Review

Iron-Dependent Regulation of Tryptophan Metabolism in Depression

Yan Zhang [1,†], Jinping Liu [2,†], Mingqian Fang [2,*], and Ren Lai [2,*]

[1] College of Life Science, Zhengzhou University, Zhengzhou 450001, China
[2] Engineering Laboratory of Peptides of Chinese Academy of Sciences, Key Laboratory of Bioactive Peptides of Yunnan Province, KIZ-CUHK Joint Laboratory of Bioresources and Molecular Research in Common Diseases, Sino-African Joint Research Center, and Kunming Institute of Zoology, Chinese Academy of Sciences, No. 17 Longxin Road, Kunming 650201, China
* Correspondence: fangmingqian@mail.kiz.ac.cn (M.F.); rlai@mail.kiz.ac.cn (R.L.)
† These authors contributed equally to this work.
Received: 7 January 2026; Revised: 6 March 2026; Accepted: 10 March 2026; Published: 24 April 2026

Abstract: Major depressive disorder (MDD) ranks among the leading causes of disability worldwide. Current treatments often yield suboptimal outcomes, largely due to an incomplete understanding of its underlying pathology. There is, therefore, a pressing need to identify novel core pathological targets. Iron serves as an essential cofactor for several key enzymes in tryptophan (Trp) metabolism, playing a central role in its regulatory pathways. Iron deficiency (ID) can profoundly disrupt Trp metabolic homeostasis in both the peripheral and central nervous systems. This review synthesizes preclinical and clinical evidence to elucidate how ID drives the pathogenesis of MDD through the following interconnected mechanisms: (1) Impairing the activity of tryptophan hydroxylase (TPH), thereby reducing the synthesis of serotonin (5-hydroxytryptamine, 5-HT) and melatonin; (2) Skewing the kynurenine pathway (KP) flux toward neurotoxic metabolites via the "dysfunctional activation" of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO); (3) Disrupting gut microbiota-mediated indole metabolism, compromising intestinal barrier integrity, and amplifying neuroinflammatory responses. These metabolic disturbances collectively contribute to a vicious pathological cycle involving neurochemical imbalance, a neurotoxic microenvironment, peripheral-central inflammatory crosstalk, and ferroptosis-mediated neuronal damage, ultimately entrenching the depressive phenotype. Furthermore, this review outlines multidimensional therapeutic strategies targeting the iron-Trp metabolic axis for depression. In conclusion, we propose that the iron-Trp metabolic axis represents a promising cross-diagnostic target for MDD, offering new theoretical insights and practical avenues for its precision treatment.

Keywords: tryptophan metabolism; iron deficiency; depression

1. Introduction

Major depressive disorder (MDD) is a leading global cause of disability [1], with a lifetime prevalence of 15–20% according to the World Health Organization. Notably, approximately 30–40% of patients exhibit a poor or inadequate response to first-line antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) [2]. This clinical dilemma may stem from the longstanding focus on the "monoamine deficiency" hypothesis, which has arguably overshadowed the more complex, multisystem pathophysiology involving dynamic interactions among nutritional, metabolic, immune, and neural systems [3]. Consequently, identifying core metabolic hubs that integrate these interconnected dysregulations has become crucial for advancing both the mechanistic understanding and therapeutic management of MDD.

Tryptophan (Trp), an essential amino acid, serves as a central metabolic node linking nutritional status, immune activation, gut microbiota, and central nervous system function. Its metabolism proceeds through three major pathways: (1) the serotonin synthesis pathway [4], which yields the key neuromodulator serotonin and the circadian hormone melatonin; (2) the kynurenine pathway (KP) [5], responsible for Trp catabolism and the generation of both neuroprotective (e.g., kynurenic acid, KYNA) and neurotoxic (e.g., quinolinic acid, QA) metabolites that critically influence central homeostasis [6]; and (3) the gut microbial indole pathway [7], in which bacterial tryptophanases produce indole derivatives that help maintain intestinal barrier integrity and mediate

gut-brain crosstalk. The balance of metabolic flux among these pathways is highly dependent on iron-sensitive enzymes; iron acts as an essential cofactor for TPH, IDO, TDO, and microbial tryptophanase, thereby directly governing the direction and efficiency of Trp metabolism [8,9].

Iron deficiency (ID)—the world's most prevalent nutritional disorder, affecting an estimated two billion people globally—shows a significant and independent association with MDD risk [10]. Clinical observations indicate that the incidence of depressive symptoms is two to three fold higher in individuals with ID than in those with sufficient iron stores. Notably, even "hidden" (subclinical) iron deficiency, defined as serum ferritin <30 μg/L in the absence of anemia, can lead to reduced central 5-HT levels and promote depressive-like behaviors [11]. Preclinical models further support that early-life ID could induce irreversible intracerebral Trp metabolic remodeling and increase MDD susceptibility in adulthood [12]. However, existing studies have largely examined the impact of ID on individual Trp pathways in isolation, lacking a systematic integration of the complete mechanistic cascade from "ID → Trp metabolic imbalance → multisystem pathological interaction → MDD". As a result, a coherent, mechanism-based intervention framework targeting the iron-tryptophan metabolic axis has yet to be established.

Against this backdrop, the present review systematically outlines the molecular mechanisms through which ID dysregulates the three major Trp metabolic pathways. We analyze how resulting imbalances converge into a self-sustaining pathological network—encompassing neurochemical disturbances, neurotoxic injury, amplified neuroinflammation, and ferroptosis—that drives MDD progression. Furthermore, we summarize emerging multi-dimensional therapeutic strategies aimed at this axis, including precision iron repletion, pathway-specific modulation, and gut microbiota intervention. By synthesizing this evidence, we aim to clarify the scientific rationale for positioning the iron-tryptophan metabolic axis as a core pathological target in MDD and to provide a conceptual framework for shifting its management from predominantly symptomatic treatment toward more precise, etiology-informed therapies.

