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Vitamin D/VDR, probiotics, and gastrointestinal diseases

Mei Shang[1,2] and **Jun Sun**[1]

[1]Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

[2]Department of Parasitology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, People's Republic of China

Abstract

Vitamin D is an important factor in regulating inflammation, immune responses, and carcinoma inhibition via action of its receptor, vitamin D receptor (VDR). Recent studies have demonstrated the role of vitamin D/VDR in regulating host-bacterial interactions. Probiotics are beneficial bacteria with the power of supporting or favoring life on the host. In the current review, we will discuss the recent progress on the roles of vitamin D/VDR in gut microbiome and inflammation. We will summarize evidence of probiotics in modulating vitamin D/VDR and balancing gut microbiota in health and gastrointestinal diseases. Moreover, we will review the clinical application of probiotics in prevention and therapy of IBD or colon cancer. Despite of the gains, there remain several barriers to advocate broad use of probiotics in clinical therapy. We will also discuss the limits and future direction in scientific understanding of probiotics, vitamin D/VDR, and host responses.

Keywords

Autophagy; bacteria; colon cancer; colitis; Lactic Acid Bacteria; IBD; Inflammation; probiotics; NF-κB; vitamin D; VDR

1. Introduction

Probiotics are ingestible nonpathogenic living microorganisms, and when consumed in adequate amounts as food components, confer some beneficial effects to the host by inhibiting or treating diseases, according to the World Health Organization [1]. Recent laboratory studies and clinical trials have shown the potential health benefits of probiotics in treating various human diseases[2–4]. In this review, we focus on the recent progress on the mechanisms of probiotics actions that modulate vitamin D and VDR in inflammatory response and development of human diseases, such as inflammatory bowel diseases (IBD), colon cancer, gastritis, and liver diseases. We summarize etiologic and clinical evidence of probiotic in modulating vitamin D/VDR and balancing gut microbiota. The limits and future direction in studying probiotics and vitamin D/VDR are also discussed.

Address correspondence to: Jun Sun, PhD, AGA Fellow, Associate Professor, Division of Gastroenterology and Hepatology, Department of Medicine, University of Illinois at Chicago, 840 S Wood Street, Room 704 CSB, Chicago, IL, 60612, Tel: 312-996-5020, junsun7@uic.edu.

2. Vitamin D and VDR

Vitamin D is converted to the dihydroxylated derivative, 1,25-dihydroxyvitamin D3 [1,25$(OH)_2D_3$] by successive hydroxylations in the liver and kidney. The active form of vitamin D exerts an important role in modulating both mucosal immunity and normal growth of epithelial cells [5]. VDR, as a member of the nuclear receptor superfamily, mediates the biological activity of 1,25$(OH)_2D_3$ [6]. The vitamin D-VDR endocrine system has been identified in nearly all nucleated cells [7]. VDR can regulate a variety of illnesses in intestine, kidney, bone, skin, heart, and various other organs. For example, loss of VDR specifically in the mammary epithelium significantly inhibits pubertal mammary gland development [8]. Deficiency of VDR in mouse lungs leads to an early onset of COPD/emphysema associated with chronic inflammation response, immune dysregulation, and lung destruction [9]. VDR activation protects against myocardial ischemia/reperfusion injury, via reducing oxidative stress and inhibiting cardiomyocyte apoptotic and autophagic pathways [10].

Vitamin D is associated with the severity of intestinal injury of colitis models [11]. Vitamin D deficiency is common in IBD patients [12]. For patient with Crohn's disease, vitamin D deficiency has been recognized as an environmental risk factor since the early 80s [13]. Patients with vitamin D deficiency displayed increased UC clinical disease severity and a lower quality of life (QOL) in a cohort of patients with IBD [14, 15]. After supplementation with recommended doses of vitamin D and reserving saturation of 1,25(OH) D_3, the serum concentration of vitamin D and health related quality of life can be improved [16, 17]. However, more recently, a study showed that daily supplementation with 1000 IU of vitamin D3, 1200 mg of calcium, or both did not significantly reduce the risk of recurrence of colorectal adenomas after its removal over a period of 3 to 5 years [18].

