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Review Article

The Effects of Gut Microbiota and Virome on the Gut Barrier and its Mucus Layer, A Review Article

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Abstract

Background: The gut barrier comprises physical, chemical, and immunological components that collaborate to safeguard the gastrointestinal tract. The mucus layer is considered the most important layer of the gut barrier that plays an important role in maintaining the gut barrier integrity and any changes in the structure and unity of the mucosal layer lead to impairment of the gut barrier which is related to hazardous intestinal tract disease. On the other hand, the human gut microbiota and sometimes gut virome plays a vital role in maintaining gut barrier integrity. Any dysbiosis can disrupt this balance, affecting the mucus layer's function and the gut barrier.

Method: A thorough search of 169 papers was carried out across databases including PubMed, Google Scholar, and Web of Science. Out of these, 57 articles published up to 2017 were chosen for the study. Furthermore, 6 papers from before 2017 were included as there were no recent studies available. The titles, abstracts, and full texts of these articles were reviewed using the Mendeley application.

Conclusion: In normal status of body, gut microbiota can maintain the structure and function of the gut mucus layer through various mechanism while dysbiosis negatively affect the expression, structure, and function of, disrupting the mucus layer's role as a critical component of the gut barrier. Limited research has been done on the virome in the gut, and its effects on the gut barrier and mucus layers are still under investigation.

Keywords: Gut microbiota; Gut barrier; Gut virome; Mucus layer; Mucins; Trefoil factors family.

Introduction

The gut microbiota, a community of bacteria in the human gut, is essential for maintaining health by supporting digestion, the immune system, and providing energy to host cells. On the other hand, the gut barrier is crucial for gut function and serves as the primary interface for interactions between the microbiota and the host (1). Any disruptions in gut barrier function can lead to diseases such as inflammatory bowel diseases and in this regard, the gut microbiota helps maintain gut barrier integrity by influencing the production of gut barrier-associated components. Research indicates that the gut microbiota can enhance mucus layer restoration, increase mucus production, and impact the glycosylation profiles of mucins. Additionally, the gut microbiota can uphold the integrity of the epithelial barrier, reduce intestinal permeability, and exhibit anti-inflammatory properties (1). Such that any imbalances in the gut microbiota are linked to chronic diseases and increased gut barrier

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permeability. Preserving intestinal barrier function is crucial for overall health, and the gut microbiota plays a pivotal role in maintaining gut barrier integrity by modulating its elements to support gut homeostasis.

This review focuses on the structure of the gut barrier, its components, and the gut microbiota's role in maintaining gut barrier integrity (2). The gut virome consists of viruses in the gastrointestinal tract, including bacteriophages, eukaryotic viruses, and archaeal viruses. It regulates the gut microbiome, bacterial populations, gene transfer, and immune responses. A balanced virome supports gut health, while disruptions are linked to diseases like inflammatory bowel disease, obesity, and infections. Research on the virome holds potential for novel therapies, such as using phages to treat bacterial imbalances (3).

Gut Barrier Components

Physical Barrier

The gut barrier comprises physical, chemical, and immunological components that work together to maintain its integrity. The mucosal layer acts as the primary barrier where microbiota interact and play a crucial role in preserving gut function (4). It is a physical barrier protecting underlying layers from harmful stimuli and facilitating food transfer. The mucus layer also influences inflammation-related cell signaling pathways and regulates processes like proliferation, differentiation, and apoptosis. Additionally, the presence of chemical barrier components in the mucous layer gives it antimicrobial properties. The mucous layer is primarily composed of proteins, water, carbohydrates, and lipids, and is distributed differently in the gastrointestinal tract (5). Any changes in the mucosal layer can lead to structural and functional impairments, creating conditions for infections like IBD. The epithelial layer forms a key physical layer of the gut barrier, consisting of enterocytes, goblet cells, enteroendocrine cells, Paneth cells, microfold cells, and tuft cells (6). Enterocytes play a crucial role in digestion and immune responses, while goblet cells produce mucins and molecules essential for the immune response (7). Enteroendocrine cells produce gut hormones that regulate host metabolism, and alterations in their function can impact digestion (6). Paneth cells maintain the stem cell niche and produce antimicrobial peptides, contributing to the innate immune system (8). Microfold cells initiate immune responses by capturing and transporting antigens, while tuft cells function as chemosensory cells with neuromodulatory and immunomodulatory activities (9). The epithelial layer regulates the passage of water, electrolytes, and nutrients while blocking harmful antigens through paracellular and transepithelial permeability mechanisms. Tight junction proteins play a crucial role in maintaining the integrity of the gut barrier, and dysfunction in these proteins is associated with diseases like IBD. The vascular barrier, composed of intestinal endothelial cells, regulates the passage of antigens, gut microbiota, fluids, and solutes into the blood-stream, maintaining the barrier's integrity (10).

Chemical barrier

The chemical barrier in the gut consists of bile acids, secretory Immunoglobulin A (SIgA), and antimicrobial peptides (AMPs) that help maintain gut homeostasis. Bile acids, produced during cholesterol metabolism, are converted into secondary bile acids by an enzyme called bile salt hydrolase in the gastrointestinal microbiota. Secondary bile acids play a role in killing bacteria by disrupting their membranes and regulating various receptors and signaling pathways (11). Intestinal plasma cells produce and secrete SIgAs into the gut lumen, preventing bacterial attachment to intestinal cells and countering pathogens. SIgAs also influence the microbiota composition and reduce mucosal immunity stimulation (12).

Antimicrobial peptides, produced by Paneth cells in the gastrointestinal tract, target bacterial cell wall components and help maintain gut barrier integrity. Generally, dysfunction of antimicrobial peptides has been associated with intestinal bowel disease (13).

