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REVIEW

Gut microbiota-derived tryptophan metabolism mediates renal fibrosis by aryl hydrocarbon receptor signaling activation

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Abstract

The gut microbiota has a crucial effect on regulating the intestinal mucosal immunity and maintaining intestinal homeostasis both in health and in disease state. Many effects are mediated by gut microbiota-derived metabolites and tryptophan, an essential aromatic amino acid, is considered important among many metabolites in the crosstalk between gut microbiota and the host. Kynurenine, serotonin, and indole derivatives are derived from the three major tryptophan metabolism pathways modulated by gut microbiota directly or indirectly. Aryl hydrocarbon receptor (AHR) is a cytoplasmic ligand-activated transcription factor involved in multiple cellular processes. Tryptophan metabolites as ligands can activate AHR signaling in various diseases such as inflammation, oxidative stress injury, cancer, aging-related diseases, cardiovascular diseases (CVD), and chronic kidney diseases (CKD). Accumulated uremic toxins in the body fluids of CKD patients activate AHR and affect disease progression. In this review, we will elucidate the relationship between gut microbiota-derived uremic toxins by tryptophan metabolism and AHR activation in CKD and its complications. This review will provide therapeutic avenues for targeting CKD and concurrently present challenges and opportunities for designing new therapeutic strategies against renal fibrosis.

Keywords Intestinal flora · Tryptophan metabolites · Chronic kidney disease · Natural products

Abbreviations

AHR	Aryl hydrocarbon receptor
AHRR	AHR repressor protein
ARNT	AHR nuclear translocator
CKD	Chronic kidney disease
COX-2	Cyclooxygenase-2
CVD	Cardiovascular diseases
CYP	Cytochrome P450 family
DKD	Diabetic kidney disease
ESRD	End-stage renal disease
I3A	Indole-3-aldehyde
IAA	Indole-3-acetic acid
IDO	Indoleamine 2,3-dioxygenase
ILA	Indole-3-lactic acid
IS	Indoxyl sulfate
HIF	Hypoxia-inducible transcription factor
NF-κB	Nuclear factor kappa B
PAHs	Polycyclic aromatic hydrocarbons
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TF	Tissue factor

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Introduction

With the development of the economy, environmental pollution has become one of the most serious problems that threaten human health [1, 2]. Some persistent organic pollutants, such as polycyclic aromatic hydrocarbons (PAHs),

halogenated aromatic hydrocarbons, and coplanar polychlorinated biphenyls are usually derived from waste incomplete combustion and pyrolysis and as by-products of industrial manufacturing processes. As early as the 1950s, PAHs have been noted to affect the substance metabolism and various physiological functions [3, 4]. Later, aryl hydrocarbon receptor (AHR) was initially reported based on the study of PAHs metabolism [5, 6]. Furthermore, many environmental carcinogens, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), benzo(a)pyrene and hexachlorobenzene, were reported to activate AHR signaling [7–9].

AHR is a member of the family of basic helix-loop-helix transcription factors [10]. Under normal circumstances, the inactive AHR combine with a dimer of the 90 kDa heat shock protein (HSP90), X-associated protein 2 (XAP2), and the co-chaperone p23 to constitute a stable protein complex in the cytoplasm [11]. When the cognate ligands bind to AHR, the complex is activated by a conformational change exposing its amino-terminal nuclear localization sequence and an adjacent nuclear export sequence. After phosphorylated by protein kinase C, the ligand-bound AHR complex is translocated into the nucleus in which it combines with the AHR nuclear translocator (ARNT) through HSP90 displacement. The AHR/ARNT heterodimer is able to bind to the special xenobiotic responsive elements (XREs) or dioxin responsive elements, which locate in the regulatory regions of many AHR target genes [10]. Subsequently, it leads to the transcription of downstream target genes including phase I metabolism enzymes, such as cytochrome P450 family (*CYP*) 1 enzyme and a few phase II conjugation enzymes [12]. In addition, in the regulatory regions of the above-mentioned target genes, those special DNA enhancer sequences also include AHR repressor protein (AHRR) [13]. AHRR inhibits AHR signal transduction through binding to ARNT or binding to XREs emulously. The expression of AHRR is activated by AHR, which forms a negative feedback loop to regulate AHR conversely [14, 15] (Fig. 1). AHR signaling pathway can interact with other transcriptional factors such as activator protein 1, nuclear factor-erythroid-2-related factor 2 (Nrf2), and nuclear factor kappa B (NF-κB), which boosts the inflammatory response [16–18]. Additionally, AHR in the cytoplasm can activate other cytoplasmic proteins, like Smads, β-catenin, mitogen-activated protein kinase (MAPK) family p38 [19], NADPH oxidase, and extracellular signal-regulated kinase. And the activation of AHR and related pathways would induce and aggravate various diseases such as cancer, cardiovascular disease (CVD), and chronic kidney disease (CKD). In this review, we will discuss gut microbiota-derived tryptophan metabolites (indole metabolites) as AHR ligands to activate AHR signaling and mediate renal fibrosis. Therapeutic potential of natural products as AHR antagonists is also highlighted to provide a new perspective for clinical treatment of CKD.

Renal fibrosis

Renal fibrosis, mainly characterized by glomerulosclerosis and tubulointerstitial fibrosis, is the common ultimate pathological feature of CKD [20]. The progression of CKD indicates that patients inevitably reach end-stage renal disease (ESRD) and need renal replacement treatment such as dialysis and transplantation. Renal fibrosis is associated with the activation of renin–angiotensin system, IκB/NF-κB, keap1/Nrf2, AHR, TGF-β/Smad and Wnt/β-catenin signaling pathways as well as the dysregulation of metabolism such as lipid metabolism, purine metabolism, and amino acid metabolism [21–27]. For patients with CKD, the higher risk cannot be completely explained by traditional risk factors such as tobacco use, obesity, high blood pressure, diabetes mellitus, and hypercholesterolemia. The uremic circumstance itself is harmful and uremic toxins have emerged as a key factor to explain CKD and its complication. In CKD patients, uremic toxins contributed to progressive renal fibrosis. Tryptophan metabolism is one of the most important sources of uremic toxins. Several seminal publications have highlighted that a plethora of uremic toxins derived from tryptophan metabolism are produced by host and gut microbiota and were implicated in renal fibrosis [9, 28–30].