2. Iron-Dependent Regulation of Tryptophan Metabolism

2.1. Serotonin Synthesis Pathway

Serotonin is a key neurotransmitter within the emotional regulatory networks of the central nervous system (CNS). Its biosynthesis is initiated and rate-limited by tryptophan hydroxylase (TPH) [13]. TPH exists in two functionally specialized subtypes: TPH1, predominantly expressed in peripheral tissues (e.g., intestine and pineal gland), mediates the synthesis of peripheral 5-HT and melatonin; TPH2, specifically localized in raphe nucleus neurons of the CNS, serves as the exclusive rate-limiting enzyme for central 5-HT synthesis, thereby directly regulating 5-HT homeostasis in emotion-related brain regions such as the prefrontal cortex (PFC) and hippocampus (HPC) [14]. Both TPH isoforms belong to the aromatic amino acid hydroxylase family. Their catalytic activity critically depends on iron (Fe), which acts as an essential cofactor alongside the pterin coenzyme tetrahydrobiopterin (BH4). Together, Fe and BH4 stabilize the enzyme's active conformation and activate its catalytic site, facilitating the hydroxylation of tryptophan's aromatic ring to produce 5-hydroxytryptophan (5-HTP)—the immediate precursor of 5-HT [15].

ID directly and reversibly impairs the catalytic activity of tryptophan hydroxylase (TPH) by depriving it of the essential cofactor, Fe^{2+} (as demonstrated in in vitro enzymatic studies) [16]. This biochemical impairment initiates a proposed pathological cascade: ID-driven TPH inhibition reduces central serotonin synthesis, which may subsequently downregulate the hippocampal glucocorticoid receptor (GR) signaling pathway. The resultant impairment in negative feedback is hypothesized to contribute to hypothalamic-pituitary-adrenal (HPA) axis over-activation, ultimately leading to the manifestation of depression-related phenotypes in preclinical models. Clinical observations corroborate the association between ID and depressive symptoms, supporting the biological plausibility of this mechanistic pathway [17,18].

Preclinical studies have confirmed that early-life ID in rodents can reduce the concentration of 5-HT in PFC, HPC and other brain regions, and this effect has a direct causal relationship with the decrease of hippocampal neuron injury and neurogenesis [17]. In mechanism, decreased central 5-HT inhibits the transcriptional expression and ligand-binding activity of hippocampal GR [19], which weakens the negative feedback regulation of GR on the HPA axis and leads to the continuous increase of cortisol [20] and HPA axis dysfunction is the core pathological characteristics of MDD.

Clinical longitudinal evidence supports this pathway. A 15-year follow-up study of 236 infants found that individuals diagnosed with ID in early life exhibited a significantly higher incidence of depressive behaviors (e.g., anhedonia and social withdrawal) during school age and adolescence compared to iron-sufficient controls. Furthermore, cerebrospinal fluid levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) were

inversely correlated with depression scale scores [21]. The long-term neural sequela may involve ID-induced persistent suppression of TPH activity, leading to irreversible remodeling of emotion-regulating circuits such as the HPC-PFC projection [22], which ultimately heightens susceptibility to MDD in adulthood [23].

2.2. Kynurenine Pathway

The kynurenine pathway (KP) serves as the major catabolic route for tryptophan (Trp), accounting for over 90% of Trp degradation under physiological conditions and undergoing significant upregulation in inflammatory microenvironments [24]. A core function of the KP is to maintain the balance between neuroprotective metabolites (e.g., kynurenic acid, KA) and neurotoxic metabolites (e.g., quinolinic acid, QA), thereby regulating homeostasis within the central nervous system (CNS) [25]. The initial and rate-limiting step of the KP is co-catalyzed by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). IDO is predominantly expressed in immune cells (e.g., macrophages and microglia) and is potently induced by inflammatory signals, whereas TDO is mainly located in the liver and CNS and is regulated by feedback from Trp concentration [26]. Critically, both enzymes are iron-dependent heme proteases. Their catalytic activity requires Fe^{2+} to coordinate with the heme prosthetic group to form a stable active center, which mediates the oxidative cleavage of the Trp indole ring and initiates the KP cascade [27].

ID disrupts KP function through a dual mechanism of "direct enzymatic inhibition" and "indirect inflammatory activation", ultimately triggering metabolic imbalance. On one hand, ID depletes bioavailable Fe^{2+} pools, directly depriving IDO and TDO of their essential cofactor and reducing their catalytic activities [28]. On the other hand, ID-induced systemic inflammation promotes the release of pro-inflammatory cytokines (e.g., interferon-γ, TNF-α), which markedly upregulate IDO transcription via pathways such as NF-κB [29]. This combination of enzyme inhibition and paradoxical transcriptional upregulation—termed "dysfunctional activation"—results in an abnormal KP metabolic flux. The consequence is systemic Trp depletion, reflected by an increased kynurenine/Trp (Kyn/Trp) ratio (a core biomarker of KP activation), alongside a shift in metabolic flux toward the neurotoxic branch, evidenced by a decreased KA/QA ratio and pathological accumulation of QA within the CNS [30].

This KP imbalance is particularly prominent in chronic inflammation-associated depression [31] and contributes to MDD pathology through three interconnected mechanisms: (1) QA, a potent agonist of the N-methyl-D-aspartate (NMDA) receptor, accumulates in regions like the HPC and PFC, leading to receptor over-activation, aberrant Ca^{2+} influx, and excitotoxic neuronal damage [32]; (2) Concurrent relative KA deficiency diminishes its inhibitory modulation of the glutamatergic system, thereby amplifying excitotoxicity and exacerbating microglia-driven neuroinflammation [33]; (3) A bidirectional interaction exists between KP imbalance and HPA axis dysfunction: QA accumulation can directly stimulate the HPA axis, while HPA axis over-activation further promotes IDO expression via inflammatory signaling. This creates a vicious cycle where KP disturbance disrupts HPA axis regulation, which in turn amplifies inflammation and perpetuates further KP dysregulation, thereby sustaining a chronic depressive phenotype [34].

Both preclinical and clinical evidence support this mechanistic framework. In rodent models of depression, CNS and peripheral Trp depletion, elevated QA, and a reduced KA/QA ratio correlate positively with the severity of depressive-like behaviors [35]. Consistently, patients with MDD exhibit significantly higher serum Kyn/Trp ratios and QA levels compared to healthy controls, and a decreased KA/QA ratio is inversely correlated with Hamilton Depression Rating Scale (HAMD) scores [36].

