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## Dairy starters and fermented dairy products modulate gut mucosal immunity

Nassima Illikoud<sup>a</sup>, Marine Mantel<sup>a,b</sup>, Malvyne Rolli-Derkinderen<sup>b</sup>, Valérie Gagnaire<sup>a</sup>, Gwénaél Jan<sup>a,\*</sup>

<sup>a</sup> INRAE, Institut Agro, STLO, Rennes, France

<sup>b</sup> Université de Nantes, Inserm, TENS, The Enteric Nervous System in Gut and Brain Diseases, IMAD, Nantes, France

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### ABSTRACT

The gut microbiota plays a crucial role in the regulation of mucosal immunity and of the function of the intestinal barrier. Dysbiosis is accordingly associated with rupture of mucosal immune homeostasis, leading to inflammatory intestinal diseases. In this context, probiotic bacteria, including a new generation of intestinal probiotics, can maintain intestinal homeostasis and promote health. Surprisingly, little is known about the impact of fermented dairy products in this context, while they represent our main source of live and active bacteria. Indeed, they provide, through our daily diet, a high number of bacteria whose effect on mucosal immunity deserves attention. Among bacteria ingested in fermented dairy products, *Streptococcus thermophilus*, *Lactobacillus delbrueckii*, *Lactobacillus helveticus*, *Lactococcus lactis* and *Propionibacterium freudenreichii* are on top, as they are ingested in high concentrations (close to 10<sup>9</sup> per gram of product) in fermented milks or cheeses. This review gives an overview of the potential immunomodulatory effects of these main dairy starters. It further explores studies dealing with fermented dairy products containing these starters, in a context of inflammation.

### Evolution of lifestyle leads to rupture of intestinal homeostasis and barrier function

Our lifestyle has changed dramatically since the last 70 years in terms of diet, medication, and increased sedentary lifestyle. One main point is the change in the food processing and eating habits associated with the worldwide Western diet, long-lasting settled in the everyday life. This western diet is mainly marked by ultra-processed foods, including refined and modified food components, as oils, fats hydrogenated or not, sugars and sweeteners, starch more or less modified, processed proteins, and various food additives, rendering the food highly palatable with empty and unnecessary calories [32]. As a consequence, such a diet leads to numerous dramatic changes in the overall food quality. Depletion of fiber, deficiency of vitamins, increase of saturated fatty acids and sugars, as well as the frequent addition of food additives, are particularly noticed. They can alter the human health in a short term, and particularly affect the intestinal homeostasis as illustrated in Fig. 1. The intestinal homeostasis is a fragile balance, finely regulated by complex interactions between the intestinal epithelial barrier (IEB), the gut microbiota, the immune system, and the enteric nervous system

(ENS) [75]. In case of deregulation, i.e. dysbiosis, prevalence of inflammatory chronic diseases, diabetes and cardiovascular higher risks and obesity increase [62].

Fiber depletion can change the homeostasis by directly or indirectly influencing the gut microbiota. The richness of the microbiota can actually be decreased, with a higher Firmicutes to Bacteroidetes ratio observed [38] as well as the production of short chain fatty acids, which helps to lower the luminal pH and inhibit the growth of pathogenic bacteria [80], while a higher mucus degradation can be observed, lowering the overall mucosal protection [23]. For the food additives, the consequences are numerous and depend on the type of additives used. For example, maltodextrin, largely used as thickening agent, change bacterial mucosal colonization in mice, leading to higher levels of pathogenic bacteria as *Salmonella* and *Escherichia coli* [91,92]. Emulsifiers as polysorbate 80 and carboxymethylcellulose have a pro-inflammatory potential in human [14] and in colitis-induced context in mice [13]. Regarding the non-caloric artificial sweeteners, their short- or long-term use in humans or mice results in dysbiosis of the gut microbiota associated with glucose intolerance as shown for saccharin [130]. Prenatal exposure to sucralose resulted in altered

\* Corresponding author.

E-mail address: [gwenael.jan@inrae.fr](mailto:gwenael.jan@inrae.fr) (G. Jan).

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composition and metabolism of the gut microbiota in pups [103], and changes in the tryptophan metabolism, essential for regulation of digestive functions, were notably observed in mice [7]. Another worrying feature of Western-diet is the presence of large quantities of micro-particles (> 10<sup>12</sup>/day) derived from food additives, that can affect intestinal homeostasis. Among them, titanium dioxide (TiO<sub>2</sub>) is one of the most widely used whitening food colorants. Studies support the pro-inflammatory effects of TiO<sub>2</sub>, a shift in the gut microbiota as well as an alteration of the IEB with bacterial translocation [6,76,115]. In rats, TiO<sub>2</sub> accumulates in the liver and Peyer’s patches following short-term exposure (7 days). Besides, a long duration of exposure contributed to a low-grade inflammation [6]. This inflammation can be explained by effects on the microbiota and the intestinal barrier. Indeed, rats exposed to TiO<sub>2</sub> had a decrease in SCFA as well as an increase in antimicrobial peptides. This suggests an alteration of the gut microbiota in rats. In addition, TiO<sub>2</sub> altered the IEB, decreased Muc-2 biosynthesis and altered colonic crypt length [76].

