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Review Article

Indole metabolism and its role in diabetic macrovascular and microvascular complications

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ABSTRACT

Tryptophan (Trp), an essential amino acid obtained through dietary sources, plays a crucial role in various physiological processes. The metabolism of Trp branches into three principal pathways: the serotonin pathway, the kynurenine pathway, and the indole pathway. The kynurenine and serotonin pathways are host pathways while the indole pathway is solely the result of bacterial metabolism. Trp metabolites extend their influence beyond protein biosynthesis to affect a spectrum of pathophysiological mechanisms including, but not limited to, neuronal function, immune modulation, inflammatory responses, oxidative stress regulation, and maintenance of intestinal health. This review focuses on indole derivatives and their impact on vascular health. Trp-containing dipeptides are highlighted as a targeted nutraceutical approach to modulate Trp metabolism, enhance beneficial metabolite production, and mitigate risk factors for vascular diseases. The importance of optimizing Trp intake and dietary strategies to harness the benefits of Trp-derived metabolites for vascular health is underscored, bringing to light the need for further research to refine these therapeutic approaches.

1. Introduction

Trp is an essential aromatic amino acid that cannot be synthesized by the body and must be obtained from dietary sources [1]. Upon absorption, Trp undertakes divergent metabolic fates: a small proportion is allocated for protein synthesis, while a significant amount is directed towards specialized metabolic routes within host cells, primarily the kynurenine and serotonin pathways, or is transformed by gut microbiota into indole and its derivatives [2]. Trp metabolites extend their influence beyond protein biosynthesis to affect a spectrum of pathophysiological mechanisms including neuronal function, immune modulation, inflammatory responses, oxidative stress regulation, and maintenance of intestinal health [3–6]. These effects span across various medical specialties, making Trp metabolism a subject of interest in fields such as cardiology, neurology, psychiatry, immunology, and gastroenterology [7].

The metabolism of Trp branches into three principal pathways: the serotonin pathway, the kynurenine pathway, and the indole pathway [2]. The serotonin pathway converts Trp into serotonin, a neurotransmitter integral to mood regulation, sleep, and appetite control [8]. The kynurenine pathway modifies Trp into several metabolites involved in immune regulation and neuroactive processes [2]. Remarkably, the microbial metabolism of Trp leads to the formation of indole and its derivatives, accounting for 4–6 % of dietary Trp metabolism [9]. These microbial metabolites are essential in sustaining host health and ensuring homeostatic balance.

In the forthcoming sections, a comprehensive review of the metabolism of Trp into indole derivatives and the implications of indole derivatives on vascular health will be discussed specifically their role in macrovascular and microvascular complications. Indole metabolites, while intended for beneficial roles, can be synthesized into detrimental metabolites. At the conclusion of this review, the potential therapeutic

Abbreviations: AGE, advanced glycation end-products; AhR, aryl hydrocarbon receptor; CMD, coronary microvascular disease; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; I3A, indole-3-aldehyde; IA, indole-3-acrylate; IAA, indole-3-acetate; IAM, indole-3-acetamide; IAN, indole-3-acetonitrile; ILA, indole-3-lactate; IPA, indole-3-propionate; IPyA, indole-3-pyruvic acid; IS, indoxyl sulfate; Kyn, kynurenine; QA, quinolinic acid; ROS, reactive oxygen species; TnaA, tryptophanase; Trp, tryptophan; VEGF, vascular endothelial growth factor; nNOS, neuronal nitric oxide synthase; eNOS, endothelial nitric oxide synthase.

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and dietary interventions targeting Trp to enhance health outcomes in individuals with micro and macrovascular complications of diabetes will be discussed.

2. Tryptophan and indole pathways

The Trp to indole pathway occurs in the gastrointestinal tract and is catalyzed by distinct intestinal microorganisms. Based on the intestinal organisms responsible and the specific metabolites produced, this pathway can be categorized into three main sub-pathways: the tryptophanase (TnaA) pathway, the transamination pathway, and the decarboxylation pathway. A summary of the key metabolites involved in each of these sub-pathways is provided in Table 1 and shown in Fig. 1. Trp can be catabolized via TnaA to indole, which subsequently mediates key effects on intestinal barrier function by modulating epithelial cell signaling and enhancing tight junction integrity. Various members of the gut microbiota, including species from the genera *Escherichia*, *Clostridium*, and *Bacteroides*, participate in this process [10]. Among these, *Escherichia coli* has been extensively studied as a key intestinal bacterium responsible for generating indole [10,11]. The expression of TnaA in *Escherichia coli* is tightly controlled by the Trp operon, a well-coordinated regulatory system that responds to the levels of Trp in the intestine. The Trp operon consists of a series of genes that are responsible for the biosynthesis of Trp, as well as TnaA [12]. Increased levels of TnaA have been shown to be beneficial in promoting both endothelial health by inducing claudin-mediated tight junction proteins and by decreasing inflammation induced by TNF-α–mediated NF-κB activation in epithelial cells such as in studies using the human enterocyte cell line HCT-8 [13]. Similarly, in mouse models, increased expression of TnaA has been shown to support the development of the colonic intestinal barrier by commensal microbiota, leading to increased expression of tight junction proteins such as claudin-7, occludin, and zonula occludens (ZO)-1 [14,15]. These effects are primarily attributed to the production of indole, a key mediator in this process. However, it must be considered that while physiological concentrations of indole support gut barrier function and homeostasis, excessively high levels may induce cytotoxic effects, compromise epithelial integrity, and contribute to gut dysbiosis, potentially exacerbating inflammatory conditions [16].

