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Mechanisms and Molecular Targets of Gut Microbiota-Derived Tryptophan Metabolites in Regulating Intestinal Mucosal Barrier Homeostasis

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ABSTRACT: Host intestinal microorganisms generate a series of bioactive molecules, including indoles and their derivatives, through the tryptophan metabolic pathway, and these microbial metabolites play an essential role in the regulation of intestinal homeostasis through the ligand-receptor interaction mechanism. This paper provides a systematic review of indole derivatives (such as indole-3-lactic acid, indole-3-propionic acid, and indole-3-acetic acid) produced by gut microbiota via the tryptophan metabolic pathway, with particular emphasis on their pivotal role as aryl hydrocarbon receptor (AhR) ligands. These metabolites activate the AhR signaling pathway to maintain the functional integrity of the intestinal mucosal barrier. Further summarizing their mechanisms of action-including regulating tight junction protein expression, promoting mucus secretion, modulating immune responses, and influencing gut microbiota composition-thereby enhancing intestinal barrier integrity. The potential therapeutic applications in inflammatory bowel disease, metabolic syndrome, and related conditions are explored. Finally, it envisions future precision intervention strategies based on the nutrition-microbiota-metabolite interaction axis, offering novel translational approaches for targeted therapies in gut barrier-related diseases.

Keywords: Gut microbes; Trp metabolism; Indole derivatives; Intestinal mucosal barrier function; Aryl hydrocarbon receptor

1. Introduction

The gut microbiome is essential for the intestinal health of the host and regulate a wide range of physiological processes that significant impact the host's overall health, including metabolism, the intestinal-brain axis, and the intestinal-liver axis ^[1]. Recent research has revealed that the small molecule metabolites produced by intestinal microorganisms play a crucial role in maintaining intestinal homeostasis. Several studies have found that small molecules such as short-chain fatty acids, indole and indole derivatives produced by microbial metabolism can cross the intestinal mucosa, act on a variety of cells (intestinal epithelial cells, intestinal stem cells, macrophages, and T lymphocytes, etc.), and bind to a variety of receptors, activate

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multiple signaling pathways, and exert beneficial functions such as enhancing intestinal mucosal barrier function, promoting cell proliferation, modulating inflammatory responses, and suppressing tumors^[2-6].

Tryptophan (Trp), an essential amino acid, is ingested exogenously as dietary protein, and its metabolism occurs mainly in the small intestine, where most of the protein is digested and absorbed through trypsin-mediated enzymatic degradation^[7]. However, some protein and amino acids still make their way to the colon, where they are broken down by different commensal bacteria^[7]. Trp plays an essential role in maintaining intestinal immunity and balance of the intestinal microbiota, and indole compounds produced by microbial metabolism of Trp, as specific ligands of aryl hydrocarbon receptor (AhR), play a key role in the maintenance of intestinal mucosal barrier function and homeostasis through the targeted regulation of AhR signaling pathway^[8]. In this paper, we systematically reviewed the mechanism of regulation of AhR pathway by indole derivatives (e.g., indole-3-acetic acid (IAA), indoleacrylic acid (IA)) produced by intestinal commensal bacteria (e.g., *Clostridium* spp., *Lactobacillus* spp., and *Bacteroides* spp.) catalyzed by Trp metabolizing enzymes (including tryptophanase, aromatic amino acid aminotransferase and tryptophan decarboxylase, etc.) and their probiotic functions in the maintenance of intestinal homeostasis. In addition, the molecular mechanisms by which indole derivatives modulate intestinal mucosal barrier function and their potential therapeutic applications are reviewed, with a focus on elucidating the effects of this class of compounds on the integrity of the intestinal mucosal barrier by regulating key pathways such as expression of tight junction proteins, homeostatic balance of immunity, and microbiota-host interactions. Based on the pathological analyses of diseases related to intestinal mucosal barrier dysfunction, this study provides an important theoretical basis and translational medical research framework for the development of novel drugs to repair the intestinal mucosal barrier damage and to prevent and control related metabolic and inflammatory bowel diseases.

2. The role of tryptophan metabolites in maintaining host intestinal health

2.1. Tryptophan metabolic pathway

The intestinal Trp metabolic system consists of two main metabolic pathways, endogenous and bacterial. In the endogenous metabolic pathway, Trp is metabolically converted via the kynurenine pathway (KP) and serotonin pathway, in which approximately 95% of ingested Trp is degraded through the KP to small molecule actives such as kynurenine, 3-hydroxykynurenine, o-aminobenzoic acid, 3-hydroxy-o-cyanobenzoic acid, and xanthuronic acid a series of bioactive metabolites^[9]. Only less than 2% of Trp is converted to serotonin through the serotonin pathway^[10]. It is worth noting that the intestinal microbiota converts Trp into physiologically active small molecule compounds such as indole, and its derivatives through a specific metabolic enzyme system, and these microbial metabolites are regulated through ligand-receptor interaction mechanism. It plays an important role in regulating the homeostasis and physiological function of the host gastrointestinal tract^[11].

2.2 Gut microorganisms and their indole derivatives

As the first indole metabolite identified to be biosynthesized by *Escherichia coli* (*E. coli*) via the Trp metabolic pathway, the specific synthesis mechanism of indole is a landmark in microbial taxonomy, and this characteristic metabolic marker has been established as a key biochemical indicator for the differential diagnosis of *E. coli* from other intestinal flora^[7-12]. However, current studies have shown that many microorganisms, in the presence of aromatic amino acid transaminase (AraT), tryptophan decarboxylase, tryptophan-2-monooxygenase, or tryptophanase, directly use Trp to convert it into indole derivatives^[13]. In general, microbes convert Trp to indole derivatives mainly through four branches (Figure 1). Different microorganisms produce different indole derivatives due to differences in the pathway of metabolizing Trp, such as indole, tryptamine, indole-3-propionic acid (IPA), IA, indole-3-carbaldehyde (I3C), indole-3-lactic acid (ILA), IAA and other indole derivatives. It is worth noting that the molecular mechanism of indole derivatives production through Trp catabolism and its metabolic regulatory network have not been systematically elucidated. In particular, the key rate-limiting enzymes and their regulatory factors in different microbial involved in this metabolic pathway need to be thoroughly analyzed genera through integrated multi-omics analysis.

