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The relationship between tryptophan metabolism and gut microbiota: Interaction mechanism and potential effects in infection treatment

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ABSTRACT

Human health is influenced by the gut microbiota, particularly in aspects of host immune homeostasis and intestinal immune response. Tryptophan (Trp) not only acts as a nutrient enhancer but also plays a critical role in the balance between host immune tolerance and gut microbiota maintenance. Both endogenous and bacterial metabolites of Trp, exert significant effects on gut microbial composition, microbial metabolism, the host immunity and the host-microbiome interface.

Trp metabolites regulate host immunity by activating aryl hydrocarbon receptor (AhR), thereby contributing to immune homeostasis. Among Trp metabolites, AhR ligands include endogenous metabolites (such as kynurenine), and bacterial metabolites (such as indole and its derivatives). Here, we present a comprehensive analysis of the relationships between Trp metabolism and 14 key microbiota, encompassing fungi (e.g., *Candida albicans*, *Aspergillus*), bacteria (e.g., *Ruminococcus gnavus*, *Bacteroides, Prevotella copri*, *Clostridium difficile*, *Escherichia coli*, lactobacilli, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Helicobacter. Pylori*), and viruses (e.g., SARS-CoV-2, influenza virus). This review clarifies how the gut microbiota regulates Trp metabolism and uncovers the underlying mechanisms of these interactions. And increased mechanistic insight into how the microbiota modulate the host immune system through Trp metabolism may allow for the identification of innovative therapies that are specifically designed to target Trp absorption, Trp metabolites, the gut microbiota, or interactions between Trp and gut microbiota to treat both intestinal and extra-intestinal inflammation as well as microbial infections.

1. Introduction

In humans, the essential amino acid tryptophan (Trp) is only obtained through dietary sources, which plays a critical role in the synthesis of proteins and acts as a precursor for the production of various important bioactive compounds. Trp impacts multiple physiological processes, including neuronal function, metabolism, inflammatory responses, oxidative stress, immune responses, and intestinal homeostasis (Xue et al., 2023).

The gut contains a highly diverse and densely populated microbial community, collectively known as the gut microbiota, which has evolved alongside the host to establish a interactional relationship (Agus et al., 2018). The gut microbiota contains a diverse range of microorganisms, including bacteria, fungi and viruses (Sommer and Bäckhed, 2013). These microorganisms play a role in food digestion and energy metabolism, as well as influencing the host immune response and homeostasis (Nicholson et al., 2012; Rooks and Garrett, 2016). Changes in the gut microbiota can contribute to the onset and progression of various diseases (Dixit et al., 2021). The metabolism of Trp is significantly influenced by gut microbiota, as they have the ability to convert Trp into different molecules like indole and its derivatives (Zhang et al., 2021). And regulation of gut homeostasis is achieved by these indoles and its derivatives through the modulation of pro-inflammatory and anti-inflammatory cytokine expression (Xue et al., 2023). In turn, Trp metabolism occurring in the host can also influence composition and colonization of gut microbiota and microbial infection. Recent studies

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have highlighted the significant impact of dietary intake and nutrients on gut microbiota composition and their interactions with the host immune system (Thorburn et al., 2014). The metabolism of Trp and the important enzymes involved have an impact on a range of cellular functions, such as immune response, cell growth, and movement through interacting with downstream molecules or pathways (Triplett et al., 2018).

This review aims to provide an overview of the advances in comprehending Trp metabolism under different conditions of gut microbial colonization or infections. We focus on the impact of Trp in maintaining gut and systemic immune homeostasis, particularly its influence on gut microbiota-related infections, and hope to find new strategies based on utilizing Trp metabolism in host and gut microbiota to treat gut microbiota-related infections. In this review, we examine researches that enhances our understanding of the interaction between Trp metabolism and the gut microbiota, the role of Trp in host-microbiota interactions, and its effects on immune homeostasis in gut, as summarized in Table 1. Furthermore, we highlight the impact of Trp on intestinal and peripheral inflammation and examine the intersections between Trp metabolites and host immunity. A better understanding of these interactions may reveal novel therapeutic targets for managing infections associated with gut microbiota and Trp metabolism.

2. Metabolism of Trp

Trp has three isomers, including L-Trp, D-Trp and DL-Trp, and L-Trp is the only amino acid with an indole structure (Modoux et al., 2021). The metabolism of Trp can currently be roughly divided into three ways: the kynurenine (Kyn) pathway, the 5-HT pathway and the indole pathway (Fig. 1). The Kyn pathway is the primary pathway and more than 95 % of Trp is metabolized into various bioactive catabolites through this way. Indolamine 2,3-dioxygenase (IDO, expressed in various body organs) and Trp 2,3-dioxygenase (TDO, almost exclusively expressed in liver) used as rate-limiting enzymes to convert Trp into N-formylkynurenine (NFK), which is subsequently catalyzed into Kyn by arylformamidase (O'Mahony et al., 2015). Due to mediating Trp metabolism, IDO has a complex and important role in immunoregulation during infection, neoplasia, pregnancy, autoimmunity and transplantation (Grohmann et al., 2003; Mellor and Munn, 2004). Kyn is metabolized in three directions. The first is the conversion of Kyn to kynurenic acid (KYNA) under Kyn aminotransferase I-IV. KYNA is a critical glutamate receptor antagonist and has potential antioxidation functions in neuron diseases (Lim et al., 2017). The second pathway involves Kyn being catalyzed into anthranilic acid by kynureninase (KYNU). The Third is the conversion of Kyn to 3-hydroxy-kynurenine (3-HK) and 3-HK, which is eventually metabolized into pyruvate, NAD^+ and xanthurenic acid (XA) respectively through different catabolism direction (Busse et al., 2018; Hestad et al., 2022). In the 5-HT pathway, Trp is converted into 5-HTP by Trp hydroxylase (TPH), and then aromatic L-amino acid decarboxylase interacts with the cofactor pyridoxal-50-phosphate to convert 5-HTP to 5-HT (Daubert and Condron, 2010). This metabolism pathway accounts for little fraction of Trp metabolism and mainly takes place in both brain and gut (Watts et al., 2012). The indole pathway is that gut microflora converts Trp into indole and its derivatives, such as tryptamine, indole-3-acetaldehyde (IAld), indole-3-propionic acid (IPA), indole-3-acetic acid (IAA) and indoleacrylic acid (Wei et al., 2021).

3. Many Trp metabolites function by binding AhR

Many Trp metabolites are ligands of aryl hydrocarbon receptor (AhR) and exert their functions in intestinal immunity through AhR. AhR is a ligand-dependent transcriptional factor widely expressed in barrier tissues, including immune cells, epithelial cells, endothelial cells, and stromal cells (Zhou et al., 2019). The AhR usually exists in a resting state in the cytoplasm associated with chaperone and immunophilin-like

Table 1
Key microbiota species and their interactions with tryptophan metabolism.

Microbiota Species	Interaction between Trp metabolism and microbiota	References
Fungi		
Candida albicans	Through IDO inhibition, *C. albicans* shifted host Trp metabolism toward 5-HT pathway, reducing IL−17 and promoting infection.	(Cheng et al., 2010, 2012; Krause et al., 2015)
	Lactobacilli-derived I3A activated AhR, enhancing IL−22 and resistance to *C. albicans* infection.	(Zelante et al., 2013)
	DADS ameliorated intestinal *C. albicans* infection through increasing indoles and their derivatives.	(Hu et al., 2021)
	Picolinic acid enhanced neutrophils to inhibit *C. albicans* growth.	(Abe et al., 2004)
	KYNA and indoleacetic acid decreased inflammatory activities and protected gut barrier function in intestinal *C. albicans* infection, through reducing IL−22 produced by ILC3.	(Peng et al., 2024)
	KYNA activated AhR to improve intestinal barrier function in *C. albicans* infection.	(Wang et al., 2022b)
	IPA induced Ca^{2+}-dependent apoptosis in *C. albicans*.	(Han and Lee, 2022)
Aspergillus	Host IDO activity increases Kyn, suppressing Th17 responses and promoting *Aspergillus* persistence.	(Romani et al., 2008; Zelante et al., 2009b)
	Fungal IDO expression redirects Trp metabolism to reduce *Aspergillus* pathogenicity.	(Zelante et al., 2021)
	Ochratoxin A secreted by *Aspergillus* disrupts host Trp metabolism.	(Ma et al., 2023)
Bacteria		
Ruminococcus gnavus	Convert Trp to tryptamine, increasing GI motility and secretion.	(Bhattarai et al., 2018; Zhai et al., 2023)
	Produce tryptamine to prevent barrier disruption and ameliorate weight loss in DSS-induced colitis mice.	(Bhattarai et al., 2020)
Bacteroides	Produces IAA, promoting IL−22 and ameliorating colitis.	(Ihekweazu et al., 2021)
Prevotella copri	Deplete IPyA, promoting tumor growth.	(Su et al., 2024)
Clostridium difficile	Induce indole production in other bacteria, altering colonization resistance.	(Darkoh et al., 2019)
Escherichia coli	Trp metabolites produced through indole pathway activated AhR to alleviate *E. coli* infection.	(Zhao et al., 2021a, 2022)
	Higher Trp level in *E. coli* inhibited biofilm formation and Trp added in *E. coli* culture degraded the preformed biofilm.	(Shimazaki et al., 2012)
	Trp metabolites produced by gut microbiome could activate dopamine receptor D2 on intestinal epithelium to promote host colonization resistance against *E. coli*	(Scott et al., 2024)

(*continued on next page*)

Table 1 (*continued*)

Microbiota Species	Interaction between Trp metabolism and microbiota	References
	E. coli could metabolize Trp into "indolokines" to enhance persisting *E. coli* biofilm formation under antibiotics treatment.	(Kim et al., 2020)
Lactobacilli	Produce AhR ligands (e.g., ILA, IAld) to enhance IL−22 and suppress Th17 polarization.	(Zelante et al., 2013; Wilck et al., 2017; Bender et al., 2023; Wang et al., 2024)
	Indoles produced by *L. reuteri* can promote intestinal flora capable of producing indoles and increasing AhR expression.	(Fang et al., 2022)
	L. murinus restricts Th17 cell differentiation via producing ILA	(Wilck et al., 2017)
	L. murinus preferentially metabolized Kyn into KYNA, which could regulate the host immune system and effectively scavenge ROS.	(DiNatale et al., 2010; Lugo-Huitrón et al., 2011; Kubicova et al., 2019; Schwarcz et al., 2024)
Mycobacterium tuberculosis	*M. Tuberculosis* infection-caused Trp depletion in host increased Kyn, promoting Treg differentiation and immune tolerance.	(Mellor and Munn, 2004; Suzuki et al., 2012, 2013)
	Gut microbiota metabolite IPA inhibited *M. Tuberculosis* growth by blocking Trp biosynthesis in *M. Tuberculosis.*	(Negatu et al., 2018, 2019)
Pseudomonas aeruginosa	Metabolizes Trp via Kyn pathway to produce anthranilate (biofilm virulence factor).	(Bortolotti et al., 2016)
	Kyn produced by *P. aeruginosa* scavenged ROS to evade immune responses.	(Genestet et al., 2014)
	Bacterial Trp metabolite indoles enhanced biofilm formation of *P. aeruginosa* in a quorum sensing-independent manner.	(Lee et al., 2007; Kim et al., 2015)
	Trp metabolite anthranilate can induce dispersion of *P. aeruginosa* biofilm.	(Li et al., 2017)
Staphylococcus aureus	Trp inhibited *S. aureus* biofilm formation.	(Paul et al., 2021)
	KYNA (via GPCR35) reduced inflammation caused by *S. aureus.*	(Zhao et al., 2021b)
	Trp metabolite violacein disrupts bacterial membranes.	(Cauz et al., 2019)
Helicobacter pylori	Upregulate IDO expression in gastric mucosa, suppressing Th1/Th17 immunity.	(Larussa et al., 2015)
Viruses		
SARS-CoV−2	Reduce ACE2-dependent Trp uptake in host, depleting IPA and increasing Kyn.	(Essex et al., 2024)
	AhR activated by Trp metabolites could exacerbate cytokine storms in COVID−19.	(Anderson et al., 2021)
Influenza virus	Induce IDO1 expression, increasing Kyn and suppressing antiviral immunity.	(Fox et al., 2015; Huang et al., 2016; Lin et al., 2020; Zhang et al., 2024b)
	Microbial Trp metabolite IPA level was negatively associated with viral load of influenza virus.	(Heumel et al., 2024)

Trp - tryptophan; IDO - indolamine 2,3-dioxygenase; I3A - indole-3-aldehyde; AhR - aryl hydrocarbon receptor; DADS - diallyl disulfide; KYNA - kynurenic acid; ILC3 - group 3 innate lymphoid cells; IPA - indole-3-propionic acid; Kyn - kynurenine; GI - gastrointestinal; DSS - dextran sulfate sodium; IPyA - indole-3-pyruvic acid; ILA - indole-3-lactic acid; IAld - indole-3-carboxaldehyde; ACE2 - angiotensin-converting enzyme 2.

proteins, such as heat shock protein-90 (HSP90), X-associated protein-2 (XAP2) and HSP90 co-chaperone p23, forming a complex (Hubbard et al., 2016). Upon ligand binding, AhR is activated with a conformation change that exposes a nuclear localization signal (NLS), and HSP90 is released from the complex. The bound AhR then translocate into nucleus and forms a heterodimer with AhR nuclear translocator (ARNT) (Hidaka et al., 2017). This heterodimer binds to the xenobiotic response element (XRE) of genes and alters these genes' expression (such as IL-22 and CYP1A1).(Mescher and Haarmann-Stemmann, 2018) This cascade of responses regulates various developmental and physiological events, including gut immunity and homeostasis (Villa et al., 2016). Trp metabolite-activated AhR participates in immune responses through a variety of mechanisms because final effects of AhR are ligand-specific and different ligands have different effects and directions (Qiu et al., 2013).