Further downstream, indole is absorbed from the intestine into the bloodstream and transported to the liver. In the liver, indole undergoes oxidation by the enzyme cytochrome P450, particularly CYP2E1, converting it into indoxyl. Indoxyl is then further processed by sulfotransferase enzymes, which add a sulfate group to form indoxyl sulfate [17]. However, indoxyl sulfate can function as a uremic toxin. The likelihood of indole being converted to indoxyl sulfate may vary between individuals, as this conversion is influenced by factors such as gut microbiota composition, liver enzyme activity, and the individual's metabolic state [18]. For example, while sulfur-containing amino acids are essential for various metabolic processes, their intake has paradoxically been associated with lower serum concentrations of indoxyl sulfate, possibly due to their role in supporting sulfate conjugation and excretion pathways [19]. Healthy kidney function is critical for the removal of uremic toxins like indoxyl sulfate. When kidney function is compromised, as in CKD, indoxyl sulfate clearance is impaired, resulting in its accumulation in the bloodstream [20]. Indoxyl sulfate induces oxidative stress and inflammation within vascular endothelial cells, contributing to endothelial dysfunction. Because the compound stimulates the production of reactive oxygen species (ROS) it can lead to lipid peroxidation, vascular calcification, and the progression of atherosclerotic plaques [21]. Additionally, indoxyl sulfate activates AhR pathway and the effect of AhR activation is influenced by factors such as cell type and metabolite concentration. In endothelial cells, indoxyl sulfate concentrations of approximately 500 μM have been shown to activate AhR, leading to significant alterations in cell proliferation [22]. In contrast, in monocytes, indoxyl sulfate concentrations as low as 250 μM can induce trained immunity, characterized by enhanced cytokine production upon subsequent stimulation [23]. In other contexts, AhR activation may promote anti-inflammatory responses, as described below when activated by indole-3-aldehyde.

Trp can be converted to tryptamine by L-amino acid decarboxylase

Table 1
Detailed table of major indole metabolites.

Metabolite	Biological function	Optimal concentration levels	Molecular target	Metabolic pathway	Effect on vascular health
Indole	Regulates immune function and maintains epithelial integrity	Elevated beneficial, excess may induce toxicity	AhR	Tryptophanase pathway	Mitigates inflammation, potentially enhancing vascular health
Indoxyl sulfate	Uremic toxin from hepatic sulfation of indole and contribute to oxidative stress, inflammation, and fibrosis.	Low levels are preferred due to its toxic effects	AhR	Tryptophanase pathway (liver)	Promotes vascular calcification, endothelial dysfunction, and contributing to the progression of cardiovascular diseases
Tryptamine	Acts as a neuromodulator, impacts mood and motility	Highly beneficial; monitor to prevent toxicity	Serotonin receptors	Decarboxylation pathway	Excessive levels can lead to hypertensive episodes, impacting vascular health
Indole-3-acetic acid (IAA)	Serves as an antioxidant, modulates inflammatory responses	Elevated levels are advantageous for anti-inflammatory effects	Liver enzymes, systemic inflammation pathways	Decarboxylation pathway	Protects endothelial functions, lowering atherosclerosis risks
Indole-3-aldehyde (I3A)	Enhances intestinal barrier function, modulates immunity	Elevated levels recommended for immune modulation	AhR	Decarboxylation pathway	Crucial for reducing complications in diabetes-related vascular issues
Methylindole	Influences gut motility, toxic at high concentrations	Maintain low levels to avoid carcinogenic risks	Intestinal and liver enzymes	Decarboxylation pathway	High concentrations linked to vascular inflammation and endothelial damage
Indole-3-pyruvate (IPyA)	Precursor for the bioactive indole derivatives	Typically as a transient intermediate in the metabolic pathway	NA (functions primarily as a metabolic intermediate)	Transamination pathway	Indirectly supports vascular health by facilitating the production of beneficial indole metabolites, such as IPA.
Indole-3-lactate (ILA)	Provides antioxidant effects, supports mucosal immunity	Elevated levels enhance antioxidant capacity	Gut mucosa, immune cells	Transamination pathway	Beneficial in reducing oxidative stress, aids in vascular health maintenance
Indole-3-acrylate (IA)	Protects the gut barrier, modulates systemic inflammation	Elevated levels crucial for maintaining intestinal health	Intestinal barrier, immune system	Transamination pathway	Guards against microvascular damage particularly in metabolic disorders
Indole-3-propionate (IPA)	Neuroprotective, regulates metabolic functions	Elevated levels preferred for neural and metabolic regulation	Brain, metabolic pathways	Transamination pathway	Mitigates microvascular damage associated with metabolic syndrome and diabetes

