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Pitching Edge of Cellular and Molecular Process of Kynurenine Pathway in Neuronal and Non-Neuronal Conditions

[1]Sneha KK, [2]Venkatesh G, [3]Chandrasekar V, [4]Deepika R, [5]Swarnabala S

[1]M. Pharm, Department of Pharmacology, KMCH College of Pharmacy, Coimbatore, India
[2]Associate Professor, Department of Pharmacology, KMCH College of Pharmacy, Coimbatore, India
[3]M. Pharm, Department of Pharmacology, KMCH College of Pharmacy, Coimbatore, India
[4]M. Pharm, Department of Pharmacology, KMCH College of Pharmacy, Coimbatore, India
[5]M. Pharm, Department of Pharmacology, KMCH College of Pharmacy, Coimbatore, India

Abstract: Tryptophan has several metabolic pathways, about 95% of tryptophan involves in the kynurenine pathway. Organs including the brain, liver, and immune cells are involved in this pathway. Many substances of biological importance are formed on the kynurenine pathway which involves kynurenine, quinolinic acid, kynurenic acid and anthranilic acid. In recent years, this pathway has received attention in the scientific community due to its involvement in neurotoxic, neuroprotective, anti-inflammatory, antidiabetic, anti-cancer, Huntington's disease, seizures, cardiovascular disease, osteoporosis, and immune properties. An imbalance of this pathway causes immune system activation and the production of different compounds such as neurotoxic compounds, which makes the kynurenine pathway a promising target for therapeutic intervention. This review aims to correlate migraine, Parkinson's disease, Alzheimer's disease, Inflammation, Rheumatoid arthritis, and Acute and chronic kidney diseases with the Kynunerine pathway.

Keywords: **Tryptophan, Kynurenine pathway, Kynurenic acid, Quinolinic acid.**

1. INTRODUCTION:

Tryptophan (TRP), an essential amino acid, is converted into several bioactive compounds, including serotonin also known as 5-hydroxytryptamine (5-HT), nicotinamide adenine dinucleotide (NAD^+), and melatonin (MT). About 1 to 5 percent of TRP takes part in the methoxy indole pathway, which results in the creation of MT and 5-HT, whereas 90 to 95 percent of TRP is used in the TRP-KYN pathway, which produces NAD^+ and other beneficial chemicals. Many organs and cell types, including the brain, liver, gut, and immune cells contribute significantly to the pathway. Adenosine triphosphate (ATP) production occurs through NAD^+ which is a crucial compound in the electron transport process of mitochondrial respiratory chain. A number of enzymatic processes and the storage of glycogen in the brain are both aided by ATP. The process also generates a variety of other bioactive compounds in addition to NAD^+ [1].

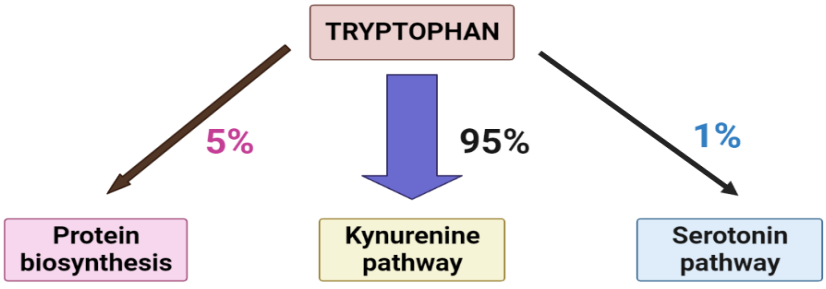

Figure 1: Tryptophan Degradation

In the 1990s, breakthrough findings increased the study of Trp. Significantly, research from Munn and Mellor 1998 demonstrated that Indoleamine 2,3-dioxygenase (IDO) is necessary for maternal immunological tolerance during pregnancy and that pharmacological suppression of IDO causes abortion [2]. Research in the field was expanded beyond neurological problems as a result of this, the Kynurenine pathway (KP) can be brought on by inflammation. For example, it has been known since the 1950s that the KP is activated in particular cancer types [3, 4]. IDO has been thought of as a crucial immune-escape mechanism of these cells, although it wasn't established that malignancies can express IDO until the 2000s [5].

The KP's immune-regulatory abilities are now reported in autoimmune and chronic inflammatory disorders, including atherosclerosis, even outside the central nervous system (CNS). It has been hypothesized that enhanced IDO expression and activity result in microenvironmental Tryptophan (Trp) depletion and a larger intracellular pool of uncharged transfer ribonucleic acid that binds tryptophan ($trna^{Trp}$) as one of the mechanisms through which the KP modulates immunity. The General Control Nonderepressible 2 (GCN2) detects uncharged tRNAs, which inhibits ribosomal mRNA translation, protein synthesis, and immune cell division by phosphorylating Eukaryotic Initiation Factor 2 Kinase (eIF2K) [6].