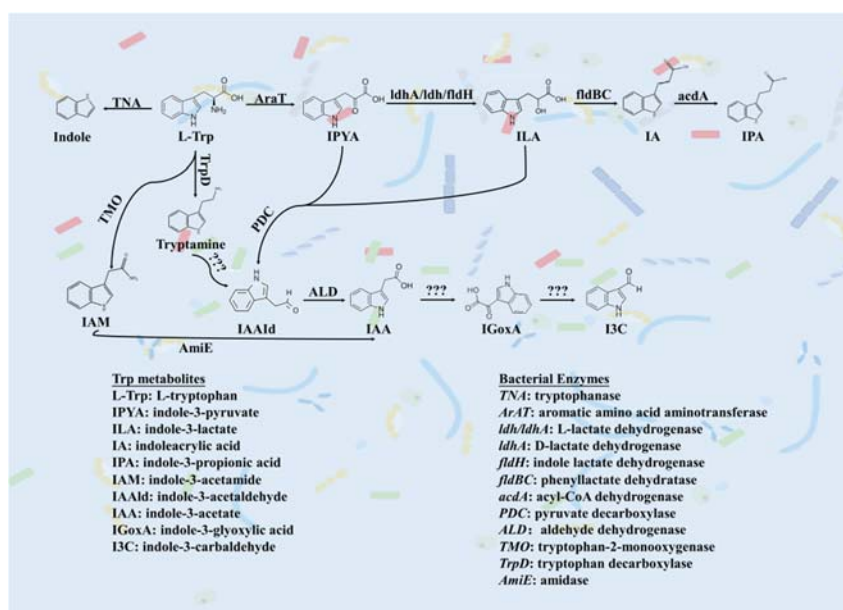


Fig. 1. When the host ingests a food rich in Trp, the gut microbes convert a small amount of Trp into indole derivatives through four pathways.

2.2.1 Synthesis of indole derivatives of microbial origin driven by a multi-enzyme

Some studies found that most microorganisms carry tryptophanase genes, which can metabolize Trp to produce indole, such as *Aeromonas salmonicida*, *Porphyromonas gingivalis*, *Salmonella*, *E. coli* and so on^[14-16]. *Peptostreptococcus* spp. convert Trp into IA and IPA mainly due to the presence of the phenyllactate dehydratase gene cluster (*fldBC*) on its chromosomes^[17]. *Clostridium sporogenes* convert Trp to indole-3-pyruvate, which in turn can be converted to indole-3-acetaldehyde (IAAld) by indole pyruvate decarboxylase^[18]. Some strains encode indole-pyruvate decarboxylase or phenylpyruvate decarboxylase to further convert IAAld to IAA^[19].

2.2.2 Synthesis of indole derivatives of *Lactobacillus* origin driven by a multi-enzyme

In recent years, it has been found that most *Lactobacillus* convert Trp into ILA, I3C and IAA, such as *Lactiplantibacillus plantarum* (*L. plantarum*), *Lactobacillus casei*, *Limosilactobacillus reuteri* (*L. reuteri*), *Lacticaseibacillus rhamnosus* (*L. rhamnosus*), *Lactobacillus acidophilus*, and *Ligilactobacillus salivarius* and so on, but there are a small number of *Lactobacillus* convert Trp into IA or tryptamine^[17, 20-22]. Therefore, the types and quantities of indole derivatives produced by different *Lactobacillus* species are different, but the reason for this difference is not clear at present. Pan et al.^[19] studies found that ILA and I3C levels were significantly correlated with the amount of AraT and amidase, respectively, but the large amount of ILA produced by *L. salivarius* was mainly related to its unique indole lactate dehydrogenase. Jia et al.^[23] reported that the enzyme that produces ILA in *Lactobacillus johnsonii* is D-2-hydroxy acid dehydrogenase (ldhA). In addition, some *Lactobacillus* strains encode indole pyruvate decarboxylase, phenylpyruvate decarboxylase or amidase, which promote the conversion of Trp to IAA^[19-24]. It is evident that indole derivatives produced by *Lactobacillus* using Trp are closely related to the enzymes they encode. Therefore, the identification of genes encoding key regulatory enzymes for indole derivative production by *Lactobacillus* metabolism Trp can help to overcome the technical challenges associated with the targeted screening of probiotics producing specific metabolites, and ultimately to establish a high-throughput screening method for specific functional probiotics.

2.2.3 Synthesis of indole derivatives of *Bifidobacterium* origin driven by a multi-enzyme

As early as 1979, Aragozzini et al.^[25] reported *Bifidobacterium* convert Trp into ILA. However, there was no report on the enzymes related to the regulation of Trp to produce ILA by *Bifidobacterium*. Recent studies have shown that *Bifidobacterium* spp. can catalyze the biotransformation process of Trp to ILA through its encoded aromatic lactate dehydrogenase, such as *Bifidobacterium longum* subsp. *longum*, *Bifidobacterium longum* subsp. *infantis*, *Bifidobacterium breve*, and *Bifidobacterium bifidum* (*B. bifidum*)^[25-27]. In addition, in the nutrient-simple M9 medium, *B. bifidum* can produce I3C, which may be related to the fact that under different nutrient substrate conditions, the strains selectively regulated the Trp catabolism pathway by activating the differentially expressed metabolic enzymes, which eventually led to the diverse expression of characteristic secondary metabolites^[19-28]. Therefore, these studies show that different indole derivatives can be obtained by adjusting the nutrients of *Bifidobacterium* spp.

In summary, heterogeneity among microbial populations due to Trp metabolizing enzyme systems drives the biosynthesis of diverse indole metabolites. However, existing studies have shown that the large number of unidentified microbial resources with the potential to produce indole derivatives, as well as novel indole derivatives that have not yet been structurally characterized, still exist in the intestinal microorganism. Therefore, the establishment of a high-throughput screening platform based on the association of genome mining and metabolomics, and the development of an identification system for indole based on the association of mass spectrometry molecules and nuclear magnetic resonance technology have become the key research

directions for elucidating the mechanism of microbial-Trp metabolism interactions and mining novel bioactive molecules.

3. Intestinal health and indole derivatives

3.1. Factors affecting the integrity of the intestinal mucosal barrier

The monolayer columnar epithelium and closely connected intestinal cells together constitute the intestinal mucosal barrier against the harsh environment in the intestinal cavity^[29]. The mechanical barrier, chemical barrier, immune barrier, and microbial barrier together constitute a complete intestinal mucosal barrier, which can effectively prevent harmful substances such as bacterial toxins and pathogenic microorganisms from entering the intestinal cavity^[30]. Once the intestinal mucosal barrier is damaged, it increases the risk of intestinal infection and promotes the introduction of bacteria and toxins into the epithelial tissues, leading to inflammation and gastrointestinal diseases^[29]. Pathophysiological or environmental factors may be key factors in disrupting normal physiology and increasing barrier permeability.

A variety of factors can threaten our intestinal health, leading to an imbalance in the structure of the intestinal flora and damage to the intestinal mucosal barrier, such as poor dietary habits, alcohol consumption, medications, bacterial toxins, and stressful life situations^[31]. When the intestinal mucosal barrier function is impaired, harmful substances enter the bloodstream through the intestinal epithelium, leading to the onset or development of a variety of diseases, such as autism disease (AD), Parkinson's disease (PD), Alzheimer's disease (AZM), celiac disease (CD), irritable bowel syndrome (IBS), chronic heart disease (CHD), inflammatory bowel disease (IBD), type 1 diabetes (T1D) and other diseases (Figure 2)^[32-34]. Psychological stress plays a role in the course of gastrointestinal disorders such as IBS and IBD^[35-36]. Stress not only leads to changes in microflora and increased intestinal permeability, but also compromises the intestinal immune system, all of which can lead to damage to the intestinal epithelial barrier^[36-38]. It was found that a high-fat diet can lead to increased intestinal permeability in mice or rats, resulting in decreased expression of intestinal tight junction proteins^[39, 40]. Also, high-fat or high-sugar diets can lead to increased abundance of Proteobacteria in the gut^[41]. These changes caused by a high-fat or high-sugar diet are more likely to cause diseases such as IBD, atherosclerosis and T1D^[42-44]. Consequently, the development of precision-targeted intervention strategies aimed at modulating Claudin/Occludin protein expression, enhancing Mucin (MUC)2 secretion from goblet cells, and regulating lamina propria immune cell functions has emerged as a cutting-edge research direction for reversing leaky gut syndrome and preventing its multi-system complications.

