Review

The Intersection between Tryptophan-Kynurenine Pathway Metabolites and Immune Inflammation, Hormones, and Gut Microbiota in Perinatal Depression

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Abstract

Perinatal depression is a prevalent mental disorder among pregnant women, characterized by sleep disturbances, appetite changes, negative emotions, cognitive impairment, and suicidal or homicidal tendencies. These symptoms severely compromise personal well-being, disrupt family life, and burden society. Early detection and intervention are thus crucial. The tryptophan-kynurenine (TRP-KYN) pathway is central to the inflammatory hypothesis of depression and has gained significant attention in perinatal depression research. This pathway encompasses numerous metabolic enzymes and neuroactive metabolites that interact with other physiological systems, influencing neurotransmitter synthesis and neuronal development. Through these interactions, the TRP-KYN pathway exerts psychotropic effects. This article reviews the key metabolites and enzymes of the TRP-KYN pathway and examines its intersection with immune inflammation, hormones, and gut microbiota.

Keywords

tryptophan-kynurenine pathway; perinatal depression; immune inflammation; gut microbiota; sex hormones; hypothalamic-pituitary-adrenal axis

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Introduction

Perinatal depression, as defined by the American Psychiatric Association, is a severe depressive episode occurring during pregnancy or within four weeks after delivery. It is one of the most common mental health complications among women of reproductive age, with prevalence rates ranging from 6.9% to 12.9% in high-income countries and exceeding 20% in low- and middle-income countries [1]. A history of mental disorders is a significant risk factor for perinatal depression, along with other factors such as inadequate family and social support, economic stress, mother-infant relationship challenges, and adverse life events. Perinatal depression disrupts maternal health and negatively impacts family dynamics and the development of future generations. Research has shown that the prevalence of paternal perinatal depression fluctuates between 2.3% and 8.4% [2] and shares many risk factors with maternal depression [3]. Chronic and severe perinatal depression impairs the emotional, language, and cognitive development of infants and young children [4].

Tryptophan (TRP) is one of the essential amino acids in the human body and can be metabolized into various biologically active substances, with 5-hydroxytryptamine (5-HT) being the most well-known [5]. The depletion of 5-HT is a well-established pathophysiological mechanism of depression [6], and its upregulation is the primary mode of action for selective serotonin reuptake inhibitors [7].

This review examines the primary metabolites and enzymes of the TRP-kynurenine (KYN) pathway and explores their intersection with immune inflammation, hormones, and gut microbiota. By providing an updated analysis, this review offers insights into potential treatment strategies and future research directions for postpartum depression.