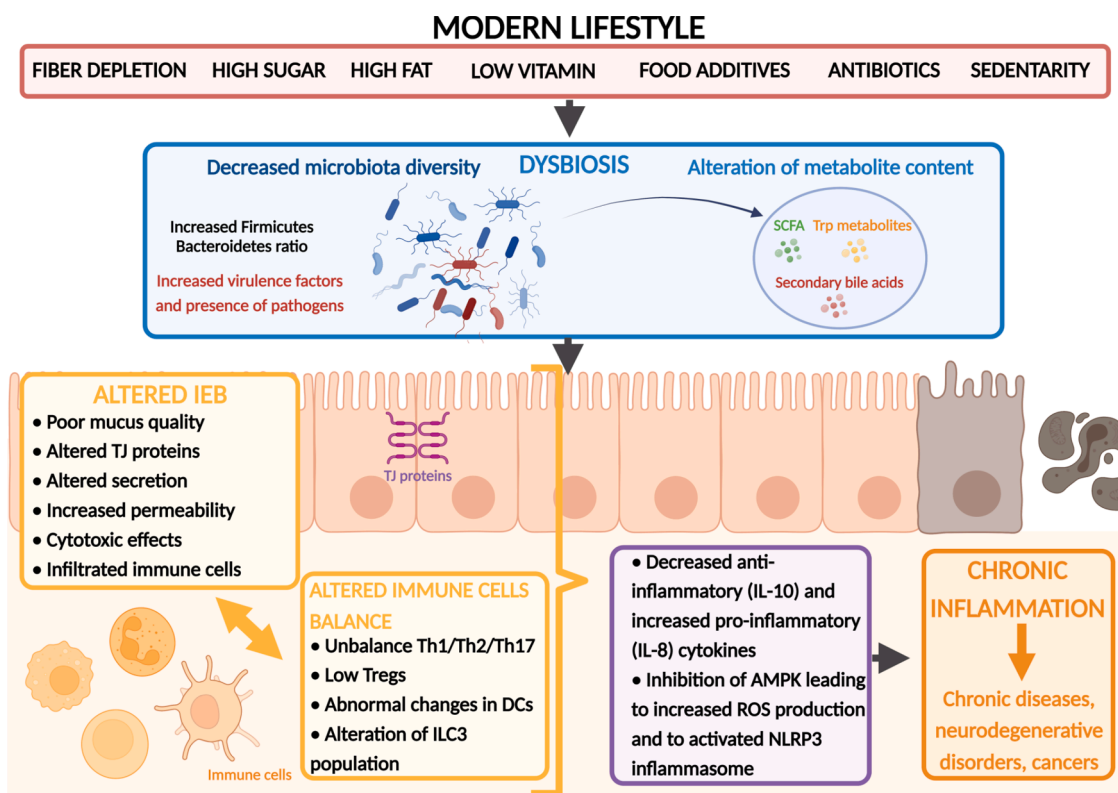
Western diet is also facing opposing disadvantages: excess of some components as fat and sugar and deficiency in vitamins. Excessively rich diet leads to an alteration of the IEB, which contributes to intestinal dysbiosis, inflammatory status, and even enhanced intestinal permeability [42,139]. Vitamin D deficiency is associated with IBD [34], while vitamin A therapies control intestinal inflammation [10]. In case of celiac diseases, the vitamin D deficiency can aggravate the reduction of bone mineral density, the increase in proinflammatory cytokines and the intestinal calcium malabsorption via a reduction of the vitamin receptor in the IEB and of some proteins involved in the tight junctions [2].

Finally, beside the role of the food component other parameters of our lifestyle, as sedentary lifestyle and medication with the increasing

use of antibiotics, also negatively impacts the gut homeostasis (Fig. 1). Thus, sedentary lifestyle led to low intestinal motility, fecal diversity and higher inflammatory status in elderly population [18]. The physical activity has been proposed as a way to alleviate some intestinal bowel syndromes [51] and seems to positively affect the gut microbiota and promote an anti-inflammatory state [19]. Regarding the antibiotics, they directly act on the gut microbiota and an excessive use of antibiotics promotes the development of chronic diseases like IBD, IBS [47], causes impairment of IEB and increase inflammation. Actually, they induce a decrease in the microbial diversity by killing pathogenic as well as collaterally beneficial microorganisms, which in turn leads to a decrease in T cells in the gut. In addition, the use of antibiotics inhibits the expression of mitochondrial genes and the number of active mitochondria, which ultimately induced cell death in the GI epithelium [88].

**Bacteria within the gut lumen modulate intestinal homeostasis and barrier function**

The human gastrointestinal tract harbors about 10<sup>14</sup> microbes belonging to 1000 species. This number is more than 10-fold the number of eukaryotic human cells [122]. This intestinal microbiota is crucial to human health since it influences host nutrition development and modulation of the immune system, and intestinal barrier function [39]. The results of various studies demonstrated a link between intestinal barrier dysfunction and human gastrointestinal diseases [52,95]. Furthermore, several studies have documented the beneficial effects of probiotics in diverse gastrointestinal diseases including IBD [39,118]. They provide the preservation of intestinal barrier by various mechanisms including (i) the decrease in pathogenic bacterial adhesion (ii) the increase of the



**Fig. 1. Consequences of changes in modern lifestyle on the gut dysbiosis, intestinal epithelial barrier (IEB) and immune system.** Changes occurring during transition to a modern lifestyle include modification of the eating habits, with reduced intake of fibers, of vitamin, yet enhanced intake of sugar, of food additives, and of fat. These changes also include sedentarity and medication, including the use of antibiotics. They favor dysbiosis, a dysregulation of the gut microbiota, with decreased microbial diversity and alteration of the content in microbial metabolites. This in turn leads to an altered intestinal epithelial barrier, which is involved in an altered balance of immune cells. All these changes finally favor chronic inflammation.

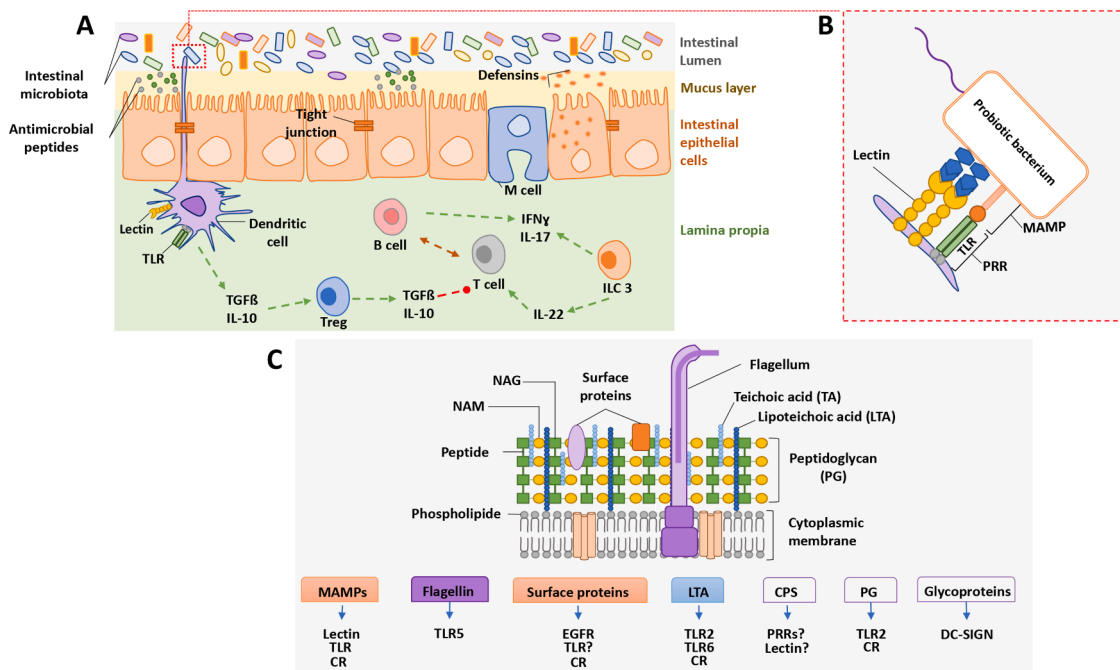
SCFA: short chain fatty acids; TJ: tight junction; IEC: intestinal epithelial cells; DCs: dendritic cells; ILC3: type 3 innate lymphoid cells; AMPK: Adenosine monophosphate-activated protein kinase; ROS: reactive oxygen species; NLRP3: Nucleotide-binding Oligomerization Domain-like Receptor Protein 3.