A variety of factors may reduce vitamin D absorption, including limited exposure to sunlight, dark skin, obesity, and problems with absorption or the ability to convert vitamin D to its active form. Given the various immune-modulatory properties of vitamin D, vitamin D deficiency increases the risk of various gastrointestinal diseases, It is likely that deficient levels lead to intestinal barrier dysfunction [11], mucosal damage [19], and susceptibility to infectious agents, thus affecting the development and maintenance of gut homeostasis [20]. 1,25$(OH)_2D_3$ and VDR may maintain integrity of junction complexes and protect the intestine from injury [21, 22].

3. Vitamin D/VDR regulation of gut microbiome

1,25$(OH)_2D_3$ has been reported to induce expression of the antimicrobial peptide gene cathelicidin [23] and β2-defensins [24] in colon cancer cell lines, bone marrow-derived macrophages and fresh bone marrow cells. Oral 1,25$(OH)_2D_3$ supplementation has an effect on the human gut microbiome of the upper GI tract, which displays a reduction in opportunistic pathogens and an increase in bacterial richness [25].

Vitamin D status is associated with the composition and function of the intestinal microbiome [26]. 1,25$(OH)_2D_3$ treatment shifts the composition of the gut bacterial

microflora and protects against experimental IBD [27]. Vitamin D and VDR regulate the innate immune response to the microbiome. They control the microbiota dysbiosis, maintain tolerance in the gut and protect the vitamin D-deficient host from IBD symptoms [28].

Our recent data show that VDR status regulates the composition and functions of the bacterial community in the intestine. We investigated fecal and cecal stool samples from whole-body VDR knockout ($VDR^{-/-}$) and wild-type (WT) mice, aiming to profile the intestinal microbiome of animals with different VDR status. In the $VDR^{-/-}$ mice, *Lactobacillus* was depleted in the fecal stool, whereas *Clostridium* and *Bacteroides* were enriched [29]. Our recent *Gut* paper has demonstrated that intestinal epithelial VDR conditional knockout ($VDR^{\Delta IEC}$) leads to dysbiosis [30] and susceptibility to chemical injury induced by dextran sulfate sodium (DSS). Deletion of VDR can increase bacterial loads and induce dysbiosis (increased *E. coli* and *Bacteroides* and decreased butyrate-producing bacteria), thus developing a severe DSS-induced colitis. We have also demonstrated that intestinal epithelial VDR plays a fundamental role in intestinal and microbial homeostasis through its actions on the autophagy gene *ATG16L1* [31]. Further, Our recent study [32] in *Nature Genetics* has demonstrated that human VDR is a key host factor to shape gut microbiome. We observe significant shifts in the microbiota of $VDR^{-/-}$ mice and correlations between the microbiota and serum measurements of selected human bile- and fatty acids [32]. Insights from microbiome and vitamin D/VDR studies can be exploited to develop novel strategies to treat or prevent various diseases by restoring VDR function and healthy microbe-host interactions.

4. Probiotics in GI health and digestive diseases

Probiotics are known to improve the balance of intestinal microbiota by regulating microbial components and metabolites [2]. They may stimulate the immune system, balance commensal and pathogenic bacteria to decrease the incidence of infections, reduce symptoms, restore homeostasis, and modify toxic compounds and host products. Recent trials using *Lactobacillus rhamnosus* GR-1 pretreatment demonstrated counteraction in the *E. coli*-induced production of various cytokines and chemokines in ameliorating inflammation and cell damage [33]. Zhang et al [34] demonstrated that pre-treatment with *L. rhamnosus* suppressed apoptosis of intestinal epithelia cells, which is consistent with the study in which *Lactobacillus rhamnosus* GG prevents cytokine-induced apoptosis in intestinal epithelial cell models [35]. Strains of Lactobacilli inhibit growth of lots of Gram-negative pathogenic bacteria solely by promoting the production of acetic, lactic, and propionic acid that decrease the local pH [36].

