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Original Research Article

# Tryptophan metabolism and piglet diarrhea: Where we stand and the challenges ahead

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ABSTRACT

The intestinal architecture of piglets is vulnerable to disruption during weaning transition and leads to diarrhea, frequently accompanied by inflammation and metabolic disturbances (including amino acid metabolism). Tryptophan (Trp) plays an essential role in orchestrating intestinal immune tolerance through its metabolism via the kynurenine, 5-hydroxytryptamine, or indole pathways, which could be dictated by the gut microbiota either directly or indirectly. Emerging evidence suggests a strong association between piglet diarrhea and Trp metabolism. Here we aim to summarize the intricate balance of microbiota–host crosstalk by analyzing alterations in both the host and microbial pathways of Trp and discuss how Trp metabolism may affect piglet diarrhea. Overall, this review could provide valuable insights to explore effective strategies for managing piglet diarrhea and the related challenges.


## 1. Introduction

Early weaning in swine production has garnered widespread adoption due to its potential to expedite the pig slaughter cycle and enhance sows' reproductive efficiency (Campbell et al., 2013). However, pigs confront an array of biological stressors spanning physiological, environmental, and social challenges upon separation from the sows. It is imperative to recognize that the stress induced by early weaning can give rise to unfavorable outcomes, particularly concerning piglets, as compromised intestinal health results in diarrhea and amplifies mortality rates (Zhao et al., 2020). Throughout the weaning process, the intestinal microbiota coexisting in the gut responds to environmental and lifestyle stimuli within short timescales, ranging from hours to days. The intestinal microbiota, composed of myriad microbes facilitating host health, provides colonization resistance against gastrointestinal disorders (Chen et al., 2020; Fassarella et al., 2020). Due to underdeveloped gastrointestinal systems and limited immunity, weaned piglets are more susceptible to the external environment and are more prone to pathogens (Meng et al., 2020). Consequently, their susceptibility to intestinal infection and frequent intestinal diseases is heightened, contributing to elevated morbidity, and mortality rates, primarily through diarrhea.

Disruptions in host–microbiota crosstalk reinforce disease development. Diet and nutrients profoundly impact intestinal microbiota composition, localization, and their interaction with host immunological pathways (Tilocca et al., 2017; Fan et al., 2023). Tryptophan (Trp) is an essential amino acid that serves as the precursor for synthesizing multiple pivotal bioactive compounds (Xue et al., 2023b). Trp and its metabolites play roles in pathophysiological processes, including metabolism, inflammatory responses, immune responses, and intestinal equilibrium. It should be noted that Trp is primarily metabolized through three pathways: the kynurenine (KYN) pathway, the 5-hydroxytryptamine (5-HT) pathway, and the indole pathway (Fan et al., 2023). The KYN pathway is the predominant metabolic route for Trp, with over 95%

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of Trp converted into an array of bioactive compounds (Vecsei et al., 2013), and the indoleamine 2,3-dioxygenase (IDO) subset of the KYN pathway has long been acknowledged to contribute substantially to the control of general inflammation (Mellor and Munn, 2003). The 5-HT pathway is involved in various physiological processes throughout the body. Notably, gut microbes can directly convert Trp into various molecules, such as indole and its derivatives, which maintain intestinal homeostasis by regulating inflammatory responses.

Growing evidence suggests the dysregulation of Trp metabolism plays a role in disease pathogenesis of swine production. In this article, we provide a contemporary overview of how Trp metabolism interfaces with microbiota–host crosstalk, specifically focusing on its implications for heightened diarrhea morbidity in weaning piglets. Beyond the direct conversion of Trp into bioactive molecules by the gut microbiota, we delve into how the gut microbiota regulates host Trp metabolism. Thus, gaining insight into these interactions could reveal novel targets for addressing gut-related disorders during the weaning transition.

## 2. Trp metabolism: pathways and physiology

Trp consists of a carbon bonded to an indole group in the third position. There are two Trp metabolic pathways: one for synthesizing tissue proteins, and the other for undergoing metabolic decomposition or conversion into other functional molecules. Trp is not autonomously synthesized in animals, which therefore need to rely on exogenous sources-primarily the diet (Agus et al., 2018). In addition to synthesizing tissue proteins, the metabolites of Trp play a crucial role in the regulation of physiological processes. For example, disease progression is influenced by the KYN pathway, 5-HT pathway, and indole pathway, which regulate inflammation, immune cell activity and the structure and functionality of epithelial cells (Zelante et al., 2013; Xue et al., 2023a).

### 2.1. Trp metabolism via the KYN pathway

The KYN pathway is governed by two rate-limiting enzymes, including Trp 2,3-dioxygenase (TDO) (mainly present in the liver) and (IDO1/2) (which participate in metabolizing Trp through the KYN pathway in the intestine). In comparison to IDO1, IDO2 exhibits significantly lower enzymatic efficiency. Therefore, it is believed that IDO2 may act as a negative regulator of IDO1 through a competitive mechanism. IDO can be regulated by pro-inflammatory cytokines (Bigelman et al., 2023) and bacterial lipopolysaccharides (Koopmans et al., 2006). Proinflammatory mediators like interferon-gamma (IFN-$\gamma$), interleukin-2 (IL-2), and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) upregulate the expression of *IDO* in intestinal epithelial cells upon exposure to intense immunological activation and inflammatory damage (Haq et al., 2021). Through IDO and TDO, Trp is swiftly converted to KYN. The stimulation of various enzymes leads to the formation of relevant metabolic branches, resulting in the production of kynurenic acid (KYNA), 3-hydroxyanthranilic acid (3-HAA), quinolinic acid (QA) and $NAD^+$ (Fig. 1). In the KYN pathway, Trp plays a complex regulatory role in the immune system through the production of metabolites such as KYN and $NAD^+$ which regulate immune cell metabolism (Minhas et al., 2019). Some metabolites, such as KYN, KYNA, and xanthurenic acid have been proven to act as aryl hydrocarbon receptor (AhR) ligands with the capacity to stimulate AhR-dependent gene expression (Romani et al., 2014).