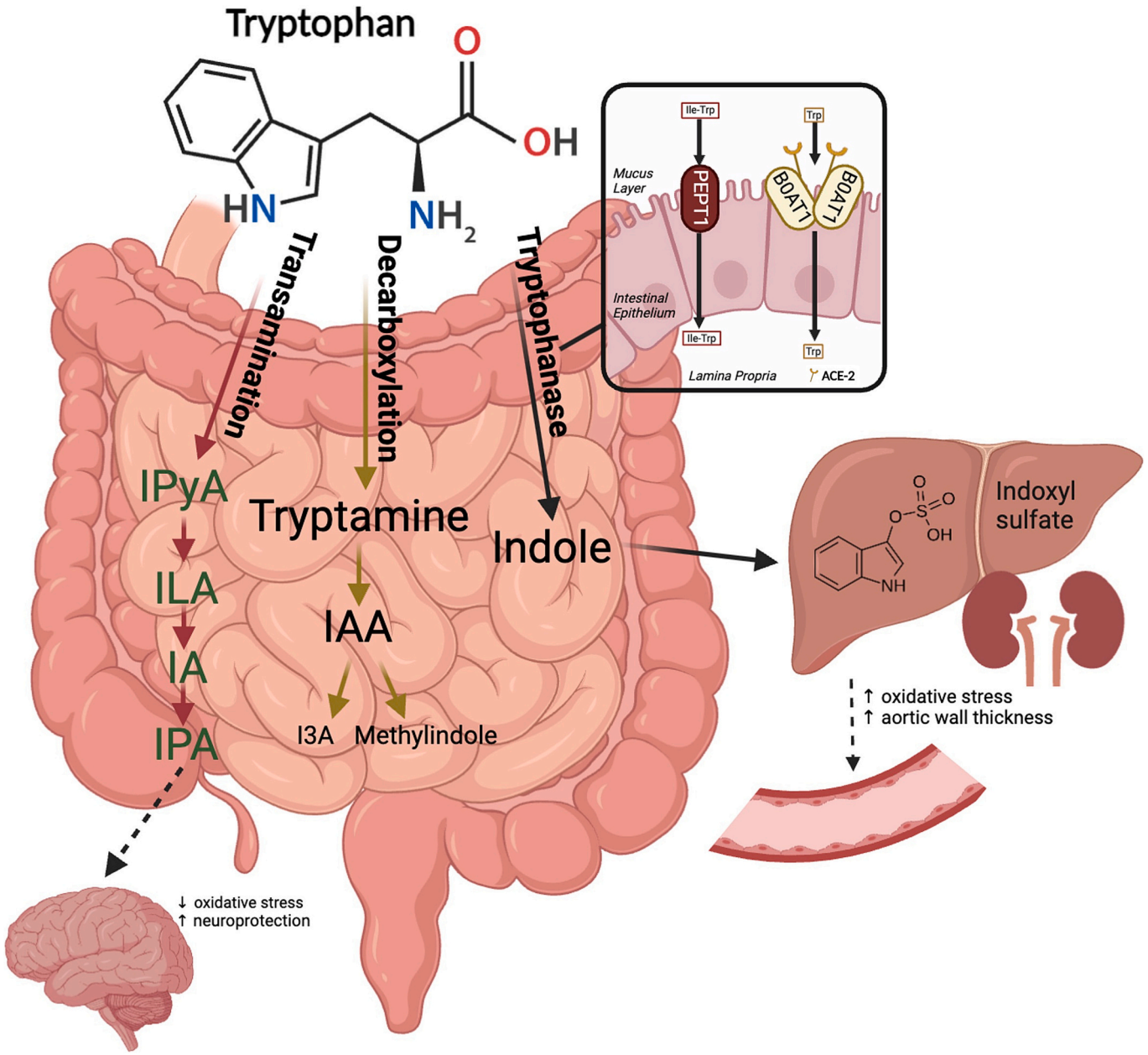

Fig. 1. Metabolic pathways of Trp to indole derivatives. IAA: indole-3-acetate, IA: indole-3-acrylate, I3A: indole-3-aldehyde, ILA: indole-3-lactate, IPA: indole-3-propionate, IPyA: indole-3-pyruvate; PEPT-1: peptide transporter 1.

[24]. Tryptamine plays multiple roles within the gut and the body as a whole. Locally, it can influence gut motility and interact with the enteric nervous system [25]. Systemically, tryptamine can act as a neuromodulator by affecting serotonin receptors, given its structural similarity to serotonin [26]. This interaction with serotonin receptors can influence various physiological processes including mood regulation, emotional responses, and potentially pain perception [27]. As tryptamine can cross the blood-brain barrier, excessive amounts might influence neurological functions and contribute to disorders linked to serotonin regulation due to the similarity in their chemical structures [28]. Elevated tryptamine levels can increase gut motility leading to irritable bowel syndrome [29]. Tryptamine has also been implicated in the pathophysiology of hepatic encephalopathy, where impaired liver function leads to the accumulation of various neurotoxic substances, including excessively high levels of tryptamine [30]. This accumulation contributes to neurotoxicity and may result in altered mental status, confusion, and impaired cognitive function, which are characteristic of hepatic encephalopathy [31]. The tryptamine decarboxylation pathway leads to formation of indole-3-acetate (IAA) and then to indole-3-aldehyde (I3A) via dehydrogenation. This process is vital to bacterial Trp metabolism, with I3A playing a key role in immune modulation [32]. I3A engages the AhR located on intestinal and immune cells, facilitating a cascade of immunological responses that are discussed below. Activation of AhR by I3A enhances mucosal barrier integrity and stimulates the production of anti-inflammatory cytokines [33]. AhR activation by this metabolite and others is known to regulate intestinal stem cell (ISC) activity and is essential for safeguarding the ISC niche and maintaining the integrity of the intestinal barrier [34,35]. By activating AhR, these metabolites promote the differentiation of ISCs into specialized epithelial cells maintaining a balance between proliferation and differentiation which is essential for gut health. The anti-inflammatory properties of I3A, along with its roles in cell proliferation and apoptosis modulation, underscore its potential in cancer prevention and managing chronic inflammation-related respiratory

syndromes, particularly those originating from the gastrointestinal tract [33,36,37]. Another indole derivative, indole alcohol, has also been shown to be crucial for maintaining gut homeostasis by enhancing the regenerative capacity of the intestinal epithelium.

By promoting the proper differentiation and turnover of the intestinal epithelium, Trp metabolites contribute to maintaining gut integrity and reducing the translocation of harmful pathogens and inflammatory signals into circulation. This reduction in systemic inflammation can subsequently mitigate the risk of vascular complications, especially in conditions such as atherosclerosis and diabetes.