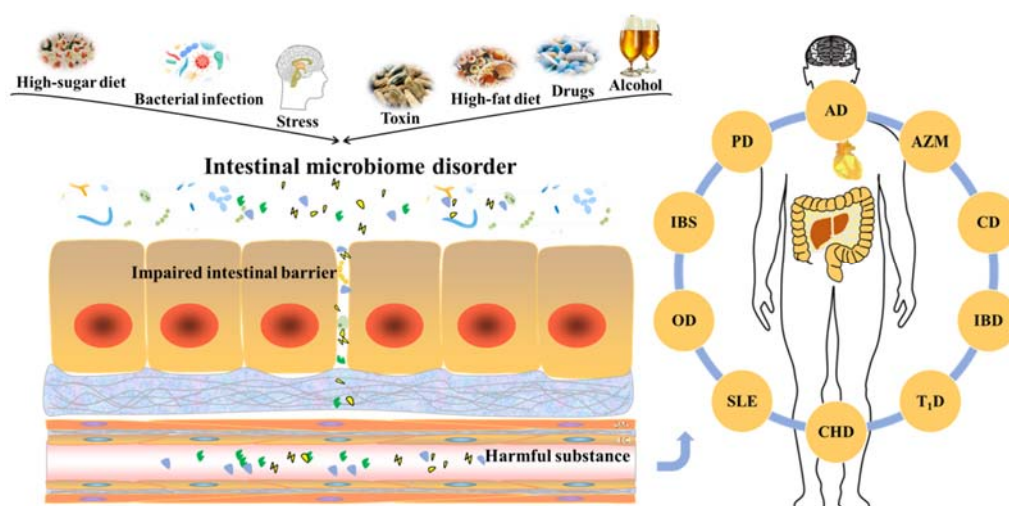


Fig. 2. A variety of factors will threaten our intestinal health, leading to an imbalance in the structure of the intestinal flora and damage to the intestinal mucosal barrier, such as poor dietary habits, alcohol consumption, medications, bacterial toxins, and life stress. When the intestinal mucosal barrier function is impaired, harmful substances pass through the intestinal cavity and enter the blood, causing a variety of diseases. Autism disease (AD), parkinson disease (PD), irritable bowel syndrome (IBS), obesity disease (OD), systemic lupus erythematosus (SLE), chronic heart disease (CHD), type 1 diabetes (T1D), inflammatory bowel disease (IBD), crohn's disease (CD), Alzheimer's disease (AZM).

In recent years, *in vivo* and *in vitro* studies have shown that indole and its indole derivatives enhance the function of intestinal epithelial cell^[45-46]. Therefore, here we have summarized and classified some bacterial strains that have been discovered in recent studies to be capable of converting tryptophan into indole derivatives, as well as the beneficial functions of the corresponding indole derivatives (see Table 1).

Table 1 Intestinal microorganisms producing indole derivatives and their functional properties

Metabolite	Bacterial Species	Major findings	References
ILA	<i>B. infantis</i>	upregulated immunoregulatory galectin-1 in Th2 and Th17 cells	[6, 20, 47-58]
	<i>L. plantarum</i>	during polarization	
	<i>L. reuteri</i>	ameliorated intestinal inflammation, tumor growth, and gut dysbiosis	
	<i>B. bifidum</i>	a developmental function in immature mature intestinal cells	
	<i>B. longum</i> subsp. <i>Infantis</i>	promote the expression of tight junction protein	
	<i>Akkemansia</i>	activating AhR and Nrf2 signaling pathways	
	<i>L. gallinarum</i>	protect epithelial cells from oxidative stress	
	<i>L. murinus</i>	inhibiting NLRP3 inflammasome and NF-κB signaling pathways	
	<i>B. breve</i>	exerts anti-tumor effects by down-regulating IL-17 signaling pathway	
	<i>L. curvatus</i>	modulates immune responses of human CD4 ⁺ T cells and monocytes	
I3C	<i>L. acidophilus</i>	block transcription of the inflammatory cytokine IL-8 by interacting with AhR	[17, 53, 59-62]
	<i>L. salivarius</i>	Inhibition of food-borne pathogens	
	<i>L. pentosus</i>	accelerate proliferation of intestinal epithelial	
	<i>Staphylococcus epidermidis</i>	promotion IL-22 transcription and balances the mucosal response	
		mediation antitumor interferon-γ-producing CD8 T cell immunity	
IAA	<i>L. reuteri</i>	Inhibition of food-borne pathogens	[53, 63-68]
	<i>Akkemansia</i>	Inhibition of TLR4/NF-κB/p38 signaling pathway	
	<i>L. plantarum</i>	Promote the expression of tight junction protein	
	<i>L. acidophilus</i>	Inhibit inflammatory damage	
	<i>Bacteroides ovatus</i>	Promote IL-22 production by immune cell	
	<i>L. plantarum</i>	upregulated AhR expression and activated the IL-22/STAT3 signaling pathway	
	<i>Akkemansia</i>	Inhibition of food-borne pathogens	
IAA	<i>E. coli</i>	affect the biofilm formation and virulence of <i>Pseudomonas aeruginosa</i>	[53, 63-68]
	<i>Azospirillum brasilense</i>	mitigates inflammatory responses	
	<i>Acinetobacter baumannii</i>		
	<i>Rubrivivax</i>		
	<i>benzoatilyticus</i>		

IA	<i>Peptostreptococcus</i>	promote intestinal epithelial barrier function	[69-71]
	<i>Species</i>	alleviate type 2 diabetes via activation of AhR to repair intestinal	
	<i>Clostridium sporogenes</i>	mucosal barrier	
	<i>Parabacteroides distasonis</i>	increase the expression level of IL-22	
Indole	<i>Parabacteroides distasonis</i>	mitigates inflammatory responses	[53, 72]
	<i>Escherichia coli</i>	promoted the expression of mucosal barrier and mucin-producing genes	
	<i>Akkemansia</i>	decreased TNF- α -mediated NF- κ B activation.	
IPA	<i>Peptostreptococcus</i> <i>Clostridium sporogenes</i>	Participate in immune regulation	[12, 69, 70, 73-77]
		Promote IL-25 production and maintain intestinal integrity	
		Promote macrophage phagocytosis	
		anti-inflammatory, antioxidant, proapoptotic responses and abating DNA damage	
Tryptamine	<i>Clostridium sporogenes</i>	anti-inflammatory	[78, 79]

Abbreviations: *Escherichia coli* (*E. coli*), *Clostridium sporogenes* (*C. sporogenes*), *Bacteroides ovatus* (*B. ovatus*), *Peptostreptococcus russellii* (*P. russellii*), *Lactiplantibacillus plantarum* (*L. plantarum*), *Limosilactobacillus reuteri* (*L. reuteri*), *Lacticaseibacillus rhamnosus* (*L. rhamnosus*), indoleacrylic acid (IA), indole-3-propionic acid (IPA), Indole-3-lactic acid (ILA), indole-3-carboxaldehyde (I3C), indole acetic acid (IAA), aryl hydrocarbon receptor (AhR), nuclear factor erythroid 2-related factor 2 (Nrf2), NOD-like receptor thermal protein domain associated protein 3 (NLRP3), nuclear factor kappa-B (NF- κ B), interleukin (IL), toll like receptor 4 (TLR4), signal transducer and activator of transcription 3 (STAT3), tumor necrosis factor- α (TNF- α).