### 2.2. Trp metabolism via the 5-HT pathway

Roughly 1% to 2% of the ingested Trp undergoes conversion to 5-HT and melatonin through the 5-HT pathway (Gao et al., 2018; Roager and Licht, 2018). The gastrointestinal tract is the primary site of 5-HT production (Daubert and Condron, 2010). Trp is enzymatically converted by Trp hydroxylase to produce 5-hydroxytryptophan (5-HTP), which is subsequently decarboxylated to form 5-HT. Further conversion of 5-HT can yield melatonin, which plays a crucial role in immune regulation (Chen et al., 2011; Xia et al., 2019). 5-HT binds to receptors (5-HTR) in the intestine to regulate intestinal motility and endocrine activity (Fig. 1). The 5-HT pathway regulates the gut–brain axis and intestinal homeostasis by triggering numerous functions in the gastrointestinal tract (Watts et al., 2012). Specifically, metabolites such as 5-HT are an important gastrointestinal signaling molecule that conveys signals from the gut to neurons and influences intestinal peristalsis, secretion, and the absorption of nutrients (Chen et al., 2011; Muller et al., 2016).

### 2.3. Trp metabolism via indole pathway

Approximately 4% to 6% of Trp undergoes conversion by gut microbiota, yielding various indole derivatives, including indole, indole acetaldehyde (IAM), indole acrylic acid (IA), indole acetic acid (IAA), indole-3 aldehyde (IAld), tryptamine (TAM), indole pyruvate (IPYA), indole lactic acid (ILA), and indole-3 propionic acid (IPA) (Fig. 1). *Clostridium* and *Lactobacillus* have been demonstrated to convert Trp into IPYA; and under the action of Trp enzymes in *Bacteroides*, *Escherichia coli*, and *Clostridium*, they are catalyzed to produce indole (Roager and Licht, 2018). *Clostridium* and *Ruminococcus* can decarboxylate Trp to TAM, while *Lactobacillus* can metabolize Trp to indole-3-formaldehyde, and *Bifidobacterium* can convert Trp to IAA. Within the biological system, the activity of a pathway depends on both Trp content in the diet and whether the corresponding metabolic enzyme system is present in the gut microbiota. Different microbes have distinct enzymes, which necessitates collaborative interactions between multiple microbes to generate particular indole derivatives from Trp (Gao et al., 2018). Some indole derivatives can bind to AhR on the surface of intestinal cells, leading to cytokine release, including interleukin-6 (IL-6), interleukin-17 (IL-17), and interleukin-22 (IL-22), which further regulate intestinal mucosal immunity, intestinal barrier, and intestinal homeostasis (Wei et al., 2021).

### 2.4. Gut microbiota regulation of Trp metabolism

Intestinal microbiota plays a central role in maintaining metabolic homeostasis. Trp metabolites are crucial mediators facilitating communication between the host and the microbiota. The rate at which circulating Trp is utilized by the host is contingent upon the delicate balance between bacterial Trp metabolism and Trp production. As previously outlined, the microbiota significantly influences the indole pathway. Genus carrying the *TAM* gene can metabolize Trp into indole and its derivatives, and these metabolites can be used as ligands of AhR and retinoid-related orphan receptor $\gamma$t (ROR$\gamma$t), thus regulating intestinal homeostasis (Wyatt and Greathouse, 2021). Furthermore, their regulatory roles in the 5-HT pathway have been substantiated in germ-free mice, presenting impaired 5-HT production, particularly in the colon, consequently leading to lower 5-HT concentrations in the blood (Yano et al., 2015). Moreover, compelling evidence supports the pivotal role of the intestinal microbiota in stimulating IDO1 activity. This

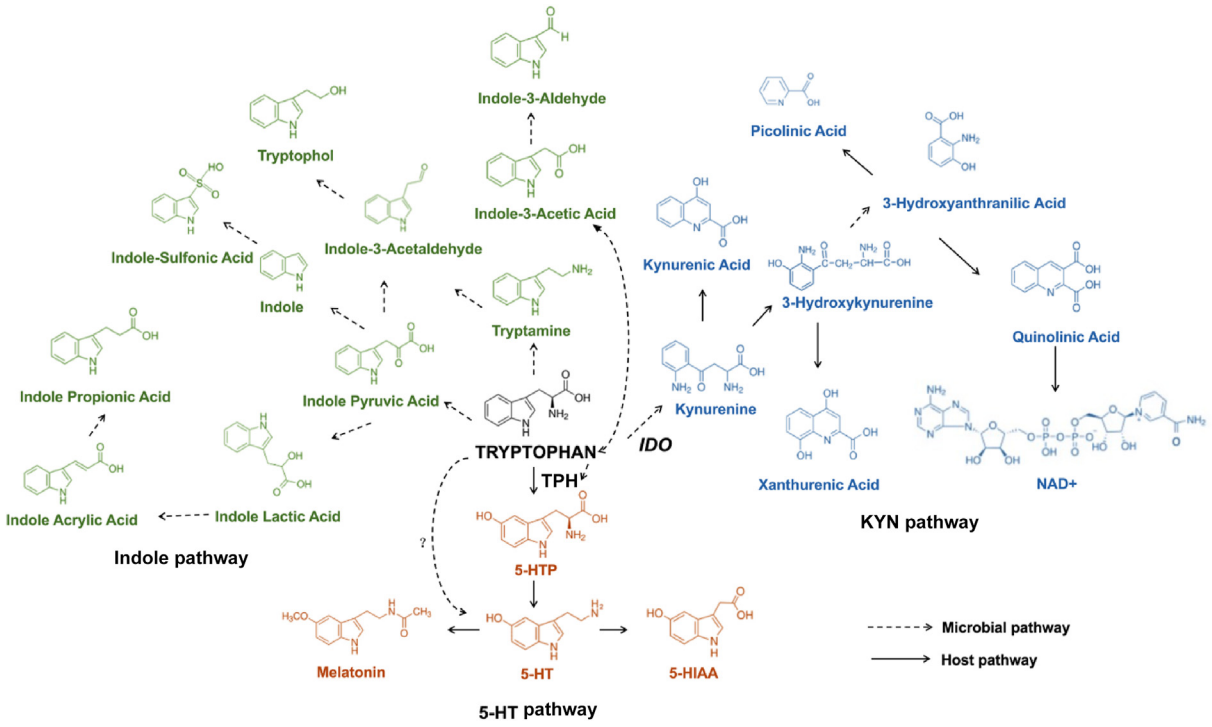


**Fig. 1.** Pathways of Trp metabolism through the 5-HT, KYN, and indole pathways. 5-HIAA = 5-hydroxyindole acetic acid; 5-HT = 5-hydroxytryptamine; KYN = kynurenine; 5-HTP = 5-hydroxytryptophan; IDO = indoleamine 2,3-dioxygenase; TPH = Trp hydroxylase.

