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Review Article



## Involvement of gastrointestinal tract associated microbiota in direct and indirect immunomodulation: An overview

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### Abstract

Gastrointestinal Tract (GIT) associated microbiota is a diverse community of trillions of microorganisms, which homeostatically co-exist with the host in normal conditions and interact actively with the physiological processes of the host. Among them, some microorganisms impart beneficial effects on the host while pathogens and opportunistic pathogens always tend to invade host body cells. Many studies have now established that probiotic bacterial strains can modulate our overall immunity and play crucial roles in digestion, metabolism, brain-gut communication, etc. Talk about immunomodulation by probiotics, studies have revealed that many bacterial strains regulate innate and adaptive immunity either directly engaging immune cells of the host body or indirectly by blocking the entry of pathogens and viruses into the host body. In this overview, we will talk about how probiotics affect immunity by promoting the creation of tight junctions (TJs), raising mucin secretion, and improving the cytotoxicity of macrophages and Natural Killer (NK) cells. The discussion will give us a holistic idea about immunomodulation by gut microbiota (GM) and provide an opportunity to use the information for human welfare.

**Keywords:** Cytokines, Dysbiosis, Gut Microbiota, Immunomodulation, Macrophages, NK cells, Probiotics

### Introduction

The growth of microbiota research has made it abundantly clear that interactions between microbes in the gut mucosa are crucial for the immune system's development and preservation. The functional microbiome continuously provides secreted or physical mediators that are necessary for an appropriate "bridge" between the immune system and the microbiota, while variations in the microbiota can impair homeostasis and worsen inflammation and illness (Bernardeau et al., 2017). The Gut Microbiota (GM) is defined as the whole of the symbiotic, commensal, and pathogenic micro-organisms that are living in our gastrointestinal tract. Among them, Bacteroidetes, Firmicutes, *Actinomycetota* (mainly the genus *Bifidobacterium*) and Proteobacteria are the predominant phyla (Blaak et al., 2020). They live there and interact relentlessly with the host. The interaction may be beneficial for the host from many aspects. The microbes that when administered in an adequate number, impart beneficial effects

on the host are referred to as probiotics. In humans as well as in other mammals, it has been established that probiotics have a crucial role in digestion, metabolism, brain-gut communication, immunomodulation, competitive exclusion of pathogens, etc (Casula et al., 2002). *Lactobacillus* species and *Bifidobacterium* species are most commonly used for probiotic supplementation in food (Catinean et al., 2020).

In our daily routine, we consume many foods from which microorganisms are entering our gut. Among them both probiotics and pathogens are present. Through faeces, microbes are excluded from the body. Thus, the cycle revolves. At times the interaction between GM and host becomes harmful for the host, as pathogenic bacteria especially opportunistic pathogens become predominant (Finucane et al., 2014). The whole microbiota homeostasis disrupts and this condition is called dysbiosis. Dysbiosis mainly occurs when the host suffers from a disease or is in an immune-compromised condition. As the host recovers, the GM returns to its initial homeostasis

(Fukuda et al., 2011). Consequently, the understanding of how the microbiome and immune systems interact will enable the development of new delivery platforms and far more options for modifying delivery strategies for the introduction of sensitivity (Larsen et al., 2010).

The current review process aims to talk about the GM's useful role. We have examined the roles played by GM in both direct (raising macrophage and NK cell activity) and indirect (improving the gut epithelial barrier and regulating mucus formation) immunomodulation in people. This review will provide an updated scientific work carried out along this line which helps our understanding of the role of GM in human health.

### The Interdependent Relationship Between GUT microbiota and the Host Immune System

Every day, the gut is exposed to a huge number of foreign antigens via food and gut-dwelling microorganisms. It would be inefficient and may be hazardous to produce protective

immune responses to these benign substances (Magne et al., 2020). Abnormal immune responses to commensals and dietary antigens can cause bowel inflammation and food allergies, respectively. Additionally, peripheral inflammatory illnesses such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and Parkinson's disease are more likely to develop in those who have gut inflammation (Catinean et al., 2019). The gut must develop ways to preferentially tolerate benign antigens while retaining the ability to defend against pathogenic invasion to cohabit with external entities. Leukocytes of the innate and adaptive immune systems, as well as intestinal epithelial cells, coordinate these homeostatic controls (Anderson et al., 2010). Commensal contacts, relations with epithelial cells, and interactions with sub-epithelial mononuclear phagocytes all play a significant role in the unusual microenvironment that exists in the mucosa (Cutting, 2011). The populations of intestinal macrophages are constantly being refilled by circulating monocytes. Fig. 1 below indicates the interdependent relationship between host immunity and gut microbes.

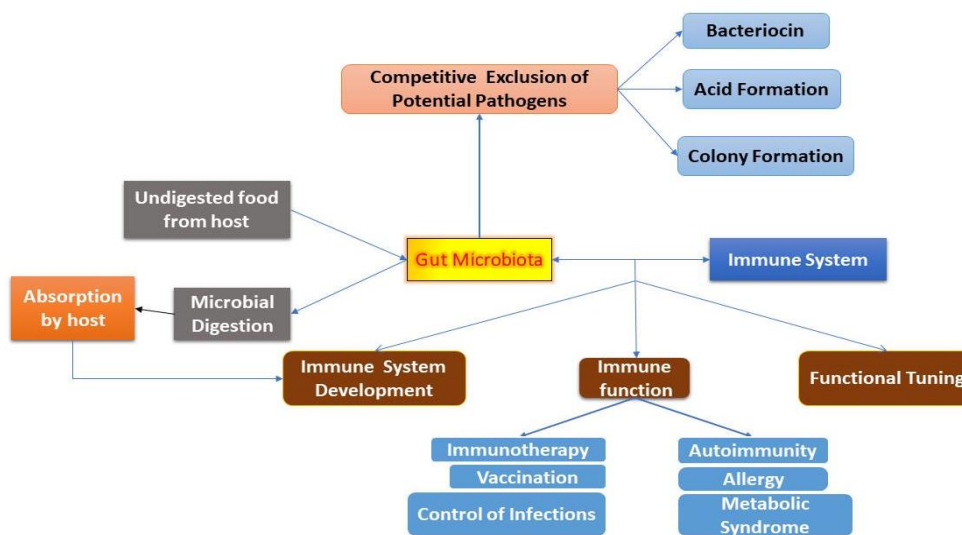


Fig. 1 Interdependent relationship between host immunity and gut microbes

If we talk about the histology of the gastrointestinal tract (GIT), it generally consists of four concentric layers which are in the following order: mucosa, submucosa, muscularis, and serosa. Among them, the mucosal layer is the innermost layer which is again in contact with the GIT lumen. Included in the mucosa is the lamina propria layer, made up of connective tissues, which is the interface between GIT and the host immune system. Lamina propria, being part of the gut-associated lymphoid tissue (GALT) consists of immune system cells that are dendritic cells, intraepithelial dendritic cells, macrophages, plasma cells, NK cells, T and B lymphocytes, etc (Hyser et al., 2019). Now that the GM and the host immune system are nearby, it is very much natural to

have interactions although these complex interactions are still not known completely rather researchers have confirmed a vibrant interdependent relationship between GM and the host immune system. Probiotic secretions can be beneficial for the host and provide various metabolic and immunological opportunities. For example, probiotics can digest undigested food or exhibit immune-modulatory effects directly or indirectly (de Goffau et al., 2013). In the case of direct immunomodulation, host immune cells are directly involved like humoral immune response while indirect immunomodulation enhances immunity without direct interference of immune cells like enhancing gut epithelial barrier. On the other hand, many pathogenic or opportunistic

pathogenic strains and their secreted toxic molecules can hamper host health as well as the health of humans (Duysburgh et al., 2019). Therefore, the host immune system must strike the ideal balance between vigilance to prevent the spread of infectious diseases and opportunistic infections and tolerance to the gut commensal microbiota (Feng et al., 2018). When the host immune system establishes the balance gut homeostasis is achieved.