intestinal epithelial barrier function via inhibition of epithelial apoptosis, preservation of tight junctions protein expression, increase in mucus production and defensin secretion, and (iii) reduced proinflammatory cytokines [26,65,101]. These probiotics may be commensals, a fraction of the natural human microbiota, or provided by either fermented foods or food supplements [112,119]. They can interact with intestinal epithelial cells (IECs) and dendritic cells (DCs) in the mucus layer (Fig. 2A). Some surface components of probiotic bacteria, named microbe-associated molecular patterns (MAMPs), play an important role in these interactions (Fig. 2C). These components are recognized by the corresponding pattern recognition receptors (PRR), present at the surface of the host cells [65]. From the bacterial side, MAMPs include flagellins, pilins, surface proteins, lipoteichoic acid, peptidoglycan, and cell wall-associated polysaccharide (CPS). From the host side, PRRs include Toll Like Receptors (TLRs) and C-type lectin DC specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN). The interaction between a MAMP and a PRR allows the induction of signaling cascades which initiate a molecular response against the detected microorganism. This response leads particularly to the secretion of immunomodulatory cytokines and other immune mediators. Subtle structural variations exist between MAMPs found in different bacteria, while their basic structure remains similar. However, these variations do not allow discrimination between the functional classes of microorganisms [26,65,124]. Of note, interaction between host DC-SIGN and surface glycoproteins of probiotic gut lactobacilli was shown to induce an anti-inflammatory response [141].

**Fermented dairy products constitute our main source of bacteria**

Fermented dairy products exist since millennia as an outstanding

way to preserve milk, provide safe food with desirable sensorial properties and numerous health benefits [78,79,116]. These fermented products are found worldwide and constitute an essential part of living bacteria arising from food in the everyday life diet [135,136]. Even if spontaneous fermentation exists, technical practices have largely evolved to use starters, either by back slopping of the previous batch of production, or by using commercial lyophilized direct-in-vat starters. The main bacteria, used as starters in many dairy processes, are lactic acid bacteria (LAB) required to produce yogurts, fermented milks, cream, butter, and cheeses. The main role of the LAB is to acidify the milk through the fermentation of lactose into lactic acid, which inhibits spoilage and/or pathogenic flora. Moreover, LAB are also responsible for the production of desirable aroma compounds such as diacetyl or acetoin for example. The presence of LAB is highly variable in the fermented dairy products, as shown for some examples in Table 1 and in greater details in the review of Rezac et al. [112]. It largely depends on the conservation time, the shorter time used the higher counts observed, and on the technological process used. Among LAB, the main species encountered in fermented dairy products are *Lactococcus lactis*, *Streptococcus salivarius* subsp. *thermophilus* (*S. thermophilus*) and lactobacilli such as *Lactobacillus delbrueckii* ssp in yogurts and fermented milks and *Lactobacillus helveticus* in Swiss cheeses. Many other microorganisms are also present within the cheeses such as propionibacteria (PAB) in Swiss-type cheeses, or at the surface of the cheeses, as moulds and yeasts (see for more details [8,81]). Among the internal ripening flora, PAB, and specially *Propionibacterium freudenreichii*, are generally growing after the LAB by using lactic acid as their main carbon source to produce propionic acid, acetic acid and carbon dioxide, visualized by holes in Emmental cheeses. Among other metabolites produced, PAB synthesize B<sub>9</sub> and B<sub>12</sub> vitamins [11]. The propionic acid is often used for food



**Fig. 2. Schematic view of possible interactions between ingested bacteria and the host. A:** drawing of the key layers of the intestinal epithelial barrier. The intestinal barrier includes: (i) the intestinal lumen with the intestinal microbiota; (ii) the mucus layer that serves as a microbial and biochemical barrier; (iii) the intestinal epithelial cells (IECs) monolayer, maintained by tight junctions, forming a physical barrier; (iv) and the lamina propria which contains different immunological cells that interact together (DCs, T cell, or ILC3). Green arrows represent cytokine secretion or stimulation, brown represents interaction and red represents inhibition. **B: Focus on the interaction between a probiotic bacterium and dendritic cell (DC).** Probiotic bacteria interact with DC via microbe-associated molecular patterns (MAMPs) and pattern recognition receptors (PRR). **C: Schematic representation of the main surface components (MAMPs) of Gram-positive probiotic bacteria and the corresponding PRRs in IECs and DCs.** Host pattern recognition receptors (PRRs) that recognize probiotic MAMPs include Toll Like Receptors (TLRs), C-type lectin DC specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN). CR, co-receptors; CPS, cell wall-associated polysaccharide; PG, peptidoglycan; TA, teichoic acid; LTA, lipoteichoic acid; EGFR, epidermal growth factor receptor; NAG, N-acetylglucosamine; NAM, N-acetylmuramic acid.

**Table 1**

Counts of some lactic acid bacteria and ripening flora in fermented dairy products.

Type of fermented milk products at the end of production	Species studied	Count range (log <sub>10</sub> CFU.g <sup>-1</sup> of product)	Reference
Plain yogurt (n = 5)	<i>S. salivarius</i> subsp.	8.20–8.36	[53]
Flavored yogurt (n = 5)	<i>thermophilus</i> ( <i>S. thermophilus</i> )	8.34–8.60 8.41–8.56	
Liquid yogurt (n = 5)		8.34–8.59	
Fermented milk (n = 5)		8.45–8.53	
Biogarde®3 (n = 5)			
Commercial yogurt	<i>S. thermophilus</i> <i>Lactobacillus delbrueckii</i>	7.54 ± 0.05- 8.88 ± 0.06 6.90 ± 0.09 - 8.56 ± 0.01	[87]
Commercial Emmental cheeses (West part of France at 51 and 61 d of ripening)	Thermophilic streptococci including <i>S. thermophilus</i> Thermophilic lactobacilli including <i>Lactobacillus helveticus</i> Propionibacteria including <i>Propionibacterium freudenreichii</i>	Not detected 6.4; 5.7 8.0; 8.6	[140]
Swiss Gruyère-type cheese manufactured with natural whey cultures (6-month ripening)	Thermophilic streptococci including <i>S. thermophilus</i> Thermophilic lactobacilli including <i>L. helveticus</i> <i>Lactobacillus helveticus</i> <sup>2</sup>	2.56 ± 0.07 −6.42 ± 0.01 3.0–7.86 ± 0.02 7.59 (±0.86)	[90]
Cantal cheeses (120 d of ripening)	Lactococci including <i>Lactococcus lactis</i> <i>S. thermophilus</i> Mesophilic lactobacilli Facultative heterofermentative lactobacilli Propionibacteria including <i>P. freudenreichii</i>	6.5 ± 0.5 6.3 ± 0.6 6.7 ± 0.3 7.4 ± 0.2 5.6 ± 0.3	[22]
Manchego cheese (150 d of ripening)	<i>L. lactis</i> subsp. <i>lactis</i> Commercial lactococci starter	~7 ~6	[108]

<sup>1</sup>CFU, colony forming unit.