stimulation results in the inhibition of the KYN pathway and a subsequent reduction in Trp levels, a phenomenon notably observed in germ-free mice. Trp metabolism through the KYN pathway is notably augmented following supplementation with intestinal microbiota. Several studies have illuminated the relationship between Toll-like receptors (TLR) and metabolic alterations in the KYN pathway (Clarke et al., 2012; Fila et al., 2021). Changes in the intestinal microbiota composition can trigger abnormal TLR activation, thus augmenting the KYN pathway. In addition, certain gut microbes possess enzymes homologous to those in the KYN pathway, enabling them to produce KYN and downstream metabolites (Agus et al., 2018). In turn, the modulation of host Trp levels in the microenvironment is believed to involve the arrest of microbial proliferation, which significantly benefits the host. Interestingly, Trp supplementation in piglets can improve gut microbiota diversity, decrease conditional pathogens, and increase Trp-metabolizing bacteria (such as *Lactobacillus*) (Liang et al., 2018, 2019).

## 3. Piglet diarrhea

Diarrhea is a significant and increasing cause of mortality among weaned piglets, inflicting substantial economic losses on swine farming. The occurrence of diarrhea in piglets is a complex interplay involving invasion by foreign pathogens, diet alterations, and separation stress (Vogt and Finlay, 2017; Gao et al., 2019). The intestine, which is the principal organ for digestion and absorption in pigs, is often the frontline in dealing with the challenges imposed by diarrhea. These challenges manifest as disturbances in intestinal barrier function, mucus secretion, the mucosal immune system, and the intestinal microbiota (Xie et al., 2019). Once the epithelial barrier is damaged, the vulnerability to pathogen invasion escalates, ultimately leading to intestinal inflammation and diarrhea.

### 3.1. Diarrhea induces intestinal injury

In terms of physiological structure, intestinal villi play a vital role as the initial line of defense since they have direct and prolonged contact with the luminal contents of the intestine, thereby increasing the susceptibility to pathogen invasion (Jayaraman et al., 2013; Bai et al., 2023). Studies have shown that diarrhea can lead to an increase in crypt depth (CD) and a decrease in villus height, along with alterations in the relative weight of the intestine. These changes in intestinal morphology indicate the impact of diarrhea on the structure and health of the pig intestine.

The intestinal barrier, crucial for gut health, is comprised of the epithelial layer and mucus. The epithelium consists of various cell types like enterocytes, goblet cells, paneth cells, and enteroendocrine cells, each with specific functions contributing to nutrient absorption, mucus secretion, antimicrobial peptide production, and hormone secretion respectively (Yu et al., 2018). These cells are tightly bound to each other with tight junctions, gap junctions, adherent junctions, and desmosomes, forming a selective and semipermeable barrier. Weaning, a pivotal event for piglets, can impair this physical barrier, disrupting tight junctions and increasing intestinal permeability (Wang et al., 2020). Decreased expression of critical tight junction proteins like claudin-1, occludin, and zona occludens-1 (ZO-1) is a hallmark of intestinal barrier injury. Elevated intestinal permeability allows pathogens, endotoxins, and other antigens to breach the intestinal mucosal barrier, ultimately causing intestinal ailments like diarrhea and enteritis (Deng et al., 2022). Mucins (MUC) and antimicrobial proteins form the mucus layer, secreted by goblet cells and epithelial cells, respectively. As the chemical barrier, the mucus layer can effectively impede the invasion of microbial pathogens, contributing to maintaining intestinal homeostasis (Tang et al., 2022). In contrast, MUC2 forms the bulk of the mucus needed to function properly. Piglet diarrhea causes the destruction of the mucus layer, impairs

the intestinal microenvironment, and further destroys intestinal barrier integrity, leading to inflammation (Xia et al., 2022). Moreover, a decrease in the number of goblet cells results in decreased MUC secretion, and the mucus layer becomes thin, which contributes to pathogens passing by the mucus layer to disrupt the chemical barrier while accelerating the damage to the physical barrier, mucosal immune barrier, and microbial barrier (Tang et al., 2022). These alterations in physical and chemical barriers are critical features of intestinal barrier injury and contribute to piglet gastrointestinal disorders.

The mucosal immune system, a complex but orderly local immune system, can provide protection against over 90% of intestinal pathogens, mainly composed of immune organs, immune cells, and immune molecules (Yang et al., 2022b). Immune cells in the intestine may recognize either intestinal autoantigens or foreign antigens via pattern recognition receptors (PRR), including nucleotide-binding oligomerization domain (NOD) like receptors and TLR (Wang et al., 2019b). Pattern recognition receptors can directly regulate numerous inflammatory pathways, such as peroxisome proliferator-activated receptor-γ (PPAR-γ), mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF-κB), which enhance immunocompetence and alleviate damage. Weaning stress activates the intestinal immune system to contribute to the production of proinflammatory cytokines, which accelerate intestinal damage and dysfunction and lead to diarrhea (Tang et al., 2022). These immune factors include TNF-α, IFN-γ, interleukin-1β (IL-1β), IL-6, interleukin-8 (IL-8), and secretory immunoglobulin A (sIgA). Diarrhea can promote colonic inflammatory responses by activating recombinant myeloid differentiation factor 88 (MyD88)-dependent TLR4 signaling in pig macrophages (Zhou et al., 2022). Moreover, the increased T cell count and matrix metalloproteinase indicate the onset of intestinal inflammation and the decreased $CD4^+/CD8^+$ T lymphocyte ratio (Tang et al., 2022). These immune responses underscore the intricate interplay between the mucosal immune system and gut health, particularly in the context of diarrhea and its associated inflammation.

