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Review

The Tryptophan–AhR Circuit in the Gut: Microbial Indoles, Kynurenines, Serotonin, and Therapeutic Opportunities in Inflammatory Bowel Disease–A Comprehensive Review

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Abstract

Tryptophan (Trp) metabolism serves as a pivotal interface linking diet, microbiota, and host immunity in the gut. Through three interconnected pathways—the kynurenine, indole, and serotonin branches—Trp is converted into bioactive metabolites that act as endogenous ligands for the aryl hydrocarbon receptor (AhR). Activation of AhR orchestrates epithelial repair, mucosal tolerance, and cytokine programs such as IL-22 and IL-10, maintaining intestinal homeostasis. Dysregulation of this circuit, characterized by enhanced kynurenine flux, depletion of microbial indoles, and disturbed serotonergic balance, contributes to the pathogenesis of inflammatory bowel disease (IBD). Microbiota-derived metabolites like indole-3-aldehyde and indole-3-propionic acid enhance barrier integrity, while kynurenine derivatives regulate immune signaling and serotonin pathways exert context-dependent effects. Restoring AhR tone through dietary ligands, microbial modulation, or metabolic targeting has demonstrated therapeutic potential in preclinical colitis models. This review synthesizes current mechanistic insights into the Trp–AhR axis, emphasizes microbiota–immune interactions in IBD, and discusses translational opportunities for biomarker-guided and personalized therapeutic interventions.

Keywords

Tryptophan metabolism, Aryl hydrocarbon receptor, Indoles, Kynurenine pathway, Serotonin, Inflammatory bowel disease

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1. Introduction

The mammalian intestine hosts a remarkably diverse community of microorganisms—including bacteria, fungi, archaea, and viruses—that coexist with epithelial and immune cells of the host [1]. This complex ecosystem has co-evolved with the host to maintain a delicate equilibrium known as intestinal homeostasis. Disruption of this balance, or dysbiosis, has been consistently linked to the pathogenesis of multiple human disorders, ranging from metabolic and gastrointestinal diseases to neurological conditions and cancer [2].

Beyond their structural diversity, gut microbes exert profound influence on host physiology by producing a broad spectrum of metabolites [3]. These bioactive molecules function as messengers in the host–microbiota cross-talk and regulate immune, nutritional, and metabolic processes both locally in the gut and systemically [4]. Among the most intensively studied microbial-derived metabolites are short-chain fatty acids (SCFAs) generated from dietary fiber fermentation, secondary bile acids derived from hepatic bile conversion, and a wide array of tryptophan (Trp) catabolites [5].

Inflammatory bowel disease (IBD), encompassing ulcerative colitis and Crohn's disease, exemplifies a chronic disruption of intestinal homeostasis driven by an imbalance between host immunity, microbiota, and metabolic signaling. Altered Trp metabolism and impaired activation of aryl hydrocarbon receptor (AhR) have emerged as central features of IBD pathogenesis, linking dietary inputs and microbial ecology to mucosal inflammation and epithelial dysfunction. Understanding how the Trp-AhR axis integrates these components provides a key framework for exploring therapeutic opportunities in IBD [3,6].

Trp metabolism, in particular, has gained attention as a central regulator of intestinal homeostasis. Microbial and host pathways convert Trp into diverse derivatives, such as indoles, kynurenine, and serotonin, each with distinct physiological effects [7,8]. Aberrant regulation of these pathways has been associated with inflammation, metabolic dysfunction, and tumorigenesis [9,10]. A growing body of evidence highlights the AhR, a ligand-activated transcription factor, as a pivotal mediator translating Trp-derived signals into immune regulation [11]. Once activated, AhR translocates into the nucleus and drives gene expression in a cell- and context-dependent manner [12].

Recent discoveries indicate that AhR activation by Trp metabolites contributes to shaping gut immunity, modulating inflammatory responses, and preventing microbial dysbiosis [13]. However, the precise mechanisms by which the Trp-AhR axis influences intestinal health remain incompletely understood. It is important to note that AhR exhibits marked species-specific ligand selectivity; for instance, human and murine receptors differ significantly in their sensitivity and response profiles to indole-derived metabolites. These interspecies variations represent a major translational challenge, as findings derived from rodent models may not fully recapitulate human AhR biology. Recognizing this limitation early provides essential context for interpreting model-based insights throughout this review. In this review, we summarize current insights into Trp metabolism and AhR signaling in gut immunity and inflammation, emphasizing nutritional strategies that may therapeutically target this pathway.

2. Tryptophan Metabolism and AhR Signaling in the Gut

2.1 Dietary Sources and Metabolic Roles of Tryptophan

L-Trp is an essential aromatic amino acid for humans and must be obtained from the diet because animal cells do not synthesize it. Rich sources include fish, poultry, cereal grains, and dairy products. Current guidance from international health authorities recommends an intake of roughly 4 mg/kg/day [14]. Beyond its role in protein synthesis, Trp is the obligate precursor for multiple host and microbial metabolites, notably serotonin and melatonin, as well as nicotinamide/nicotinic acid (vitamin B3) and downstream NAD^+ cofactors [15].

2.2 Intestinal Pathways of Tryptophan Metabolism

Trp is metabolized through three major interconnected pathways—the kynurenine, serotonin, and indole branches—each regulated by distinct enzymatic and microbial mechanisms. Although the relative contribution of microbial versus host enzymes varies among these routes, gut microorganisms influence all three pathways by modulating substrate availability, generating intermediate metabolites, and converting host-derived compounds into bioactive ligands for the aryl hydrocarbon receptor [3,16]. The gastrointestinal tract represents the central site of Trp catabolism, where ingested Trp is funneled into three interconnected metabolic routes. Through the kynurenine pathway (KP), initiated mainly by indoleamine 2,3-dioxygenase 1 (IDO1) in immune and epithelial cells and complemented by hepatic Trp 2,3-dioxygenase (TDO) and, in some tissues, indoleamine 2,3-dioxygenase 2 (IDO2), Trp is converted into a range of kynurenine metabolites such as kynurenine, kynurenic acid (KYNA), and quinolinic acid (QUIN), ultimately contributing to niacin and NAD^+ biosynthesis [17]. In parallel, within enterochromaffin cells, Trp undergoes hydroxylation by Trp hydroxylase 1 (TPH1) to form 5-hydroxyTrp, which is then decarboxylated to serotonin, a signaling molecule that regulates both local intestinal functions and systemic processes after entering the circulation [18]. At the same time, commensal microorganisms directly metabolize Trp into diverse indole derivatives—including indole-3-acetic acid, indole-3-aldehyde, IPA, indole-3-lactic acid, indole-3-acetaldehyde, and indole-acrylic acid—many

of which serve as ligands for the AhR, thereby influencing microbial ecology, epithelial integrity, and host immune regulation [19].