Tryptophan metabolism in renal fibrosis

Tryptophan is an essential amino acid that cannot be synthesized in the body but is commonly found in regular diets [9]. Recently, the most compelling evidence has suggested that the intestinal metabolites of tryptophan play a crucial role in AHR activation [31, 32]. Most of tryptophan is metabolized by the kynurenine metabolic pathway, and others are metabolized to melatonin through the serotonin pathway and to indole components through the indolic pathway [29, 33]. First, the kynurenine pathway occurs mainly in the liver, where tryptophan will be metabolized by indoleamine 2,3-dioxygenase (IDO)1, IDO2 and tryptophan 2,3-dioxygenase, producing the intermediate N-formyl kynurenine, and then converting into kynurenine by arylformamidase. Further, kynurenine can be metabolized to kynurenic acid, cinnabarinic acid, xanthurenic acid, picolinic acid, quinolinic acid, and NAD^+ [29]. These products in the kynurenine pathway are involved in the regulation of quite a few host biological responses including inflammation, immune response, and neurotransmission. Moreover, kynurenic acid was reported to exert a mucosal protective effect in the gut, which was mediated only by IDO1 [34]. Some studies have focused on the role of kynurenic acid and kynurenine as

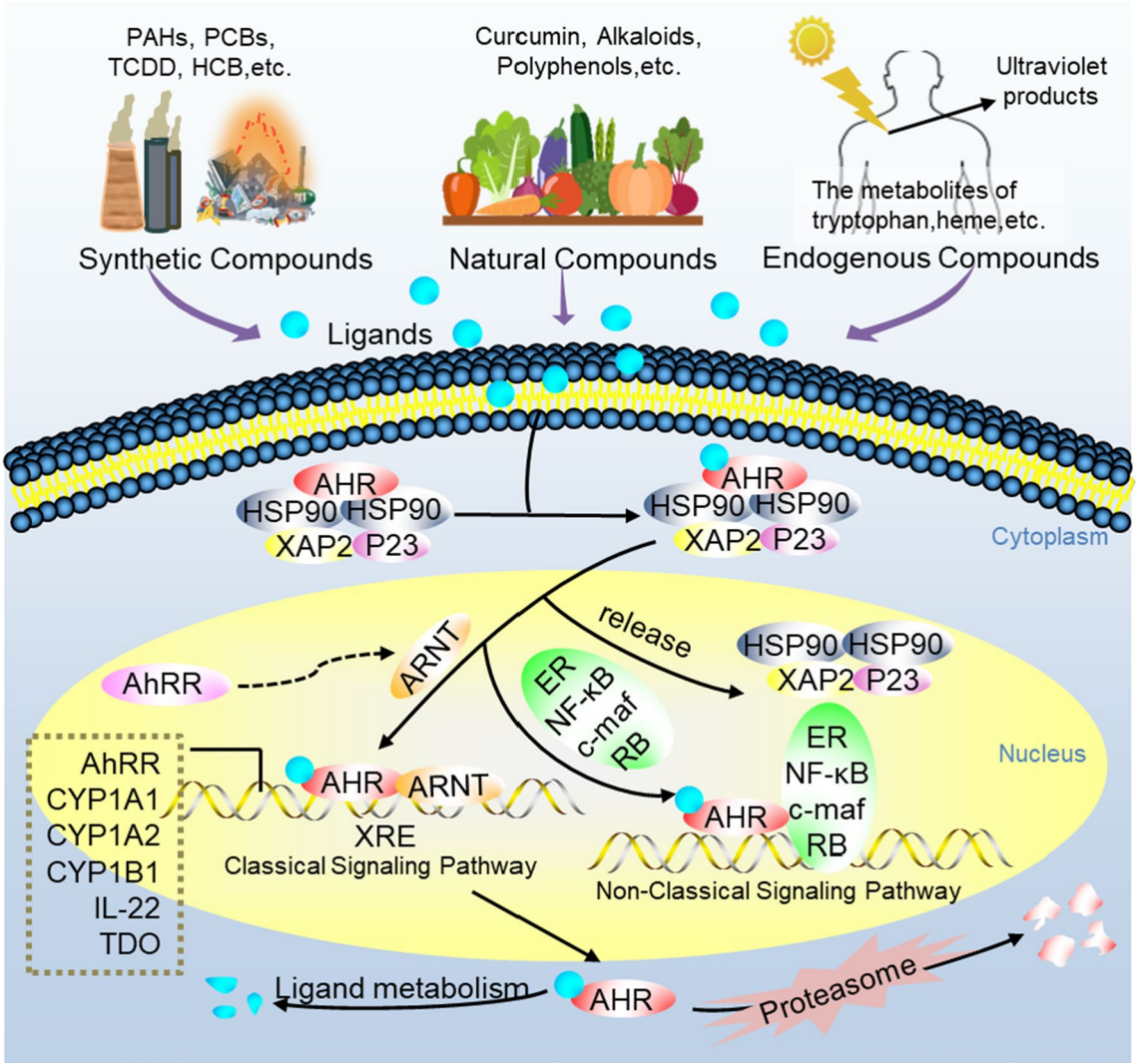

Fig. 1 The AHR signaling pathway. Inactive AHR is complexed with HSP90, XAP2, and p23 to maintain stability and keep it in a high-affinity state for its ligands. When the ligands bind to AHR, the complex translocates to the nucleus where it combines ARNT through HSP90 displacement. The AHR-ARNT heterodimer binds to XREs to induce the transcription of downstream target genes, such as CYP1A1, CYP1B1, AHRR, etc. AhRR is also a negative regulator of AHR that can bind to ARNT but does not induce transcription. Besides, the ligands–AHR complex also interacts with other regulator proteins, such as NF-κB, etc