### 3.2. Changes of intestinal microbiota in diarrheal piglets

The intestinal microbiota of pigs presents obvious dynamic changes in composition and diversity over time after birth. Piglets are born with a sterile environment in the intestine, and the microbes start colonizing after birth (such as *E. coli* and *Streptococcus* spp.) (Luo et al., 2022). Within two days after birth, facultative anaerobes, obligate anaerobes, and aerobic bacteria gradually colonize the gastrointestinal tract, which is associated with the vaginal microbiota, breast milk and the living environment (Beaumont et al., 2020; Teng et al., 2020). Weaning is considered one of the most critical periods in pig production; it triggers remodeling in the intestinal microbiota and tends to be stable at the late stage (Beaumont et al., 2020; Luo et al., 2022). The feed of piglets is switched from liquid milk toward solid-based feed after weaning, while the immature gastrointestinal tract fails to adapt to dietary changes to utilize these nutrients. Undigested nutrients by the host enter the large intestine for microbial fermentation and facilitate the propagation of pathogens, eventually resulting in diarrhea and pathological intestinal damage in piglets (Gresse et al., 2017; Tang et al., 2022).

*E. coli* is the most common microbe in the intestinal microbiota and consists of diverse strains, some of which possess pathogenic features (Hermann-Bank et al., 2015). Enterotoxigenic *E. coli* (ETEC) is mainly responsible for postweaning diarrhea in piglets (Kim et al., 2022; Wang et al., 2022). ETEC strains colonize the intestinal mucosa by adhesins, and then induce diarrhea by releasing enterotoxins that cause fluid-electrolyte disturbance and acid-base imbalance of piglets (Bin et al., 2018). Of the enterotoxins, the excretive STa (heat-stable toxin A) is the main culprit in causing diarrhea (Wang et al., 2022; Wu et al., 2023). Moreover, more abundant *Enterococcus* in diarrheal piglets than healthy piglets mean *Enterococcus* increases the risk of piglet diarrhea (Hermann-Bank et al., 2015). Indeed, previous researchers have reported that *Enterococcus* (*E. hirae* and *E. durans*) and *E. coli* co-contributed to the development of diarrhea (Gryaznova et al., 2022), which might be due to the villous atrophy in the small intestine of piglets (Jonach et al., 2014; Larsson et al., 2014). *Salmonella* can also induce intestinal barrier injury via inflammatory reactions, eventually leading to diarrhea (Thiagarajah et al., 2015). Furthermore, a metagenomic analysis shows diarrheic piglets have increased *Sutterella*, *Campylobacter*, and Fusobacteriaceae (Yang et al., 2017). Moreover, *Fusobacterium* can inhibit T-cell responses and promote inflammation, which contributes to piglet diarrhea (Nosho et al., 2016). It has been reported that *Veillonella*, Campylobacterales, and *Salmonella typhimurium* as pathogens can also induce inflammatory bowel disease, leading to piglet diarrhea (Li et al., 2018; Huang et al., 2019).

Hermann-Bank found that the relative abundance of Actinobacteria (*Bifidobacterium boum* and *Corynebacterium kutscheri*) and Firmicutes (*Lactobacillus acidophilus* and *Streptococcus gallolyticus* subsp) is decreased in diarrhetic piglets (Hermann-Bank et al., 2015). Actinobacteria and Firmicutes can digest various carbohydrates to produce short-chain fatty acids (SCFA), which are beneficial for regulating the host's intestinal immunity by divining T cells, neutrophils, and macrophages (Wang et al., 2021; Xie et al., 2023). The decreased Actinobacteria and Firmicutes abundance reduces SCFA production and weakens immune regulatory function, ultimately causing diarrhea. Another study similarly found that the abundance of Firmicutes in the diarrhetic piglets is decreased, including *Blautia*, *Ruminococcus*, *Enterococcus*, *Clostridium*, *Streptococcus*, and *Lactobacillus* (Yang et al., 2017). In addition, the lower ratio between Bacteroidetes and Firmicutes is also a contributing factor in the etiology of piglet diarrhea (Bin et al., 2018). This variation is most likely due to the increased oxygen level in the intestine caused by ETEC infection or *Vibrio cholera* infection, which inhibits the growth of anaerobes and supports facultative anaerobes (e.g., Bacilli, member of Firmicutes) (Albenberg et al., 2014; David et al., 2015). It is also evident that *Alloprevotella* and *Oscillospira* are decreased in weaned piglets (Li et al., 2018), which are producers of succinate, acetate, and butyrate, which can improve gut barrier function and exhibit anti-inflammatory properties (Gophna et al., 2017; Wang et al., 2021). In conclusion, decreased richness and diversity in the intestinal microbiota is the leading cause of piglet diarrhea.

## 4. Perturbations in Trp metabolism of diarrheal piglets

Trp metabolism disorder is strongly associated with diarrhea in piglets. The development of diarrhea is usually accompanied by Trp metabolic disorder, which alters Trp-associating metabolite levels in host and microbial pathways, ultimately causing intestinal inflammation and diarrhea and leading to a decrease in the survival rate and growth retardation of piglets. In recent years, the roles and underlying mechanisms of Trp metabolism in diarrhetic piglets have gradually been unraveled (Fig. 2). When inflammation occurs, the metabolites of Trp in the intestine can exert anti-inflammatory and immunosuppressive effects by acting on AhR. Aryl hydrocarbon receptor is a ligand-activated transcription factor belonging to the family of the Per-Arnt-Sim proteins and is widely expressed in many leukocytes (such as macrophages and dendritic cells), T lymphocytes, innate lymphoid cells, and intestinal epithelial cells