### Indirect Immunomodulation

### Probiotics and GUT barrier

The mucosa of GIT is composed of epithelial cell layers with different types of cells that include Paneth cells, goblet cells, enterocytes, dendritic and intraepithelial dendritic cells, etc

(Fig. 2). If we talk about a particular part of GIT like the intestine, it also has a monolayer of simple columnar epithelial cells. The epithelial layer is crucial as it has many functions that include nutrient uptake, ion exchange, etc (Faille et al., 2002). Most importantly, it establishes a physical barrier between the external environment (GIT lumen) and the host immune system. If the host is in a compromised condition, then this layer becomes 'leaky', it may then allow pathogens and toxic molecules to enter into the inner cells of the mucus layer (Manichanh et al., 2006). The layer prevents them by vigorous cellular regulations like forming tight junctions (TJs) between adjacent cells in the luminal epithelial layer, making it semi-permeable. Some diseases due to 'leaky' gut conditions are Inflammatory Bowel diseases (like Crohn's disease and ulcerative colitis), irritable bowel syndrome, and some kind of food-borne diseases (Marzorati et al., 2020).

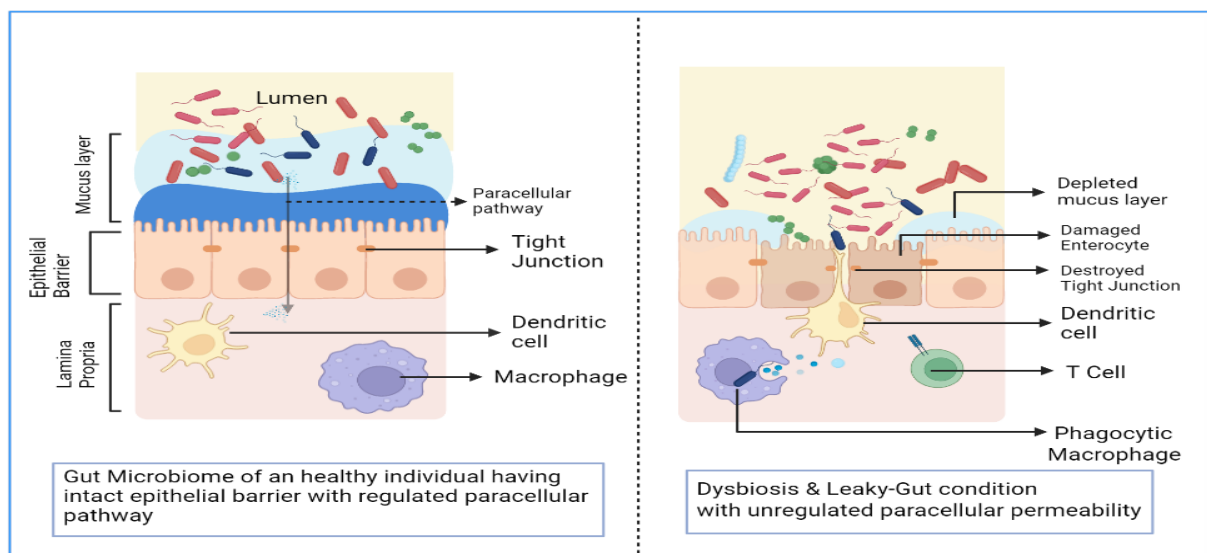


Fig. 2 Gut microbiota in healthy individuals as well as during dysbiosis and leaky-GUT condition

Trans-Epithelial Electrical Resistance (TEER) parameter and the Intestinal Permeability Test (IPT) can both be used to assess leaky situations (in vivo). The two simplest methods to treat microbial dysbiosis are probiotics, which involve consuming bacteria with known health benefits, or FMT, which entails the mass transfer of fresh or cryopreserved (stabilized frozen or freeze-dried) fecal-derived bacteria from healthy individuals into patients (El Hage et al., 2019). Improvements in obesity, diabetes, lung disease, cancer, and viral/bacterial infections have been linked to probiotics and FMT. In addition, IBD, allergies, neurological conditions, and cardiac issues have all been treated with them. *Streptococcus*, *Bifidobacterium*, and *Lactobacillus* have historically been the three most used genera for oral probiotic delivery (McFarlin et al., 2017). Thanks to developments in metagenomics technology, *Faecalibacterium prausnitizii*, *Ruminococcus bromii*, and *Akkermansia muciniphila* have been discovered to

be present in significant numbers in the gut (Molly et al., 2003). In addition to affecting gut immune responses directly, indirectly, through secreted products like SCFAs and AHR ligands, or directly, viable bacteria also manage the balance of intestinal flora by the space-occupying effect, competition, or antagonism. Major barriers to the oral distribution of live bacteria include the retention of viability during manufacturing, on the shelf, and after administration, as well as its specific transit to the small or large intestine (Wang et al., 2007). This problem is exacerbated when working with fastidious, hard-to-grow bacteria such as those in the *Faecalibacterium*, *Bacteroides*, or *Akkermansia* families. Probiotics are frequently enclosed in materials such as alginate, plant/microbial gums, chitosan, starch, k-carrageenan, cellulose acetate phthalate, milk and gelatin proteins, and lipids (Mosca et al., 2016). Although this hasn't been tested yet, probiotic strains may be introduced to "living

gels" for higher therapeutic effects. Together, probiotics and FMT encapsulation technologies have increased the efficiency and longevity of oral delivery, and they are likely to be used in the future to treat other diseases as our knowledge of the connection between the microbiome and pathology deepens. Live bacteria will likely cause inflammatory reactions elsewhere in the body as a result of unchecked expansion, rendering probiotics unsuitable for treating allergies or autoimmune diseases despite the overwhelming evidence that they increase the regulatory effects of oral immunotherapies (Wang et al., 2008). Contrarily, compounds derived from commensals may be used in treatments requiring non-oral delivery methods and enhance antigen-specific immunotherapy for autoimmune illnesses. According to a recent study (Mortensen et al., 2000), exopolysaccharide isolated from *Lactobacillus rhamnosus* KL37 might truly dramatically reduce collagen-induced arthritis and collagen II-specific antibody production even before being injected intravenously. However, it's likely that when given outside of the gut, commensal molecules will need to be individually screened for immunogenicity (Fig 2). The idea that tolerogenic polysaccharides, which were first identified in the gut, can still lessen inflammation in peripheral tissues is raised by this finding. It also suggests that additional commensal compounds might still be able to alter the immune system under different conditions (Possemiers et al., 2004). To treat inflammatory diseases in both the gut and systemic regions, researchers may be able to use compounds derived from commensals much more often. In autoimmune and allergy immunotherapy, the induction of antigen-specific trigs is critical for the control of inflammatory diseases. New strategies that combine antigen-specific therapies with tolerogenic cues from the microbiota may improve these strategies (Menni et al., 2018). As a result, knowing how the immune and microbiome systems interact will make it possible to create novel delivery platforms and more tools for adjusting delivery methods for the introduction of tolerance.

TJs play a significant part in creating a barrier between the gut and the GIT lumen, as was previously stated. The 40 different proteins that have been identified as being a part of the TJ complex include transmembrane proteins such as Claudin, Occludin, and JAM proteins (Junction Adhesion Molecules); peripheral membrane proteins such as ZO-1 and ZO-2 (Zona Occludens); and other proteins such as CPSF2 (Cleavage and Polyadenylation Specific Factor 2) protein, CD2 associated protein, CDK4 (Cyclin (Pyne et al., 2015). Numerous *in vivo* and *in vitro* animal studies have shown that probiotic bacteria can improve the development and stabilization of TJs by controlling the expression and localization of the proteins mentioned above. Sasaki et al. specifically looked into how intestinal epithelial cells were affected by *Lactobacillus plantarum* MB452. They employed a monolayer of Caco-2 (human colon cancer) cells in this *in vitro* experiment (Sasaki et al., 2020). In these kinds of experiments, this model is typical. The experimental outcomes were ascertained using a variety of methods, including TEER-assay, whole-genome microarray analysis,

and fluorescence microscopy. They claimed that some genes associated directly or indirectly with the development of the TJ complex showed altered expression when *Lactobacillus plantarum* MB452 was present (Sasaki et al., 2020; Scher et al., 2015). Table 1. lists some of the genes that are upregulated to promote TJ complex formation. They also measured the downregulation of several genes, including the CDK4 gene, which is crucial in this context.

