

The Footprint of Kynurenine Pathway in Cardiovascular Diseases

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ABSTRACT: Kynurenine pathway is the main route of tryptophan metabolism and produces several metabolites with various biologic properties. It has been uncovered that several cardiovascular diseases are associated with the overactivation of kynurenine pathway and kynurenine and its metabolites have diagnostic and prognostic value in cardiovascular diseases. Furthermore, it was found that several kynurenine metabolites can differently affect cardiovascular health. For instance, preclinical studies have shown that kynurenine, xanthurenic acid and cis-WOOH decrease blood pressure; kynurenine and 3-hydroxyanthranilic acid prevent atherosclerosis; kynurenic acid supplementation and kynurenine 3-mono-oxygenase (KMO) inhibition improve the outcome of stroke. Indoleamine 2,3-dioxygenase (IDO) overactivity and increased kynurenine levels improve cardiac and vascular transplantation outcomes, whereas exacerbating the outcome of myocardial ischemia, post-ischemic myocardial remodeling, and abdominal aorta aneurysm. IDO inhibition and KMO inhibition are also protective against viral myocarditis. In addition, dysregulation of kynurenine pathway is observed in several conditions such as senescence, depression, diabetes, chronic kidney disease (CKD), cirrhosis, and cancer closely connected to cardiovascular dysfunction. It is worth defining the exact effect of each metabolite of kynurenine pathway on cardiovascular health. This narrative review is the first review that separately discusses the involvement of kynurenine pathway in different cardiovascular diseases and dissects the underlying molecular mechanisms.

KEYWORDS: Kynurenine pathway, cardiovascular disease, hypertension, atherosclerosis, myocardial infarction, transplantation

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Introduction

Cardiovascular diseases, particularly ischemic heart disease and stroke, account for a major proportion of total deaths and disability-adjusted life years (DALYs).^{1,2} In addition, there has been an increase in the prevalence of leading cardiovascular risk factors such as hypertension, dyslipidemia, and hyperglycemia during the last decades.¹ So far, many studies have attempted to discover new markers and therapeutic targets for early diagnosis and better management of cardiovascular diseases.^{3,4} This progress in the prevention, detection, and treatment of cardiovascular diseases resulted in a remarkable decrease in the incidence and mortality of cardiovascular diseases during recent years.⁵

Kynurenine pathway, as a major route of tryptophan degradation, is involved in several biological processes such as immune-regulation, cancer, inflammation, and metabolism.^{6,7} Different metabolites produced in kynurenine pathway such as kynurenine, kynurenic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid were shown to be involved in such effects. For instance, the immunomodulatory effects of kynurenine and kynurenic acid and their function through aryl hydrocarbon receptor (AHR) have been extensively studied in different types of cancer.⁸⁻¹¹ Recent studies showed that kynurenine and its metabolites are markedly involved in the pathophysiology of cardiovascular diseases, and pharmacological interventions to modulate kynurenine pathway possess therapeutic value in several cardiovascular diseases.¹²⁻¹⁶ Furthermore, several cardiovascular risk factors such as obesity, hyperglycemia, dyslipidemia,

high blood pressure, smoking, and aging lead to the overactivation of kynurenine pathway.¹⁶⁻²⁰ Moreover, higher levels of kynurenine and its metabolites are found in other diseases such as cancer, CKD, cirrhosis, diabetes, and depression that are known for their cardiovascular complications.^{10,21-23} Regarding these findings, a deep insight into the involvement of kynurenine pathway in the pathophysiology of cardiovascular diseases can help expand its clinical application and improve the management of cardiovascular diseases. This narrative review aimed to illuminate the diverse effects of kynurenine and its metabolites on different cardiovascular diseases and illustrate the underlying molecular mechanisms. Thereafter, it would be explained how kynurenine may link cardiovascular diseases to senescence, cancer, CDK, cirrhosis, diabetes, and depression which are heavily linked to cardiovascular health.

Kynurenine Pathway

Tryptophan is an essential amino acid that is mainly catabolized through kynurenine pathway in the human body.²⁴ Besides, tryptophan is the substrate for the synthesis of serotonin, melatonin, and indole metabolites.²⁴⁻²⁶ IDO and tryptophan 2,3-dioxygenase (TDO) are the first and rate-limiting enzymes of kynurenine pathway. TDO is predominantly expressed in the liver and IDO in other organs.²⁷ IDO and TDO produce formylkynurenine, which will be converted to kynurenine by kynurenine formidase. Kynurenine undergoes 3 different enzymatic activities. Kynurenine aminotransferase (KAT) converts kynurenine to kynurenic acid.



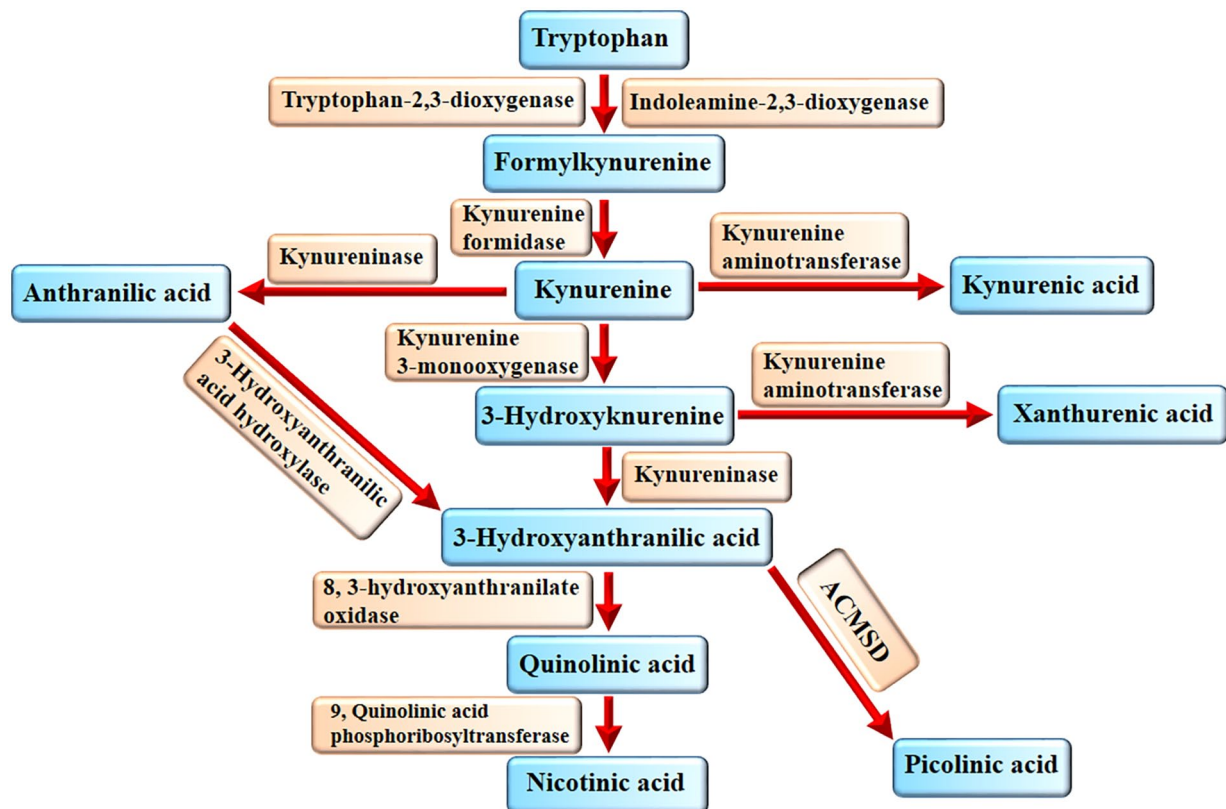


Figure 1. Kynurenine pathway. IDO and TDO convert tryptophan into formylkynurenine, which then will be converted into kynurenine by kynurenine formidase. From this point, the pathway divides into 3 arms. Anthranilic acid, 3-hydroxykynurenine and kynurenic acid are the first products of these arms. Kynureninase and 3-hydroxyanthranilic acid hydroxylase can convert 3-hydroxykynurenine and anthranilic acid into 3-hydroxyanthranilic acid, respectively. Quinolinic acid is produced by 3-hydroxyanthranilate-3,4-dioxygenase from 3-hydroxyanthranilic acid. Phosphoribosyltransferase produces nicotinic acid from quinolinic acid and 7, 2-amino-3-carboxymuconic acid semialdehyde decarboxylase (ACMSD) produces picolinic acid from 3-hydroxyanthranilic acid.

In addition, kynurenine can be converted to anthranilic acid and 3-hydroxykynurenine by kynureninase and KMO, respectively (Figure 1). Thereafter, 3-hydroxykynurenine can be converted to 3-hydroxyanthranilic acid and xanthurenic acid by kynureninase and KAT, respectively. Also, 3-hydroxyanthranilic acid hydroxylase can convert anthranilic acid to 3-hydroxyanthranilic acid.²⁸⁻³⁰ Eventually, quinolinic acid, nicotinic acid, and picolinic acid are produced from 3-hydroxyanthranilic acid in the last of kynurenine pathway.²⁸⁻³⁰ Quinolinic acid is produced by 3-hydroxyanthranilate-3,4-dioxygenase from 3-hydroxyanthranilic acid.

Phosphoribosyltransferase produces nicotinic acid from quinolinic acid and 7, 2-amino-3-carboxymuconic acid semialdehyde decarboxylase (ACMSD) produces picolinic acid from 3-hydroxyanthranilic acid.³¹

However, IDO1, IDO2, and TDO catalyze the same reaction, they have different patterns of tissue expression. IDO1 is expressed in different organs throughout the body, TDO is mainly expressed in the liver and IDO2 is mainly expressed in the liver, kidney and antigen-presenting cells.³¹ IDO in this article is considered IDO1 unless otherwise mentioned.