4. The interaction between Trp metabolism and fungi, and its potential effects on infection treatment

4.1. Trp metabolism and Candida albicans

C. albicans is a normal component of the human gut microbiota and become pathogenic under opportunistic conditions. Because of recent years' extensive use of organ transplantation, immunosuppressants, glucocorticoids, broad-spectrum antibiotics and tumor chemotherapy, the incidence of invasive candidiasis infections has been on the rise (Mohamed et al., 2019). Trp and its metabolites have crucial effects on mammalian physiology, such as gastrointestinal and immune systems (Modoux et al., 2021). As a result, the relationship between Trp metabolism and *C. albicans* and their interaction mechanisms have aroused a lot of interest.

In a mouse gastrointestinal infection model caused by *C. albicans,* inhibition of IDO significantly aggravated infection and associated inflammation because of deregulated immune responses. In vitro experiment also found that blockade of Trp catabolism promoted yeast-to-hyphal transition of *C. albicans* (Fig. 2a) (Bozza et al., 2005). Through inhibition of IDO expression, live *C. albicans* could modulate host Trp metabolism, shifting it away from Kyn pathway and towards 5-HT pathway to produce more 5-hydroxytryptophan to inhibit IL-17 production, which is a pivotal cytokine in host defense against *C. albicans* infection (Fig. 2b) (Cheng et al., 2010, 2012; Krause et al., 2015). These researches suggest that Trp metabolism plays an important role in preventing *C. albicans* infection. Some metabolites of Trp show inhibitory effects on *C. albicans* invasion. For instance, IL-22, in combination with IL-17A, induces a vital innate anti-fungal resistance in both mice (De Luca et al., 2010) and humans (Puel et al., 2010). Indole-3-aldehyde (I3A), a Trp metabolites produced by lactobacilli under condition of unrestricted Trp availability, could bind to AhR and promote IL-22 transcription, thereby enhancing colonization resistance to *C. albicans* (Fig. 2c) (Zelante et al., 2013). Additionally, amelioration of intestinal *C. albicans* infection through applying diallyl disulfide (DADS) has been accompanied with increased indoles and their derivatives (Hu et al., 2021). Picolinic acid, another Trp metabolite, enhances murine neutrophils' role to inhibit *C. albicans* growth (Abe et al., 2004). In dextran sulfate sodium (DSS)-induced *C. albicans* intestinal infection, Trp metabolites such as KYNA and indoleacetic acid markedly decreased inflammatory activities, protected gut barrier function, reduced levels of IL-22 produced by group 3 innate lymphoid cells (ILC3) in colonic lamina propria and decreased expression of other associated inflammatory cytokines (Fig. 2d) (Peng et al., 2024). In candidemia patients, Trp metabolites, including quinaldic acid, quinoline-4,8-diol and KYNA, were significantly decreased. In Caco-2 cells co-cultured with

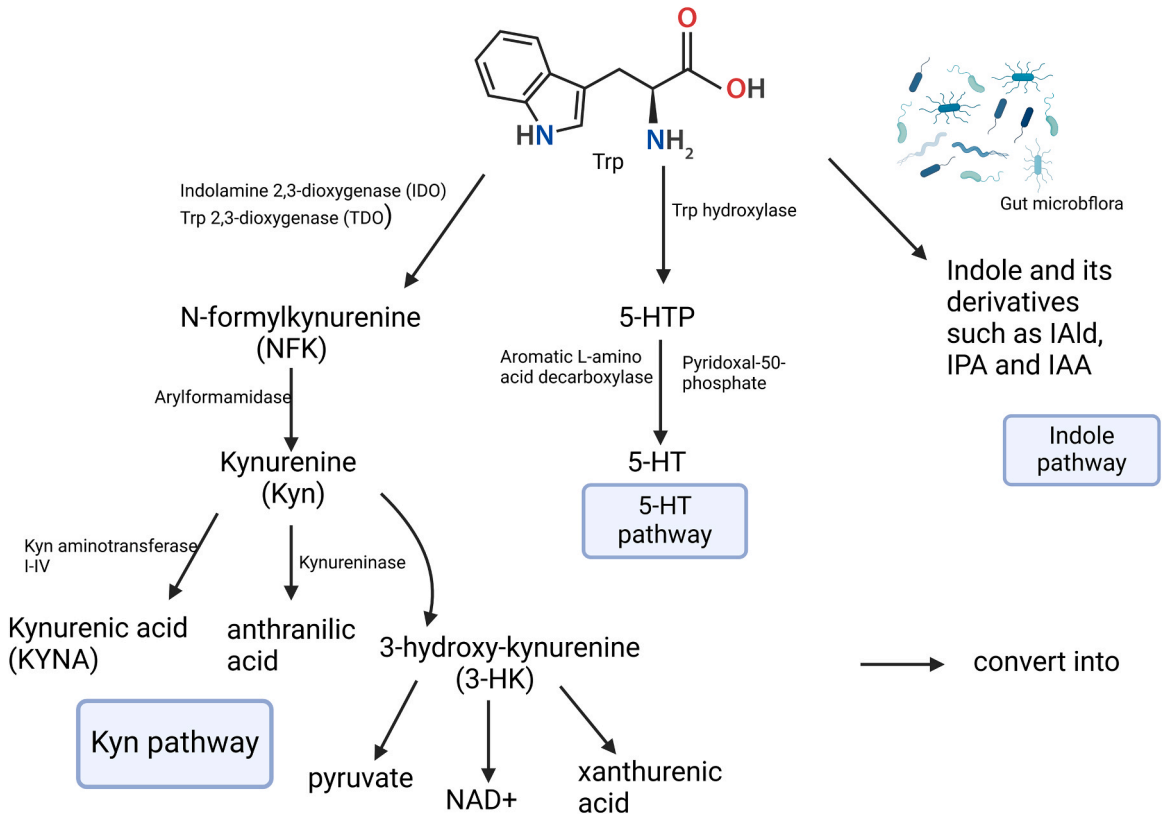

Fig. 1. Overview of Trp metabolism. Trp: tryptophan; IDO: indolamine 2,3-dioxygenase; TDO: Trp 2,3-dioxygenase; NFK: N-formylkynurenine; Kyn: kynurenine; KYNA: kynurenic acid; 3-HK: 3-hydroxy-kynurenine; NAD: nicotinamide adenine dinucleotide; 5-HTP: 5-hydroxy-L-tryptophan; 5-HT: 5-hydroxytryptamine; IAld: indole-3-acetaldehyde; IPA: indole-3-propionic acid; IAA: indole-3-acetic acid.

C. albicans, KYNA could activate AhR to inhibit MLCK-pMLC signaling pathway, promoting intestinal tight junction protein expression and enhancing intestinal barrier function. And KYNA could also increase tristetraprolin expression, suppressing MK2-p-MK2 signaling pathway and alleviating intestinal inflammation (Fig. 2e) (Wang et al., 2022b). Additionally, IPA generated by gut microbiota has been found to induce Ca^{2+}-dependent apoptosis in *C. albicans* (Fig. 2f) (Han and Lee, 2022). These experiment findings indicate that Trp metabolites may be promising therapeutic agents for treating gut infections caused by *C. albicans*.

4.2. Trp metabolism and Aspergillus

The rise of nosocomial infection frequency is becoming the main problem for public health, especially in immunocompromised individuals. *Aspergillus* is an opportunistic fungus normally present in the environment and is directly responsible for lethal nosocomial infections (Dindo et al., 2018).

Increased IDO activity in the host can alleviate inflammation and but also suppress antifungal Th17 responses, thereby favoring *Aspergillus* growth (Romani et al., 2008; Zelante et al., 2009b). Kyn can activate AhR to induce $Foxp3^+$ Treg differentiation while suppressing Th17 cells, dampening intestinal inflammation. (Díaz-Díaz et al., 2016) Similar mechanisms occur in *Aspergillus* infections, where IDO-driven Kyn suppresses antifungal Th17 responses, favoring fungal persistence. For example, epithelial IDO suppresses the functions of $CD4^+$ T cells via Kyn production during *Aspergillus fumigatus* antigen exposure (Paveglio et al., 2011). However, defective IDO activity reduces Kyn production also induces Th17 overactivation and also increases susceptibility to *Aspergillus* infection. Treatments with IDO agonists, prevention of Th17-cell activation can restore anti-fungal protective immunity in this situation (Iannitti et al., 2013). And during *Aspergillus fumigatus* pneumonia, 5-HT, a Trp metabolite produced by mast cells, promotes IDO1/Kyn pathway in host, restricting microbial activation of the indole/AhR pathway and contributing to pathogen clearance and immune homeostasis (Renga et al., 2023). These contradictory results indicate that maintaining IDO activity in host at a reasonable level is very important for their immune homeostasis and anti-fungal infection immunity. Extreme up-or-down regulation of the Kyn pathway can have adverse effects on anti-fungal defenses. In addition, *Aspergillus* itself also express IDO to synthesize nicotinamide adenine dinucleotide (NAD^+) through Kyn pathway and contribute to fungal growth (Wang et al., 2016). *Aspergillus fumigatus* without IDO expression will catabolize Trp via the indole pathway to produce indole derivatives which targets host AhR, resulting in aggravating fungal pathogenicity and inflammation in mouse aspergillosis models. Pharmacologically inducing IDO expression in *Aspergillus* improves infection outcome (Zelante et al., 2021), suggesting that targeting Trp pathway enzymes in host or *Aspergillus* may provide novel antifungal therapies.

Aspergillus ochraceus could secret ochratoxin A, a kind of widely presented mycotoxin that increases intestinal *Bacteroides plebeius* abundance. Increased *B. plebeius* then decreased intestinal Kyn metabolism, and inhibited liver Kyn metabolism revealed by decreased ATP level (Ma et al., 2023). This energy deficit in liver induced by abnormal Trp metabolism could activate AMPK to inhibit the mTOR signaling (Ma et al., 2023), reducing protein synthesis, and increasing autophagy, ultimately causing inflammation and weight loss in animal models (Chalkiadaki and Guarente, 2015; Kim et al., 2019; Kaushal et al., 2020; Xia et al., 2021). Trp treatment can attenuate the damaging effects of ochratoxin A on intestinal morphology, suggesting Trp supplementation may be an available mean to reduce the harmful effects of ochratoxin A on the intestinal mucosa (Ricci et al., 2020). These results show that Trp metabolism disturbance is part of ochratoxin A toxic mechanism and Trp metabolism might be a promising target for treatment of *Aspergillus ochraceus* infection.