AHR agonists [35]. Second, in the serotonin pathway, tryptophan is catalyzed by tryptophan hydroxylase to 5-hydroxytryptophan, then metabolized to 5-hydroxytryptamine (5-HT, serotonin) by IDO subsequently converting into melatonin [36]. Serotonin is not an AHR ligand, but it can bind with AHR ligands, as a *CYP1A1* substrate, to prevent ligand inactivation and promote sustained AHR signaling [37]. Third, another important pathway occurs in the human gastrointestinal tract, which contains more than 10^{14} kinds of microorganisms [38]. The diverse and dynamic gut microbiota in human gastrointestinal tract played a critical role in host health and diseases [39, 40]. These intestinal microorganisms can not only regulate host immune response by affecting immune tolerance and autoimmune diseases, but also play an important role in the regulation of gut homeostasis. In the healthy state, the human intestinal flora carries out a variety of activities to the human body. Intestinal flora has a symbiotic relationship with the host, which protects the body against pathogenic bacteria, regulates the immune system, regulates endogenous lipid and carbohydrate metabolism, and maintains the nutritional balance of the body. Many bacterial species have been revealed to metabolize tryptophan into indole and indole derivatives such as tryptamine, indole-3-acetic acid (IAA), indole-3-aldehyde (I3A), indole-3-lactic acid (ILA), and indole-3-propionic acid (IPA) [9]. For instance, tryptophan could be metabolized to I3A by *Lactobacillus* spp., to ILA by *Bifidobacterium* spp., to IAA by *Bacteroides* spp. and *Clostridium* spp. and to tryptamine

by *Clostridium sporogenes* and *Ruminococcus gnavus*. In addition, *Peptostreptococcus* spp. could convert tryptophan into IPA in the gut [9] (Fig. 2). Tryptophan is metabolized by bacterial tryptophan enzymes to produce the precursor indoles, which are absorbed and converted into indoles sulfate (IS) by *CYP2E1* and sulfotransferases in the liver [41]. One research had found a tryptophanase gene in *Bacteroides thetaiotaomicron* and it was a kind of common tryptophanase gene existing in the human gut. And the relative abundance of the tryptophanase gene is closely related to the relative abundance of *Bacteroidetes* in intestinal flora [41]. Additionally, many types of bacteria in the gastrointestinal tract, such as *Escherichia coli*, can metabolize tryptophan into indoles, and indoles play a key role in the progress of diseases as an important intercellular and interspecific bacterial signaling molecule [9]. Pathologically, tryptophan is metabolized to indolic compounds, such as indole, IAA and I3A, via intestinal bacteria and then absorbed into blood circulation, which commonly are accumulated in CKD patients [28]. It is also reported that IS and IAA bind with AHR, induce the complex to translocate to nuclear, and upregulate eight genes regulated by AHR, including *CYP1A1* and *CYP1B1* [42]. Taken together, tryptophan metabolites from gut microbiota have been demonstrated to participate in renal fibrosis as AHR ligands (Fig. 3).