However, the fact that Interferon-gamma (IFN-γ) stimulation not only produces IDO but also tryptophanyl-tRNA synthetase [7] (which replenishes the pool of uncharged $tRNA^{Trp}$) and that Trp depletion-mediated responses can only happen when this amino acid is "non-physiologically" absent and almost entirely absent [8] suggests that mechanisms other than Trp depletion could be triggered upon the induction of the KP. It has been found that some Trp metabolites in this state are bioactive and affect both immune and non-immune cells. Trp supplementation was prohibited by the US Food and Drug Administration (FDA) in the late 1980s because it was associated with an elevated risk of eosinophilia-myalgia syndrome (EMS) [9]. EMS was later connected to an impurity, 3-(phenylamino)-L-alanine (PAA), of L-Tryptophan (L-Trp) production from a single source, according to epidemiologic tracing investigations [10]. The FDA removed the restrictions on L-Trp dietary supplements in 2005.

It's interesting to note that Trp has recently been discovered to be an endogenous ligand for G-protein coupled receptor 139 (GPR139) and G-protein coupled receptor 142 (GPR142) [11, 12]. It has been demonstrated that GPR142 ligation controls immunological function as well as glucose homeostasis [13]. It is interesting that using a GPR142 agonist or having a GPR142 deficit has been associated with less severe collagen antibody-induced arthritis (CAIA) in mice [13], which urges further research. Activated T cells, monocytes, and epithelial cells can undergo apoptosis when exposed to 3-Hydroxy kynurenine (3-HK), 3-hydroxy anthranilic acid (3-HAA), and Quinolinic acid (QA) [14,15,16]. Nitric oxide (NO) generation [17] and adherence of monocytes in flow circumstances [18] are two examples of how Kynurenine acid (KynA) and Kynurenine (Kyn) modify endothelial cell responses.

Moreover, Kyn has been linked to the development of Tregs in the thymus [19] and the suppression of T cell interferon (IFN) production [20, 21] through its interaction with aryl hydrocarbon receptor (AhR). Surprisingly, dendritic and cancer cells have been found to have an autocrine IDO-Kynurenine/AhR-IDO loop that functions

as an inhibitory feedback mechanism [22, 23]. KynA can counteract the effects of 3-HK, 3-HAA, and QA on the central nervous system (CNS) [24], as well as interactions with the aryl hydrocarbon receptor (AhR) [25], G protein-coupled receptor 35 (GPR35) [26], and possibly the alpha-7 nicotinic receptor [27].

2. KYNURENINE PATHWAY:

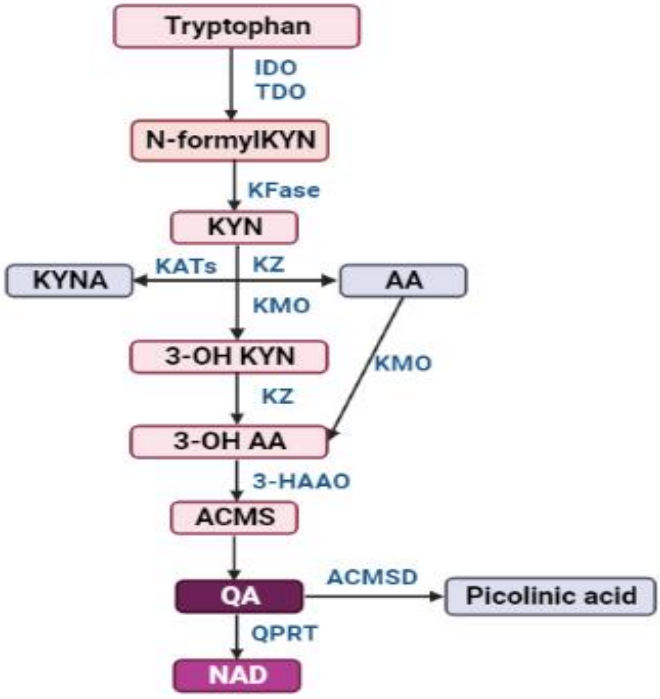

Figure 2: Kynurenine pathway. IDO or TDO converts tryptophan into serotonin or N-formyl KYN. Later, the synthesized Kynurenine can be converted into AA, 3-OHKYN, or KYNA. The final product, NAD, is produced after the 3-OHKYN has been converted into XA and QA. *IDO indoleamine 2,3-dioxygenase, TDO Tryptophan 2,3-dioxygenase, N-formylKYN N-formyl kynurenine*, *KYN* kynurenine, *KYNA* kynurenic acid, *AA* anthranilic acid, *KAT* kynurenine aminotransferase, *KZ* kynureninase, *KMO* kynurenine 3-monooxygenase (Kynurenine 3-hydroxylase), *3-OHKYN* 3-hydroxykynurenine, 3-OH AA 3-hydroxy anthranilic acid, 3-*HAAO* 3-hydroxy anthranilic acid dioxygenase, ACMS α-amino-β-carboxymuconate semialdehyde, *QA* quinolinic acid, ACMSD α-amino-β-carboxymuconate semialdehyde decarboxylase, *QPRT* quinolinic acid phosphoribosyltransferase, *NAD* nicotinamide adenine dinucleotide.