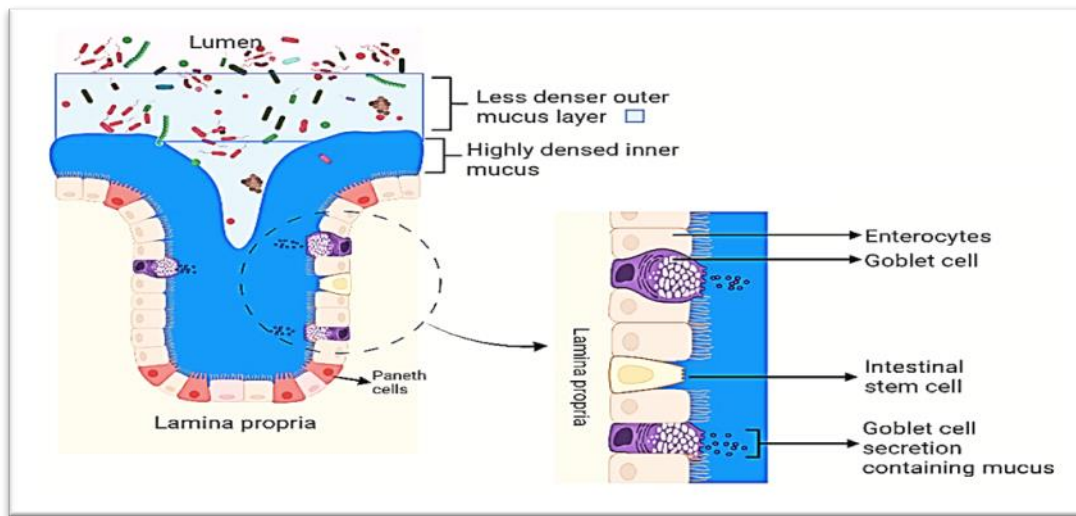
According to Sasaki et al. study on "healthy subjects," the *Lactobacillus plantarum* WCFS1 strain improves the gut epithelium by controlling the expression and distribution of TJ proteins (Sasaki et al., 2020). According to reports, "Escherichia coli Nissle 1917 (EcN) colonisation of mice increased ZO-1 proteins in Intestinal epithelial cells" (Mortensen et al., 2000). Table 2 below lists the various bacterial strains' contributions to indirect immunomodulation.

### GUT microbiota and modulation of mucus secretion

While discussing host immunity, the mucus layer plays an important role in protecting the host from infiltrating pathogens, toxic molecules, digestive enzymes, and several other factors. This layer is among the body's first line of defense. For the stomach, small intestine, and colon, the mucus layer is extremely essential, it generally decreases bacterial interaction, entraps toxin molecules, etc, thus, protecting the host body (Sidhu et al., 2017).

The mucus in GIT is secreted from goblet cells that are present in the epithelial layer. It is mainly made up of water and mucin glycoprotein. The intestinal mucus contains 95% of water and the rest are mucin (Muc2) glycoprotein (expressed by the MUC2 gene), a little number of lipids & other proteins. In the colon, the Muc3 protein is also found along with Muc2 (Suzuki et al., 2004). Alteration of intestinal mucin secretion can lead to several inflammatory health issues for humans. several diseases like ulcerative colitis (UC) (reduced synthesis and secretion of mucins, leading to a decrease in the thickness of mucus layer with increased bacterial penetration), Crohn's disease, and several other gastrointestinal diseases can occur (Sze et al., 2016). Fig. 3 depicted the mucus layer of an individual with a healthy gut microflora.

From many studies, it has been reported that gut bacteria that naturally inhabit the gut can modulate mucin secretion. Neag et al. 2020 reported that *Bifidobacterium dentium* directly modulates Muc2 production by enhancing MUC2 gene expression (Neag et al., 2020). *In vivo* experiment on germ-free Swiss Webster mice which were Monoassociated with life or heat-killed *B. dentium* revealed that mice that were mono associated with live bacteria have "filled goblet cell numbers for crypt" comparatively to germ-free mice and heat-killed *B. dentium* treated mice. To define the effects of the bacteria their study revealed that, in presence of life *B.*



**Fig. 3 The mucus layer of an individual with a healthy gut microflora**

*dentium* several goblet cell markers which are - Trefoil factor 3 (Tff3), Relm-Beta, Kruppel-like factor 4 (Klf4), and MUC2 gene exhibited an increase in colonic expression. They also identified Gamma-aminobutyric acid (GABA) which promotes mucin secretion from goblet cells (Picard et al., 2005). Although many *B. dentium* species have been identified, which secrete mucin-related glycosyl hydrolases, can degrade mucin-glycans. But studies have shown that *B. dentium* cannot grow in host epithelium having mucin as the only carbon source. This finding clears that this species is not involved in the extensive degradation of mucus (Sasaki et al., 2020).

Another probiotic *Escherichia coli* Nissle 1917 has been reported which alters mucin gene expression. An *in vitro* study performed on HT-29 cells using EcN showed enhancement in MUC2, MUC3, MUC5AC, & MUC5A gene expression. Thus, mucin secretion is increased. Other probiotic bacteria, *Lactobacillus plantarum* 299V & *Lactobacillus casei* GG have been studied and confirmed that they play an active role in enhancing mucin secretion (McFarlin et al., 2017; Possemiers et al., 2004).

Mutualistic relationships between host and microorganisms are governed by a precise balance between protective and tolerogenic immune responses that continuously fluctuate in response to changes in microbial population subgroups of the gut microflora. The density and makeup of the microbiota are influenced by chemical and nutritional gradients in the gut (Vincent et al., 2013). Fast-growing, mucus-adhering facultative anaerobes like those in the *Lactobacillaceae* family prevail in the small intestine because of the high concentrations of acids, oxygen, and antimicrobials there. Contrarily, colonic conditions support a rich and diverse community of anaerobic fermenters, such as *Bifidobacterium*, *Prevotellaceae*, *Lachnospiraceae*, *Eubacteriaceae*, and *Rikenellaceae*, that may utilise complex

carbohydrates that are undigested in the small intestine (Picard et al., 2000; Scher et al., 2015). At relatively stable, commensals help their host by neutralising toxins, converting indigestible nutrients and starches into useful metabolites, and producing short-chain fatty acids that can influence host reactions (Possemiers et al., 2004; Schipp et al., 2010). Some commensals also produce unique proteins and polysaccharides on their surface and/or secrete metabolites that can interact with immune cells to cause tolerogenic and homeostatic responses that are typically characterised by an excess of Tregs, decreased production of pro-inflammatory cytokines (e.g., TNF- and IL-6), an increased supply of anti-inflammatory cytokines (e.g., IL-10 and TGF), and improved intestinal barrier function. The basic classifications of tolerogenic commensal-derived substances are short-chain fatty acids, Aryl hydrocarbon receptor (AHR) ligands, and glycans (Possemiers et al., 2004; Schloss et al., 2011).

