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Exercise-driven changes in tryptophan metabolism leading to healthy aging

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ABSTRACT

Tryptophan metabolism is a critical regulator of physiological and pathological processes, primarily through the kynurenine (KYN), serotonin and indole pathways. Dysregulation of indoleamine 2,3-dioxygenase 1 (IDO1) activity, serotonin and indole gut-microbial metabolism has been linked to a broad range of age-related chronic conditions, including cancer, cardiovascular disease, sarcopenia, and neurodegenerative disorders. Exercise emerges as a potent modulator of these pathways, redirecting tryptophan utilization to limit the accumulation of KYN metabolites while maintaining balanced indole and serotonin production. By regulating IDO1 activity and KYN flux, exercise alleviates inflammation, restores metabolic homeostasis, improved muscle integrity, neuroprotection, and overall systemic health. Mounting evidence supports the notion that lifestyle-based interventions targeting IDO1 and its downstream metabolites, particularly by physical activity, may offer a promising avenue for extending health span and mitigating the burden of chronic disease. This review synthesizes current advances in understanding the regulation of tryptophan metabolism (KYN, Serotonin and Indole) and highlights the unique capacity of exercise to remodel these pathways, underscoring their therapeutic potential in the context of healthy aging.

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1. Introduction

Aging is associated with chronic, low-grade inflammation, commonly known as inflammaging. As the immune system becomes dysregulated with age, it produces excessive pro-inflammatory cytokines, leading to several pathological conditions such as neurodegeneration, cognitive decline, muscle dysfunction, osteoporosis, and cardiovascular disease [1,2]. Exercise has consistently been shown to be one of the most effective non-pharmacological interventions to reduce chronic inflammation, preserve muscle health, improve brain function and delay age-related comorbidities [3].

Regular physical activity, including both resistance and aerobic training, enhances muscle protein synthesis, improves mitochondrial function, and promotes metabolic flexibility [4,5]. In addition to its effects on muscle, exercise acts as a potent anti-inflammatory stimulus, lowering circulating pro-inflammatory cytokines and stimulating the release of bioactive molecules known as exerkines [6,7]. Exerkines comprising proteins, peptides, and metabolites promote systemic adaptations that regulate inflammation, bolster immune function, enhance metabolism [8,9] and improve overall health. Among the most studied exerkines are interleukin-6 (IL-6), irisin, and brain-derived neurotrophic factor (BDNF), all of which have demonstrated significant anti-inflammatory properties [9,10]. For example, exercise-induced IL-6 promotes the release of anti-inflammatory cytokines such as IL-10 and suppresses TNF-α production [11], while irisin and BDNF are involved in improving mitochondrial function, brain health, and neuromuscular communication [12].

Emerging evidence suggests that the anti-inflammatory effects of exercise may, in part, be mediated through modulation of the indoleamine 2,3-dioxygenase 1 (IDO1)-kynurenine (KYN) pathway [13]. IDO1 is a critical enzyme that catalyzes the degradation of tryptophan into KYN, a metabolite known to influence immune homeostasis and inflammatory signaling [14]. While this pathway typically serves a protective role in maintaining immune tolerance, its chronic overactivation during aging has been linked to heightened inflammation, immune suppression, and muscle wasting [15,16]. Elevated KYN levels are particularly concerning as they impair muscle function and reduce mitochondrial efficiency, compounding the effects of muscle decline [17,18]. Dysregulated tryptophan metabolism also affects central nervous system function, contributing to cognitive decline and neurodegenerative processes [19,20]. Pharmacological inhibition of IDO1 has emerged as a promising therapeutic avenue to combat inflammaging, preserve muscle integrity, and promote healthy aging [21,22].

Recent studies highlight the beneficial effects of exercise in modulating tryptophan metabolism and counteracting the negative effects of KYN accumulation [23,24]. Concurrently, exercise appears to naturally attenuate KYN accumulation by upregulating skeletal muscle kynurenine aminotransferases (KATs), which convert KYN into kynurenic acid a neuroprotective and less toxic metabolite that cannot cross the blood-brain barrier [25,26]. This exercise-induced metabolic shift not only reduces peripheral KYN toxicity but may also alleviate inflammation, decrease neurodegeneration, and improve brain and muscle health. Several preclinical studies have demonstrated the positive impact of exercise on brain and muscle health by regulating IDO1-KYN signaling pathways [13,27].

This review aims to examine the relationship between exercise, and tryptophan metabolism (KYN, Serotonin and Indole) in the context of inflammation, brain, and muscle function. By synthesizing current findings, we seek to offer insights and probe into how these interventions can combat age-related comorbidities. Exploring how exercise influences the TRP signaling pathway could elucidate novel strategies to promote healthier aging and reduce the burden of comorbidities associated with aging.

2. Overview of tryptophan metabolism

2.1. KYN signaling pathway

The essential amino acid tryptophan is not only used for protein synthesis but also serves as a precursor for several important biological processes [28,29]. The IDO1-KYN signaling pathway is the main route through which the essential amino acid tryptophan is broken down in the body (Fig. 1) [29]. Central to the regulation of the KYN pathway are two key enzymes: Indoleamine 2,3-dioxygenase 1 (IDO1) and Tryptophan 2,3-dioxygenase (TDO) [14,30,31]. TDO is found primarily in the liver and helps to regulate baseline levels of tryptophan by catalyzing the first and rate-limiting step of the KYN pathway, while IDO1 is more ubiquitous; it becomes active when the immune system is triggered, especially during inflammation [31,32]. By converting tryptophan into KYN, IDO1 not only limits the availability of tryptophan for T cells but also produces metabolites that directly influence immune behavior [33]. Once tryptophan is converted into KYN, a cascade of downstream metabolites are produced [34].