During inflammation, several inflammatory mediators such as interleukin (IL) 1 β , tumor necrosis factor- α (TNF- α), and

particularly interferon- γ (IFN- γ) instigate janus kinase (JAK)/signal transducer and activator of transcription 1 (STAT1)-mediated expression of IDO and activate kynurenine pathway.³²⁻³⁶ Furthermore, the inflammatory response may augment particular branches of kynurenine pathway and result in increased concentration of specific metabolites of kynurenine pathway.³³ IDO is produced by dendritic cells, macrophages and other inflammatory cells, which produces kynurenine, stimulates AHR and enhances T regulatory (Reg) cells differentiation.^{37,38} AHR is a nuclear receptor that regulates target gene expression. It alters immune cells differentiation in favor of T Reg cells differentiation and provides an immune-suppressive microenvironment in inflammatory diseases and cancer.^{11,39} Increased T Reg cells abundance downregulates immune response and partly alleviates the initial inflammation.⁴⁰ However, this scenario is not always helpful and kynurenine/AHR axis exerts various effects on different organs. Moreover, kynurenine pathway consists of several metabolites with various biologic effects. However, alleviation of immune response can be helpful in inflammatory and autoimmune disease, cancer cells take advantage of this opportunity and silently grow and proliferate in the immune-suppressive microenvironment produced by kynurenine/AHR.¹⁰ Indeed, cancer cells

have an increased expression of IDO and TDO that allows them to consume tryptophan and produce a higher amount of kynurenine and its metabolites.⁴¹ Hence, they can increase T Reg cells response and prevent T cells cytotoxic response. In addition, it was observed that some metabolites of kynurenine such as 3-hydroxyanthranilic and quinolinic acid can selectively induce apoptosis in murine Th1 cells in vitro.⁴² This warrants the higher plasma kynurenine/tryptophan ratio in patients with cancer.^{10,41} Herein, several inhibitors of the kynurenine pathway particularly IDO inhibitors such as indoximod, epacadostat, and navoximod are used in cancer clinical trials.¹⁰

Kynurenine Pathway and Blood Pressure

Recently, it has been uncovered that kynurenine pathway is involved in regulating blood pressure and certain metabolites of kynurenine modulated blood pressure in animal studies.^{16,43,44} Higher plasma concentrations of kynurenine and its metabolites such as kynurenic acid, 3-hydroxykynurenine, and anthranilic acid were detected in the rat model of renovascular hypertension.⁴³ Renal artery occlusion increased the plasma level of angiotensin (Ang) II, which was positively correlated with the plasma level of kynurenine and negatively correlated with the plasma level of tryptophan.⁴³ Recently, Wu et al⁴⁵ reported that a higher kynurenine/tryptophan ratio ($\geq 54.7 \times 10^{-3}$) predicts the effectiveness of Ang receptor blockers (ARBs) on macroalbuminuria (sensitivity 90.0%, specificity 50%) in patients with diabetic kidney disease. In addition, it was shown that ARBs decrease kynurenic acid production and KAT activity in rats' kidneys in vitro.⁴⁶ Likewise, it was found that patients with CKD who receive renin-Ang-aldosterone system (RAAS) inhibitors have a lower kynurenine/tryptophan ratio compared with those not receiving these drugs.²¹ These findings show that Ang II positively regulates kynurenine pathway. Also, kynurenine pathway activation in hypertension can be a sign of RAAS overactivity.

Endothelial dysfunction upregulates IDO and increases kynurenine production. Kynurenine activates adenylate and soluble guanylate cyclase pathways and dilates arteries.¹⁶ Endotoxemia enhanced endothelial IDO production in the mice model, thereby increasing kynurenine level and decreasing blood pressure.¹⁶ Consistently, pharmacological inhibition of IDO increased blood pressure in mice with systemic inflammation.¹⁶ In addition, in a dose-dependent manner, kynurenine lowered blood pressure in spontaneously hypertensive rats.¹⁶ Kynurenine, in an endothelial-independent manner, and tryptophan, in an endothelial-dependent manner, led to vasorelaxation in precontracted coronary arteries in a porcine model.¹⁶ Similarly, it has been observed that IDO is considerably overexpressed in inflamed heart tissue and endothelial cells in the heart and kidney of patients with sepsis.⁴⁷ Additionally, kynurenine/tryptophan ratio was positively and vigorously correlated with inotrope requirements in those patients.⁴⁷

Kynurenine is strongly produced in patients with idiopathic pulmonary arterial hypertension (PAH) and contributes to

lower pulmonary arterial blood pressure by activating nitric oxide (NO)/cGMP and cAMP pathways in the pulmonary arteries.⁴⁸ In response to hypoxia, IDO^{-/-} mice showed significantly more increase in mean pulmonary arterial pressure and medial thickness of pulmonary arteries.⁴⁹ Endothelial IDO serves as a protective mechanism against PAH and pulmonary arterial remodeling.⁴⁹ In addition, IDO overexpression provided more protection against PAH in a mice model.⁴⁹ IDO activity led to increased apoptosis of vascular smooth muscle cells (VSMCs) in pulmonary hypertension by depolarizing mitochondrial membrane and releasing cytochrome C.⁴⁹ Besides, IDO activity modulated the pathologic differentiation of VSMCs in PAH.⁴⁹

IDO is downregulated in endothelial cells of patients with preeclampsia.⁵⁰⁻⁵² In addition, it was uncovered that low IDO expression in the human placenta is correlated with more severe maternal hypertension or proteinuria in patients with preeclampsia.⁵² Consistently, IDO knockout has been associated with slightly increased blood pressure and preeclampsia phenotypes such as renal glomerular endotheliosis and proteinuria in mice.⁵³ Even in the presence of lower IDO expression, increased tryptophan availability for IDO contributed to vasorelaxation.⁵⁰ Kynurenine activated large-conductance Ca²⁺-activated K⁺ channels (BK_{Ca}) channels in VSMCs of women with or without preeclampsia.⁵⁴ Kynurenine enhances the amplitude but not the frequency of spontaneous transient outward currents through BK_{Ca}.⁵⁴ Sakakibara et al⁵⁵ also revealed that kynurenine activates voltage-dependent K⁺ channels (Kv7 channels) in VSMCs of both humans and rats to induce hyperpolarization of these cells and accelerate vasodilation. These effects have been associated with dilatation of omental and myometrial resistance arteries.⁵⁴ Consistently, the hypotensive effect of kynurenine in rats was partly attenuated by linopiridine, a selective inhibitor of Kv7 channel.⁵⁵

Fazio et al⁴⁴ uncovered that xanthurenic acid is the most effective metabolite of kynurenine for vasorelaxation. They found that the serum level of xanthurenic acid is increased by several folds in lipopolysaccharide (LPS)-mediated endotoxemia. Furthermore, systemic administration of xanthurenic acid reduced blood pressure in mice.⁴⁴ Xanthurenic acid upregulated endothelial nitric oxide (eNOS) to induce hypotension and its effect was reversed by eNOS inhibitor. In addition, administration of KMO inhibitors increased the serum levels of kynurenine, whereas attenuated LPS-induced hypotension in mice.⁴⁴ These findings suggest that xanthurenic acid is a highly effective vasodilator metabolite of kynurenine pathway that can be used for future drug development. Additionally, Kwok et al⁵⁶ found that the KAT-1 gene possesses a missense mutation, E61G, in every strain of spontaneously hypertensive rats. This finding may justify the importance of kynurenic acid in hypertension.

Previously, it has been shown that stimulation of Ang II type 1 receptor, a G protein-coupled receptor, internalizes and degrades BK_{Ca}, increases intracellular Ca²⁺, inhibits NO/

