	Described in vitro	Described ex vivo	Described in animals	Described in humans
Immunomodulation	2) Induction of NKG2D ligand expression on human-activated T lymphocytes by *P. freudenreichii* and *P. acidipropionici* [5].		2) Stimulation of lymphocyte proliferation in mice by *P. freudenreichii* and *P. jensenii* [3, 65]. 1E+08 cfu·day^{-1} [3]. 1E+09 and 1E+12 cfu·kg^{-1} body weight·day^{-1} [65].	2) Induction of IL-4 secretion in infants PBMC with CMA by *P. freudenreichii* [109]. 2E+09 cfu·day^{-1}.
	3) Induction of TNF-α and IL-10 in PBMC by *P. freudenreichii* [63].		3) Increase in the level of secreted IgA by *P. acidipropionici* in mice* [4]. 1.2E+09 cfu·day^{-1}.	3) Prevention of IgE-associated allergy in caesarean-delivered children by *P. freudenreichii*† [68]. 2E+09 cfu·day^{-1}.
			4) Anti-inflammatory effect of DHNA [99].	4) Increase in the resistance to respiratory infections during the first two years of life by *P. freudenreichii*† [70]. 2E+09 cfu·day^{-1}.
				5) Prevention of atopic eczema/ dermatis syndrome in infants by *P. freudenreichii*† [69, 138, 139]. 4E+09 cfu·day^{-1}.

N.D.: not determined.
* Propionibacteria alone.
† Propionibacteria in combination with other probiotic bacteria.
Ingested quantities of propionibacteria are given when available.

NADH oxidase in bifidobacteria. ACNQ, which may derive from DHNA, is an electron acceptor of NAD(P)H diaphorase and an electron donor of NAD(P)H peroxidase in bifidobacteria [61, 89, 148, 149]. NAD(P)+ regeneration is thought to be responsible for the ability of propionibacteria to stimulate bifidobacteria growth via DHNA and ACNQ. It is also worth noting that propionate, the main end-product of propionibacteria fermentation, is considered to favour the growth of bifidobacteria [62]; a property used in bifidobacteria selective culture media [38].

As regards modulation of gut enzyme activity, some bacterial species including yoghurt starters are efficient in treating lactose intolerance by enhancing β-galactosidase activity in the intestine [18]. *Propionibacterium acidipropionici* and *P. freudenreichii* have a high level of β-galactosidase activity at 37 °C [152] which was even improved in the presence of bile [151, 152], by permeabilisation of cells. The authors conclude that the environment in the human intestine may be adequate for β-galactosidase synthesis and activity. They also suggested that a fermented dairy product constitutes a good vector for high β-galactosidase activity. Moreover, the enzyme withstood the cooking temperature of Swiss-type cheeses and proved to be stable during storage at low temperatures.

Propionate was recently shown to enhance expression of epithelial calcium channel $ECaC_2$, which is involved in the transcellular route of intestinal calcium absorption in Caco-2 cells [30]. This would at least partly explain why propionate was shown to enhance calcium absorption from the human colon [133]. Intestinal absorption of lipids may be modulated by the consumption of probiotics, including dairy propionibacteria. Somkuti and Johnson found evidence of adsorption of cholesterol to *P. freudenreichii* cells. This adsorption was mainly passive, as 70% of the cholesterol removed from the medium could be recovered by solvent extraction from washed cells [125]. This suggests, however, that the presence of dairy propionibacteria in the gut may reduce the bioavailability of cholesterol.

