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Kynurenine pathway metabolites as biomarkers in major depressive disorder

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Abstract. The kynurenine pathway (KP) is the main route of tryptophan (TRP) degradation and an important axis of neuroimmune communication. This narrative review summarises clinical and preclinical evidence supporting KP metabolites as candidate biomarkers in major depressive disorder (MDD), with emphasis on KP imbalance and NAD^+ homeostasis. Inflammation-driven activation of indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO), and kynurenine-3-monooxygenase (KMO) can divert flux toward the neurotoxic branch, increasing quinolinic acid (QA) and 3-hydroxykynurenine (3-HK) and reducing kynurenic acid (KYNA) formation. This pattern has been linked to higher symptom burden, phenotype-specific signals (including painful symptoms and suicidality), and impaired neuronal energetics [1, 2, 3]. QA-related excitotoxicity and oxidative stress may converge with NAD^+ depletion and increased NAD^+ consumption under cellular stress, amplifying metabolic vulnerability [3, 4]. We propose that KP dysregulation and NAD^+ deficiency constitute a clinically relevant metabolic-energetic axis in MDD and that biomarker-stratified modulation of KP enzymes and/or NAD^+ support warrants further translational study [4].

Keywords: *Kynurenine pathway; tryptophan; NAD^+; neuroinflammation; depression.*

Introduction. Major depressive disorder (MDD) is increasingly conceptualised as a heterogeneous condition in which inflammatory and metabolic mechanisms contribute to symptom burden and treatment resistance. The kynurenine pathway (KP) metabolises the majority of tryptophan (TRP) and represents an immunometabolic interface linking peripheral immune activation with neuroactive metabolites and brain function [1,2]. A clinically relevant feature of KP is its branching into metabolites with opposing profiles: quinolinic acid (QA) and 3-hydroxykynurenine (3-HK) are associated with oxidative stress and excitotoxic mechanisms, while kynurenic acid (KYNA) is often discussed as relatively neuroprotective,

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albeit context- and concentration-dependent [2,3]. In addition, KP provides the de novo route of NAD^+ biosynthesis from TRP, connecting immune-driven KP changes with cellular energetics and mitochondrial resilience [4].

Aim of the study. To summarise clinical and translational evidence supporting KP metabolites/indices as candidate biomarkers in MDD and to outline metabolic (NAD^+-linked) and therapeutic implications.

Materials and Methods. A narrative review of peer-reviewed clinical and translational literature was performed with emphasis on KP enzymes (IDO/TDO, KMO, KATs, QPRT), KP metabolites (KYN, QA, 3-HK, KYNA), ratio-based indices (KYN/TRP; KYNA/QA), and evidence linking KP activity to inflammation, mitochondrial dysfunction, and NAD^+ homeostasis in MDD [1-4].

Key Findings and Discussion. Inflammatory signalling can upregulate TRP degradation through IDO/TDO and promote a shift of downstream flux (via KMO) toward QA and 3-HK, which aligns with oxidative stress and mitochondrial vulnerability described in mechanistic and review-level evidence [2,3]. This framework supports a plausible immune→KP→brain coupling in biologically defined subgroups of MDD, although directions and magnitudes of individual markers vary across cohorts [5]. Clinical work suggests that KP metrics may better reflect phenotype-defined subgroups rather than a universal MDD signature. For example, higher QA and elevated KYN/TRP have been reported in MDD patients with painful physical symptoms [6], and altered TRP availability with higher KYN/TRP has been linked to suicidality-relevant phenotypes [7]. Central (brain) evidence further supports biologically meaningful subgrouping: sex- and suicide-specific KP alterations, including reduced KYNA-related indices in women, have been described in corticolimbic regions implicated in mood regulation [8]. Importantly, meta-analytic evidence across mood disorder studies highlights substantial heterogeneity and cautions against relying on single KP markers; instead, it supports stratified, multi-marker approaches incorporating clinical covariates (e.g., inflammation, metabolic context, sex) [5]. Because KP contributes to de novo NAD^+ synthesis, sustained inflammatory KP activation may couple with impaired neuronal energetics, particularly when oxidative stress and immune activation increase NAD^+ consumption and destabilise mitochondrial homeostasis [4]. This supports a model in which