Oral administration of probiotics, alone or with prebiotics, may modulate colonic microbiota and maintain the intestinal environmental homeostasis, and prevent the host from preneoplastic or neoplastic lesions. Similarly, other studies have also found probiotics reducing the risk of initiation of cancer in the early-stage [37–39], but not after the carcinogen. However, in one study probiotics administration was associated with the occurrence of CRC and of precursor lesions [40].

Probiotics, such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*, are commonly used as an alternative approach to prevent and treat severe intestinal inflammatory disorders. *Lactobacillus GG* (*LGG*) and *Saccharomyces boulardii* are two well-studied probiotic strains in the prevention of antibiotic-associated diarrhea (AAD) in adult patients and children [41, 42]. Mixed probiotic strains VSL#3 was used in in the treatment of active UC and irritable bowel disease [43]. VSL#3 treated UC patients displayed a combined induction with either remission or a response rate of 77 ? [44]. After VSL#3 was used to patients with diarrhea-predominant IBS, the bloating symptom was relieved, but not colonic transit [45]. Administration of VSL#3 in IBS with bloating patients resulted in reduced flatulence and increased colonic transit time. A randomized, placebo-controlled trial valuing effect of *Lactobacillus GG* on antibiotic-associated diarrhea [46] showed that oral administration of LGG had a protective effect on the development of AAD. Participants receiving intravenous antibiotics in the study displayed serious infection. It is speculated that LGG therapy does not benefit individuals with severe infections. *Lactobacillus GG* does not influence AAD-induced diarrhea.

Not all the probiotics are the same. Various strains of probiotics could control microbiota, reduce colitis symptoms, protect barrier integrity and inhibit the release of proinflammatory cytokines [47], resulting in preventing or repairing gut damage and inflammatory responses induced by pathogens [48]. However, the mechanisms behind these probiotics are complicated.

The clinical efficacy and safety of probiotic on patients have long been a contentious issue. There are potential adverse effects of probiotics. Thus, the accurate identification of “normal” and “diseased” microbiota and understanding the specific mechanisms of actions of individual probiotic strains are needed.

5. Molecular mechanisms of probiotics in GI diseases

5.1. Probiotics in IBD

The molecular mechanisms of probiotics in prevention or treatment of GI diseases include immunomodulatory mechanisms, metabolite effects, and maintenance of intestinal homeostasis [49]. The probiotic regulation of the proinflammatory nuclear factor kappa B (NF-κB) pathway is well represented in literature [2]. Probiotic bacteria, *L. reuteri* [50] and LGG [51] suppress TNF-α/ S. Typhimurium-induced IL-8 expression in intestinal epithelial cells. This effect depends on the NF-κB signaling pathway. VSL#3 intervention in the experimental IL-10 colitis mice upregulated PPAR, xenobiotic, and lipid signaling genes, which are potential antagonists of the NF-κB inflammatory pathway[52]. NF-κB pathway is also involved in the probiotic role of *E. faecalis in vitro and in vivo* [53]. Interestingly, this study also indicates the potential of probiotic bacterial *E. faecalis* in initiating pro-inflammatory responses in the disease-susceptible host, but not in the normal healthy host.

Wu *et al* [54] shows *Lactobacillus plantarum* may maintain TEER, inhibit the reduction of TJ proteins and reduce the expression of proinflammatory cytokines induced by ETEC K88 via modulation of TLRs, NF-κB and MAPK pathways, thus improving epithelial barrier. Some probiotic species appear to activate specific TLRs to influence the host cells [55, 56].