3.2 Indole derivatives and mechanical barrier

The mechanical barrier is the most important component of the intestinal mucosal barrier, which consists of intact intestinal mucosal epithelial cells and tight junction proteins between epithelial cells. It is a selective osmotic barrier that allows the absorption of nutrients, electrolytes, and water while maintaining an effective defense against endotoxins, antigens, and the intestinal microbiota^[80]. Once the mechanical barrier is damaged, the tight junction protein is destroyed, resulting in increased intestinal mucosal permeability, resulting in bacterial translocation and intestinal flora imbalance, and ultimately intestinal injury and inflammation^[81].

It has been found that indole derivatives can maintain the integrity of the intestinal mucosal barrier by regulating the mechanical barrier^[82]. *E. coli* inhibits pathogen adhesion to epithelial cells by increasing the expression of genes involved in intestinal epithelial function, such as actin cytoskeleton, adhesion junctions and tight junctions^[71]. Reducing pathogen adhesion to intestinal epithelial cells, resisting the invasion of pathogenic microorganisms, and maintaining the integrity of the intestinal mucosal barrier is essential for maintaining intestinal homeostasis^[83]. Studies have found that IPA, indole-3-ethanol, indole-3-pyruvate and I3C can improve intestinal mucosal barrier function by reducing cell layer permeability and promoting the expression of tight junction proteins (Figure 3)^[3, 19, 61, 84]. Type 2 diabetes is a metabolic disease characterized by chronic inflammation, insulin resistance, and damage to islet cells. IA activates the AhR signaling pathway and increases the expression level of interleukin (IL)-22, thereby improving the expression of intestinal mucosal barrier -related proteins, repairing the intestinal mucosal barrier and reducing inflammation in type 2 diabetes^[71]. In a high-fat diet-induced model of obesity and metabolic disorders, oral administration of IPA increases the expression of tight junction protein, promotes the production of IL-25, maintains the integrity of the intestinal mucosal barrier, and down-regulates colon inflammation blocking its development^[75].

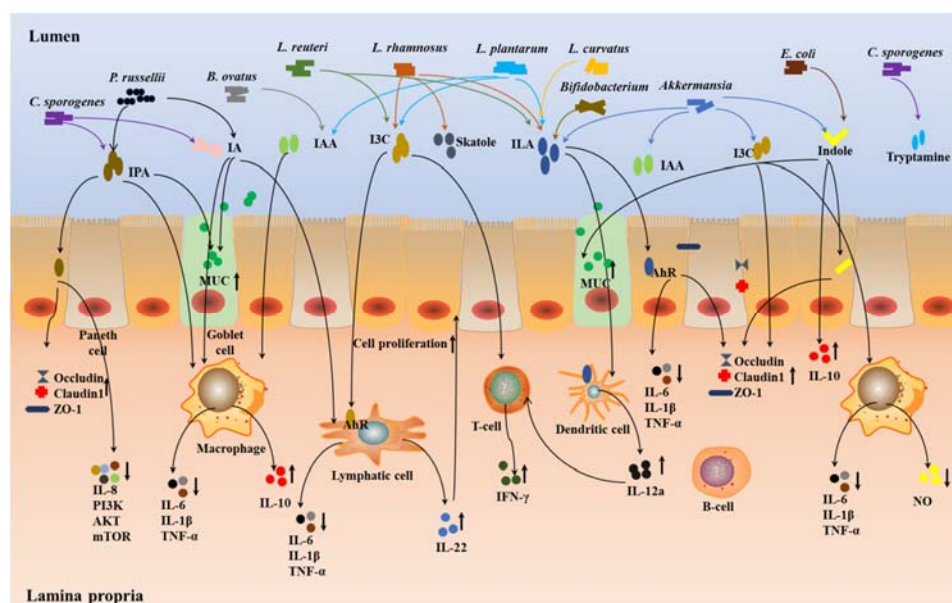


Fig. 3. Trp -derived metabolites of intestinal microorganisms and their effects on intestinal mucosal immune regulation and stable epithelial barrier function. Here we present eight Trp-derived microbial metabolites, and demonstrate the mechanisms by which some indole derivatives exert immune regulation and enhance intestinal mucosal barrier function. Indoleacrylic acid (IA), indole-3-propionic acid (IPA), Indole-3-lactic acid (ILA), indole-3-carboxaldehyde (I3C), indole acetic acid (IAA), Interferon- γ (IFN- γ), phosphatidylinositol 3-kinase (PI3K), Protein Kinase B (AKT), mammalian target of rapamycin (mTOR), mucin (MUC), zonula occludens (ZO-1).

Lactobacillus and *Bifidobacterium* have received extensive attention due to their ability to metabolize Trp to produce indole derivatives. Cui et al.^[50] showed that the AhR ligand ILA produced by *B. bifidum* FL-276.1 and *B. bifidum* FL-228.1 can modulate the AhR/nuclear factor erythroid 2-related factor 2 (Nrf2)/NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome pathway in the monomolecular layer of Caco-2, thus upregulating tight junction proteins and protecting the integrity of the epithelial barrier. The colon epithelium acts as a dynamic barrier, blocking the entry of microorganisms and food-derived antigens while mediating crosstalk between the intestinal microbiota and the host^[85]. To maintain homeostasis, intestinal stem cells at the base of the crypt proliferate and subsequently differentiate as they migrate to the surface of the lumen^[86]. Hou et al.^[59] found that the *L. reuteri* metabolite I3C stimulates the secretion of IL-22 by intestinal organs and lamina propria lymphocytes through AhR, and then induces signal transducer and activator of transcription 3 phosphorylation to accelerate the proliferation of intestinal epithelial cells, thereby restoring the damaged intestinal mucosa. In addition, it has been found that substances such as dietary black rice and β -glucan can improve intestinal mucosal barrier damage by adjusting the abundance of beneficial intestinal microorganisms, promoting the production of ILA, and promoting the expression of tight junction proteins^[87-88]. Therefore, in addition to supplementing some indole derivative-producing probiotics in daily life, intestinal stability can also be maintained by supplementing some dietary fibre-rich foods by up-regulating the abundance of beneficial flora and promoting the production of indole derivatives.