The liver has a significant degradative process called the kynurenine pathway that produces NAD^+ from tryptophan. The key rate-limiting stages that result in a number of illnesses include the formation of N′-formyl kynurenine (NFK) from tryptophan (TRP) by TDO either in the liver or extra hepatically by IDO-1 [28]. In this process, the enzyme NFK formamidase converts NFK into Kynuneurine (KYN). Additionally, the enzymatic activity leads to the hydroxylation of KYN to 3-HK by means of KMO, then to 3-HAA by kynureninase through hydrolysis. In addition to 3-HAA, this route also produces 2-amino-3-carboxymuconoate semialdehyde. Desalination of kynurenine to KYNA occurs through KAT (I, II, and III), kynureninase can also hydrolyze kynurenic acid (KYN) to anthranilic acid (AA) [29].

Most of the KP metabolites in the brain generate 3-HK in the microglia and astrocytes. By producing free radicals in normal cells, 3-HK causes neurodegeneration and neuronal death. Kynureninase changes 3-HK into quinolinic acid (QUIN) in the afflicted cells, which may contribute to neurotoxicity and neurological dysfunction. However, QUIN and other excitotoxins are observed to be blocked by the KYNA metabolite [30]. In addition to providing protection from excitotoxicity that was brought on by NMDA receptor-mediated excitotoxicity, glutamatergic signaling is also altered by the ratio of KYN metabolites. These findings proof that KP plays a significant part in physiological circumstances.

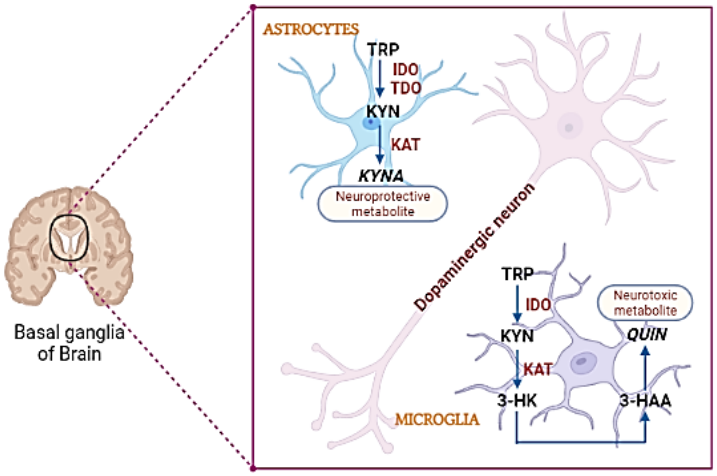

Figure 3: Kynuneurine pathway in the brain and its effects. *TRP* Tryptophan *IDO indoleamine 2,3-dioxygenase, TDO Tryptophan 2,3-dioxygenase, KYN* kynurenine, *KAT* kynurenine aminotransferase, *KYNA* kynurenic acid, *3-HK* 3-hydroxykynurenine, *3-HAA* 3-hydroxy anthranilic acid, *QUIN* quinolinic acid.

The Kynuneurine (KYN) pathway generates a number of and bioactive molecules with a variety of activities, including anti-inflammatory, neurotoxic, oxidative, neuroprotective, antioxidative, and antidiabetic, as well as activities against Huntington's disease, seizures, cardiovascular disease, osteoporosis, and immune properties and also a number of small receptor agonists [31].

Enzymes	Clinical Condition
TDO	Cancer, porphyria, major depressive disorder.
IDO	Cancer, neurodegenerative disorders, neurological diseases, and immune diseases.
KMO	Schizophrenia, drug dependence, infectious diseases
KAT	Schizophrenia
3-HAAO	Neurological diseases
QPRT	Inflammatory disorders

Table :1 Enzymes involved in the Kynurenine pathway targeted for treatment purposes.

3. MIGRAINE:

Migraine is a common brain illness that causes excruciating headaches and other neurological indications. It can be episodic or chronic, with or without aura, and it can happen before, during, or without a headache attack [32]. Trp metabolites have the potential to affect the glutamatergic system, which plays a role in cortical spreading depression (CSD), central sensitization, and pain transmission [33]. The pathophysiology of migraines is influenced by the glutamatergic ionotropic and metabotropic receptors [34]. A subset of these receptors known as N-methyl-D-aspartate receptors (NMDA) is required for the onset of CSD and the

stimulation of the migraine generator, an area of the brainstem that is specifically active during a migraine attack. [35].

In many neuropathological conditions, including migraine pain, KYNA, and its analogs may have modulatory effects by antagonistically binding to NMDA receptors [36]. Nitroglycerin-induced hyperalgesia was abolished by kynurenic acid homolog-enhanced Calcitonin gene-related peptide expression (CGRP) in a rat model of migraine. At the trigeminal level, Kynurenic acid analog A1 (KYNA-A1) inhibits Nitroglycerin (NTG) induced hyperalgesia by modifying the transcriptional activity of genes involved in the production of CGRP, Neuronal nitric oxides synthase (nNOS), and proinflammatory cytokines in Thyroglobulins (TGs) and central regions. In the nucleus trigeminal caudalis (NTC), KYNA-A1 additionally inhibited the rise in nNOS proteins and the decrease in CGRP release. It also shows that it reduced the mRNA expression of cytokines after NTG injection [37].