The Trp-Indole-3-Propionate (IPA) pathway starts with the conversion of Trp to indole-3-pyruvate (IpyA) by Trp aminotransferases [38]. From IpyA, the pathway progresses to the formation of indole-3-lactate (ILA) via phenyl lactate dehydrogenase enzymes [39]. ILA has antioxidant properties that protect cells from oxidative stress and support gut health by regulating the immune system and reducing inflammation [40–42]. Indole-3-acrylate (IA), formed by the action of a phenyl lactate dehydratase, enhances gut barrier function, modulates the immune response, and has anti-inflammatory properties [43]. The final step in this pathway is the reduction of IA to IPA, which is known to be neuroprotective and beneficially influence metabolic pathways, including glucose homeostasis to improve blood glucose and increase insulin sensitivity [44]. IPA activates AhR, strengthens tight junctions to enhance gut barrier function, and maintains gut integrity. It also has anti-inflammatory effects, reducing the chronic inflammation linked to various metabolic disorders [45]. IPA also functions as an agonist for the pregnane X receptor (PXR), which is particularly important in the context of exposure to harmful substances, such as deoxynivalenol (DON), a mycotoxin commonly found in contaminated food sources. IPA's binding to PXR has been shown to mediate and modulate the hepatocellular response to DON exposure, thereby attenuating oxidative stress and its damaging effects on liver cells. Studies conducted both in vitro liver cell cultures and in vivo animal models have demonstrated that IPA's activation of PXR can significantly reduce the oxidative damage induced by DON, thereby suggesting a protective role for IPA in hepatic health and potentially contributing to the mitigation of liver toxicity associated with mycotoxin exposure [46]. Due to these mechanisms of action, IPA has been linked to a lower risk of Type 2 diabetes and a slower the development of non-alcoholic fatty liver disease [44].

3. Macro- and micro-vascular complications

Understanding what drives the metabolic pathways leading from Trp to indole and the subsequent metabolites described above is crucial for exploring the connection between the gut microbiome and the vasculature as indole metabolites maintain vascular health by modulating inflammation and enhancing endothelial function. The generation of micro and macrovascular diabetic complications are driven by increased inflammation, permeability, advanced glycation end-products (AGEs), and ROS [47]. The gut microbiome is associated with the development of diabetic complications thus examining indole and its various metabolites represents a prominent strategy to combat the oxidative stress typically associated with diabetes [48]. By studying how Trp metabolism in the gut influenced the production of beneficial indole metabolites, a better understanding can be gained of the potential for these compounds to mitigate or prevent the progression of diabetic vascular complications.

4. Atherosclerosis

Atherosclerosis is a metabolic process consisting of the buildup of cholesterol-based deposits in arteries, with clinically significant manifestations being coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (CVD). Across multiple studies, the presence of diabetes dramatically increases the risk of atherosclerosis, demonstrating a 2 to 4 fold increase in CAD, PAD, and CVD [49–51]. The risks are so demonstrable, that diabetes is considered to be equivalent in risk to CAD when determining need for anti-atherosclerotic therapy, which is key in the prevention of life threatening complications such as myocardial infarction (MI) and death [52]. PAD is a similar atherosclerotic process in peripheral arteries and manifests with diminished/absent distal pulses, claudication, abnormal ankle-brachial indices, and limb ischemia [53,54]. CVD is an atherosclerotic disease affecting cerebral arteries and most often manifests as cerebrovascular accident or stroke. Not only is diabetes associated with higher rates of stroke, it is also associated with worse stroke-related outcomes such as dementia, recurrence, and mortality [55–57]. Treatment of atherosclerotic complications of diabetes focuses on the treatment of dyslipidemia with statins, [58,59]. Interestingly, glycemic control via oral hypoglycemic agents and insulin has not been shown to improve rates of macrovascular complications [60]. However, aggressive blood pressure control has been demonstrated to reduce risk of stroke and MI in individuals with diabetes [61].

The pathophysiology of atherosclerosis is complex and multifactorial. Chronic hyperglycemia, insulin resistance, and dyslipidemia cause dysfunction in multiple vascular structures including endothelial cells, vascular smooth muscle cells, and platelets. In the endothelial cells, hyperglycemia impairs production of nitric oxide (NO) via decreased eNOS synthase activation and increased ROS production [62]. Impaired NO and increased ROS activated transcription factors related to NF-κB, in turn increases recruitment of lymphocytes and monocytes into the vascular wall as well as increasing release of proinflammatory cytokines like IL-1 and TNF-α [62–64]. Impaired vascular smooth muscle function is marked by the formation of plaques around deposits of lipid filled macrophages. Once these fatty streaks form in the arterial wall, the smooth muscle cells begin to create a collagen rich extracellular matrix (ECM), strengthening the atherosclerotic plaque [65]. Platelet dysfunction in diabetes induces a prothrombotic state via multiple biochemical mechanisms, including altered calcium homeostasis and increased expression of glycoprotein Ib (GpIb), both leading to increased platelet aggregation [66].

Carson et al. found that Trp and indole derivatives IPA and I3A were lower in the serum of individuals with advanced atherosclerosis (requiring endarterectomy, revascularization, or amputation) when compared to an age- and risk factor-matched healthy cohort and an inverse association was observed between serum levels of Trp/IPA/I3A and ankle-brachial index, a marker of atherosclerotic disease burden [67]. The inverse association of Trp and IPA with atherosclerotic disease was shown by Teunis et al. as well. They also found a positive association between serum levels of the detrimental metabolite IAA levels and mortality associated with CAD, CVD, and PAD [68]. Most recently, Ballanti et al. demonstrated that low serum IPA was associated with insulin resistance and low-grade inflammation in humans and found that in a mouse model with diet induced insulin resistance, treatment with IPA demonstrated a significant improvement in glucose tolerance [69]. They proposed that IPA scavenged hydroxyl radicals and reduced inflammatory/metabolic transcriptional factors like NF-κB and PXR. The potential favorable metabolic properties of Trp, IPA, and other indole derivatives is compelling and their observed associations with favorable outcomes in atherosclerotic disease continue to make them an interesting target for further research.