KYN serves as a central intermediate in the KYN pathway and is further metabolized into several biologically active downstream compounds through the action of specific enzymes [34,35]. KYN aminotransferases (KATs) convert KYN into kynurenic acid (KYNA), a neuroprotective metabolite that acts as an antagonist at NMDA and α7-nicotinic receptors [36]. Alternatively, KYN 3-monooxygenase (KMO) converts KYN into 3-hydroxykynurenine (3-HK), which can generate reactive oxygen species and contribute to oxidative stress [37]. 3-HK is further metabolized by kynureninase (KYNU) into 3-hydroxyanthranilic acid (3-HAA), which is then converted into quinolinic acid (QUIN) by 3-hydroxyanthranilic acid oxidase (3-HAO) [38]. These enzymatic

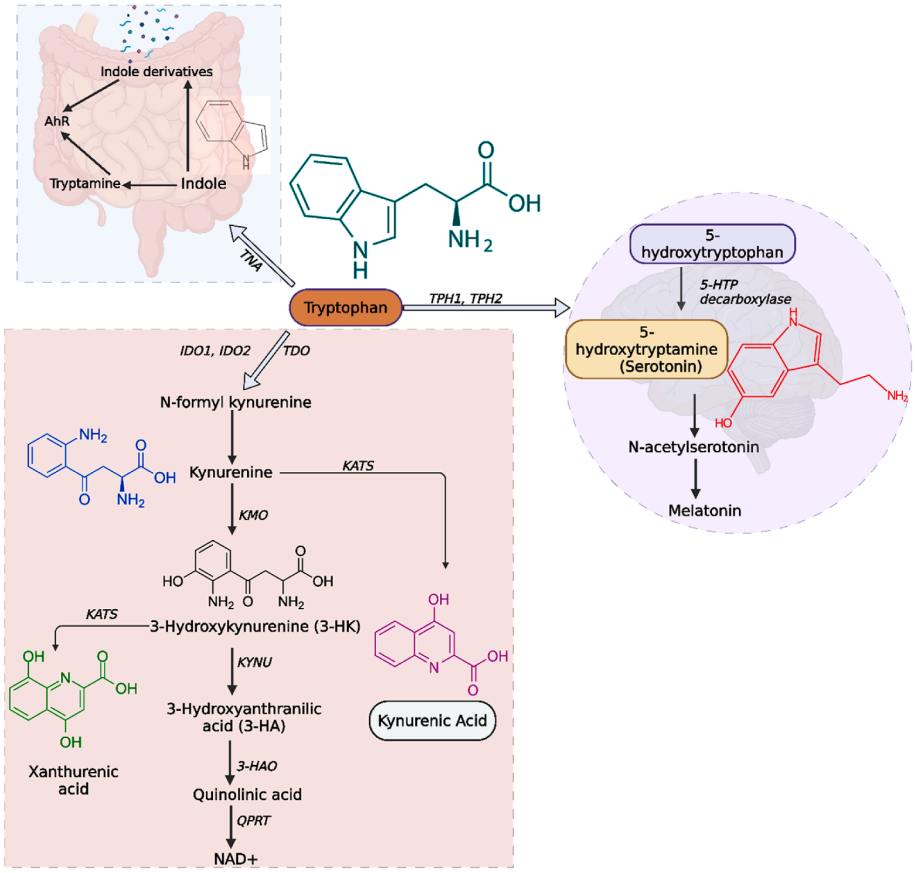

Fig. 1. Schematic diagram showing major metabolites of tryptophan in serotonin and kynurenine pathways. (IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; KAT, kynurenine aminotransaminase; KMO, kynurenine 3-monooxygenase; KYNU, kynureninase) (Created using https://BioRender.com).

steps create a balance between protective and harmful metabolites, and dysregulation of this pathway has been implicated in several pathological conditions, including neurodegenerative diseases, chronic inflammation, and aging-related muscle loss [34,39].

Some of these metabolites are quite powerful in their effects. For instance, kynurenic acid (KYNA) has protective roles in the brain; it helps alleviate excessive excitatory signals and prevents neurons from overactivation [40]. On the other hand, quinolinic acid (QUIN) is a neurotoxic metabolite, which has the capability to overstimulate neurons and contributes to oxidative stress and neurodegeneration [41]. This dynamic interplay between KYNA and QUIN is essential in the development of neurological conditions like depression, Alzheimer's disease, and other disorders of the brain.

Beyond the nervous and immune systems, the KYN pathway also plays a major role in musculoskeletal health [42]. With age or chronic inflammation, IDO1 becomes persistently active, and levels of KYN rise [15]. These elevated metabolites can interfere with muscle regeneration, impair mitochondrial function, and contribute to muscle weakness and loss, particularly in aging individuals [15,18]. Interestingly, exercise can alter how this pathway functions. Physical activity has been shown to increase the expression of enzymes that convert KYN into its protective form, KYNA, particularly in skeletal muscle [23]. This does not only diminish the effects of neurotoxic metabolites but also helps protect the brain and muscles from inflammation-related damage [43]. In this way, exercise acts almost like a natural modulator of the KYN pathway, offering benefits far beyond fitness [44].