3.1. TRYPTOPHAN – INDOLE – KYNURENINE - NIACIN PATHWAY IN MIGRAINE:

The synthesis of proteins, serotonin, tryptamine, melatonin, and kynuramines, as well as other metabolic processes, all require the amino acid tryptophan [38]. Two fundamental metabolic pathways such as the indole-kynurenine-niacin pathway and the serotonin-melatonin pathway are used by the organism to break down tryptophan [39]. Tryptophan is metabolized and destroyed through the kynurenine route, where 99% of it is converted into neuroactive substances known as kynurenines that inhibit the NMDA receptors [40]. The KP metabolites and the enzyme involved in this pathway have been shown in several studies of neurological illnesses to be up-regulated or down-regulated in association with disease [41]. A correlation between kynurenine metabolite changes and 21 patients with cluster headaches was recently found by Curto et al., [42]. Studies also discovered kynurenine metabolite alteration in the serum of individuals who had persistent migraines [43]. In fact, the accumulation of kynurenines within the CNS and inhibition or activation of enzymes in kynurenine pathway have been proposed as potential therapeutic approaches. However, this therapy approach's promise for treating migraines has not yet been tested [44].

Researchers have used the tryptophan depletion approach to examine depressed mood stages and peripheral and central serotonin turnover in Acute Tryptophan Depletion (ATD). Research in healthy individuals revealed a link between a reduction in central serotonin turnover and tryptophan depletion. The tryptophan-serotonin relationship was first discovered in 1970 and has been established in animal models [45], suggesting that this mechanism may play a role in human serotonin-related illnesses. [46]. Variations in the serotonin-dependent brain processes and depression that occurs in the peripheral blood plasma can affect the nervous system functions [47]. Dietary and nutritional changes can affect the level of precursors for neurotransmitter production in the brain as well as the rates at which neurons synthesize these neurotransmitters. Migraine sufferers who lack tryptophan experience more nausea, headaches, and photophobia [48]. With L-tryptophan supplementation, headache indices were significantly lower than with a placebo, according to two investigations conducted in the 1970s on headache sufferers [49, 50]. Tryptophan has not been fully utilized for both therapeutic and scientific objectives. Understanding the complicated serotonergic biochemistry of migraine will

benefit from more investigation of the link between tryptophan (plasma) and serotonin metabolism (brain) in healthy and pathological conditions.

4. PARKINSON'S DISEASE:

Parkinson's disease (PD) is the most prevalent neurological movement disorder. Tremor, rigidity, bradykinesia/akinesia, and postural instability are its primary motor symptoms, although the clinical evidence also includes other motor and non-motor symptoms (NMS). Loss of dopaminergic neurons located in the pars compacta of substantia nigra (SNpc) and accumulation of misfolded α-synuclein, which is present in intracytoplasmic aggregates known as Lewy bodies (LBs), are the pathological hallmarks of PD [51]. In animal models of PD, increased levels of KYNA in the brain can protect nigrostriatal dopamine neurons from damage brought on by excitotoxins like QUIN. They used QUIN infusions to lower the levels of KYN and KYNA in the rat brain. Furthermore, the excitotoxicity limit can be lowered by low KYNA concentrations. When L-dopamine (L-DOPA) and D-amphetamine were combined, there was a noticeable drop in KYNA levels in rat brains [52]. While KATs were shown to be more abundant in PD patients' RBCs, their KAT-I and KAT-II activity decreased along with their levels of KYNA in their plasma. Additionally, KAT-II inhibition raises striatal dopamine levels by a factor of two to three, which can be guarded against by taking KYNA concurrently [53].

Therapy with L-DOPA can modify the glutamatergic pathway that results in L-DOPA-induced dyskinesia (LID) as well as the concentration of kynurenine metabolites. The first indication of KP impairment in PD appeared in the early 1990s. Ogawa et al. stated that TRP/KYN and KYNA/TRP ratios in the frontal cortex, putamen, and SNpc of PD patients were significantly elevated and the 3-HK levels were higher in the putamen and SNpc [54]. PD patients who had been administered L-dopa had considerably low KYN and KYNA levels in their frontal brains. Similarly, the KYN/3-HK ratio was considerably reduced in the frontal cortex and pars compacta of substantia nigra of PD patients treated with L-dopa, and solely in the putamen of patients not given L-dopa. Another research observed a drop in KYNA levels in the cerebellum, cortical areas and caudate of PD patients [55].

The expression of KAT-I is decreased in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated mice of SNpc [56]. The same group also showed that *6-hydroxydopamine* (6-OHDA) injections into adult rats' lateral ventricles result in the loss of the majority of their nigral neurons and that tyrosine hydroxylase (TH) and KAT-I are co-expressed in the same SNpc neurons. The authors also found that microglia only developed immunoreactive KAT-I after 6-OHDA, astrocytes in the SNpc expressed KAT-I under normal circumstances and elevated after 6-OHDA injection. In comparison to age- and gender-matched healthy controls, elevated KYN/TRP ratios have also been seen in the cerebral spinal fluid (CSF) and serum of people with Parkinson's disease [57].