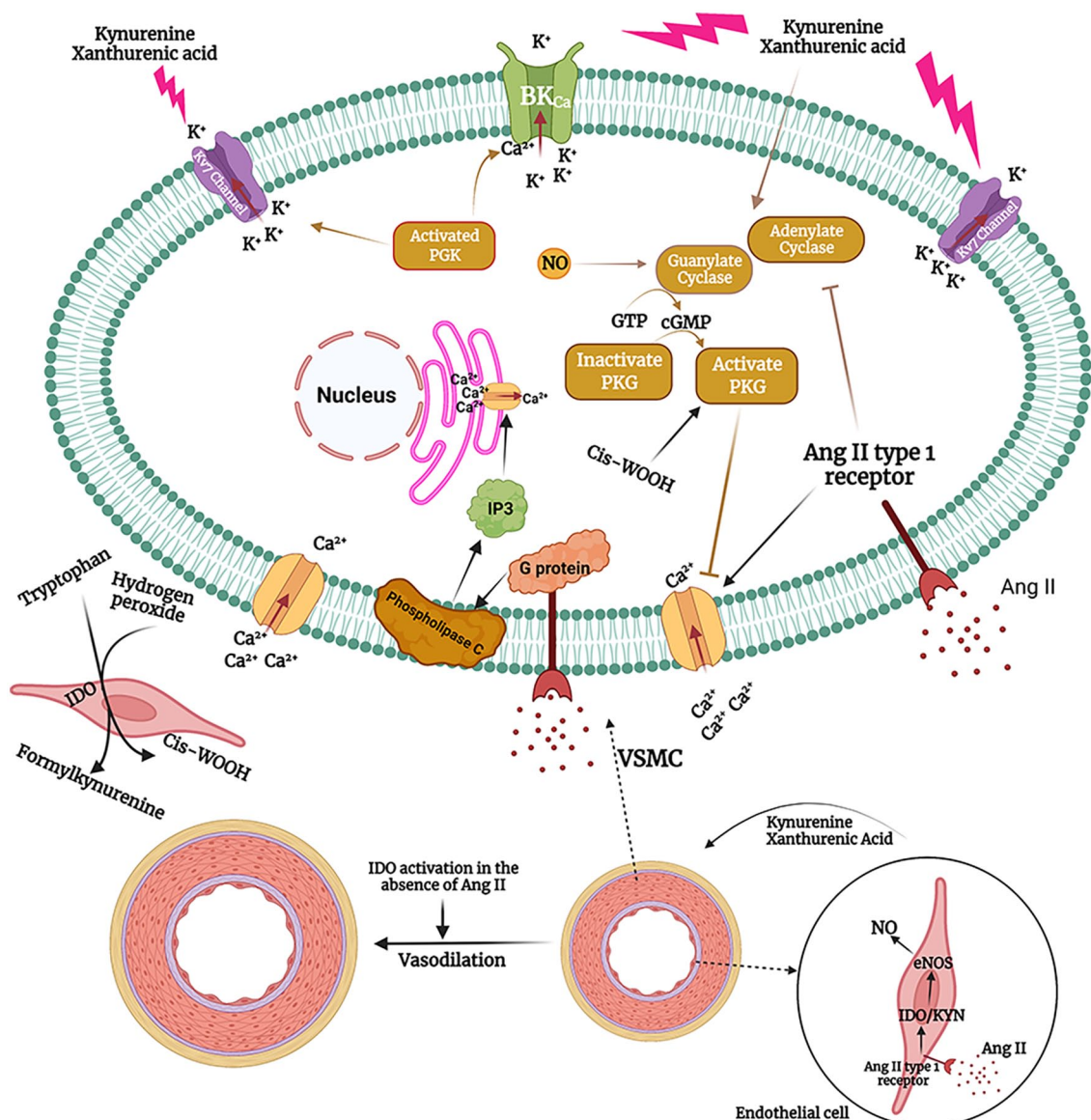


Figure 2. The effect of Ang II and kynurenine pathway on vascular tonicity and blood pressure. Ang II stimulates Ang II type 1 receptor on VSMCs, which is a G protein-coupled receptor. G protein activates phospholipase C, leading to IP₃ production from membrane phospholipids. IP₃ opens the Ca²⁺ channels on sarcoplasmic reticulum membrane and increases cytoplasmic Ca²⁺ concentration. In addition, Ang II type 1 receptor stimulation leads to inhibition of guanylate cyclase, downregulation of BK_{Ca} and extracellular Ca²⁺ influx. In the endothelial cells, Ang II upregulates IDO and activates kynurenine pathway. Kynurenine metabolites, particularly kynurenine itself and xanthurenic acid, activate guanylate cyclase and adenylate cyclase. Guanylate cyclase converts GTP into cGMP, thereby activating PKG. PKG activates K⁺ channels and leads to VSMCs hyperpolarization and relaxation. Furthermore, kynurenine pathway can enhance eNOS function in endothelial cells to lower blood pressure. In addition to its hypertensive effects, Ang II activates kynurenine pathway, which acts as a counter-regulatory mechanism. Pharmacological augmentation of kynurenine pathway or attenuation of Ang II signaling pathway helps to lower blood pressure. In addition, overactivation of kynurenine pathway in the absence of increased concentrations of Ang II such as those observed in sepsis leads to hypotension. Interestingly, inflammatory response and increased concentration of hydrogen peroxide can lead to cis-WOOH production as a by-product of kynurenine pathway in the endothelial cells. Cis-WOOH can readily activate PKG1 α , induce vasorelaxation and decrease blood pressure.

guanylate cyclase system, and leads to vasoconstriction in VSMCs, whereas Ang II receptors in endothelial cells may activate compensatory vasodilation mechanisms⁵⁷⁻⁶¹ (Figure 2). Ang II type 1 receptor stimulation activates G protein-coupled receptor, subsequently activates phospholipase C and increases inositol-1,4,5-triphosphate (IP₃) in VSMCs.⁶¹ IP₃ stimulates sarcoplasmic reticulum Ca²⁺ efflux and begins contraction.⁶¹ Ang II type 1 receptor stimulation also leads to extracellular Ca²⁺ influx.⁶¹ IDO overexpression in endothelial cells,

subsequent to Ang II stimulation, activates NO/guanylate cyclase. Guanylate cyclase converts GTP to cGMP, which subsequently activates protein kinase G (PKG), opens K⁺ channels, hyperpolarizes VSMCs, and blocks the Ca²⁺ channels.⁶² Hence, IDO is mechanistically acting against Ang II to decrease blood pressure (Figure 2).

IDO needs the reduction of Fe³⁺ to Fe²⁺ for its enzymatic activity.⁶³ Interestingly, Stanley et al⁶³ showed that oxidation of tryptophan by IDO in the presence of hydrogen peroxide can

produce a byproduct named cis-WOOH. Cis-WOOH is generated by oxidatively activated dioxygenase activity of IDO. Inflammation results in the increased concentration of hydrogen peroxide and IDO produces singlet molecular oxygen (1O_2) from hydrogen peroxide. This reaction is associated with stereoselective oxidation of l-tryptophan to a tricyclic hydroperoxide via the oxidatively activated dioxygenase activity of IDO. Cis-WOOH decreases arterial tonicity and reduces blood pressure through PKG1 α .⁶³ PKG1 α function accelerates vasorelaxation and it is also deeply involved in the long-lasting blood pressure-lowering effect of NO.⁶⁴ Cis-WOOH can be generated in the endothelial cells. Cis-WOOH effectively and readily reacts with PKG1 α , but it reacts slowly with arterial types of glutathione peroxidases and peroxiredoxins which prolongs its function.⁶⁵ Developing new drugs based on Cis-WOOH may be helpful for adequate control of blood pressure in hypertensive subjects.

Regarding these findings, IDO, kynurenine and kynurenine metabolites serve as both prognostic markers and therapeutic targets in hypertension. Kynurenine pathway is upregulated by Ang II and helpfully attenuates the deleterious effects of Ang II on hypertension. Future studies can further illuminate the clinical application of kynurenine, its metabolites and inhibitors of kynurenine pathway in the management of systemic hypertension, PAH, preeclampsia, and hypotension.

Kynurenine Pathway and Atherosclerosis

Atherosclerosis is a prevalent vascular condition and a major cause for the initiation and progression of other cardiovascular diseases.^{66,67} It is a local but chronic inflammatory response of the immune system that crucially endangers cardiovascular health in the long-term.⁶⁸ Both progression of atherosclerosis and rupture of an atherosclerotic plaque can result in major cardiovascular events^{67,68} and pharmacological management of atherosclerosis markedly prevents cardiovascular death.^{69,70}

Both innate and adaptive immune cells, particularly macrophages, are markedly involved in the pathogenesis of atherosclerosis.⁷¹ Oxidized lipoproteins stimulate immune response and lead to the release of numerous inflammatory cytokines such as IL1 β , IL6, and TNF- α .⁷¹ Furthermore, decreased abundance of T Reg cells and overactivity of T helper (Th)1, Th17, and B cells in response to ApoB, as a core protein of low-density lipoprotein (LDL), contribute to atherosclerosis progression.⁶⁷

It has been uncovered that Kynurenine and its metabolites are heavily implicated in the pathophysiology of atherosclerosis.⁷² Overactivation of kynurenine pathway and increased plasma levels of kynurenic acid, 3-hydroxykynurenine, anthranilic acid, and 3-hydroxyanthranilic acid have been associated with a higher risk of acute myocardial infarction in patients with stable angina pectoris, particularly in diabetic and pre-diabetic subgroups.⁷³

Cason et al¹⁵ measured the correlation between tryptophan, indole metabolites and kynurenine metabolites and the

presence of advanced atherosclerosis in 100 patients who underwent carotid endarterectomy or limb revascularization. The study revealed that tryptophan, indole, indole-3-propionic acid, and indole-3-aldehyde levels were significantly associated with decreased risk of advanced atherosclerosis, whereas kynurenine/tryptophan ratio significantly and positively correlated with the presence of advanced atherosclerotic plaque.¹⁵ Furthermore, kynurenine/tryptophan ratio was positively associated with a postoperative cardiac complication and major adverse events during the follow-up period.¹⁵ Interestingly, it was shown that deviation within kynurenine pathway, particularly overproduction of quinolinic acid and decreased production of kynurenic acid, were associated with aggravation of local inflammatory response, carotid artery atherosclerosis, and increased need of patients for surgery because of an unstable carotid plaque.⁷² It was observed that kynurenic acid and AHR could suppress the immune response, thereby improving carotid plaque stability.⁷² KAT-1 (95% CI, OR 0.058 [0.006-0.541]) and KAT-2 (95% CI, OR 0.395 [0.146-1.069]) independently protected against carotid atherosclerotic plaque being symptomatic, while KMO (95% CI, OR 1.460 [0.896-2.377]) and kynureninase (95% CI, OR 1.540 [0.942-2.519]) were associated with non-significant increase in the risk of atherosclerotic plaque being symptomatic.⁷² These enzymes may be useful markers for screening patients who will need therapeutic intervention in the near future.

IDO deletion decreased blood levels of IL10 and accelerated atherosclerosis plaque formation in hypercholesterolemic ApoE^{-/-} mice.⁷⁴ Likewise, IDO inhibition by 1-methyl tryptophan (1-MT), an IDO inhibitor, has been associated with larger atherosclerotic lesions in the aortic root, increased levels of TNF- α , monocyte chemoattractant protein 1 (MCP-1), and vascular cell adhesion protein 1 (VCAM1) and increased CD68+ macrophage infiltration into the atherosclerotic lesion.⁷⁵ A derivative of anthranilic acid, 3,4-dimethoxycinnamoyl anthranilic acid (3,4-DAA), decreased the production of IL6, TNF- α , C-X-C motif ligand 1 (CXCL1) and granulocyte macrophage colony-stimulating factor (GM-CSF) in human atheroma cells and reduced atherosclerotic plaque size and lesional macrophage abundance in ApoE^{-/-} mice.⁷⁴

Polyzos et al⁷⁶ indicated that systemic attenuation of IDO by 1-MT increases vascular inflammation and augments the expression of MCP-1 and VCAM1 in ApoE^{-/-} mice. IDO inhibition also accelerated M1 subtype macrophages polarization and expedited aortic atherosclerotic plaque formation (Figure 3). IDO inhibition also increased total cholesterol and very low-density lipoprotein (VLDL)/high-density lipoprotein (HDL) ratio in ApoE^{-/-} mice. Supplementation of exogenous 3-hydroxyanthranilic acid alleviated vascular inflammation and reversed the atherogenic effect of 1-MT.⁷⁶ Attenuation of inflammatory cells infiltration into the vessel's wall is a crucial mechanism involved in the protective effects of IDO.⁷⁷ Increased activity of inflammatory cells, in particular

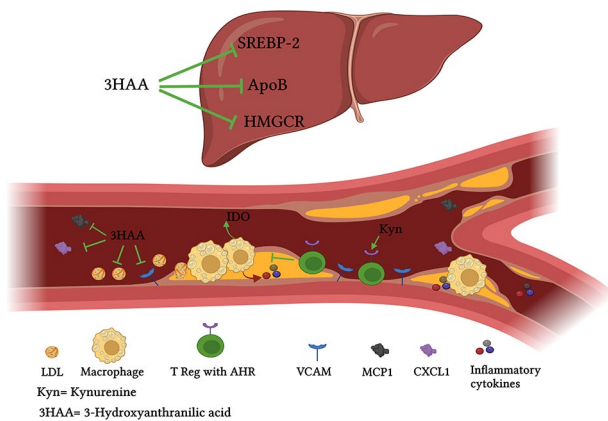


Figure 3. The effect of kynurenine and its metabolites on atherosclerosis. Inflammation and accumulation of oxidized lipoprotein stimulate the expression of IDO in inflammatory cells such as macrophages. Increased production of kynurenine accelerates T Reg cells differentiation and alleviates local inflammatory response. Kynurenine metabolites, particularly 3-hydroxyanthranilic acid, can vigorously decrease inflammatory cytokines release. In addition, 3-hydroxyanthranilic acid prevents the uncontrolled release of chemokines and hinders the infiltration of inflammatory cells into the vessel's wall. It has been reported that 3-hydroxyanthranilic acid can attenuate hepatic lipogenesis and decrease blood level of LDL by downregulating SREBP-2, HMGCR, and ApoB.