2.2.1 Kynurenine Pathway

In the intestine, IDO1 catalyzes the first and rate-limiting step, channeling Trp toward kynurenine and onward to metabolites including KYNA, QUIN, niacin/nicotinamide, and ultimately NAD^+ [17]. While TDO and IDO2 can also generate Kyn, they are not major gut enzymes. In mammals, the bulk of dietary Trp (often estimated at ~95%) is ultimately funneled through the KP [20].

Microbiota shape KP activity at several levels: microbial signals and inflammatory tone upregulate IDO1; conversely, Trp availability and certain bacterial products can tune flux through downstream nodes [21]. Some intestinal bacteria harbor enzyme homologs capable of Kyn production and of generating neuroactive or immunoactive downstream products (e.g., 3-hydroxyanthranilic acid) [22]. Functionally, Kyn metabolites influence cell differentiation, neurotransmission, inflammation, and immune responses—and several act as endogenous AhR ligands, linking the KP to transcriptional programs that maintain or, when dysregulated, disrupt mucosal homeostasis [23].

2.2.2 Serotonin Pathway

Most peripheral serotonin originates in the gut. Enterochromaffin cells convert Trp to serotonin via TPH1, releasing 5-hydroxytryptamine (5-HT) into the lamina propria and circulation [24]. Peripheral 5-HT is a key paracrine and endocrine signal regulating motility, secretion, vasodilation, and nutrient absorption, and it communicates with the enteric nervous system [25]. The gut microbiota is integral to this axis: germ-free animals show reduced colonic and circulating 5-HT, while microbial metabolites—particularly SCFAs—have been shown to stimulate TPH1 expression. Secondary bile acids (e.g., deoxycholate) can also enhance 5-HT biosynthesis [26]. In the central nervous system, serotonin is synthesized from Trp by TPH2 in serotonergic neurons and modulates mood, appetite, and sleep, highlighting the compartment-specific control of Trp hydroxylation [27].

2.2.3 Direct Microbial Conversion to Indoles

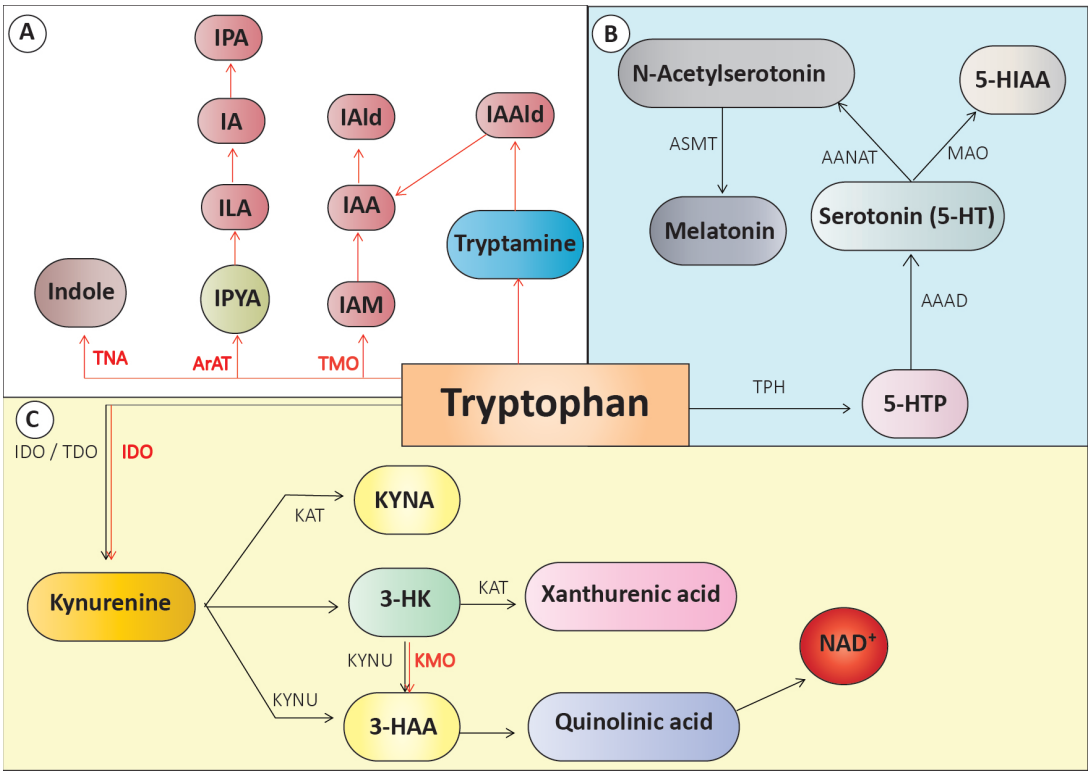

Figure 1. Overview of Trp metabolism via three interconnected branches: A = indole pathway, B = serotonin pathway, and C = kynurenine pathway. Black arrows denote host enzymatic conversions, while red arrows represent microbial reactions. Key metabolites of the indole branch (e.g., indole-3-aldehyde, indole-3-acetic acid, indole-3-propionic acid, indole-3-lactic acid, tryptamine) are known to act as AhR ligands, linking microbial metabolism to mucosal immunity.

A diverse set of commensals degrade Trp to indole and indole-derived molecules such as indole-3-acetic acid (IAA), indole-3-aldehyde (IAId), IPA, indole-3-lactic acid (ILA), indole-3-acetaldehyde, and indole-acrylic acid [28]. These metabolites can reshape bacterial physiology (antibiotic tolerance, sporulation, biofilm dynamics) and signal to the host. Well-characterized contributors include *Bifidobacterium*, *Peptostreptococcus russellii*, and multiple Lactobacillus species (e.g., *L. reuteri*, *L. johnsonii*), which use oxidative/reductive routes (often via aromatic amino acid aminotransferases) to generate AhR-active ligands [6, 29-31]. IPA and IAA are repeatedly linked to enhanced barrier

integrity and immunoregulatory effects. Classic Trpase-positive organisms (e.g., *E. coli*, many lactobacilli) convert Trp into indole, which diffuses across membranes or is exported via transporters (e.g., AcrEF-TolC, Mtr). Diet-derived indolic substrates, including glucobrassicin from crucifers, augment the pool of AhR ligand precursors (Figure 1) [22,32].

2.3 Gut Microbiota–Trp Metabolites–AhR Axis

The intestinal microbiota uses Trp (and, indirectly, SCFAs) to generate signaling molecules that converge on the AhR. In the healthy state, AhR activation supports epithelial barrier function, anti-inflammatory programs (e.g., IL-22-dependent mucosal defense), and balanced host–microbe mutualism [33]. SCFAs can also enhance expression of AhR pathway components, further reinforcing this crosstalk [34].