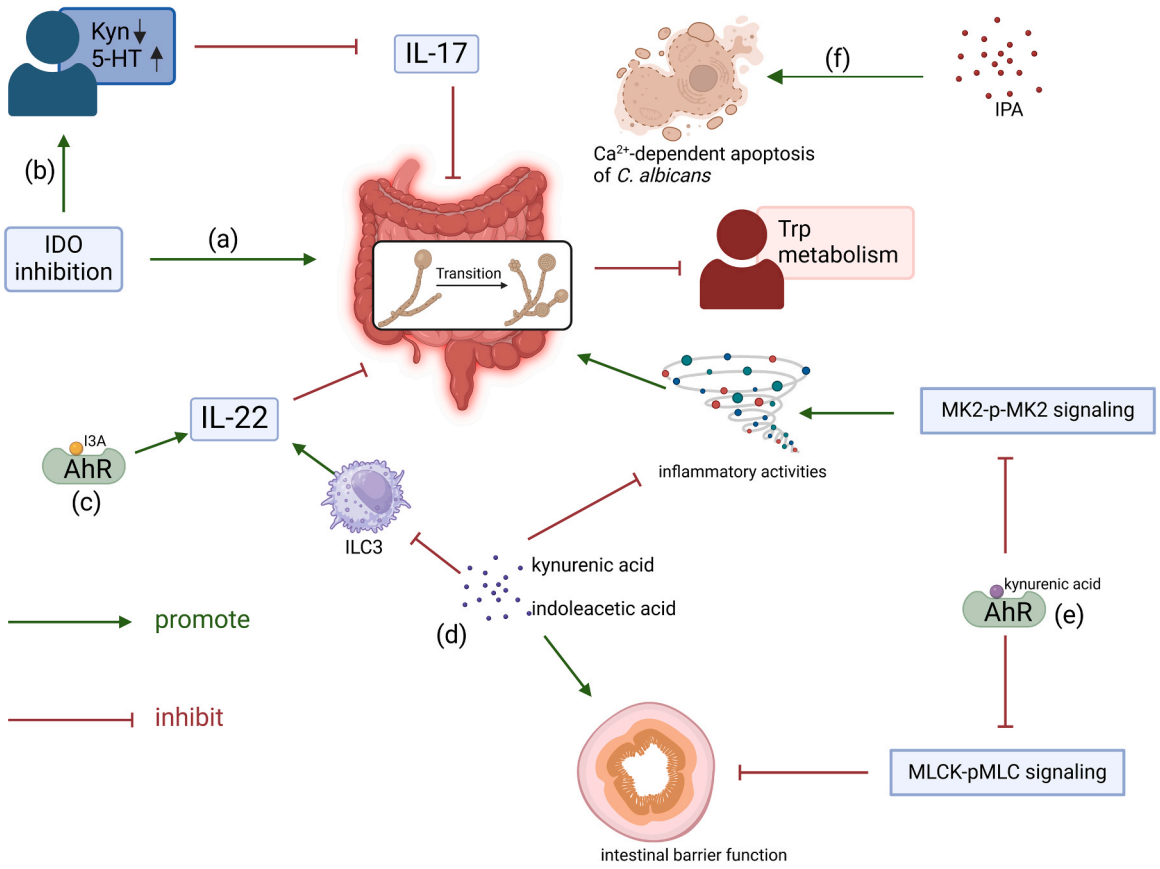

Fig. 2. Interactions between Trp and *C. albicans*. (a) IDO inhibition aggravates *C. albicans* infection and promoted the yeast-to-hyphal transition of *C. albicans*; (b) IDO inhibition caused by *C. albicans* shifts host Trp metabolism toward increased 5-HT production, which inhibited IL-17 production and thereby promoted infection; (c) I3A binds to AhR enhancing IL-22 transcription and providing colonization resistance to *C. albicans*; (d) In DSS-induced *C. albicans* intestinal infection, kynurenic acid and indoleacetic acid decrease inflammatory activities, protect intestinal barrier function and reduce IL-22 produced by ILC3; (e) Kynurenic acid activates AhR to inhibit MLCK-pMLC signaling pathway, promoting intestinal barrier function, and suppresses MK2-p-MK2 signaling pathway to alleviate intestinal inflammation caused by *C. albicans*; (f) IPA induces Ca^{2+}-dependent apoptosis in *C. albicans*. Trp: tryptophan; IDO: indolamine 2,3-dioxygenase; Kyn: kynurenine; 5-HT: 5-hydroxytryptamine; AhR: aryl hydrocarbon receptor; I3A: indole-3-aldehyde; ILC3: group 3 innate lymphoid cells; IPA: indole-3-propionic acid.

5. The interaction between Trp metabolism and bacteria, and the potential effects of Trp on infection treatment

5.1. Trp metabolism and Ruminococcus gnavus

R. gnavus, a ubiquitous human gut symbiont, is an early colonizer in the infant gut and exists throughout adulthood (Juge, 2023). While tryptamine generated from bacterial Trp metabolism (Marcobal et al., 2013) is uncommon among human commensal bacteria, *R. gnavus* is responsible for conversion of Trp into tryptamine (Williams et al., 2014). Trp metabolism mediated by *R. gnavus* plays an important role in regulating intestinal homeostasis. Tryptamine produced by *R. gnavus* activates epithelial serotonin receptor-4, a kind of G-protein-coupled receptor, to increase anion-dependent proximal colon secretion, thereby accelerating gastrointestinal transit (Fig. 3a) (Bhattarai et al., 2018). Tryptamine produced by *R. gnavus* also binds to trace amine-associated receptor 1 (TAAR1) to promote serotonin biosynthesis in intestinal enterochromaffin cells, which increases gastrointestinal (GI) motility and secretion, suggesting a mechanistic insight in irritable bowel syndrome-diarrhea(IBS-D) (Fig. 3b) (Zhai et al., 2023). Additionally, bacterially derived tryptamine prevents barrier disruption and ameliorates weight loss in DSS-induced colitis mice (Fig. 3c), demonstrating its potential as a therapeutic pathway for treat inflammatory conditions of the gut (Bhattarai et al., 2020).

5.2. Trp metabolism and Bacteroides

Bacteroides species consist of approximately 40 % of healthy children's gut microbiome and their abundance can increase with age (Hollister et al., 2015). *Bacteroides* usually beneficially affect metabolic, immune and physiological homeostasis in the host (Mazmanian et al., 2005). The low abundance of *Bacteroides* can decrease the activity of Dopa decarboxylase, leading to the decrease of skatole produced from microbial metabolism of Trp. The reduced skatole may further down-regulate glucagon-like peptide-1 expression in intestinal endocrine L cells, resulting in increased blood glucose levels and contributing to Type 2 diabetes mellitus (Fig. 4a) (Liu et al., 2024). Research has shown that *Bacteroides ovatus* can metabolize Trp into IAA and suggests that IAA produced by *Bacteroides ovatus* promotes IL-22 expression in immune cells to improve colitis (Fig. 4b) (Ihekweazu et al., 2021). Similarly, this beneficial effect is also found in other *Bacteroides* species. *Bacteroides thetaiotaomicron* moderates colitis in IL-10 knockout and DSS-induced colitis models (Delday et al., 2019). *Bacteroides fragilis* treatment ameliorates inflammation in DSS and trinitrobenzene sulfonic acid (TNBS)-induced colitis models (Round and Mazmanian, 2010; Chiu et al., 2014). Additionally, tryptamine catabolized by *Bacteroides thetaiotaomicron'* s Trp decarboxylase is similar to 5-HT and can bind to the 5-HT_4 receptor on colonic epithelium to increase intestinal secretion and accelerate GI transit (Bhattarai et al., 2018), and this mechanism is like the former mentioned interaction between Trp and *Ruminococcus gnavus* (Fig. 4c) (Bhattarai et al., 2018).

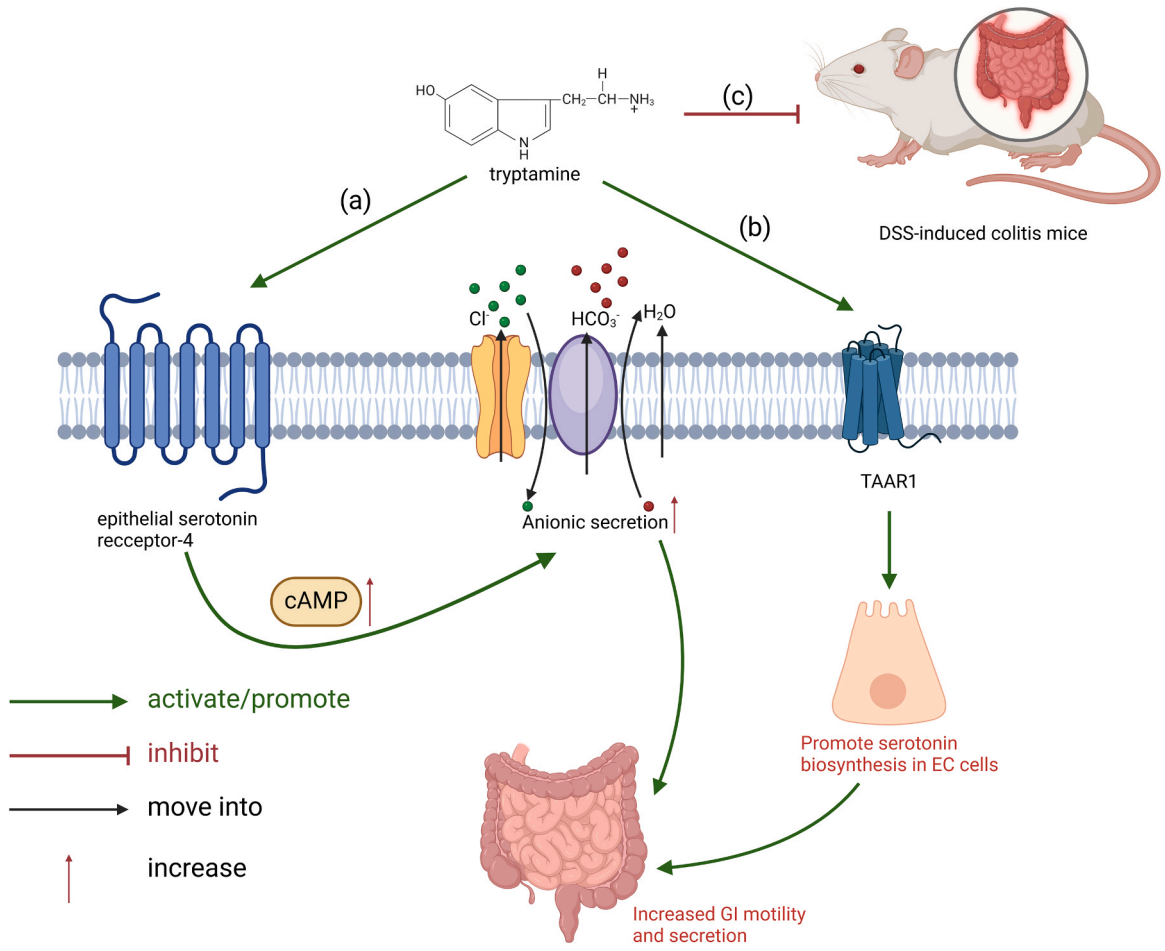

Fig. 3. Interactions between Trp and *R. gnavus*. Tryptamine produced by *R. gnavus* can (a) activate epithelial serotonin receptor-4 to increase anion-dependent colon secretion, thereby accelerating gastrointestinal transit; (b) bind to TAAR1 to promote serotonin biosynthesis in intestinal enterochromaffin cells, increasing GI motility and secretion; (c) ameliorate weight loss in DSS-induced colitis mice. Trp: tryptophan; TAAR1: trace amine-associated receptor 1.

5.3. Trp metabolism and Prevotella copri

Prevotella copri, a gram-negative anaerobe, is the primary species of the *Prevotella* genus in gut microbiota (Tett et al., 2021) and associated with various diseases including gout (Chu et al., 2021) and obesity (Dong et al., 2022). Indole-3-pyruvic acid (IPyA) is an indole compound derived from interaction between the host and gut microbiota in Trp metabolism, and is usually accumulated in host at normal levels (Agus et al., 2018). IPyA is an intrinsic anti-cancer agent in the host at physiological levels and excessive *P. copri* can exhaust intrinsic IPyA to promote tumor growth, highlighting importance of the interaction between Trp metabolism and *P. copri* in the gut as a pathway in tumor progression (Su et al., 2024).

5.4. Trp metabolism and Clostridium difficile

C. difficile is the primary reason of globally hospital- and antibiotic-associated diarrhea and is unique among gut pathogens due to its characteristic tendency to persist in the gut and recur after antimicrobial therapy (Stanley et al., 2013; Cole and Stahl, 2015). Although *C. difficile* itself doesn't produce indole, it can promote indole production in other bacteria via secreting quorum signaling to beneficial gut-protective and indole-sensitive microbiota. Increasing indole levels in the gut reduces colonic microbial diversity and alters colonization resistance, leading to sustained or recurrent *C. difficile* infection (Darkoh et al., 2019). In view of this mechanism, a study found that compared with vancomycin, fecal microbiota transplantation (FMT) could not only ameliorate *C. difficile* infection-induced clinical symptoms and intestinal tissue damage, but also could better replenish intestinal microbiota and reduce Trp metabolism in the gut metabolome to promote the recovery of colonization resistance in *C. difficile* infected mice, thus offering a new insight for the prevention of recurrent *C. difficile* infection (Xu et al., 2022). Kyn produced by IDO1 expressed in cecal lamina propria cells can limit IFNγ-expressing neutrophil accumulation via Kyn-triggered apoptosis, thereby leading to less severe immunopathology in *C. difficile* infection. While IDO1 inhibitors used in cancer immunotherapy may exacerbate the severity of *C. difficile* colitis (El-Zaatari et al., 2014). These researches indicate that though *C. difficile* itself doesn't metabolize Trp into indole compounds, Trp metabolites produced by host or other gut microbiota have pivotal influence on *C. difficile* colonization and infection.

5.5. Trp metabolism and Escherichia coli

Escherichia coli is the Gram-negative, rod-shaped bacterium (Croxen et al., 2013) and this bacterium can become pathogenic via mobile virulence genes' expression (Croxen and Finlay, 2010). Recent studies have found that Trp metabolism plays a vital role in ameliorating GI infection caused by *E. coli*. Increased Trp content in the feed is useful in preventing and controlling pathogenic *E. coli* intestinal infections (Peng et al., 2020).