2.3. Intestinal Microbial Pathway

The intestinal microbiota plays a central regulatory role in the host tryptophan (Trp) metabolic network, producing indole and its derivatives such as indole-3-lactic acid (ILA) and indole-3-propionic acid (I3P) [37]. Acting as high-affinity natural agonists of the aryl hydrocarbon receptor (AhR), these indole metabolites specifically activate the AhR signaling pathway in intestinal epithelial cells. This activation serves dual functions: it maintains intestinal mucosal barrier integrity by upregulating the transcriptional expression and stability of tight junction proteins, including occludin and zonula occludens-1 (ZO-1) [38,39], and exerts systemic anti-inflammatory effects by inhibiting the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α from peripheral immune cells including macrophages and dendritic cells. Additionally, through the microbiota-gut-brain axis (MGBA), these metabolites help regulate central nervous system (CNS) neurotransmitter homeostasis and modulate neuroinflammation [40].

Iron status represents a crucial environmental determinant regulating both the composition and metabolic activity of the intestinal microbiota. ID disrupts the intestinal Trp-indole metabolic equilibrium through direct and

indirect mechanisms [41]: (1) Direct effects: ID significantly reduces the abundance and metabolic activity of indole-producing commensal bacteria such as *Akkermansia muciniphila* and *Bifidobacterium* spp., leading to diminished synthesis of intestinal indole derivatives [42]; (2) Indirect effects: ID alters luminal iron bioavailability, promoting the proliferation of iron-tolerant pathogenic bacteria (e.g., Escherichia coli) while inhibiting colonization by beneficial indole-producing species, thereby exacerbating microbiota structural imbalance and metabolic dysregulation [43].

The reduction in indole derivatives directly limits the availability of AhR ligands, substantially impairing AhR signaling pathway activation [44]. This downregulates intestinal epithelial tight junction protein expression, compromises barrier integrity, and permits translocation of pro-inflammatory substances including lipopolysaccharide (LPS) and unmethylated CpG DNA into systemic circulation. These molecules activate peripheral innate and adaptive immune responses, triggering systemic low-grade inflammation [45]. Peripheral inflammatory signals subsequently access the CNS via two primary routes: transcellular transport across the blood-brain barrier (BBB) or inflammation-mediated paracellular pathways [46]; and through circumventricular organs (CVOs), which lack a complete BBB and can directly sense peripheral cytokines [47].

Within the CNS, inflammatory signals activate microglia and astrocytes, induce neuroinflammation, and disrupt bidirectional MGBA communication, ultimately leading to central neurochemical homeostasis imbalance [48,49]. Notably, a self-reinforcing vicious cycle emerges between ID-induced microbiota metabolic disruption and gut-brain axis dysfunction: peripheral inflammation further suppresses intestinal indole-producing bacterial proliferation and metabolism, reduces indole derivative synthesis, and exacerbates intestinal barrier damage [50]. Concurrently, CNS inflammation modulates intestinal motility and secretion via autonomic pathways (e.g., vagal signaling), further destabilizing microbiota homeostasis [51]. This closed-loop pathological amplification constitutes the key upstream mechanism through which iron-tryptophan metabolic axis dysregulation drives major depressive disorder (MDD) pathogenesis.

3. The Pathological Network of Depression Driven by Imbalance of the Iron–Tryptophan Metabolic Axis

3.1. Neurochemical Disorder: Dysfunction of Emotional and Sleep Regulation

As the central pathological node in MDD driven by an imbalance of the iron-tryptophan metabolic axis, neurochemical disturbances primarily manifest as the inhibition of key enzymes. This inhibition triggers a deficit in neurotransmitter synthesis, directly leading to emotional and sleep dysfunction, thereby initiating and sustaining the depressive phenotype (Figure 1).

Serotonin is a core modulator of the central emotional circuitry, and its insufficient synthesis constitutes a key pathological basis for core MDD symptoms—namely, depressed mood and anhedonia [52]. ID specifically impairs the activity of TPH2 in CNS raphe-nucleus serotonergic neurons by depriving the enzyme of its essential Fe^{2+} cofactor. This impaired TPH2 function directly reduces the firing frequency of serotonergic neurons and diminishes 5-HT release into the PFC and HPC [53] (Figure 1). Concurrently, ID also disrupts melatonin (MT) biosynthesis by inhibiting peripheral TPH1, which is predominantly expressed in the pineal gland [54]. MT is a key hormonal regulator of the sleep-wake cycle; its deficiency leads to circadian rhythm disruption characterized by prolonged sleep latency, sleep fragmentation, reduced deep-sleep proportion, and early awakening—all core diagnostic features and typical phenotypes of MDD [55]. Mechanistically, pineal TPH1 activity depends on Fe^{2+} to mediate tryptophan hydroxylation. ID-induced iron depletion directly obstructs the Trp → 5-HTP → MT synthesis pathway, resulting in decreased peak cerebrospinal-fluid MT concentration and blunted circadian fluctuation [56].

Notably, sleep disturbance in MDD is not merely a concomitant symptom but acts as an amplifier that exacerbates the imbalance of the iron-tryptophan metabolic axis, creating a self-reinforcing positive-feedback cycle: (1) Sleep disturbance activates the HPA axis, leading to sustained cortisol elevation, which suppresses expression of the intestinal iron-absorption transporter divalent metal transporter 1 (DMT1) and aggravates ID [57]; (2) Sleep deprivation increases intestinal-barrier permeability, triggering low-grade inflammation. Pro-inflammatory cytokines (e.g., IL-6, TNF-α) further inhibit TPH activity and reduce 5-HT and MT synthesis [58]; (3) Sleep disturbances directly impair hippocampal neuroplasticity, weakening emotional-regulation capacity and making depressive symptoms more resistant to remission [59].

Thus, ID-induced TPH inhibition → deficient 5-HT and MT synthesis → depression and sleep disturbance → further aggravation of ID and iron-tryptophan metabolic imbalance forms a closed-loop amplification circuit. This self-perpetuating cycle represents a core mechanistic driver underlying the progression of major depression from acute episodes toward chronicity and treatment resistance.