This axis is bidirectional and tightly regulated. Inflammation upregulates IDO1/TDO, increasing KP flux and producing additional AhR agonists (e.g., Kyn), while AhR signaling can, in turn, induce IDO1 expression—creating a positive feedback loop [35]. During inflammation, up-regulation of IDO1 substantially redirects Trp flux toward the kynurenine pathway, thereby depleting the substrate pool available for both microbial indole formation and host serotonin synthesis. This metabolic rerouting alters the composition of AhR-active ligands, shifting the balance from short-lived indolic agonists toward longer-acting kynurenines. Accumulating kynurenine and downstream metabolites can further enhance IDO1 transcription through AhR-dependent feedback, reinforcing a self-amplifying inflammatory circuit. Conversely, reduced indole and serotonin outputs weaken IL-22–mediated mucosal protection and barrier repair, sustaining inflammatory signaling[3,36]. Collectively, these reciprocal feedbacks exemplify how inflammatory cues dynamically remodel the Trp–AhR circuit and determine whether its outcome is homeostatic or pathogenic.

When chronically amplified, these circuits can propagate beyond the gut: sustained mucosal inflammation drives Trp metabolites and cytokines into the circulation, with downstream effects reported in distal organs such as brain and kidney [37]. For example, microbially derived indoles can circulate to the liver and kidney, where they are processed into uremic toxins (e.g., indoxyl sulfate); such compounds accumulate in chronic kidney disease [38, 39] and have been implicated in vascular and neural pathologies [40]. In the nervous system, circulating AhR ligands—including microbial indoles, tryptamine produced by certain microbes, and KP-derived agonists—may access or influence the brain and have been associated in some studies with features observed in neurodegenerative conditions.

In inflammatory contexts, IDO1 upregulation exerts a profound rerouting effect on Trp flux, creating a metabolic competition among the kynurenine, serotonin, and microbial indole pathways. As IDO1 consumes available Trp to generate kynurenine, substrate scarcity limits both host serotonergic synthesis and microbial conversion of Trp into indole derivatives. This redistribution of Trp flow not only alters the pool of AhR-active ligands but also feeds back on immune regulation, as reduced indole signaling weakens IL-22–mediated epithelial protection, while excessive kynurenine accumulation drives tolerogenic or immunosuppressive responses. Together, these interlinked feedbacks define the dynamic "Trp-AhR circuit," in which inflammation-driven enzymatic shifts reshape ligand availability and receptor activation patterns across host and microbial compartments.

3. Molecular Structure and Regulation of the AhR

As a central receptor mediating the effects of Trp-derived ligands, the AhR is a ligand-activated transcription factor and a member of the basic helix-loop-helix/Per-Arnt-Sim (bHLH-PAS) superfamily of proteins. This evolutionary ancient receptor has been conserved for more than 600 million years, underscoring its fundamental role in cellular signaling and homeostasis [41]. Structurally, AhR is organized into distinct domains that mediate DNA binding, protein–protein interactions, ligand recognition, and transcriptional activation. The N-terminal region harbors the basic DNA-binding motif, followed by a helix-loop-helix (HLH) domain that facilitates dimerization with partner proteins. Two highly conserved PAS domains (PAS-A and PAS-B) confer specificity for ligand binding and heterodimerization, particularly with the AhR nuclear translocator [42]. The PAS-B domain, in particular, forms the canonical ligand-binding pocket and determines receptor activation in response to both exogenous and endogenous ligands [43]. At the C-terminal end, AhR contains a glutamine-rich transactivation domain responsible for recruiting co-regulators and initiating gene transcription [44].

In its inactive state, AhR is retained in the cytoplasm as part of a multiprotein complex that includes the chaperone heat-shock protein 90 (HSP90), the co-chaperone p23, and the X-associated protein 2 (XAP2, also known as AIP). This complex stabilizes AhR, prevents its proteasomal degradation, and maintains it in a conformation competent for ligand binding [45]. Upon binding of an agonist ligand—such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), I3C derivatives, or Trp metabolites—AhR undergoes conformational rearrangements that expose its nuclear localization signal [46]. The activated receptor then translocates into the nucleus, where it dissociates from chaperones and forms a heterodimer with ARNT. The AhR/ARNT complex binds to specific DNA motifs known as dioxin- or xenobiotic-response elements (DRE/XRE) located in the promoter regions of target genes [47]. This interaction drives the transcriptional activation of a broad gene network, including phase I xenobiotic-metabolizing enzymes such as CYP1A1, CYP1A2, and CYP1B1, as well as inflammatory mediators like COX-2 [48].

AhR signaling is tightly regulated to prevent excessive or prolonged activity that may result in toxicity or pathological immune responses. Three principal feedback mechanisms contribute to this regulation. First, the AhR protein itself undergoes ubiquitin-mediated proteasomal degradation following prolonged activation, ensuring receptor turnover and limiting sustained signaling [49]. Second, AhR activation induces the transcription of the AhR repressor, a competitive inhibitor that binds ARNT and displaces AhR, thereby attenuating gene expression [50]. Third, many AhR ligands are rapidly metabolized by AhR-inducible enzymes, particularly cytochrome P450 family members such as CYP1A1, which create an auto-regulatory loop limiting ligand availability [51].

In addition to its classical genomic functions, AhR also exerts non-genomic effects. Ligand binding can activate cytoplasmic signaling cascades independent of direct DNA binding. Notably, AhR activation has been linked to phosphorylation and activation of Src kinase, which subsequently influences focal adhesion kinase (FAK) and downstream pathways involved in cell adhesion, migration, and proliferation [52]. These non-genomic activities expand the scope of AhR beyond xenobiotic metabolism, integrating environmental and metabolic cues with cellular stress responses, immunity, and tissue remodeling.