M1 macrophages, not only contributes to atherosclerotic plaque formation, but also leads to plaques destabilization.⁷⁸

It was found that 3-hydroxyanthranilic acid prevents inflammasome activation and IL1 β production in macrophages.^{14,79} In addition, Berg et al¹⁴ showed that 3-hydroxyanthranilic acid could suppress the expression and nuclear translocation of sterol regulatory element binding protein-2 (SREBP-2) and secretion of apolipoprotein B in hepatocytes. Furthermore, 3-hydroxyanthranilic acid prevented inflammasome activation and IL1 β production in macrophages.^{14,79} Prevention of 3-hydroxyanthranilic acid degradation by inhibiting 3-hydroxyanthranilic acid 3,4-dioxygenase (HAO) downregulated hepatic expression of SREBP-2 and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), decreased hepatic lipid accumulation, reduced plasma levels of triglyceride and cholesterol and ameliorated atherosclerosis in *LDLR*^{-/-} mice.¹⁴ SREBP-2 is a transcription factor that increases the expression of HMGCR to enhance the synthesis of cholesterol⁸⁰ (Figure 3). Interestingly, 3-hydroxyanthranilic acid can strongly inhibit the oxidation of LDL and lower oxidized LDL intake in macrophages, thereby ameliorating the initiation and progression of atherosclerosis^{79,81} (Figure 3).

Previously, it was observed that plasmacytoid dendritic cells are markedly involved in preventing atherosclerosis in both humans and animals.⁸² Plasmacytoid dendritic cells produce IDO and stimulate T Reg cells differentiation.⁸² IDO expression in dendritic cells is associated with increased activity of T Reg cells in vessels' walls and reciprocally T Reg cells with their cytotoxic T-lymphocyte-associated protein 4 (CTLA4) surface

receptor instigate IDO expression in dendritic cells.⁸³ The self-augmentation cycle between T Reg cells and IDO mitigates vascular inflammation and protects against atherosclerosis.⁸³ Consistently, it has been observed that IDO is significantly overexpressed in atherosclerotic plaques, particularly in lesional macrophages and in coordination with T Reg cells activity.⁸⁴ Even it was observed that the beneficial effects of eicosapentaenoic acid on the repression of atherosclerosis are mediated by induction of IDO and differentiation of T Reg cells in the lesion. Likewise, IDO inhibitor reversed the protective effects of eicosapentaenoic on atherosclerosis.⁸⁵ Similarly, it has been revealed that the protective effects of mesenchymal stem cells on atherosclerosis also rely on IDO.⁸⁶

In an NF- κ B-dependent manner, IDO increases the expression of tissue factor in macrophages of atherosclerotic plaques which can increase the risk of thrombogenesis and acute cardiovascular events. Consistently, inhibition of IDO or AHR decreases tissue factor expression in macrophages.⁸⁷ It was shown that kynurenine but not 3-hydroxyanthranilic and quinolinic acids could induce tissue factor expression in macrophages in the presence of an IDO inhibitor.⁸⁸

These findings suggest that the kynurenine pathway is a compensatory mechanism that is activated in atherosclerosis and attempts to protect against atherosclerosis. Metabolites and enzymes of kynurenine pathway can help to find patients who are at high risk of atherosclerotic plaque formation or instability. Moreover, targeted therapy for kynurenine pathways, such as those increasing anthranilic acid and 3-hydroxyanthranilic acid, have therapeutic value in atherosclerosis.

Kynurenine Pathway in Ischemic Heart Disease and Cardiac Remodeling

Hordaland Health Study uncovered that increased kynurenine/tryptophan ratio predicts a higher risk of acute coronary events such as unstable angina, non-fatal or fatal myocardial infarction, and sudden death among patients.^{89,90} In addition, the adjusted hazard ratio (HR) was 1.57 (1.03-2.39) for the fourth quartile, compared with the first quartile of kynurenine/tryptophan ratio.⁸⁹ Similarly, 55 months follow-up of 3224 patients after elective coronary angiography revealed that urine kynurenine/tryptophan ratio is significantly and positively correlated with major coronary events, acute myocardial infarction, and all-cause and cardiovascular mortality.⁹¹ In addition, increased levels of kynurenine, 3-hydroxykynurenine, anthranilic acid, and 3-hydroxyanthranilic acid predict a higher risk of acute myocardial infarction in patients with stable angina pectoris, particularly in those with impaired glucose metabolism.⁷³

It was unveiled that the plasma levels of kynurenine pathway metabolites such as kynurenine, kynurenine acid, and 3-hydroxyanthranilic acid increase after cardiopulmonary resuscitation in rats and pigs.^{92,93} In addition, it was observed that increased plasma levels of kynurenine acid and 3-hydroxyanthranilic acid

correlate with markedly lower ejection fraction and stroke volume.⁹² Interestingly, 6 months follow-up of 292 patients after myocardial infarction showed that increased activity of IDO is significantly associated with left ventricular remodeling.⁹⁴ Moreover, IDO activity was superior to N-terminal Pro-BNP (NT-proBNP), suppression of tumorigenicity 2 (ST2), Galectin 3, or C-reactive protein (CRP) for predicting cardiac remodeling after myocardial infarction.⁹⁴

Melhem et al¹³ reported that pharmacological inhibition or genetic deletion of IDO could improve myocardial injury, and dysfunction after myocardial infarction. The study exhibited that distinct loss of function of IDO in endothelial cells but not in smooth muscle cells, inflammatory cells, or cardiomyocytes can ameliorate cardiomyocytes contractility, cardiac function and ventricular remodeling after myocardial infarction in mice.¹³ Furthermore, kynurenine reversed the protective effects of IDO deletion, stimulated AHR-mediated production of reactive oxygen species (ROS), and activated apoptosis.¹³

Liu et al⁹⁵ found that IDO is upregulated in cardiac hypertrophy. They uncovered that pharmacological inhibition of IDO with PF-06840003, an IDO inhibitor, partly attenuates Ang II-mediated cardiac hypertrophy in mice. Adenoviral overexpression of IDO enhanced Ang II-mediated hypertrophic cardiomyopathy *in vitro*.⁹⁵ Furthermore, siRNA-mediated knockdown of IDO prevented Ang II-mediated cardiomyocytes growth and decreased the expression of hypertrophy-associated genes such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and β -myosin heavy chain (β -Mhc) in rat cardiomyocytes *in vitro*.⁹⁵ It was illuminated that IDO activates ribosomal protein synthesis through activation of phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin complex 1 (mTORC1) in cardiomyocytes and pharmacological inhibition of PI3K by picilisib, AKT by perifosine or mTORC1 by rapamycin abrogates the effect of IDO on Ang II-mediated cardiomyopathy.⁹⁵ Additionally, 1-MT stimulated apoptosis in human cardiac myofibroblasts that can profoundly prevent cardiac fibrosis.⁹⁶

On the contrary, there are studies claiming that kynurenine is responsible for the protective effects of remote ischemic preconditioning in myocardial infarction.^{97,98} IDO inhibition by 1-MT reverted the protective effects of remote ischemic preconditioning in rats.⁹⁸ In addition, administration of kynurenine (300 mg/kg body weight) before myocardial ischemia reduced infarct size in the rat model.⁹⁷

However controversial, it was shown that kynurenine pathway is enormously involved in the pathogenesis of myocardial infarction. Furthermore, kynurenine and its metabolites can be used as prognostic markers for surveillance of myocardial infarction or detect patients who are at high risk of coronary artery disease and post-intervention adverse events.⁹⁹ Although IDO and kynurenine have been well-studied in ischemic heart disease and cardiac hypertrophy, the effect of other enzymes and metabolites of kynurenine pathway in these conditions remains

to be known. Future studies in this regard may help to develop new medications for the treatment of myocardial infarction by targeting specific members of kynurenine pathway.

Kynurenine Pathway and Heart Failure

Recently it was shown that heart failure is associated with increased plasma levels of kynurenine, kynurenic acid, 3-hydroxykynurenine, quinolinic acid, kynurenine/tryptophan ratio, and 3-hydroxykynurenine/xanthurenic acid ratio.^{100,101} Dschietzig et al¹⁰² evaluated the predictive value of plasma kynurenine in 114 patients with congestive heart failure (CHF). The plasma levels of kynurenine and NT-proBNP increased in patients with greater New York Heart Association (NYHA) grade. Moreover, 6 months follow-up of these patients revealed that elevated plasma levels of kynurenine but not NT-proBNP were associated with increased risk of death among patients with CHF.¹⁰² Konishi et al¹⁰³ revealed that kynurenine significantly and negatively correlates with hand-grip strength, peak oxygen consumption, and 6-minute walk distance in patients with heart failure. Ten years follow-up of 202 patients with heart failure showed that baseline kynurenine (95% CI, HR 1.4 (1.1-1.9)) quinolinic acid (95% CI, HR 1.8 [1.1-2.9]), 3-hydroxykynurenine (95% CI, HR 1.8 [1.2-2.6]), 3-hydroxykynurenine/xanthurenic acid ratio (95% CI, HR 1.7 [1.3-2.2]), and kynurenine/tryptophan ratio (95% CI, HR 1.55 [1.1-2.2]) are associated with significant increase in mortality among these patients.¹⁰⁰ However, xanthurenic acid showed a negative correlation with heart failure-related mortality.¹⁰⁰

Previously, it was mentioned that the plasma level of kynurenine is elevated in patients with heart failure with either reduced or preserved ejection fraction.¹⁰³ Patients with heart failure have elevated levels of inflammatory cytokines suggesting that chronic and systemic inflammation may be a precipitating factor for heart failure progression.¹⁰⁴ Systemic inflammation can be a consequence of heart failure, as well.¹⁰⁴ Higher levels of inflammatory cytokines such as IL1 β and TNF- α are common findings in heart failure.¹⁰⁵ Previously, it has been mentioned that inflammatory cytokines such as IL1 β , TNF- α , and particularly IFN- γ can induce IDO expression and activate kynurenine pathway.³²⁻³⁶ Garcia et al¹⁰⁶ showed that IFN- γ knockout exacerbates left ventricular hypertrophy and diastolic dysfunction and increases myocardial fibrosis in the mice model of diastolic heart failure. Furthermore, recombinant IFN- γ ameliorated cardiac hypertrophy in both IFN- γ knockout mice and wild-type mice.¹⁰⁶ Moreover, Kimura et al¹⁰⁷ revealed that IFN- γ /STAT5 axis, an inducer of IDO expression, protects against pressure overload-mediated cardiac hypertrophy in mice. Similarly, kynurenine can prevent fibroblast and collagen deposition in damaged tissue and improve the healing process.¹⁰⁸ In contrast, IDO/kynurenine pathway aggravated post-ischemic ventricular remodeling in mice.¹³ Besides, kynurenic acid, anthranilic acid, 3-hydroxykynurenine,

and 3-hydroxyanthranilic acid impair myocardial mitochondrial respiration, which heavily disrupts cardiac energy and calcium homeostasis, increases ROS production, and contributes to the development of heart failure.¹⁰⁹⁻¹¹¹ Nevertheless, more studies are necessary to define the exact role of kynurenine pathway in the development and progression of heart failure.