### Direct Immunomodulation

The host's immune system is shaped by the microbiota, particularly the gut microbiota, through the modulation of both local and systemic immunological responses. Being the largest interface between the host body and the external environment, the GIT is the most common path for microorganisms to enter the host body. Thus, to defend the body from pathogenic strains, only gut-epithelial barrier or mucus entrapment is not adequate. So, it becomes very important to directly engage the pathogens (Walters et al., 2014). Various innate and adaptive immunity cells of the host body elicit an immune response against these pathogens and kill them by engaging directly. GALT is the site where this immune response begins. The gut natural killer cells (NK cells), dendritic cells (DCs), and macrophages are important immune cells. They are part of the innate immune system and kill pathogens via cell lysis and phagocytosis (Windey et al., 2012). They can identify both pathogenic and non-pathogenic

**Table 1. Various bacterial strains are involved in indirect immunomodulation**

Name of the bacterial strains	Experimental Conditions	Results	Significant Observations	References
<i>Escherichia coli</i> Nissle 1917 (EcN)	In vivo (Gnotobiotic BALB/c mice Model).	Upregulated expression of ZO-1 mRNA and protein in the intestinal epithelial cells of the test mice.	Prevention of leaky gut condition.	Finucane et al., 2014; Duysburgh et al., 2019; Possemiers et al., 2004; Scher et al., 2015
	In vitro (T84 cells & Caco-2 cells).	Upregulation of ZO-2 protein expression and increased localization pattern for the same protein were observed.	Intestinal epithelial permeability maintenance and also restoration of the disrupted epithelial barrier.	
	In vitro (HT 29 cell)	Enhanced expression of MUC2, MUC3, MUC5AC, MUC5A genes.	Maintenance of a healthy mucus layer.	
<i>Lactobacillus plantarum</i> WCFS1	Both in vivo (human study) and in vitro (Caco-2 cells).	Increased localization of ZO-1 and occludin proteins in the TJs of the intestinal epithelial cells.	Enhancement of TJ formation thus maintaining the epithelial permeability.	Hyser et al., 2019; Faille et al., 2002; McFarlin et al., 2017; Possemiers et al., 2004
<i>Lactobacillus plantarum</i> MB452	In vitro (Human colon cancer cells/Caco-2 cells).	A vigorous alteration of gene expression was observed, among them 19 were involved in TJ formation.	Increasing the integrity of the intestinal epithelial barrier by enhancing the expression of TJ-forming proteins.	
<i>Bifidobacterium infantis</i> and <i>Lactobacillus acidophilus</i>	In vivo (mouse model)	A mixture of both of the strains enhanced the expression of Claudin-1 and Occludin proteins and also suppressed the expression of Proinflammatory cytokines IL-6 and IL-17 in the mouse model of post-infectious IBD (Irritable Bowel Syndrome).	Recovery of integrity as well as a normal gut function after a certain physiological imbalance.	Possemiers et al., 2004; Scher et al., 2015; Neag et al., 2020; Hyser et al., 2019
<i>Lactobacillus reuteri</i> E	In vitro (HT 29)	<i>L. reuteri</i> E, Pre-cultivated with mucin significantly upregulates MUC2, MUC5AC gene expression, and anti-inflammatory IL-10.	Maintenance of the mucus layer.	Hyser et al.,2019.; Faille et al.,2002; McFarlin et al.,2017;
<i>Bifidobacterium dentium</i>	In vivo (Swiss Webster mice)	Upregulation of MUC2 gene expression of intestinal epithelial cells, secretion of microbial metabolites like acetate and GABA, along with stimulating the autophagy-mediated CA++ stimulation collectively enhance mucus production.	Increased production of mucin thus increasing the amount of mucus in gut mucosa resulting in better entrapment of pathogens.	
VSL#3	In vivo (Wistar rats)	Enhanced expression of MUC2 gene resulting in higher mucin secretion	Increased mucin production and maintenance of mucus layer	Duysburgh et al., 2019; Possemiers et al., 2004; Scher et al., 2015
	In vivo (BALB/c mice)	Maintained the expression of ZO-1, claudin-1,3,4,5 proteins during acute colitis condition (induced by Dextran Sodium Sulphate) in test animals, as these proteins are downregulated during colitis.	Prevention of increased colonic epithelial permeability during acute colitis.	
<i>Lactobacillus casei</i> GG	In vitro (Human Caco-2 cell layer)	LGG increased the MUC2 gene expression.	Prevention of bacterial translocation	Duysburgh et al., 2019; Hyser et al., 2019; Faille et al., 2002
<i>Lactobacillus rhamnosus</i> GG	Both in vivo and in vitro	P40, a soluble protein derived from the strain upregulates MUC2 gene expression thus enhancing mucus production.	Enhanced mucin production may protect the intestinal epithelium from injury and intestinal inflammatory diseases.	

strains via Pattern Recognition Receptors (PRRs) like, Toll-like receptors (TLRs). Pathogenic strains exhibit specific markers (molecules like peptidoglycan, lipopolysaccharide (Lps), and other membrane-associated virulence factors (patterns) on their outer surface that help immune cells distinguish them (Yang et al., 2015).

The development of CD4<sup>+</sup> T lymphocytes depends on the gut microbiota both inside and outside the intestine. LP CD4<sup>+</sup> cells are consequently much less prevalent in germ-free mice. Systematically, germ-free animals also have defective spleens and mesenteric lymph nodes because they lack lymphocyte zones. In 18 germ-free mice, there is an imbalance between the Th1 and Th2 immune responses, with the Th2 response being more pronounced. Recent studies have even discovered a connection between a certain bacterial species and the development of various T-cell subtypes (Yoshida et al., 2018). It has been established that the systemic Th1 response emerges as a result of the polysaccharide A (PSA) molecules generated by *Bacteroides fragilis*. Contrarily, it was found that segmented filamentous bacteria (SFB) were potent inducers of LP Th17 cells (Sche et al., 2015; Zhang et al., 2019). In the dataset of human gut metagenome sequences, only a small number of reads, or 0.31% of the mouse SFB genome, were discovered in a recent study. This finding raises the possibility that other bacteria may operate as the main inducers of human Th17 cells. This underscores the importance of identifying other microorganisms in humans as Th17 inducers. Another possibility is that the lack of SFB finding in humans is caused by the human metagenome data set's removal of samples obtained from young children during weaning periods (Pyne et al., 2015). In mice, SFB colonisation spreads widely at weaning age. *Clostridia*, especially those from clusters IV and XIVa, have recently been shown to be able to aid in the induction of colonic Tregs. Another study discovered that intestinal Treg cell conversion is prevented by TLR9 signaling triggered by DNA from the gut microbiota. This helps to maintain immune homeostasis. It's intriguing to learn that *B. fragilis* PSA can stimulate Tregs via TLR2 and then block a Th17 response (Rinttila et al., 2004).

Multiple studies have shown that particular microbiota species change the ratio of different immune cell subtypes, such as Foxp3<sup>+</sup> regulatory T cells and Th17 cells, showing that the microbiota's composition may have a substantial effect on the immune response (Scher et al., 2015; Schloss et al., 2011). Numerous studies have shown that alterations in the gut microbiota can promote the activation of effector T cells over iTregs, which can result in the development of autoimmune and inflammatory illnesses. This study identified specific gut commensals that can either activate Th17 or Treg responses, which are linked to the onset of disease or its prevention, respectively (Suzuki et al., 2004; Vincent et al., 2013). Several investigations utilising animal models have shown that TLR2 mediates the regulatory immune responses in the gut. The treatment of ethanol or AT1002 (*V. cholera* zona occludens toxin hexapeptide)

results in limited disruption of the epithelial barrier in addition to producing persistent CD4<sup>+</sup> LAP<sup>+</sup> (latent TGF—associated with latency-associated peptide) cells. It has been demonstrated that the development of these cells is reliant on the presence of a healthy intestinal flora, which works, at least in part, by activating CD11c<sup>+</sup> lamina propria DCs with Th2 (Arboleya et al., 2016). Hence, it is likely that activating these cells enhances the maintenance of homeostasis against the possible intestinal bacterial invasion before Foxp3<sup>+</sup> iTreg cells respond. The microbiota, TLRs, and Th17. Despite extensive study, it is still unknown how TLRs influence the control of gut-adaptive Th17 cells. It has been shown that intestinal Th17 cell growth is aided by the addition of flagellin, a TLR5 ligand, and that TLR9-deficient mice have fewer lamina propria Th17 cells (Azad et al., 2018). These results suggest that Th17 differentiation may also be influenced by TLR5-dependent signaling. Contrarily, in the large and small intestines of MyD88 and TIR domain containing adaptor-inducing IFN- (Trif) doubly deficient animals, a normal number of LP Th17 cells are detected. The role of TLRs in the activation of intestinal Th17 cells must therefore be further studied because other chemicals signaling through MyD88 or Trif may have an effect that is in opposition to TLR9's (Backhed et al., 2005).