2.2. Serotonin pathway

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a biologically active monoamine neurotransmitter synthesized from the essential amino acid tryptophan through a two-step enzymatic process (Fig. 1) [45]. This biosynthetic pathway is critical for regulating various physiological functions, including mood, cognition, sleep, thermoregulation, appetite, and gastrointestinal motility [46]. The first and rate-limiting step in serotonin synthesis is the hydroxylation of tryptophan [47]. This reaction is catalyzed by the enzyme tryptophan hydroxylase (TPH), which exists in two isoforms: TPH1, predominantly expressed in peripheral tissues (such as the gut and pineal gland), and TPH2, primarily found in serotonergic neurons of the central nervous system [48]. TPH requires molecular oxygen and the cofactor tetrahydrobiopterin (BH_4) to convert tryptophan into 5-hydroxytryptophan (5-HTP) [48]. In the second step, 5-HTP is decarboxylated to serotonin by the enzyme aromatic L-amino acid decarboxylase (AADC), also referred to as DOPA decarboxylase [45]. This reaction occurs in both peripheral tissues and the brain and requires pyridoxal phosphate (vitamin B6) as a coenzyme [45,48].

Surprisingly, about 90–95 % of the body's total serotonin is localized in the gastrointestinal (GI) tract rather than the central nervous system (CNS) [49]. This peripheral serotonin is produced by enterochromaffin cells that line the intestinal walls [49,50]. Serotonin synthesized in the gastrointestinal tract is unable to cross the blood-brain barrier and therefore does not exert direct effects on the central nervous system [51]. However, it plays a critical role in peripheral physiological processes, particularly in

regulating intestinal motility, coordinating smooth muscle contractions, and maintaining overall gastrointestinal function [49,51]. Dysregulation of this system can contribute to disorders like irritable bowel syndrome (IBS) and chronic constipation [52]. The remaining serotonin, about 5 %, is synthesized in the central nervous system, where it functions as a key neurotransmitter influencing mood and behavior [51]. In the brain, serotonin is produced primarily in the raphe nuclei of the brainstem, and it plays a critical role in mood regulation, emotional processing, sleep, and cognitive function [53]. Dysregulation of central serotonergic signaling has been strongly implicated in the pathophysiology of various neuropsychiatric disorders, including depression, anxiety, and other mood disorders [54]. Consequently, pharmacological agents such as SSRIs (Selective Serotonin Reuptake Inhibitors), which enhance synaptic serotonin availability, are commonly employed as first-line treatments for these conditions [55].

Even though serotonin in the gut and the brain operate independently in terms of biosynthesis, they are functionally interconnected through the gut-brain axis [56]. This bidirectional communication network, which integrates neural (e.g., vagus nerve), endocrine, and immune signaling pathways, enables physiological states in the gut to influence brain function and vice versa [56]. This may help explain why people with digestive disorders often also experience anxiety or depression. Serotonin serves diverse physiological roles: centrally, it regulates mood, cognition, and sleep; peripherally, it modulates gastrointestinal motility and homeostasis [57]. Several studies have reported that exercise enhances cognitive health in part by increasing serotonin levels [46]. Understanding the mechanisms by which exercise influences serotonin levels both centrally and peripherally may provide valuable insights into therapeutic strategies that target the gut-brain axis to promote both mental and physical health.

2.3. Indole pathway

Beyond the kynurenine and serotonin pathways, tryptophan metabolism also proceeds through the indole pathway, primarily mediated by the gut microbiota. In this pathway, intestinal bacteria metabolize tryptophan into a variety of indole derivatives and related compounds such as indole-3-lactic acid (ILA), indole-3-propionic acid (IPA), and indole-3-acetic acid (IAA) [58–60] These microbiota-derived metabolites exert potent immunomodulatory and anti-inflammatory effects, establishing a critical molecular interface between the gut microbiome and host physiology. Indole derivatives act as natural ligands for the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor expressed in multiple tissues [61,62]. Upon binding to AhR, these metabolites trigger transcriptional programs that regulate immune tolerance, mucosal integrity, and xenobiotic metabolism [62]. Activation of AhR by indole derivatives induces the expression of genes such as CYP1A1, IL-22, and Claudin-1, which collectively improve intestinal barrier function, and suppress pro-inflammatory cytokine production [63].

Interestingly, physical activity modulates this indole-AhR axis in an intensity-dependent manner [64]. Exercise alters the composition and metabolic activity of the gut microbiota, [64]. As a result, enhances the production of beneficial indole metabolites such as IPA and IAA, leading to a sustained activation of AhR and its downstream target genes that mediate anti-inflammatory, antioxidant, and metabolic regulatory functions. This mechanism provides a compelling explanation for how exercise contributes to systemic health not only by improving cardiovascular and musculoskeletal health but also by modulating microbiota-derived signaling pathways.

3. Overview of age-related alteration in KYN metabolites

We [65,66] and others [14,67] have reported dysregulation of IDO1 activity and expression with age in several tissues. KYN levels increase with age and are associated with frailty [68], as well as higher mortality in older adults [69]. Our group demonstrated elevated levels of serum kynurenine precursor, N-formylkynurenine (NFK) with age [70]. We also reported elevated levels of KYN-induced muscle (Kaiser et al., 2019) and bone loss [70]. Chronic intraperitoneal administration of KYN (10 μg/kg, 4 weeks) in young mice reduced muscle mass and strength while increasing lipid peroxidation. Earlier studies had already hinted that changes in tryptophan metabolism might contribute to osteoporosis (Forrest et al., 2006). This idea was supported by several strong clinical evidences. In the Hordaland Health Study (1998–2000), they discovered that older adults (ages 71–74) with higher KYN-to-tryptophan ratios had lower hip bone density, while this link wasn't seen in middle-aged adults (ages 46 to 49). In a follow-up study, they also found that older adults with higher levels of the KYN metabolites 3-hydroxykynurenine (3-HK) and anthranilic acid had a greater risk of hip fractures [71]. In vitro, KYN exposure elevated reactive oxygen species (ROS) production in mouse and human myoblasts. Conversely, pharmacological inhibition of IDO with 1-methyl-D-tryptophan in aged mice enhanced muscle fiber size and contractile strength [66]. A recent review by Ballesteros et al. [72] provides a comprehensive overview of IDO-KYN signaling in sarcopenia and osteoporosis.