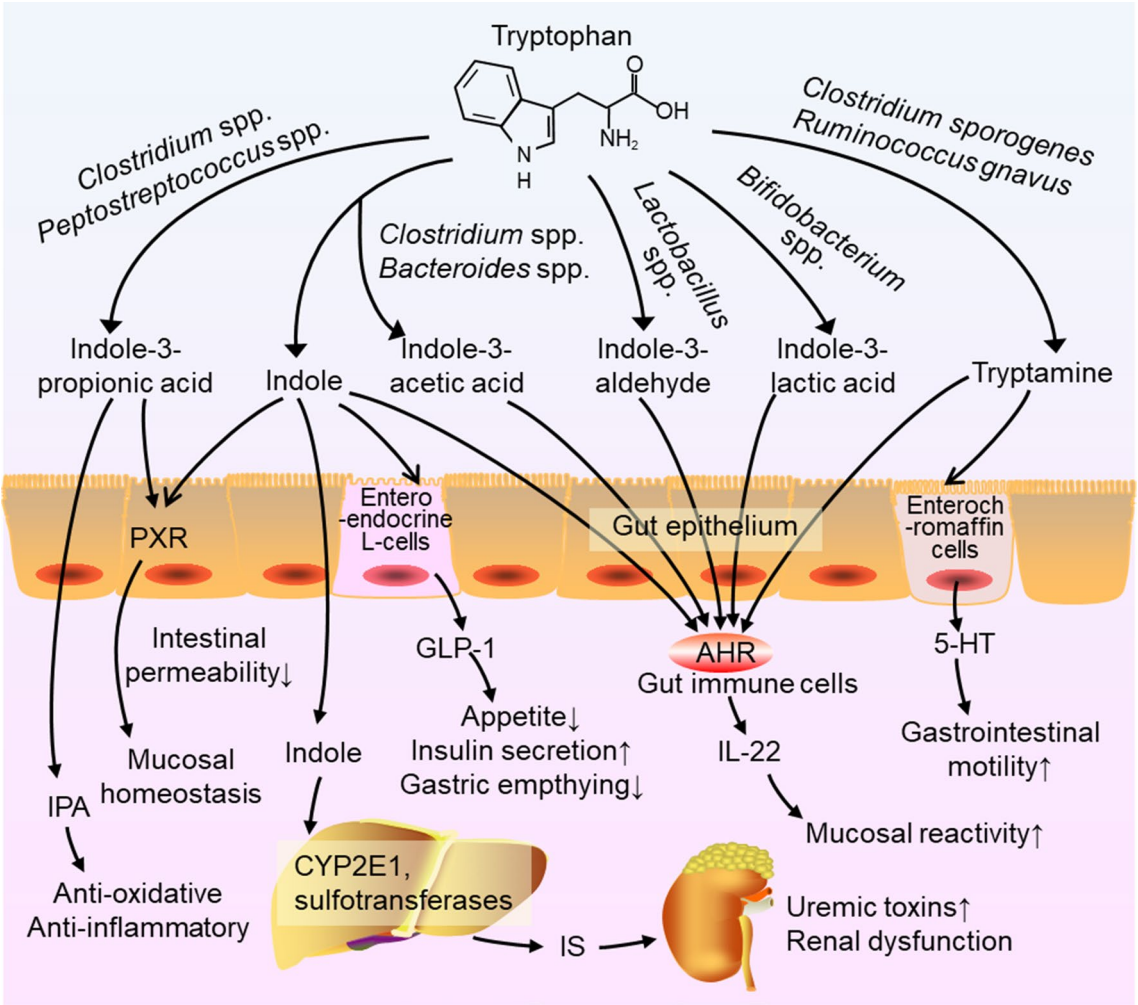

Fig. 2 Mechanisms of action of microbial tryptophan catabolites on host physiology and disease. Tryptophan in the colonic lumen is converted into various catabolites by the gut microbiota. Indole and indole-3-propionate (IPA) may mediate the pregnane X receptor (PXR) to decrease intestinal permeability and affect mucosal homeostasis. Indole is metabolized to indoxyl sulfate by CYP2E1 and sulfotransferases in the liver leading to the accumulation of IS, which is toxic and associated with renal dysfunction. Indole also induces the release of glucagon-like peptide 1 (GLP-1) in enteroendocrine L-cells, suppressing appetite and insulin secretion and slowing gastric emptying. Several tryptophan catabolites activate AHR in intestinal immune cells to alter innate and adaptive immune responses maintaining mucosal reactivity. In enterochromaffin cells, tryptamine induces the release of 5-HT stimulating gastrointestinal motility by acting on enteric nervous system neurons

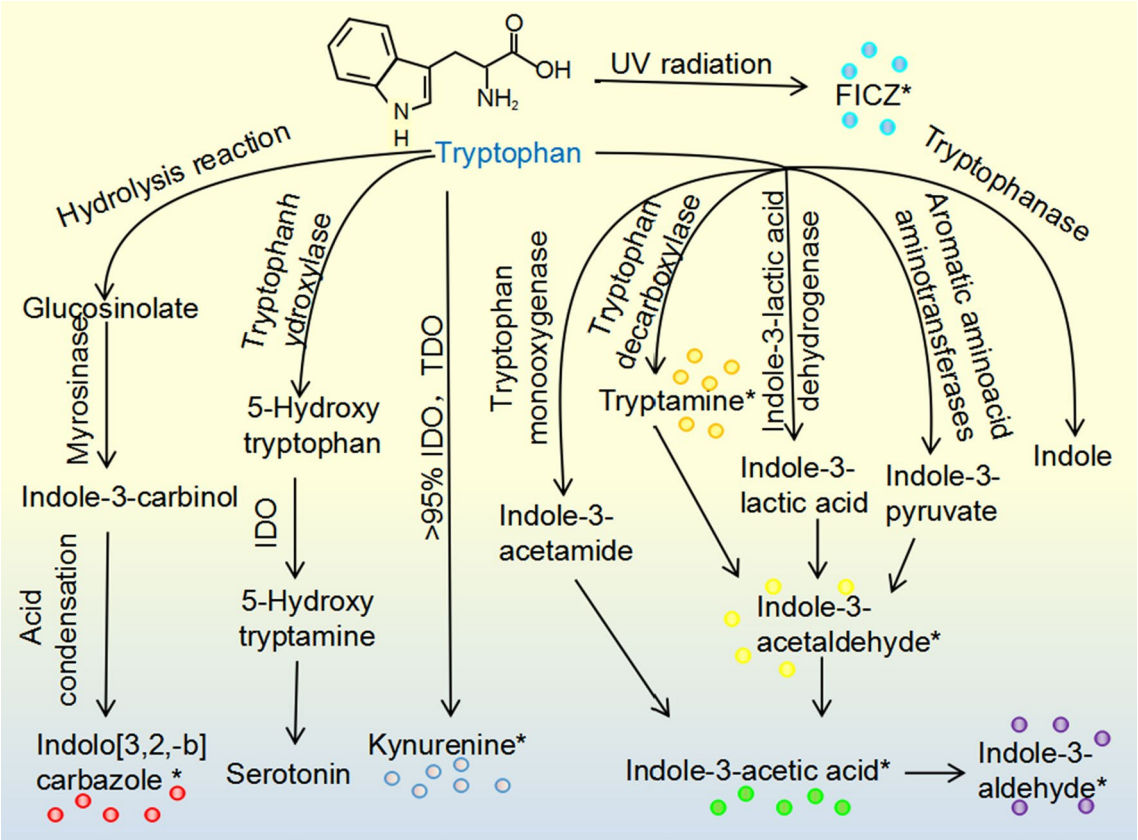

Fig. 3 AHR ligands from tryptophan metabolism. Tryptophan in cruciferous vegetables produce glucosinolate via hydrolysis reaction, yielding indolo[3,2,-b]carbazole. 95% tryptophan can be metabolized to kynurenine, which is mediated by IDO and TDO. In the gastrointestinal tract, metabolites such as tryptamine, indole-3-acetaldehyde, indole-3-acetic acid, and indole-3-aldehyde are from the microbial metabolic process. Besides, tryptophan can be metabolized to 6-formylindolo-(3,2-b)-carbazole from ultraviolet radiation. Asterisks indicate metabolites with AHR agonistic activity

AHR in renal fibrosis

The roles of AHR have gradually been demonstrated in renal fibrosis. First, activation of AHR can result in progressive glomerular and renal tubular cells damage, which can cause glomerulosclerosis and renal interstitial fibrosis, thereby exacerbating CKD [43]. In the classical AHR signaling pathway, the activated AHR can induce the transcription of downstream target genes including *CYP1A1*, the main enzyme involved in drug metabolism and biological activation. Second, CKD patients generally have microinflammatory state and lipid metabolism disorder, which would affect each other and accelerate the progression of the disease. *CYP1A1* can metabolize many exogenous precancerous substances into electron-friendly compounds, combine with macromolecular substances in vivo to form DNA adductions, and eventually lead to mutation and genotoxicity [44]. Meanwhile, the body also initiates the immune response, when *CYPlAl* metabolizes endogenous and exogenous substances, which can induce oxidative stress and inflammation. Third, activation of AHR also can explain the high risk of CVD in patients with CKD. AHR activated by uremic toxins increased the expression and activity of cyclooxygenase-2 (COX-2), a key enzyme in the synthesis of prostaglandin and thrombin by arachidonic acid, promoting platelet aggregation in vascular endothelial cells [13]. And in vascular smooth muscle cells, it also induced the increased expression and activity of tissue factor (TF), thus inducing a procoagulant state [45]. Vascular dysfunction caused by AHR activation plays a crucial role in the increased risk of multiple CVD, like peripheral artery disease, myocardial infarction, and stroke in CKD patients [46].