Intestinal AhR activation mediated by microbiota plays a pivotal role in host-microbiota interactions and disease progression (Zhao et al., 2022). IAld and indole produced by gut microbiota-mediated Trp

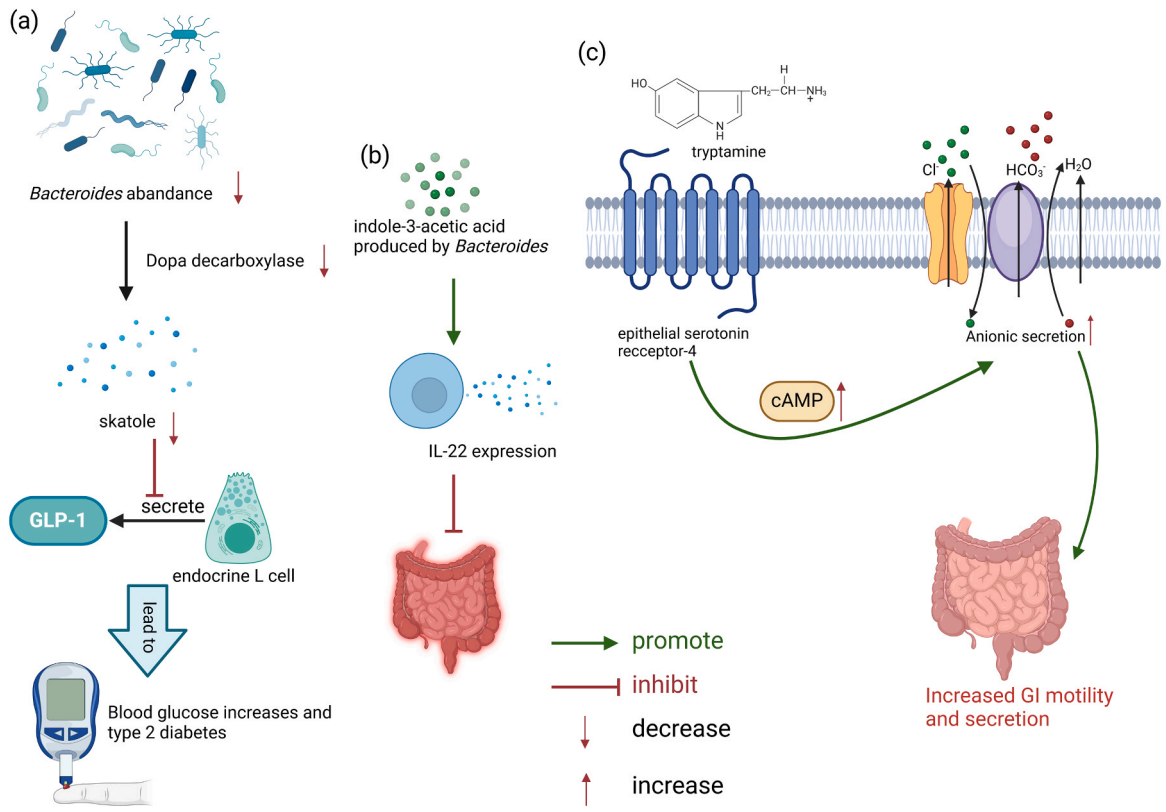

Fig. 4. Interactions between Trp and *bacteroides*. (a) The low abundance of *Bacteroides* leads to the decrease of skatole produced from Trp. The reduced skatole may further down-regulate GLP-1 expression in endocrine L cells, resulting in increased blood glucose levels and contributing to Type 2 diabetes mellitus; (b) Indole-3-acetic acid produced by *Bacteroides ovatus, Bacteroides thetaiotaomicron* and *Bacteroides fragilis* could promote IL-22 expression in immune cells to improve colitis; (c) Tryptamine catabolized by *Bacteroides thetaiotaomicron* can bind to 5-HT_4 receptor on colonic epithelium to increase GI secretion and transit. Trp: tryptophan.

metabolism can activate AhR to alleviate *E. coli*-induced mastitis in a mouse model through reinforcing epithelial barrier function and restricting NF-κB activation (Fig. 5a) (Zhao et al., 2021a). Similarly, administration of indole and indole aldehyde could also bind to AhR to ameliorate *E. coli*-induced endometritis through restoring barrier function and suppressing inflammatory responses (Zhao et al., 2022). Overexpressed IDO1 in the epithelium was also found to non-enzymatically interact with AhR to inhibit NOTCH1 signaling, increasing intestinal secretory cell differentiation, resulting in a thicker mucus layer and thus resisting enteropathogenic *E coli* infection (Fig. 5b) (Alvarado et al., 2019).

A high-fat diet can promote *E. coli* gut colonization (Wotzka et al., 2019) through increasing pathogen's antibiotic tolerance, and the indole pathway metabolite IAA supplementation could significantly reverse this effect (Fig. 5c) (Liu et al., 2021). Generally speaking, biofilm formation confers bacteria resistance to some physical treatments and antibiotics (Zottola and Sasahara, 1994; Costerton et al., 1995, 1999; Kumar and Anand, 1998; Davey and O'Toole., 2000) and thus has become a serious problem for medical and food hygiene. Research found that lower Trp level in *E. coli* promotes biofilm formation and higher intracellular Trp level inhibits biofilm formation. Additionally, Trp added in *E. coli* culture degraded the preformed biofilm (Fig. 5d) (Shimazaki et al., 2012).

Recently, Trp metabolites were found to regulate pathogenic *E. coli* infection through targeting dopamine receptor D2 on intestinal epithelium. *E. coli* serotype O157:H7 is an attaching and effacing food-related pathogen that can cause severe bloody diarrhea, gastroenteritis, enterocolitis and acute renal failure (Kaper et al., 2004; Croxen and Finlay, 2010). Trp metabolites produced by gut microbiome can promote host colonization resistance against *Citrobacter rodentium*, a kind of *E. coli*, through activating dopamine receptor D2 on intestinal epithelium. These activated receptors then decrease the expression of a host actin regulatory protein which involved in the colonization of *C. rodentium* and *E. coli* on gut epithelium (Fig. 5e), implying a new targeted pathway to create new prophylactics or therapeutic agents focusing on improving gut health and treating GI infection caused by pathogenic *E. coli* (Scott et al., 2024).

Trp can also metabolized by *E. coli* itself to ensure survival. Under inflammation-mimetic conditions in host, *E. coli* could produce indole metabolites named "indolokines"to enhance persisting *E. coli* biofilm formation under antibiotics treatment (Fig. 5f) (Kim et al., 2020). These findings provide clues for finding innovative therapeutic strategies to treat *E. coli* infections.

5.6. *Trp metabolism and lactobacilli*

Some lactobacilli (such as *Limosilactobacillus reuteri*) have been demonstrated to be probiotic, and proper application of them can benefit host health (Mu et al., 2018). Through metabolomics, researchers have found that, in addition to IAA, other Trp metabolites of lactic acid bacteria exhibit high species specificity. The concentration of Trp metabolites remains steadily within the same species, while only a small fraction of strains shows strain-specific Trp metabolism (Pan et al., 2023).

Trp catabolism is one of the mechanisms used by *L. reuteri* to exert anti-infection and anti-inflammatory properties. *L. reuteri* has the ability to produce AhR ligands (Lamas et al., 2016; Natividad et al., 2018), especially transforming Trp into AhR ligands such as IAld and indole cpmpounds (Zelante et al., 2013; Agus et al., 2018). Administration of *L. reuteri* in healthy newborn mice elevated Trp metabolite levels, including indoles and adenosine, which improve immune tolerance to inflammatory stimuli (Liu et al., 2019). Additionally, *L. reuteri*

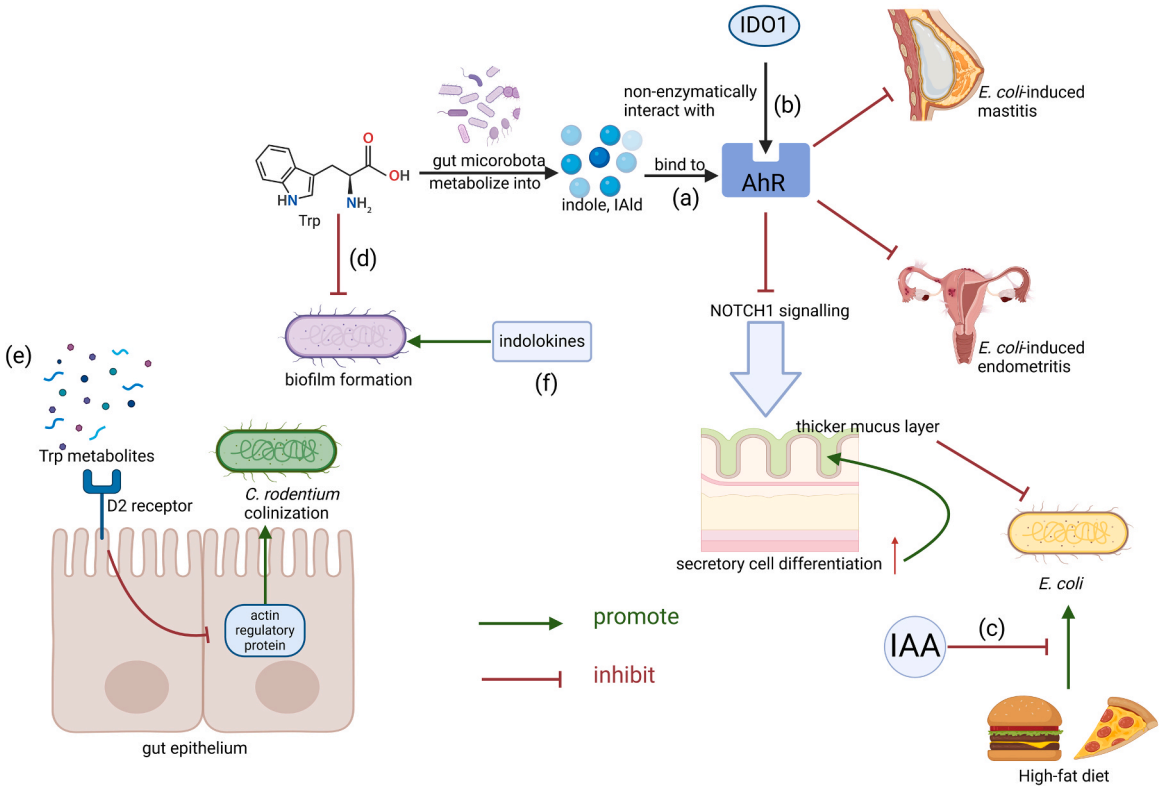

Fig. 5. Interactions between Trp and *E. coli*. (a) IAld and indole produced by gut microbiota can bind to AhR to alleviate *E. coli*-induced mastitis and endometritis; (b) Overexpressed IDO1 in epithelium could non-enzymatically interact with AhR to inhibit NOTCH1 signaling to increase intestinal secretory cell differentiation, resulting in a thicker mucus layer to resist *E. coli* infection; (c) IAA supplementation could significantly reverse high-fat diet-induced *E. coli* gut colonization; (d) High intracellular Trp level inhibits biofilm formation; (e) Trp metabolites produced by gut microbiome can activate dopamine receptor D2 of intestinal epithelium to decrease expression of a host actin regulatory protein, thus promoting host colonization resistance against *C. rodentium*; (f) *E. coli* could produce"indolokines"to enhance persisting *E. coli* biofilm formation under antibiotics treatment. Trp: tryptophan; IAld: indole-3-carboxaldehyde; IDO1: indolamine 2,3-dioxygenase 1; AhR: aryl hydrocarbon receptor; IAA: indole-3-acetic acid.

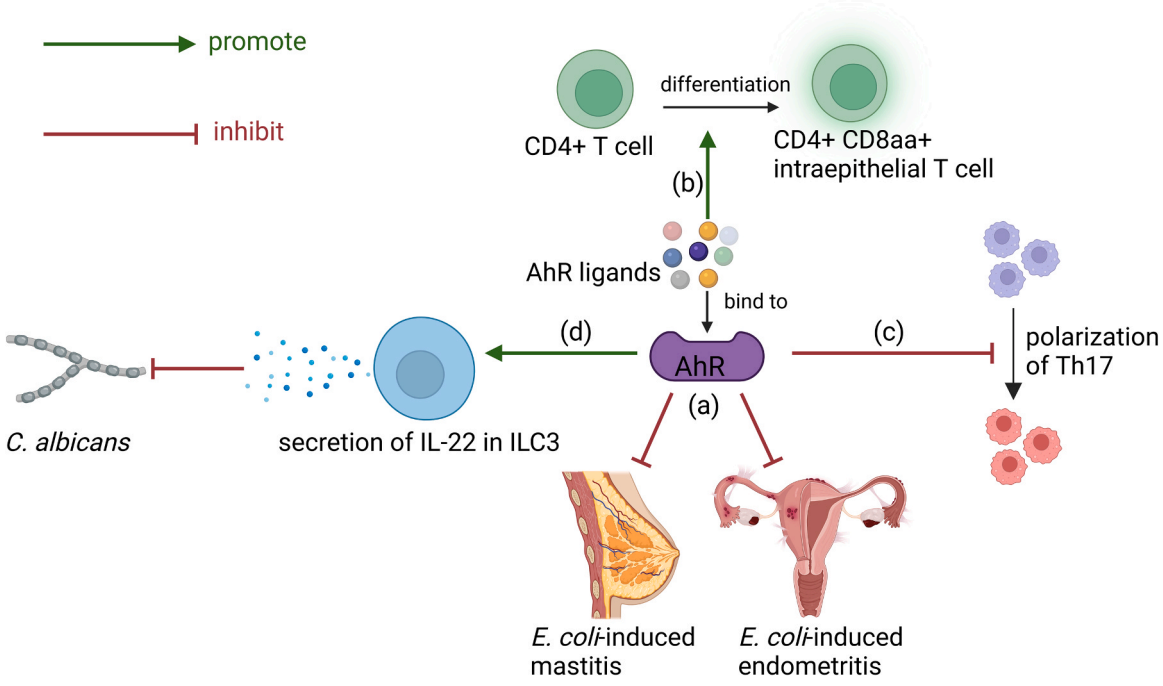

Fig. 6. Interactions between Trp and *L. reuteri*. (a) *L. reuteri* produces AhR ligands to ameliorate *E. coli*-induced mastitis and endometritis in an AhR-dependent manner; (b) *L. reuteri* produces ILA to activate AhR to enhance the differentiation of $CD4^+$ T cells into $CD4^+$ $CD8aa^+$ double positive intraepithelial lymphocytes; (c) ILA inhibits the polarization of Th17 cells in mouse; (d) IAld acts as a ligand for AhR, promoting ILC3 to secrete IL-22, thereby protecting the host against *C. albicans* infection. Trp: tryptophan; AhR: aryl hydrocarbon receptor; IAld: indole-3-carboxaldehyde; ILC3: group 3 innate lymphoid cells.