Lactobacillus upregulated TLR2 expression in Caco-2 cells and the effect can be reversed by treatment with OxPAPC, a TLR inhibitor [57]. Shimazu *et al* [58] showed that *Lactobacillus jensenii* TL2937 negatively regulated TLRs to reduce the expression of proinflammatory cytokines and chemokines caused by ETEC or LPS challenge, thus mitigating damaging immune response during ETEC infection.

Intestinal barrier dysfunction has been implicated in IBD. Studies have showed that probiotics can possibly recover barrier integrity by altering tight-junctions expression of IECs (summarized in Table 1).

Peroxisome proliferators activated receptor (PPAR)- γ, a nuclear receptor, forms obligate heterodimers with the retinoid X receptor (RXR) [59]. Recent researches reveal that activation of PPAR γ is another mechanism of probiotic regulation of NF-κB transcriptional activity in the nucleus [60]. *L paracasei* F19 can upregulate Fiaf expression in IECs through the PPAR-α and PPAR-γ dependent pathways [61]. Studies also reported that VSL#3 modulated gut microbial diversity and CLA production in the colon [62] and corrects the inflammation-driven metabolic dysfunction [63] by targeting PPAR **y** to suppress colitis. However, *Lactobacillus rhamnosus* CNCMI-4317 modulates Fiaf expression in IECs in a PPAR-γ independent, but PPAR-α dependent manner.

1.1. Probiotics and colorectal cancer (CRC)

Colon tumorigenesis is the second largest cause of cancer death in western countries . Epidemiological evidence points to the fact that environmental and genetic factors far outweigh hereditary factors in the occurrence of CRC [64]. Mutations in tumor-suppressor genes such as Adenomatous polyposis coli (APC), β-catenin (cadherin-associated protein), K-ras, and p53 induce the initiation of CRC [65]. In addition, intestinal microbiome can affect colon cancer lesions [66]. Probiotics, as beneficial non-pathogenic lactic acid bacteria, have been used as food or supplement in the prevention and treatment of CRC. *In vitro* studies show that probiotics *Bacillus polyfermenticus* SCD inhibited the growth of colon cancer cells [67]. Furthermore, *in vivo* study demonstrated that daily oral administration of the microencapsulated *Lactobacillus acidophilus* significantly suppressed colon tumor incidence/multiplicity and size in DMH-induced animal colon cancer model and increased cellular apoptosis during the therapy [68]. However, in many clinical trials, effects of the probiotics in suppressing CRC have been inconsistent. After 2–4 years consuming *Lactobacillus casei*, it was observed that suppression of colorectal tumor growth in patients [69], whereas *Bifidobacterium longum* has no influence [69]. Jenab *et al* [70] used enzyme immunoassay to measure circulating vitamin D concentration (25-(OH)D) in 1248 cases of incident colorectal cancer. The results indicated a strong inverse dose-response association between risk of colorectal cancer and levels of pre-diagnostic 25-(OH)D concentration. It seems like that the effects of both probiotics and vitamin D/VDR in colorectal cancer patients are not conclusive, e.g. as recently reviewed by Dou et al [71], epidemiological studies have consistently demonstrated a strong inverse association of plasma 25(OH)D concentration with colorectal cancer incidence and mortality. However, the effect of vitamin D intake on colorectal cancer prevention is controversial [72–74]. There has

been and continues to be considerable research into the evaluation of probiotics in clinical treatment.

1.2. Probiotics and gastritis

After gastric damage, some tissues show oxidation phenomena. Probiotics have inhibitory effects on gastric injury. *Lactobacillus rhamnosus* GG reduced ethanol-induced mucosal lesion. The effect may be due to the significant increase of the basal mucosal prostaglandin E2 level [75]. Suo et al [76] also demonstrated that *Lactobacillus fermentum* Suo, a new lactic acid bacterial strain found in yak yoghourt, prevents HCl/Ethanol induced gastric injury via its antioxidant effects. Probiotic *BIFICO* cocktail inhibited the expression of cytokines and chemokines to ameliorate *H.pylori*-induced gastritis [77].