Propionibacteria may contribute to reduction of risk factors for cancer development particularly through the ability to bind, in vitro, carcinogenic compounds like mycotoxins [22, 98] and especially aflatoxin B_1 [24, 35–37, 39, 76], cyanotoxins such as microcystin-LR [37], plant lectins such as concanavilin A and jacalin [154], and also some heavy metals such as cadmium and lead [37, 50]. The organic toxins cited above are particularly associated with colorectal cancer. Heavy metals have many deleterious effects on human health including kidney or other cancers. These data suggest that dairy propionibacteria may help to reduce gut absorption of carcinogenic compounds and so limit the emergence or development of cancer. In addition, these bacteria may be used as detoxifying additives in food contaminated by high levels of this kind of carcinogenic compound which are very difficult to remove. Vorobjeva et al. [140–142] demonstrated the antimutagenic properties of dairy propionibacteria.

P. freudenreichii subsp. *shermanii* prevented mutations caused by various mutagenic agents. The suggested active component is a cysteine synthase of 35 $kg{\cdot}mol^{-1}$, secreted into the extracellular environment [142]. Another potential anti-cancer property is the ability of *P. freudenreichii* and *P. acidipropionici* to induce apoptosis of colorectal carcinoma cells owing to the action of short-chain fatty acids, especially propionate, on cancer cell mitochondria [52, 73]. These data suggest that the use of dairy propionibacteria could reduce the incidence of colon cancer or help to treat this cancer, which is the second most fatal cancer in Europe. In addition, *P. freudenreichii* and *P. acidipropionici* induced NKG2D ligand expression on various cancer cells and the authors speculate that the pro-apoptotic effect may also be mediated by this overexpression [5].

P. freudenreichii has been observed to modulate the immune system in vitro by inhibition of *H. pylori*-induced IL-8 and PGE_2 release in human intestinal epithelial cells [95]. These anti-inflammatory effects did not persist when *P. freudenreichii* subsp. *shermanii* JS was used in combination with *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC-705 and *B. breve* Bbi99. The authors stress the importance of characterising the individual strains to improve the therapeutic response of probiotics used in combination. In addition, *P. freudenreichii* and *P. acidipropionici* induced NKG2D ligand MICA/B expression on human-activated T lymphocytes without affecting this expression on resting peripheral blood cells. This effect was also observed with propionate alone and to a lesser extent by acetate [5]. Expression is stimulated by higher promoter activity due to a mechanism that depends on intracellular calcium. The authors suggest that preoperative treatment with cutaneous propionibacteria strains may produce beneficial immunostimulation and increased survival of patients with colorectal carcinoma. As regards cytokine production, *P. freudenreichii* subsp. *shermanii* JS was able to induce TNF-α and IL-10 production in human PBMCs [63]. The anti-inflammatory actions of IL-10 could be helpful in the treatment of inflammatory conditions or diseases. Interestingly, *P. freudenreichii* subsp. *shermanii* JS induced the expression of IL-12 (pro-inflammatory cytokine) only weakly [63], suggesting useful implication to treat colitis as reported earlier [29]. *E. coli* DH5α-induced IFN-γ production was also reduced when it was combined with *P. freudenreichii* subsp. *shermanii* JS [63].

4. PROBIOTIC POTENTIALITIES OF DAIRY PROPIONIBACTERIA STUDIED EX VIVO

P. freudenreichii enhanced iron absorption from the rat proximal colon ex vivo, via the production of short-chain fatty acids (SCFA), especially propionate [8]. The authors suggest that this absorption may be enhanced in vivo by local production of SCFA. This suggests a positive effect of dairy propionibacteria on the bioavailability of dietary iron for uptake by the liver and spleen.

The ability of dairy propionibacteria to bind carcinogenic compounds like aflatoxin B_1 has also been described ex vivo [24, 34, 35]. A mixture of *P. freudenreichii* subsp. *shermanii* JS and *L. rhamnosus* LC-705 was able to bind aflatoxin B_1 and tissue uptake of this carcinogen was reduced when probiotic bacteria were present in a duodenal loop. Consequently, this probiotic mixture could delay, but not prevent, aflatoxin B_1 absorption in duodenal loops. Hence, ingestion of dairy propionibacteria may limit bioavailability, absorption and metabolisation of these carcinogenic compounds and so decrease cancer emergence risk.