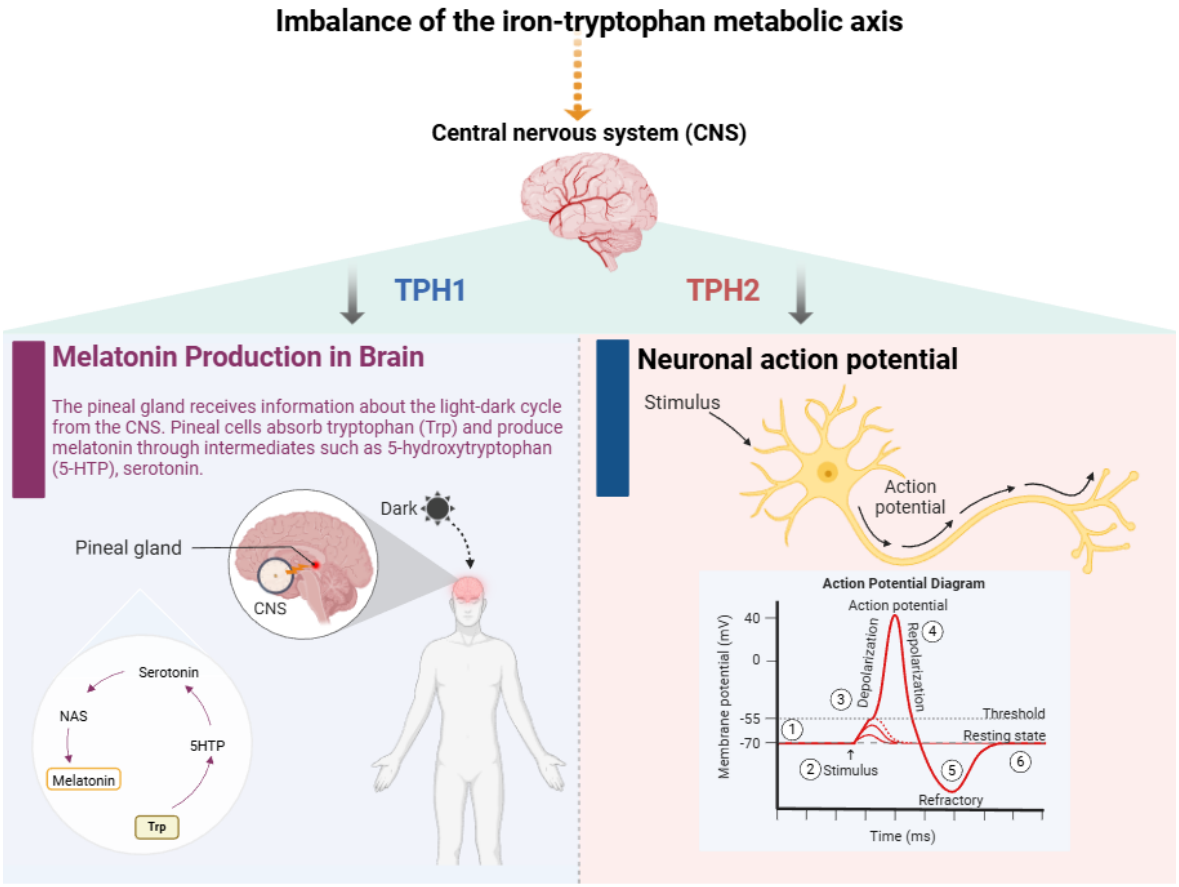

Figure 1. Iron-tryptophan axis disruption promotes mood and sleep disorders.

3.2. Neurotoxic Microenvironment: Neuronal Damage and Circuit Disruption

As a central downstream consequence of the imbalanced iron-tryptophan metabolic axis (detailed in Section 2.2), the neurotoxic bias of KP induces neuronal damage and disrupts circuit function through a synergistic interplay of neurotoxic metabolite accumulation, diminished neuroprotection, and amplified neuroinflammation (Figure 2).

Quinolinic acid (QA)-mediated over-activation of NMDA receptors represents the core initiating mechanism of neurotoxic injury [60]. Excessive binding of QA to NMDA receptors leads to sustained channel opening, resulting in abnormal neuronal Ca^{2+} influx and activation of downstream calcium-dependent signaling pathways (e.g., calcineurin, protein kinase C) [61]. This cascade subsequently triggers oxidative stress, lipid peroxidation, and the activation of apoptosis-related genes such as caspase-3 [62]. Such damage exhibits regional specificity, preferentially targeting key brain regions involved in emotional regulation and cognitive processing—notably the HPC and PFC—and culminates in selective, often irreversible, neuronal death (Figure 2). Clinical studies confirm that neuron counts in the PFC and HPC of MDD patients are reduced compared to healthy controls, with the extent of neuronal damage positively correlating with intracerebral QA levels [63].

Concurrently, the relatively diminished levels of kynurenic acid (KA) weaken its modulatory inhibition of the glutamatergic system [64]. KA competitively binds to the glycine site of the NMDA receptor, inhibiting both presynaptic glutamate release and postsynaptic receptor activation. Its deficiency thus lifts this inhibitory brake, resulting in excessive glutamate release and further amplification of NMDA receptor-mediated excitotoxicity [65] (Figure 2). The combined increase in QA (promoting excitation) and decrease in KA (reducing inhibition) directly destabilizes the central nervous system's excitatory-inhibitory (E-I) balance [66], compromising synaptic integrity and functional connectivity within emotion-relevant neural circuits.

Of particular pathophysiological significance, QA can directly polarize microglia toward a pro-inflammatory phenotype by binding to Toll-like receptor 4 (TLR4) on their surface [67]. This interaction promotes the secretion of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) and chemokines [68]. Activated microglia, in turn, further upregulate IDO expression via the NF-κB pathway, accelerating the catabolism of tryptophan toward QA and thereby establishing a self-amplifying vicious cycle of neurotoxicity → neuroinflammation → KP imbalance [69] (Figure 2). In rodent models of depression, the expression of the microglial activation marker Iba-1 correlates

positively with intracerebral QA levels [70], while pharmacological inhibition of microglial activation significantly reduces QA concentration and ameliorates depressive-like behaviors [71].