3.3 Indole derivatives and chemical barrier

The chemical barrier consists of mucus secreted by intestinal epithelial cells, digestive fluid, and bacteriostatic substances produced by normal parasitic bacteria in the intestinal lumen, in which intestinal epithelial cells proliferate and differentiate in a highly coordinated manner along the villus axis, and which act as an important chemical barrier to prevent the entry of harmful molecules into the systemic circulation through the secretion of fluids, mucus, and antimicrobial peptides, among other chemicals^[89]. Paneth cells secrete lysozyme have antibacterial activity and can protect the intestinal epithelial cells from being attacked by pathogenic bacteria and their related harmful products^[90]. MUC2 is mucus secreted by mammalian intestinal epithelial cells and is essential to maintain intact mucosal barrier function^[91].

Recent studies have shown that IPA and IA can enhance mucus barrier function and alleviate inflammation by improving goblet cell function (promoting the expression of trefoil factor 3 (TFF3) and resistin-like molecule beta (RELMβ)) and promoting mucus production (MUC2 and MUC4)^[65, 69, 82]. In addition, in order to induce goblet cell differentiation, indole interacts with AhR to increase the expression of cytokine IL-10, and indole increases intestinal cell renewal and promotes goblet cell differentiation through AhR and IL-10 to change intestinal homeostasis, a process that is dysregulated with age^[92]. Indole derivatives can improve DSS-induced colitis by activating the AhR signaling pathway to promote goblet cell differentiation^[53, 93]. Li et al.^[94] found that the gut microbiota metabolite IAA ameliorates intestinal mucosal barrier damage and maintains intestinal epithelial homeostasis via MUC sulfation.

3.4 Indole derivatives and immune barrier

The immune barrier is composed of intestinal epithelial cells, intestinal intraepithelial lymphoid tissue, lamina propria lymphocytes, mesenteric lymph nodes, and immunoglobulin A secreted by intestinal plasma cells^[95]. When some bacteria, viruses, and toxin antigens in our living environment stimulate the intestinal mucosa, the intestinal mucosal immune system can rapidly identify the antigens in the body, and produce humoral immunity and cell immunity to effectively remove the antigens, which has the effects of resisting invasion of pathogenic microorganisms, antiallergic reaction, and inhibiting the immune response^[4, 7, 96].

It has been found that indole increases the transepithelial resistance of the polarized intestinal epithelium of HCT-8 and decreases tumor necrosis factor (TNF)-α mediated nuclear factor kappa-B (NF-κB) activation and IL-8 secretion, thus promoting epithelial function^[72]. AhR binding to its ligand I3C plays a protective role in DSS-induced colitis mice by modulating or toll-like receptor 4/NF-κB/p38 signaling pathways and reducing TNF-α, IL-1β, IL-6, and IL-8 expression^[97]. In the intestines of breastfed infants, *Bifidobacterium infantis* (*B. infantis*) can produce ILA, which significantly inhibits the expression of IL-8 in intestinal epithelial cells induced by TNF-α and lipopolysaccharide (LPS)^[52]. Furthermore, indole derivatives can act on a variety of immune cells in the intestinal microenvironment, including macrophages, dendritic cells, T cells, and natural immune cells^[6, 54, 97]. A recent study found that IA has anti-inflammatory and antioxidant effects in LPS-activated human peripheral blood mononuclear cells, mainly by reducing the secretion of IL-6 and IL-1β^[69]. ILA has the potential to modulate intestinal homeostasis by regulating epithelial-macrophage interactions, and ILA derived from *E. coli*-reduced the susceptibility of mice to sodium dextran sulfate-induced colitis^[98]. ILA

or I3C, produced by *L. reuteri* metabolizing Trp, can not only be reprogrammed into immunoregulatory T cells through intraepithelial CD4⁺ T cells to regulate the inflammatory response but also stimulate the secretion of IL-22 by intestinal organoids and laminae propria lymphocytes through AhR to regulate intestinal inflammation^[59, 97]. Li et al. found that the proportion of Tregs in intestinal tissue increased significantly after IAA administration, suggesting that IAA improves colitis by influencing Tregs to regulate intestinal immunity^[99]. Supplementation of *Lactobacillus acidophilus* or its metabolite ILA in cesarean section offspring reduced intestinal inflammation and restored group 3 innate lymphoid cell frequency and IL-22 levels^[55]. Therefore, as shown in Figure 3, indole derivative treatment acts outside epithelial cells and can also maintain intestinal homeostasis by acting on a variety of immune cells.

3.5 Indole derivatives and gut microbiota

The balance of intestinal flora and the stability of the intestinal mucosal barrier system is the basis of intestinal physiological functions. A large number of microorganisms exist in the intestine, which help maintain a favorable intestinal environment, and their physiological functions have become an indispensable part of the host's physiological functions, playing an active role in the anabolism and catabolic metabolism of substances^[100]. Furthermore, they prevent the invasion of foreign bacteria and stimulate the establishment, improvement, and maintenance of the immune function of the organism^[101-102]. However, when intestinal microorganisms are subjected to dietary factor or pharmacological stresses, their function can be severely compromised, inducing disturbances in intestinal metabolism, increasing pathogen invasion, and increasing the risk of diseases such as inflammation, diabetes, obesity, and metabolic syndrome. Once the balance of the intestinal microbiota is disturbed, conditionally pathogenic intestinal bacteria begin to harm the organism, which in turn causes a series of inflammatory responses due to a compromised intestinal mucosal barrier^[103-104].

Small molecule active substances produced by intestinal microbial metabolism can, in turn, regulate intestinal microbial composition^[82, 105-107]. In recent years, it has been found that supplementation of Fu brick tea, Fu brick tea theabrownin, turmeric powder, black rice and β -glucan can promote the growth of beneficial microorganisms *Lactobacillus*, *Bifidobacterium* or *Bacteroides uniformis* by adjusting intestinal microorganisms, and improve the level of microbial Trp metabolites I3C, IAA, IPA or ILA^[87-88, 108-110]. However, in addition to maintaining the integrity of the intestinal mucosal barrier by regulating the immune barrier, mucus barrier and mechanical barrier, it has been found that indole derivatives can also maintain intestinal homeostasis by adjusting the composition of intestinal microbes^[99, 111-112]. Indole as an intercellular signaling molecule that plays an important role in microbial communities by influencing spore formation, plasmid stability, drug resistance, biofilm formation, and virulence^[113-114]. The pathogenesis of bacteria involves complex mechanisms, and understanding the multifactorial nature of bacterial infections is critical to developing effective interventions^[115]. Indole and its indole derivatives modulate the expression of the number of enteric bacterial virulence factors, and indoles being used as ToxR agonists to modulate *Vibrio cholerae* virulence in intestinal gene expression and biofilm production^[115-116]. Additionally, indole, IAA also

down-regulates virulence production in pathogenic *E. coli*^[116]. IAA can effectively inhibit the formation and virulence of *Pseudomonas aeruginosa* biofilm^[117]. ILA has been reported to have antimicrobial activity against *Penicillium*, *E. coli*, *Salmonella* spp., *Staphylococcus* spp., *Listeria monocytogenes* and *Bacillus cereus*^[22, 107, 118].