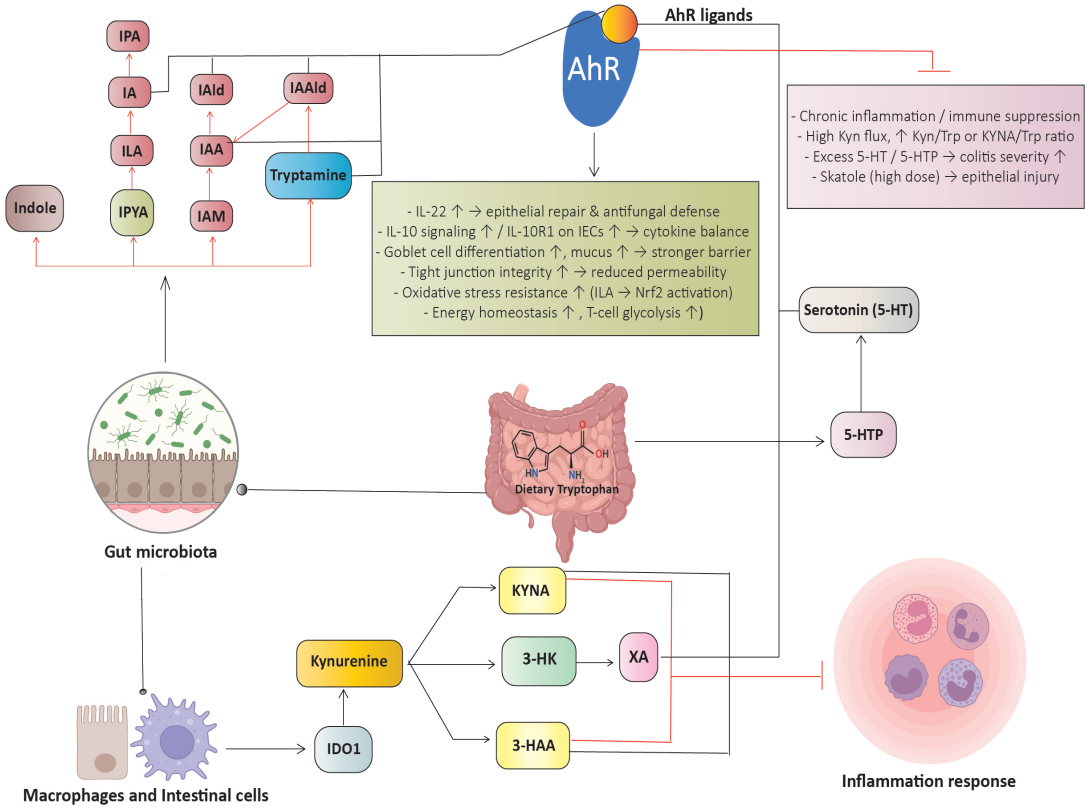

Figure 2. Canonical and non-canonical AhR signaling pathways. Upon ligand binding, cytoplasmic AhR dissociates from its chaperone complex (HSP70, p23, XAP2, Src) and translocates into the nucleus. In the canonical pathway, AhR heterodimerizes with ARNT and recruits coregulators to bind dioxin-responsive elements, driving transcription of target genes. In the non-canonical pathway, AhR interacts with other transcription factors and coregulators or functions as an E3 ubiquitin ligase, thereby modulating diverse immune and inflammatory responses.

In canonical signaling, AhR acts as a transcription factor after nuclear translocation and ARNT dimerization, directly regulating gene expression through DRE motifs. In contrast, non-canonical signaling involves cytoplasmic or protein–protein interactions independent of DNA binding, modulating kinase cascades, ubiquitination, and inflammatory signaling [53,54]. These complementary modes explain the dual genomic and cytoplasmic actions summarized in Figure 2.

Collectively, the structural organization and multi-layered regulatory mechanisms of AhR provide the molecular basis for its dual role as both an environmental sensor and a central mediator of physiological homeostasis. Its ability to integrate signals from diverse ligands—including synthetic pollutants, dietary compounds, and endogenous metabolites such as those derived from Trp—highlights AhR as a versatile signaling hub with implications across toxicology, immunology, and metabolism.

3.1 AhR Ligand Classes and Origins

Many ligands with varying chemical structures, affinities, and biological effects can activate the AhR. Despite having a variety of sources, these compounds are often hydrophobic and loaded with aromatic rings. From a biological perspective, AhR ligands can be roughly divided into two groups: endogenous ligands, which are produced inside the body by host or microbial metabolism, and exogenous ligands, which come from outside the host. This classification

offers a conceptual framework for understanding the role of AhR signaling in both physiological and pathological settings [55].

3.2 Exogenous Ligands

All substances that are brought into the body from the outside world are referred to as exogenous ligands. Generally speaking, they are divided into two major categories: those that are created by synthetic and industrial processes and those that are found in food as naturally occurring substances. Although both groups are capable of activating AhR, their physiological effects, signaling length, and potency vary significantly.

Among the best-characterized high-affinity agonists of AhR are synthetic exogenous ligands. These comprise polychlorinated biphenyls (PCBs), halogenated aromatic hydrocarbons (HAHs) like TCDD, and polycyclic aromatic hydrocarbons (PAHs) like benzo[a]pyrene (BaP) and benz[a]anthracene (BA). These substances are released through the burning of garbage, the exhaust from automobiles, the manufacture of pesticides, the burning of PVC plastic, and the smelting of steel. They are byproducts of contemporary industrial activity [56, 57]. These pollutants have significant immunotoxic effects, such as the inhibition of humoral and cellular immune responses and the development of carcinogenesis, due to their high receptor-binding affinity and metabolic persistence [58]. Interestingly, despite its toxicity, the synthetic ligand TCDD has been reported to alleviate DSS (dextran sulfate sodium)-induced colitis by enhancing Treg differentiation and suppressing Th17 cell induction through epigenetic mechanisms [59]. The TCDD–AhR-ARNT heterodimer binds to dioxin response elementsin the regulatory areas of genes like CYP1A1, CYP1A2, and CYP1B1, causing a strong induction of enzymes that metabolize xenobiotics, according to mechanistic studies. One of the most reliable indicators of TCDD activity is still the increase of CYP1A1 [60]. TCDD-induced CYP1A1 expression can be inhibited by other synthetic ligands, such as 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F-203), which exhibit a high binding affinity to AhR [61]. PCBs are equally powerful: PCB 153 has been demonstrated to cause DNA damage, raise IL-6 expression 15.5-fold ($p < 0.01$), and activate NF-κB via ATM/NEMO signaling pathways in intestinal epithelial cells (IECs) [62], whereas coplanar PCBs increase intestinal epithelial permeability and alter junctional protein integrity [63]. PAHs make things even more complicated: Through the AhR and ERK pathways, BaP, a component of cigarette smoke, stimulates the growth and metastasis of gastric cancer cells [64]; BA binds AhR tightly and affects melanin formation by controlling tyrosinase activity [65]. Furthermore, new small compounds such as VAF347 bind AhR, activate CYP1A1, and reduce inflammation in monocytes [66]. Altogether, artificial exogenous ligands represent long-term, high-affinity AhR activation, which usually results in pathogenic rather than advantageous effects [52].