It is important to note that IDO exhibits tissue-specific regulation: its activity rises in the brain but declines in the liver and kidney. Consequently, KYN and its downstream metabolites including kynurenic acid (KYNA), quinolinic acid (QUIN), and picolinic acid (PIC) accumulate in the aging brain, while hepatic and renal KYN levels decline. In disease states, similar tissue specificity is observed, IDO is strongly upregulated in tumors, where it promotes immune suppression [73], while in neurodegenerative conditions such as Alzheimer's disease, enhanced IDO activity contributes to elevated neurotoxic kynurenine metabolites [74]. It has been reported that elevated levels of IDO1 is found in atherosclerotic plaques [75]. They found that plaques rich in pro-inflammatory (M1) macrophages exhibited higher kynurenine levels, driven by sustained IDO1 activation. Several clinical and pre-clinical studies have highlighted age-related dysregulation of IDO1 across pathological conditions, as summarized in several recent reviews [15,65,76–80]. Given the emerging role of exercise as a modulator of IDO1 activity, this review expands on its relevance to aging and exercise physiology.

4. Exercise as a modulator of IDO1-KYN metabolism

4.1. Human clinical studies demonstrating modulation of IDO1-KYN metabolism

It is interesting to note that exercise has been demonstrated to meaningfully alter this pathway (Table .1), providing a non-pharmacological means of reversing the negative effects of KYN buildup [13]. Frequent exercise seems to both lower IDO1 expression and change KYN's downstream processing to less toxic metabolites [81]. Several studies have found that physical activity, particularly endurance or aerobic exercise, can lower systemic inflammation, a major cause of IDO1 activation [23]. A recent study by Valente-Silva and group (2021) examined the interaction between TRP supplementation and endurance exercise training on KYN pathway metabolism in both animal model (mice) and humans [26]. In the mice study, chronic TRP supplementation elevated circulating concentrations of all KYN pathway

Table 1
Clinical evidence of exercise-induced remodeling of tryptophan metabolism. Summary of human studies showing how different exercise interventions influence tryptophan metabolism, particularly within the kynurenine pathway.

Population Type	Exercise Intervention	Sample type	Main findings (TRP/KYN/QUIN)	Reference
Old men	Resistance + HIIT	Muscle, plasma	Plasma KYN, KYNA, QUIN, QUIN/KYN dec.	[82]
YA, OS	Endurance, Acute	Muscle, plasma	KYNA inc. in OA vs YA. TRP inc. in OS, KYN/TRP no diff. QUIN dec. in OS vs YA.	[18]
Multiple Sclerosis patients	HIIT, MCT	Plasma	Dec. in KYN in MCT and HIIT. KYNA dec. in MCT but inc. in HIIT. Inc. in QA in both	[90]
Male	Endurance, Eccentric	Muscle, plasma	Higher levels of KAT isoforms in ES vs control. Plasma KYNA inc. after exercise.	[25]
Male & Female	Endurance	Sweat	KYN dec. KYNA inc.	[24]
Pancreatic cancer patients	Resistance (supervised/home group)	Serum	KYN dec.,KYN/TRP dec., TRP inc. in supervised group. KYN inc., KYN/TRP inc. in home group	[91]
Male & Female	Endurance	Plasma	TRP & KYN inc.	[26]
Old Male & Old Female with MCI	Resistance	Plasma, hippocampus	KYN inc.	[88]
Male & Female	Exhaustive aerobic	Serum	TRP dec., KYN inc.,KYN/TRP inc.	[83]
Male	Acute endurance & resistance	Serum	KYN/TRP inc., KA, KA/KYN inc. in EE, QA inc., in EE	[84]
Old men and women (50–70yrs)	12 weeks combined strength & endurance + nutritional intervention	Plasma & serum	KA inc., in EXR, KA dec., in CON, QA/KA dec., in EXR, inc., in CON	[85]
Male & female (between 30 & 60yrs)	Increasing intensity endurance exercise & moderate continuous training	Serum	Inc., in 3-HAA in both EXR group.	[87]
Old men	Treadmill	Plasma & serum	TRP inc.,	[112]
Healthy Old men	12-week progressive exercise	Blood, muscle	Dec., in KAT1-4, no change in plasma kynurenines	[82]

metabolites, whereas exercise selectively attenuated metabolites associated with neurotoxicity. Apart from an increase in voluntary wheel running, TRP supplementation did not influence training adaptations, energy metabolism, or behavioral outcomes. In human volunteers, acute TRP administration during aerobic exercise resulted in higher plasma TRP and KYN levels in trained individuals compared with untrained counterparts. These findings indicate that endurance training modulates TRP metabolic fate and potentially mitigates neurotoxic KYN pathway activity [26].

Extending these observations, Hinkley et al. (2023) investigated resting and exercise-induced metabolite profiles in skeletal muscle from cohorts comprising young active adults, older active adults, and older sedentary individuals [18]. The biopsies of the vastus lateralis were collected at rest, immediately post-exercise, and 3 h following an acute bout of endurance cycling. At baseline, older adults displayed elevated muscle KYN levels compared to young participants, while tryptophan concentrations were significantly higher in sedentary older adults relative to both active groups. Notably, the KYN-to-tryptophan ratio did not differ significantly across groups, suggesting that KYN accumulation in older muscle may reflect increased substrate uptake rather than enhanced IDO1-mediated conversion. Interestingly, physically active individuals, regardless of age exhibited higher intramuscular levels of downstream KYN metabolites, including kynurenic acid and quinolinate, both of which are involved in NAD + biosynthesis and mitochondrial function. Although baseline metabolite differences were evident, the acute exercise bout elicited comparable shifts in muscle metabolite pools across all cohorts. These findings underscore the role of habitual endurance exercise in promoting favorable adaptations in skeletal muscle KYN metabolism, potentially enhancing mitochondrial health and contributing to improved systemic resilience during aging [18]. Complementary findings come from Allison et al. (2019), who reported that 12 weeks of supervised resistance and interval training in older men markedly upregulated transcriptional regulators (PGC-1α, PPARα, PPARδ) and kynurenine aminotransferases (KAT1-4) in muscle [82]. Interestingly, **plasma concentrations of KYN metabolites did not** change significantly despite the robust transcriptional adaptations. These results indicate that skeletal muscle is primed for enhanced peripheral clearance of KYN via elevated KAT activity [82].