Indole derivatives can not only regulate the intestinal flora by regulating the expression of virulence genes of intestinal pathogens and by altering the physiological functions of the pathogenic bacteria, but also they can also modulate intestinal flora by increasing the abundance of beneficial flora and decreasing the abundance of harmful ones^[10]. The I3C has the ability to modulate gut flora and inhibit *Candida albicans* colonization^[17, 81]. IPA was found to modulate intestinal microbiota composition and inhibit microbial ecological dysbiosis in rats fed a high-fat diet^[119]. IAA can not only enhance the intestinal health of the host by inhibiting the proliferation of *Salmonella typhimurium*, but also further maintain intestinal homeostasis by adjusting the composition of intestinal microorganisms^[112]. In summary, indole and its indole derivatives play a key role in inhibiting the colonization of harmful microorganisms and regulating the composition of intestinal microorganisms. Therefore, the mechanism and characteristics of indole and its indole derivatives inhibiting harmful organisms and regulating intestinal microorganisms can be further explored in future studies, so as to provide a means to treat infections and other diseases caused by pathogenic microorganisms by targeting the growth inhibition of pathogenic microorganisms.

4. Indole derivatives and AhR

Indole derivatives maintain the integrity of intestinal mucosal barrier function by regulating chemical barrier, mechanical barrier, immune barrier and intestinal microorganism. We further summarized the mechanism of indole derivatives enhancing intestinal mucosal barrier function. AhR is a ligand-dependent transcription factor widely expressed in immune cells, epithelial cells, endothelial cells, and stromal cells, and is a key regulator of immunity and inflammation, playing a critical role in adaptive immunity, mucosal barrier function, and maintenance of intestinal homeostasis^[5, 120]. AhR activation prevents chemically induced impairment of barrier integrity and cytokine expression in Caco-2/TC7 cells via the protein kinase C and p38 signaling pathways^[121]. 6-formylindolo (3, 2-b) carbazole (Ficz) is recognized as the most potent ligand for the AhR, and Ficz, by activating the AhR, can increase MUC2 expression and the number of goblet cells, and reduce bacterial infiltration in order to ameliorate DSS-induced colitis^[93]. In addition, Ficz also ameliorates colonic inflammation, reduces IL-6 and claudin-2 expression, and maintains intestinal mucosal barrier function through activation of AhR in a DSS-induced colitis mouse model^[122].

IPA regulates intestinal immune homeostasis by activating AhR to significantly induce the IL-10 receptor ligand-binding subunit on intestinal epithelial cells^[123]. It has been reported that ILA produced by *B. infantis* activates the intestinal epithelial AhR signaling pathway by increasing its nuclear localization and upregulating cytochrome P450, family 1, subfamily A, polypeptide 1 (Cyp1a1) protein expression^[52]. IL-22 is a key regulator of epithelial homeostasis that protects the host from inflammatory damage, and its primary function in the gut is to maintain intestinal epithelial integrity and improve defense mechanisms against

bacterial pathogens^[124]. IL-22 has been implicated in multiple aspects of epithelial barrier function, including regulation of epithelial cell growth and permeability, mucus and antimicrobial protein production^[125]. Indole derivatives induce IL-22 through AhR, which promotes stem cell-mediated epithelial barrier repair and prevents infection and damage caused by a high inflammatory response^[92]. *Salmonella typhimurium* can cause severe foodborne illness, but the ILA produced by *Bacillus velezensis* JT3-1 was found to contribute to the protection of mice against gastrointestinal infections induced by *Salmonella typhimurium* through activation of the AhR/IL-22 pathway^[126].

4.1 AhR interactions with Nrf2/NF- κ B

The AhR, Nrf2, and NF- κ B are crucial intracellular transcription regulators that play pivotal roles in maintaining cellular homeostasis, responding to exogenous stimuli, and in the onset and progression of disease. In the latest study, it was found that activation of the AhR signaling pathway can further promote the activation of the Nrf2 signaling pathway, and inhibit the activation of NF- κ B and NLRP3 inflammasome signaling pathways, playing a role in the regulation of the inflammatory response and improving intestinal mucosal barrier function (Figure 4)^[20, 50, 127].

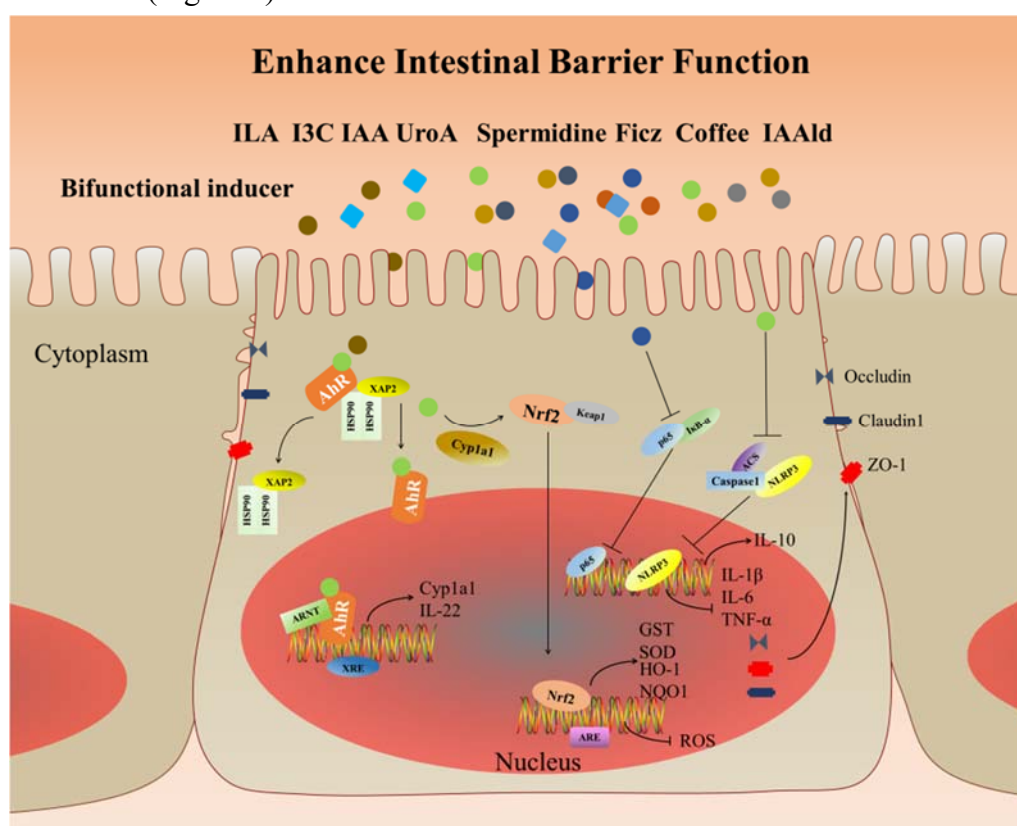


Fig. 4. Mechanisms by which some bifunctional inducers enhance intestinal mucosal barrier function. Aryl hydrocarbon receptor (AhR) and nuclear factor erythroid 2-related factor 2 (Nrf2) are two signaling pathways related to gastrointestinal cell metabolism, and they have certain regulatory roles in intestinal inflammation and oxidative stress-related responses.