<sup>2</sup> The quantitation of *L. helveticus* was performed by quantitative PCR, which specifically targets the *pheS* gene encoding the  $\alpha$ -subunit of the phenylalanine-tRNA synthetase and expressed as log<sub>10</sub> copies g<sup>-1</sup>.

preservation in industry and has a positive role in the gut health [111].

Beyond their role in the genesis of the overall qualities of the fermented dairy products, LAB and PAB have also an essential role in the human health and the gut homeostasis as shown in the following sections. This review gives an overview of the potential immunomodulatory effects of these main dairy starters. It further explores studies dealing with fermented dairy products containing these starters, in a context of inflammation.

#### Dairy starters as single strains: evidence *in vivo* and mechanisms *in vitro*

##### *Streptococcus thermophilus*, demonstrated effects *in vivo*

*S. thermophilus* strains have been mainly studied in colitis-induced context. As a now well-established animal model of immune homeostasis rupture, colitis can be induced in mice by introducing dextran sulfate sodium (DSS) into drinking water. This model of colitis, among various chemically-induced models, is widely used to investigate gut inflammation as well as means to counteract it. Indeed, it is simple to implement, rapid, reproducible, and controllable, and it shares many

similarities with human ulcerative colitis [29].

Compared to a placebo, the consumption of *S. thermophilus* YIT2001, before colitis induction, was able to prevent colitis, to decrease the disease activity index, as well as the content of lipid peroxide in the colonic mucosa, as evaluated by quantifying the thiobarbituric acid reactive substance content [48]. Interestingly, other strains of *S. thermophilus* that were tested in this study, revealed no protective effect, which indicates the strain-dependent properties of immunomodulatory effects. These authors suggest that the antioxidative activity of active strains of *S. thermophilus* is involved in reducing colitis severity.

In the same model of DSS-induced colitis, other strains were tested: *S. thermophilus* ST28, [96] and *S. thermophilus* NCIMB 41,856 [3]. While DSS induced IL-17 in lamina propria lymphocytes, *S. thermophilus* ST28 consumption significantly decreased this production, as well as the percentage of Th17 cells in this lymphocytes population [96]. This strain thus suppresses Th17 response in the context of intestinal inflammation. The *S. thermophilus* NCIMB 41,856 consumption delayed onset of colitis, reduced bacterial translocation into the colon tissue, reduced clinical signs of the disease, including bodyweight loss and gastrointestinal bleeding. However, it had no effect on gross pathology, histopathology or cytokine production in either colitis or control animals [3]. Authors suggest that this strain promotes maintenance of mucosal barrier, preventing bacterial translocation, thus reduced immune stimulation and inflammation, allowing healing of colitis. In addition, Chen et al. [17] compared the effects of *S. thermophilus* MN-BM-A01 and of exopolysaccharides (EPS) produced by this strain. Isolated EPS, composed of rhamnose, glucose, galactose and mannose, alleviated the severity of colitis [17]. This included decreased disease activity index and colonic epithelial cell injury, reduced pro-inflammatory cytokines levels (tumor necrosis factor- $\alpha$ , interleukin-6, and interferon- $\gamma$ ) and restored expressions of tight junction protein (claudin-1, occludin, and E-cadherin).

*S. thermophilus* CRL803 was tested in another model of colitis induced in mice by intrarectal administration of trinitrobenzene sulfonic acid (TNBS). Consumption of this strain is reported to lower macroscopic and histologic damage scores, microbial translocation to liver, iNOs<sup>+</sup> (inducible nitric oxide synthase positive) cells in their large intestines, and proinflammatory cytokines, compared with colitis mice without probiotic [66]. Authors report the same effect for other lactic acid bacteria (including *L. delbrueckii* subsp. *bulgaricus*) producing riboflavin, as well as for the administration of pure riboflavin. Authors suggest that riboflavin-producing lactic acid bacteria strains prevent intestinal damage and colitis.

*S. thermophilus* was also reported to mitigate another ailment characterized by an inflammation of the digestive tract, mucositis. This last is a painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer. A now well recognized rodent model of mucositis is based on the injection of the cancer chemotherapy drug 5-fluorouracyl (5-FU) to rodents. In this model of intestinal digestive disease, consumption of *S. thermophilus* CRL 808 mitigated induced mucositis. This included reduction in diarrhea score and restoration of the intestinal architecture, while no effect was observed concerning blood levels of cytokines. By contrast, another strain of *S. thermophilus*, CRL 415, failed to exert similar protective effect [67]. Another consistent study reported the amelioration of 5-FU mucositis in mice as a result of consumption of *S. thermophilus* ST4, including reduction of body weight loss, of appetite loss and of diarrhea, as well as maintenance of the epithelium structure in small intestines and colons, and reduced intestinal inflammation [126]. These *in vivo* experiments suggested that protective mechanisms of *S. thermophilus*, in the context of intestinal inflammation, may involve the production of folate, riboflavin, of exopolysaccharide, modulation of the immune response, including suppression of Th17 response. Further molecular mechanisms of action were sought *in vitro*.

*Streptococcus thermophilus*, mechanisms elucidated in vitro

In order to explain the healing effect of selected strains of *S. thermophilus* in the context of intestinal inflammation, the mechanisms potentially involved in its immunomodulatory properties were sought. As an example, *S. thermophilus* ST28 was tested *in vitro* on murine splenocytes stimulated by TGF- $\beta$  and IL-6. While these cytokines induced the production of IL-17, addition of ST28 repressed this induction, as well as the number of Th17 cells in the stimulated splenocytes. By contrast, the type strain *S. thermophilus* ATCC 19,258 failed to do so. Such an immunomodulatory property coincided with the healing effect of *S. thermophilus* ST28 in the context of DSS-induced colitis *in vivo* [96]. This suppressive effect of *S. thermophilus* ST28 was further characterised in murine splenocytes. It was shown to induce transcription of interferon (IFN)- $\gamma$  mRNAs, and anti-IFN- $\gamma$  antibodies suppressed the immunosuppressive effect of *S. thermophilus* ST28. Genomic DNA from this strain accordingly suppressed IL-17 production. Authors hypothesized that this was mediated by the Toll-like receptor 9 and suggest that modulation of Th1/Th17 balance would be involved in ST28 anti-inflammatory effect [97].