Kynurenine Pathway, Heart Rate, and Arrhythmias

Bądzińska et al¹¹² indicated that kynurenic acid 25 mg/kg/day for 3 weeks could selectively decrease heart rate in rats without a significant impact on mean arterial pressure. Shayesteh et al¹¹³ revealed that 1-MT, in a dose-dependent manner, ameliorates cirrhosis-induced chronotropic dysfunction and improves heart response to epinephrine. Metabolomics analysis of 502 patients showed that quinolinic acid was positively correlated with atrial fibrillation (95% CI, OR 1.15 [1.01-1.32]).¹⁰¹ Quinolinic acid impairs cellular Ca²⁺ homeostasis and increases intracellular Ca²⁺ concentration.¹¹⁴ Quinolinic acid also contributes to lipid peroxidation¹¹⁵ and ROS production.¹¹⁶

ROS plays an important role in the pathophysiology of atrial fibrillation.¹¹⁷ ROS induces arrhythmogenic effects through several mechanisms, including alteration in Na⁺ currents, increasing intracellular Ca²⁺ concentration, impairment of gap junctions, fibrosis, and extracellular matrix disruption.¹¹⁸ These mechanisms contribute to early afterdepolarization, ectopic, and re-entry arrhythmias.¹¹⁸

On the other hand, inflammation upregulates IDO and increases kynurenine production. Inflammation and cardiac arrhythmia have a highly complex association, and inflammation contributes to arrhythmia.¹¹⁹ Moreover, inflammation participates in atrial remodeling through several pathways.¹²⁰ Since the kynurenine pathway is usually activated in inflammation, uncovering the association between kynurenine metabolites and arrhythmias can be helpful for better management of arrhythmias.

Kynurenine Pathway and Stroke

Stroke is defined as the sudden onset of neurological symptoms, including motor, sensory, and cognitive symptoms due to ischemia or hemorrhage in the central nervous system (CNS).¹²¹ Ischemic stroke constitutes the major proportion of stroke.¹²¹ Stroke is a leading cause of death and disability worldwide.¹²² Several mechanisms are involved in the pathophysiology of neuronal damage after stroke, including mitochondrial dysfunction, neuroinflammation, glutamate-induced excitotoxicity, and oxidative stress.^{123,124}

Studies on mice models indicated that ischemic stroke is associated with increased expression of IDO in the neuronal tissue of hippocampus and cerebral arterioles.^{125,126} IDO activity positively correlated with high sensitivity C-reactive protein (hs-CRP), national institute of health stroke scale (NIHSS), and infarct volume in patients with stroke.^{127,128} Furthermore, patients with poor outcomes possessed higher kynurenine/

tryptophan ratios.¹²⁸ Brain resident phagocytes, including monocytes, macrophages, dendritic cells, and microglia express IDO. As previously mentioned, IDO is upregulated in inflammation.¹²⁹ In addition, it was shown that IDO expression increases in neuronal progenitor cells after 3 and 8 hours of oxygen and glucose deprivation.¹³⁰ IDO overexpression predicted neuronal progenitor cells death and IDO inhibition improved neuronal progenitor cells survival during oxygen and glucose deprivation *in vitro*.¹³⁰ However, Jackman et al¹²⁶ revealed that either IDO inhibition or deletion could not change the neurological function, total brain infarct size, and edema following ischemic stroke in mice.

It has been reported that post-ischemic activation of AHR increases astrogliosis and downregulates neurogenesis in adult mice, whereas AHR knockout decreases inflammatory markers such as IL1 β , IL6, IFN- γ , CXCL1 and upregulates neurogenesis factors such as neurogenin 1 and neurogenin 2 after stroke.¹³¹ Consistently, AHR antagonist significantly alleviated neurogenic inflammation, decreased oxidative stress and inflammatory cytokines release, and reduced infarct size after ischemic stroke in mice and rats.^{132,133} Ischemia increased total and nuclear AHR levels in neurons both *in vivo* and *in vitro*. Pharmacological inhibition or genetic loss of AHR reduced infarct size and decreased neurological deficit 48 hours after ischemia.¹³⁴ AHR inhibits cAMP response element (CRE)-binding protein (CREB) mediated neuronal brain-derived neurotrophic factor (BDNF) gene expression.^{134,135} CREB signaling prevents apoptosis and prolongs neuronal cells survival.¹³⁶ Hence, AHR stimulation accelerates the apoptosis of neurons.¹³⁴ Kynurenine, as an AHR agonist, is increased after stroke and may induce neurologic damage via AHR activation.¹³⁴

Conversely, intraperitoneal administration of kynurenine sulfate (30, 100, and 300 mg/kg) before middle cerebral artery occlusion dose-dependently decreased infarct size and hippocampal CA1 pyramidal cells loss in mice, as well as preventing post-stroke behavioral changes and hypermobility in gerbils.¹³⁷ Even post-ischemic chronic administration of kynurenine sulfate (300 mg/kg/day) ameliorated neuronal damage in rats.¹³⁸ However, Gellért et al¹³⁹ reported that post-ischemic single-dose administration of kynurenine sulfate (300 mg/kg/day) aggravated the outcome of focal cerebral ischemia/reperfusion mediated by middle cerebral artery occlusion. Intraperitoneal injection of KMO inhibitors such as (*m*-nitrobenzoyl)-alanine (400 mg/kg) or Ro 61-8048 (40 mg/kg) 3 times at 1, 30, and 180 minutes after bilateral carotid artery occlusion significantly decreased infarct size in rats and markedly confined pyramidal neurons lesion in the hippocampal CA1 region of gerbils.¹⁴⁰ In addition, intraperitoneal administration of 1 mmol/kg of kynurenic acid analog 1 hour before and 2, 5, 23, and 29 hours after global forebrain ischemia significantly prevented pyramidal neurons damage in the hippocampus CA1 zone and improved synaptic response and

electrophysiological function of neurons.¹⁴¹ Interestingly, it was found that patients with post-ischemic cognitive decline have a higher quinolinic acid/kynurenic acid ratio.¹⁴² Quinolinic acid and kynurenic acid are the agonist and antagonist of N-Methyl-D-aspartate (NMDA) receptor, respectively.¹⁴³ Excessive NMDA receptor stimulation by glutamate leads to intracellular Ca²⁺ overload, ROS production, mitochondrial damage, and mediates excitotoxic neuronal death in ischemic stroke.¹⁴⁴

KMO leads to the conversion of kynurenine into quinolinic acid, a neurotoxic metabolite of the kynurenine pathway.¹⁴⁵ KMO inhibition not only prevents the production of quinolinic acid but also increases the substrate for KAT and kynurenic acid production.¹⁴⁶ KMO inhibitors prevent neuronal loss and behavioral changes in several neurodegenerative diseases and psychiatric conditions such as Alzheimer's disease, Huntington's disease, and depression.^{146,147} KMO inhibitors, particularly JM6 and Ro 61-8048, do not cross the blood-brain barrier. Accordingly, it seems that peripheral inhibition of KMO is responsible for the protective effects of KMO inhibitors.¹⁴⁶

All in all, previous findings from preclinical studies show that kynurenic acid supplementation, KMO inhibition, AHR inhibition or simultaneous kynurenine supplementation and AHR inhibition may improve the outcome of stroke. In addition, the opposite effects of kynurenine and kynurenic acid supplementation and AHR inhibition on stroke can indicate that kynurenine has major biological functions that are not mediated through AHR.

Kynurenine Pathway and Aneurysm

Ang II is a major instigator of the aneurysm or at least accelerates its progression.¹⁴⁸ Ang II activates several inflammatory signaling pathways such as nuclear factor kappa B (NF- κ B) signaling pathway, upregulates matrix metalloproteinases, and damages the vessel's wall.¹⁴⁸ Ang II is widely used to induce abdominal aorta aneurysm in animal studies.^{148,149} Ang II, in an IFN- γ -dependent manner, stimulates the expression of IDO in the vessel's wall.¹⁵⁰ Ang II infusion notably increased the risk of abdominal aorta aneurysm in Apoe^{-/-} mice, but not in Apoe^{-/-} mice with IDO deletion.¹⁵⁰ IDO overactivity has been reported to be involved in the apoptosis of VSMCs.^{49,151} Consistently, IDO knockout improved the survival of VSMCs and protected against Ang II-mediated abdominal aorta aneurysm in LDLR^{-/-} mice.¹⁵¹ It was observed that 3-hydroxyanthranilic acid, IDO, and kynureninase are vigorously expressed in the neighboring non-aneurysmal segments of human abdominal aorta aneurysm samples.¹⁵⁰ Similarly, kynureninase and KMO were upregulated in macrophages of aortic atherosclerotic aneurysm in patients who underwent aortic surgery.¹⁵² Furthermore, 3-hydroxyanthranilic acid, in an NF- κ B-dependent manner, increases the expression of matrix metalloproteinase 2 in VSMCs and accelerates the formation and exacerbation of Ang II-mediated abdominal aorta aneurysm in

both Apoe^{-/-} and Apoe^{-/-}/IDO^{-/-} mice.¹⁵⁰ Moreover, kynureninase knockdown strongly decreased 3-hydroxyanthranilic acid and matrix metalloproteinase 2 and partly prevented Ang II-mediated abdominal aorta aneurysm in mice.¹⁵⁰ Abdominal aorta aneurysm remains without an effective medication and large size and symptomatic aneurysms are repaired by open or endovascular surgery.¹⁵³ Maybe pharmacological intervention targeting kynurenine pathway, particularly targeting kynureninase, KMO, and 3-hydroxyanthranilic acid, contribute to the management of abdominal aorta aneurysm.