5. Diabetic nephropathy

DN is characterized by increased albuminuria or decreased glomerular filtration rate (GFR) and occurs in 20–40 % of diabetics [70]. It is the most common single cause of end-stage renal disease (ESRD) and typically presents after an individual has been diagnosed with diabetes for 10–20 years. The typical progression consists of a steady decline in renal function that eventually becomes irreversible requiring dialysis [70]. The pathogenesis of kidney disease in diabetes is remarkably like retinal disease, and the two often coincide. Chronic hyperglycemia,

AGEs, ROS, and inflammation lead to endothelial dysfunction in the glomerulus. Additionally, DN patients experience glomerular basement membrane (GBM) thickening, glomerular mesangial matrix proliferation, and nodular glomerulosclerosis [71]. Unlike DR, advanced DN is characterized by a loss of VEGF secondary to destruction of glomerular podocytes where it is produced. In the kidneys, VEGF is responsible for endothelial growth and survival, and its absence contributes to renal fibrosis [71]. The current standard treatment consists of glycemic control, inhibition of the renin-angiotensin system (RAS), blood pressure control, and cardiovascular risk reduction [72].

The indole pathway tends to be anti-inflammatory and protective against microangiopathic disease. However certain metabolites such as IAA and indoxyl sulfate are considered uremic toxins and can worsen progression of DN [73]. Inflammation in DN, driven by factors such as AGEs, ROS, and hyperglycemia, exacerbates the accumulation of these harmful metabolites, particularly indoxyl sulfate and IAA. This accumulation occurs because, in DN patients, there is impaired renal clearance of indoxyl sulfate in the proximal convoluted tubule, leading to elevated levels of these metabolites in the bloodstream [74–77]. Increased levels of IAA in DN induce cyclooxygenase-2 and ROS stimulating glomerular sclerosis and interstitial fibrosis leading to progressive renal disease [1,78]. Indoxyl sulfate acts via stimulation of NF-κB and plasminogen activator inhibitor type 1, leading to nephrotoxicity and tubulointerstitial fibrosis [79].

However, it's important to note that other indole metabolites, particularly IPA, have shown promise in protecting against kidney damage, including in conditions DN. IPA, produced by gut microbiota, possesses antioxidant and anti-inflammatory properties that help mitigate oxidative stress and inflammation—two major contributors to kidney damage in DN. Zeng et al. suggested that IPA may reduce fibrosis and glomerulosclerosis, hallmarks of DN [80]. In the same study, IPA's mitochondrial protective effects was observed by reducing ubiquitination-mediated degradation of SIRT; thereby protecting kidney cells from damage associated with DN [80]. Additionally, IPA supplementation can improve blood glucose levels and increase insulin sensitivity, which are vital in preventing and managing DN [81].

Thus, while the harmful effects of IS and IAA are recognized in DN, other indole metabolites such as IPA may play a protective role, suggesting that the overall impact of indole metabolism in kidney disease is context-dependent and influenced by the balance of different metabolites.

6. Diabetic retinopathy

Diabetic retinopathy, a spectrum of disease ranging from mild, moderate, and severe non-proliferative (NPDR) to proliferative (PDR), is associated with microaneurysms, dot-blot hemorrhages, hard exudates, cotton wool spots, macular edema (DME), arterial/venous changes, and neovascularization [82]. The presence of neovascularization marks the transition from NPDR to PDR. DR is the most common cause of severe vision loss affecting adults. Diabetes is also strongly linked to coronary microvascular disease (CMD) with 72 % of patients with the triad of DM, nonobstructive coronary artery disease, and angina being found to have CMD [83].

The mechanism behind DR, CMD and DN in diabetic individuals is currently unknown, but was found to be associated with hyperglycemic induced oxidative stress, insulin resistance, chronic inflammation, and, for DR and DN, the formation of AGEs which results in the release of cytokines and VEGF [83,84]. Cytokine release contributes to increased vascular permeability, occlusion, and eventual ischemia. Ischemia leads to VEGF secretion that contributes to retinal neovascularization. Current management is centered on glycemic control, intravitreous injections of anti-VEGF agents, panretinal photocoagulation and vitrectomy [85].

Indole and its metabolites play a significant role in the pathogenesis of DR. Metabolomic analyses have revealed that the tryptophan metabolism pathway, is disturbed in DR patients. Elevated levels of indole and its metabolites, such as indoleacetic acids, have been observed in the serum of individuals with DR. [86]. One specific metabolite, indoxyl sulfate, has been identified as a contributor to retinal microvascular injury in DR. Metabolomic studies have shown that indoxyl sulfate levels are significantly increased in the vitreous humor of diabetic patients as indoxyl sulfate levels can breach the blood-retinal barrier, leading to endothelial apoptosis and disruption of cell junctions [87]. The increased levels of indole metabolites such as indoxyl sulfate and the activation of inflammatory pathways in DR suggest that manipulating indole metabolism may offer therapeutic benefits [88]. In line with this, recent research has focused on exploring how indole derivatives could mitigate some of the negative effects associated with DR. In 2020, Platania et al. discovered that artificially synthesized indole derivatives VP12/14 and VP12/110 inhibited VEGF and TNF-α release in human retinal epithelial cells challenged with high glucose levels in vitro [89]. These molecules were chosen for testing based on structural similarity to dihydrotanshinone (DHTS), a known inhibitor of human antigen R (HuR), which stabilizes the mRNA of several genes including those responsible for VEGF and TNF-α production [90,91]. Additionally, Platania et al. demonstrated that VP12/14 and VP12/110 demonstrated anti-angiogenic effects in HREC stimulated with VEGF-A. Further research needs to be done to demonstrate if this effect translates in vivo, but the anti- inflammatory and anti-angiogenic effects of VP12/14 and VP12/110 demonstrate favorable characteristics as a potential target for the development of future treatments for DR.

7. Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a neurodegenerative complication affecting peripheral nerves, which is characterized by pain, diminished sensation, non-healing ulcers, and limb ischemia. Although observed rates vary between studies, the estimated lifetime prevalence of DPN is up to 50 % of adults with diabetes, with rates tending to be higher in type 2 vs. type 1 diabetes [92]. DPN is believed to be caused by peripheral nerve dysfunction and cell death due to ROS-mediated oxidative stress, AGEs, and chronic inflammation, particularly within the mitochondria, which leads to the characteristic axonal injury [93]. The unmyelinated C fibers are typically the first affected, leading to pain, hyperesthesia, and allodynia [94]. As the disease progresses, demyelination outpaces remyelination and axonal injury of myelinated nerves occurs, resulting in loss of distal sensation in the limbs [95]. The current mainstay of treatment is duloxetine, pregabalin, and glycemic control, as well as improvement in modifiable cardiovascular risk factors, wound care for ulcers and revascularization/amputation for limb ischemia [96,97].

Gundu et al. investigated the ability of IPA to decrease endoplasmic reticulum stress (ERS)-induced neuronal cell death [98]. The accumulation of misfolded proteins in the ER is typically mitigated via the unfolded protein response (UPR) which increases translation of ER chaperone proteins, helping to restore homeostasis [99]. When prolonged stress exceeds the ability of the UPR to compensate, it activates the apoptotic signaling pathway leading to neuronal cell death [100]. IPA has demonstrated potential as a protective factor in ER stress due to its action as a chaperone chemical, preventing the aggregation of denatured proteins associated with ERS-induced neuronal damage [101]. IPA also acts as a free radical scavenger, allowing it to mitigate major avenues of ERS induced neuronal damage [102]. More research is required, but IPA poses an exciting potential treatment for reducing the burden of DPN.

8. Review of clinical and experimental findings on drugs impacting indole metabolism

In therapeutic settings, Trp-containing dipeptides could serve as the basis for developing dietary strategies or supplements aimed at preventing or managing conditions such as hypertension, atherosclerosis,

and diabetic vascular complications. Dipeptides and tripeptides exhibit superior absorption compared to single amino acids, as exemplified by the preferential uptake of tryptophan in dipeptide form via peptide transporter 1 (PEPT-1). Tryptophan in its single amino acid form is absorbed less efficiently through B0AT1 which dimerizes with angiotensin-converting enzyme 2 (ACE2). ACE2 expression at the intestinal brush border membrane facilitates interaction with B0AT1 (Fig. 1) [103]. Therefore, dipeptides offer a targeted approach to enhancing the production of specific metabolites like indole derivatives, which can support endothelial function, reduce inflammation, and improve blood vessel health: key factors in mitigating the risk of vascular disease complications. Table 2 provides a summary of intervention studies utilizing Trp-containing dipeptides and their effects on the macrovascular and microvascular complications. Most studies have focused on the protective effects of tryptophan-histidine (Trp-His) dipeptide on cardiovascular health. Recent research highlights the significant potential of particularly Trp-His, in managing atherosclerosis through various mechanisms. Studies have shown that Trp-His reduces atherosclerotic lesions in apo E-deficient mice without affecting growth parameters or lipid profiles [104]. It is absorbed intact into the blood and localized in the intestinal membrane in rats [105]. Trp-His exhibits dose-dependent anti-proliferative effects on rat vascular smooth muscle cells and regulates intracellular calcium levels, suppressing CaMK II activity [106,107]. Additionally, Trp-Lys increases CYP7A1 mRNA levels, which can prevent hypercholesterolemia and atherosclerosis [108]. Trp-His also shows synergistic effects with catechins, enhancing vasorelaxation, which can be reversed by TNF-α and restored by ferulic acid [109]. These findings underscore the potential of tryptophan-derived dipeptides in atherosclerosis. However, limited research exists on the effects of Trp dipeptides on microvascular diseases such as retinopathy (0 studies), neuropathy (1 study [110]), and nephropathy (2 studies [111,112]).

By utilizing Trp in dipeptide form to affect metabolic pathways, it is feasible to influence both systemic and local factors that contribute to vascular diseases. This strategy not only targets the underlying mechanisms of these conditions but also provides a potential preventive and therapeutic advantage in managing vascular health.

9. Dietary factors that modulate the gut microbiota, Trp metabolism and micro/macro vascular complications

As an essential amino acid, Trp cannot be endogenously synthesized and must be acquired through dietary intake, making its intake through food crucial for maintaining health. Dietary interventions are recognized as safe and effective alternatives to conventional therapies and thus represent an ideal strategy for maintaining adequate Trp levels, promoting a healthy gut microbiota, and consequently treating macrovascular and microvascular complications.

Trp has relatively low tissue storage in humans, and its overall concentration is the lowest among all amino acids [113,114]. Although only small amounts are necessary for general health, a typical diet provides 1000–1500 mg of protein-sourced Trp per day [115]. The recommended daily allowance for adults ranges from 250 mg/day to 425 mg/day, translating to a dietary intake of 3.5 to 6.0 mg/kg of body weight per day to maintain nitrogen balance [1].

Trp in dietary sources exists in a wide variety protein-containing foods, including eggs, cheese, meat (especially turkey), fish, wheat, rice, potatoes, and bananas [1,116]. Dairy products, such as whole milk, are particularly rich in Trp, along with seafood like canned tuna and various types of poultry, such as turkey and chicken (both light and dark meat). Plant-based sources such as oats and peanuts, and cheddar cheese are also notable for their Trp content. Among fruits, bananas, dried prunes, and apples contain smaller amounts of Trp, while foods like white bread and sweet chocolate contribute modestly to Trp intake [1,116,117]. However, it is important to note that while dietary intake has an impact on Trp availability, its absorption and utilization are highly regulated and influenced by the presence of other large neutral amino acids (LNAAs) [118]. The transport mechanism for Trp across the blood-brain barrier (BBB) is shared with other LNAAs, such as tyrosine, valine, isoleucine, leucine, and phenylalanine [119]. Since Trp is the rarest of all essential amino acids, most proteins contain insignificant amounts of Trp compared to competing LNAAs. Thus, the supplementation of Trp has been extensively studied in numerous clinical research investigations to enhance Trp absorption and subsequent indole metabolism.