1.3. Probiotics and liver disease

Bacterial overgrowth, intestinal barrier function impairment and an increased pathogen toxicity are involved in the early phases of liver diseases, such as steatosis, steatohepatitis or liver injury [78]. It is demonstrated that *Lactobacillus casei* Shirota (Lcs) protects mice from NAFLD-induced liver steatosis through modulating the activation of PPAR γ and attenuation of the TLR4 signaling cascade [79]. *Lactobacillus casei* Zhang (LcZ) protected host against endotoxin- and D-galactosamine-induced liver injury in rats. These effects are associated with the antioxidative and anti-inflammatory functions in a TLR4-independent mechanism [80]. Zheng et al [81] studied the relation of feeding probiotic *Enterococcus faecium* with hepatic metabolism. Probiotics improved the metabolic efficiency of broiler chickens and decreased inflammatory responses.

1.4. Probiotics in immune responses

Immune disorder is supposed to be one of the main pathogenic mechanisms of autoimmune diseases, such as IBD [82] and rheumatoid arthritis (RA) [83]. Probiotics modulate the host-pathogen interactions by effecting on the innate immune responses, which involve the TLR, NF-κB, MAPK, and c-Jun NH2-terminal kinase (JNK) pathways. Supplementation of probiotics, especially *Lactobacillus* and *Bifidobacterium* species, can recover host health by excluding pathogens and modulating immune responses in IECs [84, 85]. Two independent clinical trials have demonstrated that two probiotic strains (*Bifidobacterium breve* and *Bifidobacterium infantis* 35624) could enhance the TGFβ signaling and increase peripheral Treg cells numbers [86, 87]. In addition, Xie *et al* assessed the expression levels of Th17 and Treg immune response specific transcription factors ROR γ t and Foxp3 in *Lactobacillus plantarum* NCU116 treated mice. Exposure to this strain led to increased immunity of intestinal mucosa and regulated the Th17/Treg balance, which was owed to TLR pathway in DCs [88]. Another aspect with regard to immunomodulation is that pretreatment with probiotics may decrease various cytokines and chemokines production and induce anti-inflammatory molecules, mainly through Th17/Treg, TLRs, or NF-κB signaling pathways [89, 90]. Probiotic *Lactobacillus rhamnosus* GR-1 ameliorated *E. coli* induced disruption of cellular structure and inflammation, partly by promoting TLR2 and NOD1 synergism and decreasing NLRP3 inflammasome activation [33].

In summary, probiotics protect the host from tumor and inhibit inflammation responses mainly in three mechanisms: (1) immune modulation, including the adhesion of probiotics to host cells, the interferation of cellular metabolism and cytokine production and the protection of tissue barrier integrity [91]; (2) gut microbiome. As probiotics may induce antimicrobial substance production, compete for limiting resources, prevent invasion and protect the host against toxins, thus altering the profile and functions of the gut microbiome [92]; and (3) the activity of genotoxin inhibition, involving in chronic inflammation inhibition, DNA repair, mutagenic substance inactivation, reducing the levels of carcinogenic compounds and binding to certain mycotoxins and cyanobacterial toxins [93, 94].

2. Probiotic modulate vitamin D and VDR

Collected data from recent studies demonstrate that probiotic treatment could increase vitamin D, VDR expression, and VDR activity in the host. Jones et al [95] reported that oral supplementation with bile salt hydrolase (BSH)-active *L.reuteri* NCIMB 30242 increases levels of circulating 25(OH)D. Although it has long been known that the gastrointestinal tract plays an active role in the absorption of vitamin D, these findings showed an orally delivered probiotic strain improves vitamin D level.