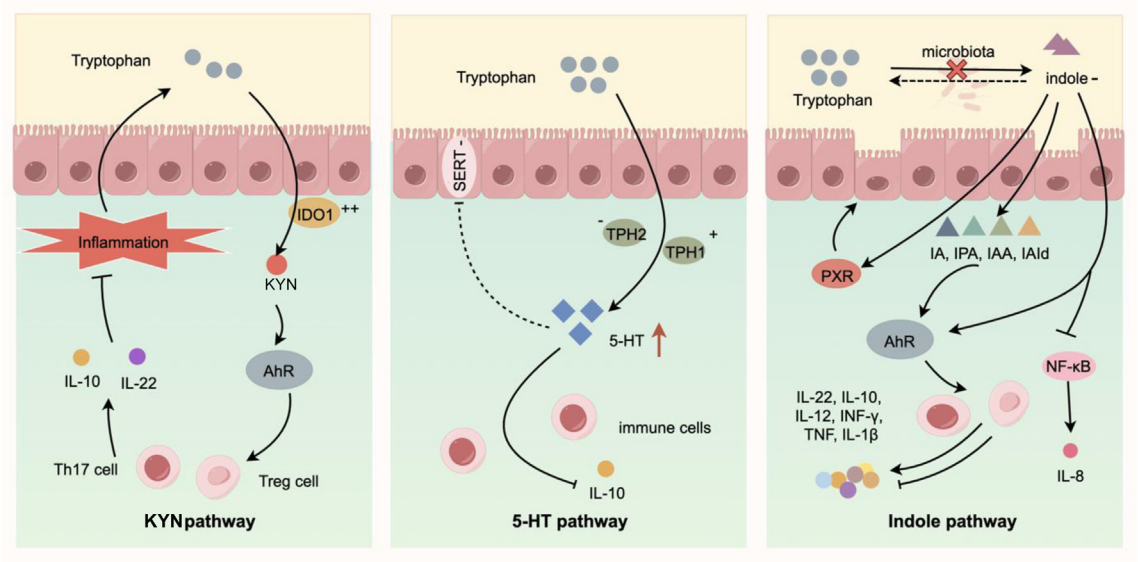


**Fig. 2.** Perturbations to Trp metabolism in diarrheal piglets. The three major pathways of Trp metabolism are differentially affected in diarrhea. 5-HT = 5-hydroxytryptamine; AhR = aryl hydrocarbon receptor; IA = indole acrylic acid; IAA = indole acetic acid; IAld = indole-3 aldehyde; IDO1 = indoleamine 2,3-dioxygenase-1; IL-1β = interleukin-1β; IL-8 = interleukin-8; IL-10 = interleukin-10; IL-12 = interleukin-12; IL-22 = interleukin-22; INF-γ = interferon-γ; IPA = indole-3 propionic acid; KYN = kynurenine; NF-κB = nuclear factor-kappa B; PXR = pregnane X receptor; SERT = serotonin transporter; Th17 = T helper cell 17; TNF = tumor necrosis factor; TPH1 = Trp hydroxylase1; TPH2 = Trp hydroxylase2.

(IEC) (Hukkanen, 2012; Pernomian et al., 2020). Weaning-associated intestinal inflammation induces aberrant AhR signaling in weaned piglets. As AhR ligands, the metabolites of Trp associated with the KYN and indole pathways may regulate inflammation by mechanisms dependent on AhR activation to relieve diarrhea in piglets (Zhang et al., 2022; Han et al., 2023). Therefore, AhR has recently been postulated as a molecular target for controlling intestinal inflammation and diarrhea, although the underlying mechanisms have not yet been elucidated.

### 4.1. Host endogenous Trp metabolism and diarrhea

The KYN pathway is the major route for Trp metabolism in the host and has a multilevel association with inflammatory bowel disease (IBD), with diarrhea being a frequent consequence of IBD. Diarrhea and inflammation can activate the KYN pathway, leading to elevated serum KYN levels (Li et al., 2020). Indoleamine 2,3-dioxygenase-1 is the initial rate-limiting enzyme in Trp catabolism within the KYN pathway and plays an important role in regulating adaptive immunity (Nayak-Kapoor et al., 2018; Grifka-Walk et al., 2021). When inflammation occurs in the mucosa, activated IDO1 can exert anti-inflammatory and immunosuppressive through KYN production, immune reactivity, and gut microbial composition, suggesting the acceleration of Trp metabolism to KYN (Wolf et al., 2004; Gao et al., 2018). Kynurenine and its derivatives act as direct ligands of AhR and can contribute to the activation and transcription targeted genes, including *IL-6*, *IL-22*, vascular endothelial growth factor A (*VEGFA*), and cytochrome P450 1A1 (*CYP1A1*) (Hubbard et al., 2015), thereby inducing the generation of regulatory T cells to resist hyper-inflammatory responses (Bessede et al., 2014). Li et al. have also found that KYN can exert immunosuppressive effects via AhR to realize the regulation of immune responses by suppressing effector T cell proliferation and increasing regulatory T cell development (Li et al., 2019). Meanwhile, KYN, XA, and KYNA can facilitate the proliferation of IEC and improved barrier function through their interactions with AhR and an increased expression of *IL*-22. These derivatives such as KYNA can regulate intestinal inflammation via the glycolysis of T cells and mitochondrial respiration of IEC (Michaudel et al., 2023). In addition, activated AhR regulates the Treg/Th17 axis to resist inflammatory responses and differentiate innate immune cells like dendritic cells and macrophages (Lamas et al., 2018; Grifka-Walk et al., 2021). The KYN pathway may also control the balance between anti-inflammatory and proinflammatory responses in intestinal immune cells by regulating the secretion of IDO1 (Kaszaki et al., 2008). In colitis, IDO-deficient mice display more severe colitis and significantly increased proinflammatory cytokines (Takamatsu et al., 2013). More importantly, the lower IDO activity leads to both decreased KYN and increased 5-HT concentrations (Machado et al., 2017). The pathological injury induced by IDO deletion is probably due to increased 5-HT synthesis in the intestines and the activation of proinflammatory cytokines, as well as a decrease in the number of $CD4^{+}Foxp3^{+}$ regulatory T cells (Chen et al., 2021; Craig et al., 2022). In summary, IDO is activated during inflammation, thus increasing KYN levels by consuming more Trp, which goes on to serve as an AhR ligand activating AhR to exert anti-inflammatory and immunosuppressive effects.