Many naturally occurring food chemicals also act as AhR ligands, in addition to industrial contaminants. These can nonetheless have a big impact on immune modulation and barrier integrity even though they are typically weaker agonists or partial antagonists than synthetic ligands. Glucobrassicins, which are found in cruciferous vegetables like broccoli and Brussels sprouts, are hydrolyzed during digestion to produce indole-3-carbinol (I3C), a weak AhR agonist [67]. I3C condenses into stronger AhR agonists such as diindolylmethane (DIM), indolo[3,2-b]carbazole (ICZ), and LTr-1 in acidic stomach circumstances; ICZ has a high receptor affinity [68]. Dietary flavonoids also play a role; fruits, tea, cocoa, and vegetables contain substances such as quercetin, kaempferol, and baicalin. Quercetin and kaempferol suppress TCDD-induced AhR transactivation and control CYP1A1 transcription. Quercetin also improves AhR signaling by preventing 6-Formylindolo[3,2-b]carbazole (FICZ) breakdown [69]. One of Scutellariae Radix's main active ingredients, baicalin, lowers AhR expression and prevents cigarette smoke from activating AhR, hence reducing inflammation and preventing myocardial ischemia injury [70]. A partial AhR agonist, resveratrol is found in large quantities in grape skin and red wine. It is known to stimulate CYP1A1 and to have anti-inflammatory and anti-tumor properties [71]. Notably, resveratrol supplementation in piglets increased the expression of CYP1A1 in the jejunal mucosa [72]. Similarly, I3C has been shown to mitigate colitis by promoting Treg induction and suppressing pro-inflammatory Th17 responses, while both I3C and quercetin reduced chronic DSS-induced colitis in C57BL/6 mice via AhR-dependent anti-inflammatory mechanisms [73,74]. Other dietary ligands include curcumin, which both promotes AhR–ARNT heterodimerization and inhibits DRE binding and CYP1A1 induction [75]; berberine, a plant alkaloid that temporarily activates AhR at high concentrations [76]; and carotenoids, which influence AhR–RAR/RXR crosstalk and act as AhR antagonists after conversion to retinoids [77]. In contrast to the hazardous permanence of industrial ligands, these natural dietary ligands show how nutrition and plant-derived chemicals can fine-tune AhR activity, frequently balancing pro- and anti-inflammatory responses [78]. In line with this, oral administration of β-naphthoflavone significantly decreased the severity of DSS-induced colitis and reduced pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β [79].

3.3 Endogenous Ligands

AhR reacts to a broad range of endogenous ligands made by the body in addition to foreign compounds. These ligands are produced by oxidative and chemical changes, microbiota-derived activities, or host metabolic pathways. Examples include heme metabolites like bilirubin and biliverdin, which, although having a lower receptor affinity than TCDD, directly activate AhR to induce CYP1A1 transcription and have anti-inflammatory effects [80]. Lipoxin A4 and other metabolites of arachidonic acid also influence AhR activity and serve as competitive substrates for CYP1A1 [81].

L-Trp, an essential amino acid that functions as a pseudo-endogenous precursor, is the source of a significant subset of endogenous ligands. Despite not being a strong AhR ligand in and of itself, Trp's breakdown produces a variety of metabolites that, in physiological settings, can interact with AhR [82]. This process involves three main metabolic pathways. First, kynurenine, KYNA, QUIN, cinnabarinic acid (CA), and xanthurenic acid (XA) are produced by the kynurenine route, which is mediated by IDO1 and TDO. Among these, kynurenine and KA are well-known AhR agonists that play important roles in T cell development and immunological tolerance. Second, Trp produces FICZ, a high-affinity AhR agonist that is metabolically unstable and functions as a physiological ligand that is tightly controlled when exposed to UV radiation or oxidative stress [83]. Third, dietary Trp is converted by the intestinal microbiota into a wide variety of indole derivatives, such as tryptamine, skatole (3-methylindole), IAA, IPA, ILA, indole-3-aldehyde (IAld), indole-3-acetaldehyde (IAAld), and indole-3-carboxaldehyde (3-IAld) [84-86]. These compounds are a significant ligand pool in the gut that connects AhR signaling to microbial activity and food consumption. For example, Lactobacillus reuteri's IAld increases mucosal defense and guards against Candida albicans colonization by activating AhR-dependent IL-22 transcription [36]. In animal models, it has been demonstrated that several microbial metabolites, including indole, IPA, and ILA, improve intestinal inflammation and epithelial barrier function [87]. Indirubin and indigo, two others naturally occurring compounds produced by oxidative processes, are likewise strong AhR agonists; indirubin's activity is even greater than that of TCDD [88,89].

All things considered, endogenous ligands, especially those made from Trp, constitute a dynamic interface between immune control, microbial ecology, and host metabolism. Under healthy settings, they support immune tolerance and epithelial homeostasis by regulating AhR signaling, whereas immunological dysfunction and chronic inflammation have been linked to deregulation of their synthesis.

4. The Trp–AhR Axis in IBD: From Metabolism to Inflammation

IBD, encompassing ulcerative colitis (UC) and Crohn's disease (CD), represents a chronic relapsing inflammation of the gastrointestinal tract driven by epithelial barrier dysfunction, immune dysregulation, and microbial imbalance. Clinically, IBD manifests with abdominal pain, diarrhea, rectal bleeding, and extraintestinal symptoms affecting the joints, skin, and liver. Pathophysiologically, the disease results from a complex interplay between genetic susceptibility, microbiota composition, and host immune responses, ultimately leading to loss of intestinal homeostasis [90,91].