Immunological Barrier

More than 70% of immune cells are located in the gut, where the gut and its immune system

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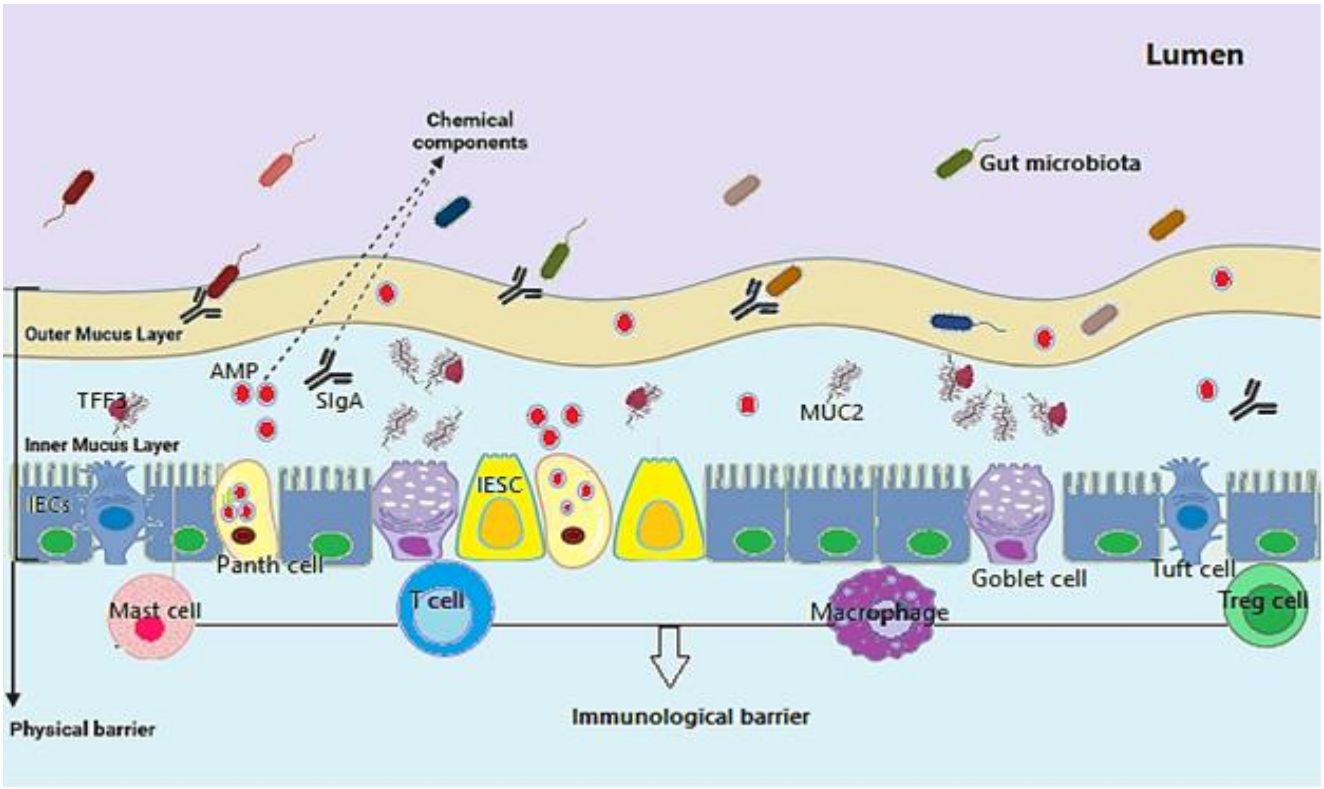

Fig.1. Different components of Gut barrier

work together to promote overall health. These cells, including Type-I interferon-producing plasmacytoid dendritic cells, innate lymphoid cells, and mucosa-associated invariant T cells, play a crucial role in maintaining gut health (14,15).

The Gut-Associated Lymphoid Tissue (GALT) which is a significant component of the immune system, works in conjunction with the gut microbiota to protect against foreign substances, regulate intestinal balance, and preserve the integrity of the intestinal barrier. When harmful antigens breach the gut barrier, inappropriate immune responses can lead to inflammation and disrupt the barrier's integrity, increasing the risk of gastrointestinal and metabolic diseases (16) (Fig.1).

The Effect of Gut Microbiota on Gut Barrier Components

The gut microbiota plays a vital role in regulating gut barrier function by influencing various components of physical, chemical and immunological barriers (17). Colonization by beneficial microbes and the production of metabolites (postbiotics) positively impact the gut mucus layer, the initial barrier against pathogens. For instance, *Escherichia coli Nissle 1917* (EcN), a probiotic, enhances epithelial barrier integrity by modulating tight junction protein expression. Its Outer Membrane Vesicles (OMVs) protect against enteropathogenic Escherichia coli-induced damage by increasing transepithelial resistance and promoting tight junction protein expression (18). *Bifidobacterium infantis*, another probiotic, prevents increased epithelial barrier permeability and maintains TJ proteins, crucial in diseases like necrotizing enterocolitis (19).

Additionally, *Roseburia intestinalis* and *Bacteroides faecis* reduce intestinal inflammation by enhancing epithelial barrier integrity and tight junction protein expression in various cell lines (20, 21). *Faecalibacterium prausnitzii* is a key indicator of human health and a crucial member of the gut microbiota. Numerous clinical and animal studies have shown a lower presence of this bacterium in the fecal samples of patients and mice compared to control groups. It exerts protective effects on the epithelial barrier through its extracellular vesicles and a