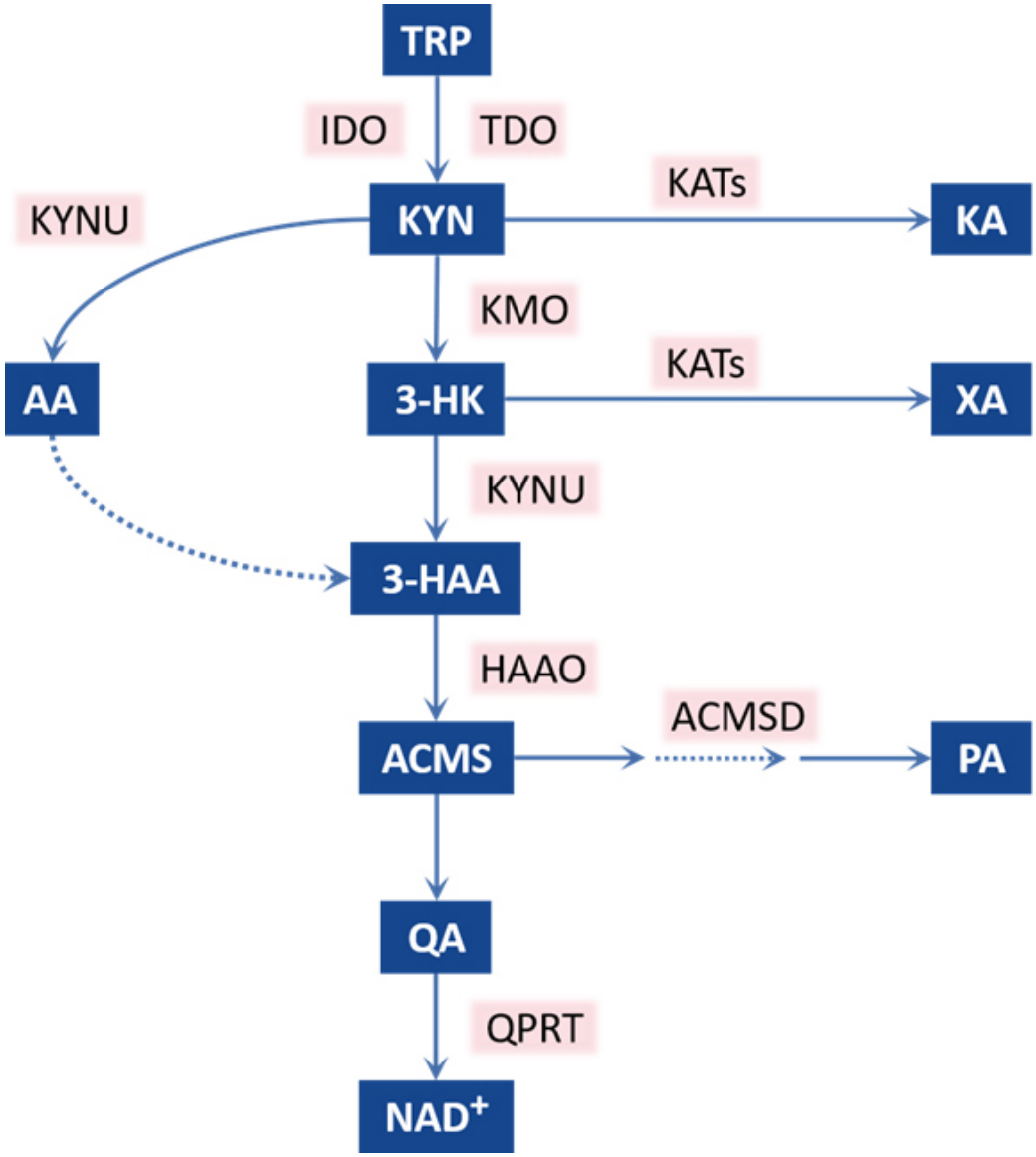

Fig. 1. Schematic diagram of the TRP-KYN pathway. The diagram illustrates the central role of kynurenine within the TRP-KYN pathway, where it undergoes degradation through three specific routes (via KATs, KYNU, and KMO) to generate various neuroactive metabolites. Abbreviations: TRP, tryptophan; IDO, indoleamine-2,3-dioxygenase; TDO, tryptophan-2,3-dioxygenase; KATs, kynurenine aminotransferase I–III; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; 3-HAA, 3-hydroxyanthrenillc acid; KMO, kynurenine 3-monooxygenase; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; XA, xanthurenic acid; ACMS, 2-amino-3-carboxymuconate-6-semialdehyde; ACMSD, ACMS decarboxylase; PA, picolinic acid; QA, quinolinic acid; NAD^+, nicotinamide adenine dinucleotide; TRP-KYN, tryptophan-kynurenine. **Note**: The graphics are produced using MedPeer software (V1.3240320, Beijing Maidipel Information Technology Co., Ltd., Beijing, China).

Tryptophan-Kynurenine (TRP-KYN) Pathway and its Metabolites

Approximately 95% of free TRP follows the kynurenine (KYN) pathway, where it is metabolized and broken down by two rate-limiting enzymes, indoleamine 2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) [8]. The downstream metabolites of KYN include two major branches. The first branch is mediated by kynurenine-3-monooxygenase (KMO), converting KYN into 3-hydroxykynurenine (3-HK), which is subsequently metabolized to 3-hydroxyanthranilic acid (3-HAA) by kynureninase (KYNU). 3-HAA is then processed by 3-hydroxyanthranilic acid 3,4-dioxygenase (HAAO)

to produce 2-amino-3-carboxymuconate-6-semialdehyde (ACMS), the precursor of quinolinic acid (QA). Through a non-enzymatic reaction, this precursor generates QA, which is further processed by quinolinic acid phosphoribosyltransferase (QPRT) to form the final product, nicotinamide adenine dinucleotide (NAD^+). NAD^+ is involved in a series of important cellular energy metabolism processes. Additionally, ACMS can also convert to picolinic acid (PA) by ACMS decarboxylase (ACMSD). KYN is converted to kynurenic acid (KA) by kynurenine aminotransferases (KATs). Furthermore, KATs break down 3-HK into xanthurenic acid (XA) and KYN into anthranilic acid (AA), which are minor branches of canine urine acid metabolism (Fig. 1).