There is an interdependent relationship between the two pathways, and some bi-functional inducers can simultaneously activate the AhR and Nrf2 signaling pathways, encoding downstream cytochrome P450, family 1, subfamily A, polypeptide 1 (Cyp1a1), interleukin (IL)-22, heme oxygenase 1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO1), glutathione S-transferases (GST), superoxide dismutase (SOD), respectively, to enhance intestinal mucosal barrier function. In addition, these bifunctional inducers can also inhibit the activation of nuclear factor kappa-B (NF- κ B) and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) Inflammasome signaling pathways, and alleviate intestinal inflammation and oxidative stress.

4.1.1 The interaction mechanism between AhR and Nrf2

In addition to playing an important role in maintaining intracellular oxidation balance and resisting damage from oxidative stress, the Nrf2 signaling pathway also plays an important role in stabilizing intestinal homeostasis and maintaining intestinal mucosal barrier integrity^[49, 128]. In several studies, it has been found that some bifunctional inducers act to improve intestinal mucosal barrier function and inhibit inflammation by activating the AhR and Nrf2 signaling pathways through a two-pronged mechanism^[129]. The molecular basis for this dual functionality lies in the multi layered crosstalk between the AhR and Nrf2 pathways. Direct transcriptional regulation occurs through reciprocal promoter binding: AhR can bind to xenobiotic-response-element (XRE)-like sequences in the Nrf2 gene promoter, thereby up-regulating Nrf2 transcription^[130]. Conversely, Nrf2 may enhance AhR expression via antioxidant-response-element (ARE)-mediated mechanisms, establishing a positive feedback loop^[127]. Indirect crosstalk is also prominent; for instance, AhR activation induces cytochrome P450 (CYP) enzymes, whose metabolic products can generate mild oxidative stress that modifies Keap1, leading to Nrf2 stabilization and nuclear translocation^[131]. Meanwhile, Nrf2-driven antioxidant defenses help maintain AhR protein stability by reducing oxidative inactivation, further reinforcing pathway synergy. Bifunctional inducers are compounds that can activate both phase I and phase II metabolic pathways, in particular the AhR/XRE and Nrf2/ARE pathways^[132]. A variety of bifunctional inducers have been reported, such as xanthones, spermidine, coffee, and urolithin A(UroA), ILA, IAAld, Ficiz and IAA^[20, 123, 125, 133-135]. In our previous study, we found that the Trp metabolite ILA of *L. plantarum* DPUL-S164 activates the Nrf2 signaling pathway in intestinal epithelial cells, and that promotion of tight junction proteins is dependent on AhR expression^[20]. Furthermore, it has been found that the ILA produced by *B. bifidum* can enhance intestinal mucosal barrier function and alleviate intestinal inflammation by promoting the activation of the AhR-Nrf2 signaling pathway and inhibiting the NLRP3 inflammasome signaling pathway^[50].

4.1.2 The interaction mechanism between AhR and NF- κ B

The AhR and NF- κ B signaling pathways exhibit intricate and multi-layered interactions, with AhR primarily inhibiting NF- κ B through transcriptional regulation and signal interference. Upon activation, AhR directly competes for binding to the promoter regions of NF- κ B target genes, thereby suppressing their transcriptional activity. Research indicates that coptisine, as a potent AhR agonist, can dose-dependently inhibit TNF- α -induced ROS production and NF- κ B activation in HT-29 cells by promoting Cyp1a1 nuclear translocation and transcriptional activation^[136]. Conversely, AhR knockdown abrogated berberine's suppression of NF- κ B and barrier protective effects, unequivocally confirming AhR pathway dependency for this effect^[136]. Alternatively, AhR activation may suppress pro-inflammatory phenotype conversion in macrophages by regulating their metabolism and polarization, thereby inhibiting the NF- κ B pathway^[137]. Furthermore, AhR can induce the production of anti-inflammatory cytokines (such as IL-10), indirectly suppressing NF- κ B mediated inflammatory responses^[138-139]. These mechanisms not only deepen our

understanding of the balance mechanisms governing intestinal and systemic inflammation but also provide crucial theoretical foundations for targeting the AhR-NF- κ B axis in the treatment of metabolic and inflammatory diseases.

5. Clinical research case

Occurrence or development of a variety of diseases is related to impaired intestinal mucosal barrier function or the phenomenon of intestinal leakage. Recent studies have elucidated the potential mechanisms of atorvastatin in colon cancer intervention and its association with gut microbial metabolites. Studies indicate that following atorvastatin intervention in colon cancer mice, it enhances the availability of tryptophan to gut microbiota by suppressing the expression of indoleamine 2,3-dioxygenase 1^[49]. This subsequently promotes an increase in *Lactobacillus* abundance and significantly enriches IAA. And a corresponding marked elevation in IAA levels was also observed in colorectal cancer patients undergoing atorvastatin intervention^[49]. Further clinical studies employing metagenomic sequencing and targeted tryptophan metabolomics analysis revealed abnormal levels of ILA in colorectal cancer patients, with this abnormality correlating with tumor progression^[140]. And, *in vitro* experiments have demonstrated that ILA can inhibit tumor cell proliferation and migration while diminishing their anti-apoptotic capacity^[140]. Moreover, multiple clinical data indicate that levels of other indole derivatives, such as IA and IPA, are also generally lower in patients with colorectal cancer and inflammatory bowel disease compared to healthy individuals^[141-142]. This evidence collectively indicates that reduced levels of indole derivatives may be closely associated with the onset and progression of intestinal diseases.

In recent years, extensive clinical research has demonstrated that diminished levels of indole derivatives are closely associated with psychiatric disorders such as cognitive impairment and depression. In patients with mild cognitive impairment and AZM, serum IPA levels are lower than in healthy controls and show a significant positive correlation with cognitive scores. Animal models further confirm that IPA can cross the blood-brain barrier, exert anti-inflammatory effects, and inhibit β -amyloid deposition, revealing neuroprotective potential^[143]. Moreover, ILA levels are generally reduced in AZM patients. Administration of a synbiotic formulation comprising *Lactobacillus suilingensis* and inulin to mice significantly improved cognitive function in female AZM model mice. This effect was achieved by enhancing tryptophan metabolism, promoting ILA biosynthesis, activating the AhR signaling pathway, suppressing neuroinflammation, and reducing β -amyloid deposition^[144]. Among patients experiencing depression and anxiety triggered by methamphetamine addiction, serum levels of indole derivatives are similarly markedly reduced. Animal studies further indicate that gut microbiota and disrupted tryptophan metabolism play a pivotal role in the development of such psychiatric symptoms^[145]. Similarly, abnormalities in the metabolism of indole and its derivatives are also commonly observed in patients with chronic disease-related cognitive impairment and clinical depression^[146-147]. These findings suggest that targeting the regulation of the gut microbiota-tryptophan metabolism axis may offer novel intervention strategies for the prevention and treatment of psychiatric disorders.