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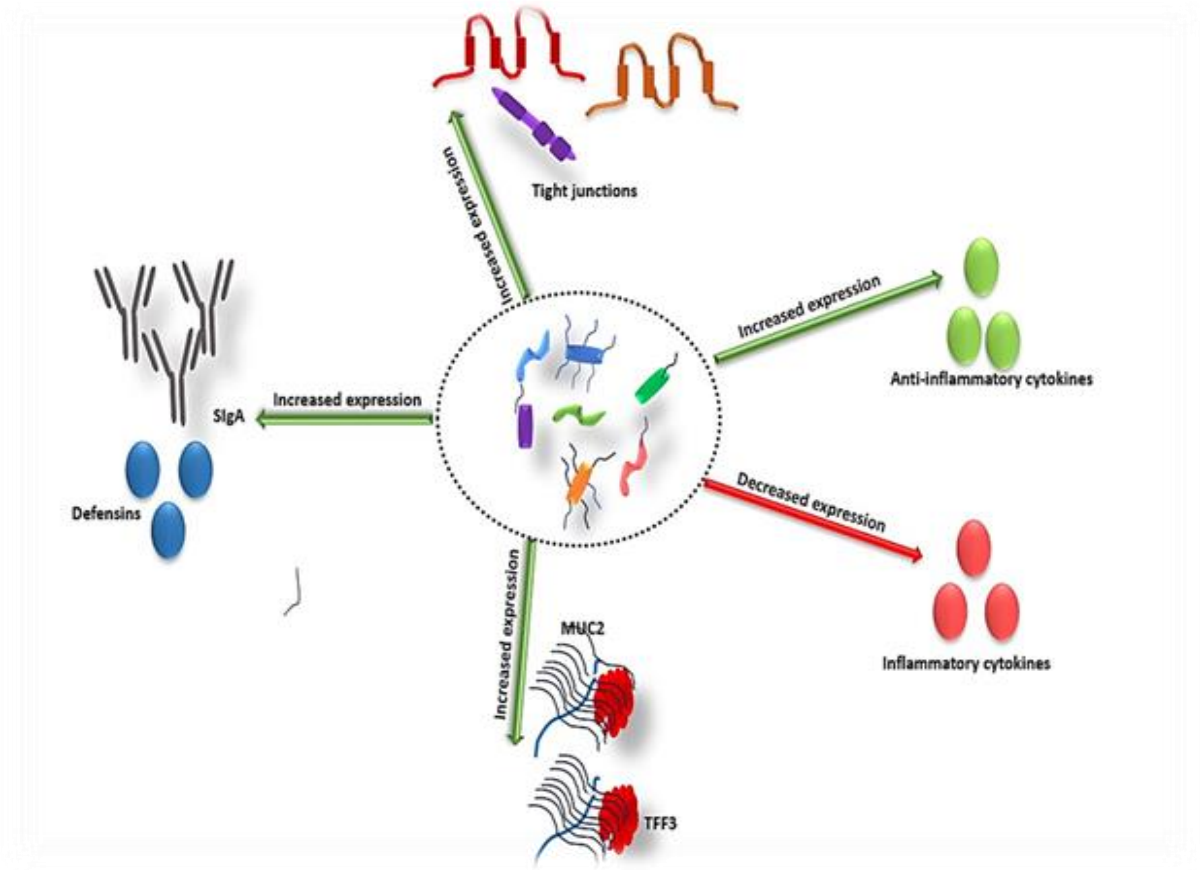

Fig. 2. Effects of gut microbiota on different components of gut barrier

novel protein found in its supernatant (22).

The extracellular vesicles derived from *Faecalibacterium prausnitzii* lead to an increase in the transcriptional levels of the genes of tight junctions in the enterocyte-like cells. Microbial anti-inflammatory molecule (MAM) is a novel protein found in *Faecalibacterium prausnitzii* supernatant and it helps maintain gut barrier integrity by upregulating the expression of a gene of tight junctions in Caco2 and HT-29 cells transfected with FLAG-tagged MAM plasmid (23). Additionally, in db/db mice that received recombinant His-tagged MAM protein, MAM also increased ZO-1 expression, further supporting its role in gut barrier function modulating immune responses is crucial for maintaining gut barrier integrity and preventing intestinal inflammation (24).

Modulating immune responses is crucial for gut barrier function, and certain gut microbiota and their postbiotics have been shown to stimulate anti-inflammatory cytokine production. *Bacteroides fragilis* and its outer membrane vesicles have anti-inflammatory properties (25). It is also reported that *F. prausnitzii* and its metabolite butyrate induce anti-inflammatory effects by regulating immune responses (26). The presence of gut microbiota leads to increased production of chemical barrier components such as SIgA and beta-defensin. Studies on high-fat diet-fed mice and rat models with intestinal obstruction have shown changes in the composition and abundance of gut microbiota, as well as reduced levels of SIgA. Studies have shown that changes in gut microbiota composition can impact the levels of these components (27,28) (Figure 2).

The Effect of Gut Virome on the Gut Barrier

The gut virome, a key component of the gut microbiota, consists of a diverse population of viruses in the gastrointestinal tract, including bacteriophages, eukaryotic viruses, and archaeal viruses. Bacteriophages are the predominant viruses in this ecosystem, regulating bacterial populations through lytic and lysogenic cycles,

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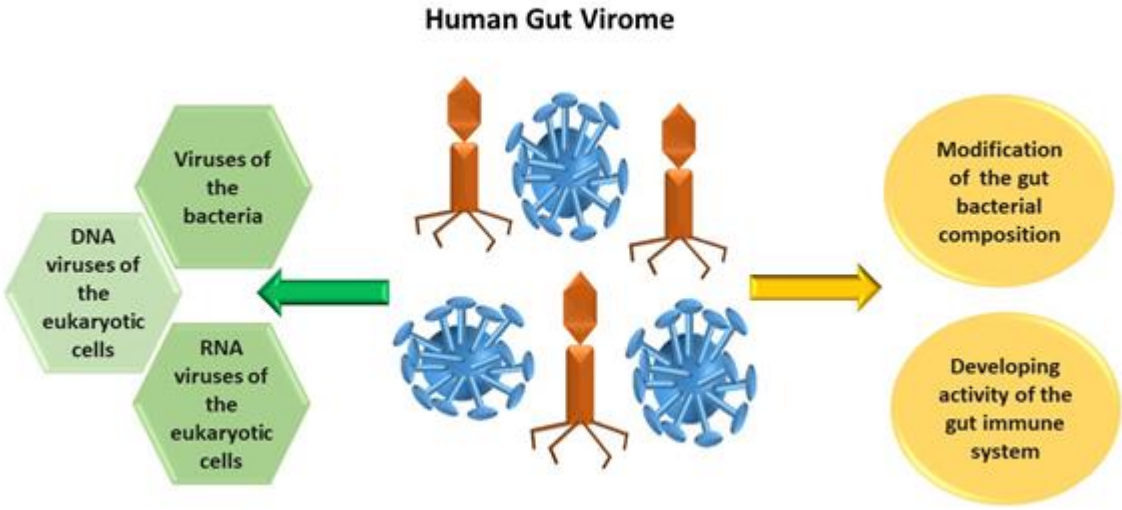

Fig. 3. Gut virome and gut barrier

influencing microbial diversity, and facilitating horizontal gene transfer, which drives bacterial adaptation and evolution. Eukaryotic viruses like norovirus and rotavirus can impact gut health by infecting host cells directly or interacting indirectly with the microbiota and immune system. The gut virome plays a crucial role in maintaining gut homeostasis, supporting microbial balance, regulating immune responses, and contributing to the metabolic and functional stability of the microbiome. Disruptions in the virome, known as virome dysbiosis, are associated with diseases such as inflammatory bowel disease, obesity, metabolic disorders, and the spread of antibiotic resistance (3,29).