In the central nervous system, microglia and astrocytes are key regulators of TRP metabolism. Microglia primarily produce QA, while astrocytes, lacking KMO, mainly synthesize kynurenic acid (KA). KA is neuroprotective and acts as a free radical scavenger [9]. At low concentrations, KA exhibits a high affinity for the glycine binding site of N-methyl-D-aspartic acid (NMDA) receptors. At supraphysiological concentrations, it can antagonize NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), and kainate receptors (KARs), thereby reducing the sensitivity of hippocampal neurons to kainic acid [10].

In addition to QA and KA, other products in this pathway can also influence neuronal activity. AA, 3-HK, and 3-HAA have been shown to have pro-oxidant effects, inducing neuronal apoptosis through the generation of free radicals [11]. Paradoxically, Su *et al*. [12] reported that 3-HK and 3-HAA have strong free radical scavenging capabilities. They found that these metabolites inhibit cytokine-induced neuronal death in mixed human fetal central nervous system cultures. Specifically, 3-HAA has a unique role in inducing the cytoprotective enzyme heme oxygenase-1 (HO-1) in astrocytes and microglia [13].

Immune Inflammation and the TRP-KYN Pathway in Perinatal Depression

The immune system undergoes significant adaptive changes during different stages of pregnancy [14].

The drastic changes in the immune system of women during the perinatal period are essential for maternal and infant health and survival. In recent years, increasing evidence has emphasized the significant role of immune-inflammatory dysregulation in the etiology of perinatal depression [15]. This has created a unique susceptible "window of opportunity", where women during the perinatal period are more prone to mood disorders. The TRP-KYN pathway connects perinatal depression with immune inflammation. Inflammation upregulates IDO activity and activates TRP metabolism, creating a local and systemic environment with high KYN and low TRP levels. The KYN/TRP ratio is commonly used to measure the metabolic levels of TRP along the KYN pathway and IDO activity in plasma [16].

Immune activation upregulates KMO expression but does not induce KATs, disrupting the balance between QA and KA and altering the TRP-KYN metabolic homeostasis [17]. TRP is preferentially metabolized in an inflammatory environment along the neurotoxic TRP-KYN-QA pathway. Systemic inflammation increases the influx of neurotoxic QA into the brain. Under normal conditions, the L-type amino acid transporter (LAT) in the blood-brain barrier mediates the uptake of peripheral KYN and 3-HK into the brain. AA can also enter the brain to a certain extent through passive diffusion. QA, KA, and 3-HAA have limited blood-brain barrier permeability [18]. Approximately 40% of KYN is synthesized in the brain, while the remaining comes from the periphery [19]. Inflammatory responses increase blood-brain barrier permeability, facilitating excessive QA to enter the central nervous system, further exacerbating excitatory neurotoxicity.

Some researchers have proposed that cytokines and TRP metabolites can be considered biomarkers for perinatal depression (with an accuracy rate of up to 83%). Among them, interleukin-6, tumor necrosis factor, QA, and KYN exhibit strong individual accuracy in predicting future disease risk and severity [14]. Quan *et al*. [20] found that women with postpartum depressive symptoms had notably elevated levels of KYN on the day before delivery and a higher QA/KA ratio on the third day postpartum compared to healthy participants, along with lower KAT activity. In contrast, Achtyes *et al*. [21] found that the decrease in plasma QA not only increased the risk of postpartum depression but was also associated with the severity of symptoms. There are contradictory findings regarding the changes in QA and KA in perinatal depression, which may be due to differences in sample size, participants' history of mental illness, and variations in assessment and detection methods. Further exploration is needed in this regard. Lastly, from the perspective of the "new 5-HT hypothesis" [22], the KYN pathway competes with serotonin (5-HT) for the same precursor, TRP. Immune activation-induced IDO increases TRP consumption, leading to a decrease in 5-HT, which may further contribute to the development of depression.