5-hydroxytryptamine, as an essential signaling molecule in organisms, triggers multiple signals in the intestine and nervous system and is implicated in a wide range of physiological functions through activating specific 5-HT receptors (Mawe and Hoffman, 2013). Intestine-derived 5-HT can convey signals from the intestine to intrinsic or extrinsic neurons, modulating intestinal peristalsis and motility, secretion, and the absorption of nutrients through 5-HTR signaling, vasodilatation, and platelet function (Hu et al., 2023; Liu et al., 2023). Additionally, 5-HT participates in the regulation of diarrhea by affecting intestinal inflammation. The inhibition of serotonin transporter (*SERT*) expression in the intestine is a sign of inflammation induced by an enteric source of 5-HT, which leads to the secretion-enhancing effect promoted by 5-HT in the mucosa and promotes colon inflammation induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS) or the deletion of the anti-inflammatory factor interleukin-10 (IL-10) (Gershon, 2013). This is due to the lack of SERT, which increases the release of 5-HT from

enterochromaffin cells, promoting intestinal inflammation, therefore 5-HT is unmistakably proinflammatory (Liu et al., 2021). Notably, inflammation can raise the concentration of 5-HT in the serum and gastrointestinal tract wall of piglets, which is further accompanied by diarrhea (Bulc et al., 2022; Yang et al., 2022a; Wang et al., 2023). Trp hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of 5-HT, contains two isoforms, of which TPH1 is mainly expressed by specialized gut endocrine cells (Jones et al., 2020). Typically, an elevated 5-HT level is associated with the upregulation of TPH1 in the small intestinal mucosa, implying that TPH1 plays an important role in this physiological process. Thus, inhibiting TPH1 is an attractive strategy to curb inflammation and attenuate diarrhea (Chojnacki et al., 2021; Zhai et al., 2023). Previous studies have found that the increasing 5-HT content activates the innate immune system by binding to 5-HTR, eventually bringing adaptive immunity to bear and mediating the full force of inflammation in the bowel (Faba et al., 2022; Liu et al., 2023). These subtle changes in immune activation may contribute to the diarrhea caused by 5-HT. Unlike *TPH*1, *TPH*2 is primarily expressed in neurons of the raphe nuclei of the brain stem and a subset of neurons in the enteric nervous system (Jones et al., 2020). Interestingly, the deletion of TPH2 seems to increase the severity of inflammation, emphasizing the immune protective effect of neuronal 5-HT. Studies have found that the 5-HT produced by TPH2 can protect the enteric nervous system from the neurotoxic effects of inflammation (Gershon, 2012). This suggests that 5-HT plays both offence and defense in the intestine, depending on the site of 5-HT synthesis (Najjar et al., 2023). However, there is no direct evidence to show the mitigating effect of TPH2 on diarrhea, and this area of study should be investigated using more targeted techniques. Although the relationship between endogenous Trp metabolism and diarrhea has not yet been reported, the changes in endogenous Trp metabolites and the corresponding enzymes in the inflammatory responses function as indicators of diarrhea.

### 4.2. Microbial Trp metabolism and diarrhea

The gut microbiota can directly utilize Trp, which partially limits Trp availability for the host. Microbial metabolites of Trp, such as indole and indolic acid derivatives, play a dominant role in intestinal AhR and pregnane X receptor (PXR) activity, modulating mucosal immune responses or mucosal barrier integrity which ultimately impacts diarrhea (Lamas et al., 2016). Additionally, gut microbiota can stimulate IDO1 activity, which affects the decomposition of Trp. Namely, AhR and IDO1 participate in connecting microbial Trp catabolism and host endogenous Trp metabolites with regulatory T cells' functions. Interestingly, in the absence of IDO1, AhR/IL-22 activities are not reduced (Bessede et al., 2014). The upregulation of AhR/IL-22 activity in response to the absence of IDO1 suggests a compensatory or alternative mechanism. Therefore, AhR and IL-22 are associated with maintaining mucosal immunity and responding to signals from the gut microbiota. In addition, AhR stimulation may in turn affect IDO1. The positive feedback loop between IDO1 and AhR is required for the coevolution of the gut microbiota and the mammalian immune system, which is beneficial for the host under strong inflammatory conditions and prevents dysregulated immunity.

Microbial Trp metabolites can affect intestinal homeostasis by regulating the secretion of IL-22, promoting the production of antimicrobial peptides, and protecting the intestine against pathogenic infection via AhR (Levy et al., 2017). Indole derivatives such as ILA and IAld can activate AhR in $CD4^+$ T cells and subsequently regulate intraepithelial lymphocytes via $CD4^+$ $CD8\alpha\alpha^+$ (Cervantes-Barragan et al., 2017). Furthermore, indole is considered to be a beneficial signaling molecule in IEC and ameliorates intestinal inflammation by modulating inflammation-mediated via alterations in the gut microbiota composition and innate immune responses (Whitfield-Cargile et al., 2016). Indole can reduce the expression of *Salmonella* pathogenicity island-1 (*SPI-1*) genes to weaken the invasion and colonization capabilities of enteric bacteria. Indole treatment can increase the expression of genes associated with strengthening the mucosal barrier and MUC production and the secretion of the anti-inflammatory cytokine IL-10, as well as decrease activation of NF-κB mediated by *TNF-α*, *IL*-8 expression (a proinflammatory), and the adherence of pathogenic *E. coli* to HCT-8 cells, rather than other indole-like molecule treatments, such as H-indole-2,3-dione, 7-hydroxyindole, 5-hydroxyindole, 2-hydroxyindole, and indole-3-acetic acid (Bansal et al., 2010). This suggests that variations in NF-κB activation and cellular resistance are highly associated with indole (Gao et al., 2018).