5. PROBIOTIC POTENTIALITIES OF DAIRY PROPIONIBACTERIA IN ANIMAL MODELS

Sarkar and Misra [119, 120] showed a decline in the total number of faecal bacteria in rats fed a fermented milk containing *Bifidobacterium bifidum*, *P. freudenreichii* subsp. *shermanii* and either *L. acidophilus* or not. Especially, the number of coliforms was decreased, but an increase in the bifidobacteria population was observed. Perez-Chaia et al. [108] noticed a similar microbiota modulation in mice consuming *P. acidipropionici*, with fewer anaerobes and coliforms in the caecal content. Moreover, Alvarez et al. [4] reported that feeding a *P. acidipropionici* CRL 1198 supplement to mice prior to *Salmonella typhimurium* administration afforded a partial protection against the pathogen colonisation. Indeed, a decrease in tissue colonisation

by *S. typhimurium* and an increase in the mice survival rate were observed. The *P. freudenreichii* component DHNA ingested by mice presenting a dextran sodium sulphate (DSS)-induced colitis led to a modulation of the microbiota, including a weaker drop in the *Lactobacillus* and *Enterobacteriaceae* intestinal populations caused by DSS [100]. DHNA also increased intestinal bifidobacteria population in mice suffering from non-steroidal anti-inflammatory drug (NSAID)-induced colitis [99]. *Bifidobacterium* is probably the most amply documented genus of the human microbiota studied for probiotic properties. Thus, stimulation of bifidobacteria growth by dairy propionibacteria therefore constitutes a key probiotic potential.

Metabolic activity of *P. freudenreichii* has been described in the gastrointestinal tract of human microbiota-associated rats [72]. Transcriptional activity within the intestine was demonstrated by the presence of *P. freudenreichii*-specific transcarboxylase mRNA. Transcarboxylase is involved in propionic acid metabolism. Strain TL133 also increased the concentrations of acetate, propionate and butyrate in rat caecal contents [72]. In another study, mice fed *P. acidipropionici* CRL 1198 showed increased β-galactosidase activity and enhanced propionic acid levels in the caecum [107]. This strain also tends to reverse the hyperlipidemic effect of a high lipid diet [106]. This effect can be attributed to modulation of liver metabolism by absorbed propionic acid but can also be linked to the cholesterol-binding activity described above [125]. Hypolipidemic effects of dairy propionibacteria should be confirmed in human studies.

Many bacterial enzymes, including β-glucosidase, β-glucuronidase, azoreductase and urease, are involved in producing carcinogens within the gut. Many probiotic studies have monitored the activity of these faecal enzymes. A potential modulation of risk factors for carcinogenesis has been observed in animal models. In mice fed *P. acidipropionici*, β-glucuronidase activity was lower than in controls on a conventional diet [108]. With a red cooked meat supplement, the β-glucuronidase activity increased in the control mice. In the faeces of propionibacteria-supplemented mice, β-glucuronidase activity increased much less than in the control at the beginning of the meat diet and decreased thereafter. Propionibacteria supplementation prevented the increase in β-glucuronidase activity with the red meat diet. The authors also describe a slight reduction in azoreductase and nitroreductase activity [108]. Lan et al. [71] report that *P. freudenreichii* TL133 increased induction of apoptosis in colonic mucosal crypts of human microbiota-associated rats treated with the carcinogen 1,2-dimethylhydrazine (DMH). The administration of propionibacteria alone did not increase the number of apoptotic cells in healthy colonic mucosa. This study demonstrates the ability of *P. freudenreichii* to favour apoptotic depletion of damaged cells at an early stage of malignant cell transformation in rats.