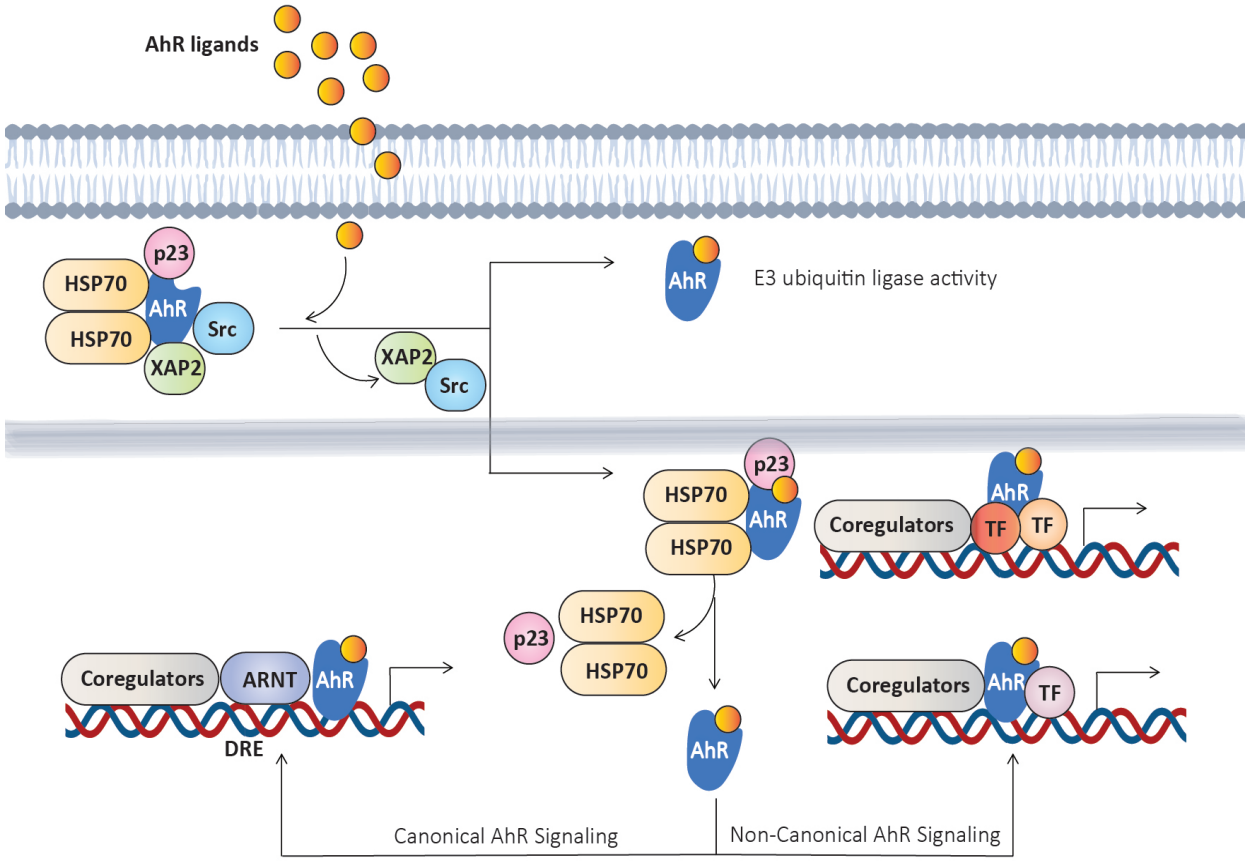

Figure 3. Intestinal Trp metabolism through the kynurenine, indole, and serotonin pathways. Microbial catabolism generates indole derivatives (IAld, IAA, IPA, ILA, IA, tryptamine), while host cells produce kynurenine metabolites (KYN, KYNA, 3-HAA) and serotonin (5-HT). These metabolites act as endogenous AhR ligands, driving either protective outcomes (IL-22 induction, barrier repair, immune homeostasis) or pathogenic responses under dysregulated conditions (chronic inflammation, excessive 5-HT, high Kyn flux).

Recent evidence highlights metabolic–immune crosstalk, particularly involving the Trp-AhR axis, as a key regulator of this inflammatory process [3,92]. Trp and its downstream metabolites–including kynurenines, serotonin, and microbial indole derivatives–act as AhR ligands that influence epithelial integrity, cytokine balance, and immune tolerance. Dysregulation of these pathways has been consistently linked with disease activity, relapse, and extraintestinal manifestations in IBD patients (Figure 3) [93,94]. Animal studies have shown that a deficiency in dietary AhR ligands worsens intestinal inflammation, whereas oral supplementation with Trp or I3C in the DSS model resulted in a mild improvement of colitis [74,95].

The gut microbiota plays a pivotal role in this process by shaping both the production and the downstream effects of Trp-derived metabolites. Alterations in microbial composition influence the balance between kynurenine, serotonin, and indole branches, thereby modifying AhR ligand availability and signaling tone. Understanding these host–microbe interactions provide essential context for therapeutic strategies aimed at restoring intestinal homeostasis through modulation of the Trp–AhR axis.

4.1 The Kynurenine Pathway in IBD

The kynurenine pathway represents the primary route of Trp catabolism in mammalian systems, accounting for more than 95% of dietary Trp degradation. This pathway is initiated by IDO1 and TDO, producing kynurenine as a central intermediate, which can then be further metabolized into downstream derivatives such as KYNA, XA, QUIN, and CA [96]. Many of these metabolite's function as ligands for the AhR, positioning the kynurenine pathway as a major immunometabolic regulator in the intestinal mucosa [97].

In patients with IBD, particularly UC and CD, kynurenine metabolism is markedly dysregulated. Multiple clinical studies have shown that IDO1 is overexpressed, circulating Trp levels are reduced, and both the Kyn/Trp and KYNA/Trp ratios are significantly elevated in inflamed tissues [98]. These metabolic signatures are not only biochemical hallmarks of disease activity but also correlate with key clinical parameters. For example, elevated KYNA/Trp ratios have been associated with inflammation severity, histological injury, and increased hospitalizations in UC patients [99]. Similarly, KYNA levels are consistently higher during active flares compared to remission phases in both UC and CD [100].

Microbial interactions further amplify this axis. Pathogenic Escherichia coli, a frequent etiological factor in UC, can convert kynurenine to KYNA via aspartate aminotransferase, thereby directly increasing KYNA concentrations in the inflamed gut [101]. Such pathogen-driven amplification may exacerbate inflammatory cascades and mucosal injury. Genetic studies also support the clinical relevance of this pathway: nonsynonymous single-nucleotide polymorphisms (SNPs) in IDO1 are associated with extraintestinal manifestations, perianal involvement, and increased CD risk [102].

Mechanistically, kynurenine and its downstream products exert context-dependent effects through AhR signaling. KYNA and XA, for example, promote intestinal epithelial cell proliferation and enhance IL-22 secretion, supporting epithelial regeneration and mucosal protection [103]. Additionally, KYNA and XA improve mitochondrial respiration in IECs and enhance glycolytic capacity in T cells, thereby contributing to energy homeostasis under inflammatory stress [104]. CA and KYNA can also engage AhR to modulate T-cell differentiation toward anti-inflammatory phenotypes. Conversely, excessive kynurenine flux–manifested as persistently high KYNA/Trp ratios–has been implicated in immune suppression and chronic inflammation.

Kynurenine itself can activate AhR to upregulate IL-10 receptor 1 expression on IECs, enhancing responsiveness to the anti-inflammatory cytokine IL-10 [9]. Through these mechanisms, the kynurenine pathway helps shape a tolerogenic environment that counterbalances proinflammatory signals. However, microbial dysbiosis or genetic alterations amplifying kynurenine flux may perpetuate pathology.

Emerging data also indicate that Trp-derived ligands trigger non-genomic AhR signaling through phosphorylation of cytoplasmic kinases such as Src and FAK, influencing epithelial repair and immune migration. This rapid, transcription-independent signaling may explain the protective effects observed shortly after AhR ligand exposure in colitis models [54,105,106]. Reports showing kynurenine and microbial indoles (e.g., IAld, IPA) enhancing tight-junction dynamics support such mechanisms [107]. Overall, the kynurenine pathway acts as both a biomarker and a therapeutic target in IBD–protective when balanced, but pathogenic under excessive activation.

4.2 The Microbial Indole–AhR Axis in IBD

Microbiota-driven catabolism of dietary Trp generates a diverse pool of indole derivatives–such as indole, IAld, IAA, IPA, ILA, tryptamine, and 3-methylindole–that engage the AhR to coordinate epithelial repair, immune modulation, and barrier integrity [108]. Landmark studies demonstrated that commensal Lactobacillus species convert Trp into IAld, which activates AhR to induce IL-22, protecting the intestine against fungal overgrowth and barrier disruption [36]. Indole chemistry thus represents a key molecular language mediating host–microbe communication and maintaining intestinal homeostasis [16].