Kynurenine Pathway and Myocarditis

Acute viral myocarditis has been associated with decreased serum levels of tryptophan, elevated serum levels of kynurenine and increased IDO activity in the heart and spleen of mice.¹⁵⁴ Furthermore, both IDO^{-/-} and 1-MT-treated mice had significantly better survival, higher IFN- γ and lower viral load than IDO^{+/+} mice in acute viral myocarditis.¹⁵⁴ Moreover, treatment with kynurenine attenuated the beneficial effects of IDO deletion on mice survival.¹⁵⁴ Previously, it was found that IDO deletion upregulates type I interferon, subsequently hinders viral replication.¹⁵⁵ The expression of IDO also increased in the mice model of chronic viral myocarditis.¹⁵⁶ IDO overexpression in macrophages co-cultured with cardiomyocytes revealed that IDO overactivity increases the release of IL1 β , IL6, and TNF- α and ROS. In addition, IDO overactivity was associated with enhanced lactate dehydrogenase (LDH) activity and treatment of macrophages with 1-MT ameliorated these alterations.¹⁵⁶ Kubo et al¹⁵⁷ revealed that KMO^{-/-} mice have better survival and lower inflammatory cells infiltration in the mice model of viral myocarditis, compared with KMO^{+/+} mice. KMO^{-/-} mice also had markedly higher serum levels of kynurenine, anthranilic acid, and kynurenic acid, and significantly lower levels of chemokines such as chemokine ligand (CCL) 1, CCL2, CCL3, CCL4.¹⁵⁷ Based on these findings, IDO inhibition, KMO inhibition, or a combination of KMO inhibition with supplementation of specific metabolites of kynurenine pathway may help to improve the outcome of myocarditis.

Kynurenine Pathway and Heart Transplantation

During a 1-year follow-up of 98 patients with heart transplantation it was found that compared with those without acute rejection, patients with acute rejection had significantly higher serum IDO activity 1 month after transplantation (3.32 ± 1.56 vs 2.62 ± 1.35). Additionally, it was reported that serum IDO activity was significantly (95% CI, OR 1.4 [1.033-1.876]) associated with cardiac allograft rejection among patients, independent of gender, age or renal function.¹⁵⁸

As mentioned previously, activation of kynurenine pathway increases T Reg cells differentiation and induces immune tolerance.^{10,159,160} Based on this theory, Yang et al¹⁵⁹ investigated the effect of kynurenine pathway on heart transplantation.

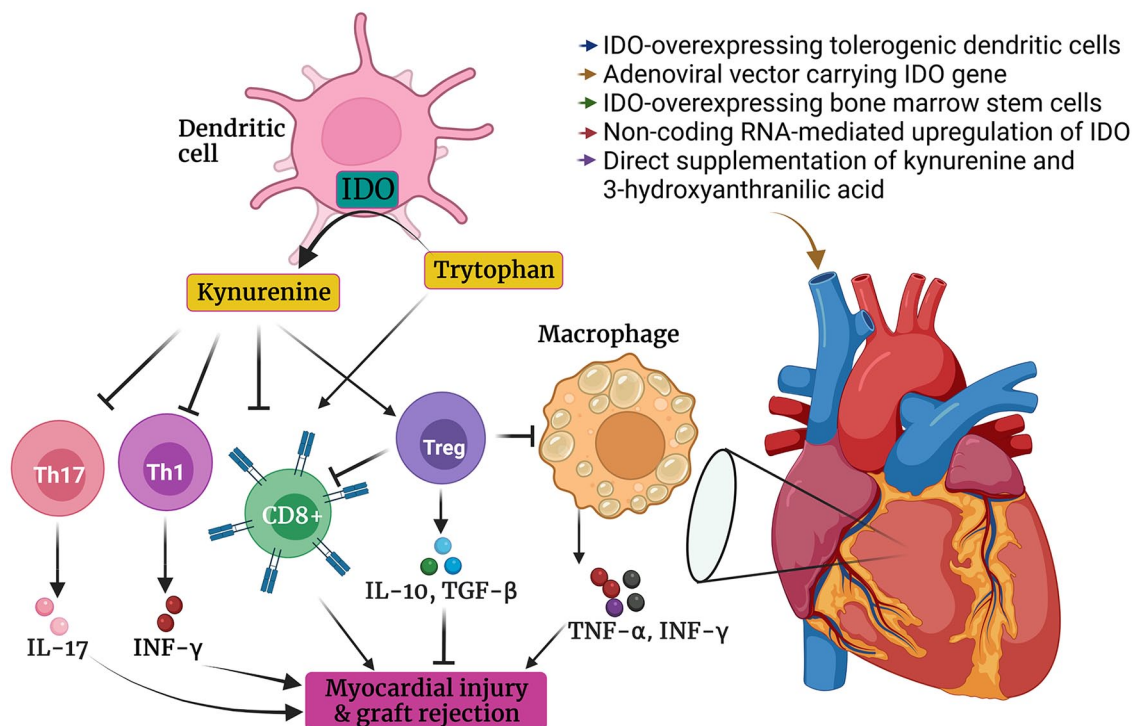


Figure 4. The protective effect of IDO/kynurenine on heart transplantation. Enhancing IDO expression by different methods can induce tolerance in the immune system. Kynurenine accelerates T Reg cells differentiation and suppresses the function of CD8+ cell, T helper 1 and T helper 17 cells in heart transplantation. In addition, IDO overexpression leads to tryptophan depletion. Sufficient amount of tryptophan is necessary for competent function of effector T cells. Subsequently, IDO overexpression increases anti-inflammatory cytokines such as IL10 and TGF- β and decreases pro-inflammatory cytokines such as IL17, TNF- α , and IFN- γ . These alterations prolongs graft survival.

It was observed that increased expression of IDO and activation of kynurenine pathway is associated with a higher abundance of T Reg cells and predicts decreased risk of graft rejection in rats. Consistently, a higher rejection rate was reported among rats receiving 1-MT. It was shown that adenoviral vector-mediated IDO overexpression by dendritic cells significantly postpones heart allograft rejection in mice and prolongs the survival of animals.¹⁶¹ Likewise, treatment of heart transplanted rats with IDO-overexpressing bone marrow stem cells markedly improved their ejection fraction and prolonged their survival.¹⁶² In addition, IDO overexpression was associated with a significant increase in IL10, transforming growth factor (TGF)- β 1, TGF- β 2 and TGF- β 3 and T Reg cells abundance.¹⁶² IDO overexpression also decreased IL2, IFN- γ , major histocompatibility complex (MHC) II, CD8+ and CD86+ cell.¹⁶² Intracoronary injection of adenoviral-mediated IDO overexpressing dendritic cells enhanced heart allograft survival in rats and decreased IFN- γ , IL-1, and TNF- α levels¹⁶³ (Figure 4). Likewise, several studies indicated that IDO overexpression in the immune cells, induced by gene transfection techniques, protects against heart allograft rejection, reduces CD8+ cells response, prevents inflammatory cytokines release, potentiates T Reg response, and enhances the immunomodulatory effect of other drugs such as cyclosporine to prevent heart allograft rejection in mice and rats¹⁶⁴⁻¹⁶⁹ (Table 1). Interestingly, tolerogenic dendritic cells transfer

from one heart transplant recipient to another significantly improved graft survival mediated through upregulation of IDO expression, increased T Reg cell differentiation, and suppressed anti-donor T cells response.¹⁷⁰ Interestingly, pretreatment with a single dose of 3-hydroxyanthranilic acid and allogeneic dendritic cells 7 days before transplantation markedly augmented the survival of cardiac allograft in rats and induced tolerance in recipients T cells.¹⁷¹ Li et al¹⁷² uncovered that intravenous administration of either tryptophan catabolic metabolites or dendritic cells transfected with adenovirus vector carrying IDO gene could downregulate anti-donor T cells function and prolong cardiac allograft survival in mice. Also, their combination was notably superior, compared with each one of them separately. Accordingly, the authors concluded that both tryptophan depletion and accumulation of kynurenine and its metabolites are crucial for cardiac allograft survival¹⁷² (Figure 4). Consistently, it was shown that both tryptophan starvation and tryptophan catabolites lead to general control nonderepressible 2 (GCN2) kinase-dependent downregulation of T cell receptor (TCR) ζ -chain in CD8+ T cells of mice and suppresses T cell-mediated cytotoxic activity.¹⁷³ Alloreactive CD8+ T cells are enormously involved in graft rejection and suppression of CD8+ T cells response can markedly prolong heart transplant survival.¹⁷⁴ IDO overexpression ameliorates T helper 17 response, decreases IL17 levels, shifts T cells response toward T Reg response in heart

Table 1. Implication of tryptophan/kynurenine pathway in the survival of heart transplantation.