As regards intestinal inflammation, in some studies, colonic infusion with *P. acidipropionici* [88] or oral supplementation with a milk whey culture of *P. freudenreichii* ET-3 [135] reduced the severity of TNBS-induced colitis in rats. The healing of TNBS-induced colitis was also observed with oral administration of propionate [135]. In therapeutic and preventive studies, DHNA improved the survival rate and histological damage scores of mice with DSS-induced colitis [100]. DHNA attenuated colonic inflammation not only by balancing intestinal bacterial ecosystem but also by suppressing lymphocyte infiltration [100]. Okada et al. [99] report that DHNA had an anti-inflammatory effect on NSAID-induced colitis in IL-10-knockout mice through increased numbers of *Bifidobacteria* and suppression of inflammatory cell infiltration.

As regards immunomodulation, Perez-Chaia et al. [106] observed an improvement in carbon clearance in mice fed with *P. acidipropionici* CRL 1198, indicating an enhanced phagocytic function of the reticulo-endothelial system. Administration of this strain prior to *S. typhimurium* pathogen inoculation led to an increase in both anti-*S. typhimurium* IgA levels and numbers of cells producing the antibody [4]. Moreover, *P. acidipropionici* enhanced the phagocytic activity of isolated mouse peritoneal macrophages [106], which was higher with mice fed propionibacteria than in the controls. The orally administered *P. acidipropionici* showed this immunostimulating activity with isolated cell wall but not with isolated peptidoglycan [91]. Immune system modulation by dairy propionibacteria may be related to the chemical composition of the cell walls, particular molecules protruding from the surface. Oral treatment of mice with *P. freudenreichii* subsp. *shermanii* JS in combination with *L. rhamnosus* GG increased T-cell and B-cell proliferation after stimulation with concanavalin A (T-cell mitogen), and lipopolysaccharide (B-cell mitogen), respectively [65]. The authors suggest that these results may indicate that the splenic lymphocytes acquired a higher tolerance to the cytotoxic effects of the mitogens. They suggest that they are related to the capacity of dairy propionibacteria to bind this lectin in vitro, as cited above. Another study showed a higher T-cell proliferation of splenic lymphocytes with *P. jensenii* 702 in mice receiving soluble *Mycobacterium tuberculosis* antigens [3]. The strain has been patented as an adjuvant for oral vaccines [1, 2].

6. PROBIOTIC POTENTIALITIES OF DAIRY PROPIONIBACTERIA IN HUMAN

Many teams have studied the impact of dairy propionibacteria on the human microbiota. In several independent studies, ingestion of *P. freudenreichii* in the form of whey cultures, whether heat-inactivated [61, 121] or not [43], or as freeze-dried live bacteria forms [7, 116], resulted in a higher faecal bifidobacteria population in human beings. Sarkar and Misra [119, 120] showed that a fermented milk containing *B. bifidum*, *P. freudenreichii* subsp. *shermanii* and either *L. acidophilus* or not led to a decline in coliforms and to an increase in bifidobacteria in the faeces of infants receiving the product. Whey cultures with *P. freudenreichii* ET-3 also triggered a decrease in *Clostridium perfringens* [122] and *Bacteroides* populations [89]. In children suffering from intestinal dysbacteriosis, consumption of a milk containing *P. freudenreichii* subsp. *shermanii* and *L. acidophilus* restored of the microbiota, thus shortening the convalescence period during antibiotherapy [124]. Hatakka et al. [40] report that a cheese containing a mixture of probiotics (*L. rhamnosus* GG, *L. rhamnosus* LC705 and *P. freudenreichii* ssp. *shermanii* JS) reduced the risk of high yeast counts, especially *Candida* sp., in the mouth of elderly people. These authors also observed that probiotic intervention reduced the risk of hyposalivation and a dry mouth sensation and can therefore be considered beneficial to oral heath in general. In fact, the authors suggest that the absence of protective probiotics and increased hyposalivation might explain the enhanced *Candida* growth in the control group. A probiotic supplementation with *L. rhamnosus* GG, *L. rhamnosus* LC70, *B. breve* Bb99 and *P. freudenreichii* ssp. *shermanii* JS did not significantly reduce the frequency of new or aggravated symptoms caused by antibiotic treatment during *H. pylori* eradication [97], although this probiotic combination has exhibited promising anti-*Helicobacter* properties in vitro (see section above). However, taking total symptom severity into account, this study suggests improved tolerance of the anti-*H. pylori* treatment. The authors also