5. ALZHEIMER'S DISEASE:

Wide portions of the hippocampus and cerebral cortex are affected by Alzheimer's disease (AD), which is a neurodegenerative disorder that progresses unabatedly and without remission. Typically, abnormalities are first found in the frontal and temporal lobes of the brain before progressively spreading to other sections of the

neocortex at rates that vary greatly between persons. AD is characterized by the buildup of tau protein aggregates in neurofibrillary tangles and the deposition of insoluble forms of amyloid (A) in plaques in extracellular spaces as well as in blood vessel walls [58]. In addition to activating NMDA receptors, quinolinic acid may trigger the expression of many immunologically active molecules, such as Interleukin-8 (IL-8), Chemokine Ligand-5 (CCL5), Macrophage Inflammatory Protein-1 (MIP-1) in astrocytes and several chemokine receptors, including CXCR4, CXCR6, CCR3, and CCR5, which help leukocytes pass the blood-brain barrier [59, 60]. It has been proposed that KYN pathway may be implicated in the cause of AD because of the finding that β-amyloid promotes IDO production and the fact that patients with Alzheimer's condition have higher levels of numerous of these proteins in their brains. This hypothesis is reinforced by the fact that these proteins are found in greater amounts in the brains of these patients [61, 62].

Quinolinic acid has the ability to start a positive feedback cycle that results in the production of more quinolinic acid, cell activation, the induction of mediators, and further stimulation from which it might be difficult for cells to break out. Quinolinic acid activates NMDA receptors, which increases glial growth and intensifies these processes [59, 63]. The elevated kynurenine pathway activity in Alzheimer's disease [64-67] has been associated with tau hyperphosphorylation and β-amyloid formation, both of which can be triggered by quinolinic acid [63-65, 68-70]. Also, there is solid evidence that kynurenines contribute to the development of neurofibrillary tangles and senile plaques [67]. Plaque growth, neuronal death, and cognitive impairment are all suppressed by IDO1 inhibition [71].

In order to regulate the release of inflammatory mediators, neuronal ACMSD **(Figure 2)** causes 3HAA to be diverted from quinolinic acid to picolinic [72-74]. Additionally, it guards against some of the negative consequences of quinolinic acid, including its toxicity against cholinergic and dopaminergic neurons [71-73]. Studies proposed components of the KYN pathway had a crucial part in the development of suicidal thinking and behavior [78].

Inflammatory mediators such as IDO-1, which is produced by IFN-γ, cytosine-phosphate-guanosine (CpG) in antigen-presenting cells (APC) and lipopolysaccharide (LPS) [79-81], tightly regulate a number of enzymes in the KP. Reduced Trp levels inhibit microbial growth, as well as T cell proliferation and the accumulation of downstream KP metabolites, KYN, which can activate AhR in lymphoid tissues and promote the formation of Treg cells [82]. As the KP is activated, more NAD^+ is produced, which increases energy generation, DNA repair, and genomic signaling, and plays a significant part in antioxidant defense processes [83]. After being shielded from reactive oxygen species (ROS), Caenorhabditis elegans have been shown to survive longer when supplemented with NAD^+ [84]. The sirtuins (SIRT 1-7) play a role in mediating cellular adaptations like an enhanced function of mitochondria and maintaining genomic stability, which helps to explain in part how calorie restriction lengthens lifetime. With aging, the activity of these proteins may decrease, which could cause a decrease in NAD^+ [85, 86]. Many researchers have examined various NAD^+ precursors as possible AD treatments. In 3xTg AD mice, nicotinamide (NAM) treatment enhanced cognitive function, reduced Aβ and tau

pathologies, and increased NAD^+ levels and proteins associated with cell survival and plasticity, such as ERK42 and cAMP-response element (CREB) [87].

However, the development of neurodegenerative diseases like AD may be particularly relevant to persistent KP activation [88]. For example, Amyloid β (Aβ) plaques are frequently surrounded by active microglia in the CNS and IDO-1 colocalizes with Neurofibrillary tangles (NFT) and Aβ plaques [89]. QUIN is an NMDA receptor agonist which is produced downstream of KMO and causes glutamatergic excitotoxicity when used in excess. It also increases glutamate release by neurons and inhibits glutamate reuptake by astrocytes, which results in elevated glutamate concentrations in the microenvironment [90]. Additionally, it has been demonstrated that QUIN causes tau hyperphosphorylation in human cortical neurons [91].

Additional findings showing a connection between the KP and AD include raised 3-HK in AD patient serum [92], higher KYN/Trp ratio in AD serum in relation to elderly controls [93], reduced Trp, 3-HAA, and XA in histopathologically confirmed AD plasma [94], the build-up of QUIN in the hippocampus of AD patients [62], and enhanced expression of TDO and IDO-1 immunoreactivity in both the hippocampus and the cortex of AD patient [67, 89]. In addition, compared to controls who had identical age and gender but no obvious risk of developing AD, female participants with pre-clinical AD (characterized by high neocortical amyloid-β load) had greater serum levels of KYN and AA [95].

6. INFLAMMATION:

KP is the only pathway in typical human physiology that can create nicotinamide adenine dinucleotides (NAD^+) from scratch. It also serves as a counter-regulatory mechanism that decreases immune responses during inflammation. Growing evidence suggests that inflammation plays a significant role in TRP influx into the KYN pathway and that KP metabolites play a significant regulatory role in the inflammatory response. By promoting IDO expression during inflammation, pro-inflammatory cytokines, particularly tumor necrosis factor (TNF) and interferon (IFN), lift the catabolism of TRP down the KP [96]. This leads to an increase in all KP metabolites from the sub-branches, including KYNA and NAD+. Increased flux down the KP during inflammation is believed to serve two vital purposes: it stimulates immune responses and exists as a counter-regulatory mechanism for controlling inflammation [97].