10. Effect of direct Trp supplementation on indole metabolites

Trp metabolism is governed by the Trp operon and is influenced by a variety of factors including diet, host genetics, environmental conditions, the composition of the host microbiota, and systemic health conditions, each contributing to its complex regulatory dynamics. In bacteria, when Trp levels are low, the operon is activated to increase Trp synthesis and its conversion into indole and other metabolites. This process involves a negative feedback mechanism: when Trp is present, it stabilizes the repressor protein, which binds to the operator and inhibits transcription. In low Trp conditions, the repressor dissociates, allowing transcription to proceed and increasing tryptophanase production.

Understanding the genetic and biochemical control of Trp metabolism through the Trp operon provides a foundational perspective for exploring the effects of Trp supplementation and its impact on indole production. Under an in vitro simulation of the human intestinal microbial ecosystem (SHIME), researchers observed higher amounts of beneficial metabolites, namely tryptophol, IAA, I3A, and tryptamine, at the end of the Trp supplementation period compared to the control period [120]. There was a larger increase in indole, 3-methylindole, and oxindole compared to other Trp metabolites, suggesting a higher rate of conversion for reactions catalyzed by tryptophanases [121]. Among these increased metabolites, which are known to be AhR ligands, only tryptamine induced a relatively high concentration-dependent AhR activation, while indole did not cause a significant increase in AhR activation [122]. This observation partially contrasts with another in vitro study conducted by Jin et al., in which Trp metabolites including indole, tryptamine, and indole-3-acetate were found to modulate AhR-mediated responses in CaCo-2 cells [123]. These findings underscore the complex roles of bacterial species with distinct Trp metabolic pathways, as evidenced by the observed decrease in the relative abundance of the *Bacteroidetes* and *Verrucomicrobia* phyla during the Trp supplementation period in both cellular and animal studies. For instance, in studies using rat hepatoma-derived reporter cells with Trp concentrations ranging from 0.1 to 100 μM, and in adenosine-induced chronic kidney disease models where pregnant rats received intragastric administration of Trp at doses of 200 mg/kg BW/day, a reduction in harmful bacterial populations was observed [120,124]. Both the Bacteroidetes and Verrucomicrobia phyla are known to contribute significantly to maintaining intestinal integrity, supporting that Trp supplementation has effects on gut microbiota composition and intestinal health that warrant further investigation [125]. In contrast, DSS-colitis mice models have demonstrated beneficial outcomes following dietary supplementation with 200 mg/kg BW/day additional L-Trp, which led to the restoration of AhR ligand production by the gut microbiota, increased AhR mRNA expression, reduced pro-inflammatory cytokine levels, and upregulated anti-inflammatory cytokine IL-22 production in both mouse and porcine models [126,127]. Similarly, in a dietary-induced Non-Alcoholic Fatty Liver Disease mouse model, Trp supplementation of 400 mg/kg BW/day showed a protective effect by enhancing tight-junction protein expressions to stabilize the intestinal barrier and higher 5-HT, 5-HT transporter (SERT) and motility [128]. In a mouse model of experimental autoimmune encephalomyelitis, Trp supplementation improved disease scores and curtailed CNS inflammation in wild-type mice. Importantly, AhR-deficient mice did not exhibit any improvement after supplementation

Table 2
Summary of articles employing dipeptides in macro/micro complications.