These cells can distinguish commensals from pathogens (RLRs) thanks to pattern recognition receptors (PRRs), which include the families of toll-like receptors (TLRs), nucleotide-binding oligomerization domain- (NOD-) like receptors (NLRs), C-type lectin receptors (CLRs), cytosolic DNA receptors (CDRs), and RIG-I-like receptors (Faille et al., 2002). Particularly, enteric cells' cytoplasm and the membranes of immunological and epithelial cells' respective membranes contain TLRs and NODs. As pathogen-associated molecular patterns (PAMPs, expressed by pathogens), and microbe-associated molecular patterns (MAMPS, expressed by resident microbiota), TLRs and NODs are able to recognize common molecular motives (PAMPS, produced by microbial invaders). They are activated by a variety of intracellular signaling cascades, which result in the production of cytokines, chemokines, and transcription factors required to preserve gut homeostasis and/or fight infection (Molly et al., 2003; Mortensen et al., 2000). To preserve the harmony of intestinal homeostasis, TLRs are essential for both enhancing inflammatory responses to infections and inhibiting the activation of the inflammatory cascade. To maintain the equilibrium of intestinal homeostasis, TLRs are essential for both enhancing inflammatory responses to infections and inhibiting the activation of the inflammatory cascade (Scher et al., 2015). There are eleven unique members of the transmembrane protein family known as TLR. Even though they are constantly exposed to a lot of commensal bacteria, they can manage inflammation in steady-state conditions by acting in a way that is hyporesponsive to the intestinal flora (Picard et al., 2005). According to recent studies, interactions between host effector molecules and bacteria may be important in the mechanisms that control immune activation. These molecules

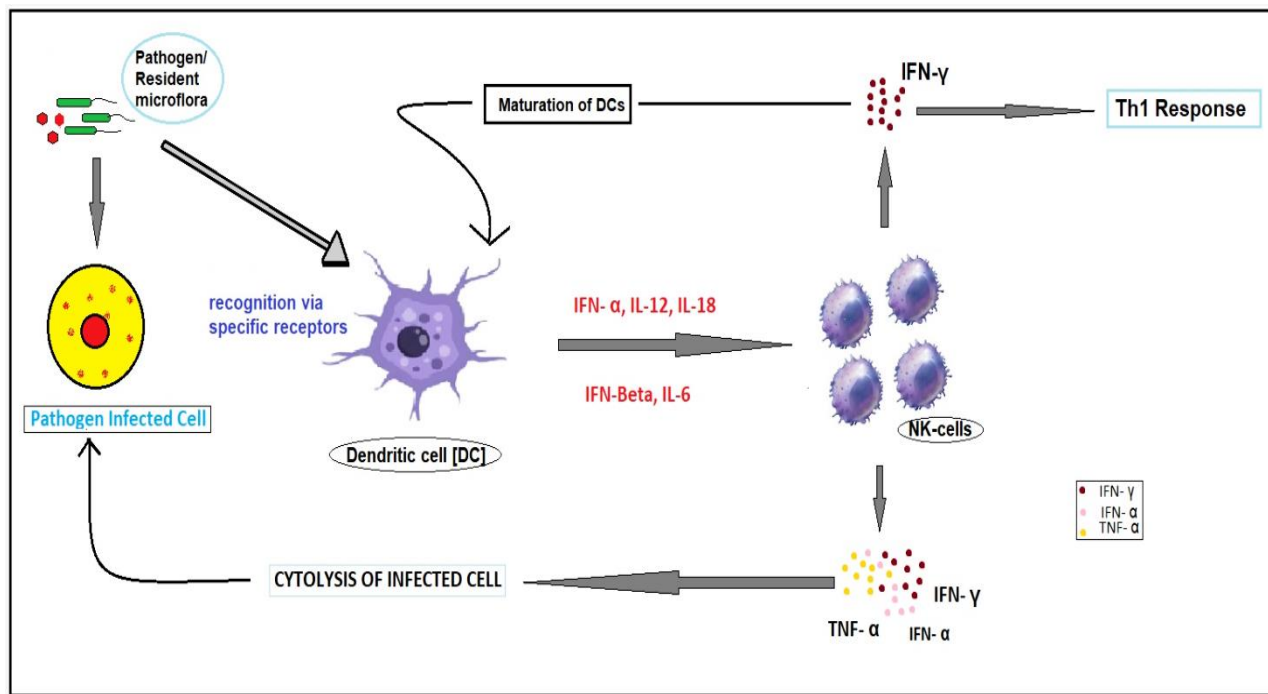
have the power to interfere with and change the signal transmission mediated by TLRs by interfering either at the level of effector molecule synthesis or along the signal transduction from the TLRs (Vincent et al., 2013; Schloss et al., 2011). TLR2 makes it easier to find both Gram-positive and Gram-negative bacteria as well as yeast. According to many pieces of evidence, TLR2 can dimerize with a variety of different coreceptors, such as TLR2 itself, TLR1, TLR6, and TLR10, to produce pro- or anti-inflammatory responses (Mortensen et al., 2000; Possemiers et al., 2004). According to recent studies, TLR2/TLR6 dimerization activates the TLR2-MyD88-IRAK-TRAF-NIK-IKK-NF- $\kappa$ B signal transduction pathway, which induces the transcription of proinflammatory molecules, while TLR2/TLR1 dimerization promotes the anti-inflammatory pathway, which results in the expression of IL-10 and the transdifferentiation of Th17 and iTreg cells (Pyne et al., 2015; Arboleya et al., 2016; Backhed et al., 2005).

Surprisingly, Th17 cells cause harm in many inflammatory diseases despite being essential for the non-inflammatory maintenance of the intestinal barrier integrity (Arboleya et al., 2016). This dichotomy follows a similar pattern to that of macrophages and dendritic cells: long-lived intestine resident Th17 cells support barrier maintenance and homeostasis, whereas Th17 cells generated by the infection have a highly inflammatory nature and are effective in combating pathogenic bacteria. They are mostly determined by these special bacteria that cause the differentiation of these Th17 populations (Vincent et al., 2013; Backhed et al., 2005). A recent study found that Th17 cells produced by segmented filamentous bacteria (SFB) are homeostatic and do not participate in inflammatory responses. There are two stages to SFB's Th17 manufacture. Dendritic cells in the mLN that are loaded with SFB antigens first activate naive T cells, which are then induced to generate ROR $\gamma$ t before returning to the small intestine (Cutting, 2011; Faille et al., 2002). As a result of SFB interaction with intestinal epithelial cells, serum amyloid A (SAA) is then formed, maturing T cells into overexpressing ROR $\gamma$ t/IL-17A. (Finucane et al., 2014). Memory cells and tissue-resident homeostatic Th17 cells have comparable metabolic profiles. Contrarily, Th17 cells that have been stimulated by pathogens carry out aerobic glycolysis, which is frequently associated with inflammatory cells. Even though there is mounting evidence that specific bacterial species are essential for the development and maintenance of intestinal Th17 and Treg cells' homeostatic nature, research into the molecules produced by commensals that are in charge of upholding this equilibrium has only recently begun to pick up steam.