*S. thermophilus* being shown to promote maintenance of mucosal barrier function [3], its effect on gut epithelial cells was further investigated. In cultured human intestinal epithelial cells (HIEC) Caco-2, barrier integrity was disrupted by the addition of pro-inflammatory lipopolysaccharide (LPS). By contrast, EPS isolated from *S. thermophilus* MN-BM-A01 protected Caco-2 cells barrier integrity from such disruption, in line with increased expression of tight junction proteins, and alleviated pro-inflammatory response in these cells [17]. *S. thermophilus* EPS were further shown to modulate the antiviral innate immune response in porcine intestinal epitheliocytes [86]. EPS more precisely increased the expression of interferon  $\beta$  (IFN- $\beta$ ), interleukin 6 (IL-6), and C-X-C motif chemokine 10 (CXCL10) in response to TLR3 stimulation in these cells. Monitoring of mucus biosynthesis and immune response in human colonic epithelial cells further indicated that *S. thermophilus* upregulates goblet cell activity [125]. *S. thermophilus* EPS were also shown to inhibit adhesion of the pathogen *Helicobacter pylori* to gastric AGS cells and to attenuate *H. pylori*-induced inflammatory response in these cells [77]. D-Alanylation of teichoic acid (TA), a component of bacterial cell wall, was also shown to play a role in gut barrier protection by *S. thermophilus*. Indeed, inhibition of TA D-Alanylation in *S. thermophilus* suppressed its ability to maintain the trans epithelial electrical resistance (TEER) in Caco-2 cells, when challenged by TNF- $\alpha$  [85].

*Lactobacillus delbrueckii*, demonstrated effects in vivo

In a pioneer research work, the immunomodulatory properties of a series of strains of the dairy starter *Lactobacillus delbrueckii* were screened. Promising anti-inflammatory properties were evidenced, in a strain-dependent manner, in both the *bulgaricus* and the *lactis* subspecies, on cultured HIEC, by monitoring the Nuclear Factor NF- $\kappa$ B activity. A selected strain, *L. delbrueckii* subsp. *lactis* CNRZ327, was then shown to mitigate gut inflammation *in vivo* (Santos [121]). Its consumption reduced the macroscopic and microscopic symptoms of DSS-induced colitis in the mouse intestinal tract, diminished body weight loss, and improved survival (Santos [121]). The same authors then showed that it modulates the production of cytokines such as TGF- $\beta$ , IL-6, and IL-12, at the colon level, as well as that of TGF- $\beta$  and IL-6 in the spleen. It further caused an expansion of CD4<sup>+</sup>FOXP3<sup>+</sup> regulatory T cells in the cecal lymph nodes (Santos [120]). In another study, *L. delbrueckii* subsp. *bulgaricus* was shown to inhibit colitis-associated cancer. It inhibited total tumor volume and mean size of tumors, attenuated the clinical signs of intestinal inflammation, and decreased intestinal and tumor levels of IL-6, TNF- $\alpha$ , IL-17, IL-23 and IL-1 $\beta$ , in an azoxymethane / DSS mice model [127].

Oxidative stress playing a role in the progression of IBD, *L. delbrueckii*

subsp. *bulgaricus* A13, an exopolysaccharide-producing strain, was tested in a rat model of colitis induced by intracolonic administration of acetic acid, and oxidative stress markers were followed. Colitis caused oxidative damage, associated with enhanced level of malondialdehyde (MDA) activity and reduced antioxidant enzyme activities. Consumption of *L. delbrueckii* subsp. *bulgaricus* A13 restored antioxidant enzyme activities. It also improved the oxidative stress parameters [123]. In line with these *in vivo* studies, a clinical study reported the healing effect of a combination of *L. delbrueckii* with *L. fermentum*, in ulcerative colitis patients. Consumption of these probiotics for eight weeks ameliorated inflammation, decreased colonic concentration of IL-6, expression of TNF- $\alpha$  and NF- $\kappa$ B p65, leukocyte recruitment and the level of fecal calprotectin, compared to the control group [43].

In germ-free mice, mono-association with *L. delbrueckii* UFV-H20b20 stimulates the immune system and protects towards experimental infections, including *Salmonella enterica* and *Listeria monocytogenes* (dos [28]). In influenza A virus-infected mice, *L. delbrueckii* feeding enhances humoral immune response [134]. In weaning piglets, *L. delbrueckii* improves intestinal integrity and antioxidant ability [15]. Accordingly, an immunobiotic feed developed with *L. delbrueckii* improves health and growth in piglets [129].

*Lactobacillus delbrueckii*, mechanisms elucidated in vitro

In the above-cited study by Santo Rocha et al., [121] the immunomodulatory properties, evidenced on cultured HIEC (HT29), were shown to be dependent on surface proteins. Indeed, shaving of the bacterial surface proteins by the protease trypsin suppressed these properties (Santos [121]). From a mechanistic point of view, they affect the central part of the NF- $\kappa$ B activation pathway and reduce I- $\kappa$ B phosphorylation (Santos [121]).

Exopolysaccharides produced by *L. delbrueckii* may also be involved in its immunomodulatory properties. Both *L. delbrueckii* and its exopolysaccharide attenuate enterotoxigenic *E. coli*-induced inflammatory response in porcine intestinal cells [143]. Such a treatment leads to enhanced resistance towards rotavirus infection [54]. In these porcine cells, *L. delbrueckii* exopolysaccharides differentially modulate immune response triggered by TLR3 activation. They enhanced the expression of interferon (IFN)- $\alpha$  and of IFN- $\beta$  after the stimulation with the TLR agonist polyinosinic-polycytidylic acid (poly(I:C)), as well as the expression of the antiviral factors MxA and RNase L. They may thus improve intestinal innate antiviral response [55].

Considering immune cells, incubation of immature human dendritic cells with *Lactobacillus delbrueckii* ssp. *bulgaricus* induced secretion of the cytokines of IL-1 $\beta$ , IL-10, IL-12 and TNF $\alpha$  [30]. In such cells, generation of tolerogenic dendritic cells was stimulated by *Lactobacillus delbrueckii*, described as a tolerogenic probiotic [31]. In splenocytes isolated from C57BL/6 and BALB/c mice, *L. delbrueckii* modulated the production of interleukin 12p40 (IL-12p40), of tumor necrosis factor alpha and of IL-10. This effect was shown to depend, at least partly, on Toll-like receptor 2 (TLR2) and on phagocytosis [12].

*Lactobacillus helveticus*, demonstrated effects in vivo

*L. helveticus* NS8, isolated from Koumiss, a traditional fermented milk from Inner Mongolian pasturing area, revealed anti-inflammatory properties by protecting mice from TNBS-induced colitis. It limited in particular the weight loss induced by TNBS, and reduced the Wallace score, as well as damages seen at the histologic level [114]. The same strain was then shown to suppress colitis-associated colorectal tumorigenesis by modulating inflammatory development and microbial homeostasis [113]. In this azoxymethane + DSS-induced carcinogenesis mouse model, *L. helveticus* NS8 consumption reduced the tumor number and the degree of hyperplasia, enterocytes proliferation, while enhancing apoptosis, suppressed the activation of NF- $\kappa$ B, upregulated the anti-inflammatory cytokine IL-10 and downregulated

IL-17-producing T cells [113].