Among these metabolites, IAld emerges as a potent AhR agonist that upregulates IL-22 and antimicrobial programs, constraining inflammation and dysbiosis [109]. Similarly, IPA, a Clostridium-derived metabolite, attenuates

experimental colitis, tightens epithelial barriers, and reduces oxidative stress via AhR- and PXR-dependent mechanisms [36]. Administration of the high-affinity AhR agonist FICZ markedly alleviates TNBS- and DSS-induced colitis through enhanced IL-22 production and suppression of proinflammatory cytokines [6,110]. Other indoles such as IAA, ILA, and tryptamine improve mucus production, goblet-cell differentiation, and antioxidant responses via AhR–Nrf2 signaling, collectively strengthening the epithelial barrier [3,111].

At the host–microbiota interface, microbial indoles sustain IL-22-producing ILC3 cells, reinforcing epithelial regeneration and mucosal defense [112]. SCFAs, produced by fiber-fermenting commensals, further augment IL-22 via HIF-1α and AhR coactivation, illustrating a cooperative metabolite network [113]. CARD9 deficiency, which disrupts Trp-metabolizing Lactobacillus species, blunts indole-AhR–IL-22 signaling and heightens colitis susceptibility—effects reversible by microbial or metabolite complementation [36]. AhR activation by dietary I3C similarly restores IL-22 signaling and corrects dysbiosis in colitis models [114].

Table 1. Major Trp-derived metabolites in IBD, highlighting their AhR-mediated mechanisms and dual context-dependent roles based on current clinical and experimental evidence.

Metabolite	Primary source / pathway	Protective vs. pathogenic role in IBD	Mechanistic insights (AhR-related)	Contextual modifiers (Inflammation, microbiota, genetics)	Ref
Kynurenine	Host (IDO1/TDO → kynurenine pathway)	Dual – protective (tolerogenic, IL-10R1) vs. pathogenic (when excessively activated)	Activates AhR to upregulate IL-10R1 in IECs and enhance IL-10 responsiveness; excessive IDO1 activity may cause sustained immune suppression	Increased IDO1 expression and Kyn/Trp ratio in active IBD; microbial dysbiosis and IDO1 SNPs amplify pathway flux	[9, 96, 118, 119]
Kynurenic acid	Host kynurenine pathway	Mostly protective	Enhances IL-22 signaling, IEC proliferation, and mitochondrial metabolism; supports epithelial regeneration	Elevated KYNA/Trp ratio in UC/CD flares; *E. coli* may convert Kyn to KYNA under inflammatory stress	[99, 103, 104]
Cinnabarinic acid	Host kynurenine pathway	Protective	Engages AhR to promote anti-inflammatory T-cell differentiation	Host-dependent; represents fine balance within kynurenine flux	[96, 103, 104]
Indole-3-aldehyde	Microbial (mainly Lactobacillus spp.)	Protective	Activates AhR–IL-22 axis to enhance epithelial repair and antifungal defense; modulates mast-cell Trp metabolism toward serotonin synthesis	Reduced Lactobacillus abundance (e.g., CARD9 deficiency) lowers IAld-AhR signaling; restored by probiotic complementation	[36, 120]
Indole-3-propionic acid	Microbial (e.g., Clostridium spp.)	Protective	Tightens epithelial barrier, reduces oxidative stress, and shifts macrophages toward M2 polarization via AhR-PPARγ crosstalk	Depleted in active IBD and dysbiosis; restored by microbiota recovery or postbiotic supplementation	[36, 121, 122]
Indole-3-acetic acid	Microbial indole branch	Protective	Enhances mucus production, goblet-cell differentiation, and anti-inflammatory cytokine balance through AhR signaling	Effect strengthened under restored microbial diversity and indole-pool synergy	[111, 123]
Indole-3-lactic acid	Microbial (e.g., Lactobacillus, Bifidobacterium)	Protective	Activates AhR and Nrf2 pathways in IECs, increasing tight-junction integrity and reducing oxidative injury	Activity potentiated by symbiotic microbiota and fiber-rich diet; contributes to indole-pool cross-amplification	[29, 112, 123]
Serotonin	Host enterochromaffin cells (TPH1 pathway)	Dual – epithelial repair vs. pro-inflammatory (receptor-dependent)	Acts as endogenous AhR agonist inducing CYP1A1; TPH1/5-HTP increase inflammation; 5-HT$_4$R promotes restitution, 5-HT$_7$R enhances immune activation	Phase-dependent: protective during repair, pathogenic in acute inflammation; modulated by SCFAs, SERT status, and CARD9-related dysbiosis	[120, 124, 125]

Clinical evidence parallels these findings. IBD patients show reduced fecal AhR ligands and decreased mucosal AhR expression in inflamed regions [115]. Fecal-transplant and postbiotic interventions increasing IAld, IAA, or IPA restore AhR–IL-22 pathways, expand Tregs, and mitigate colitis severity [116]. Nutritional and pharmacological enhancement of the microbial indole pool consistently improves outcomes, while inhibition of AhR signaling (e.g., by CH-223191) abrogates these effects [117]. Altogether, microbial indoles represent a therapeutic axis integrating dietary inputs, microbiota metabolism, and mucosal repair. Collectively, metabolites from both host and microbial Trp pathways demonstrate diverse, context-dependent effects on intestinal inflammation through AhR signaling. Table 1 summarizes the major Trp-derived metabolites characterized to date, highlighting their source, mechanistic actions, and modulatory roles in IBD pathophysiology.

4.3 The Serotonin-AhR Axis in IBD

The serotonin (5-hydroxytryptamine, 5-HT) branch of Trp metabolism intersects closely with AhR signaling in colitis. TPH1, the enzyme converting Trp to 5-hydroxyTrp and subsequently to 5-HT, regulates both serotonergic tone and Trp availability for AhR-related pathways. Inhibition or deletion of TPH1 mitigates DSS-induced colitis, whereas supplementation with 5-HTP exacerbates inflammation [124].

Serotonin modulates AhR activity directly and indirectly. Intracellular 5-HT accumulation via SERT enhances AhR nuclear translocation and CYP1A1 induction in IECs, while SERT deficiency disrupts this process [126]. Furthermore, 5-HT inhibits CYP1A1-mediated ligand clearance, prolonging AhR signaling [127]. These findings indicate that serotonin acts both as a ligand and as a regulator of AhR persistence.

Cross-talk between microbial metabolites and serotonin further refines this axis. Microbial IAld promotes mast-cell TPH1-dependent serotonin synthesis through AhR activation, forming a positive feedback loop between microbial Trp catabolites and serotonergic flux [120,128]. In parallel, butyrate stimulates 5-HT release from enterochromaffin cells via AhR signaling, linking microbial SCFAs to gut motility and homeostasis [18,26]. Serotonin itself functions as an endogenous AhR agonist, inducing CYP1A1 expression in a SERT-dependent manner [129].