Advances in metagenomics and virome research have improved our understanding of this complex viral community and highlighted its potential for therapeutic applications, such as phage therapy to target pathogenic bacteria, the development of viral-based probiotics, and the identification of virome-based biomarkers for early disease detection. As a dynamic and integral part of the microbiome, the gut virome represents a frontier in understanding human health and exploring innovative medical interventions. The gut virome plays a significant role in maintaining the integrity of the gut barrier, which is essential for protecting the body from harmful pathogens while allowing the absorption of nutrients. The gut barrier consists of a physical layer of epithelial cells, tight junctions that seal the spaces between them, and the underlying immune system that constantly monitors and responds to potential threats. Disruptions to this barrier are linked to various diseases, including inflammatory bowel disease (IBD), leaky gut syndrome, and metabolic disorders. The gut virome, through its interactions with the microbiota and the host, can influence the structure and function of this barrier in both beneficial and detrimental ways (29,30).

Bacteriophages, the most abundant viruses in the gut, affect gut barrier function primarily by modulating microbial populations. Phages help maintain a balance in the microbial community by controlling the abundance of specific bacteria, including pathogenic strains that may disrupt the gut lining. By preventing the overgrowth of harmful bacteria, phages indirectly contribute to maintaining the integrity of the intestinal epithelium and preventing an inflammatory response that could compromise the barrier. Furthermore, phages may influence the production of microbial metabolites like short-chain fatty acids (SCFAs), which are critical for gut health and epithelial cell function. SCFAs have been shown to strengthen tight junctions between epithelial cells, thereby rein-

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forcing the gut barrier. Disruptions to the gut virome, such as an imbalance or depletion of beneficial phages, can contribute to a compromised gut barrier. For example, an overgrowth of pathogenic bacteria due to reduced phage activity could trigger an immune response that damages the epithelial lining. Additionally, some viruses, particularly eukaryotic viruses like rotavirus, can directly infect intestinal epithelial cells, causing damage and increasing intestinal permeability. This may lead to a "leaky gut" scenario, where the barrier becomes permeable to harmful substances, triggering systemic inflammation and immune dysregulation.

The gut virome can also influence the immune system, which plays a critical role in gut barrier function. Phages can modulate immune responses by interacting with the microbiota and influencing the production of antimicrobial peptides and cytokines that regulate the permeability of the gut barrier. An altered virome may contribute to an inflammatory state, weakening the gut barrier and making it more susceptible to injury or infection (3,29,30) (Figure 3).

MUC2 and TFF3 in the Mucus Layer of the Thysical Barrier

MUC2 and its Function

There are two categories of mucins in the mucus layer: secreted mucins and transmembrane mucins. Secreted mucins contribute to mucus gel formation, while transmembrane mucins are involved in signaling pathways and barrier defense. Transmembrane mucins adhere to the apical surfaces of enterocyte cells (31). Human-secreted mucins MUC2, MUC5AC, MUC5B, MUC6, and MUC19 share structural similarities with their murine counterparts. These mucins are located at specific chromosomal loci in both humans and mice. In the large intestine, there are two layers of mucus covering it, unlike the small intestine.

The main component of the mucus layer in the colon is MUC2, which is produced and secreted by goblet cells along with other forms of mucin (32). MUC2, found in the mucus layer of the colon, acts as a barrier against harmful substances and bacterial translocation (33). So that, mice lacking MUC2 exhibit increased inflammation and colitis due to a loss of the mucus layer (34). Additionally, MUC2 is essential for intestinal homeostasis and immune regulation by influencing dendritic cells and suppressing inflammatory responses.

So, any changes in glycan glycosylation, particularly in MUC2, are associated with mucosal inflammation and inflammatory bowel disease (IBD) because glycans in MUC2 serve as adherence sites for commensal bacteria, enhancing the protective effects of the mucus layer (35). MUC2, in the large intestine, interacts with proteins from the trefoil factors family known as TFF3, which stabilizes the mucus hydrogel, increasing its viscosity and thickness, and repairing the mucosal layer in the mucus layer (36).

TFF3 and its Function

Trefoil factors (TFFs) are essential components of the mucus layer that are resistant to proteases and are widely distributed in the gastrointestinal tract. TFF1 and TFF2 are prominently expressed in the stomach and duodenum, respectively, while TFF3 is extensively expressed in the small and large intestines, particularly in the colon. These factors act as divalent lectins that bind to the GlcNac-α-1,4Gal disaccharide on mucins, preserving the mucosal layer, increasing mucus viscosity, and stabilizing mucin. Additionally, TFFs play a crucial role in promoting cell migration, epithelial cell restitution, nitric oxide (NO) production, and anti-apoptotic features (37). Among the TFFs, TFF3 stands out as a key protein essential for the restoration of epithelial cells. It plays a vital role in repairing intestinal mucus, promoting wound healing, and exhibiting anti-inflammatory properties in the gut. Research has shown that TFF3 can induce the recovery of tight junction proteins.

The gastrointestinal mucosal layer can be damaged, affecting gut barrier function, with two types of injuries: deep and superficial. Mitosis is a repair process for large lesions, while epithelial restitution is crucial for rapid primary

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repair, involving cell detachment and migration to the injury site. Various factors, including transforming growth factor-β (TGF-β), human growth factor (HGF), and epidermal growth factor (EGF), stimulate cell migration in mucosal epithelial cells. EGF activates the ERK/MAPK signaling pathway, essential for cell dispersion and migration (38).

TFFs, particularly TFF3, are vital for inducing restitution and promoting migration into wound areas, with protective effects enhanced by mucins. In vitro studies have shown that TFF3 accelerates epithelial migration and prevents necrosis of gastric mucosal epithelial cells. Animal studies have demonstrated that mice lacking intestinal trefoil factor (ITF) experience impaired mucosal healing and increased apoptosis in colonocytes (39). ITF, in conjunction with decay-accelerating factor (DAF), protects host tissue against autologous complement damage. TFF3 has therapeutic potential in inflammatory bowel disease by inhibiting the TLR4/NF-κB signaling pathway. Understanding the mechanisms regulating TFF3 and MUC2, key components of the mucus layer, is crucial for maintaining gut barrier integrity and promoting healing in the gastrointestinal tract (40).