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the most prevalent chronic liver diseases, its development being closely associated with metabolites derived from the gut microbiota. Clinical studies indicate that levels of both IPA and IAA in the feces of patients with hepatic steatosis are lower than those observed in healthy controls^[137]. In animal models of diet-induced MAFLD, supplementation with IPA and IAA effectively reduces endotoxin levels and suppresses macrophage activity, thereby improving hepatic steatosis and inflammation. This suggests that these two microbial metabolites hold potential for the prevention or treatment of MAFLD^[137]. Beyond hepatic disorders, multiple clinical studies further indicate that metabolic abnormalities in indole derivatives are also implicated in various pathological processes, including atherosclerosis, ageing-related phenotypes, and high myopia. Plasma I3C levels are markedly reduced in patients with atherosclerosis; metagenomic analysis in mouse models reveals this alteration is closely associated with decreased abundance of the Bacteroidetes and Lactobacillaceae families within the gut microbiota^[148]. Recent ageing research reveals that the abundance of *Lactobacillus* species is generally reduced in ageing intestines, with a significant decrease in the key tryptophan metabolite IAA. Multi-omics analysis identified *Lactobacillus salivarius* as a key strain, which converts tryptophan into IAA via its unique aldehyde dehydrogenase. Animal studies confirmed that the anti-aging effect of IAA in the gut depend on the AhR-poly (ADP-ribose) polymerase 1 (PARP1) signaling axis^[149]. Furthermore, markedly reduced plasma IAA levels were observed in patients with high myopia, with this decrease negatively correlated with reduced *Akkermansia* abundance and myopia severity^[150].

In summary, intestinal microbial tryptophan metabolites play a crucial regulatory role across multiple systemic diseases. Future research may further focus on the signaling pathways of key indole metabolites, their causal associations with specific bacterial strains, and the translational potential of intervening in relevant metabolic pathways through dietary, probiotic, or metabolite supplementation.

6. Perspectives

Taken together, the available evidence suggests that indole metabolites play a key role in intestinal immunomodulation and homeostasis maintenance. The gut microbiota generates a series of bioactive indole derivatives through the tryptophan metabolic pathway. These molecules not only directly participate in host signaling but, more significantly, form a cascade transformation relationship of metabolic division of labor and cooperation among different microbial communities within the complex gut microbiome network. This entails certain microbial communities utilizing intermediate products produced by other microorganisms to further synthesize or modify them into final products with diverse functions. Jia et al.^[23] found that the ILA produced by *Lactobacillus johnsonii* was used by *Clostridium sporogenes* further converted to IPA. This discovery not only reveals the complexity of material transfer between microorganisms from the perspective of metabolic interactions, but also suggests that intestinal indole metabolism constitutes a dynamic, interconnected network whose overall output function depends upon the structural and functional equilibrium of the microbiota. Consequently, systematically deciphering the dynamic interaction mechanisms between the microbiome-tryptophan metabolic axis-host physiology axis and its dysregulation characteristics under

pathological conditions has become a central scientific proposition in research on gut microbiome-host interactions.

Indole derivatives, as potentially pharmacologically active compounds, have not received sufficient attention for their application in the prevention and treatment of intestinal mucosal barrier dysfunction. In contrast, probiotics have received widespread attention for their modulatory effects on intestinal mucosal barrier function. It is worth noting that the probiotic strains that produce high levels of indole derivatives may play a synergistic protective role in maintaining the homeostasis of the intestinal mucosal barrier through the tryptophan-indole metabolic axis. In addition, in recent years, it has been found that supplementation with β -glucan, Fubrick tea theabrownin, black rice, turmeric powder and dietary fibre can maintain the integrity of the intestinal mucosal barrier by adjusting the abundance of beneficial microorganisms and metabolizing Trp to produce indole derivatives. These findings collectively point to a cross-level regulatory network, namely the nutrient-microbiota-metabolite interaction system.

Based on the above understanding, future research should focus on systematically constructing and analyzing this interaction network, concentrating on the following scientific questions: 1) how specific nutrients or dietary patterns selectively promote the growth and metabolic activity of indole-producing bacterial strains, and whether the molecular mechanisms involve regulation of bacterial surface receptors, signaling pathways, or quorum sensing systems; 2) how key enzymes and metabolic nodes in the microbial tryptophan metabolic pathway are regulated by the nutritional environment, including substrate availability, co-metabolic factors, and dynamic regulation of local physicochemical conditions within the gut; and 3) what is the structure-activity relationship between the chemical properties (including polarity, receptor affinity, membrane permeability, etc.) of indole derivatives with different structures (such as ILA, IPA, IAA, etc.) and their functions in maintaining intestinal barrier integrity, regulating immune responses, and providing antioxidant effects? To thoroughly investigate the aforementioned issues, it is necessary to integrate multi-omics technologies (microbiome, metabolome, transcriptome) with nutritional intervention experiments. This approach should incorporate in vitro co-culture models, organoids, and animal models to construct a predictive nutritional-microbiome interaction network. This framework will facilitate the establishment of precision nutrition strategies grounded in microbiome function. It will enable the targeted enrichment of functional microbial communities through specific dietary components, thereby optimizing the output spectrum of their beneficial metabolic products. Furthermore, by employing synthetic biology techniques to engineer probiotics or commensal bacteria in conjunction with microbiota transplantation technology, it is anticipated that next-generation microbial therapies capable of stably and controllably producing specific indole derivatives may be developed. Such functionally defined living biological drug formulations could complement dietary interventions, thereby generating synergistic effects.

Therefore, from the perspective of host-microbiota co-metabolism, systematically designing combined nutritional-microbiota interventions targeting intestinal mucosal barrier function not only deepens our understanding of mechanisms underpinning gut homeostasis, but may also offer innovative preventive and

therapeutic approaches for diseases closely linked to barrier impairment, such as inflammatory bowel disease and metabolic syndrome. This interdisciplinary research direction will propel microbiome therapy towards precision, functionalization, and personalization.

7. Conclusion

In summary, this review highlights the central role of gut microbiota-derived tryptophan metabolites—particularly indole derivatives—in the maintenance and regulation of intestinal mucosal barrier function. These metabolites, produced through species-specific enzymatic pathways in bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Clostridium*, function as key AhR ligands. Through AhR activation, they enhance epithelial barrier integrity by upregulating tight junction proteins, stimulating mucus secretion, and modulating immune responses, thereby upholding intestinal homeostasis. Furthermore, clinical and preclinical evidence links altered levels of indole metabolites to various gastrointestinal, metabolic, and even neuropsychiatric disorders, underscoring their systemic relevance. Future research should focus on elucidating the precise microbial enzymes involved, the diet - microbiota - metabolite axis, and the potential of targeted nutritional or probiotic interventions to restore indole-mediated barrier function. Ultimately, harnessing microbial tryptophan metabolism offers a promising avenue for developing novel therapies for barrier-related diseases, including inflammatory bowel disease, metabolic syndrome, and beyond.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

Data availability is not applicable to this paper.

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