supplementation produces AhR ligands that ameliorate *E. coli*-induced mastitis in an AhR-dependent manner. (Zhao et al., 2021a) And *L. reuteri* was also observed to repress *E. coli*-induced endometritis in mice model by metabolizing Trp into AhR agonists (Fig. 6a) (Zhao et al., 2022). Indole-3-lactic acid (ILA) is a key Trp metabolite of *L. reuteri* in the amelioration of inflammation and gut microbiota modulation. (Wang et al., 2024) *L. reuteri* colud enhance the differentiation of $CD4^+$ T cells into $CD4^+$ $CD8aa^+$ double positive intraepithelial lymphocytes through producing ILA (Fig. 6b), which activates AhR and represses the transcription factor Thpok (Cervantes-Barragan et al., 2017). In vitro, ILA has been demonstrated to inhibit polarization of Th17 cells in mice (Fig. 6c) (Wilck et al., 2017). Additionally, IAld and ILA reprograms intraepithelial $CD4^+$ T helper cells into immunoregulatory T cells via AhR activation (Cervantes-Barragan et al., 2017). IAld from *L. reuteri* dietary Trp metabolism acts as a ligand for AhR activation on $CD4^+$ T cell surface (Zelante et al., 2013) and promote ILC3 to secrete IL-22 (Spits et al., 2013), protecting host against *C. albicans* infection and mucosal inflammation (Fig. 6d) (Zelante et al., 2013). Through bacterial cross-feeding, ILA promotes the proliferation of bacteria encoding Trp metabolism-relevant enzymes, thereby increasing microbial Trp metabolites (such as IPA and IAA) synthesis in vivo and in vitro. Then IPA activates pregnane X receptors (PXR) to exert anti-inflammation and intestinal barrier-strengthening functions, while IAA modulates gut microbiota independently of AhR activation (Wang et al., 2024). Trp metabolite indoles produced by *L. reuteri* can also result in an elevation in proportion of intestinal flora that are capable of producing indole and increasing AhR expression (Fang et al., 2022), thereby repressing intestinal inflammation and regulating host immunity (Alexeev et al., 2018; Pernomian et al., 2020).

Some lactobacilli can excellently regulate immune functions, not only improving the gut immune function but also regulate immunity of other organs (Chong et al., 2019; Hojsak, 2019; Gao et al., 2021). *Ligilactobacillus murinus* restricts Th17 cell differentiation in the spinal cord and spleen via increasing the production of ILA (Wilck et al., 2017). Indole compounds, such as IA and IAId produced by *L. murinus*, activate AhR to regulate Th17/Treg imbalance via decreasing the proportion of Th17 cells and increasing Treg cells in lung tissues. This process alleviates polycyclic aromatic hydrocarbon-induced lung inflammation, ultimately influences lung homeostasis through gut-lung axis, and highlights *L. murinus*' potential as a novel therapeutic approach for treating environmental pollution-induced lung diseases (Zhu et al., 2024). In addition to producing indole compounds, *L. murinus* preferentially metabolizes absorbed Kyn into KYNA (Schwarcz et al., 2024), which regulates the host immune system through its agonistic effects on AhR (DiNatale et al., 2010) and effectively scavenges ROS (Lugo-Huitrón et al., 2011; Kubicova et al., 2019).

Some *L. reuteri*-mediated dietary Trp metabolites can unexpectedly exacerbate experimental autoimmune disease, mechanistically as these Trp-derived metabolites produced by *L. reuteri* activate AhR and enhance T cell production of IL-17 (Montgomery et al., 2022). *L. reuteri*-produced I3A which can activate AhR to promote IL-22-dependent mucosal protection paradoxically exacerbates autoimmune diseases by enhancing IL-17 production (Zelante et al., 2013; Bender et al., 2023). At the same time, some Trp metabolites produced by lactobacilli can improve the progression of some immune-mediated diseases. Membranous nephropathy (MN), a distinct organ-limited autoimmune glomerular disease (Wang et al., 2022a; Hua et al., 2023), can be alleviated by Trp metabolites such as IpyA, IAld, and tryptamine produced by lactobacilli (including *L. johnsonii, L. murinus, L. vaginalis and L. reuteri*), which act as antagonists to inhibit intrarenal AhR signaling activation (Miao et al., 2024).

5.7. Trp metabolism and Mycobacterium tuberculosis

Tuberculosis (TB), caused by *M. tuberculosis* is the leading cause of global death, and new strategies are urgently needed to eradicate TB. Many studies found increased catabolism of converting Trp to Kyn in both active and latent TB infection (Collins et al., 2020). As a result, the ratio of Kyn/Trp has been proposed to predict the prognosis of TB disease (Suzuki et al., 2012).

The innate immune system induces IFNγ-mediated cellular Trp depletion in response to *M. tuberculosis* infection through promoting IDO1 expression and Kyn production (Fig. 7a) (Suzuki et al., 2012, 2013). IDO-mediated Trp depletion activates the GCN2 kinase pathway, leading to T-cell anergy and immunosuppression in tumors and chronic infections (Mellor and Munn, 2004). Kyn are effective molecules negatively regulating T-cell activity and inflammation. Dendritic cells produce Kyn to inhibit the active T-cell proliferation and induce Treg cell expansion, leading to immune tolerance which may contribute to chronic bacterial infection (Fig. 7b) (Mellor, 2005; Zelante et al., 2009a). Thus, IDO-1 inhibition can reduce the bacterial burden and severity of TB disease, and promote $CD4^+$ and $CD8^+$ memory T cell proliferation. In addition, IDO-1 inhibition initiates granulomas remodeling, allowing $CD4^+$ T cells to have greater access to the necrotic and bacteria-rich central region, thus markedly raising immune-related *M. tuberculosis* elimination (Fig. 7c) (Gautam et al., 2018). IFN-γcan also induce expression of Interleukin-4 induced 1 (IL4i1), an L-amino acid oxidase, resulting in the conversion of Trp into IPA, IAA, and KYNA. This effect is linked to M2 macrophage polarization, which is associated with anti-inflammation and promoting TB disease progression (Fig. 7d) (Zhang et al., 2024a). The gut microbiota metabolite IPA also can inhibit *M. tuberculosis* growth in vitro and in vivo (Negatu et al., 2018). Trp biosynthesis in *M. tuberculosis* is essential for *M. tuberculosis* proliferation and survival (Zhang et al., 2013; Wellington et al., 2017) and is regulated by Trp itself, which is a cooperative allosteric inhibitor of TrpE, and an anthranilate synthase that catalyzes the first step of Trp biosynthesis (Morollo and Eck, 2001; Bashiri et al., 2015). IPA, the deaminated form of Trp, can mimic Trp to bind to TrpE to inhibit Trp biosynthesis regardless of intracellular Trp concentrations, thus exerting antibacterial activity (Fig. 7e) (Negatu et al., 2019). These studies suggest that Trp metabolism and synthesis has a vital role in the development of TB infection and governing Trp metabolism may be a new strategy targeted to teat TB disease.

5.8. Trp metabolism and Pseudomonas aeruginosa

P. aeruginosa, a gram-negative bacterium, mainly infects burnt or immunocompromised patients and is one of the main reasons of nosocomial infections (Lyczak et al., 2000).

Unlike most bacteria catabolizing Trp anaerobically into indole compounds (Yanofsky, 2007), *P. aeruginosa* metabolizes Trp through Kyn pathway (Stanier et al., 1951) to produce anthranilate, a crucial precursor of pseudomonas quinolone signal, which acts as a kind of virulence factor in infection (Fig. 8a). When anthranilate production is impaired, Trp metabolism of *P. aeruginosa* turns to produce KYNA (Bortolotti et al., 2016). Due to metabolites in Kyn pathway known to modulate host immune responses, the Kyn pathway in *P. aeruginosa* may allow immunomodulatory interplay between bacteria and host. Kyn produced by *P. aeruginosa* can scavenge reactive oxygen species produced by neutrophile granulocytes to circumvent the innate immune response in the acute phase of *P. aeruginosa* infection (Fig. 8b). Additionally, Kyn is also the essential precursor of quinolone signal as former mentioned, and is involved mainly in chronic infections. (Genestet et al., 2014) In contrast, some studies also have found that Trp and its derivatives can assist host immunity to against *P. aeruginosa* invasion. A study found that AhR ligands (Trp and indole) supplementation can enhance intestinal IKKβ/NF-κB activation and intestinal ROS production to promote alveolar macrophage activity and lung defense mechanisms against antibiotic-induced *P. aeruginosa* infection (Fig. 8c) (Tsay et al., 2019). Indole can increase the uptake of antimicrobials in *P. aeruginosa* through interacting with Mtr permease, a Trp specific importer (Fig. 8d) (Wu et al., 2022).

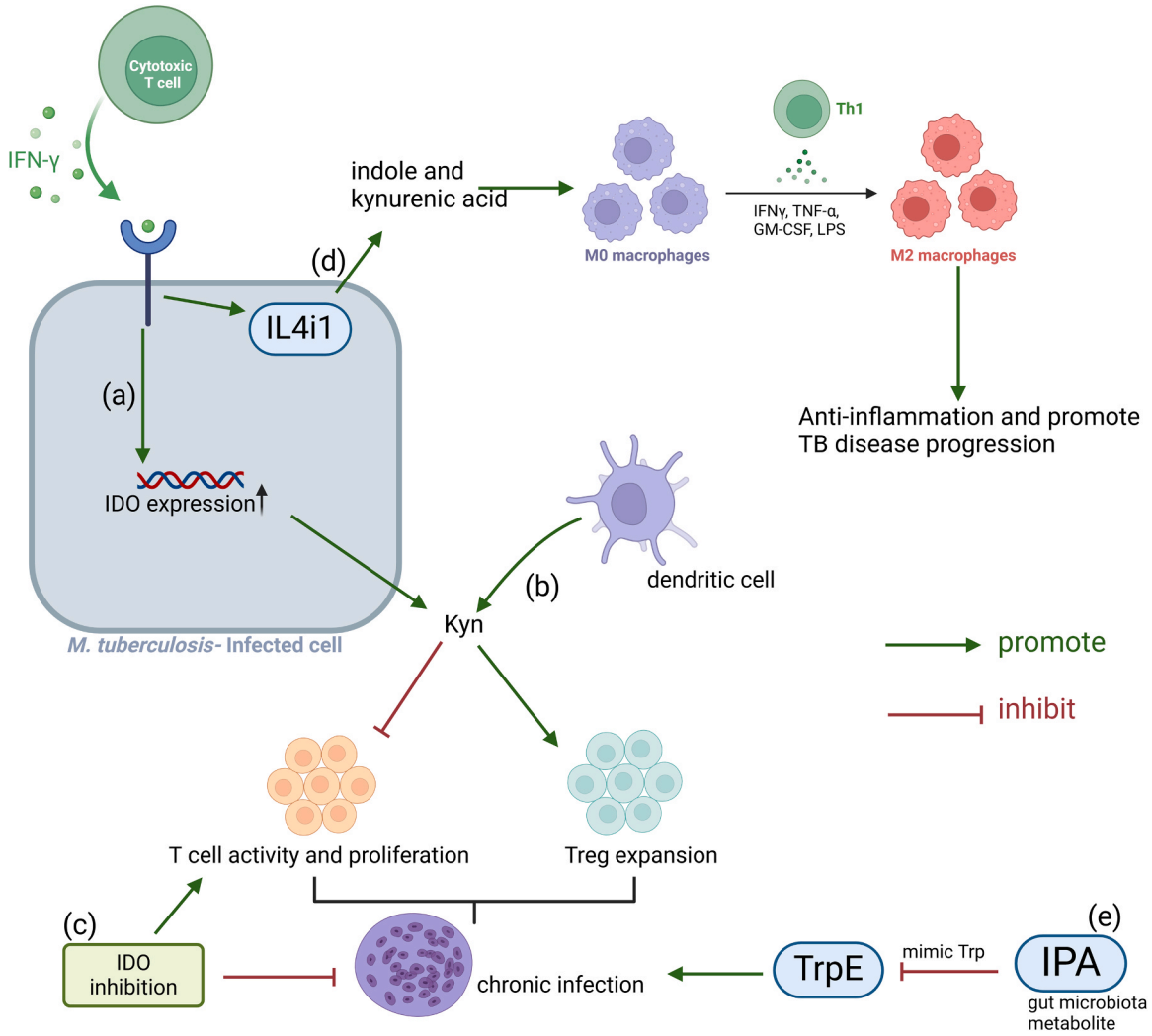

Fig. 7. Interactions between Trp and *M. tuberculosis*. (a) IFNγ can induce cellular Trp depletion in response to *M. tuberculosis* infection through promoting IDO1 expression and Kyn production; (b) Kyn produced by IDO can inhibit the active T-cell proliferation and induce Treg cell expansion, contributing to chronic bacterial infection; (c) IDO-1 inhibition can reduce the bacterial burden and severity of TB disease, and promote $CD4^+$ and $CD8^+$ memory T cells proliferation; (d) IFNγ can induce the expression of IL4i1, promoting the production of IPA, IAA, and kynurenic acid which are linked to M2 macrophage polarization; (e) IPA can inhibit *M. tuberculosis* growth through inhibiting TrpE to inhibit Trp biosynthesis in cells, thus exerting antibacterial activity. Trp: tryptophan; IDO: indolamine 2,3-dioxygenase; Kyn: kynurenine; IL4i1: Interleukin-4 induced 1; TB: Tuberculosis; IPA: indole-3-propionic acid; TrpE: Trp operon E.