Gut microbiota-derived tryptophan metabolites as AHR ligands in renal fibrosis

IAA as AHR ligand in renal fibrosis

IAA is a kind of tryptophan metabolite mainly produced by *Clostridium* spp. and *Bacteroides* spp. in the gut. A growing body of research has demonstrated the deleterious effect of

IAA on renal and vascular cells, and AHR was identified as the cellular receptor of toxins [8]. However, IAA could not directly activate the AHR pathway to increase the expression or activity of IF compared with IS. Tawfik et al. found that IAA at 50 μM could activate AHR to induce TF expression but the level of TF was significantly decreased when inhibited the NF-κB pathway, which was suggested that the NF-κB was essential in the process of IAA inducing TF. Moreover, the nuclear translocation of the NF-κB p50 subunit was reduced by p38 MAPK inhibition. It is concluded that AHR did not directly bind to the TF gene promoter, but IAA modulated AHR/p38 MAPK/NF-κB pathway to increase TF in human endothelial cells [47]. Gondouin et al. found that TF levels in human umbilical vein endothelial cells (HUVECs) and peripheral blood mononuclear cells (PBMCs) were increased by 52% when incubated with IAA at a concentration of 50 μM compared with the control group [48]. Further studies found IAA enhanced AHR-dependent gene expression and the level of TF mRNA in endothelial and peripheral blood mononuclear cells by activating AHR. Additionally, indolic uremic solutes could increase TF procoagulant activity [48]. These thrombotic mechanisms induced by toxins include not only increasing the levels of procoagulant microparticles, but also impairing endothelial healing [49]. Also, endothelial dysfunction, oxidative stress, and inflammation induced by uremic solutes could result in increased cardiovascular risk [50]. Dou et al. reported that high levels of IAA (IAA > 3.73 mM)-treated endothelial cells increased COX-2 expression and this raised COX-2 would enhance the synthesis of prostaglandin E2 in endothelial cells, promoting platelet aggregation [51]. Meanwhile, it is verified that IAA increased the mRNA expression of *CYP1A1*, *CYP1B1*, and *AHRR* and increased reactive oxygen species production in endothelial cells. IAA activated the AHR/p38MAPK/NF-κB pathway and upregulate the expression and activity of COX-2 to induce oxidative stress and inflammation, suggesting the prooxidant and proinflammatory effects of the uremic solute IAA.

In diabetic kidney disease (DKD) rats, oxidative stress, metabolic abnormalities, and matrix accumulation lead to glomerular mesangial cell activation and tubular cell function changes. And the activation of AHR has been involved in DKD. Lee et al. found that the chow and water intake, urine output, urine albumin, and albumin to creatinine ratio were obviously increased in streptozotocin-induced diabetic mice, which were alleviated in AHR-knockout mouse [52]. Furthermore, the number of macrophages, macrophage infiltration, and ECM accumulation were significantly higher in the diabetic group than in the control group, and were attenuated in AHR-knockout mouse or AHR inhibitor treatment mouse. Meanwhile, AHR deficiency reduced the levels of COX-2 and prostaglandin E2, lipid peroxidation and oxidative stress. These results suggested that AHR could mediate pathologic alterations of renal function and structure in diabetic mouse [52]. The Nrf2 plays a key role in combating diabetes-induced oxidative stress and inflammation, which are the main causes of diabetes-induced endothelial dysfunction. It is known that endothelial dysfunction is a key first step in the development of diabetic macrovascular complications [53]. Wu et al. found Nrf2 knockout diabetic mice-induced diabetes by streptozotocin showed more severe aortic endothelial oxidative stress, inflammation, and dysfunction than wild-type diabetic mice. And sodium butyrate, an activator of Nrf2, obviously alleviated these effects in the wild-type mice, but not in the Nrf2 knockout mice. Moreover, sodium butyrate could increase Nrf2 mRNA and protein but did not promote Nrf2 nuclear translocation in high glucose-treated aortic endothelial cells. Further, sodium butyrate increased occupancy of AHR and the co-activator P300 at the Nrf2 gene promoter. It was suggested that Nrf2 is necessary to protect against diabetic-induced aortic endothelial dysfunction [53]. Nrf2 and NF-κB signaling pathways are mutually regulated. Nrf2 deficiency up-regulates NF-κB activity and causes proinflammatory factor expression, which in turn regulates Nrf2 transcription and activity. Abnormalities of Nrf2 and NF-κB signaling pathways are closely related to renal fibrosis [24].

Reducing oxidative stress and inflammatory response is important to slow or improve the development of CKD. It is noted that the effects of IAA to induce oxidative stress and endothelial inflammation were significant stimuli of cardiovascular events in clinical studies. Some researchers have studied CKD patients with long-term exposure to urinary toxins and found that elevated TF levels in vessel walls may accelerate atherosclerosis, which probably explains the high cardiovascular mortality observed in this population [54]. It is reported that those patients with higher IAA levels (> 3.73 μM) have an increased risk of cardiovascular disease in CKD patients compared to patients with lower IAA levels (<= 3.73 μM) [51]. Brito et al. also found a positive correlation between AHR protein expression and IAA plasma levels in CKD patients [55]. IAA also can activate the AHR/MAPK pathway to regulate cell proliferation, differentiation, and immune function and induce CVD in ESRD patients [56].