NK cells are mostly located in the spleen, bone marrow, and blood. They are distinguished by the surface expression of the immunoglobulin superfamily member and NK cell surface marker CD56, but not by the expression of CD3. When compared to those found in peripheral blood, the NK cells associated with the stomach are frequently immature (McFarlin et al., 2017). This is due to the fact that NK cells

in peripheral blood are usually CD16-positive, but NK cells in the gut are not always CD16+ (McFarlin et al., 2017; Mortensen et al., 2000). Through the FC regions of antibodies, the CD16s, sometimes referred to as Fc-RIII, bind to targets that are coated with antibodies, mediating antibody-dependent cellular cytotoxicity (ADCC) (Sasaki et al., 2020). Additionally, the gut NK cells express CD56 at a high density. Large amounts of IFN- (Interferon-) are produced by CD56-bright (high density) NK cells, which stimulates T-helper 1 (Th1) cells, DCs, and macrophages for the phagocytosis and lysis of pathogen or virus-infected cells (Fig.4). They also produce TNF (Tumor Necrosis Factor), IL-2, IL-17, and IL-22 in addition to IFN. These cytokines trigger the innate immune system and the immature NK cells' cytolytic function (Sidhu et al., 2017; Vincent et al., 2013). Probiotics have been shown in numerous studies to increase NK cell function. Yang et al. (2015) investigated the effects of the *Bispan* strain of *Bacillus polyfermenticus* to determine whether it had any positive impacts on NK cell function. 25 males between the ages of 22 and 35 were chosen to participate in the test. Twelve of them were chosen as the control group, while the remaining 13 guys received either a placebo or *B. polyfermenticus* supplements for a period of eight weeks. After the research, it was discovered that the *Bispan* strain-supplemented group displayed 35% increased CD56+ NK cell activity (Azad et al., 2018). Additional links exist between DC-secreted cytokines and NK cell activation. DCs can actively recognize pathogen-affected cells and respond by secreting cytokines and chemokines such as IL-12, IL-18, type I IFNs, among others. Due to the frequent interactions between GM and the host immune system at mucosal surfaces like the colon and intestine, this role becomes essential. These DC-secreted cytokines and chemokines are important for inducing NK cell activity, according to numerous studies. IL-12 released by DCs increases NK cell INF- production (Fig.4 and 5). This secretion is induced by the interaction of IL-18 and IL-12, and these two factors also increase the cytotoxicity of NK cells. IFN- (type I interferon), which is secreted by plasmacytoid DCs (pCDCs), promotes NK cell-mediated cell lysis of virus-infected target cells. NK-DC crosstalk refers to these interactions between NK and DC cells, and it is essential for our immune system (Hyser et al., 2019). Studies have shown that several *Lactobacillus* species (LAB) cause DCs to produce more TNF, IL-6, and IL-12. Additionally, they support DC maturation. These probiotics are crucial to the function of NK cells since they are partially dependent on DCs. It has been specifically discovered that *Lactobacillus acidophilus* stimulates DCs to secrete IL-12, which then boosts NK cells' production of IFN-. In addition to LAB, some *Bifidobacterial* species also cause little DC maturation (Wang et al., 2008; Sasaki et al., 2020). Innate immunity also includes macrophages in addition to NK cells and DCs. They also eliminate infections through cell lysis and phagocytosis. Reactive oxygen species (ROS) and other pro-inflammatory cytokines, including as TNF-, IL-8, and others, are released by macrophages in response, which hinders pathogen invasion (Picard et al., 2005; Vincent et al.,



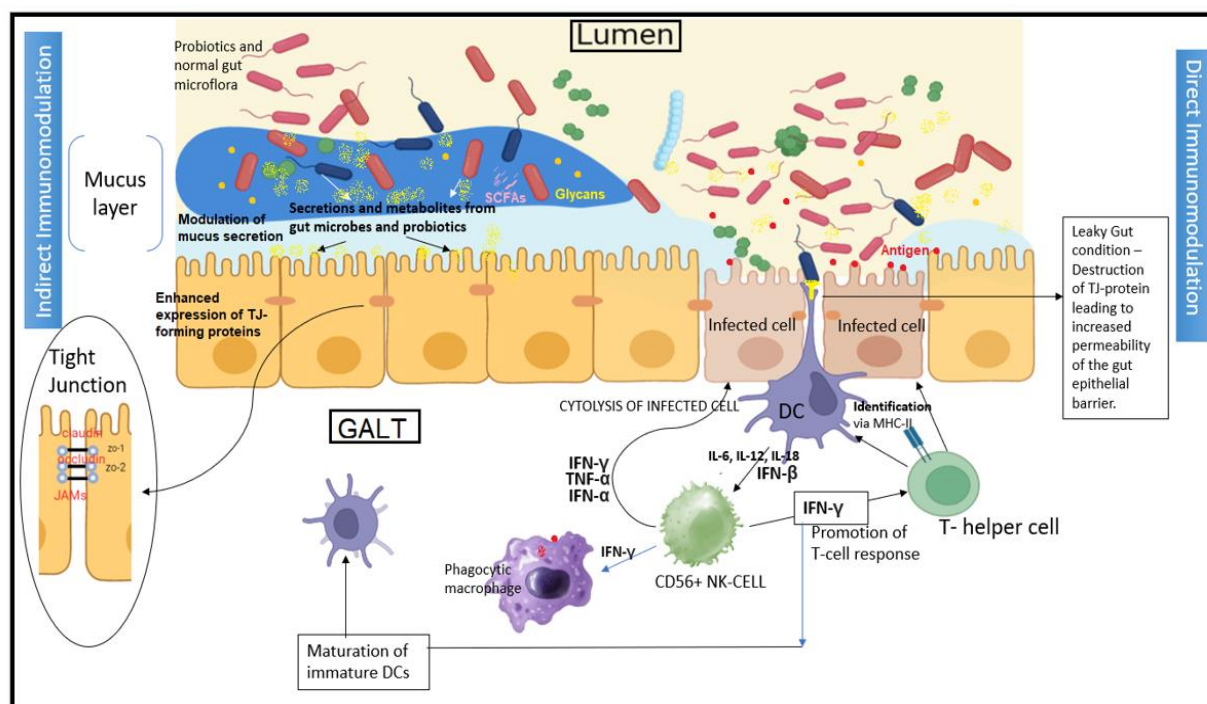


**Fig. 4 Representation of NK-DC crosstalk as discussed earlier. DCs recognizes infected cells via specific receptors and secrete IL-12, IL-18, and type I IFNs and other cytokines and chemokines which in turn trigger the cytotoxicity of NK cells**

2013). By triggering NF- $\kappa$ B, STAT-1, and STAT-3 DNA binding activity, Mortensen et al. (2000) demonstrated that both viable and non-viable *Lactobacillus rhamnosus* GG improve macrophage functions (Mortensen et al., 2000). Additionally, research has demonstrated that specific *Lactobacillus* species cause macrophages to release cytokines (IL-8 by *Lactobacillus casei*, & IL-1 by *Lactobacillus helveticus*). Probiotics aid in the improvement of macrophage activity in this way (Menni et al., 2018).

The existence of commensal microorganisms that are "beneficial" and can lower sickness shouldn't come as a surprise. For instance, *B. fragilis* can lessen the colitis that *Helicobacter hepaticus* causes in immunocompromised mice by producing PSA, which prevents illness by stimulating the production of the anti-inflammatory IL-10 from CD4+ T cells and reducing the production of the pro-inflammatory IL-17 in the colonic mucosa (Sasaki et al., 2020). Furthermore, it has been demonstrated that the bacteria *Bacteroides thetaiotaomicron* inhibits *Salmonella* enterica-induced inflammation by enhancing the nuclear export of PPAR-, a transcription factor crucial for regulating lipid metabolism and inflammation (Yang et al., 2015). Short-chain fatty acids (SCFAs) produced by the gut microbiota have also been shown to reduce inflammation in the dextran sulfate sodium (DSS)-induced colitis model. To have this anti-inflammatory effect, SCFAs have to bind with the G-

protein-coupled receptor, which is expressed on immune cells (Yang et al., 2015; Azad et al., 2018). Given that *Clostridium*'s anti-inflammatory effects coincided with a decline in DSS-induced colitis, it's plausible that Tregs are at fault for these effects (Suzuki et al., 2004). The composition of the gut microbiota has been significantly influenced by a variety of practices that have been adopted throughout the history of human civilization. In addition to the autoimmune disorders described in this study, alterations in the gut microbiota may also influence many other health-related conditions, such as obesity and allergies. Therefore, these practices require careful evaluation (Yang et al., 2015). Dietary choices are one of the major factors that affect the variety of gut microbiota, for example. Significant scientific and therapeutic interest has grown in the regulation of immune function by commensals and how it impacts well-being and disease. For the organism's defense (mostly symbionts), strict surveillance that can distinguish between microbes with pathogenic potential (pathobionts) and nonpathogenic microbes is required (Pyne et al., 2015). Understanding the relationship between gut microbes and the host immune system is important for maintaining good health because the incidence of various diseases, including several immunological disorders, is rising alarmingly quickly and may be triggered by commensal dysbiosis.