One of the most prevalent inflammatory diseases is Rheumatoid arthritis (RA), whose therapy has been transformed by the development of substances that block the Tumor Necrosis Factor alpha's (TNF-α) proinflammatory action. Alternative methods of modifying TNF-α levels or receptors are being researched because, in up to 50% of RA patients, these medications do not work as well as they should or cause response loss over time. The inflammatory processes in arthritic joints may be controlled by kynurenic acid. SZR72, a synthetic analog of KYNA, has been demonstrated in studies to increase levels of TNF-stimulated gene 6 while lowering the production of TNF in whole blood samples of RA patients. IDO1 activation has been reported in another investigation to alleviate the signs and symptoms of experimental arthritis. In fact, systemic administration of the same analog and kynurenic acid alone mitigates a lot of the negative effects of pancreatic inflammation and acinar cell death in an animal model [98].

The authors were able to prevent pulmonary inflammation by extending the theory to explain why there were fewer inflammatory-activated $CD11c^{+}$ cells in the lungs. It is widely known that kynurenines, especially the active form, kynurenine, promote the growth of regulatory T cells while suppressing the development of pro-inflammatory Th17 cells. TRP metabolism inhibits long-lasting immunological tolerance and regulates hyperinflammation. These results rely on IDO's capacity to change the regional and systemic KYN/TRP balance. This equilibrium has a direct effect on the metabolic and immunological signalling pathways that regulate defence against inflammation in IDO-competent cells which include epithelial cells and antigen-presenting cells. Furthermore, it creates a local (rarely systemic) milieu that is rich in KYN and low in TRP, altering the function of neighbouring cells (like T cells). Several biochemical processes serve as the mediating agents for immunological and non-immune responses to changes in intracellular TRP and KYN levels [99].

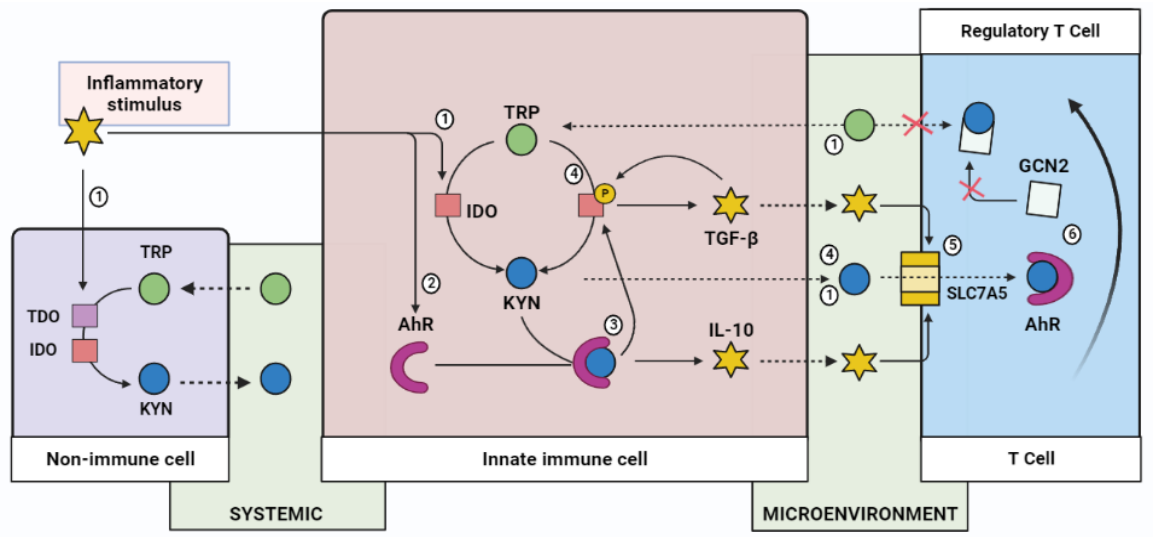

Figure 4: TRP metabolism-related mechanisms for controlling inflammation. IDO (and occasionally TDO) is activated when immune and non-immune cells are subjected to inflammatory stimulation, which results in decreased local and systemic Tryptophan levels and increased intracellular and extracellular KYN levels (1). AhR expression is raised through inflammation (2), and the production of anti-inflammatory cytokines like IL-10 is induced by AhR's ligand KYN (3). When AhR ligands are activated, IDO is phosphorylated as a result, which also causes persistent IDO activity and the production of TGF-β, which takes part in a feedback loop that facilitates the phosphorylation of IDO (4). Inflammatory cytokines like TGF-β and IL-10 stimulate the amino acid transporter SLC7A5 on the plasma membrane of naive T-cells, which then allows KYN to enter the T cell (5); Naive T cells become differentiated into regulatory T cells as a result of TRP depletion-induced activation of GCN2 and KYN-induced AhR ligand activation (6). The regulation (transcription or translation) and enzymatic actions of TRP and KYN are indicated by solid arrows, while active or passive cross-compartmental and cross-cellular transport are indicated by dashed arrows. Trp Tryptophan, Kyn Kynurenine, IDO indoleamine 2,3-dioxygenase, TDO tryptophan 2,3-dioxygenase, TGF-β tissue growth factor beta, IL-10 interleukin 10, AhR aryl hydrocarbon receptor, GCN2 General Control Nonderepressible 2 Kinase, SLC7A5 solute carrier transporter 7a5.