AUTHOR	HUMAN/ANIMAL	METHOD	FINDINGS
Suarez-Fuentetaja et al ¹⁵⁸	Human	An observational study measuring serum IDO activity in patients with heart transplantation	Patients with acute rejection had higher IDO serum activity after 1 month of transplantation. Also, IDO serum activity independently (95% CI, OR 1.4 [1.033-1.876]) predicted graft rejection among patients with heart transplantation
Li et al ¹⁶⁴	Mouse	Treating animals with dendritic cells transfected with adenovirus vector carrying IDO gene	IDO overexpression improved survival, postponed graft rejection, reduced IFN- γ production, and accelerated CD4 ⁺ cell death
He et al ¹⁶²	Rat	Treating animals with bone marrow stem cells transfected with lentiviral vector carrying IDO gene	IDO overexpression prolonged survival, enhanced ejection fraction, decreased CD86 ⁺ , CD80 ⁺ cells, MHC II, IL2 and IFN- γ and increased T Reg cells abundance and the expression of CD274, IL10, TGF- β 1, TGF- β 2, TGF- β 3 in the heart allograft
Yang et al ¹⁵⁹	Rat	Treating rats with immutol, cyclosporine and 1-MT	1-MT significantly blocked kynurenine pathway and decreased graft survival. Activation of kynurenine pathway has been associated with increased abundance of T Reg cells, higher concentrations of IL10, and TGF- β , as well as decreased abundance of CD8 ⁺ cells
Dai et al ¹⁷¹	Rat	A single-dose intravenous administration of 3-hydroxyanthranilic acid + allogeneic dendritic cells 7 days before heart transplantation	Pretreatment with the combination of 3-hydroxyanthranilic acid + allogeneic dendritic cells enhanced cardiac allograft survival and suppressed T cells activity
Lv et al ¹⁶¹	Mouse	Treating mice with dendritic cells transfected with adenovirus vector carrying IDO gene	IDO overexpression enhanced both cardiac graft survival and function. Higher IL10/IL6 ratio and lower levels of IFN- γ and IL-2 were found in treated group
Li et al ¹⁷⁰	Mouse	Transferring tolerogenic dendritic cells from a tolerant recipient to secondary recipient in mice heart transplantation model	Tolerogenic dendritic cells transfer from a tolerant recipient to another recipient significantly enhanced IDO expression, induced T Reg differentiation, suppressed anti-donor T cells activity and increased graft survival in the secondary recipient
Li et al ¹⁷²	Mouse	Treating mice with intravenous injection of tryptophan catabolic metabolites, dendritic cells transfected with adenovirus vector carrying IDO gene and their combination	Treating mice with tryptophan catabolic metabolites or adenoviral transfected dendritic cells significantly increased cardiac graft survival, decreased IL2, TNF- α and IFN- γ and increased IL10. Significantly greater improvement was observed in combination therapy
Yu et al ¹⁶⁹	Mouse	Cardiac allograft injection with adenovirus vector carrying IDO gene.	Higher IDO expression was detected in treated mice. Increased IDO expression was associated with decreased expression of IL2, IL17, and IFN- γ . IDO enhanced T Reg cells differentiation and prolonged graft survival
He et al ¹⁶⁶	Rat	Intravenous injection of DO1-BMSC-exosomes 48 h after heart transplantation	Treated rats showed better cardiac function. Treatment with DO1-BMSC-exosomes augmented T Reg response and suppressed CD8 ⁺ response
Li et al ¹⁷⁶	Mouse	Measuring microRNAs in mice cardiac transplantation and assessing their effect on cardiac allograft rejection and IDO expression	miR-669b-3p decreased IDO expression, thereby expediting graft rejection
Sucher et al ¹⁶⁷	Mouse	Treating heart transplanted mice with cytotoxic T lymphocyte-associated antigen-4 Ig (CTLA4Ig)	CTLA4Ig promoted IDO expression, thereby increasing graft survival. IDO gene deletion accelerated graft rejection. Furthermore, IDO inhibition since transplantation or 50 days after transplantation attenuated the beneficial effects of CTLA4Ig on graft survival. In addition, T Reg cells depletion impairs CTLA4Ig-mediated graft survival
Zhang et al ¹⁶⁵	Mouse	Intravenous injection of dendritic cells transfected with adenovirus vector carrying GDF15 gene 7 days before transplantation	GDF15 overexpression upregulated IDO in dendritic cells, thereby inducing tolerance in T cells and delaying graft rejection

transplantation.¹⁶⁹ IL17 severely instigates inflammatory response in heart transplants and accelerates graft rejection¹⁷⁵ (Figure 4).

Even, it was demonstrated that IDO and kynurenine pathway are the target of other molecules such as growth/differentiation factor-15 (GDF15) and non-coding RNAs for regulation of cardiac graft survival. They negatively or positively modulate IDO expression, thereby regulating the immune system and graft survival.^{165,176} Therefore, kynurenine pathway has both prognostic and therapeutic value in heart transplantation. Besides, pharmacological augmentation of kynurenine pathway can ameliorate immune response and prolong the survival of heart transplants.

Kynurenine Pathway and Vascular Transplantation

Similar to heart transplantation, several studies have shown the beneficial effects of kynurenine and its metabolites on vascular transplantation. Herein, Juli et al¹⁷⁷ revealed that post-transplantation mesenchymal stem cells (MSCs) injection into the soft tissue surrounding femoral artery transplant significantly prevented perivascular lymphocyte infiltration, intimal hyperplasia, and graft occlusion in a porcine model of femoral artery transplantation. It was found that MSCs increased IFN- γ , IDO, IL10, and T Reg cells abundance in the vascular graft.¹⁷⁷ IDO expression by VSMCs induces an immune-privileged condition in the medial layer of the artery, which prevented allogeneic T cells infiltration and prolonged graft survival in a mice model.¹⁷⁸ Perivascular infiltration of leukocytes particularly neutrophils and T lymphocytes leads to vascular rejection.¹⁷⁹ The beneficial effect kynurenine on the prevention of perivascular infiltration and vascular graft rejection can generally benefit several organs transplantation.¹⁸⁰

Kynurenine Links Cardiovascular Diseases With Other Diseases

In previous sections, it has been discussed how kynurenine pathway is involved in different cardiovascular diseases. In addition to cardiovascular diseases, kynurenine pathway is involved in a wide variety of other medical conditions which can directly or indirectly affect cardiovascular health. In this section, we briefly discuss the role of kynurenine and its metabolites in some medical conditions and explain their possible interactions with cardiovascular diseases.

Kynurenine Pathway in Aging and Frailty

Aging is related to the impaired function of cells and organs, leading to several diseases such as cardiovascular and metabolic diseases, neurodegenerative diseases, and cancer.¹⁸¹ Chronic low-grade inflammation or “inflamm-aging” accelerates cardiac and vascular aging, increases the risk of atherosclerosis and atherothrombosis.^{182,183} Frailty and cardiovascular diseases have mutual interaction, that is, cardiovascular diseases are prevalent among older people with frailty and patients with

cardiovascular disease are at higher risk of frailty.¹⁸³ Likewise, the removal of senescent cells from tissues was shown to improve several chronic diseases.¹⁸¹

Frail subjects possess higher serum concentrations of kynurenine, compared to those with robustness and pre-frailty.¹⁸⁴ Overactivation and dysregulation of kynurenine pathway are vigorously associated with aging, frailty, weaker grip strength, slower walking speed, and increased inflammatory markers such as TNF- α R1 and IL6.¹⁸⁵ Studies showed that the inhibition of kynurenine pathway prolongs lifespan in *Drosophila* and worms.¹⁸⁶⁻¹⁸⁸ Aging is associated with elevated kynurenine and kynurenine/tryptophan ratio, which correlates with an increased mortality rate among the elderly population.^{189,190} Increased kynurenine and kynurenine/tryptophan ratio are associated with cardiovascular diseases mortality and all-cause mortality in the Hordaland Health Study.⁹⁰ Kynurenine impairs autophagy and induces senescent phenotype in MSCs, which are involved in the regulation of adipogenesis, bone and bone marrow homeostasis.¹⁹¹ Higher kynurenine levels in older age may be a sign of organs dysfunction such as cardiovascular dysfunction.⁹⁰ Also, the increased production of kynurenine and its metabolites can change the clinical course of several cardiovascular diseases, as previously mentioned.

Kynurenine links depression to cardiovascular diseases

Depression and cardiovascular diseases have a bidirectional relation and the underlying mechanism is complex and multifactorial.¹⁹² Patients with depression are at higher risk of cardiovascular diseases and patients with hypertension, coronary artery diseases and other cardiovascular diseases are more susceptible to depression.¹⁹² In addition, it has been demonstrated that depression increases cardiovascular mortality among patients.^{193,194} Depression is one of the significant risk factors for coronary artery disease-related mortality.¹⁹⁵ Tryptophan concentrations have been negatively associated with the presence of depression among patients with heart failure.¹⁹⁶ Interestingly, it has been shown that mice with heart failure, particularly those having high kynurenine serum levels and kynurenine/tryptophan ratios, are more susceptible to developing depression.¹⁹⁷ Furthermore, increased expression of KMO and decreased expression of KAT in the heart were strongly associated with depressive behavior in mice with heart failure.¹⁹⁷

Tryptophan depletion and accumulation of toxic metabolites of the kynurenine pathway or shifting from serotonin to kynurenine are involved in the pathophysiology of inflammation-induced depression.^{198,199} Serotonin regulates the function of the CNS and cardiovascular system. Depletion of tryptophan, as a precursor for serotonin, interferes with the normal function of the CNS and cardiovascular system.^{200,201} Additionally, toxic metabolites of kynurenine pathway affect

the CNS in several ways, including production of ROS, enhancing lipid peroxidation, increasing excitotoxicity, and altering glutamatergic activity.^{202,203} Intraperitoneal injection of kynurenine in mice resulted in depressive-like behavior.²⁰⁴ Endotoxin-induced depressive-like symptoms were attenuated in the presence of IDO inhibition, IDO deletion, or IFN- γ receptor deletion.^{205,206} Depressed patients with co-morbid cardiovascular diseases exhibited greater serum kynurenine/tryptophan ratio, compared to patients with cardiovascular diseases but without depression, which indicates the role of depression in shifting tryptophan metabolism to kynurenine pathway.²⁰⁷ A meta-analysis by Hunt et al²⁰⁸ showed that increased risk of depression after treatment with IFN- α in patients with chronic medical conditions could be mediated by the kynurenine pathway activity. Raison et al²⁰⁹ revealed that the administration of IFN- α elevated the cerebrospinal fluid (CSF) levels of kynurenine and quinolinic acid, which related to the severity of depressive symptoms. Selective serotonin reuptake inhibitors (SSRIs) relieve cytokine-induced depression.²¹⁰ Interestingly, Halaris et al²¹¹ revealed that the levels of 3-hydroxykynurenine and quinolinic acid were decreased following treatment with escitalopram, which shows the neuroprotective effect of SSRIs can partly be due to their effect on kynurenine and its metabolites. Kocki et al²¹² also uncovered that different antidepressants such as fluoxetine, citalopram, amitriptyline, and imipramine increase the expression of KAT and decrease the expression of KMO in the primary astroglial culture. In addition, these antidepressants increased kynurenic acid/3-hydroxykynurenine ratio.²¹²

Deregulation of kynurenine pathway seems to be a common finding in depression and cardiovascular diseases which predicts their co-existence. Kynurenine metabolites converge the effect of inflammation and immune system on the CNS and cardiovascular system and can be used as therapeutic and diagnostic targets for both depression and cardiovascular diseases.