**Fig. 5 An overview on gastrointestinal tract associated microbiota in direct and indirect immunomodulation**

### Conclusion and Future perspective

How the microbiota affects the activation and control of T cells' functions are still being investigated. It is still unclear exactly how commensals affect immune responses and diseases caused by immunological-mediated processes. The growth and "maintenance" of a healthy gut depend on the gut microbiota and the immune system it continuously stimulates. The immune system defends the host against many infectious agents such as bacteria, viruses, fungi, and parasites, making it an essential part of the host organism. A healthy human gut with a homeostatic relationship between GM and host immunity confers a healthy human life. Age, diet, medication, and way of life are just a few examples of the many different variables that might have an impact on the microbiota in the gut. Prebiotics are non-digestible food ingredients that can alter the gut microbiota with a potentially positive impact on the human body. Probiotics are commensal microorganisms that support and maintain the host intestinal cell wall's permeability. Mucosa-associated bacteria are thought to need to adhere to the intestinal mucus layer to colonise, and this serves as a selection criterion for probiotic microbes. Understanding the biology of probiotics has made it possible to decipher the dynamics of the gut's microflora and the variations in bacterial composition when these advantageous strains are administered. Dendritic cells (DCs) are in charge of scanning the environment for any pathogenic intruders and releasing cytokines or chemokines to elicit an immune response. Probiotics and other commensal bacteria found in the gut lumen are crucial in the regulation role of DCs. Probiotics do not seem to have much

of the desired effect on acquired immunity, however, some probiotic strains have been demonstrated to improve innate immunity (particularly, phagocytosis and NK cell activity). The health benefits of probiotics could be supported by a better understanding of the functions of the gut immune system.

### Conflict of Interest

The author hereby declares no conflict of interest.

### Consent for publication

The author declares that the work has consent for publication.

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### References

- Anderson, R.C., Cookson, A.L., McNabb, W.C., Park, Z., McCann, M.J., Kelly, W.J., Roy, N.C. (2010). Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. *BMC Microbiol* 10(316). DOI: 10.1186/1471-2180-10-316.
- Arbolea, S., Watkins, C., Stanton, C., & Ross, R. P. (2016). Gut Bifidobacteria populations in human health and aging. *Frontiers in Immunology*, 7(1204). <https://doi.org/10.3389/fmicb.2016.01204>.
- Azad, M. A. K., Sarker, M., Li, T., & Yin, J. (2018). Probiotic Species in the Modulation of Gut Microbiota: An Overview. *Biomed Research International*, 1–8. <https://doi.org/10.1155/2018/9478630>.
- Backhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A., & Gordon, J. I.

- (2005). Host bacterial mutualism in the human intestine. *Science*, 307(5717), 1915–1920. <https://doi.org/10.1126/science.1104816>.
- Bernardeau, M., Lehtinen, M. J., Forssten, S. D., & Nurminen, P., (2017). Importance of the gastrointestinal life cycle of *Bacillus* for probiotic functionality. *Journal of Food Science and Technology*, 54(8), 2570–2584. <https://doi.org/10.1007/s13197-017-2688->
- Blaak, E. E., Canfora, E. E., Theis, S., Frost, G., Groen, A. K., Mithieux, G., Verbeke, K. (2020). Short chain fatty acids in the human gut and metabolic health. *Benef Microbes*, 11(5), 411–455. <https://doi.org/10.3920/BM2020.0057>.
- Casula, G., & Cutting, S. M. (2002). *Bacillus* probiotics: Spore germination in the gastrointestinal tract. *Applied and Environment Microbiology*, 68(5), 2344–2352. <https://doi.org/10.1128/aem.68.5.2344-2352.2002>.
- Catinean, A., Neag, A. M., Nita, A., Buzea, M., & Buzoianu, A. D. (2019). *Bacillus* spp. spores—a promising treatment option for patients with irritable bowel syndrome. *Nutrients*, 11(9). <https://doi.org/10.3390/nu11091968>.
- Catinean, A., Neag, M. A., Krishnan, K., Muntean, D. M., Bocsan, C. I., Pop, R. M., Buzoianu, A. D. (2020). Probiotic *Bacillus* spores together with amino acids and immunoglobulins exert protective effects on a rat model of ulcerative colitis. *Nutrients*, 12(12), 3607. <https://doi.org/10.3390/nu12123607>.
- Cutting, S. M. (2011). *Bacillus* probiotics. *Food Microbiology*, 28(2), 214–220. <https://doi.org/10.1016/j.fm.2010.03.007>.
- de Goffau, M. C., Luopajarvi, K., Knip, M., Ilonen, J., Ruohtula, T., Harkonen, T., Vaarala, O. (2013). Fecal microbiota composition differs between children with beta-cell autoimmunity and those without. *Diabetes*, 62(4), 1238–1244. <https://doi.org/10.2337/db12-0526>.
- Duysburgh, C., Van den Abbeele, P., Krishnan, K., Bayne, T. F., & Marzorati, M. (2019). A synbiotic concept containing spore-forming *Bacillus* strains and a prebiotic fiber blend consistently enhanced metabolic activity by modulation of the gut microbiome in vitro. *International Journal of Pharmaceutics*: X, 1, 100021. <https://doi.org/10.1016/j.ijpx.2019.100021>.
- El Hage, R., Hernandez-Sanabria, E., Calatayud Arroyo, M., Props, R., & Van de Wiele, T. (2019). Propionate-producing consortium restores antibiotic-induced dysbiosis in a dynamic in vitro model of the human intestinal microbial ecosystem. *Frontiers in Microbiology*, 10(1206). <https://doi.org/10.3389/fmicb.2019.01206>.
- Faille, C., Membre, J. M., Kubaczka, M., & Gavini, F. (2002). Altered ability of *Bacillus cereus* spores to grow under unfavorable conditions (presence of nisin, low temperature, acidic pH, presence of NaCl) following heat treatment during sporulation. *Journal of Food Protection*, 65(12), 1930–1936. <https://doi.org/10.4315/0362-028x-65.12.1930>.
- Feng, Y., Wang, Y., Wang, P., Huang, Y., & Wang, F. (2018). Short-chain fatty acids manifest stimulative and protective effects on intestinal barrier function through the inhibition of NLRP3 inflammasome and autophagy. *Cellular Physiology and Biochemistry*, 49(1), 190–205. <https://doi.org/10.1159/000492853>.
- Finucane, M. M., Sharpton, T. J., Laurent, T. J., Pollard, K. S., & Heimesaat, M. M. (2014). A taxonomic signature of obesity in the microbiome? Getting to the guts of the matter. *PLoS ONE*, 9(1), e84689. <https://doi.org/10.1371/journal.pone.0084689>.
- Fukuda, S., Toh, H., Hase, K., Oshima, K., Nakanishi, Y., Yoshimura, K., Ohno, H. (2011). Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature*, 469(7331), 543–547. <https://doi.org/10.1038/nature09646>.
- Hyser, M., James V. (2019). Bifidobacterium dentium Fortifies the Intestinal Mucus Layer via Autophagy and Calcium Signaling Pathways. *mBio* 10: e01087-19. DOI: 10.1128/mBio.01087-19.
- Larsen, N., Vogensen, F. K., van den Berg, F. W. J., Nielsen, D. S., Andreasen, A. S., Pedersen, B. K., Bereswill, S. (2010). Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS ONE*, 5(2), e9085. <https://doi.org/10.1371/journal.pone.0009085>.
- Magne, F., Gotteland, M., Gauthier, L., Zazueta, A., Pesoa, S., Navarrete, P., & Balamurugan, R. (2020). The Firmicutes/Bacteroidetes ratio: A relevant marker of gut dysbiosis in obese patients? *Nutrients*, 12(5). <https://doi.org/10.3390/nu12051474>.
- Manichanh, C., Rigottier-Gois, L., Bonnaud, E., Gloux, K., Pelletier, E., Frangeul, L., Dore, J. (2006). Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut*, 55(2), 205–211. <https://doi.org/10.1136/gut.2005.073817>.
- Marzorati, M., Abbeele, P. V. D., Bubeck, S. S., Bayne, T., Krishnan, K., Young, A., DeSouza, A. (2020). *Bacillus subtilis* HU58 and *Bacillus coagulans* SC208 probiotics reduced the effects of antibiotic-induced gut microbiome dysbiosis in an M-SHIME (R) model. *Microorganisms*, 8(7). <https://doi.org/10.3390/microorganisms8071028>.
- McFarlin, B. K., Henning, A. L., Bowman, E. M., Gary, M. A., & Carbajal, K. M. (2017). Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers. *World Journal of Gastrointestinal Pathophysiology*, 8(3), 117–126. <https://doi.org/10.4291/wjgp.v8.i3.117>.
- Menni, C., Lin, C., Cecelja, M., Mangino, M., Matey-Hernandez, M. L., Keehn, L., Valdes, A. M. (2018). Gut microbial diversity is associated with lower arterial stiffness in women. *European Heart Journal*, 39(25), 2390–2397. <https://doi.org/10.1093/eurheartj/ehy226>.
- Molly, K., Vande Woestyne, M., & Verstraete, W. (1993). Development of a 5-step multichamber reactor as a simulation of the human intestinal microbial ecosystem. *Applied Microbiology and Biotechnology*, 39(2), 254–258. <https://doi.org/10.1007/BF00228615>.
- Mortensen, P. B., & Clausen, M. R. (1996). Short-chain fatty acids in the human colon: Relation to gastrointestinal health and disease. *Scandinavian Journal of Gastroenterology. Supplement*, 31(sup216), 132–148. <https://doi.org/10.3109/00365529609094568>.
- Mosca, A., Leclerc, M., & Hugot, J. P. (2016). Gut microbiota diversity and human diseases: Should we reintroduce key predators in our ecosystem? *Frontiers in Microbiology*, 7(455). <https://doi.org/10.3389/fmicb.2016.00455>.
- Neag, M. A., Catinean, A., Muntean, D. M., Pop, M. R., Bocsan, C. I., Botan, E. C., & Buzoianu, A. D. (2020). Probiotic *Bacillus* spores protect against acetaminophen-induced acute liver injury in rats. *Nutrients*, 12(3), 632. <https://doi.org/10.3390/nu12030632>.
- Picard, C., Fioramonti, J., Francois, A., Robinson, T., Neant, F., & Matuchansky, C. (2005). Review article: Bifidobacteria as probiotic agents – physiological effects and clinical benefits. *Alimentary Pharmacology & Therapeutics*, 22(6), 495–512. <https://doi.org/10.1111/j.1365-2036.2005.02615.x>.
- Possemiers, S., Verthe, K., Uyttendaele, S., & Verstraete, W. (2004). PCR-DGGE-based quantification of stability of the microbial community in a simulator of the human intestinal microbial ecosystem. *FEMS Microbiology Ecology*, 49(3), 495–507. <https://doi.org/10.1016/j.femsec.2004.05.002>.
- Pyne, D. B., West, N. P., Cox, A. J., & Cripps, A. W. (2015). Probiotics supplementation for athletes - clinical and physiological effects. *European Journal of Sport Science*, 15(1), 63–72. <https://doi.org/10.1080/17461391.2014.971879>.
- Rinttila, T., Kassinen, A., Malinen, E., Krogius, L., & Palva, A. (2004). Development of an extensive set of 16S rDNA-targeted primers for quantification of pathogenic and indigenous bacteria in faecal samples by real-time PCR. *Journal of Applied Microbiology*, 97(6), 1166–1177. <https://doi.org/10.1111/j.1365-2672.2004.02409.x>.
- Sasaki, K., Sasaki, D., Inoue, J., Hoshi, N., Maeda, T., Yamada, R., & Kondo, A. (2020). *Bacillus coagulans* SANK 70258 suppresses Enterobacteriaceae in the microbiota of ulcerative colitis in vitro and enhances butyrogenesis in healthy microbiota. *Applied Microbiology and Biotechnology*, 104(9), 3859–3867. <https://doi.org/10.1007/s00253-020-10506-1>.
- Scher, J. U., Ubeda, C., Artacho, A., Attur, M., Isaac, S., Reddy, S. M., Abramson, S. B. (2015). Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis & Rheumatology*, 67(1), 128–139. <https://doi.org/10.1002/art.38892>.
- Schippa, S., Iebba, V., Barbato, M., Di Nardo, G., Totino, V., Checchi, M., Conte, M. (2010). A distinctive 'microbial signature' in celiac pediatric patients. *BMC Microbiology*, 10(1), 175. <https://doi.org/10.1186/1471-2180-10-175>.
- Schloss, P. D., & Westcott, S. L. (2011). Assessing and improving methods used in operational taxonomic unit-based approaches for 16S rRNA gene sequence analysis. *Applied and Environment Microbiology*, 77(10), 3219–3226. <https://doi.org/10.1128/AEM.02810-10>.
- Sidhu, M., & van der Poorten, D. (2017). The gut microbiome. *Australian Family Physician*, 46(4), 206–211. <https://www.ncbi.nlm.nih.gov/pubmed/28376573>.