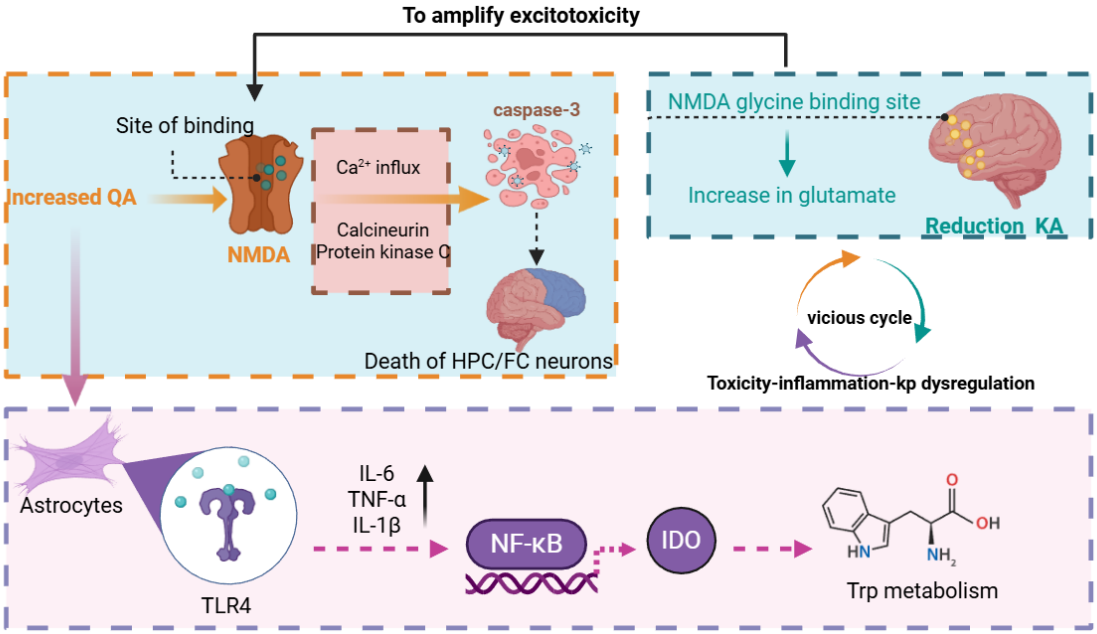

Figure 2. Imbalance in the iron-tryptophan metabolic axis induces neuronal damage and disruption of neural circuit function. Dysfunctional activation of IDO and TDO disrupts the KP metabolic pathway, leading to accumulation of the neurotoxic substance QA in the HPC and PFC. This excessively activates NMDA receptors, causing abnormal neuronal Ca^{2+} influx and inducing excitotoxic damage. Relatively insufficient KA levels weaken its inhibitory effect on the glutamatergic system, further amplifying excitotoxicity and exacerbating glia-mediated neuroinflammation. Inflammatory signals subsequently promote IDO expression, causing further imbalance in tryptophan metabolism and forming a vicious cycle of neurotoxicity-neuroinflammation-KP dysregulation.

3.3. Activation of Neuroinflammation: A Peripheral-Central Inflammatory Cycle

As a key regulatory loop in the pathological progression of MDD mediated by the imbalance of the iron-tryptophan metabolic axis, the cascade amplification of neuroinflammation establishes a bidirectional positive-feedback loop between peripheral and central inflammation via the microbiota-gut-brain axis (MGBA), directly driving the disease toward chronicity and severity [72]. As outlined in Section 2.3, ID impairs intestinal synthesis of indole derivatives, weakens aryl-hydrocarbon-receptor signaling, and compromises intestinal-barrier integrity, thereby promoting translocation of lipopolysaccharide into the systemic circulation. Binding of LPS to TLR4 activates the NF-κB pathway, inducing secretion of pro-inflammatory cytokines. These cytokines can enter the central nervous system (CNS) directly through transcellular transport or paracellular pathways across the blood-brain barrier (Figure 3).

Once inside the CNS, pro-inflammatory cytokines rapidly activate resident glial cells (microglia and astrocytes). Microglia release centrally derived pro-inflammatory cytokines and up-regulate the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), generating excess reactive oxygen species (ROS) and nitric oxide (NO) [73,74]. Concurrently, astrocytes down-regulate the expression of the glutamate transporter GLT-1 [75], leading to accumulation of synaptic glutamate and further amplifying neurotoxicity [76]. Activated microglia also significantly up-regulate IDO expression via the JAK-STAT/NF-κB pathway [77], critically linking neuroinflammation to further dysregulation of the iron-tryptophan metabolic axis. Enhanced IDO activity accelerates the catabolism of Trp to QA, resulting in reduced 5-HT synthesis [78]. Moreover, central pro-inflammatory factors (e.g., IL-1β and IL-6) feedback to the periphery via the MGBA, suppressing expression of intestinal DMT1 and ferroportin, reducing iron absorption, further disrupting epithelial tight junctions, and exacerbating both ID and intestinal permeability [79]. This series of events reinforces a self-amplifying cycle of neuroinflammation (Figure 3).