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KP dysregulation and NAD^+ deficiency reinforce each other (inflammation → neurotoxic KP shift/oxidative stress → NAD^+ depletion/energy deficit → vulnerability to persistent inflammation), providing a mechanistic rationale for combining KP-oriented and NAD^+-supportive strategies in selected subgroups [4,5].

Table 1

Key enzymes of the kynurenine pathway

Enzyme	Localisation (main)	Reaction catalysed	Key regulator/ inductor	Clinical significance
Tryptophan 2,3-dioxygenase	Liver, CNS	Oxidation of tryptophan to N-formylkynurenine	Glucocorticoids, tryptophan	Regulation of systemic tryptophan levels, activation during stress
Indoleamine 2,3-dioxygenase (two isoforms)	Lungs, small intestine, placenta	Oxidation of tryptophan to N-formylkynurenine	IFN-γ	An immunometabolic enzyme plays a role in immune defence, often expressed by tumour cells
Kynurenine-3-monooxygenase	Neurons, microglia	Conversion of kynurenine to 3-hydroxykinurenine	Vitamin B2-dependent enzyme	Formation of a neurotoxic metabolite
Kynurenine aminotransferases (4 isoforms)	Astrocytes	Conversion of kynurenine to kynurenic acid	Vitamin B6-dependent enzyme	Formation of neuroprotective metabolite
Quinolinic acid phosphoribosyl transferase	Neurons, microglia	Conversion of quinolinic acid to nicotinic acid mononucleotide (precursor of NAD^+)	Energy deficiency	Key step in the de novo synthesis of NAD^+ and the detoxification of quinolinate

Therapeutic Implications. Given heterogeneity, KP biomarkers are most promising for stratification and monitoring rather than universal diagnosis. Mechanism-guided directions include: (1) reducing neurotoxic flux by targeting branch-point enzymes (notably KMO) and upstream activation (IDO/TDO) in relevant phenotypes, (2) attenuating downstream excitotoxic signalling where QA-related mechanisms are suspected, and (3) supporting metabolic resilience via NAD^+-linked interventions, ideally in a biomarker-defined framework [2,4,5].

Conclusions. To date, the serotonin theory of major

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depressive syndrome remains dominant, so SSRIs remain first-line therapy. However, meta-analytic clinical evidence indicates substantial heterogeneity among KP biomarkers for depression, and some markers (e.g., KYN/TRP) do not show consistent differences across studies, supporting cautious causal interpretation and biomarker-stratification approaches. Nevertheless, current data convincingly show that an imbalance in the kynurenine pathway and reduced NAD^+ constitute an independent metabolic-energetic axis in the pathogenesis of depression. The interaction among immune activation shifting toward neurotoxicity, quinolinic acid accumulation, reduced quinolinate phosphoribosyltransferase, and NAD^+ deficiency leads to chronic metabolic exhaustion of neurons. One approach that already accounts for kynurenine pathway disturbance in depression is ketamine use, which affects NMDA receptors and reduces the neurotoxic effect of quinolinic acid on them. Prospects for depression treatment targeting the kynurenine pathway will likely include drugs that inhibit enzymes promoting a shift toward neurotoxicity, such as indoleamine 2,3-dioxygenase, tryptophan 2,3-dioxygenase, and kynurenine-3-monooxygenase; drugs that stimulate quinolinate phosphoribosyltransferase; or approaches that directly modulate quinolinic acid levels in the CNS. Diagnosis of depressive disorders may include measuring kynurenine levels, pathway intermediates, and products to prescribe more specific and individualised therapy for patients.

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