The TRP-KYN pathway also plays a role in immune regulation. Various metabolites of IDO and this pathway can "dampen" immune responses and promote apoptosis in effector cells. Eroğlu and Eroğlu [23] suggested that placental cells with high expression of IDO suppress maternal T-cell activity. KYN-treated natural killer (NK) cells exhibit reduced functionality [19], and 3-HAA and QA can induce selective apoptosis in mouse thymocytes and Th1 cells *in vitro* [24]. Additionally, IDO and TDO in the placenta help maintain maternal-fetal immune tolerance, exhibit antimicrobial activity, and promote placental vascular relaxation, contributing to fetal survival and improving placental perfusion [25]. These findings highlight the role of the TRP-KYN pathway in adaptive immune suppression during pregnancy.

A longitudinal study on healthy pregnant women showed that TRP metabolism increased significantly during pregnancy and gradually returned to the baseline after delivery [13]. Theoretically, maternal immunosuppression will also be released after delivery. However, Osborne *et al*. [26] found that T-cells are significantly activated in healthy women after delivery, with increases observed in Th1 cells and regulatory T-cells (Tregs). However, in women with postpartum depression, there are defects in the T cell system, preventing physiological T cell immune activation. This is consistent with the findings of Groer and Morgan [27], who reported that postpartum depressed women have lower Th1/Th2 ratios in serum samples and supernatants from whole blood *ex vivo* cultures, indicating suppressed cellular immunity. These findings have also been confirmed in animal experiments. In comparison to normal rats, both the thymus index and spleen index (which roughly estimate the strength of immune function based on the extent of lymphocyte proliferation) are notably decreased in a hormone-induced postpartum depression rat model. However, after treatment with antidepressant drugs, both indices increase [28].

These observations suggest that postpartum TRP-KYN metabolism in depressed women remains relatively "overactive" and cannot return to normal levels. The relatively high activity of IDO and relatively high concentrations of KYN, QA, 3-HAA, and other metabolites weaken the activities of immune cells such as T cells and NK cells. On the other hand, suppressing immune inflammation may reduce TRP metabolism along the neurotoxic branch. Overall, the TRP-KYN pathway and the immune system interact and counterbalance each other, which may reflect a degree of disease "self-limitation" and the body's attempt at "self-rescue".

Contrary to these findings, Kruse *et al*. [29] argued that changes in TRP-KYN metabolites do not mediate the relationship between cytokines and depressive mood. However, their study focused on healthy participants, and inflammation-induced depressive symptoms may not fully represent clinical depression. Further research is needed to confirm the role of the TRP-KYN pathway in mediating inflammation and depression, especially in perinatal depression.

Hormones and the TRP-KYN Pathway in Perinatal Depression

Epidemiological research has shown that women are more prone to depression than men [29]. After puberty, the likelihood of women developing severe depression is approximately twice that of men [30]. Hou *et al*. [31] demonstrated direct evidence for the involvement of estrogen and progesterone withdrawal in the development of postpartum depression. However, some studies suggest that perinatal depression may be associated with high levels of postpartum sex hormones.

Gender differences in TRP metabolism have also been observed [32]. A comparative study on severe depression in both sexes showed that women have notably lower levels of KA, KA/3-HK ratio, and KA/QA ratio compared to men [33]. Additionally, progesterone may play a role in immune tolerance by reducing IDO expression at the maternal-fetal interface [34]. In pregnant women, women using oral contraceptives, and men with prostate diseases, estrogen has been shown to increase the urinary excretion of TRP-KYN pathway metabolites, such as XA, 3-HAA, 3-HK, QA, and KA and to enhance the conversion of TRP to NAD^+. Yang *et al*. [35] suggested that higher levels of estradiol may offer a protective effect, while lower levels of estrogen may increase the risk of depression. Moreover, progesterone acts on human macrophages to reduce interferon-gamma (IFN-γ)-induced TRP-KYN pathway activation, leading to decreased QA levels but increased KA levels. The diminished neuroprotective effects associated with low estrogen and progesterone levels align with the hypothesis that the rapid postpartum decline in these hormones may contribute to depression.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been widely implicated in perinatal depression [36]. In individuals with severe depression who have died by suicide, a positive correlation between the KYN/TRP ratio and cortisol suggests that cortisol may enhance TRP metabolism [37]. Animal studies by Qiu *et al*. [38] demonstrated that postpartum corticosterone (CORT)