show that the probiotic bacteria survived in the gastrointestinal tract despite the intensive antimicrobial therapy [97]. A more recent study has confirmed that the same probiotic mixture counteracts the effects of antibiotic treatment against *H. pylori* [94]. In particular, reduced *H. pylori*-induced inflammation of the gastric mucosa was observed [96]. Altogether, these results strongly suggest that the tested probiotics, containing *P. freudenreichii* subsp. *shermanii* JS, may be helpful during the treatment of *H. pylori* infection.

Hojo et al. [43] report that a high faecal bifidobacteria level due to *P. freudenreichii* ET-3 supplementation was linked to an increased number of defecations in constipated female volunteers. Stool frequency was also significantly increased by administration of a *P. freudenreichii* culture in healthy human subjects [61] and in elderly subjects [122]. In another study, elderly subjects receiving a *L. rhamnosus* and *P. freudenreichii*-supplemented juice also exhibited an increase in defecation frequency [102]. This probiotic property is interesting because constipation is a common problem in elderly subjects. Another clinical study reported a limited effect on segmental colonic motility, including slower transit in the left colon [7]. The authors suggested that propionibacteria may regulate transit when this one is disturbed.

The consumption of a juice supplemented with *L. rhamnosus* LC-705 and *P. freudenreichii* subsp. *shermanii* JS led to decreased faecal azoreductase activity in elderly subjects [102]. The same probiotic combination was used in healthy men and led to a non-significant decrease in β-glucosidase activity of 10% and in urease activity of 13% [41]. In irritable bowel syndrome patients, a probiotic mixture containing *L. rhamnosus* GG, *L. rhamnosus* LC-705, *B. breve* Bb99 and *P. freudenreichii* subsp. *shermanii* JS led to a decrease in β-glucuronidase activity in most people in the probiotic group [59]. A clinical trial investigated the effect of a probiotic preparation containing *L. rhamnosus* LC-705 and *P. freudenreichii* subsp. *shermanii* JS on levels of aflatoxin B_1 in human faecal samples. Following probiotic administration, there was a significant reduction in the faecal level of aflatoxin B_1 and this decrease continued during the follow-up period [25]. Another study with the same probiotic supplementation in young men from Southern China found an increase in urinary samples with negative aflatoxin B_1-N^7-guanine and a decrease in the concentration of urinary aflatoxin B_1-N^7-guanine in the probiotic group [26]. Aflatoxin B_1-N^7-guanine is a marker for a biologically effective dose of aflatoxin. The probiotic supplementation thus reduced the organism's exposure to this carcinogen.

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 ulcerative colitis patients [89, 128]. Patients also showed a decrease in the endoscopic index and an improvement in serum haemoglobin and albumin concentrations [128]. An increase in all SCFA concentrations was measured after BGS ingestion but this was significant only for butyrate [128]. The authors suggest that BGS restores a healthy microbial balance, thus favouring beneficial competitive interactions which may prevent or treat ulcerative colitis.