A neurodegenerative condition with late onset is ALS (Amyotrophic Lateral Sclerosis). Numerous neurodegenerative illnesses, including ALS, have been functionally linked to neuroinflammation and the kynurenine pathway. In individuals with sporadic ALS, 18 genes associated with the breakdown of tryptophan

were examined by Fifita et al. for their genetic contribution. They came to the conclusion that four genes directly affected the production of KYNA from 3-OHKYN, and these genes may be closely linked to sporadic ALS and increase the likelihood of getting the condition [100].

7. ACUTE KIDNEY INJURY AND CHRONIC KIDNEY DISEASE:

Acute kidney injury (AKI) is the medical term for a brief loss of kidney function (within 7 days) that results in an accumulation of urea and other nitrogenous wastes in the blood. A wide range of etiological factors, including ischemia, sepsis, and drug-induced toxicity, are included in this clinical condition [101]. An abnormal Glomerular filtration rate (GFR) of about 60 mL/min/1.73 m^2 or chronic proteinuria is used to identify Chronic kidney disease (CKD), which can be described as a dysfunction of the kidney function or kidney structure for at least 3 months. Diabetic kidney disease, hypertensive nephrosclerosis, and glomerulonephritis are the three most prevalent forms of CKD [102].

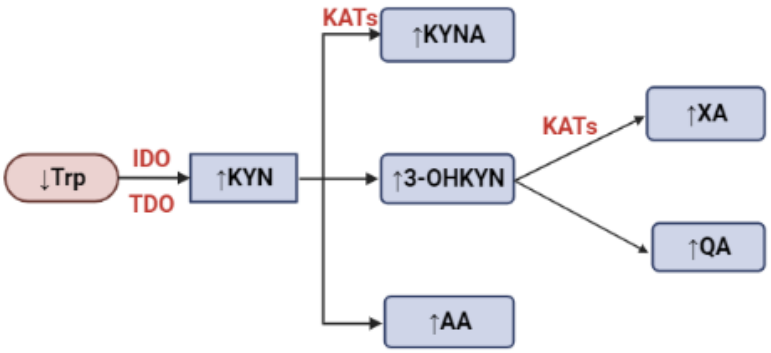

Figure 5: Alterations in the KYN pathway during CKD. Low serum concentrations of Trp were found in CKD in animal and human studies. In contrast, high serum KYN, 3-OHKYN, KYNA, AA, QA, and XA were noticed, suggesting the activation of the kynurenine pathway in CKD. *Trp* tryptophan, *KYN* kynurenine, 3-*OHKYN* 3-hydroxy kynurenine, *AA* anthranilic acid, *IDO* indoleamine 2,3-dioxygenase, *TDO* tryptophan 2,3 dioxygenase, *KAT* kynurenine aminotransferase, *KYNA* kynurenic acid, *QA* quinolinic acid, *XA* xanthurenic acid.

Metabolomics studies have demonstrated that the KP metabolites are significantly altered in animal models and human patients with AKI or CKD. Human observational studies that were both cross-sectional and longitudinal have demonstrated the diagnostic and prognostic value of the KP metabolite in both AKI and CKD. To investigate the biological effects of KP on the pathophysiology of AKI and CKD, experimental models with various aetiologies have been employed. In AKI, the etiology of the damage determines the magnitude and direction of variations in the kynurenine pathway. In CKD, KP metabolites are changed from the beginning of the disease through its advanced stages, including uremia and its associated vascular complications [103]. In animal models of glomerulonephritis, activation of the KP was reported to give protection, and may involve the regulation of T cell subsets including regulatory T cells and T helper 17 cells (Th17) via the immunomodulatory mechanism. In animal models of AKI, manipulation of the KP to boost NAD^+ synthesis or direct it towards particular benefits of KP metabolites has also been discovered.

Potential biomarkers for hypertension-related kidney damage include KP metabolites. There is a distinct difference between renovascular hypertension and hypertensive nephrosclerosis from an etiological standpoint

(hypertension secondary to kidney diseases). In an observational study, KYN was one of the top five metabolites that might differentiate people with biopsy-proven hypertensive nephrosclerosis from subjects who were healthy [104]. Increased levels of KYN, KYNA, 3-HK, and AA as well as decreased levels of TRP were seen in the renovascular hypertension of rat model, with KYN showing an independent relationship with mean blood pressure [105].

Observational research indicated that individuals with chronic glomerulonephritis-related renal failure had greater levels of KYN than healthy controls [106]. A brief pilot study on individuals suffering from IgA nephropathy revealed a correlation between proteinuria and KYN and disease severity [107]. It's interesting to note that the serum and renal tissue KYN/TRP ratios were elevated in a mouse model of crescentic glomerulonephritis. IDO was found to be upregulated in the mouse glomerulus and renal tubular epithelial cells by immunohistochemistry [108].