A study using IL10$^{-/-}$ colitis mouse model has demonstrated an association between probiotic VSL#3 and the nuclear receptor signaling pathway [2]. Pretreatment with the probiotic VSL#3 can increase VDR and angiostatin expression, decrease alkaline phosphatase to attenuate microscopic damage, and prevent development of carcinoma in a rat model of cancer [96]. Mencarelli *et al* [97] also tested the therapeutic potential of VSL#3 intervention in protecting against progress of steatohepatitis and atherosclerosis. VSL#3 conditioned medium intervention modulates the expression of nuclear receptors, such as peroxisome proliferator-activated receptor- γ , Farnesoid-X-receptors and VDR, which reverses insulin resistance and prevents development of steatohepatitis and atherosclerosis.

Our study has demonstrated that the probiotics LGG and *Lactobacillus plantarum* (LP) increased VDR protein expression, VDR transcriptional activity, which leads to increase in VDR target gene *cathelicidin* [98]. Probiotics protected the wild-type mice from *Salmonella*-induced colitis. However, probiotics had no effect of inhibiting *Salmonella*-induced colitis in VDR$^{-/-}$ mice [2]. The VDR pathway is required for probiotic protection in colitis [99]. The beneficial effects of probiotics in inhibiting intestinal inflammation and bacterial infection may depend on the VDR signaling pathway.

In conclusion, VDR plays a vital role in the effect of probiotic protection against inflammation and infection. VDR deletion may abolish the protective role of probiotics [2, 98–100]. Restoring vitamin D/VDR signaling may enhance the host's ability to modulate inflammation in patient with IBD and CRC [22].

3. Conclusion, limits, and future Direction

Probiotic supplementation with specific strains of microbes might be beneficial in the prevention of gastrointestinal disorders and other autoimmune illnesses. The mechanisms of probiotic actions are involved in regulation of innate immune functions via TLRs, NF-κB,

MAPK and secretion of anti- and pro-inflammatory molecules. Recent progress further shows that vitamin D and its receptor VDR contribute to the protective process of probiotics. It is now known that 1) Lactic acid bacteria were depleted in VDR KO intestine, 2) probiotic LGG and LP treatments enhanced VDR expression, and 3) Probiotics protected from *Salmonella*-colitis depending on the VDR signaling. Table 1 outlines representative publications on the mechanisms of protective effects of probiotic on the host.

Previously, probiotics have been used in the treatment of IBD. However, the responses to treatment and clinic outcomes are inconsistent [101–104]. The clinical efficacy and safety of probiotic on patients have long been a contentious issue. Although the side effects of probiotics tend to be mild and digestive (such as gas or bloating), serious effects have been seen in people, especially those with underlying health conditions. Our study [98] in *Salmonella*-colitis model has also demonstrated that, in the mice without VDR expression, probiotic treatment led to more severe infection. Our findings that probiotic function depends on VDR status may provide an explanation for the inconsistent clinical response of some patients with IBD. There are different groups with IBD: those with 1) dysfunctional VDR signaling; 2) vitamin D deficiency; and 3) dysbiosis. However, the current usage of probiotics is based on a generic, nonspecific approach. Thus, a more personalized approach to the use of probiotics is needed. A personalized strategy is not only applied to IBD therapy, but also to other diseases. The accurate identification of probiotics and understanding the specific mechanisms of actions of individual probiotic strains are needed. Studies demonstrate that specific probiotic strains exert specific effects in IBD therapy. Elucidating how probiotics specifically regulate VDR signaling will advance our understanding of bacterial-host interactions in IBD.

Strategies to restore VDR expression in inflamed mucosa may be important for preventing and treating IBD and other illness. As dysregulation of bacterial-host interaction can result in chronic inflammation, strategies to restore VDR expression in inflamed mucosa may be important for the prevention and treatment of various diseases. There is still a long way to go to identify the most suitable probiotics for the prevention and to develop more probiotics to fight human illnesses.