Biofilm formation of *P. aeruginosa* can cause serious infections and contribute to chronic infections. Recent studies have found that bacterial Trp metabolite indole enhance this formation in a quorum sensing-independent manner (Lee et al., 2007; Kim et al., 2015). Another Trp metabolite anthranilate can induce dispersion of *P. aeruginosa* biofilm via reducing levels of intracellular c-di-GMP and enhancing bacterial swarming and swimming motilities without showing cytotoxicity to human cells at high concentrations, suggesting anthranilate is a promising anti-biofilm agent to inhibit *P. aeruginosa* biofilm formation (Fig. 8e) (Li et al., 2017). Therefore, targeting Trp metabolism in *P. aeruginosa* may be a promising way for the therapy of *P. aeruginosa* infections.

5.9. Trp metabolism and Staphylococcus aureus

Staphylococcus aureus, a round-shaped gram-positive bacterium, is one of the main causes of nosocomial infections globally (Otto, 2008). *S. aureus* is associated with a series of infections such as folliculitis, abscesses, meningitis, pneumonia, osteomyelitis, endocarditis (Moreira et al., 2017). Many studies have shown that during the infection progression, *S. aureus* develops biofilm within the host, thereby making the therapy more difficult (Donlan, 2002; Chakraborty et al., 2020).

Trp was found to inhibit the formation of *S. aureus* biofilm through influencing the quorum-sensing property and cell surface hydrophobicity of the pathogen (Fig. 9a) (Paul et al., 2021). D-Trp can trigger biofilms of *S. aureus* disassembly and its biofilm formation by disturbing the bacterial communication and inhibiting intra-and-interbacterial aggregation between *S. aureus* and other bacteria (Ghosh et al., 2019). Trp combined with 1,4-naphthoquinone works more efficiently to repress biofilm formation and induce the disintegration of pre-existing biofilms than their individual application (Paul et al., 2023). Another Trp metabolite anthranilate can inhibit *S. aureus* biofilm formation via reducing slime production without showing cytotoxicity to human cells at high concentrations, suggesting anthranilate is a promising anti-biofilm agent for inhibiting biofilm formation in *S. aureus* infection (Li et al., 2017).

Kyn pathway in *S. aureus* can be activated by curcumin, which makes Trp required for supporting bacteria growth decreased, thereby starving *S. aureus* of an essential nutrient to exert antimicrobial function (Adeyemi et al., 2020). And administration of 1-Methyl-Tryptophan (1-MT) can effectively inhibit the activity of IDO, elevate the concentrations of Trp to permit *S. aureus* growth, and abrogate IDO-mediated

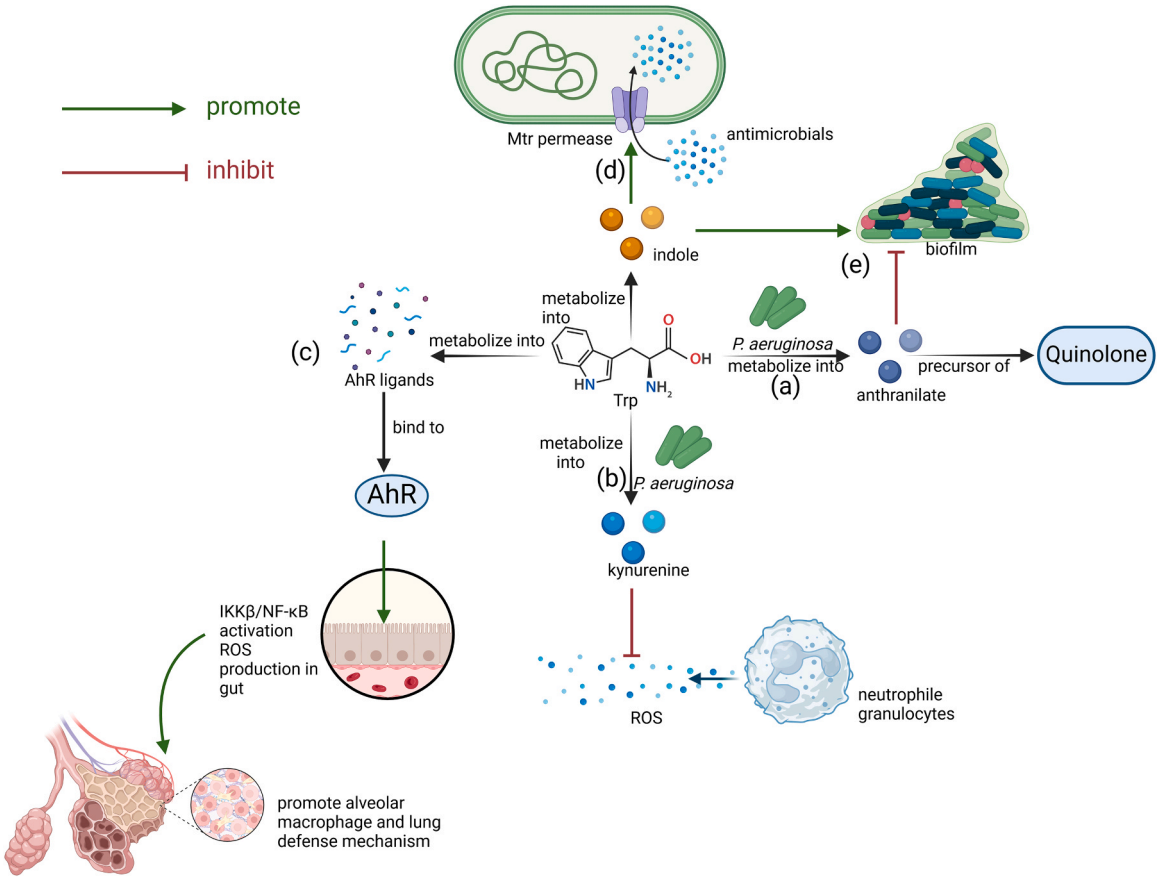

Fig. 8. Interactions between Trp and *P. aeruginosa*. (a) *P. aeruginosa* metabolizes Trp into anthranilate, a crucial precursor of pseudomonas quinolone signal that acts as a virulence factor in infection; (b) Kyn produced by *P. aeruginosa* can scavenge ROS from neutrophile granulocytes and is an essential precursor of quinolone signal; (c) AhR ligands can enhance intestinal IKKβ/NF-κB activation and intestinal ROS production to promote alveolar macrophage activity and lung defense mechanisms against antibiotic-induced *P. aeruginosa* infection; (d) Indole can increase the uptake of antimicrobials in *P. aeruginosa* through interacting with Mtr; (e) Indole enhances biofilm formation in a quorum sensing-independent manner, and anthranilate can induce dispersion of *P. aeruginosa* biofilm. Trp: tryptophan; Kyn: kynurenine; ROS: reactive oxygen species; AhR: aryl hydrocarbon receptor.

antimicrobial effects (Schmidt et al., 2012). TDO which is specifically expressed in liver has also shown antimicrobial effects against *S. aureus* (Schmidt et al., 2009) and the underlying mechanism may be similar with that of IDO. KYNA, produced by Kyn pathway of Trp metabolism, can reduce inflammatory responses and enhance the integrity of blood-milk barrier to alleviate *S. aureus*-induced mastitis through NF-κB inhibition and Nrf2/Ho-1 activation, which are probably mediated by GPCR35, rather than AhR (Fig. 9b) (Zhao et al., 2021b). In addition, 3-hydroxy-DL-kynurenine and α-picolinic acid derived from Kyn pathway have also shown strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig. 9c) (Narui et al., 2009).

Supplementation of IAA could inhibit persist *S. aureus* formation, and IAA combined with ciprofloxacin can promote the survival of high-fat-diet fed mice infected with MRSA persisters (Liu et al., 2021). Violacein, an environmental bacteria-producing bisindole formed by condensation of two Trp molecules, can quickly and dramatically permeabilize *S. aureus* to result in discontinuities or rips in the cytoplasmic membrane while not affect the cell wall, thus repressing *S. aureus* infection. The molecular mechanism is that violacein can directly bind to bacterial phospholipids and perturbs their structure and permeability (Fig. 9d) (Cauz et al., 2019).

5.10. Trp metabolism and Helicobacter. Pylori

H. pylori infection is a worldwide health problem (Malfertheiner et al., 2011) and has been demonstrated to cause a number of diseases affecting the gastrointestinal tract, such as peptic ulcer diseases.

The expression of Trp hydroxylase in gastric mucosa was found increased to produce more serotonin in symptomatic *H. pylori* infection when compared with asymptomatic infection, indicating that Trp metabolism plays a role in pathogenesis of *H. pylori* infection (Chojnacki et al., 2019). Human gastric mucosa infected by *H. pylori* was also found to express a high mount of IDO to attenuate Th1 and Th17 immune responses, promoting *H. pylori* pathogenicity and establishing an immunological tolerance condition (Fig. 10a) (Larussa et al., 2015). IDO activity in *H. pylori* infection is in vivo genetically regulated by TGFB1 and CTLA4 polymorphisms (Raitala et al., 2007) and further research has found that IDO expression could be induced by curcumin to down-regulate IL-17 levels in *H. pylori*-infected human gastric mucosa (Fig. 10b), suggesting a potential mechanism of IDO in alleviating *H. pylori*-induced immune-mediated inflammation (Larussa et al., 2018).

Trp and its metabolite melatonin, produced through 5-HT pathway, can contribute to the remedy of gastroduodenal ulcer caused by *H. pylori* infection (Fig. 10c). The probable mechanism is that Trp can promote melatonin and leptin generation in gastric mucosa, and these two hormones are involved in gastroprotection and ulcer healing due to their antioxidant and anti-inflammatory effects (Celinski et al., 2011).

H. pylori is a critical factor for gastric intestinal metaplasia (Scida et al., 2018; Zheng et al., 2022), which is characterized by enhanced caudal type homeobox 2 (CDX2) and/or mucin 2 (MUC2) expression (Chen et al., 2020, 2021). One research has found that *H. pylori* can activate cGAS/STING/TBK1/IRF3 signaling to promote KAT2-mediated Kyn pathway, resulting in XA production. XA can further enhance CDX2

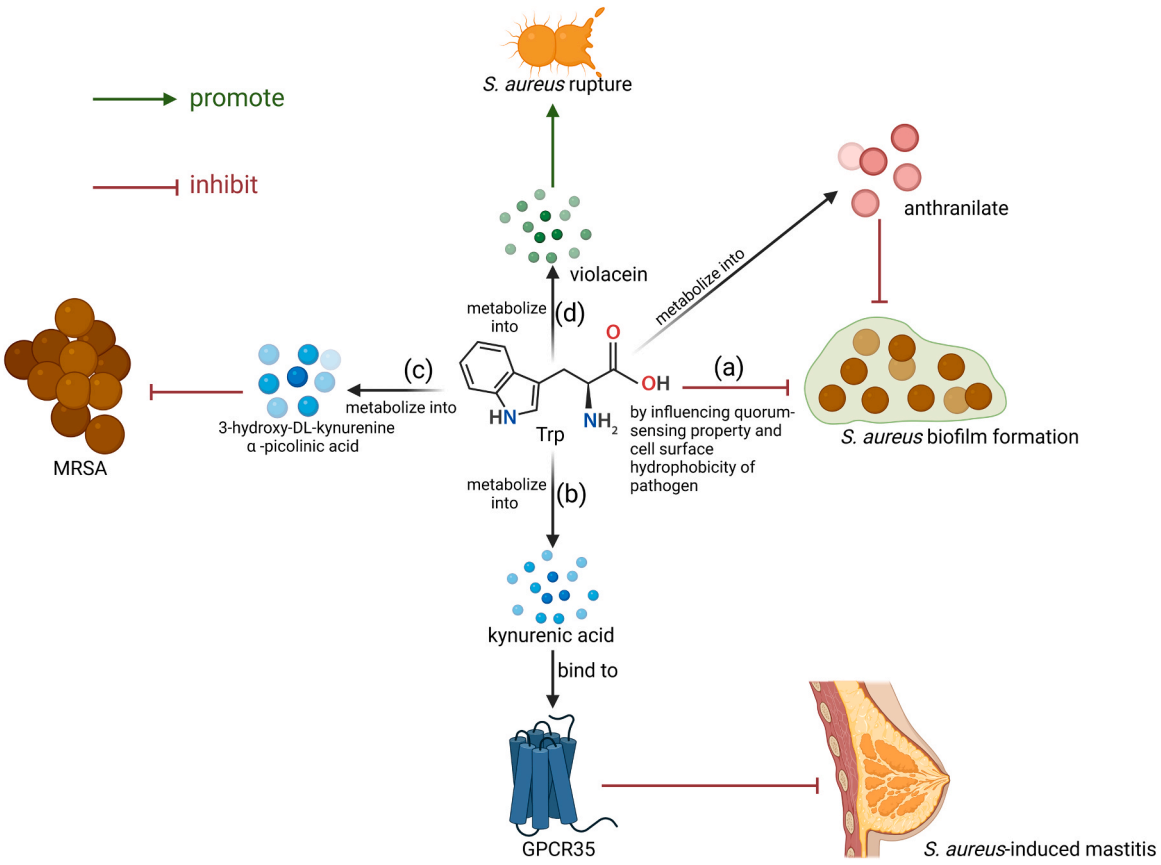

Fig. 9. Interactions between Trp and *S. aureus*. (a) Trp and its metabolite anthranilate can inhibit *S. aureus* biofilm formation; (b) Kynurenic acid derived from Trp can alleviate *S. aureus*-induced mastitis through binding to GPCR35; (c) 3-hydroxy-DL-kynurenine and α-picolinic acid have also shown strong antibacterial activity against MRSA; (d) Violacein can permeabilize *S. aureus*, resulting in ruptures. Trp: tryptophan; GPCR35: G protein-coupled receptor 35; MRSA: methicillin-resistant *Staphylococcus aureus*.