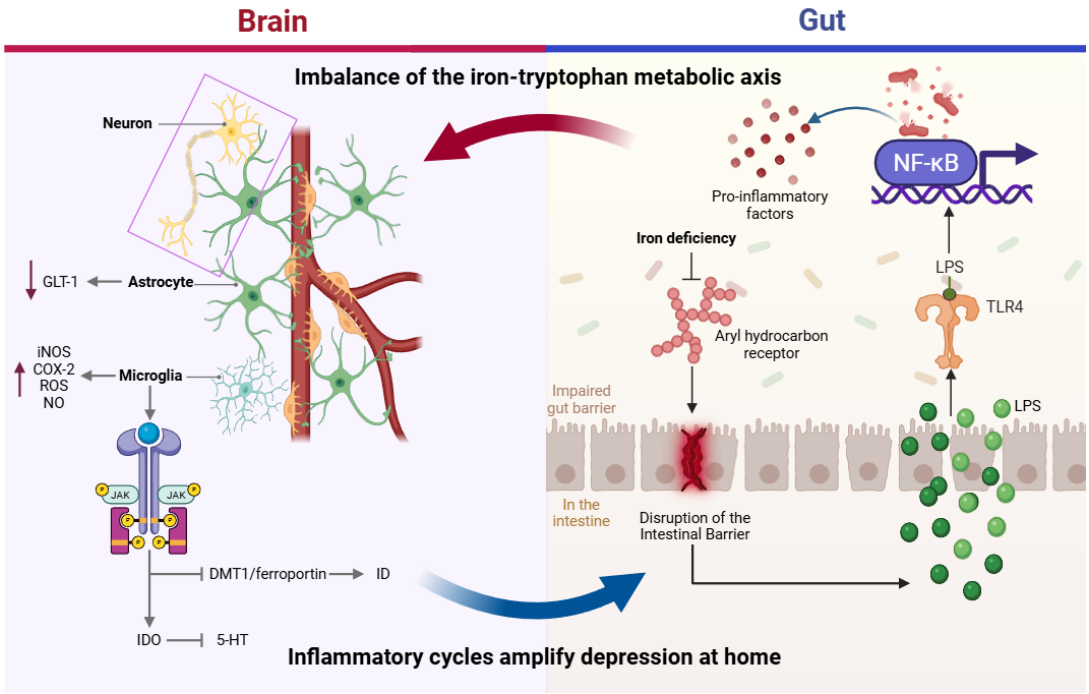

Figure 3. Imbalance in the iron-tryptophan metabolic axis promotes peripheral- central inflammation circulation. Iron deficiency leads to insufficient synthesis of intestinal indole derivatives, damaging the intestinal barrier. This promotes the secretion of pro-inflammatory cytokines that enter the CNS, thereby enhancing neuroinflammation. Neuroinflammation, via MGBA, modulates peripheral mechanisms, exacerbating iron deficiency and intestinal permeability.

3.4. Decrease in Antioxidant Capacity: Ferroptosis and Neuronal Injury

Imbalance in the iron-tryptophan metabolic axis impairs antioxidant defense system function, thereby activating ferroptosis (iron-dependent regulatory cell death). This forms a synergistic injury loop of "oxidative stress-ferroptosis-neuroinflammation," further exacerbating metabolic axis imbalance and depressive phenotypes [80]. It is important to note that the core of ferroptosis lies in the uncontrolled accumulation of lipid peroxides, rather than mere systemic iron overload. In chronic inflammation-associated ID conditions, despite low systemic iron stores, altered blood-brain barrier permeability, activated microglia releasing iron, or impaired neuronal iron recycling may lead to functional iron overload in specific brain regions or organelles. Although ID reduces total body iron reserves, it enhances neuronal susceptibility to ferroptosis by both compromising antioxidant defenses and inducing local iron accumulation. Although this pathway differs from the model where iron overload directly and massively generates lipid peroxides, both ultimately converge on the core hallmark of uncontrolled lipid peroxidation.

Trp metabolites such as 5-HT, ILA, and I3P function as natural radical-trapping antioxidants (RTAs) [81], playing a key antioxidative role by scavenging ROS and inhibiting iron-dependent lipid peroxidation. ID-mediated imbalance of the iron-tryptophan axis directly reduces the synthesis of these antioxidant metabolites, markedly weakening the CNS's capacity to suppress lipid peroxidation and thereby increasing neuronal susceptibility to ferroptosis [82,83].

The core pathological feature of ferroptosis is the abnormal accumulation of lipid peroxides, whose clearance critically depends on glutathione peroxidase 4 (GPX4) [84]. GPX4 acts as a ferroptosis suppressor by specifically catalyzing the reductive decomposition of lipid peroxides; its impairment leads to progressive lipid-peroxide accumulation and triggers cell death [85]. Animal studies confirm that expression of GPX4 in the HPC and PFC of depression-model mice is significantly down-regulated, accompanied by elevated levels of lipid peroxides such as malondialdehyde (MDA) [86]; these alterations correlate positively with the severity of depressive-like behaviors [87].

ID further enhances susceptibility to ferroptosis through two mechanisms: (1) ID disrupts intracellular iron homeostasis. Despite systemic iron shortage, dysfunction of subcellular iron transporters (e.g., DMT1 in neuronal mitochondria and lysosomes) can lead to local enrichment of Fe^{2+}. This locally accumulated Fe^{2+} may bind to the active center of GPX4, distort its conformation, inhibit its catalytic function, and thereby weaken the core clearance pathway for lipid peroxides [80]. (2) Reduced levels of tryptophan-derived antioxidant products indirectly suppress the NRF2 signaling pathway, leading to down-regulation of transcription and expression of anti-ferroptosis

proteins such as GPX4 and superoxide dismutase (SOD), ultimately collapsing the cellular antioxidant defense system [88]. This impaired RTA-mediated antioxidant defense, coupled with direct inhibition of GPX4 activity, dramatically magnifies lipid-peroxide accumulation and ultimately induces neuronal ferroptosis [86].

Furthermore, neuronal damage mediated by ferroptosis releases damage-associated molecular patterns (DAMPs), including high-mobility-group box 1 (HMGB1), ATP, and other endogenous danger signals [89]. These molecules bind to TLR4 and purinergic receptor P2X7 on microglial surfaces, activating downstream inflammatory signaling and promoting microglial polarization toward a pro-inflammatory phenotype with sustained release of pro-inflammatory cytokines [90], thereby amplifying neuroinflammation. Importantly, persistent neuroinflammation in turn inhibits the synthesis of tryptophan antioxidant metabolites and GPX4 expression, further heightening neuronal susceptibility to ferroptosis [91]. This establishes a self-reinforcing cycle of "ferroptosis → neuroinflammation → metabolic axis imbalance" that continuously exacerbates the depressive phenotype.

4. Treatment Strategies Targeting the Iron-Tryptophan Metabolic Axis

4.1. Foundational Intervention: Iron Supplementation

Iron supplementation is a fundamental intervention for correcting imbalances in the iron-tryptophan metabolic axis; however, its implementation must be carefully tailored according to the patient's iron status and comorbidities to optimize efficacy and safety. In patients with MDD comorbid with uncomplicated iron-deficiency anemia (IDA), meta-analyses show that combining iron preparations (e.g., ferrous sulfate, ferrous gluconate) with antidepressants can normalize hemoglobin levels, lower the Kyn/Trp ratio, and increase 5-HT levels [92]. Mechanistically, supplemental Fe^{2+} restores the catalytic activity of iron-dependent enzymes such as TPH and IDO, thereby rescuing 5-HT synthesis and rebalancing the kynurenine pathway [93]. Clinical cohort studies confirm that iron supplementation in IDA patients reduces the risk of depressive symptoms and improves the response rate to antidepressant treatment [94,95] (Figure 4). Notably, even in cases of simple iron-deficiency anemia, the efficacy of iron supplementation may be influenced by MDD subtypes and baseline inflammatory levels.