IS as a AHR ligand in renal fibrosis

Indole is the main bacterial tryptophan metabolite, which is generated by *Bacteroides* spp. and *Clostridium* spp. in the gut [57]. It has been demonstrated that indole inhibited the upregulation of interleukin-1β, interleukin-6, and chemokine ligand 2 induced by palmitate and lipopolysaccharide to attenuate inflammation and also decreased the secretion of the key oxidative stress inducer protein nitric oxide synthase and NADPH oxidase. Further studies indicated that

IS significantly increased the levels of *CYP1A1* and *CYP1B1* but cannot reduce the upregulation of interleukin-1β and nitric oxide synthase. It is suggested that indole itself, not IS, has anti-inflammatory effects in the liver [58]. Additionally, indole may bind with the pregnane X receptor to reduce the permeability of the intestine and maintain the stability of the intestinal mucosa. It also could induce enteroendocrine L-cell to secrete glucagon-like peptide 1, which is known to stimulate insulin secretion, suppresses appetite, and slow the rate of gastric emptying [9]. Indole is metabolized to IS by *CYP2E1* and sulfotransferases in the liver, which is toxic and gradually accumulates in the body. With the aggravation of renal damage, it would develop ESRD and even death. Recently, a great many reviews have suggested that IS plays a crucial role in AHR activation and the progress of CKD. It is noted that IS activated the AHR pathway in cells of CKD mice to upregulate the mRNA levels of *CYP1A1* and *CYP1B1* [59]. Schroeder et al. determined the expression of *CYP1A1*, *CYP1A2*, and *CYP1B1* in hepatoma cell lines after IS exposure. They found that IS would increase the levels of *CYP1A1*, *CYP1A2*, and *CYP1B1* mRNA, and the effects of 100 μM IS and 10 nm TCDD on *CYP1B1* gene expression were equivalent [60]. The activation of AHR in CKD may provide a mechanism to explain the harmful effect of toxins on cells. For example, AHR activated by IS can induce podocyte injury and glomerular damage. It is reported that mice exposed to IS for 8 weeks would exhibit progressive glomerular injury and vascular damage along with increased *CYP1A1* expression. IS could induce AHR nuclear translocation, increase *CYP1A1* levels, and decrease cell size and viability of podocytes in mice [8]. Besides, the level of IS in renal tissue of rats with chronic renal failure was increased by six times, and IS in renal homogenate was up to 71 μM. These results also reflect a significant increase of IS in the damaged kidneys [8]. Indeed, activation of AHR could lead to progressive glomerular injury and the impairment of renal function by podocyte progression. It is demonstrated that macroscopic renal cortex atrophy in IS-treated kidneys may be an end-stage feature due to the sum of glomerular and tubulointerstitial damage [61]. Although a lot of studies support the direct role of IS on podocyte injury, it is still possible that podocytes lesion is a comprehensive consequence of chronic vascular damage by toxins. Hung et al. showed that IS impaired endothelial progenitor cell function in uremia mice by inhibiting the HIF/interleukin-10/vascular endothelial growth factor signaling pathway, thereby inhibiting neovascularization and mediating peripheral arterial disease in CKD [62]. DKD is another primary cause of CKD and leading cause of ESRD, which develop many comorbidities and has a high mortality rate. Zhao et al. observed the increase of serum creatinine and blood urea nitrogen and the decrease of serum albumin in DKD rats. And in the rats treated with *Tangshen Formula*, the levels of serum creatinine and microalbuminuria were attenuated. They also detected that mesangial matrix was moderately expanded, tubules atrophy and lumens were dilated, and ECM was deposited in glomeruli and tubulointerstitium in the kidney of DKD rats, which were inhibited in *Tangshen Formula*-treated rats [63]. Additionally, the level of IS in the DKD group increased by four times compared with the sham group and markedly reduced in *Tangshen Formula*-treated group. The latter group of rats also significantly reduced the mRNA level and expression of AHR and suppressed the nuclear translocation of phosphorylated NF-κB p65 to inhibit activation of NF-κB signaling. It was demonstrated that orally administered *Tangshen Formula* significantly decreased level of IS and attenuated renal inflammation to inhibit diabetic renal injury [63].

Disturbance of intestinal flora results into the release of proinflammatory bacteria products, leading to insulin resistance, energy consumption, immune disorders, atherosclerosis in diabetic patients, and accelerating the progression of renal disease. Quite a few studies have suggested that DKD is the most severe and one of common long-term complications of diabetes. Kim et al. pointed out that the activity of serum AHR ligands was an important and independent risk factor for DKD based a multiple regression analysis [64]. Recent studies have found decreased tryptophan level and increased levels of tryptophan metabolites, including kynurenic acid, 3-hydroxykynurenine, 5-hydroxytryptophan, 3-hydroxyanthranilic acid, and 5-hydroxyindoleacetic acid in diabetic mellitus patients. Matsuoka et al. divided diabetic patients into higher and lower tryptophan groups. They found higher levels of IAA, kynurenine, kynurenic acid, 5-hydroxytryptophan, and 5-hydroxykynurenine in higher tryptophan group but 5-hydroxyindoleacetic acid was higher in lower tryptophan group [65]. The results indicated that there was more degradation of tryptophan when plasma tryptophan level was high, and more serotonin is converted to 5-hydroxyindoleacetic acid when plasma tryptophan level was low. It was also suggested that diabetic patients are often exposed to stress [65]. Additionally, there have been many clinical studies on the role of IS as an AHR ligand in CKD. IS could activate AHR to mediate the immune response to influence the progression of renal fibrosis. Kim et al. found that the production of TNF-α in macrophages of CKD patients is modulated involving the crosstalk among AHR, NF-κB, and suppressor of cytokine signaling. IS-activated AHR rapidly binds to the NF-κB p65 subunit, resulting in a mutual inhibition of AHR and NF-κB and inhibiting the production of TNF-α early. Afterward, AHR induced the expression of suppressor of cytokine signaling 2 to increase TNF-α production through NF-κB. Meanwhile, co-immunoprecipitation data showed that the direct interaction between AHR and p65 occurred 15-30 min after IS stimulation [66].

Vascular dysfunction caused by AHR activation also explained the high risk of CVD in ESRD patients. Increasing evidence showed that IS was associated with the pathophysiology of cardiovascular and renal dysfunction. More recently, IS has been considered as a vascular toxin [66]. In vascular smooth muscle cells (VSMCs), IS could induce the increased expression and activity of TF, thus inducing a procoagulant state [45]. Shivanna et al. have reported that the levels of IS in ESRD patients were 55 times higher than those in the control group on average. Moreover, the activity of TF in VSMCs increased after exposure to serum of ESRD patients, which was significantly correlated with the level of IS in ESRD patients. IS can activate AHR and then inhibit TF ubiquitination and degradation in VSMCs of patients with renal failure and then promoting thrombosis [67]. Gondouin et al. showed that the production of TF in endothelial cells was increased by 84%, 106%, and 135%, respectively following the treatment of IS at concentrations of 0.1, 0.5, and 1 mM [48]. In addition, the study also demonstrated that IS activated the classical AHR signaling that directly bound to TF, and increased TF stability and induced thrombosis [68]. Abundant evidence has shown that patients with CKD are predisposed to CVD and the emergence and development of CVD are the primary inducements of death in patients treated by dialysis [69]. Therefore, this connection is even more distinct in patients with ESRD, in which the proportion accounts for 50% of all-cause mortality [66]. Cardiovascular mortality of patients with a functioning renal transplant is two to five times higher than general population [70].