Disease type/ function	No.	Article	Model	Dipeptide	Dosage/duration	Results
Atherosclerosis (hypertension)	1	Davis, B. R. et al. [131]	Hypertensive patients	Gly-Gly + Gly-Trp; Trp-Trp	Participants were randomized to one of four treatment arms, chlorthalidone, lisinopril, amlodipine, or doxazosin, in a ratio of 1.7:1:1:1, given respectively daily.	1. Coronary heart disease incidence did not differ among treatments or genotypes. 2. Women Trp allele carriers may have increased CHD risk if treated with chlorthalidone versus amlodipine or lisinopril.
Atherosclerosis (endothelial dysfunction)	2	Morikawa, K. et al. [108]	HepG2 cells	14 types of dipeptides (1 mM) with a C terminal lysine (Lys)	1 mM of dipeptide for 24H	1. Asp-Lys, Glu-Lys, and Trp-Lys significantly increased the CYP7A1 mRNA level, which can be an effective strategy in preventing hypercholesterolemia and atherosclerosis
Atherosclerosis (vasoreactivity)	3	Tanaka, M., Tokuyasu, M., Matsui, T., & Matsumoto, K. [132]	Sprague–Dawley (SD) rats	His-Trp, Trp-His, Trp-Leu, Trp-Val	Vasoactive peptide was added in a cumulative manner (0.5–5.0 mM)	1. His-Trp, Trp-His, Trp-Leu, Trp-Val all evoked an apparent vasodilating effect in 50 mM KCl-contracted aortic rings in the descending order of Trp-His>His-Trp > Trp-Leu > Trp-Val.
Atherosclerosis (endothelial dysfunction)	4	Matsui, T et al. [104]	apo E-deficient mice	Trp-His	9 wk./0, 10 or 100 mg/kg per d	1. Atherosclerotic lesion area was significantly reduced by 27 and 38 % for Trp-His dosed at 10 and 100 mg/kg per d. 2. No effect on growth parameters such as body weight and feeding efficiency, lipid profile
Atherosclerosis (vascular smooth muscle cell function)	5	Wang, Z et al. [106]	Rat vascular smooth muscle cells	Trp-His	1 mM Trp-His for 24H	1. Trp-His significant dose-dependent anti-proliferation effect, without cytotoxicity. 2. Trp-His suppressed extracellular Ca (2+) entry into CaCl (2)-stimulated VSMCs
Atherosclerosis (vascular smooth muscle cell function)	6	Kobayashi, Y., et al. [107]	Rat vascular smooth muscle cells	Trp-His	Trp-His (300 μM) 10 min.	1. Trp-His reduced the [Ca (2+)] i elevation while corresponding constituent amino acids did not show significant reduction. 2. Trp-His suppressed CaMK II activity in Ang II-stimulated VSMCs, resulting in the inhibition of phosphorylation of voltage-dependent L-type Ca (2+) channels
Atherosclerosis (vasorelaxation)	7	Tanaka, M. et al. [133]	Rat aorta	Trp-His	single administration 0.01–4.7 mM followed by catechins	Trp-His, was synergistically enhanced in the presence of EGCG (CI = 0.51; synergistic), but not in the presence of other catechins (EC, ECG, and EGC)
Atherosclerosis (vasorelaxation)	8	Zhao, J. et al. [109]	Rat aorta	Trp-His	Single administration Trp-His (700 μM) and EGCG (300 μM) with or without FA (250 μM)	1. Synergistic enhancement of vasorelaxation in rat aorta by Trp-His and EGCg was significantly attenuated in the presence of TNF-α, an effect that was reversed by the addition of ferulic acid (FA, 250 μM)
Atherosclerosis (vasoreactivity)	9	Tanaka, M. et al. [105]	Sprague-Dawley rats	Trp-His and His-Trp	Single oral administration	1. Trp-His was absorbed intact into SD rat blood, not His-Trp. 2. Trp-His was visualized in the overall intestinal membrane, not His-Trp
Atherosclerosis (normotensive)	10	Kasier S. et al. [134]	Normotensive patients	Ile-Trp and Trp-Leu	50 mg IW or 100 mg WL	1. A significant rise in plasma concentrations was observed, reaching a peak of 2.4 ± 0.5 nm for IW and 29–36 nm for WL within 0.5 h, followed by rapid elimination.
Atherosclerosis (vasoreactivity)	9	Tanaka, M., Tokuyasu, M., Matsui, T., & Matsumoto, K. [132]	Sprague–Dawley (SD) rats	His-Trp, Trp-His, Trp-Leu, Trp-Val	Vasoactive peptide was added in a cumulative manner (0.5–5.0 mM)	1. His-Trp, Trp-His, Trp-Leu, Trp-Val all evoked an apparent vasodilating effect in 50 mM KCl-contracted aortic rings in the descending order of Trp-His>His-Trp > Trp-Leu > Trp-Val.
Neuropathy	1	Hamano, M. et al. [110]	Male ddY mice	Tyr-Trp	YW (100 mg/kg/day, twice a day)	1. YW not only reversed inflammation-related responses. 2. YW activated various molecular networks involving a transcriptional regulatory system against the neurotoxic effects of Aβ25–35
Nephropathy	1	Deplanque, G. et al. [112]	Human patients with renal cell carcinoma	Glu-Trp (IM862)	20 mg three times daily	1. Treatment with IM862 has no toxicity but does not lead to any significant objective responses in metastatic RCC. 2. The decrease in VEGF levels warrants further investigation of IM862 as an antiangiogenic therapy.

(*continued on next page*)

Table 2 (*continued*)

Disease type/ function	No.	Article	Model	Dipeptide	Dosage/duration	Results
Nephropathy	2	Hosoyamada T. [111]	Case study: 5-year-old Hartnup patient	Trp-Phe	Loading test	1. Renal clearance of neutral amino acids in this case increased to levels 5 to 35 times normal

of a 0.5 % Trp diet, suggesting that the beneficial effects of Trp are dependent on AhR signaling, highlighting that AhR ligand supplementation can also modulate inflammation beyond the gut [129]. In human studies, direct clinical trials on tryptophan supplementation on indole metabolism and risk for cardiovascular diseases are limited, several studies have explored the correlations between tryptophan levels, its metabolites, and cardiovascular health. For instance, higher plasma tryptophan levels were inversely correlated with the risk of CVD, suggesting a protective role of tryptophan in cardiovascular health [68]. Another epidemiology study indicated that plasma tryptophan and its metabolite IPA levels are significantly associated with decreased risks of cardiovascular and all-cause mortality [130]. These findings imply that maintaining adequate tryptophan levels and promoting the production of beneficial metabolites like IPA may have a protective effect against cardiovascular diseases in human studies. However, further clinical trials are necessary to establish definitive evidence regarding the efficacy of tryptophan supplementation, especially when it comes to the host's systemic health.

11. Conclusion

This review highlights the critical role of Trp metabolism in vascular health, emphasizing the impact of indole derivatives produced by intestinal microbiota on endothelial function, inflammation, and gut integrity. The therapeutic potential of Trp intake through diet and supplementation represents a promising strategy, particularly with the direct use of IPA and Trp-containing dipeptides, which offer a novel approach to modulate Trp metabolism and mitigating vascular disease risk factors. Dietary interventions and Trp supplementation represent viable alternatives to conventional treatments, fostering a healthier gut microbiota and targeting both macrovascular and microvascular complications. However, the findings discussed here also underscore the necessity for additional research studies, particularly well-designed clinical phase 1 and 2 trials, to optimize dosages and refine pharmacological approaches. Such research is essential to fully understand the efficacy and safety of Trp-derived metabolites, aiming to maximize their health benefits and improve overall vascular health outcomes.

CRediT authorship contribution statement

W. Hu: Writing – original draft, Conceptualization. **C. Garrison:** Writing – original draft. **R. Prasad:** Writing – review & editing. **M.E. Boulton:** Writing – review & editing. **M.B. Grant:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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