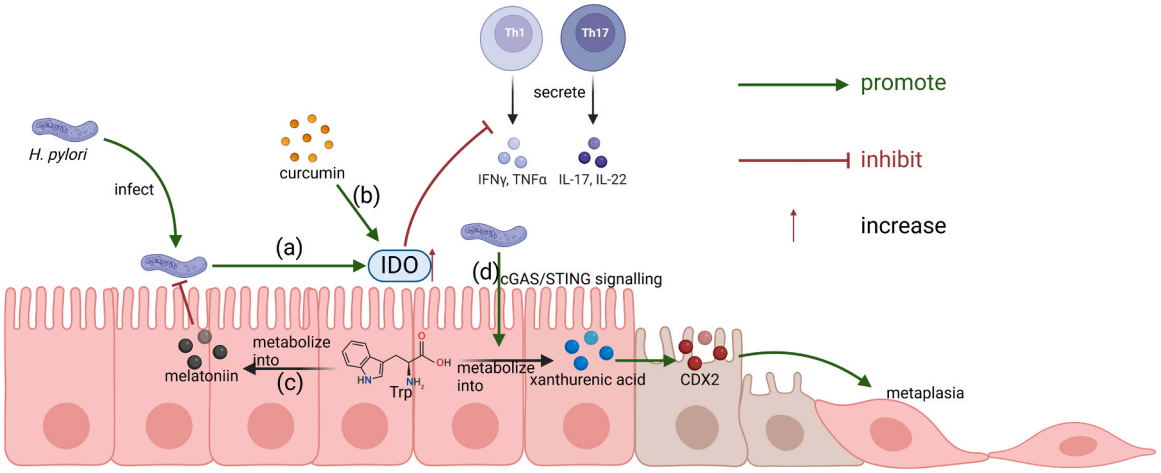

Fig. 10. Interactions between Trp and *H. pylori*. (a) When human gastric mucosa infected by *H. pylori,* expression of IDO will increase to attenuate Th1 and Th17 immune responses; (b) Curcumin can induce IDO expression to down-regulate IL-17 levels in *H. pylori*-infected human gastric mucosa; (c) Melatonin can contribute to the remedy of gastroduodenal ulcer caused by *H. pylori* infection; (d) *H. pylori* can activate cGAS/STING signaling to promote XA production, which can further enhance CDX2 expression in gastric epithelial cells to enhance intestinal metaplasia. Trp: tryptophan; IDO: indolamine 2,3-dioxygenase; XA: xanthurenic acid; CDX2: caudal type homeobox 2.

expression in gastric epithelial cells (Fig. 10d) (Liang et al., 2023). This finding suggests that targeting Kyn pathway may be a promising strategy to prevent *H. pylori*-induced gastrointestinal metaplasia. A significant increase in Kyn/Trp ratio was also found in *H. pylori*-induced gastric cancer patients, and this elevated ratio indicates that *H. pylori* might via Trp metabolism to suppress immunosurveillance to drive cancer development (Engin et al., 2015).

6. The interaction between Trp metabolism and viruses, and potential effects of Trp in infection treatment

6.1. Trp metabolism and SARS-CoV-2

Enterocytes abundantly expressing the angiotensin-converting enzyme 2 (ACE2) viral receptor is an active site for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication (Devaux et al., 2021). SARS-CoV-2 can induce vomiting, diarrhea and nausea abdominal pain as onset symptoms in severe coronavirus-19 disease (COVID-19) patients (Song et al., 2020; Wang et al., 2020), and abdominal symptoms are risk factors for severe COVID-19 (Hayashi et al., 2021).

The reduction of ACE2 expression in enterocytes, caused by SARS-CoV-2 infection, is likely to result in impaired Trp uptake, which may further cause an altered composition of gut microbiota (Fig. 11a) (Hashimoto et al., 2012). In COVID-19 patients, gut bacteria elements with immunomodulatory capacity, such as *Eubacterium rectale*, *Faecalibacterium prausnitzii* and several bifidobacterial species, were depleted (Fig. 11b) (Yeoh et al., 2021). Severe COVID-19 was linked with gut microbiota dysbiosis and elevated Kyn concentration. And increase in Kyn in COVID-19 were related to enhanced inflammatory cytokine production. (Essex et al., 2024) Studies show that Kyn and indole 3 pyruvate (I3P) can activate AhR. Activated AhR contributes to a strengthened initial pro-inflammatory "cytokine storm" to SARS-CoV-2 and suppresses the endogenous antiviral responses of natural killer cells and $CD8^+$ T cells, thereby altering the nature of immune responses to COVID-19 (Fig. 11c) (Anderson et al., 2021). Stool metabolomic analysis indicated that IPA level was significantly decreased in the critical COVID-19 patients compared to non-critical patients (Yokoyama et al., 2022). A possible explanation is that former mentioned up-regulation of the Kyn pathway in the host leads to decreased IPA production.

The expression of genes involved in Trp metabolism, including ACE2, AHR, CARD9 and IL22, were down-regulated in the ileum of critical COVID-19 patients (Yokoyama et al., 2022). This study suggests that gastrointestinal damage is potentially caused by impaired Trp metabolism in the small intestine due to SARS-CoV-2-mediated decreased expression of Trp metabolism genes (Fig. 11d). SARS-CoV-2 can destroy tight junctions between intestinal epidermal cells, increasing incidence of opportunistic infections (Otani and Furuse, 2020; Tian et al., 2020). Trp can restore tight junctions, inhibit production of pro-inflammatory cytokines, and modulate mucosal cell autophagy via mechanistically targeting mTOR signaling (Fig. 11e) (Viana et al., 2020). The Kyn pathway can provide required compounds for nicotinamide adenine dinucleotide (NAD) synthesis, which is pivotal for DNA damage repair and regulating oxidative stress. Recent studies revealed that SARS-CoV-2 infection might decrease NAD production through causing impaired Trp absorption (Fig. 11f) (Heer et al., 2020), and NAD supplementation could effectively reverse cytokine storms (Hong et al., 2018). Therefore, NAD supplementation may be a potential explanation for the therapeutic effect of Trp on SARS-CoV-2-related hyperinflammation (Qin et al., 2021).

Specific molecular mechanisms underlying the interactions between SARS-CoV-2 infection and Trp metabolism has been explored. The raised levels of pro-inflammatory cytokines in host caused by initial infection of SARS-CoV-2 will upregulate IDO expression, thereby increasing the proportion of Kyn production in Trp metabolism (Anderson et al., 2021). At the same time, SARS-CoV-2 can upregulate AhR ligands through the mechanism independent of IDO upregulation (Turski et al., 2020). Like

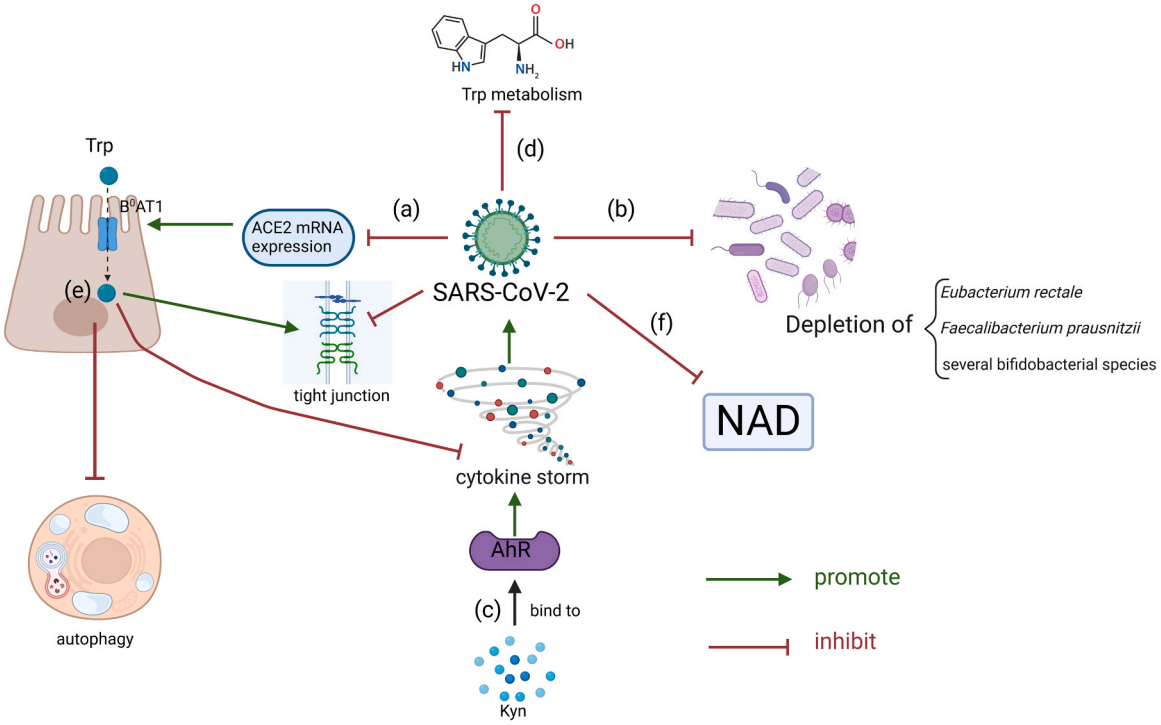

Fig. 11. Interactions between Trp and SARS-CoV-2. (a)SARS-CoV-2 infection can reduce ACE2 expression in enterocytes, which is likely to result in impaired Trp uptake; (b) In COVID-19 patients, gut bacteria such as *Eubacterium rectale*, *Faecalibacterium prausnitzii* and several bifidobacterial species were depleted; (c) Kyn can activate AhR to elicit a pro-inflammatory "cytokine storm", which underpins severity and fatality of SARS-CoV-2; (d) Expression of genes involved in Trp metabolism, including ACE2, AhR, CARD9 and IL22, were down-regulated in the ileum of critical COVID-19 patients; (e) Trp can restore tight junctions destroyed by SARS-CoV-2, inhibit production of pro-inflammatory cytokines, and modulate mucosal cell autophagy via mechanistically targeting mTOR signaling; (f) SARS-CoV-2 infection can decrease NAD production, which is pivotal for DNA damage repair and regulating oxidative stress. Trp: tryptophan; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin-converting enzyme 2; B^0AT1: broad neutral amino acid transporter1, encoded by the SLC6A19gene; AhR: aryl hydrocarbon receptor; Kyn: kynurenine; NAD: nicotinamide adenine dinucleotide.

other viral infections, SARS-CoV-2 is associated with the upregulation of IL4i1 in a number of immune cells, especially in macrophages, and thereby leading to the production of other AhR ligands such as I3P and I3A (Hu et al., 2018; Feng et al., 2019). These IDO and IL4i1-driven AhR ligands then activate AhR, altering the host immune responses to SARS-CoV-2 infection. AhR overactivation can disrupts immune homeostasis, contributing to an exacerbated and sustained initial "cytokine storm" which underpins severity and fatality of COVID-19 (Iqubal et al., 2021). In the normal course of viral infection, initial inflammatory responses mediated by macrophages, neutrophils, and mast cells are eventually replaced by specialized cytotoxic lymphocytes like natural killer (NK) cells and $CD8^+$ T cells and these cells can selectively eliminate virus-infected host cells (Anderson et al., 2020). However, AhR overactivation on NK cells and $CD8^+$ T cells can make these cells exhausted, which limits their ability of eliminating SARS-CoV-2-infected cells (Li et al., 2020). These researches indicate that Trp metabolism can regulate the host response to SARS-CoV-2 through producing AhR ligands, while SARS-CoV-2 aggravates patients' condition and evades immune clearance through AhR activation. However, the more specific molecular mechanisms of interactions between Trp metabolism and SARS-CoV-2 still need further exploration.