There were reports that uremic toxins mediated the vicious cycle between oxidative stress and inflammation aggravating the chronic inflammatory environment, thereby accelerating the progression of CVD in CKD patients [71]. For instance, it has shown that IS can alter the balance between prooxidant and antioxidant mechanisms [72], increase the release of endothelial microparticles [73], and lower the healing ability of endothelial cells, which results in the occurrence of oxidative stress [74]. Reactive oxygen species produced during the metabolism of *CYP1A1* can activate NF-κB inducing the expression of proinflammatory factors. Uremic toxin-activated AHR can induce oxidative stress and inflammation increasing the mortality of CVD in patients with CKD [75]. It is reported that NF-κB was activated and transferred into the nucleus to induce the expression of certain proinflammatory factors, thus participating in the pathological process of inflammatory and autoimmune diseases [76]. Another study demonstrated that IS-activated AHR induced monocytes to produce proinflammatory cytokine TNF-α leading to a proinflammatory state of smooth muscle cells in patients with ESRD. But it has also been reported that IS activated AHR to trigger the inflammatory response by mediate activator protein 1 transcriptional activity [77]. Therefore, the mechanism still needs further study.

Other gut microbiota-derived tryptophan metabolites as AHR ligands

Tryptamine, a tryptophan metabolite generated by *Clostridium sporogenes* and *Ruminococcus gnavus*, has been considered as AHR ligand with weak potency. It is reported that tryptamine could bind to AHR and induce the expression of AHR target genes to regulate intestinal immune response [78]. Further research showed that tryptamine induced AHR nuclear accumulation and AHR/ARNT promoter recruitment to activate the transcription of *CYP1A1* [79]. Besides, I3A has been reported to activate AHR in intestinal immune cells and increase the expression of interleukin-22 to attenuate mucosal inflammation and protect the intestinal epithelial barrier [80]. A recent study found that the combination of I3A and AHR increased the secretion of interleukin-22 by lamina propria lymphocytes and induced the phosphorylation of signal transduction factor and transduction factor 3, thus promoting the intestinal epithelial cells proliferation and restoring the intestinal mucosa injury [81]. Moreover, the treatment of macrophages with I3A reduced the production of TNF-α, interleukin-1β, and monocyte chemoattractant protein-1 induced by lipopolysaccharide to attenuate the inflammatory response obviously. It also regulated the expression of AHR target genes and modulated the hepatocyte metabolism by mediating ligand activation of the nuclear receptor [82]. The study by Yu et al. showed that I3A acted as a ligand of AHR and decreased both the protein and mRNA levels of *CYP1A1*. It is demonstrated that I3A (100 nM) could suppress the production of thymic stromal lymphopoietin, an important cytokine, reduce inflammation, and enhance antifungal abilities in patients who suffer from atopic dermatitis [83]. In the gut, *Bifidobacterium* spp. can metabolize tryptophan into ILA, another AHR ligand. It has been reported that ILA was able to inhibit inflammatory T cells and stimulate immunoregulatory T cells through AHR [84]. ILA activated AHR to inhibit the transcription of IL-8 and reduce the interleukin-8 response after interleukin-1β stimulus in immature intestinal enterocytes [85]. ILA also could clear the free radicals and reduce the production of inflammatory mediator interleukin-6 induced by ultraviolet B radiation to exert anti-inflammatory effects in human keratinocytes [86].

As discussed above, accumulated studies showed gut microbiota-derived tryptophan metabolites as AHR ligands exert an adverse influence on the occurrence and progression of renal fibrosis [36]. Moreover, some researchers suggest that AHR activated by different ligands is a bifunctional modulator of the expression of downstream target genes and the progress of many diseases. With these discoveries, we

see a promise of AHR as a therapeutic target for diseases and hope to seek therapeutic schedules of CKD to better control the increased rate of CKD based on the regulation of AHR.

The potential role of natural products as AHR antagonists

Identification of potential ligands helps to regulate the activity of AHR and improve CKD and reduce its complications. Traditionally, AHR is considered as a xenobiotic sensor that intermediates the chemical communication between environmental toxins and the homeostasis in the organism [87]. AHR ligands are abundant in many sources, such as diet, yeast and bacteria [88] (Table 1). Recent evidence has identified endogenous AHR ligand candidates, including tryptophan metabolites, indigoid (e.g. indirubin), metabolites of arachidonic acid (e.g. lipoxin 4A), heme metabolites (e.g. bilirubin), lipopolysaccharide, and cyclic AMP (cAMP) [8, 87]. Natural products are rich and important sources for drug discovery and considered as an alternative therapy for improving CKD and inhibiting renal fibrosis [89–93]. It has been demonstrated that several dietary phytochemicals are sources of AHR ligands [94]. Flavonoids derived from dietary materials such as baicalein, apigenin, chrysin, diosmetin, daidzein, genistein, quercetin, and