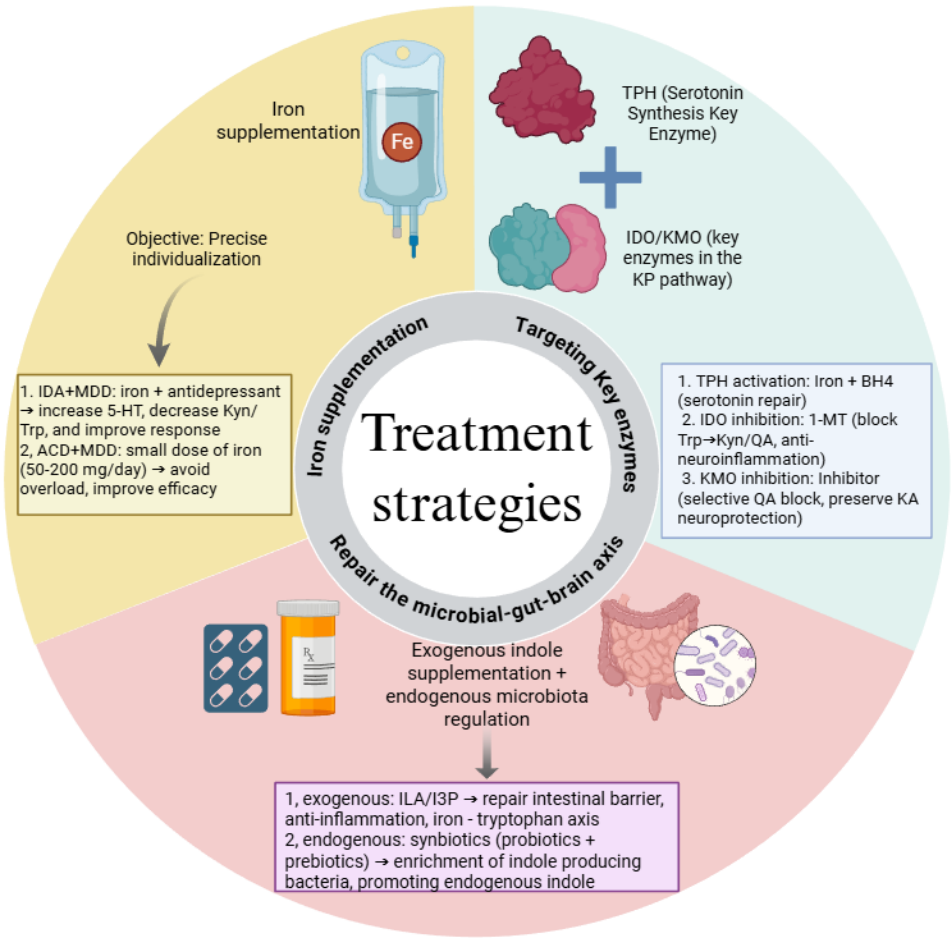

Figure 4. Depression treatment strategies targeting the iron-tryptophan metabolic axis, including foundational interventions (iron supplementation), precision interventions targeting key enzymes in metabolic pathways, and restoration of the microbiome-gut-brain axis function.

In MDD patients with anemia of chronic disease (ACD), iron supplementation requires caution. Blind supplementation may lead to iron overload (serum ferritin > 1000 μg/L), aggravating oxidative stress and amplifying neuroinflammation via the Fenton reaction [80]. Therefore, low-dose oral iron (50–200 mg iron daily) is recommended for ACD-related MDD. Clinical studies show that this regimen enhances antidepressant efficacy while reducing adverse effects such as gastrointestinal irritation [96]. This precision strategy minimizes risks associated with iron overload (e.g., neuronal oxidative damage) while promoting steady-state recovery of the iron-tryptophan metabolic axis.

4.2. Precision Modulation of Key Metabolic Enzymes

Serotonin deficiency and the neurotoxic shift in the KP are core pathological links in MDD mediated by imbalance of the iron-tryptophan metabolic axis. Specific regulation of the key enzymes has emerged as an important direction for precision intervention.

To address the central defect of impaired TPH activity, a synergistic activation strategy combining iron and tetrahydrobiopterin (BH4) shows promising potential. As an essential cofactor for TPH catalysis, BH4 stabilizes the enzyme's active conformation and promotes Fe-mediated hydroxylation of tryptophan [97]. BH4 deficiency leads to conformational instability of the CNS-specific TPH2 isoform, while Fe^{2+} deficiency further weakens metal-ion binding at its catalytic center, creating a "double hit" to TPH function [98]. Co-administration of iron and BH4 addresses both limiting factors simultaneously: Fe^{2+} directly restores TPH's catalytic core, and BH4 supplies the rate-limiting cofactor. Their synergistic action significantly improves TPH catalytic efficiency and ameliorates the pathological state of serotonin deficiency [99,100] (Figure 4).

Specific inhibitors targeting key enzymes offer precise regulation of the neurotoxic shift in the kynurenine pathway. 1-Methyl-D-tryptophan (1-MT) is a classic competitive inhibitor of IDO [101] that selectively binds the enzyme's active site, blocking oxidative cleavage of the tryptophan indole ring, inhibiting downstream flux toward Kyn and QA, reducing the Kyn/Trp ratio, and curtailing QA synthesis while restoring peripheral and central tryptophan reserves [102]. Preclinical studies demonstrate that 1-MT intervention significantly improves depressive-like behaviors in animal models and reduces hippocampal levels of neuroinflammatory factors such as IL-6 and TNF-α [103]. Compared with IDO inhibitors, kynurenine monooxygenase (KMO) inhibitors offer higher specificity. By selectively inhibiting the key rate-limiting step in QA synthesis, they do not affect upstream conversion of kynurenine to the neuroprotective metabolite kynurenic acid (KA), thereby avoiding the broad disruption of tryptophan metabolism that may accompany IDO inhibition [104]. Preclinical studies have established that KMO inhibitors effectively ameliorate depressive-like phenotypes in animal models. These favorable outcomes are attributed to their ability to selectively reduce neurotoxic QA production while preserving the neuroprotective KA branch, a mechanism largely devoid of major off-target liabilities. Consequently, KMO inhibitors are regarded as promising next-generation candidates for antidepressant development [79,105].