Kynurenine links CKD to cardiovascular diseases

The kidney and cardiovascular system have mutual interactions. CKD is a risk factor for heart failure, coronary artery disease, and arrhythmias and increases cardiovascular mortality.²¹³ In return, cardiovascular dysfunctions such as low-cardiac output, high blood pressure, and endothelial dysfunction impair the kidney's function and lead to CKD in the long-term.²¹³

Previously, it has been mentioned how kynurenine pathway is involved in the pathophysiology of hypertension, as a major driver for both cardiovascular and kidney diseases.^{214,215} Kynurenine levels were negatively correlated with glomerular filtration rate (GFR) among patients with congestive heart failure.¹⁰² The inverse correlation was also demonstrated in both subgroups of heart failure with reduced and preserved ejection fraction.¹⁰³ Higher levels of kynurenine pathway metabolites such as kynurenine itself, 3-hydroxykynurenine,

kynurenic acid, anthranilic acid, and quinolinic acid in patients with CKD have been associated with increased intima-media thickness and higher expression of inflammatory and coagulatory molecules such as thrombomodulin, von Willbrand factor (vWF), intercellular adhesion molecule 1 (ICAM1), and VCAM1.^{216,217} Furthermore, increased levels of anthranilic acid and quinolinic acid have been associated with increased plasma levels of prothrombin fragments 1 + 2 and hypercoagulable state among patients with end-stage renal disease (ESRD).²¹⁸ Furthermore, metabolomics assessment of 146 patients with ESRD uncovered that 3-hydroxykynurenine is independently associated with the presence of cardiovascular diseases among these patients.²¹⁹ Similarly, a higher kynurenine/tryptophan ratio was found among CKD patients with a history of cardiovascular diseases, compared to those without cardiovascular diseases.²¹

Higher levels of kynurenic acid, 3-hydroxykynurenine, and kynurenine were found in advanced stages of CKD, compared to primary stages of CKD.²²⁰ Low plasma tryptophan levels were associated with an increased risk of cardiovascular diseases among CKD patients.²²⁰ Likewise, 3-hydroxykynurenine and kynurenine were negatively correlated with estimated glomerular filtration rate (eGFR) among CKD patients.²²¹ By using the laboratory data of 154 patients with CKD and 42 patients without CKD, Pan et al²²² showed that the logarithm of kynurenine/tryptophan ratio is independently associated with CKD and albuminuria. Also, it was found that IDO activity higher than 0.0466 predicts CKD with a sensitivity of 83.8% and a specificity of 75%. Similarly, the analysis of metabolomics biomarkers of 1741 patients showed that kynurenine (95% CI, OR 1.98 [1.05-3.73]) and kynurenine/tryptophan ratio (95% CI OR 3.20 [1.57-6.51]) significantly predicts the incidence of CKD in the next 8 years after assessment.²²³ IDO expression increases during TGF- β -mediated renal fibrosis and partly prevents fibrogenesis.²²⁴ Furthermore, IDO overexpression was shown to be protective against renal inflammation and renal injury.^{224,225} However, recent studies showed that inhibition of kynurenine pathway ameliorates renal fibrosis.²²⁶⁻²²⁸ Pan et al²²⁶ indicated that either IDO deletion or inhibition attenuates glycogen synthase kinase 3 beta (GSK3 β) and Wnt/ β -catenin pathway, thereby decreasing the expression of pro-fibrotic factors such as smooth muscle alpha-actin (α -SMA), fibronectin, and vimentin and mitigating renal fibrosis in the mice model of acute kidney injury.

Based on previous findings, kynurenine pathway possesses prognostic value in both CKD and cardiovascular diseases. Kynurenine metabolites have therapeutic value in CKD and cardiovascular diseases, which demands future studies. Furthermore, overactivation of kynurenine pathway in CKD or cardiovascular disease may alter the incidence of the other one. Herein, targeted therapy for kynurenine pathway may be a good option to improve the function of both the cardiovascular and urinary systems.

Kynurenine links cirrhosis to cardiovascular diseases

Cirrhosis leads to cardiac dysfunction known as cirrhotic cardiomyopathy.²²⁹ Impaired β -adrenergic function, systemic inflammation, increased production of NO, endocannabinoids, and other endogenous mediators have been implicated in the pathogenesis of cirrhotic cardiomyopathy.²³⁰ In return, cardiac dysfunction due to heart failure, constrictive pericarditis, valvulopathy, myocarditis, and myocardial infarction can lead to liver damage known as cardiac hepatopathy.²³¹

Patients with acutely decompensated cirrhosis and particularly patients with acute-on-chronic liver failure have higher levels of kynurenine metabolites, compared with healthy individuals and patients with compensated cirrhosis.²² In addition, higher levels of kynurenine metabolites are associated with nosocomial infection and mortality among patients with acute decompensated cirrhosis.²² Liver inflammation and fibrosis are associated with an increased plasma kynurenine/tryptophan ratio.^{232,233} An in-vitro study by Oh et al²³⁴ revealed that inhibition of IDO by 1-MT enhances the apoptosis of hepatic stellate cells, which are the main drivers of liver fibrosis. Furthermore, carbon tetrachloride (CCl₄)-induced liver fibrosis was significantly attenuated in IDO^{-/-} mice, compared to wild-type mice.²³⁵ Consistently, treatment with 1-MT alleviates liver inflammation and fibrosis in the rat model of biliary cirrhosis.¹¹³ Treatment with 1-MT also improved cardiac chronotropic response to epinephrine in the rat model of cirrhotic cardiomyopathy.¹¹³

Regarding the involvement of kynurenine metabolites in cardiac remodeling and hepatic fibrosis and the mutual interaction between cirrhosis and cardiac dysfunction, modulation of kynurenine pathway may be a suitable therapeutic approach to preserve the function of the heart and liver.

Kynurenine links cancer to cardiovascular diseases

A higher incidence of cardiovascular events is recorded among cancer patients. For instance, the incidence of cardiovascular events between 108 215 cancer survivors and 523 541 healthy individuals revealed that venous thromboembolism has a significantly higher risk among 18 of 20 site-specific cancers (from HR 1.72 [1.57-1.89] in prostate cancer to HR 9.72 [5.50-17.18] in pancreatic cancer) for more than 5 years after cancer diagnosis.²³⁶ Additionally, higher risks of heart failure, cardiomyopathy, coronary artery diseases, arrhythmia, stroke, pericarditis, and valvular heart diseases were found among cancer survivors.²³⁶ Even, risks of venous thromboembolism, heart failure, and cardiomyopathy were higher among younger patients or those without previous history of cardiovascular diseases.²³⁶ Furthermore, a higher prevalence of cardiovascular risk factors such as hypertension and diabetes were found among cancer survivors.²³⁷ Cardiovascular death constitutes a major proportion of mortality among cancer patients. Of 1 228 328 patients with 28 cancer types, 38% died because of

cancer itself, and 11% died of cardiovascular diseases, in particular heart diseases.²³⁸ Herein, cardiovascular adverse effects of anti-cancer drugs remain a great concern in cancer chemotherapy and early detection and management of cardiovascular complications of chemotherapy can markedly improve patients' lifespan.^{239,240}

Kynurenine serves as a defensive mechanism for cancer cells and contributes to cancer cells' immune-evasion.¹⁰ Kynurenine/AHR stimulates T Reg cells differentiation and suppresses the cytotoxic function of effector T cells in different types of cancer.¹⁰ Kynurenine pathway is significantly activated in different types of cancer and correlates with the poor prognosis of the disease.¹⁰ Besides, attenuation of kynurenine/AHR signaling may be helpful in cancer chemotherapy.²⁴¹ In previous sections, we have comprehensively discussed how impaired kynurenine pathway can alleviate or exacerbate several cardiovascular diseases. As discussed previously, overactivation of kynurenine pathway can aggravate myocardial remodeling, heart failure, and myocardial infarction as the major causes of cardiovascular mortality among cancer survivors. Therefore, kynurenine pathway may be a proper target to improve cancer chemotherapy and relieve the following cardiovascular diseases.

Kynurenine links diabetes to cardiovascular diseases

Cardiovascular diseases such as hypertension, heart failure, coronary artery disease, and peripheral arterial disease are common among patients with diabetes.²⁴² Diabetes and cardiovascular diseases are affected by similar etiologic factors such as endothelial dysfunction, vascular inflammation, atherosclerosis, RAAS overactivity, and oxidative stress.²⁴² Interestingly, a 7.6-year follow-up of 2519 patients with coronary artery disease revealed that urine kynurenine/tryptophan ratio is a strong predictor of type 2 diabetes in these patients. Comparing quartile 4 with quartile 1 of kynurenine/tryptophan ratio, showed that kynurenine/tryptophan ratio was independently (95% CI, HR 2.35 [1.39, 3.96]) associated with the incidence of diabetes in the follow-up period.²⁴³ Previously, it was found that overactivity of kynurenine pathway is correlated with insulin resistance.²⁴⁴ In particular, increased plasma concentrations of xanthurenic acid are associated with the presence of insulin resistance and diabetes (OR 1.15 [1.03-1.27]) among elderly subjects.²⁴⁵ Furthermore, it was shown that alleviation of insulin resistance by metformin is associated with a decrease in kynurenine/tryptophan ratio.²⁴⁶ Feeding mice with kynurenine enhanced their weight gain and led to liver steatosis and hyperglycemia.²⁴⁷ Interestingly, inhibition of kynurenine pathway attenuated olanzapine-mediated weight gain and insulin resistance in mice.¹⁸ Insulin resistance not only leads to diabetes but also contributes to the development of cardiovascular diseases.^{248,249} Therefore, modulation of kynurenine pathway may improve insulin resistance as a common etiological factor for diabetes and cardiovascular diseases. Furthermore, increased

kynurenine metabolites in diabetes or cardiovascular diseases may help to develop the other one.

Conclusion and Future Research Direction

Dysregulation of kynurenine pathway is observed in different cardiovascular diseases and other medical conditions which have mutual interactions with cardiovascular health. Kynurenine metabolites possess diagnostic and prognostic value in cardiovascular diseases. In addition, preclinical studies have shown that augmentation or inhibition of certain branches of kynurenine pathway can alleviate the development or progression of cardiovascular diseases. However, it has been illuminated which metabolites of kynurenine are responsible for the observed effects in some cardiovascular diseases, it remains to be known in most cases. As mentioned, IDO inhibitors such as indoximod, epacadostat, and navoximod are currently used in cancer clinical trials.¹⁰ The same drugs can be used in cardiovascular clinical trials to treat myocardial infarction, heart failure and myocarditis. Furthermore, supplementation of kynurenine and its metabolites or new methods of gene and RNA delivery may be helpful for more efficient management of hypertension, atherosclerosis, heart transplantation and stroke. The kynurenine pathway includes several metabolites and now we just know the cardiovascular effects of some of the upstream metabolites and enzymes of this pathway. Additional studies are needed to provide a better knowledge of cardiovascular effects of downstream metabolites and enzymes of the kynurenine pathway. For instance, it was already shown that KMO inhibition is protective against stroke and myocarditis, 3-hydroxyanthranilic acid prevents atherosclerosis and xanthurenic acid decreases blood pressure. Future studies may show similar effects for other enzymes and metabolites of the kynurenine pathway. Furthermore, future clinical trials are needed to consolidate the results of preclinical studies.

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Author' Contributions

Moein Ala conceptualized this article. Moein Ala and Seyed Parsa Eftekhar performed the literature search and wrote the draft. Moein Ala edited the article.

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