Another strain, *L. helveticus* SBT2171, provided within a cheese, was tested in mice. In healthy mice, cheese induced regulatory T cells (Treg), which regulate immune and inflammatory responses, while suppressing production of IL-17, IL-4, and IL-10 in gut Peyer's patch cells. In mice with DSS-induced colitis, cheese alleviated the symptoms of colitis, prevented body weight loss and colon length shortening, and reduced the disease activity index, which includes diarrhea and fecal bleeding. It furthermore decreased production of proinflammatory cytokines (IL-17 and IL-6) and increased production of the anti-inflammatory cytokine transforming growth factor- $\beta$ 1 in Peyer's patch cells [45]. Its intraperitoneal administration moreover strongly alleviated symptoms of collagen-induced arthritis (CIA) in mice [46]. Such preventive effect towards induced arthritis was further evidenced as a result of oral administration of *L. helveticus* SBT2171, in line with its ability to downregulate the abundance of immune cells and the subsequent production of CII-specific antibodies and IL-6 [146].

Surprisingly, the strain-specific immunomodulatory properties of selected strains of *L. helveticus* prevented the anxiety-like behavior and negative effects on memory that were induced by a Western-style diet [98]. Furthermore, *L. helveticus* NS8 was shown to improve behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress in rats [68]. This correlated with lower plasma corticosterone and adrenocorticotropic hormone ACTH levels, higher plasma IL-10 levels, restored hippocampal serotonin and norepinephrine levels.

#### *Lactobacillus helveticus*, mechanisms elucidated in vitro

In the above-mentioned study by Rong et al., *L. helveticus* NS8, in coculture with peripheral blood mononuclear cells (PBMCs), induced secretion of the immunomodulatory IL-10 [114]. It furthermore reduced the pro-inflammatory response elicited by lipopolysaccharide (LPS) in mouse macrophage cell line RAW264.7. Concerning the above-mentioned *L. helveticus* SBT2171, it was shown *in vitro* to inhibit lymphocytes proliferation (LPS-stimulated mouse T and B cells and Jurkat and BJAB human lymphoma cell lines) via regulation of the JNK signaling pathway [46]. It moreover induced A20 expression via Toll-Like Receptor 2 signaling and inhibited the lipopolysaccharide-induced activation of NF- $\kappa$ B and mitogen-activated protein kinases in peritoneal macrophages [57]. This effect was also induced by a cell-wall fraction of the strain. The surface S-layer protein covering this strain was further shown to promote human  $\beta$ -Defensin 2 expression via TLR2-JNK signaling in Caco-2 HIECs [59]. In *L. helveticus* MIMLh5, S-layer protein SlpA mediates the stimulatory effect on innate immunity [138]. In murine bone-marrow-derived dendritic cells, *L. helveticus* MIMLh5 induced greater production of IFN- $\beta$ , IL-10, and IL-12p70, compared to S-layer-depleted MIMLh5, and S-layer promotes endocytosis by these dendritic cells [137]. In stimulated human monocyte derived dendritic cells, different strains of *L. helveticus*, isolated from Italian hard cheeses, induced release of both the pro-inflammatory cytokine IL-12p70 and the anti-inflammatory cytokine IL-10, while corresponding cell-free culture supernatants triggered a dose-dependent decrease of IL-12p70 and an increase of IL-10 [149]. Accordingly, the suppression of intestinal epithelial cell chemokine production was shown to be mediated by secreted bioactive molecules in *L. helveticus* R0389 [49]. Different immunomodulatory compounds, with contrasted effects, are thus associated with the bacteria or secreted into the external medium.

Exopolysaccharide produced by *L. helveticus* KLDS1.8701, in addition, was shown to alleviate DSS-induced colitis in mice [70]. The immunomodulatory effect of *L. helveticus* R389 on murine IEC was shown to depend on TLR, as antibodies raised against TLR2 and TLR4 both suppressed modulation by *L. helveticus*. In FaDu hypopharyngeal carcinoma cells, *L. helveticus* MIMLh5 antagonized the pro-inflammatory effect of *Streptococcus pyogenes*, reducing the induction of IL-6, IL-8, and of TNF- $\alpha$  [40].

#### *Lactococcus lactis*, demonstrated effects in vivo

Many studies dealt with recombinant genetically modified lactococci, expressing human or animal cytokines, in order to counteract inflammation, and will not be cited here, as this review only focuses on wild type, GRAS, safe bacteria that may be implemented in fermented food products. As an example, *L. lactis* NCDO2118 was given in a curative way during the remission period following DSS treatment [71]. Its consumption resulted in a milder form of recurrent colitis than that observed in control diseased mice, together with an early increase in IL-6 production and sustained IL-10 production in colonic tissue, as well as an increase in regulatory CD4(+) T cells (Tregs) bearing surface TGF- $\beta$  in its latent form (Latency-associated peptide-LAP) in the mesenteric lymph nodes and spleen. *L. lactis* healing effect was further shown to be more effective when administered in a preventive way prior to, than during and after DSS administration [5]. Such a preventive role towards DSS-colitis was confirmed by different teams [4,5,56,69,71], while another strain, *L. lactis* JCM5805, given at high doses to mice, worsened DSS-colitis, decreasing survival rate, increasing histopathological score, as well as levels of IFN- $\gamma$ , TNF- $\alpha$  and IL-6 [60]. This evidences the strain-dependent immunomodulatory effects of lactococci.

In cyclophosphamide-immunosuppressed mice, consumption of *L. lactis* subsp. *lactis* GCWB1176 elevated natural killer (NK) cell activities; concanavalin A-induced T cell proliferation; and serum levels of TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-4, IL-10 and IL-12 [50]. This strain thus improved immune function through the activation of macrophages and NK cells (see below).

*L. lactis* subsp. *cremoris* ATCC 19,257 was shown to exert cytoprotective effects on the Drosophila intestine in response to oxidative challenge [21]. It induced activation of the Nrf2 signaling pathway in the Drosophila intestine, independently of reactive oxygen species. It further exerted a cytoprotective effect against radiological injury in mice and protected the murine intestine from DSS-induced colitis.

In healthy mice, administration of *L. lactis* MG1363 during five days triggered systemic immunomodulation. It reduced splenic T helper cell cytokine responses after *ex vivo* restimulation, as well as T helper 2 cell frequencies [128].

#### *Lactococcus lactis*, mechanisms elucidated in vitro

In cultured HIEC, *L. lactis* FC significantly down-regulated IL-8 mRNA expression and inhibited NF- $\kappa$ B nuclear translocation [94], while *L. lactis* NCDO2118 was able to reduce IL-1 $\beta$ -induced secretion of IL-8 [71]. *L. lactis* ML2018, which also prevented DSS-induced colitis in mice, prevented the release of nitric oxide (NO) and the production of inflammatory factors induced by lipopolysaccharides (LPS) in RAW264.7 cells [69].