To explore the effects of exhaustive exercise on Tryptophan metabolism and the immune system, Strasser et al. (2016) engaged both male and female subjects to high-speed cycle ergometer exercises until fatigued [83]. They observed a 12 % reduction in plasma tryptophan and a 20 % increase in the KYN/TRP ratio, reflecting elevated IDO enzyme activity. Concomitantly, neopterin levels, a biomarker of immune activation rose significantly and correlated positively with the KYN/TRP ratio, indicating enhanced immune system stimulation. These findings suggest that while exercise is generally beneficial, excessive or exhaustive training can provoke adverse physiological responses, including reduced cerebral tryptophan availability for serotonin synthesis, immune dysregulation, and muscle fatigue [83].

Building on this work, Joisten et al. (2020) compared the metabolic and immunological effects of endurance exercise (EE) and resistance exercise (RE) in 24 healthy males [84]. EE involved high intensity cycling, whereas RE consisted of multi-joint movements such as chest press, lat pull, leg curl, leg extension, and back extension. Their findings revealed that EE induced stronger modulation of the kynurenine pathway than RE, with significant increases in QA, KA, and the KA/KYN ratio immediately post-exercise, followed by normalization during recovery. Moreover, IDO1 expression correlated positively with IL-6 and regulatory T cells (Tregs) but negatively with natural killer (NK) and cytotoxic T cells, indicating differential immune engagement. Collectively, these results demonstrate that the metabolic and immune consequences of exercise are highly intensity- and mode-dependent. Endurance exercise exerts more pronounced effects on kynurenine pathway metabolism, potentially invoking transient neuroprotective and adaptive immune mechanisms compared with resistance exercise [84].

To explore how exercise and diet influence the immune system and kynurenine (KYN) pathway, Boβlau, Tim Konstantin et al. (2023) examined $CD8^+$ T-cell differentiation in older adult [85]. Ninety-six elderly patients aged 50–70 comprising of both males and females were made to complete combined strength and endurance exercises. $CD8^+$ T-cells were elevated in the control group as compared to the exercise group whereas blood plasma levels of KA also showed an increment in the latter than the former [85]. These results highlight that combined exercise training may

contribute to the slowing down of T-cell differentiation and in turn strengthen the immune system in the elderly.

Beyond its effects on immune modulation, exercise appears to influence systemic aging processes through upregulation of kynurenine pathway metabolites such as 3-hydroxyanthranilic acid (3-HAA). Preclinical studies have demonstrated that 3-HAA and its associated enzymes, kynureninase and 3-hydroxyanthranilate 3,4-dioxygenase, play pivotal roles in extending lifespan and maintaining metabolic homeostasis [86]. Joisten et al. (2025) used these findings to investigate the association between 3-HAA, its enzymatic activity, and longevity, with an emphasis on how exercise affects this relationship [87]. They employed a group of both men and women, dividing them into two age groups: young and middle aged. For 26 weeks, the study evaluated two groups of exercise intensity: continuously increasing intensity (INC) and standard moderate continuous training. Blood samples were obtained at certain times and tested for 3-HAA levels and related metabolite ratios Long-term endurance exercise reversed age-related decreases in systemic 3-HAA levels in middle-aged adults. Both INC and CON resulted in a significant rise in 3-HAA levels relative to baseline. This increase persisted throughout the workout period, while anthranilic acid levels decreased [87]. This finding was consistent with prior studies on mice models in which 3-HAA supplementation increased lifespan [86]. Findings from this study imply that exercise is an important strategy to help boost 3-HAA levels in humans as well as a non-pharmacological strategy to extend lifespan.

Finally, Schlittler et al. (2016) provided direct evidence that endurance exercise acutely reshapes systemic KYN metabolism. They investigated the impact of endurance exercise using two experimental groups [25]. These groups consisted of male subjects who engaged in endurance exercise and another group who were recreationally active but did not take part in endurance training. The analysis of plasma before and after completion of the endurance exercise. They observed changes in KYN metabolism during endurance as plasma KYNA increased by 63 %, Quinolone (QUIN) by 19 %. The ratio of the QUIN/KYNA decreased after endurance exercise by 27 %. The same trend was observed in the group that ran on a hill as there was a 125 % increase in plasma KYNA [25]. These findings highlight that endurance exercise causes a significant hike in plasma KYNA concentration and a decrease in QUIN/KYNA, indicating the important role of regular and consistent endurance exercises and how they alter metabolic changes.