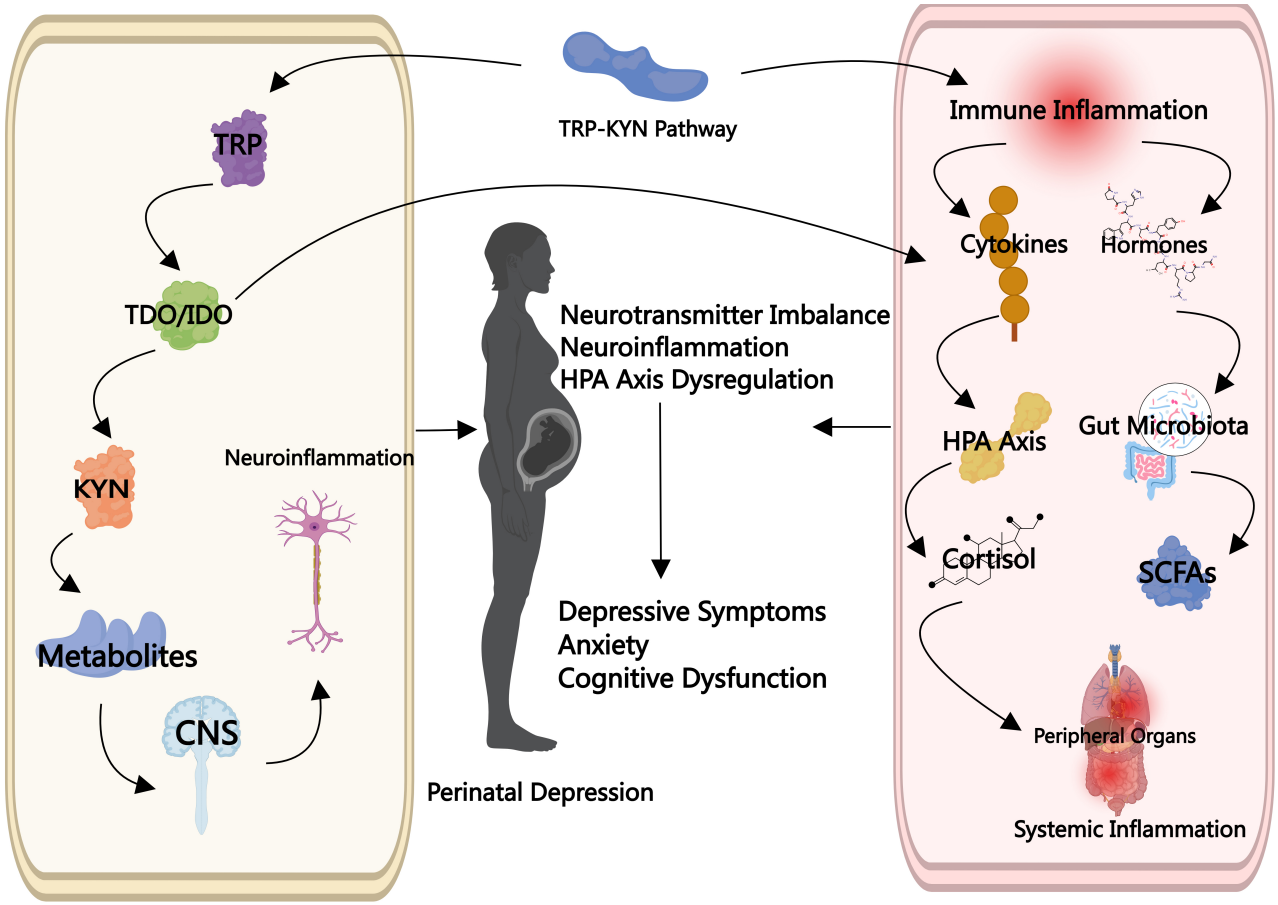

Fig. 2. Interaction of the TRP-KYN pathway with hormones, inflammation, and gut microbiota. This figure depicts the complex interactions between the TRP-KYN pathway and various physiological processes, including immune inflammation, hormones and gut microbiota. Abbreviations: IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan-2,3-dioxygenase; CNS, central nervous system; SCFAs, short chain fatty acids. **Note**: The graphics are produced by medpeer software (V1.3240320, Beijing Maidipel Information Technology Co., Ltd., Beijing, China).

activates the TRP-KYN-QA neurotoxic pathway, increasing neurotoxic metabolites (3-HK and 3-HAA) and the neurotoxic branch coenzyme vitamin B2, and its cofactor flavin adenine dinucleotide (FAD) in the maternal body. In summary, TRP-KYN pathway dysregulation may be associated with HPA axis hyperactivity in perinatal depression.