MUC2 and TFF3 in Gut Related Diseases

Studies have shown that mice lacking MUC2 experience more severe inflammation when exposed to dextran sulfate sodium. In this study, mice with an inactive Muc2 gene displayed altered intestinal homeostasis and metabolic signatures (41).Clinical research has revealed changes in MUC2 expression and quality in gastrointestinal diseases. Patients with ulcerative colitis and colitis have lower MUC2 levels compared to healthy individuals (42,43). In Barrett's metaplasia patients, MUC2 immunohistochemical tests were negative, and most ulcerative colitis patients had a thin mucus layer due to altered MUC2 glycan profiles (44). Maintaining MUC2 expression and structure is crucial for gut barrier function. TFF3, which helps stabilize MUC2 and the mucus layer, is downregulated in the affected tissue of inflammatory bowel disease patients, linked to increased miR-7-5p levels (45). Treatment with TFF3 peptides or Recombinant Human Keratinocyte Growth Factor (rHuKGF) in mice with inflammatory bowel disease can alleviate symptoms (46). Thus, balancing MUC2 and TFF3 levels is essential for pre-venting and managing gastrointestinal diseases like inflammatory bowel disease.

Regulatory and Epigenetic Mechanisms of MUC2, and TFF3

Goblet cells in the intestinal epithelium produce and secrete mucus, with MUC2 being the main component in their cytoplasmic granules. The TFF3 promoter in these cells contains the goblet cell-specific enhancer element (GCRE) and the goblet cell-silencer inhibitor (GCSI). This shared regulatory elements in the TFF3 and MUC2 promoters suggest potential co-regulation (47). Th2 cell activation increases mucus production, protecting the gut barrier from invading pathogens. In fact, IL-4 and IL-13 cytokines as the produced cytokines through the Th2 activation pathway, can enhance the production of goblet cell markers such as TFF3 and MUC2 by binding to the IL-4R and paired IL-4R/IL-13R receptors. This binding activates STAT6, which increase the transcription of the TFF3 gene (48,49).

Moreover, Phosphatidylinositol 3-kinase (PI3-K) as a modulator and activator of myogenic differentiation, playing a role in transforming enterocyte-like cells such that inhibition of PI3-K has been shown to impair mucus production processes. On the other side, ex-posure of mucus-producing cells to PI3-K leads to an increase in mRNA levels of MUC2 and TFF3, indicating a role for PI3-K in goblet cell differentiation in the intestine (50–52).

Leucine, an essential amino acid involved in protein biosynthesis, can also enhance MUC2 levels in goblet cell-like cells through the PI3-K signaling pathway. An anti-inflammatory cytokine, IL-10, plays a role in preserving the intestinal mucus layer by promoting the production of MUC2 in human goblet cell-like cells, which helps prevent MUC2 misfolding (53). Pro-inflammatory cytokines like IL-1β,

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IL-6, and TNF-α are associated with IBD. In both in vitro and in vivo experiments, IL-1β, IL-6, and TNF-α have been shown to decrease TFF3 transcription, which hinders the healing process during inflammation. Additionally, IL-6 derived from macrophages can reduce the expression of MUC2 in enterocyte-like cells (54). MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression, and their dysregulation is linked to various diseases. In inflammatory bowel disease (IBD), altered miRNA expression contributes significantly to disease progression by impacting gut barrier integrity. For example, inhibition of miR-155 in IBD models has shown promise in reducing intestinal injuries and weight loss, potentially by upregulating hypoxia-inducible factor 1α (HIF-1α) and trefoil factor 3 (TFF3) to maintain epithelial barrier function.

Moreover, miR-125b influences disease severity in ulcerative colitis (UC) by directly regulating mucus production and modulating colonic mucus layer components like MUC2 and TFF3, highlighting miRNAs' intricate roles in IBD pathogenesis alongside inflammatory cytokines (55).

The Effect of Gut Microbiota on MUC2 and TFF3

The glycans profiles of the mucins in the intestinal mucus layer play a crucial role in shaping the bacteria that rely on glycans for colonization and energy within the mucus layer. Some reports demonstrate how the gut microbiota can influence the phenotypes and integrity of the mucus layer through various mechanisms (56). The composition of gut microbiota plays a crucial role in maintaining the integrity of the mucus layer.

In animal studies, mice with impermeable mucus layers exhibited higher abundance of two species, *Allobaculum* and *Anaerostipes*, compared to the group with a permeable inner mucus layer (57) (Table 1). The composition of gut microbiota can influence the glycosylation of the mucus layer, impacting its structure and function. *Bacteroides thetaiotaomicron*, a key member of the microbiota in both mice and humans, promotes the fucosylation of glycans in the intestinal mucus layer and also enhances the transcription of glycans containing sialic acid residues.

Furthermore, *Bacteroides thetaiotaomicron*, known for its acetate production, can stimulate goblet cell differentiation. Interestingly, alterations in the glycan profile of the intestinal mucosa and goblet cell differentiation induced by Bacteroides thetaiotaomicron are reversed when it is combined with Faecalibacterium prausnitzii (58, 59) (See Table 1). Butyrate, a metabolite produced by gut microbiota that can help preserve the mucus layer.

A study found that butyrate can increase the expression of MUC2 in the human colon cancer cell line LS174T (60). Lactic acid bacteria are important in promoting the integrity of the gut barrier. Studies have shown that they can increase the production of MUC2 and TFF3 in intestinal goblet cell-like cells. For example, treating the goblet cell-like cell with four commercial probiotics, including *Bifidobacterium animalis* subsp. Lactis, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, and *Streptococcus thermophilus*, significantly increased the expression of MUC2.