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Abbreviations

AAD	Antibiotic-associated diarrhea
APC	Adenomatous polyposis coli
BSH	Bile salt hydrolase
CLA	Conjugated linoleic acid
CRC	Colon cancer

COPD	Chronic obstructive pulmonary disease
DMH	Dimethylhydrazine
DCs	Dendrtic cells
DSS	Dextran sodium sulfate
ERK	Extracellular-signal-regulated kinase
HRQOL	Health-related quality of life
IECs	Intestinal epithelial cells
IBDs	Inflammatory bowel diseases
JNK	c-Jun NH2-terminal kinase
La	*Lactobacillus acidophilus*
Lc	*Lactobacillus casei*
Lcs	*Lactobacillus casei* Shirota
LcZ	*Lactobacillus casei* Zhang
LGG	*Lactobacillus rhamnosus* GG
LP	*Lactobacillus plantarum*
LAB	Lactic Acid Bacteria
MI/R	Myocardial ischemia/reperfusion
MAPK	Mitogen-activated protein kinase
NLRP3	NOD-like receptor family member pyrin domain-containing protein 3
NF-kB	Nuclear factor kappa B
PPAR-γ	Peroxisome proliferators activated receptor gamma
PPAR-α	Peroxisome proliferators activated receptor alpha
RAS	Renin-angiotensin system
RXR	Retinoid X receptor
RA	Rheumatoid arthritis
TEER	Transepithelial electrical resistance
TJs	tight-junctions
TNF	Tumor necrosis factor
TLR	Toll-like receptor

TNBS	Trinitrobenzenesulfonic acid
UC	Ulcerative colitis
VDR	Vitamin D receptor

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Table 1

Molecular mechanisms for the beneficial roles of probiotics

Pathways	Probiotics	Subjects	Summary	Ref.
NF-kB	**(i)** LP-L2 **(ii)** LGG **(iii)** Lactobacillus reuteri **(iv)** *L.casi* [110] **(v)** *Lactobacillus fermentum* Suo	**(i-ii)** Caco-2 **(iii)** IL-10 KO mice **(iv)** HEK-293T **(v)** Gastric Injuried mice	**(i-ii)** Probiotics inhibited TNF-α-induced NF-kB translocation/IkBα degration in Caco-2 cells **(iii)** *L. reuteri* suppressed inflammatory response on human epithelial cells and inhibited colitis in IL-10 KO mice depending on NF-kB signaling pathway **(iv)** Lc inhibited the transcription of genes encoding pro-inflammatory effectors and adherence molecules induced by *S.flexneri* to confer anti-inflammation via inactivation of NF-kB pathway **(v)** LF-Suo has potential use as probiotics for its gastric injury treatment effects via modulating NF-kB pathway	[48, 51, 76, 105, 106]
NF-kB MAPK (ERK1/2/JNK /p38)	**(i)** Ocotillol **(ii)** *E.colo Nissle* 1917 (ECN) **(iii)** .fermentum **(iv)** *L.acidophilus* (La) **(v)** VSL#3	**(i)** Mice with TNBS-induced colitis **(ii-v)** Caco-2	**(i)** Treatment with *ocotillol* inhibited trinitrobenzenesulfonic acid (TNBS)-induced expression of TNF-αand IL-1β, as well as activation of NF-kB and MAPK **(ii)** Probiotic obiviously increased human β defensins-2 mRNA expression in Caco-2 cells **(iii)** Probiotic abolished Hbd-2 promoter activation via deleting NF-kB and activating AP-1	[107, 108]
TLRs	**(i)** *Lactobacillus delbrueckii* TUA4408L **(ii)** Enterococcus faecalis	**(i)** Porcine intestinal epitheliocytes **(ii)** Gnotobiotic mouse model of experimental colitis	TUA4408L and *Enterococcus faecalis* attenuate inflammatory response via TLR2/TLR4 pathways.	[53, 109]
TLRs NF-kB/ MAPK	**(i)** Lactobacillus jensenii TL2937 **(ii)** B. longum **(iii)** LGG	**(i)** PIE cells **(ii-iii)** T84 **(iii)** HT-29	**(i)** *Lactobacillus jensenii* TL2937 negatively regulates TLRs to reduce the expression of proinflammatory cytokines and chemokines caused by ETEC or LPS challenge, mitigating damaging immune response during ETEC infection **(ii)** Treatment with *B. longum* decreases TNF-α-induced NF-kB activation by reducing IkBα degradation and p38 ohosphorylation **(iii)** Its coomensal-origin DNA increased TLR9 expression in HT-29 and T84 cells	[58, 111]
TJs	**(i)** VSL#3 **(ii)** LP MB452 **(iii)** r **(iv)** a **(v)** B.lactis 420 **(vi)** ECN	**(i)** Balb/c mice **(ii-v)** Caco-2 **(vi)** ECs/DSS-induced mice	**(i)** VSL#3 decreased expression and redistribution of occluding, ZO-1, and cludin-1,3,4,5, and increase of epithelial apoptotic ratio **(ii)** LP MB452 induced TER accrossing Caco-2 cells **(iii-v)** biotics protected the tight junctions from damage **(vi)** Adding ECN restored the barrier integrity induced by EPEC-infection	[112–116]