4.2. Impact of exercise on kynurenine pathway dynamics across age-related comorbidities

Several studies have also examined the effects of exercise on KYN metabolite levels in various age-related pathological conditions, including cognitive impairment, remote ischemic preconditioning, multiple sclerosis, cancer, and chronic back pain. For example, Vints et al. (2024) examined the association between circulating KYN and the risk of mild cognitive impairment (MCI) in older adults and further evaluated the modulatory effects of resistance exercise on these metabolite levels [88]. At baseline, individuals with higher cognitive risk already had elevated KYN levels, linking low-grade inflammation with cognitive vulnerability. However, after a 12-week resistance exercise program, there were no significant changes in KYN concentrations or other related markers [88]. Similarly, Brzezińska et al. (2024) explored remote ischemic preconditioning (RIPC) prior to exercise [89]. In young runners, RIPC exaggerated the drop in tryptophan levels following intense running but reduced the KYNA/KYN ratio immediately after exercise. This suggests that not all interventions that increase metabolic stress even if they enhance athletic performance necessarily led to beneficial shifts in KYN metabolism. It also highlights that the timing and nature of physiological stressors can dramatically influence whether the pathway becomes neuroprotective or potentially harmful.

In clinical populations, Joisten et al. (2021) demonstrated that exercise can exert clear neuroprotective effects in people with multiple sclerosis (MS) [90]. In a randomized trial of individuals with an Expanded Disability Status Scale score of 3.0–6.0, the effects of high-intensity interval training (HIIT) were compared with moderate continuous training (MCT) on plasma neurofilament light chain (pNfL) and KYN pathway metabolites [90]. Acute exercise led to a reduction in pNfL and a metabolic shift toward the neuroprotective kynurenic acid (KYNA), with HIIT producing more pronounced effects than MCT. Following a 3-week intervention, sustained activation of the KYN pathway was observed only in the HIIT group. Importantly, changes in KYNA correlated positively with reductions in pNfL, suggesting that exercise-induced rerouting of KYN metabolism may contribute to neuroprotection in this population.

In pancreatic cancer patients following surgery and chemotherapy, Pal et al. (2021) reported that 6 months of supervised, moderate-to-high-intensity progressive resistance training reduced serum KYN levels and the KYN/tryptophan (TRP) ratio, while increasing TRP concentrations, compared with home-based training or standard care [91]. In contrast, home-based exercise increased KYN and KYN/TRP ratio. These findings suggest that supervised resistance exercise may downregulate IDO/TDO activity, potentially contributing to immune modulation [91]. In a different rehabilitation context, a study involving males and females aged 25–65 years with chronic (>3 months) mild to moderate low back pain found that moderate endurance training altered sweat concentrations of KYN metabolites [24]. After 14 days of training, KYN levels decreased while kynurenic acid (KYNA) increased, suggesting enhanced kynurenine transaminase activity. This sweat-based profiling highlights a potential non-invasive approach for monitoring exercise-induced changes in KYN metabolism in rehabilitation patients [24].

4.3. Acute and chronic exercise adaptations in tryptophan metabolism

Exercise serves as a powerful physiological stimulus that modulates numerous biological and immune responses in a dose-dependent manner [92]. A single exercise session is referred to as acute exercise, whereas chronic training denotes a structured and repetitive regimen performed over time with consistent frequency and duration [93]. Acute exercise typically induces transient alterations in circulating tryptophan (TRP) and kynurenine (KYN) metabolites, often increasing KYN turnover toward kynurenic acid (KA) and quinolinic acid (QA) within hours of endurance activity. The magnitude of these metabolic shifts depends largely on exercise intensity and duration [84].

Evidence further indicates that the effects of acute exercise on the kynurenine pathway vary according to metabolic and disease context. In patients with type 2 diabetes, a single bout of exercise downregulated KAT1, KAT2, and KAT4 while upregulating PGC-1α1, resulting in reduced plasma KYN and elevated KYNA levels shifting metabolism toward the neuroprotective branch of the pathway [94]. Similarly, in cancer patients undergoing chemotherapy, Pal et al. (2021) compared no exercise, unsupervised home-based exercise, and supervised resistance training [91]. They found that supervised training significantly decreased serum KYN and the KYN/TRP ratio while increasing TRP levels, whereas the unsupervised group exhibited the opposite trend [91]. These findings underscore the importance of structured, supervised exercise in

optimizing kynurenine metabolism and mitigating the accumulation of potentially neurotoxic metabolites.

In contrast, chronic exercise training (weeks to months) induces more durable adaptations. Repeated training reprograms tissues particularly skeletal muscle through PGC-1α1-dependent upregulation of kynurenine aminotransferases (KATs), enhancing peripheral KYN clearance and reducing neurotoxic load [25]. Notably, such adaptations may occur even when circulating metabolite levels remain unchanged, suggesting robust tissue-specific remodeling [95]. Overall, the influence of exercise on TRP metabolism represents a complex, multifactorial process shaped by individual physiology, training status, and disease condition. Further studies are needed to clarify interindividual variability, identify potential confounding factors, and determine how different exercise modalities can be leveraged to therapeutically modulate the kynurenine pathway.

5. Rodent studies supporting human clinical outcomes

In addition to findings from randomized clinical trials and human studies, rodent models have provided compelling evidence that exercise modulates the IDO1-KYN pathway (Table .2). Rodent studies offer several key advantages over human studies, including the ability to directly assess metabolite levels within specific tissues (such as muscle, liver, and brain), which is often not feasible in clinical settings due to ethical and technical limitations [96].

Supporting the human studies mentioned above, rodent studies also reported elevated levels of IDO-KYN signaling pathway. Agudelo et al. (2014) sheds light on the importance of exercise and how it activates the skeletal muscle transcription factors PGC1-α to combat stress-induced depression [95]. PGC1-α was overexpressed in transgenic male mice mck-PGC1-α and subjected to chronic mild stress (CMS), running wheel exercises and forced swim tests. Interestingly, mck-PGC1-α showed no signs of depressive behavior but rather a decrease in body weight [95]. They also displayed no change in the transcript levels of BDNF, VEGFA and B in the hippocampus. The exposure of mck-PGC1-α to stress caused increase in the expression of pro-inflammatory cytokines MCP-1 and TNF-α suggesting that these mice do respond to stress. Off note, there was no change in IDO-1,2, TDO-1,2 levels but rather an increase in Kynurenine aminotransferases. mck-PGC1-α also expressed the ability to metabolize KYN to KYNA [95].