6.2. *Trp metabolism and influenza virus*

Neonatal infection with influenza A virus was found to induce the Kyn pathway (Asp et al., 2010). Research on serum Trp metabolites variation in murine influenza A virus infection found that the levels of Kyn, hydroxykynurenine and quinolinic acid increased (Al-Shalan et al., 2023). In vitro research found that influenza A virus could lead to Trp depletion and Kyn accumulation in infected nasal epithelial cells through inducing IDO expression, thus attenuating host immune response (Lin et al., 2020). Influenza A virus was also found capable of up-regulating IDO1 expression in respiratory epithelial cells via IFN-λ signaling (Fox et al., 2015). Inhibition of replication of influenza A virus prior to IFN induction could suppress IDO1 expression, while inhibition after IFN induction did not (Gaelings et al., 2017). These foundlings suggest that influenza virus can facilitate Trp metabolism in infected cells via promoting IDO expression.

Influenza virus infection also causes damage in the intestine, implying an association between respiratory and intestinal tract. During influenza virus infection, although the virus was spotted solely in lungs, a notable shift in intestinal microbiota composition was observed, including increased *Enterobacteriaceae* and decreased *Lactobacillaceae* (Fig. 12a) (Zhang et al., 2024b). Experimental results also found that influenza virus infection can markedly increase IDO1 expression in colon, which facilitates the Treg production and restricts the TH17 response, thereby inhibiting immune function of intestine (Fig. 12b) (Zhang et al., 2024b). A significant decrease in IPA serum level was observed in influenza A virus. As a microbial metabolite of Trp, IPA decrease was in accordance with virus-induced reduction in the abundance of *Lactobacillaceae* and *Bifidobacteriaceae* in the gut. Further experiments have shown that IPA inhibition can enhance viral load and

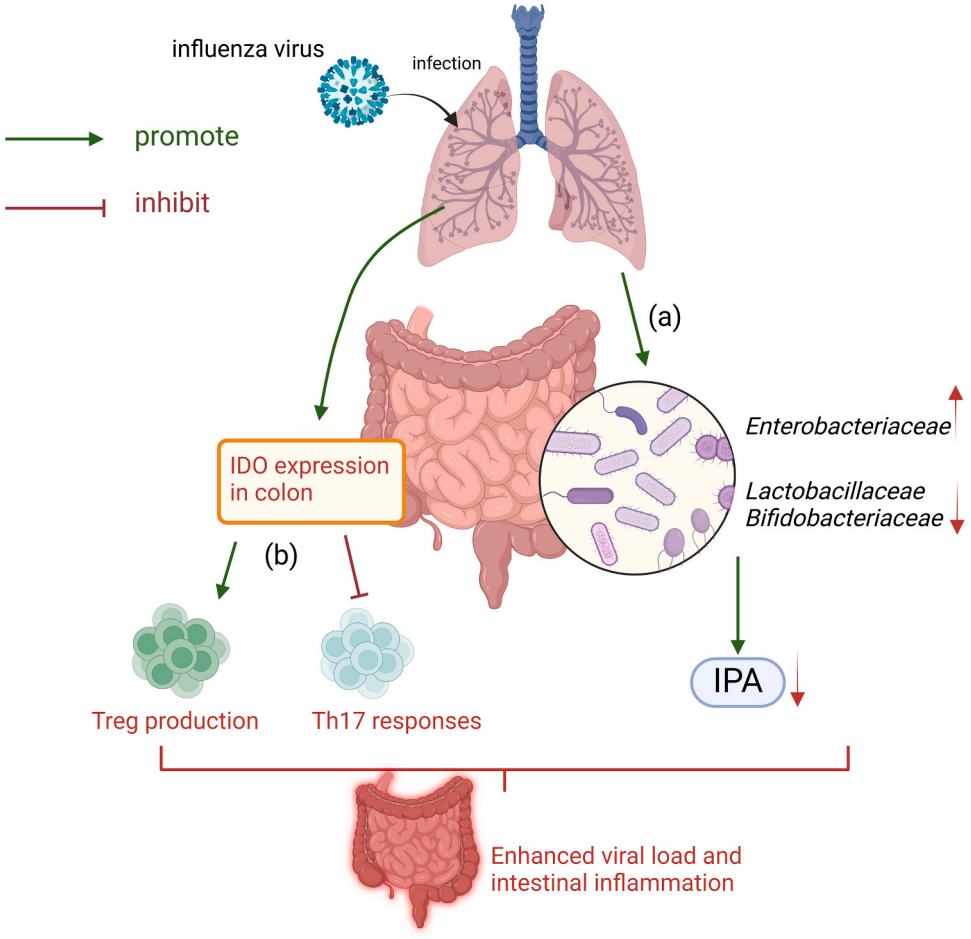

Fig. 12. Interactions between Trp and influenza virus. (a) During influenza virus infection, a notable shift in intestinal micobiota composition was observed, including increased *Enterobacteriaceae* and decreased *Lactobacillaceae* and *Bifidobacteriaceae,* which further leading to a decrease of IPA serum level; (b) Influenza virus infection can markedly increase IDO1 expression in colon, which facilitates Treg production and restricts TH17 response, thereby inhibiting immune function in the intestine. Trp: tryptophan; IDO: indolamine 2,3-dioxygenase; IPA: indole-3-propionic acid.

lung and intestinal inflammation, while supplementation can reverse this. These results highlight that IPA is a vital contributor to influenza outcomes and a potential biomarker of infection severity (Fig. 12a) (Heumel et al., 2024). The studies mentioned above suggest that influenza virus infection may disturb gut microbiota homeostasis through the lung-gut axis, thereby influencing the Trp-related metabolite levels in the gut microbiota to cause lung and intestinal damage.

Specific molecular mechanisms underlying the interactions between influenza virus infection and Trp metabolism has been explored. Influenza virus can significantly upregulate the expression of IDO1 by activating the IFN signaling pathway, especially IFN-γ, leading to Trp depletion and the accumulation of Trp metabolites such as Kyn (Fox et al., 2015; Lin et al., 2020). Trp depletion inhibits T cell proliferation by activating the GCN2 kinase (Eleftheriadis et al., 2015), while Kyn promotes the differentiation of regulatory T cells by activating AhR, thereby suppressing antiviral immune responses (Solvay et al., 2023). Influenza virus can also attenuate the IDO1 expression and Kyn production through its NS1 protein, increasing Trp to support viral replication (Gaelings et al., 2017). However, Trp metabolites such as Kyn can in turn inhibit viral replication through AhR-dependent pathways. These metabolites cause the translocation of AhR to the nucleus upon activation, where it forms a complex with ARNT, upregulating cytochrome P450 enzymes (such as CYP1A1) to generate metabolites with antiviral activity (Torti et al., 2021). At the same time, influenza virus infection can alter the composition of gut microbiota, affecting the generation of Trp metabolites (such as indole derivatives), thereby regulating systemic immune responses. IPA from gut microbiota can enhance antiviral interferon signaling in the lungs by activating AhR and suppress excessive inflammatory responses to alleviate host damage (Heumel et al., 2024). In summary, influenza virus achieves immune evasion and replication optimization by regulating Trp metabolism mediated by IDO1; whereas the host defends influenza virus infection through AhR signaling and microbiota metabolites. This interaction may provide new insights for the development of metabolism-targeted anti-influenza virus therapies.

7. Therapeutic potential of targeting Trp metabolism and gut microbiota in infection and inflammation

Sepsis patients often experience immune suppression, and IDO generating Kyn and other Trp metabolites may exacerbate this immune suppression (Platten et al., 2019) Clinical experiments have found that granulocyte-macrophage colony-stimulating factor (GM-CSF) as an IDO inhibitor can significantly reduce Kyn/Trp ratio in plasma by restoring monocyte function (increasing mHLA-DR) and reducing bacterial load (lowering procalcitonin), thereby improving the immune suppression state of sepsis patients, but it did not significantly improve the 28-day mortality rate (Schefold et al., 2010). HIV can directly activate IDO in plasmacytoid dendritic cells (pDCs) through gp120-CD4 interaction, inhibiting $CD4^+$ T cell proliferation, and this process is independent of interferon signaling. A clinical study has found that 1-MT as a competitive blocker of IDO can reverse $CD4^+$ T cell dysfunction, indicating its potential in HIV immunotherapy, especially suitable for early infection or in combination with antiretroviral therapy (ART) (Boasso et al., 2007). *Clostridioides difficile* infection (CDI) is a major concern for healthcare-associated infections, with current treatments such as antibiotics having high recurrence rates and limited effectiveness. Research has found that the Trp metabolite Indole-3-carbinol (I3C), acting as an AHR agonist, can significantly reduce mortality and severity of CDI through dietary supplementation. The specific mechanism involves the regulation of intestinal immune cells (such as Tregs, ILC3s, γδT cells) via an AhR-dependent IL-22 pathway. Currently, I3C has undergone clinical trial safety verification (e.g., NCT04116100) and is expected to be rapidly translated for use in patients at high risk for CDI (Julliard et al., 2017). Ulcerative colitis is closely associated with intestinal barrier dysfunction. IL-22 produced by ILC3s promotes barrier repair by enhancing tight junctions and mucosal defense, while AhR is a key transcription factor regulating IL-22 expression. Translational studies have found that baicalein, as an AhR agonist, activates the AhR/IL-22 pathway in ILC3s, promoting IL-22 secretion, thereby enhancing intestinal barrier function and alleviating UC, providing experimental evidence for the development of baicalein as a therapeutic drug for UC (Li et al., 2022). In addition, gut microbiota can be integrated with IDO inhibitors or AhR agonists to exert therapeutic potential in infection and inflammation. Clinical trials have found that fecal microbiota transplantation combined with IDO inhibitors can restore the gut microbiota imbalance induced by antibiotics, reducing the recurrence rate of *Clostridioides difficile* from 29 % to 11 % ($p = 0.032$) (Suez et al., 2018). *L. reuteri* can enhance AhR activity by 1.8 times through the production of IPA, promoting the improvement of intestinal barrier function in HIV-infected individuals (Vujkovic-Cvijin et al., 2020).

Targeting Trp metabolism (IDO/AhR) and gut microbiota offers new directions for the treatment of infection and inflammation. Current research indicates that AhR agonists and gut microbiota metabolites (such as IPA) have synergistic effects, both of which can enhance barrier repair. However, there are bottlenecks in clinical translation, with insufficient efficacy of monotherapy (e.g., GM-CSF does not improve survival rates in sepsis), suggesting the need for multi-target combination therapy. Future research can promote clinical translation by optimizing the timing of drug administration (e.g., the combination of ART and 1-mT), developing microbiota-targeted delivery systems, and validating personalized approaches through organoid models. At the same time, the long-term safety of targeting Trp metabolism (IDO/AhR) and gut microbiota therapy (such as the carcinogenic risk of excessive AhR activation) still needs to be strictly assessed.

8. Discussion and conclusion

Our understanding of interactions between Trp metabolism, gut microbiota, and host immunity has significantly deepened in recent years. Relevant evidences suggest that Trp, along with its endogenous host metabolites (like Kyn) and the metabolites produced by the gut microbiome (such as indole and its derivatives), have significant impacts on the composition of gut microbes, microbial functions, the host-microbiome interface, and the interactions between the host immunity and gut microbiota. The gut microbiota also, in turn, have an impact on the absorption and metabolism of Trp in the host, and they play a role in regulating the host's physiological and immune responses, either directly or indirectly. Additionally, there is potential for developing infection therapies that are specifically designed to target Trp absorption, Trp metabolites, the gut microbiota, or interactions between Trp and gut microbiota. These Trp-targeted approaches show potential in treating intestinal and extra-intestinal inflammation and microbial infections.

However, current researches about Trp metabolism and gut microbiota primarily discuss the interaction between Trp metabolism and gut microbiota in the treatment of infections based on mouse models, these researches don't fully address the differences in the composition of gut microbiota and the specificity of immune responses between mice and humans. For instance, the abundance of dominant genera in the mouse gut microbiota (such as lactobacilli) is significantly higher than in humans (Walter et al., 2011), whereas the distribution of *Bacteroides* and *Prevotella* in the human gut is more complex (Tett et al., 2019). Additionally, there are differences in the expression patterns of the key enzyme IDO1 in Trp metabolism between mouse and human (Ji et al., 2021), which may limit the extrapolation of immunoregulatory mechanisms. For example, the intensity of the antifungal effect mediated by AhR ligands (such as indole derivatives) through IL-22 in mouse models may differ in human gut ILC3 cells (Zelante et al., 2013).

Future research should prioritize human clinical studies to verify the universality of these discovered mechanisms. For instance, the concentration of IPA in human blood is only 1/5 that of mice (Dodd et al., 2017;

Wastyk et al., 2021), which may affect its efficacy against *M. tuberculosis* in human body (Negatu et al., 2019). Additionally, the human gut microbiota's ability to metabolize Trp is significantly regulated by genetic polymorphisms (such as the TPH1 gene) and dietary patterns (Rogers et al., 2016; Dodd et al., 2017), a heterogeneity that cannot be fully simulated by mouse models. It is recommended to combine multi-omics technologies and organoid models (Kanton et al., 2019) to systematically evaluate therapeutic potential of Trp-targeted interventions in human infection and inflammation.

Author contributions

T.P. conducted the literature research and wrote the first version of the manuscript. W.L. and Z.Z. reviewed the manuscript. Q.Z. provided reading comments. G.Y. and S.Y. provided reading comments. J.T. and H.C. conducted the critical reading and overall review. All authors read and approved the final manuscript.

Consent for publication

The authors have consented to publish this article.

Ethics approval and consent to participate

Not applicable.

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Declaration of Competing Interest

The authors declare no conflict of interests.

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Data Availability

Data will be made available on request.

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