Kekkonen et al. [64] report that a probiotic intervention with *P. freudenreichii* subsp. *shermanii* JS in healthy adults led to a reduction in the serum level of C-reactive protein (CRP) compared to a placebo control. CRP being a sensitive inflammation marker, this result confirms the anti-inflammatory potential of dairy propionibacteria. In a randomised, placebo-controlled, double-blind trial was performed in Helsinki on infants at high risk of allergy, a probiotic mixture containing *L. rhamnosus* GG, *L. rhamnosus* LC-705, *B. breve*

Bb99 and *P. freudenreichii* subsp. *shermanii* JS was given daily for six months after birth and compared to a placebo [68–70]. Two years after birth, less antibiotic prescription and fewer respiratory infections were reported in the supplemented infant group, whatever the mode of delivery [70]. In addition, less eczema and less atopic eczema were diagnosed in the treated group [69]. Five years following birth, significant differences were detected among caesarean-delivered children: less IgE-associated disease occurred, particularly eczema, and less IgE sensitisation was detected [68]. Thus, during the first stages of life, probiotic supplementation including propionibacteria seems to promote immune system maturation, preventing infections and allergies. In addition, such supplementation would further counteract disorders linked to caesarean delivery such as delayed colonisation of the gut by bifidobacteria and lactobacilli. Another randomised, placebo-controlled, double-blind trial tested the same probiotic mixture in infants with atopic eczema-dermatitis syndrome (AEDS) and suspected cow's milk allergy (CMA). Soluble E-selectin and plasma IL-10 levels were higher after probiotic supplementation than after placebo treatment [139] and faecal IgA levels tended to be higher in the probiotic group [138]. Another study showed that a mixture of *P. freudenreichii* subsp. *shermanii* JS, *L. rhamnosus* GG and LC-705 and *B. breve* Bbi99 increased IL-4 secretion and tended to stimulate IFN-γ secretion in PBMCs of infants with CMA [109]. This may offer clinical benefits in the treatment of allergic diseases by immunologic means. Altogether, these clinical data indicate beneficial immunomodulation by a mixture of gram-positive bacteria including *P. freudenreichii* subsp. *shermanii* JS, with a reported anti-inflammatory effect of the latter. Further clinical data should pin down the role of dairy propionibacteria per se.

7. PRODUCTION OF OTHER COMPOUNDS AND FUTURE TRENDS

Many other properties of dairy propionibacteria can be regarded as beneficial [49]. They secrete bacteriocins [44], anti-fungal compounds [81] and anti-viral compounds [16, 32, 33, 112–115] and are therefore used as food preservatives. Propionate, being an SCFA, has been investigated for its health effects. In particular, preliminary in vitro investigations suggest that propionate has a role inducing apoptosis of gastric cancer cells [85] and in preventing colon cancer cell colonisation [27]. In vivo, propionate increased secretion of intestinal mucus in rats [123] and human colorectal calcium absorption [133]. The suggested beneficial effects of propionate suggest similar properties for dairy propionibacteria, mediated by their metabolism end-products. As an example, induction of the satietogen peptide PYY by SCFAs having been reported [9], Ruijschop et al. [117] tested a dairy product fermented by lactic acid bacteria and propionibacteria in a human study. After consumption of this product, subjects felt significantly fuller, were less hungry and had less desire to eat [117]. However, the authors report no effect on ad libitum food consumption. Also of health interest is the capacity of dairy propionibacteria to improve the nutritional quality of fermented products by synthesising vitamins, trehalose and conjugated linoleic acid (CLA). Dairy propionibacteria synthesise vitamin B_8 (biotin), B_9 (folic acid) and B_{12} (cobalamin) [49]. Folic acid has been described as an agent for colorectal cancer prevention but this claim is controversial [48]. Trehalose has been observed to reduce the level of enterohaemorrhagic *Escherichia coli* O157:H7 in ruminants because this sugar can be used by commensal *E. coli* but not by the O157:H7 strain [17]. The broad spectrum of biological effects reported for conjugated linoleic acids [10, 144] includes

the anticarcinogenic properties of rumenic acid, the cis-9,trans-11 stereoisomer of CLA [75, 82]. *P. freudenreichii* has been shown to convert linoleic acid to rumenic acid [86, 110, 111, 136, 145] and the corresponding mechanisms have been identified [86]. As the authors of that study suggest, rumenic acid formation in the human gut could promote health.