Table 1 Tryptophan metabolites as AHR ligands in CKD

Ligands	Compounds	Origin	Biological effects	Molecular mechanism	References
Agonist	Indole	Indolic pathway	Alleviate inflammation and oxidative stress	Decreased IL-1β, IL-6, and chemokine ligand 2 levels	[58]
Agonist	IS	Indolic pathway	Induce podocyte injury	Increased CYP1A1 expression	[97]
Agonist	IS	Indolic pathway	Inhibit neovascularization, cause peripheral arterial disease	Inhibit TF ubiquitination, down-regulate HIF/IL-10/VEGF signaling pathway	[62, 68]
Agonist	IS	Indolic pathway	Induce inflammation	Increased expression of SOCS2 and TNF-α	[75, 77]
Agonist	IAA	Indolic pathway	Accelerate vascular dysfunction	Increased TF level via AHR/p38 MAPK/NF-κB pathway	[47, 48]
Agonist	IAA	Indolic pathway	Induce oxidative stress and inflammation	Increased CYP1A1,ROS and COX-2 expression	[50, 51, 56]
Agonist	Tryptamine	Indolic pathway	Regulate intestinal immune response	Increased CYP1A1 expression	[78, 79]
Agonist	Indole-3-aldehyde	Indolic pathway	Reduce mucosal inflammation, protect the intestinal epithelial barrier	Increased IL-22 level and STAT3 phosphorylation, decreased levels of TNF-α and IL-1β	[81, 82]
Agonist	Kynurenine	Kynurenine pathway	Accelerate arteriovenous thrombosis	Increased levels of TF and PAI-1 via AHR-TF/PAI-1 axis	[98, 99]
Agonist	Kynurenine	Kynurenine pathway	Induce chronic inflammation and oxidative stress	Increased HIF, IL-1β, and IL-6 levels, decreased EPO expression	[100, 101]
Antagonist	Indolo[3,2-b] carbazole	Dietary	Protect against oxidative DNA damage	Increased an antioxidant enzyme expression	[102]
Antagonist	6-formylindolo-[3,2-b]-carbazole	UV light	Reduce inflammation	Decreased levels of IL-6 and claudin-2	[103, 104]
Antagonist	5,7,3′,4′,5′-pentahydroxy flavanone	*Semen Plantaginis*	Ameliorate CKD and renal fibrosis	Inhibit profibrotic protein expression expression	[21]
Antagonist	Barleriside A	*Semen Plantaginis*	Ameliorate CKD and renal fibrosis	Inhibit profibrotic protein expression expression	[21]
Antagonist	Rhoifolin	*Semen Plantaginis*	Ameliorate CKD and renal fibrosis	Inhibit profibrotic protein expression expression	[21]
Antagonist	Baicalein	*Scutellaria baicalensis*	Alleviate aristolochic acid I (AAI)-mediated kidney toxicity	Induce CYP1A1 and CYP1A2 expression	[95]
Antagonist	Tanshinone I	*Salvia miltiorrhiza*	Alleviate AAI-mediated kidney injury	Increased CYP1A1 and CYP1A2 expression	[96]

galangin have been recognized as the natural AHR ligands that can activate AHR and regulate downstream target gene expressions in various diseases [87]. Extensive studies have demonstrated that flavonoids were mainly applied to cancer treatment through regulating AHR signaling [94]. However, a few studies have reported that flavonoids regulated CKD via AHR activation. Our latest study identified that endongous metabolite 1-aminopyrene showed strong positive and negative correlation with serum creatinine levels and creatinine clearance, respectively, in the 5/6 nephrectomised rats [21]. Further study demonstrated that mRNA expressions of AHR and its three target genes including *CYP1A1*, *CYP1A2*, and *CYP1B1* were significantly upregulated in both mice and NRK-52E cells induced by 1-aminopyrene, while this effect was partially weakened in AHR shRNA-treated mice and NRK-52E cells [21]. 1-aminopyrene could lead to renal function decline and fibrosis in the 1-aminopyrene-induced mice. We further showed that treatment with three flavonoids 5,7,3′,4′,5′-pentahydroxy flavanone, barleriside A, and rhoifolin isolated from *Semen Plantaginis* inhibited 1-aminopyrene-induced upregulation of profibrotic protein expression in NRK-52E cells [21]. Treatment with 5,7,3′,4′,5′-pentahydroxy flavanone and barleriside A ameliorated CKD and renal fibrosis through inhibiting AHR signaling pathway in both 1-aminopyrene-induced mice and 5/6 nephrectomised rats [21]. Structure–function relationship analysis showed that the antagonistic effect of flavonoids on AHR was deeply influenced by the number and location of hydroxyl and glycosyl groups. Previous study has demonstrated that baicalin significantly alleviated aristolochic acid I-mediated kidney toxicity via AHR-dependent *CYP1A1* and *CYP1A2* induction [95]. In addition, it has been reported that Tanshinone I promoted aristolochic acid I metabolism and prevents aristolochic acid I-mediated kidney injury by the induction of hepatic *CYP1A1* and *CYP1A2 in vivo* [96]. We expect that more flavonoids are identified as AHR ligands to retard CKD and its complication and optimize the treatment of CKD.

Conclusion

With the improving understanding of the link between AHR and its ligands, the AHR signaling pathway involved in various diseases has become more evident. The deficiency of renal function in CKD patients induces the accumulation of uremic toxins, which increase oxidative stress and proinflammatory cytokine. It is well known that the uremic toxin-AHR pathway exerts multiple adverse biological effects on the development of renal fibrosis. In the cardiovascular system, the deficiency of AHR can result in abnormal cardiac function, hypertension or hypotension, vascular dysfunction, and CVD. A large number of studies have identified gut microbiota-derived uremic toxins as potent endogenous ligands of AHR and investigated the pathophysiological role of the AHR signaling pathway in CKD and CVD. Moreover, DKD induces glomerular mesangial cell activation and tubular cell function changes to promote the progress of renal fibrosis, which has been regarded as primary cause of ESRD with a high mortality rate.

In this review, an advanced understanding of the AHR signaling pathway provides more possibilities to identify novel exogenous and endogenous ligands of AHR. Meanwhile, the integration of mass spectrometry, nuclear magnetic resonance, and other modern analytical techniques, made up of the metabonomics technology platform, had accelerated the identification of AHR ligands. Multiple studies of tryptophan metabolites as AHR agonists and antagonists have led to a clearer understanding of the adverse effects of urinary toxins on patients with CKD. Moreover, due to the importance of flavonoids in the activation of AHR, we could give more attention to study natural products as therapeutic drugs to improve the use of medicines. Importantly, these mechanisms of uremic toxins from tryptophan metabolism activate AHR inspire many new ideas of the activation of AHR signaling pathways and help to develop new treatment strategies targeting AHR and related signaling pathways. Despite advances in our understanding of diseases associated with AHR, the molecular mechanisms of AHR signaling and the crosstalk between AHR signaling and other signaling pathways require further study. Therefore, it is still meaningful for further clinical practice to study the AHR signaling and alternative pathways in the prevention and treatment of CKD.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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