Pathways	Probiotics	Subjects	Summary	Ref.
TJs MAPK/ TLRs/ PKC	**(i)** B.infantis **(ii)** LP **(iii)** LCN	**(i)** IL-10,IL-1 deficient mice **(ii)** T84 **(iii)** Caco-2	**(i)** *B.infantis* conditional medium (BiCM) increased p-ERK and decreased p-p38 to upregulate TER, ZO-1, and occluding expression **(ii)** LP induced translocation of ZO-1 to the TJ region via modulation of TLRs pathway **(iii)** LCN restored the barrier intergrity and distruption by EPEC infection	[117–120]
VD/VDR	**(i)** *L.reuteri* NCIMB 30242 **(ii)** VSL#3 **(iii)** LP **(iv)** LGG	**(i)** Human **(ii)** IL10−/− colitis mouse **(iii)** HKOs (HCT116/MEFs) and $VDR^{-/-}$ mice	**(i)** Oral supplementation with bilebile salt hydrolase (BSH)-active *L.reuteri* NCIMB 30242 increases levels of circulating 25(OH)D **(ii)** VSL#3 increaed VDR expression and activity in th IL10−/− mouse model **(iii)** LR and LGG increased VDR protein epression and its transcriptional activity, VDR deletion may abolish the protective role of probiotics	[30, 31, 52, 95, 99]
PPAR-γ/other Nuclear receptor	**(i)** VSL#3 **(ii)** Bacteroides thetaiotaomicron **(iii)** *Lactobacillus rhamnosus* GR-1	**(i)** IL-10 KO mice **(ii)** HT-29 **(iii)** *Escherichia coli*-Induced Inflammation and BMECs Damage	**(i)** VSL#3 intervention results in upregulation of PPARγ, potential antagonists of NF-kB inflammatory pathways **(ii)** *L. rhamnosus* CNCMI–4317 strain induced the expression of Fiaf gene in a PPAR-γ independent but PPAR-α dependent manner in IECs **(iii)** *L. rhamnosus* GR-1 pretreatment ameliorates E. coli-induced inflammation and cell damage via promotion of TLR2 and NOD1 synergism and attenuation of ASC-independent NLRP3 inflammasome activation	[31, 33, 63]
Immune response	**(i)** Bifidobacterium breve **(ii)** Heat-killed *Lactobacillus* acidophilus	**(i)** Murine DSS-induced colitis **(ii)** Bovine beta-lactoglobul-in-sensitized mice model	**(i)** *Bifidobacterium breve* attenuates murine dextran sodium sulfate-induced colitis and increases regulatory T cell responses **(ii)** The suppression of major allergic symptoms by oral administration of *Lacidophilus* was probably due to improve the regulatory T (Treg)/Th17 balance and inhibit the IL-6 production	[82, 121]