In a study by da Rocha, Alisson Luiz et al. (2025) investigating the physiological effects of high-intensity endurance exercise, the authors reported a marked reduction in the expression of REV-ERB-α, a circadian-regulated transcriptional repressor critical for skeletal muscle oxidative metabolism [97]. Eight-week-old male C57BL/6 mice were subjected to both acute (AEE) and chronic (CEE) exhaustive exercises. Both exercises resulted in a down-regulation of REV-ERB-α. AEE caused a reduction in the kynurenine aminotransferase in both muscle and the hippocampus while upregulating kynurenine 3-monooxygenase levels [97]. These shifts the pathway to a neurotoxic route. Also, KYN, KYN/KYNA levels were reduced in the muscle but increased in the hippocampus thus compounding the neurotoxic effects REV-ERB-α [97]. These findings highlight the interplay among exercise, REV-ERB-α and the kynurenine pathway.

The study performed on mice (C57BL/6) model by Lee et al. (2017) demonstrated that in mice aged 6 weeks to 10 months, serum levels of tryptophan metabolites and the IDO1 activities altered with age [98]. Voluntary chronic aerobic exercise was shown to mitigate these changes partially. Notably, the serum ratio of kynurenic acid (KYNA) to 3-hydroxykynurenine (3-HK) declined with advancing age, reflecting a shift in kynurenine pathway metabolism. Voluntary exercise interventions were able to restore the KYNA/3-HK ratio in 6- and 8-month-old mice [98]. Building on this [26], investigated the interaction between dietary tryptophan supplementation and exercise. They hypothesized that having excessive TRP in diet without engaging in physical exercise could have deleterious effects on health. Male mice (C57BL/6J) 6-weeks old were subjected to near free-wheel running and fed on a diet enriched with 1 % TRP. After 8 weeks of intervention, TRP-supplemented mice displayed significantly greater physical activity compared to controls. As anticipated, TRP supplementation resulted in elevated KYN pathway metabolites; however, the combination of exercise and TRP intake markedly reduced the levels of neurotoxic intermediates, including KYN, 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), and quinolinic acid (QA) [26]. These findings highlight the complex interplay between dietary supplementation and physical activity and underscore the role of the KYN pathway in mediating their combined effects.

As mentioned above, exercise is well established to reduce anxiety- and depression-like behaviors [99]. Su and group (2020) investigated the effects of voluntary exercise on depressive-like behaviors induced by KYN in mice [99]. Two weeks of voluntary

Table 2
Preclinical insights into exercise and tryptophan metabolism. Compilation of rodent studies highlighting how exercise regimens reshape kynurenine pathway metabolites and tissue-specific tryptophan utilization.

Population Type	Exercise Intervention	Sample type	Main findings (TRP/KYN/QUIN)	Reference
6wks, 3, 6 and 8 months old male C57BL/6	**Aerobic (VWR)**	**Serum**	**KYNA/3HK dec. with age, KYNA/3HK restored in 6M & 8M**	[98]
20wks C57BL/6 male	**Aerobic (VWR)**	**Fecal matter, Blood, Brain**	**VWR inc. TRP supply in blood and to brain in exercise group**	[102]
3-4M wildtype BDNFVal/Val and BDNFVal66Met homozygousknock-in male mice	**Aerobic (VWR)**	**Plasma, Hippocampus, Gastrocnemius muscle**	**IDO1 and KAT2 inc. in knockin mice not influenced by exercise. Exercise inc. plasma KYN, KAT1, KAT4 in knockin mice**	[101]
Male C57bl/6J mice, 6 weeks old	**Aerobic (VWR)**	**Plasma, muscle**	**TRP diet inc. KYN pathway metabolites. VWR dec. neurotoxic branch. VWR inc. KYN and TRP**	[26]
3M Swiss male albino mice with AD	**Swimming**	**Brain, Quadriceps**	**Swimming blocked IDO activity, dec. KYN & TRP, KYN/TRP levels**	[100]
Wild-type C57BL/6J Narl mice	**Aerobic (VWR)**	**Plasma, Soleus muscle**	**KYN metabolises faster in VWR group. KAT3 inc. in VWR gorup**	[99]
Mck-PGC-1α1 and MKO-PGC-1α mice	Chronic mild stress	Vastus lateralis muscle	KAT1-4 inc. in Mck-PGC-1α1 mice, no change in TRP, 3-HK, IDO1 & 2, TDO1 &2.	[95]
Eight-week-old male C57BL/6	Exhaustive exercise	Serum, Gastrocnemius, hippocampus	KAT1 dec., in exe, no diff in KMO between exe and control, KYN inc. in hippocampus in exe, In muscle KAT1 dec. in exe., KYN/TRP inc., in gastrocnemius	[97]

exercise significantly attenuated stress-induced helplessness. In non-stressed mice, KYN administration increased immobility in the tail suspension test and elevated failure rates in the escape test [99]. Remarkably, exercised mice were resistant to these KYN-induced behavioral deficits. Following KYN injection, plasma KYN concentrations in exercised mice were approximately one-quarter of those in sedentary controls [99]. Mechanistically they found that exercised mice exhibited higher muscle expression of kynurenine aminotransferase III (KAT3) [99]. A comparable study in an animal model of Alzheimer's disease (AD) was conducted by Souza et al. (2017), they examined the effects of physical activity on IDO activation and its potential role in preventing neurodegenerative processes [100]. AD was experimentally induced in Swiss Albino mice via intracerebroventricular injection of amyloid-β1–42 peptide [100]. The injection of Amyloid β1-42 had significantly increased IDO activity. Amyloid- β1-42 caused a significant increase of TRP which was significantly reduced by physical exercise [100]. Physical exercise restores the TRP levels in the hippocampus. KYN levels which was highly elevated in both sham and test, were significantly decreased after swimming in the prefrontal cortex region of the brain of Swiss Albino mice [100].