The above-mentioned immunostimulatory strain *L. lactis* GCWB1176, in RAW264.7 macrophages, induced phagocytic activity, increased the production of nitric oxide (NO) and expression of inducible NO synthase. Moreover, it increased the production of TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-10 and IL-12 from mouse splenocytes and RAW264.7 cells and increased the transcriptional activities of NF- $\kappa$ B and iNOS [50].

The MAMPS responsible for potential interactions between *L. lactis* and host cells, leading to immunomodulation, are yet unknown. A surface proteome analysis of a natural isolate of this bacterium however revealed the presence of pili able to bind to cultured HIECs [82]. Inactivation of the corresponding pilin gene abolished adhesion of *L. lactis* both to culture HIECs and to intestinal mucus [63,82]. Interestingly, adhesion of *L. lactis* to epithelial cells was shown to inhibit, in a strain-dependent manner, both adhesion and internalization of pathogens such as *E. coli* and *Staphylococcus aureus* [1]. Milk fermented by *Lactococcus lactis* ssp. *cremoris* JFR1 moreover inhibited Salmonella invasion into intestinal epithelial cells [151]. Competitive exclusion of pro-inflammatory bacteria, or of components thereof, by *L. lactis* may explain, at least partly, its immunomodulatory effect.

Finally, some strains of *L. lactis* were shown to produce exopolysaccharides, which display immunomodulatory properties and may also participate to this effect. EPS produced by *L. lactis* Z-2, composed of rhamnose, xylose, mannose, glucose, and galactose, was reportedly able to modulate the immune responses *in vitro* and *in vivo* [33]. *In vitro*, it enhanced proliferation and phagocytosis activities ( $P < 0.05$ ), induced production of nitric oxide (NO), pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), and anti-inflammatory cytokines (IL-10, TGF- $\beta$ ) ( $P < 0.05$ ) in fish head kidney cells. In line with this, in cyclophosphamide-immunosuppressed mice, EPS from *L. lactis* increased macrophage phagocytosis, spleen and thymus indices and haemolytic complement activity (HC(50)) [41].

#### *Propionibacterium freudenreichii*, demonstrated effects in vivo

A first report on immunomodulatory properties of *Propionibacterium freudenreichii* strains evidenced a highly strain-dependent ability to induce the anti-inflammatory IL-10 in human peripheral blood monocytes cells (PBMCs) [36]. In the same report, the most IL-10-inducing strains were further shown to protect mice from TNBS-induced colitis. This included attenuation of weight loss, of macroscopic Wallace, of colonic MPO, and of histopathological score. Moreover, consumption of *P. freudenreichii* delayed and attenuated the onset of colitis induced by the pathogen *Citrobacter rodentium*. Further screening on PBMCs identified the *P. freudenreichii* CIRM-BIA129 strain as the most immunomodulatory one [35]. This strain was used to generate a model single-strain cheese, which protected mice against TNBS-induced colitis [107]. It was further associated with a strain of *L. delbrueckii* to generate a two-strain model cheese which displayed the same protective effect [106]. Consumption of both cheeses, in a preventive way, prior to TNBS-induction, alleviated severity of symptoms, modulated local and systemic inflammation, as well as colonic oxidative stress and epithelial cell damages. By contrast, the corresponding sterile cheese matrix failed to afford such protection. An Emmental cheese was finally manufactured in industrial conditions, using *P. freudenreichii* CIRM-BIA129 as a ripening starter. Its consumption was then shown to reduce severity of DSS-colitis in mice [109]. This included reduction weight loss, of disease activity index and histological score, of small bowel immunoglobulin A (IgA) secretion, restored occludin gene expression and reduced induction of TNF $\alpha$ , IFN $\gamma$  and IL-17. Another strain, *P. freudenreichii* KCTC 1063, also protected rats from DSS-induced colitis, by stimulating MUC2 expression (mucin 2, a high molecular weight glycoprotein which forms an insoluble mucous barrier that protects the gut lumen) in intestinal goblet cell [73]. This included reduced mRNA levels of typical pro-inflammatory cytokines and decreased inflammatory state, yet increased expression of MUC2 gene and protein.

In the case of mucositis, *P. freudenreichii* CIRM-BIA129, given in a preventive way, prevented weight loss and intestinal damages, reduced inflammation and histopathological scores in mice receiving 5-FU [20]. Furthermore, it regulated key markers, including Claudin-1, as well as IL-17a, IL-12 and IL-1 $\beta$  cytokines levels, restored goblet cells and prevented a dramatic increase in gut permeability (do [25]).

#### *Propionibacterium freudenreichii*, mechanisms elucidated in vitro

The immunomodulatory effect of *P. freudenreichii* seems multifactorial, involving both surface proteins and secreted components. In *P. freudenreichii* CIRM-BIA129, guanidine-extraction of surface layer proteins, as well as proteolytic shaving thereof, suppressed such activity [36, 64]. In line with this, the guanidine-extract, enriched in surface layer proteins, was shown to induce IL-10 in a dose-dependent manner in human PBMCs [64] and in porcine ones [110]. Several mutants, affected in various surface proteins, were constructed. *P. freudenreichii*  $\Delta$ slpB, devoid of the SlpB surface layer protein, failed to induce IL-10, while the wild type (WT) parental strain did. In another *in vitro* assay, *P. freudenreichii* WT reduced expression of IL-8 and of TNF- $\alpha$  in

LPS-stimulated HT-29 HIECs, while *P. freudenreichii*  $\Delta$ slpB failed to do so (do [25]). In line with this, the mutant strain failed to adhere to cultured HIECs and to protect mice from 5-FU-induced mucositis [25,27]. Moreover, heterologous expression of *P. freudenreichii* slpB enhanced the protective potential of *L. lactis* in mice with DSS-induced colitis [4].

Secreted compounds are also involved in *P. freudenreichii* anti-inflammatory properties. Indeed, its culture supernatant reduced the disease activity in DSS-treated rats [73]. A bifidogenic secreted compound, called BGS, was identified in *P. freudenreichii* ET-3 [111]. It was identified as 1,4-dihydroxy-2-naphthoic acid (DHNA), a precursor of menaquinone (vitamin K2), which is responsible for the bifidogenic and for the immunomodulatory effects of *P. freudenreichii* ET-3 culture supernatants [44]. DHNA attenuated DSS-induced colitis by modulation of bacterial flora and lymphocyte homing in mice [99]. It furthermore reduced inflammation in IL-10-deficient mice with colitis by suppressing macrophage-derived proinflammatory cytokines [100]. It was moreover identified as an activator of the aryl hydrocarbon receptor (AhR), activating the AhR pathway in cultured HIEC and in the mouse intestine [37]. In mice, it induced anti-microbial proteins RegIII $\beta$  and  $\gamma$  in the intestine, altered gut microbiota and inhibited DSS-induced colitis.

#### What clinical studies say

As recently reviewed, human studies confirming the health benefits of fermented foods in humans are rare [116]. This constitutes an apparent incongruity, when considering the numerous evidences obtained in preclinical studies (see above). This is complicated by the fact that fermented foods are various and contain a wide variety of microbial ecosystems, while all the health properties were shown to be strain-dependent, within each microbial starter species.