Gut Microbiota and the TRP-KYN Pathway in Perinatal Depression

Digestive disorders often co-occur with depression, and individuals with gastrointestinal symptoms are significantly more likely to experience depressive symptoms [39]. Postpartum depression patients and healthy women differ significantly regarding the diversity and composition of their gut microbiota [40]. Patients with gut microbiota dysbiosis have a 2.85 times higher risk of developing depression compared to healthy control groups [41]. Therefore, gut microbiota dysbiosis may be a precursor to the development of perinatal depression.

The gut microbiota influences TRP-KYN metabolism through several mechanisms [42]: (1) by modulating the availability of circulating TRP and levels of TRP-KYN metabolism; (2) by influencing the permeability of the blood-brain barrier, thereby affecting the blood-brain barrier permeability of TRP-KYN pathway metabolites; (3) by controlling the maturation and function of microglial cells, which impacts the production of QA; (4) by regulating the expression of NMDAR in the central nervous system. These findings suggest that gut microbiota may influence the pharmacokinetics and pharmacodynamics of TRP-KYN metabolism. Changes in the diversity of the gut microbiota during depressive states can lead to fluctuations in the levels of TRP-KYN pathway metabolism. For instance,

elevated levels of KYN and QA have been observed in depression patients with small intestinal bacterial overgrowth, and antimicrobial therapy has been shown to alleviate TRP metabolism disturbances and depressive symptoms [43,44].

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays a crucial part in immune regulation, maintaining mucosal barrier function, intestinal homeostasis, cell proliferation, and differentiation [12]. TRP metabolism in the gastrointestinal tract is primarily manifested through the following pathways: (1) the gut microbiota can directly convert TRP into indole and its derivatives; (2) IDO1 mediates the activation of the TRP-KYN pathway in the gut; (3) enterochromaffin cells produce serotonin (5-HT) through the action of tryptophan hydroxylase 1 (TpH1). Metabolites from these pathways, such as indole and its derivatives, KYN, cinnabarinic acid (CA), KA, and XA, act as endogenous ligands for AhR [45]. Madison *et al*. [46] demonstrated that AhR agonists, including 3,3′-diindolylmethane (DIM) and 1,4-dihydroxy-2-naphthoic acid ester (1,4-DHNA), have antidepressant effects in female mice. However, further research revealed that transgenic mice with AhR knockout in intestinal epithelial cells were more resilient to chronic unpredictable mild stress, exhibiting less anxiety and improved spatial learning than the control group. Therefore, intestinal AhR exacerbates stress-induced depression. Moreover, the antidepressant effects of DIM and 1,4-DHNA were found to be independent of intestinal AhR expression [47]. In summary, AhR mediates the microbiota-gut-brain axis and interacts with the TRP-KYN pathway. Given the diverse effects of AhR on TRP-KYN pathway enzymes, the emotional effects of AhR intervention may also vary depending on the bias towards TRP-KYN-QA, TRP-KYN-KA, and TRP-5-HT branches. However, the mechanisms underlying the antidepressant effects of AhR agonists like DIM and 1,4-DHNA remain unclear. Questions regarding the differential impact of AhR in various body parts and the safety of these interventions in postpartum women warrant further investigation.

Conclusion

The TRP-KYN pathway plays a pivotal role as a "hub" in perinatal depression, interacting with immune inflammation, hormones, and gut microbiota, leading to systemic effects (Fig. 2). However, this pathway remains underexplored. Current research mainly focuses on the upstream and intermediate metabolites and enzymes, while the downstream substances are less studied. Additionally, existing findings are often contradictory, and specific research on perinatal depression is limited, highlighting the need for further investigation into the TRP-KYN pathway.

Future research should focus on several key areas: identifying brain region-specific or individual differences in the effects of TRP-KYN pathway metabolites, finding effective strategies to enhance the blood-brain barrier permeability of neuroprotective substances while preventing the entry of neurotoxic metabolites into the brain, and developing targeted interventions for perinatal depression that have minimal side effects, low cost, precise efficacy, and good compliance.

Availability of Data and Materials

Not applicable.

Author Contributions

KZ and HL designed the research study. HL and CY performed the research and drafted this manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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