8. RHEUMATOID ARTHRITIS:

The distinction between tissue and immune cells is clear in peripheral inflammatory diseases like rheumatoid arthritis (RA). In this condition, reduction in the joint space volume is due to pannus development, leukocyte infiltration, and local tissue trauma and degeneration. As a result of cellular infiltration and cytokine release, tissue damage eventually occurs. This creates a positive feedback cycle where the deteriorating joints worsen the inflammatory reaction, which then has the effect of hastening the erosion of the bone and joints. The kynurenine metabolites in this situation have been the subject of significant evidence on the first enzymes of the system (IDO and tryptophan-2,3-dioxygenase, TDO), whose isoforms have been widely investigated [109].

The B7 complex on dendritic cells (DCs) interacts with the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) made up in the membranes of regulatory T cells to regulate IDO1. Transforming Growth Factor (TGF) and mediators associated with inflammation act to control this ligation, which is initiated and activates IDO1 in the DCs through non-canonical Nuclear Factor-κβ (NF-κβ) actions. This route serves as a vital link between arthritic damage and the KYN pathway and is one of the key mechanisms for the steady, long-term maintenance of immunological tolerance [110]. As a result, we were able to show that RA patients had a malfunction in IDO1 induction that affected the interaction between B7 and CTLA-4 in the immune system. This defect's mechanism was determined to be abnormal DNA methylation at the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) promoter, which resulted in a loss of Treg cells and worsened symptoms in the patients [111]. As a result, in IDO1-/- animals, the effect of arthritic aggravation was replicated by genetically impaired IDO1 activation. Even though the precise aetiology of these events is yet unknown, IDO in DCs clearly plays a crucial part in the cycle of RA development, progression, and remission.

Kynurenine administration is a straightforward process that can lessen the extent of tissue damage and impairment [112], suggesting a potential route for innovative therapeutics. The ratio of KYN to TRP levels in the blood or tissues has become a recognized indicator of immune system activation despite the lack of complete knowledge of changes in the levels and relative proportions of metabolites downstream of kynurenine 3-mono-oxygenase (KMO). Evidence suggests that the decreased availability of tryptophan and other downstream

metabolites is how the effects of IDO activation are mediated. The immediate effects of these chemicals on the immune system control the initiation, progression, and termination of immunological responses to infection or tissue damage.

While the relative importance of tryptophan deprivation and KYN metabolite activity in immune system modulation are still being debated [113, 114], it is likely that both mechanisms are important to a lesser extent. Although TRP is oxidized (to KYN) by IDO or TDO, the alterations in tryptophan concentration in blood or CSF are typically negligible. The main physiologically active molecules in the kynurenine pathway are KYN and its metabolites. The statistically important parameter is the quantification of the kynurenine: tryptophan (K/T) ratio which is a common component of behavioral research in experimental animals or clinical research in people. Tryptophan depletion probably mediates its effects by activating the Generalised Controller Non-derepressible-2 Kinase (GCN2), a sensor of cellular amino acid levels [114-116]. The availability of tryptophanyl-tRNA molecules, which activate GCN2, increases as tryptophan concentrations drop. Consequently, by lowering proliferation and promoting death, IDO-expressing cells like plasmacytoid DCs can promote T-cell senescence [114, 117]. Although GCN2 is typically thought to be required for the interaction between tryptophan shortage and the suppression of the cell cycle, it's likely that this association functions differently in clusters of differentiation 4 ($CD4^+$) and clusters of differentiation 8 ($CD8^+$) T cells [118]. The kynurenine pathway tryptophan catabolites increase the effects of tryptophan deprivation [115].

Table 2: Kynunerine levels in neurodegenerative diseases, immunologic diseases, tumors & psychiatric disorders.

Disease/disorders	Neuromodulatory Kynurenines	Neurotoxic Kynunerines
Neurodegenerative Diseases		
Parkinson's disease	↑	↓
Huntington's disease	↑	↓
Alzheimer's disease	↑	↓
Vascular cognitive dementia	↑	↑
Multiple sclerosis	↑	↑↓
Immunologic Diseases		
Rheumatoid arthritis	↓	Unknown
Tumors		
Colon cancer	↑↓	↓
Brain tumor	↑	Unknown
Cutaneous malignant melanoma	↓	↑
Psychiatric Disorders		
Anxiety disorder	↓	Unknown
Schizophrenia	↑	↑
Bipolar disorder	Unknown	↑↓
Depressive disorder	↑	↓

9. CONCLUSION:

Overall, the role of KP metabolites and enzymes at various sites and in various conditions is of considerable importance. With the growing interest in disease onset and recovery, a combined knowledge of KP metabolites and enzymes might yield beneficial advancements in therapies and medicine.

10. FUTURE PERSPECTIVE:

The KP enzymes and intermediates are involved in numerous crucial physiological processes that take place all over the body and offer numerous potentials to treat a variety of disease conditions. The KP has drawn more attention in recent years from doctors, biologists, and biochemists to a variety of unique studies. Even though the precise mechanism is yet unknown, future investigations should clarify the function of the KYN pathway in the pathophysiology of many diseases.

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