Nonetheless, a clinical study pointed out to the fact that deprivation of fermented foods from the human diet has strong impacts on the human immune system, including a fall in innate immune response [102]. In this study, the fall of in the immune response, provoked by a wash-out period, was counteracted by a daily consumption of a standard yogurt containing a conventional starter. This revealed the significant impact of the daily consumption of fermented foods on human physiology.

Looking for a beneficial impact of fermented foods ingestion in healthy subjects resembles the quest for a holy grail. Clinical studies however indicated effects of yogurt consumption in subjects with metabolic and cardiovascular disorders, including obesity and overweight. In obese Chinese women with non-alcoholic fatty liver disease and metabolic syndrome, yogurt consumption decreased serum LPS, lipids, and biomarkers of inflammation and oxidative stress [16]. In overweight and obese people, yogurt reduced PBMCs expression of ROR- $\gamma$ t and serum levels of high-sensitivity C-reactive protein (hs-CRP) [150]. In the same category of subjects, yogurt decreased plasma concentration of TNF- $\alpha$ , while increasing soluble TNF- $\alpha$  receptor-1 (s-TNFR-1), indicating an impact on low-grade systemic inflammation [142]. Concerning healthy subjects, consumption of yogurt reduced postprandial inflammation and markers of endotoxin exposure in healthy premenopausal women [104,105]. Yogurt consumption was further associated with lower levels of chronic inflammation, including serum levels of IL-6 and fibrin, in both normal weight and overweight volunteers, in the Framingham Offspring study [148].

While yogurt is fermented by 2 bacterial species, *S. thermophilus* and *L. delbrueckii*, cheeses constitute a much more complex ecosystem, so that every cheese will develop different effects. This may explain why meta-analyses fail to evidence significant immunomodulatory effect of dairy products taken together, including milk, yogurt and cheeses. A review of clinical evidence, based on 52 clinical trials, defined an inflammatory score (IS), and confirmed an overall anti-inflammatory property of dairy products, taken together, in subjects with metabolic disorders [9]. The IS of the product category “fermented dairy products” indicated a beneficial anti-inflammatory effect, whatever the subject



category. Authors conclude on the possible anti-inflammatory effect of bacteria present in such fermented products. Indeed, different components of fermented dairy products appear to suppress inflammatory response.

A Randomized Controlled Cross-Over Trial (RCT) further aimed at evidencing the difference between fermented and unfermented dairy products, within high-fat meals, with respect to PBMCs' expression of inflammation-related genes, as well as circulating inflammatory markers and metabolites [117]. Based on 47 healthy subjects, this RCT evidenced that expression of genes related to lymphocyte activation, cytokine signaling, chemokine signaling, and cell adhesion was differentially affected, according to the kind of product. Fermented products cheese and sour cream reduced, while non-fermented products butter and whipped cream increased expression of these genes. Authors conclude that intake of fermented dairy products, especially cheese, induces a less inflammatory postprandial PBMC gene expression response than non-fermented dairy products.

Finally, a systematic review of the literature dealing with the effects of dairy products and proteins intake on inflammation reported contradicting results. In this review, 10 cited trials reported no effect of the intake of dairy products (milk, cheese, and yogurt) on low-grade systemic inflammation in adults without severe inflammatory disorder. By contrast, eight reported a reduction in at least one biomarker of inflammation [93]. More RCT are thus needed to specify the role of different fermented dairy products, and of the microorganisms contained therein, in the management of inflammation.

In order to elucidate beneficial effects of probiotic starters in humans, pure cultures thereof, including model fermented milks, were also implemented in clinical trials. As an example, a randomized, double blind, placebo-controlled clinical study, performed on 80 knee osteoarthritis subjects, tested the impact of *S. thermophilus* TCI633 oral intake. This probiotic improved serum collagen type II C-telopeptide and serum CRP [72]. In another clinical trial, topical application of *S. thermophilus* improved the signs and symptoms characteristic of atopic dermatitis [24]. In an RCT, oral supplementation with *L. delbrueckii* subsp. *bulgaricus* 8481 was shown to enhance systemic immunity in elderly subjects [89]. This included increased blood NK cells, decreased IL-8, yet increased antimicrobial peptide hBD-2. In the same category of patients, *L. delbrueckii* subsp. *bulgaricus* OLL1073R-1 fermented milk was shown to increase the concentration of saliva IgA [144,145]. It moreover reduced the risk of infection in the elderly, increasing NK cell activity as well as enhancing the quality of life score [74]. *L. helveticus* Lafti L10 was shown in an RCT, to modulate mucosal and humoral immunity in elite athletes, increasing anti-*Enterococcus faecalis* IgG, as well as total IgA [83]. It further reduced the duration of respiratory infection in the same population [84]. Another strain, *L. helveticus* SBT2171, alleviated perennial allergic rhinitis in Japanese adults by suppressing eosinophils in an RCT [147]. Immunomodulation was also confirmed in humans for *L. lactis*. Consumption of milk fermented by *L. lactis* JCM5805-activated plasmacytoid dendritic cells in an RCT, while enhancing the ability to produce interferons [131]. It was further shown to modulate immunity, reduce symptoms such as sneezing, and reduce cumulative days of fatigue in a male athletes RCT [61]. Moreover, consumption of a fermented milk containing *L. lactis* 11/19-B1 mitigated the severity of atopic dermatitis in children in a clinical trial [133]. Concerning *P. freudenreichii*, a pilot clinical study, performed on 12 ulcerative colitis patients, indicated that the bifidogenic growth stimulator, consisting in a dried whey culture of the ET-3 strain, improved the clinical activity index, as well as the endoscopic index [132], in line with *P. freudenreichii* immunomodulatory properties evidenced *in vitro* and *in vivo* (see above). Finally, an RCT conducted on 62 healthy adults showed that the consumption of milk fermented by *P. freudenreichii* JS reduced the serum level of hsCRP [58].

## Conclusion

The healing effect of LAB and PAB strains was clearly evidenced through the numerous *in vitro* and *in vivo* studies shown in the review. However, only elected strains, within each species, are exerting positive action of gut homeostasis. This strain-dependency implies screening numerous strains to find the rare *gem* and to explore the mechanisms underlying the complex multi-facet interactions between bacteria and host gut system. These multi facets include different MAMPS on the bacterial side, that are recognised also by different receptors on the host side, leading to many different mechanisms of regulation of the gut homeostasis. This requires to develop preclinical and clinical studies using more complex associations of strains with well-known healing effects. The next challenge will be to enhance synergistic effects by wisely combining strains able to trigger adapted ways to alleviate specific inflammatory symptoms such as IBD or IBS that are one of the main consequences of the lifestyle changes. Knowledge of these strains and of their effects opens avenues for developing targeted functional fermented foods, namely fermented dairy products.

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