Indole can be further metabolized by the intestinal microbiota into indole derivatives, which are also important for maintaining intestinal immune homeostasis. Indole acrylic acid is considered an essential factor in resisting intestinal inflammation. Inflammation can promote *Peptostreptococcus species* to produce IA, improving both *IL-10* and *MUC* gene expression to mitigate inflammatory responses (Wlodarska et al., 2017). Indole-3 propionic acid, which is metabolized by *Clostridium sporogenes*, can control inflammation by regulating the expression of immune factors, including interleukin-12 (*IL-12*), interferon-γ (*INF-γ*), *TNF*, *IL-1β*, and *IL-10*, as well as inducing the differentiation and augmented suppressive potential of Tr1 cells (Pernomian et al., 2020). *Bacteroides thetaiotaomicron* can metabolize Trp into IAA and IPA, which activate the AhR and enhance Treg cell function to inhibit intestinal inflammation (Li et al., 2021). *Lactobacillus reuteri* increases the levels of IAld and reduces intestinal inflammation via the activation of the AhR/IL-22 axis. Furthermore, IAld could stabilize and improve intestinal microbiota composition to alleviate inflammation (Xue et al., 2023b). However, diarrheal diseases are accompanied by disturbances in gut microbial diversity, which may perturb Trp metabolism in microbial pathways. Not surprisingly, low levels of indole, 5-hydroxyindole acetic acid (5-HIAA), IAA, and other derivatives were found in diarrheal piglets. They, therefore, can reduce AhR activation and further result in inflammation and diarrhea (Fu et al., 2021; Song et al., 2021; Han et al., 2023). Thus, a stable intestinal microbial community is crucial to reduce piglet diarrhea.

## 5. Trp metabolism: from a disrupted equilibrium to therapeutic strategies

Diarrhea can be classified into infectious and non-infectious types, which are caused by pathogen and stress of feeding management, respectively (Wang et al., 2019a), resulting in intestinal barrier disruption and gut microbiota dysbiosis, ultimately triggering inflammation and immune responses (Ghosh et al., 2021). Alterations in Trp levels and metabolites strongly correlate with clinical features in diarrhea, encompassing mucosal barrier dysfunction, microbiome dysbiosis, and inflammation severity. Given the impact of Trp metabolism in pathological conditions, utilizing Trp and its metabolites as biomarkers holds promise in supporting diagnosis, prognosis, and guiding therapeutic decisions. Previous studies have shown dietary Trp supplementation during the weaning period of piglets can effectively modulate diarrhea. Piglets supplemented with 0.35% Trp decreases the diarrhea rate (33.8%) compared with those of 0.14% dietary Trp (43.5%) (Rao et al., 2021). Moreover, Trp can relieve intestinal inflammation, improve barrier function, and modulate the microbiome in piglets challenged by diquat or lipopolysaccharide (Liu et al., 2019, 2022). This modulation primarily manifests through the interactions between

the host immune system and the gut microbiome (Hu et al., 2023). Conversely, high concentrations of dietary Trp (0.75%) could have the opposite effect on small intestinal structure in weaned piglets (Tossou et al., 2016).

Diarrhea triggers the synthesis of numerous proinflammatory cytokines in the intestine, such as IL-1β, IL-6, and IL-8. Excessive secretion of these cytokines can cause inflammation and disrupt intestinal barrier integrity (Zhao et al., 2022). The biological effects of Trp metabolites and their disease alterations suggest their potential as therapeutic targets. This can be achieved directly by utilizing Trp metabolites, targeting their receptors, or indirectly manipulating the gut microbiota (Fig. 3). Trp exhibits anti-inflammatory effects in mammals and is vital in regulating inflammatory responses. Studies have revealed that Trp can reduce the release of proinflammatory cytokines and increase anti-inflammatory factors (Kim et al., 2010; Shizuma et al., 2013). Dietary supplementation with 0.2% to 0.4% Trp has been observed to decrease the abundance of *Clostridium* and *Streptococcus* while increasing the levels of *Lactobacillus* and *Clostridium*. Additionally, it raises the concentration of sIgA (Liang et al., 2018). Intriguingly, L-Trp is not catabolized by porcine intestinal epithelial cells, but it can regulate intracellular protein turnover and the expression of tight junction proteins (Wang et al., 2015). Trp metabolites can regulate the expression of intestinal cytokines and consequently modulate intestinal inflammation. Trp acts as a precursor for serotonin, a neurotransmitter, and undergoes enzyme catalysis through the 5-HT pathway and the KYN pathway. This process is implicated in the onset of visceral hypersensitivity observed in diarrhea (Li et al., 2017). Oral Trp supplementation has been shown to regulate the synthesis of 5-HT and melatonin, enhancing the innate immune response in animals. Melatonin is also confirmed to possess anti-inflammatory properties. Abnormalities in 5-HT metabolism can result in gastrointestinal dysfunction, although the precise mechanism remains poorly understood. It is speculated that other Trp metabolites, primarily those of the KYN pathway, play a crucial role in regulating intestinal function. Immune cells break down Trp into KYN, a pivotal regulator of immune responses during infection and inflammation. Kynurenine exhibits antimicrobial activities, directly affecting the proliferation of intestinal microbiota (Nino-Castro et al., 2014). The interplay between the intestinal microbiota and host Trp metabolism in the KYN pathway is intertwined with the immune system. In the KYN pathway, KYN modulates intestinal homeostasis by stimulating AhR and regulating *IDO* expression (Bessede et al., 2014). This is the case in settings of intestinal inflammation, where dietary Trp supplementation alleviates colitis severity through restoration of AhR ligand production. Several bacterial Trp metabolites, including indole, IAA, IPA, IA, IAld, indole-3-acetaldehyde (IAAld), and KYN, have been proven to be AhR ligands. Approaches involving the supplementation of Trp and its metabolites have shown promising effects in treating inflammatory conditions caused by weaning diarrhea. Through AhR, these metabolites may provide essential cues to the host for resisting colonization, defending against mucosal inflammation, and targeting a range of immune cells, including epithelial lymphocytes, Th17 cells, macrophages, and dendritic cells, thus regulating immune responses to ensure immune barrier integrity.