Disruption of these interactions worsens inflammation. CARD9 deficiency reduces Lactobacillus-derived AhR ligands and IL-22 production, increasing colitis susceptibility [130]. TPH1 inhibition or 5-HT synthesis blockade ameliorates inflammation, whereas 5-HTP supplementation aggravates it [101,131]. Impaired SERT function leads to excessive mucosal 5-HT accumulation and defective AhR activation [132]. Receptor-specific pathways add another layer of complexity: 5-HT_4 signaling in epithelial cells promotes restitution, while 5-HT_7 signaling in immune cells enhances inflammation [125,133].

Thus, the serotonin–AhR interplay functions as a metabolic and immunological pivot. Balanced serotonergic flux supports epithelial repair and tolerance, whereas dysregulation amplifies inflammatory responses. Modulating TPH1 activity, serotonin reuptake, or microbial AhR ligand production offers promising strategies to restore homeostasis in IBD.

5. Future Perspectives

Despite major advances in defining the role of Trp metabolism and AhR signaling in gut immunity, translation into clinical practice remains at an early stage. Unresolved questions persist regarding ligand specificity, microbiota–host crosstalk, and patient heterogeneity. The ligand- and dose-dependent nature of AhR activation, species-specific differences in receptor affinity, and interindividual variability in diet, microbiota composition, and host genetics collectively shape how the Trp–AhR axis influences intestinal inflammation. Variations in microbial community structure and host polymorphisms in genes such as AhR, IDO1, and TPH1 alter ligand sensitivity and Trp flux, predisposing certain individuals to dysregulated immune responses. Addressing these factors will be essential for the development of precision medicine approaches tailored to patient-specific metabolic and microbial profiles.

Recent studies have highlighted the therapeutic promise of restoring AhR activity through microbial and dietary interventions. IPA, a microbiota-derived metabolite enriched in Clostridium species, protected colitic mice with reduced microbial diversity by enhancing epithelial barrier integrity, reducing luminal particle translocation, and preserving mucosal separation [121]. Mechanistic studies in DSS colitis confirmed that IPA drives macrophage polarization toward anti-inflammatory M2 states via PPAR-γ, modulating lipid and glucose metabolism through CPT1A and ACSL1 [122]. Similarly, microbiota-derived indole-3-lactic acid increased downstream indoles such as IAA and IPA, alleviating inflammation and correcting dysbiosis in IL-$10^{-/-}$ and DSS models [123]. Together, these findings highlight indole metabolites as a mucosal “language” between bacteria and the host, suggesting that dietary supplementation, engineered probiotics, or postbiotic delivery could re-establish protective AhR signaling.

Dietary compounds such as I3C–derived from cruciferous vegetables–also demonstrated efficacy in experimental colitis by inducing IL-22, enhancing butyrate levels, reducing Th17 activity, and expanding Tregs, thereby preventing colitis-associated dysbiosis. Translating these findings into clinical practice could enable dietary or supplement-based interventions that fine-tune AhR activation without the toxicity of high-affinity synthetic ligands [114].

Human studies reveal that metabolic imbalance in the kynurenine pathway persists even during remission in ulcerative colitis and Crohn’s disease. Decreased serum Trp and altered kynurenine ratios correlate with oxidative stress and disease activity [134]. Genetic studies further support causality: Mendelian randomization analyses show that higher Trp availability is protective, whereas elevated kynurenine increases disease risk [119].

These findings identify Kyn/Trp and KYNA/Trp ratios as promising biomarkers of disease activity and therapeutic response. Longitudinal plasma or stool monitoring of these ratios could dynamically reflect mucosal immune tone and predict relapses [101]. Likewise, fecal AhR activity assays integrate the total ligand potential of host and microbial metabolites, providing a functional readout of AhR signaling [26]. Combining metabolite ratios with fecal AhR assays under standardized sampling and analysis conditions [102]

could allow biomarker-guided stratification, early relapse detection, and personalized intervention tracking. Establishing robust analytical platforms for quantitative metabolomics and functional AhR testing remains a crucial step toward clinical translation.

Emerging multi-omics technologies now offer tools to resolve the complexity of the Trp-AhR-IBD network at unprecedented resolution. Metabolomics enables precise quantification of Trp-derived metabolites and identification of disease-specific signatures [102]; single-cell transcriptomics dissects AhR-dependent immune and epithelial programs [135]; and microbiome sequencing pinpoints bacterial taxa responsible for generating AhR ligands [136]. Complementary organoid and humanized mouse models allow cross-species validation of ligand function, overcoming translational gaps caused by interspecies receptor differences.

Incorporating longitudinal biomarker monitoring (Trp metabolite profiling and fecal AhR activity) into clinical trials will help optimize dosing and validate response metrics. The development of synthetic or semi-synthetic AhR ligands with defined receptor affinity, metabolic stability, and tissue specificity represents another frontier for targeted therapy with minimized risk.

In summary, future research must bridge the gap between mechanistic discoveries and clinical application. Controlled clinical trials guided by precision medicine frameworks–supported by integrated biomarker and metabolomic platforms–will be essential to establish the Trp-AhR axis as a diagnostic and therapeutic cornerstone in IBD management. The convergence of microbial ecology, metabolism, and immunology, empowered by technological innovation, now provides a clear roadmap for translating this pathway from experimental insight to clinical reality.

6. Conclusion

The Trp-AhR axis constitutes a central metabolic–immune interface linking diet, microbiota, and host signaling pathways that determine intestinal homeostasis or inflammation. In IBD, disruption of this axis–characterized by reduced protective indole ligands and elevated Kyn/Trp and KYNA/Trp ratios–correlates with impaired epithelial repair, defective IL-22 signaling, and heightened inflammation. Conversely, restoring physiological AhR tone can improve barrier function and immune tolerance.

From a therapeutic standpoint, the Trp-AhR circuit offers multiple opportunities: dietary and postbiotic supplementation to enhance microbial indole production, modulation of IDO1/TDO-driven kynurenine metabolism, and controlled targeting of serotonergic pathways to balance repair and inflammation. These interventions, together with biomarkers such as Kyn/Trp ratios and fecal AhR activity, may guide personalized therapy and disease monitoring.

Future translation requires well-designed clinical studies integrating metabolomics, microbiomics, and functional AhR assays to define safe, effective, and patient-specific strategies. Ultimately, viewing the Trp-AhR axis as a regulatory circuit provides a conceptual and practical framework for next-generation diagnostics and nutrition-based therapies in IBD.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

During the preparation of this manuscript, the authors used AI-assisted language editing tools solely to improve grammar, spelling, and readability. The authors reviewed and edited the content and take full responsibility for the integrity of the work.

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