The technological qualities of dairy propionibacteria constitute a key advantage for their uses as probiotics. They survive the technological stresses imposed during freeze-drying, spray-drying, reconstitution in milk, cheese making and storage at low temperatures. Dairy propionibacteria ferment a wide range of carbohydrate substrates. Such remarkable adaptability, robustness and versatility are consistent with the occurrence of propionibacteria in various niches and should allow their growth and/or viability in a variety of probiotic vectors.

Most of the clinical studies have been conducted using mixtures of bacteria from different genera. The development of a pure culture of dairy propionibacteria in a food grade vector will make it possible to pin down their specific probiotic potential in human beings. However, synergistic effect between different probiotics should also be investigated in the different fields of beneficial activity. In addition, complex interactions between ingested probiotics and the complex gut microbiota should be taken into consideration. In this context, the ability of dairy propionibacteria to modulate this microbiota, beyond the propionibacteria population itself, is of particular interest.

Probiotic properties "in general", including bifidobacteria and lactobacilli, differ from a species to another and are strain-dependent. It is therefore necessary to screen a large number of dairy propionibacteria in order to select strains with the best potentialities for dedicated applications. In this context, such approach to study immunomodulation of a large set of diverse single propionibacteria both in vitro (PBMC) and in vivo (experimental colitis and infectious mice models) have already been initiated and developed (Deutsch/Foligné et al., personal communication) and should fill some gaps soon. Besides classical screening methods, the first dairy *Propionibacterium* genome from a *P. freudenreichii* subsp. *shermanii* strain is expected to be available soon. Genomic data will allow new mechanistic investigations of its probiotic potential [66].

8. CONCLUSION

In conclusion, although more experimental data are available concerning probiotic applications of bifidobacteria and lactobacilli, dairy propionibacteria also deserve attention. Indeed, there is now specific promising evidence from dairy propionibacteria regarding beneficial modulation of colon microbiota and carcinogenesis together with anti-inflammatory and immune properties. Future works should focus on the development of molecular tools and appropriate delivery vectors as well as on selecting the best strains. Progress on these aspects will allow specific clinical studies. These in turn should lead to a better understanding and exploitation of the beneficial effects of dairy propionibacteria in the different compartments of the gastrointestinal tract.

Individual probiotics demonstrate unique, specific biological effects. Knowledge of the specific effects of each probiotic strain will allow the development of probiotic mixtures adapted to particular cases or pathologies. Selecting (mixtures of) probiotics for use in disease(s) treatment will be guided by improved knowledge on action mechanisms based on established experimental models from in vitro to clinic. Knowledge of probiotic mechanisms may allow us to select the strain(s) with the best possible expected biological outcome.

However, bench-to-bedside clinical trials will remain necessary to validate the chosen strain selection strategy. It will also confirm the physiological effectiveness of the proposed mechanisms in, for example, a wider population of patients suffering immune disorders, such as Inflammatory Bowel Diseases (IBD) and Irritable Bowel Syndrome (IBS), as well as other gastrointestinal infection diseases, cancers and allergies.

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Abbreviations list

ACNQ	2-amino-3-carboxy-1,4-naphthoquinone
AEDS	atopic eczema-dermatitis syndrome
BGS	bifidogenic growth stimulator
CLA	conjugated linoleic acid
CMA	cow's milk allergy
CRP	C-reactive protein
DHNA	1,4-dihydroxy-2-naphthoic acid
DMH	1,2-dimethylhydrazine
DSS	dextran sodium sulphate
EFSA	European food safety authority
GRAS	generally recognised as safe
IBD	inflammatory bowel diseases
IBS	irritable bowel syndrome
NSAID	nonsteroidal anti-inflammatory drug
QPS	qualified presumption of safety
SCFA	short-chain fatty acid
TNBS	trinitrobenzene sulphonic acid