In summary, synergistic activation of TPH and pathway-specific inhibition of IDO/KMO target two core pathological branches of the iron-tryptophan metabolic axis, respectively. By precisely modulating the activities of key enzymes, these strategies repair metabolic imbalance and provide mechanism-based directions for the precision treatment of MDD. However, it is worth noting that the efficacy, safety, and practical applicability of related drugs for treating MDD in humans remain largely unsubstantiated by robust clinical trials. The clinical translation also involves numerous challenges, including factors such as drug permeability across the blood-brain barrier, off-target effects, and patient specificity.

4.3. Restoration of Microbiota-Gut-Brain Axis Function

For intestinal-derived indole deficiency (see Section 2.3), dual strategies of exogenous indole supplementation and endogenous microbiota modulation can precisely restore MGBA function and thereby block depression-related pathological processes.

Exogenous supplementation of indole derivatives (e.g., ILA, I3P) that act as aryl-hydrocarbon-receptor (AhR) agonists represents a direct intervention route [106]. By activating AhR signaling, these compounds up-regulate expression of intestinal epithelial tight-junction proteins (e.g., occludin, ZO-1) [107], rapidly repairing damaged intestinal-barrier integrity and inhibiting translocation of endotoxins such as LPS into the systemic circulation [108]. Simultaneously, via bidirectional regulation of the MGBA, they suppress the peripheral-central inflammatory cascade and improve central neural plasticity [109]. Their antidepressant potential has been validated preclinically: ILA intervention significantly improves depressive-like behaviors in depression models [110] while concurrently reducing hippocampal levels of pro-inflammatory factors [111]; its efficacy is directly linked to regulation of the iron-tryptophan metabolic axis and alleviation of neuroinflammation (Figure 4).

Endogenous microbiota modulation precisely targets the iron-tryptophan metabolic axis through microbial remodeling. This strategy combined with biomarker-guided treatment, further enhances intervention specificity and sustainability. A core approach is the synbiotic strategy—combined administration of probiotics and prebiotics—which selectively enriches the abundance of indole-producing bacteria (e.g., *Akkermansia muciniphila, Bifidobacterium* spp.) [112], up-regulates microbial tryptophanase activity, promotes synthesis of endogenous indole derivatives, and optimizes metabolic flux within the iron-tryptophan axis [113], thereby establishing a sustained metabolic-regulatory effect. Growing evidence supports the translational value of probiotic-based interventions in diverse populations: (1) A randomized controlled trial (RCT) in 124 healthy older adults (mean age 62 years) showed that subjects receiving psychobiotic supplementation (*Lactobacillus helveticus* and *Bifidobacterium longum*) had significantly lower anxiety and depression scores than the placebo group, an effect closely associated with increased fecal indole levels [114]; (2) A large cohort study of pregnant women demonstrated that supplementation with *Lactobacillus rhamnosus* HN001 significantly reduced the incidence of postpartum depression and anxiety [115], offering a microbiota-modulation strategy for perinatal depression prevention; (3) In patients comorbid for irritable bowel syndrome (IBS) and MDD, twice-daily intervention with *Bacillus coagulans* MTCC5856 significantly improved HAMD and Patient Health Questionnaire-9 items (PHQ-9) scores and decreased serum Zonulin (a marker of intestinal-barrier permeability) [116], confirming that microbiota regulation can alleviate the depressive phenotype by repairing the intestinal barrier and modulating the iron-tryptophan axis.

In summary, dual strategies of exogenous indole supplementation and endogenous microbiota modulation can precisely restore MGBA function. By directly supplying functional molecules and persistently remodeling metabolic flora, they effectively rebalance the iron-tryptophan metabolic axis, thereby providing a novel intervention pathway targeting gut-brain interactions for MDD.

5. Conclusions and Prospects

This review systematically elucidates the scientific rationale for positioning the iron-tryptophan metabolic axis as a core pathological target in MDD. As an essential cofactor for key enzymes in the three major tryptophan metabolic pathways (serotonin synthesis, KP catabolism, and intestinal indole production), ID inhibits TPH activity, thereby reducing 5-HT and melatonin synthesis, driving a neurotoxic shift in the KP, and disrupting intestinal indole metabolism. These disturbances collectively drive MDD progression through a pathological network encompassing neurochemical disturbances, neurotoxic injury, amplified neuroinflammation, and ferroptosis. Consistent preclinical and clinical evidence confirms that imbalance of the iron-tryptophan metabolic axis is a central feature of MDD, and its related markers (e.g., ferritin, Kyn/Trp ratio, indole derivatives) hold potential as tools for diagnosis and prognosis assessment.

Multidimensional intervention strategies targeting this axis—precision iron supplementation, pathway-specific enzyme modulation, and intestinal microbiota regulation—have demonstrated considerable antidepressant potential, offering a new direction for the precision treatment of MDD. Nevertheless, current research still faces limitations: (1) The clinical translation of IDO/KMO inhibitors remains in its early stages, and their long-term safety and broad effects on systemic tryptophan metabolism require further evaluation; (2) Existing interventions largely focus on single metabolic nodes, with a lack of clinical evidence for multi-target synergistic approaches; (3) Standardized clinical assays for iron-tryptophan-axis-related markers have not been established, hindering their translation into routine practice. Furthermore, despite the promising prospects of therapeutic strategies targeting the iron-tryptophan axis, numerous challenges remain. These include the complexity of personalized iron status assessment, the blood-brain barrier permeability and off-target effects of enzyme inhibitors, as well as the individual variability and durability of effects in microbiota interventions.

Future studies should focus on: (1) leveraging single-cell sequencing, metabolomics, and related technologies to dissect subtype-specific alterations of the iron-tryptophan metabolic axis in MDD; (2) establishing standardized detection criteria for these axis-related biomarkers to facilitate their application in stratified diagnosis and treatment monitoring. Ultimately, through deep integration of mechanistic research and clinical translation, we can advance MDD management from “symptomatic treatment” toward “etiology-based therapy,” providing new scientific support for improving patient outcomes.

Author Contributions: Y.Z. and J.L. contributed equally to this work. All authors contributed to the literature review, writing, and revisions. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Ministry of Science and Technology of China (2025YFA1308900), the National Science Foundation of China (32571339, 32530016 and W2523103), Kunming Science and Technology Bureau (2022SCP007) and Shenzhen New Cornerstone Science Foundation (NCI202238).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. Given the role as Editorial Board Member, Ren Lai had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal

Use of AI and AI-Assisted Technologies: During the preparation of this work the author(s) used DeepSeek in order to improve readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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