- Suzuki, H., Watabe, J., Takeuchi, H., Tadano, Y., Masuda, S., & Maruta, K. (2004). Effect of *Bacillus subtilis* C-3102 intakes on the composition and metabolic activity of fecal microflora of humans. *Journal of Intestinal Microbiology*, 18(2), 93–99. <https://doi.org/10.11209/jim.18.93>.
- Sze, M. A., & Schloss, P. D. (2016). Looking for a signal in the noise: Revisiting obesity and the microbiome. *mBio*, 7(4), e01018–01016. <https://doi.org/10.1128/mBio.01018-16>.
- Vincent, C., Stephens, D. A., Loo, V. G., Edens, T. J., Behr, M. A., Dewar, K., & Manges, A. R. (2013). Reductions in intestinal Clostridiales precede the development of nosocomial *Clostridium difficile* infection. *Microbiome*, 1(1), 18. <https://doi.org/10.1186/2049-2618-1-18>.
- Walters, W. A., Xu, Z., & Knight, R. (2014). Meta-analyses of human gut microbes associated with obesity and IBD. *FEBS Letters*, 588(22), 4223–4233. <https://doi.org/10.1016/j.febslet.2014.09.039>.
- Wang, M., Karlsson, C., Olsson, C., Adlerberth, I., Wold, A. E., Strachan, D. P., Ahm'e, S. (2008). Reduced diversity in the early fecal microbiota of infants with atopic eczema. *The Journal of Allergy and Clinical Immunology*, 121(1), 129–134. <https://doi.org/10.1016/j.jaci.2007.09.011>.
- Wang, Q., Garrity, G. M., Tiedje, J. M., & Cole, J. R. (2007). Naive Bayesian classifier for rapid assignment of rRNA sequences into the new bacterial taxonomy. *Applied and Environment Microbiology*, 73(16), 5261–5267. <https://doi.org/10.1128/AEM.00062-07>.
- Windey, K., De Preter, V., & Verbeke, K. (2012). Relevance of protein fermentation to gut health. *Molecular Nutrition & Food Research*, 56(1), 184–196. <https://doi.org/10.1002/mnfr.v56.110.1002/mnfr.201100542>.
- Yang, H. J., Kwon, D. Y., Kim, H. J., Kim, M. J., Jung, D. Y., Kang, H. J., Park, S. (2015). Fermenting soybeans with *Bacillus licheniformis* potentiates their capacity to improve cognitive function and glucose homeostasis in diabetic rats with experimental Alzheimer's type dementia. *European Journal of Nutrition*, 54(1), 77–88. <https://doi.org/10.1007/s00394-014-0687-y>.
- Yoshida, N., Yamashita, T., & Hirata, K.-I. (2018). Gut microbiome and cardiovascular diseases. *Diseases*, 6(3), 56. <https://doi.org/10.3390/diseases6030056>.
- Zhang, T., Li, Q., Cheng, L., Buch, H., & Zhang, F. (2019). *Akkermansia muciniphila* is a promising probiotic. *Microbial Biotechnology*, 12(6), 1109–1125. <https://doi.org/10.1111/mbt2.v12.610.1111/1751-7915.13410>.

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