Specifically, Streptococcus thermophilus showed a higher increase in TFF3 expression compared to the other species in the cell line (61) (See Table 1). Treating a DSS-induced colitis-associated colorectal cancer (CAC) mouse model with a synbiotic combination of *Lactobacillus gasseri* 505 (LG) and Cudrania tricuspidata leaf extract (CT) as a novel prebiotic resulted in an increase in anti-inflammatory cytokines and a decrease in inflammatory cytokines. In addition to LG anti-inflammatory properties, this treatment also upregulated the expression of MUC2 and TFF3, contributing to its therapeutic effects on CAC (62) (See Table 1). An investigation into *Lactobacillus casei* ethyl acetate soluble supernatant (LC-EAS) showed that it has anti-inflammatory effects by inhibiting NF-κB phosphorylation in RAW 264.7 cells. Additionally, it was found to upregulate the expression of TFF3, which is known to have a regulatory effect on NF-κB (63) (Table 1). The gut microbiota can indirectly influence the expression of MUC2 and TFF3 by regulating immune system responses. key

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Table 1. Gut microbiota and their effects on the mucus layer of the gut barrier

Gut Microbiota	Effects on Mucus Layer	Ref	Gut Microbiota	Effects on Mucus Layer	Ref	Gut Microbiota	Effects on Mucus Layer	Ref	Effects on Mucus layer	Ref
Anaerostipes	Production of butyrate	(57)	*Bifidobacterium animalis*	Increase of the expression of MUC2 & TFF3	(61)	*Lactobacillus plantarum*	Increase of the expression of MUC2 & TFF3	(61)	Production of butyrate	(61)
Allobaculum	Production of butyrate	(57)	*Lactobacillus acidophilus*	Increase of the expression of MUC2 & TFF3	(61)	*Streptococcus thermophilus*	Increase of the expression of MUC2 & TFF3	(61)	Production of butyrate	(61)
Bacteroides thetaiotaomicron	Fucosylation of glycans in the intestinal mucus layer Enhancing the transcription of glycans Production of acetate	(58) (59)	*Lactobacillus gasseri* 505	Increase of the expression of anti-inflammatory cytokines	(62)	*Lactobacillus case*	Inhibition of the expression of the inflammatory cytokines Increase of the expression of TFF3	(63)	Fucosylation of glycans in the intestinal mucus layer Enhancing the transcription of glycans Production of acetate	(63)

members of the gut microbiota can stimulate the body to increase anti-inflammatory cytokines and decrease inflammatory cytokines, which in turn impact the expression of MUC2 and TFF3.

Conclusion

The mucus layer is the primary defense barrier that gut microbiota encounter in the gut. Beneficial gut bacteria play a crucial role in maintaining the gut barrier by influencing the structure and function of the mucus layer. Two key components of this layer are the trefoil factors family, specifically TFF3, and secreted or gel-forming mucins like MUC2, which protect the mucus layer and the gut barrier. Research indicates that under normal conditions, gut microbiota can positively regulate the expression of TFF3 and MUC2 through various mechanisms, preserving the structure and function of the gut barrier. In contrast, dysbiosis can negatively impact the expression, structure, and function of TFF3 and MUC2, disrupting the mucus layer's role as a critical component of the gut barrier. The viruses present in the gut microbiota are essential for the health and stability of the gut ecosystem. While much remains to be discovered, the virome represents a promising frontier in understanding human health and developing innovative therapies. Its dynamic interplay with the microbiome and host under-scores its potential as both a tool and target in medicine.

In summary, the gut virome plays a crucial role in maintaining the integrity of the gut barrier. Through its regulation of microbial communities, production of metabolites, and modulation of immune responses, the virome helps ensure proper functioning of the gut barrier. Disruptions in the virome, however, can compromise the barrier, increasing susceptibility to inflammation, infection, and various gut-related diseases. Further research into the gut virome's impact on gut barrier function may lead to new therapeutic approaches for preventing or treating disorders related to gut permeability.

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Conflict of Interest

No conflict of interest is declared.

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Ethics Approval and Consent to Participate