The pathological role of microbial Trp metabolism in diarrhea might be feasible to target, as shown by manipulation of the intestinal microbiota with diet and *L. reuteri* products inducing the AhR agonist IAA to reprogram intraepithelial $CD4^+$ T cells into immunoregulatory $CD4^+CD8\alpha\alpha^+$ T cells (Cervantes-Barragan et al., 2017). Intestinal microbes play a crucial role in developing diarrhea through interactions with Trp metabolites. Using fecal transplantation, studies have revealed that IAAld alleviates intestinal inflammation by influencing intestinal microbiota composition. *B. thetaiotaomicron* can increase the levels of IAA and IPA, inhibiting intestinal inflammation via the activation of AhR and enhancing Treg cell function (Li et al., 2021). Indole-3 propionic acid is produced by intestinal symbiotic bacteria such as *Peptostreptococcus* (Platten et al., 2019) and *Clostridium* (Lavelle and Sokol, 2020), which promote immune regulation. Recent research has highlighted the potential of IPA to promote nerve regeneration and repair when it enters the bloodstream (Serger et al., 2022). Additionally, IPA contributes to maintaining barrier function and inhibiting the production of tumor necrosis factors by activating AhR receptors and PXR. This activation induces the production of

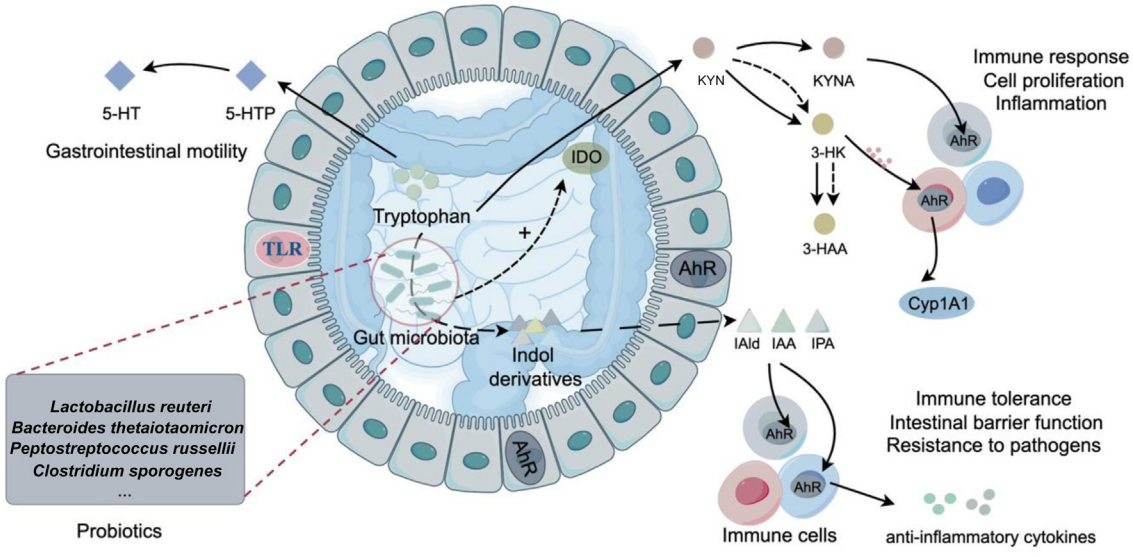


**Fig. 3.** Therapeutic strategies of utilizing Trp metabolism to diarrhea. Intestinal microbes can regulate host immunity by directly converting Trp into AhR ligands or affecting the IDO/KYN pathway. Therefore, indole derivatives and some probiotics such as *Lactobacillus rhamnosus* can be supplemented to alleviate diarrhea. 3-HAA = 3-hydroxyanthranilic acid; 3-HK = 3-hydroxykynurenine; 5-HT = 5-hydroxytryptamine; 5-HTP = 5-hydroxytryptophan; AhR = aryl hydrocarbon receptor; Cyp1A1 = cytochrome P450 1A1; IAA = indole acetic acid; IAld = indole-3 aldehyde; IDO = indoleamine 2,3-dioxygenase; IPA = indole-3-propionic acid; KYN = kynurenine; KYNA = kynurenic acid; TLR = Toll-like receptor.

immune cells that promote tolerance, ultimately reducing the inflammatory response and enhancing immune tolerance in the intestine (Flannigan et al., 2023). Furthermore, the manipulation of the KYN and 5-HT pathways in the intestine through microbiota-based approaches is also attractive. Evidence of gut microbial influence on KYN concentrations and IDO activity reveals that targeting the gut microbiome to modulate KYN pathway prevents diseases. Studies of *Bifidobacterium infantis* have reported that KYN metabolites are increased after colonization (Desbonnet et al., 2008). Although studies have shown the addition of the *Lactobacillus johnsonii* probiotic has reduced IDO activity (Marcial et al., 2017), it can also promote the transformation of the indole pathway (Roager and Licht, 2018), possibly as part of an adaptive mechanism to maintain immune homeostasis in the presence of gut microbiota. However, a better understanding of microbial processes is needed, specifically how microbiota and Trp metabolites regulate Trp metabolism to cope with diarrhea.

## 6. Conclusion and future perspective

Weaned piglets are susceptible to the external environment due to immature gastrointestinal development and low immunity. This heightened sensitivity often results in diarrhea. Additionally, there is a decrease in the abundance of beneficial bacteria in the intestine, accompanied by abnormal Trp metabolism. Tryptophan significantly influences physiology and physiopathology through three main pathways: the KYN, 5-HT, and indole pathways. These pathways can be regulated either directly or indirectly through the gut microbiota. As a result, Trp metabolism in the intestine emerges as a critical player in a therapeutic context. This could involve using molecules targeting specific Trp metabolites or leveraging microbes that manipulate Trp metabolism. Targeting Trp metabolites, including IDO1, KYN, 5-HT, indole, and their derivatives via the AhR signaling pathway, represents a novel and promising strategy for treating diarrhea and associated conditions. Considering the complex and variable nature of the intestine microbiota, it is potential to identify universal principles regarding bacterial Trp metabolites. Manipulating the intestinal microbiota to influence Trp metabolism could be a practical approach in addressing diarrhea and related challenges in weaned piglets.

## Author contributions

**Yaoyao Xia** and **Guangdong Bai** designed and guided the review. **Xuan Zhao**, **Guangdong Bai**, and **Jiaman Pang** wrote the manuscript. **Xie Peng**, **Zhenguo Yang**, **Wanghong Zhang**, and **Jiaman Pang** helped with reference collection. All authors read and approved the manuscript.

## Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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