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References

1. Wang J, Zhang P, Chen S, Duan H, Xie L. Microbiota and Gut Health: Promising prospects for clinical trials from bench to bedside. Adv Gut Microbiome Res. 2022; 2022:1–17.
2. Quesada-Vázquez S, Bone C, Saha S, Triguero I, Colom-Pellicer M, Aragonès G, et al. Microbiota dysbiosis and gut barrier dysfunction associated with non-alcoholic fatty liver disease are modulated by a specific metabolic cofactors' combination. Int J Mol Sci. 2022;23(22):13675.
3. Lecuit M, Eloit M. The Viruses of the Gut Microbiota. In: Floch MH, Ringel Y and Walker WA, editors. Microbiota Gastrointestinal Pathophysiology, Implication Human Health, Prebiotics, Probiotics, Dysbiosis. Acadimc press. 2017. p. 179–83.
4. Vancamelbeke M, Vermeire S. The intestinal barrier: a fundamental role in health and disease. Expert Rev Gastroenterol Hepatol. 2017;11(9):821–34.
5. Herath M, Hosie S, Bornstein JC, Franks AE, Hill-Yardin EL. The Role of the gastrointestinal mucus system in intestinal homeostasis: implications for neurological disorders. Front Cell Infect Microbiol. 2020;10: 248.
6. Odenwald MA, Turner JR. The intestinal epithelial barrier: a therapeutic target? Nat Rev Gastroenterol Hepatol. 2017;14(1):9–21.
7. Dickson I. Enterocyte zonation along the intestinal villus reveals a division of labour. Nat Rev Gastroenterol Hepatol. 2018;15(12):717.
8. Wallaeys C, Garcia-Gonzalez N, Libert C. Paneth cells as the cornerstones of intestinal and organismal health: a primer. EMBO Mol Med. 2023;15(2):e16427.
9. Dillon A, Lo DD. M cells: Intelligent engineering of mucosal immune surveillance. Front Immunol. 2019;10: 1–13.
10. Horowitz A, Chanez-Paredes SD, Haest X, Turner JR. Paracellular permeability and tight junction regulation in gut health and disease. Nat Rev Gastroenterol Hepatol. 2023;20(7):417–32.
11. Zhang C, Liu H, Sun L, Wang Y, Chen X, Du J, et al. An overview of host-derived molecules that interact with gut microbiota. lmeta. 2023;2(2):e88.
12. Pietrzak B, Tomela K, Olejnik-Schmidt A, Mackiewicz A, Schmidt M. Secretory IgA in intestinal mucosal secretions as an adaptive barrier against microbial cells. Int J Mol Sci. 2020;21(23):9254.
13. Gubatan J, Holman DR, Puntasecca CJ, Polevoi D, Rubin SJ, Rogalla S. Antimicrobial peptides and the gut microbiome in inflammatory bowel disease. World J Gastroenterol. 2021;27(43):7402–22.
14. Beermann C. The immune barrier: influence of food components on the intestinal barrier. In: Beermann C, editor. Food and the Immune System: molecular mechanisms and nutritional relevance in health and disease. Cham: Springer International Publishing; 2023. p. 33–72.
15. Di Sabatino A, Santacroce G, Rossi CM, Broglio G, Lenti MV. Role of mucosal immunity and epithelial–vascular barrier in modulating gut homeostasis. Intern Emerg Med. 2023;18(6):1635–46.
16. Bemark M, Pitcher MJ, Dionisi C, Spencer J. Gut-associated lymphoid tissue: a microbiota-driven hub of B cell immunity. Trends Immunol. 2024;45(3):211–23.
17. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue Barriers. 2017;5(4): e1373208.
18. Alvarez CS, Badia J, Bosch M, Giménez R, Baldomà L. Outer membrane vesicles and soluble factors released by probiotic escherichia coli Nissle 1917 and commensal ECOR63 enhance barrier function by regulating expression of tight junction proteins in intestinal epithelial cells. Front Microbiol. 2016;7:1981.
19. Abdulqadir R, Engers J, Al-Sadi R. Role of bifidobacterium in modulating the intestinal epithelial tight junction barrier: current knowledge and perspectives. Curr Dev Nutr. 2023;7(12):102026.
20. Tan B, Luo W, Shen Z, Xiao M, Wu S, Meng X, et al. Roseburia intestinalis inhibits oncostatin M and maintains tight junction integrity in a murine model of acute experimental colitis. Scand J Gastroenterol. 2019; 54(4):432–40.
21. Mohebali N, Ekat K, Kreikemeyer B, Breitrück A. Barrier protection and recovery effects of gut commensal bacteria on differentiated intestinal epithelial cells in vitro. Nutrients. 2020;12(8):2251.
22. He X, Zhao S, Li Y. Faecalibacterium prausnitzii: A next-generation probiotic in gut disease improvement. Can J Infect Dis Med Microbiol. 2021;2021.
23. Xu J, Liang R, Zhang W, Tian K, Li J, Chen X, et al. Faecalibacterium prausnitzii-derived microbial anti-inflammatory molecule regulates intestinal integrity in diabetes mellitus mice via modulating tight junction protein expression. J Diabetes. 2020;12(3):224–36.
24. Breyner NM, Michon C, de Sousa CS, Vilas Boas PB, Chain F, Azevedo VA, et al. Microbial anti-inflammatory molecule (MAM) from Faecalibacterium prausnitzii shows a protective effect on DNBS and DSS-

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induced colitis model in mice through inhibition of NF-κB pathway. Front Microbiol. 2017;8:114.
25. Gilmore WJ, Johnston EL, Bitto NJ, Zavan L, O'Brien-Simpson N, Hill AF, et al. Bacteroides fragilis outer membrane vesicles preferentially activate innate immune receptors compared to their parent bacteria. Front Immunol. 2022;13:970725.
26. Moon J, Lee AR, Kim H, Jhun J, Lee SY, Choi JW, et al. Faecalibacterium prausnitzii alleviates inflammatory arthritis and regulates IL-17 production, short chain fatty acids, and the intestinal microbial flora in experimental mouse model for rheumatoid arthritis. Arthritis Res Ther. 2023;25(1):130.
27. Pabst O, Slack E. IgA and the intestinal microbiota: the importance of being specific. Mucosal Immunol. 2020;13(1):12–21.
28. Raffaela P, Brancaccio M, Laneri S, De Biasi MG, Lombardo, Scudiero O. A novel view of human helicobacter pylori infections: interplay between microbiota and beta-defensins. Biomolecules. 2019;9(6):237.
29. Cao Z, Sugimura N, Burgermeister E, Ebert MP, Zuo T, Lan P. The gut virome: A new microbiome component in health and disease. eBioMedicine. 2022;81: 104113.
30. Jansen D, Matthijnssens J. The emerging role of the gut virome in health and inflammatory bowel disease: challenges, covariates and a viral imbalance. Viruses. 2023;15(1).
31. Paone P, Cani PD. Mucus barrier, mucins and gut microbiota: The expected slimy partners? Gut. 2020;69 (12):2232–43.
32. Berón W, Gutierrez MG, Rabinovitch M, Colombo MI. Coxiella burnetii localizes in a Rab7-labeled compartment with autophagic characteristics. Infect Immun. 2002;70(10):5816–21.
33. Kawashima H. Roles of the gel-forming MUC2 mucin and its O-glycosylation in the protection against colitis and colorectal cancer. Biol Pharm Bull. 2012;35 (10):1637–41.
34. Wu M, Wu Y, Li J, Bao Y, Guo Y, Yang W. The Dynamic Changes of Gut Microbiota in Muc2 Deficient Mice. Int J Mol Sci. 2018;19(9):2809.
35. Grondin JA, Kwon YH, Far PM, Haq S, Khan WI. Mucins in intestinal mucosal defense and inflammation: learning from clinical and experimental studies. Front Immunol. 2020;11:2054.
36. Aihara E, Engevik KA, Montrose MH. Trefoil factor peptides and gastrointestinal function. Annu Rev Physiol. 2017;79:357–80.
37. Braga Emidio N, Hoffmann W, Brierley SM, Muttenthaler M. Trefoil factor family: unresolved questions and clinical perspectives. Trends Biochem Sci. 2019;44 (5):387–90.
38. Nakov R, Velikova T, Nakov V, Gerova V, Tankova L. Trefoil factor 3 is highly predictive of complete mucosal healing independently and in combination with c-reactive protein in patients with ulcerative colitis. J Gastrointestin Liver Dis. 2019;28:169–74.
39. Šešelja K, Bazina I, Vrecl M, Farger J, Schicht M, Paulsen F, et al. Tff3 deficiency differentially affects the morphology of male and female intestines in a long-term high-fat-diet-fed mouse model. Int J Mol Sci. 2023;24 (22):16342.
40. Liu J, Yang Q, Chen Z, Lv S, Tang J, Xing Z, et al. TFF3 mediates the NF-κB/COX2 pathway to regulate PMN-MDSCs activation and protect against necrotizing enterocolitis. Eur J Immunol. 2021;51(5):1110–25.
41. Tadesse S, Corner G, Dhima E, Houston M, Guha C, Augenlicht L, et al. MUC2 mucin deficiency alters inflammatory and metabolic pathways in the mouse intestinal mucosa. Oncotarget. 2017;8(42):71456–70.
42. Leon-Coria A, Kumar M, Workentine M, Moreau F, Surette M, Chadee K. Muc2 mucin and nonmucin microbiota confer distinct innate host defense in disease susceptibility and colonic injury. Cell Mol Gasteroenterol Hospatol. 2021;11(1):77-98.
43. Kang Y, Park H, Choe BH, Kang B. The role and function of mucins and its relationship to inflammatory bowel disease. Front Med (Lausanne). 2022;9:848344.
44. Korbut E, Janmaat VT, Wierdak M, Hankus J, Wójcik D, Surmiak M, et al. Molecular profile of Barrett's esophagus and gastroesophageal reflux disease in the development of translational physiological and pharmacological studies. Int J Mol Sci. 2020;21(17): 6436.
45. Guo J, Sun M, Teng X, Xu L. MicroRNA-7-5p regulates the expression of TFF3 in inflammatory bowel disease. Mol Med Rep. 2017;16(2):1200–6.
46. Byrne FR, Farrell CL, Aranda R, Rex KL, Scully S, Brown HL, et al. rHuKGF ameliorates symptoms in DSS and CD4+CD45RBHi T cell transfer mouse models of inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol. 2002;282(4):G690–701.
47. Van Seuningen I, Pigney P, Perrais M, Porchet N, Aubert JP. **T**ranscriptional regulation of the 11p15 mucin genes. Towards new biological tools in human therapy, in inflammatory diseases and cancer? Front Biosci. 2001;6:D1216-34.
48. Blanchard C, Durual S, Estienne M, Bouzakri K, Heim MH, Blin N, et al. IL-4 and IL-13 up-regulate intestinal Trefoil factor expression: requirement for STAT6 and de novo protein synthesis. J Immunol. 2004; 172(6):3775–83.
49. Podolsky DK. Mucosal immunity and inflammation V. Innate mechanisms of mucosal defense and repair: The best offense is a good defense. Am J Physiol. 1999; 277(3):G495–9.
50. Morgos DT, Stefani C, Miricescu D, Greabu M, Stanciu S, Nica S, et al. Targeting PI3K/AKT/mTOR and MAPK signaling pathways in gastric cancer. Int J Mol Sci. 2024;25(3):1848.
51. Shi HS, Zhu WL, Liu J, Luo YX, Si JJ, Wang SJ, et al. PI3K/Akt signaling pathway in the basolateral amygdala mediates the rapid antidepressant-like effects of Trefoil factor 3. Neuropsychopharmacology. 2012;37 (12):2671–83.
52. Zhang MM, An LY, Hu WX, Li ZY, Qiang YY, Zhao BY, et al. Mechanism of endometrial MUC2 in reproductive performance in mice through PI3K/AKT

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signaling pathway after lipopolysaccharide treatment. Ecotoxicol Environ Saf. 2022;231:113177.
53. Jenkins BR, Blaseg NA, Grifka-Walk HM, Deuling B, Swain SD, Campbell EL, et al. Loss of interleukin-10 receptor disrupts intestinal epithelial cell proliferation and skews differentiation towards the goblet cell fate. FASEB J. 2021;35(6):e21551.
54. Borisova MA, Achasova KM, Morozova KN, Andreyeva EN, Litvinova EA, Ogienko AA, et al. Mucin-2 knockout is a model of intercellular junction defects, mitochondrial damage and ATP depletion in the intestinal epithelium. Sci Rep. 2020;10(1):21135.
55. Liu Y, Zhu F, Li H, Fan H, Wu H, Dong Y, et al. MiR-155 contributes to intestinal barrier dysfunction in DSS-induced mice colitis via targeting HIF-1α/TFF-3 axis. Aging (Albany NY). 2020;12(14):14966–77.
56. Schroeder BO. Fight them or feed them: How the intestinal mucus layer manages the gut microbiota. Gastroenterol Rep (Oxf). 2019;7(1):3–12.
57. Jakobsson HE, Rodríguez-Piñeiro AM, Schütte A, Ermund A, Boysen P, Bemark M, et al. The composition of the gut microbiota shapes the colon mucus barrier. EMBO Rep. 2015;16(2):164–77.
58. Tilford LE, Crost EH, Kavanaugh D, Juge N. Mucin glycan foraging in the human gut microbiome. Front Genet. 2015;6:81
59. Thomas M, Wrzosek L, Miquel S, Noordine ML, Bouet S, Chevalier-Curt MJ, et al. 264 bacteroides thetaiotaomicron and faecalibacterium prausnitzii shape the mucus production and mucin O-glycosylation in colon epithelium. Gastroenterology. 2013;144(5):S-59.
60. Jiang W, Wu J, Zhu S, Xin L, Yu C, Shen Z. The Role of Short Chain Fatty Acids in Irritable Bowel Syndrome. J Neurogastroenterol Motil. 2022;28(4):540–8.
61. Shastri MD, Chong WC, Vemuri R, Martoni CJ, Adhikari S, Bhullar H, et al. Streptococcus thermophilus uast-09 upregulates goblet cell activity in colonic epithelial cells to a greater degree than other probiotic strains. Microorganisms. 2020;8(11):1758.
62. Oh NS, Lee JY, Kim YT, Kim SH, Lee JH. Cancer-protective effect of a synbiotic combination between Lactobacillus gasseri 505 and a Cudrania tricuspidata leaf extract on colitis-associated colorectal cancer. Gut Microbes. 2020;12(1):1785803.
63.Karthikeyan T, Pravin M, Muthusamy VS, Bharathi Raja R, Lakshmi BS. In vitro investigation of the immunomodulatory potential of probiotic lactobacillus casei. Probiotics Antimicrob Proteins. 2013;5(1):51–8.

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