Genetic background further shapes exercise responses in KYN metabolism. Utilizing a mouse model with a knock-in of Brain-derived-neurotrophic-factor (BDNF) Val66Met polymorphism mice, leraci et al. (2020) assessed the KYN pathway in the skeletal muscle, plasma and hippocampus in exercising mice [101]. Wild-type and homozygous knock-in mice were at the age of 3–4 months and were given access to free running wheels for 4 weeks. Plasma KYN and KYNA metabolites in the knock-in mice were significantly higher than the wildtype mice and were not induced by exercise [101]. But exercise influenced the outcome of KYN levels. The KYNA/KYN was also significantly higher in the knock-in mice when compared to control. In the muscle, KATs were seen to be greatly induced by exercise. KAT3 increased in the exercise groups, and a greater interaction was seen in KAT1, KAT4 between the strain type and exercise group [101]. These findings suggest physical exercise can improve upon neurological deficits caused by a deficit in BDNF.

Expanding beyond tissue metabolism, Vazquez-Medina et al. (2024) examined exercise-induced alterations in the microbiota-gut-brain axis [102]. They investigated the effect of exercise and changes in the microbiota-gut-brain axis [102]. Their multi-omics data analysis revealed a significant turnover in the exercise group of TRP metabolites. There were changes in the microbial diversity in running mice such as increased levels of *Firmicutes and A. muciniphila*. These bacteria play an important role in TRP metabolism. The running exercise was seen to influence these changes in the TRP pathway degradation through the indole pathway. These findings highlight the importance of running exercise and how it influences the gut microbiome and the alterations it induces in the gut microbiota-gut-axis [102]. Collectively, both human and rodent studies demonstrate that exercise exerts a regulatory influence on the IDO1-KYN pathway, often shifting metabolism toward anti-inflammatory and neuroprotective outcomes.

6. Exercise and serotonin pathway

As mentioned above, Serotonin is a pivotal neurotransmitter derived from tryptophan, regulating mood, cognition, sleep, appetite, and motor function [103]. Dysregulation of serotonergic signaling has been implicated in a wide range of neuropsychiatric and metabolic disorders [54], highlighting the importance of interventions that can modulate this pathway. Exercise has emerged as a powerful physiological regulator of serotonin metabolism, with evidence from animal models, athletic cohorts, and clinical populations showing that physical activity enhances serotonin synthesis [104,105]. These effects are influenced by exercise intensity, duration, type, and individual physiological or pathological states. This section reviews current evidence linking exercise to serotonergic modulation, spanning mechanistic studies to clinical applications across diverse populations.

6.1. Exercise and serotonin levels in human clinical studies

As previously stated, exercise modulates KYN pathway metabolites, promoting a shift toward neuroprotective and anti-inflammatory metabolites while reducing neurotoxic intermediates [106]. Similarly, serotonin, a key neurotransmitter synthesized from tryptophan, exerts widespread positive effects on health. Exercise enhances serotonin synthesis and turnover in the brain by increasing the availability of free tryptophan and facilitating its transport across the blood-brain barrier (Table .3). [107]. Elevated central serotonin levels contribute to improved mood, reduced anxiety, enhanced cognitive performance, and better motor function [107]. Evidence for exercise-induced serotonergic modulation comes from both athletic and clinical populations. Azevedo et al. (2024) characterized the metabolomic profile of cyclists after different timepoints in their cycling training [108]. The cyclists were made to perform 3 separate time trials. Time intervals were divided into Fast, Start, even pace and End-spurt categories. It is interesting to note that the Spurt group was the only one that revealed pathways involved in serotonin metabolism [108].

Extending this notion, Zimmer et al. (2016) investigated the effects of exercise intensity on serotonin (5-HT) in young adults aged between 20 and 27 years following a three-week exercise intervention involving low, moderate and high intensity training [109]. Serum serotonin levels increased significantly only in the high-intensity group, suggesting that exercise intensity plays a critical role in regulating peripheral serotonin release [109]. Beyond intensity, the type of exercise and its integration with other interventions also appear to shape serotonergic responses. For example, Liu et al. (2024) investigated the combined effects of Chinese traditional exercise (Baduanjin) and psychotherapy (escitalopram oxalate) and their synergistic effect in people with post-stroke depression [110]. Both the Baduanjin and the escitalopram oxalate therapy groups demonstrated increased serum 5-HT levels, alongside significant improvement in their sleep and Hamilton depression rack score. [110]. Similarly, Tsang et al. (2013) explored the impact of Qigong exercise on depression over a 12-week intervention [111]. Interestingly, participants in the exercise group exhibited a reduction rather than an increase in serum 5-HT. The authors attributed this unexpected finding to variability in participant performance, concomitant medication use, and the fact that some of the participants met all the baseline functional tests requirement and needed no room for improvement [111].

In line with these observations, Melancon et al. (2012) explored the long-term effects of exercise on tryptophan metabolism and serotonergic activity in older adults [112]. The study measured the ratio of TRP to branched-chain amino acids (BCAA), a well-established indicator of central serotonin synthesis, and found a 102 % increase following exercise, which remained elevated throughout the training period. In addition, serum TRP and prolactin levels rose significantly after exercise, indicating enhanced serotonergic activity [112]. These results suggest that regular physical activity sustains serotonin synthesis and turnover in the aging brain, thereby supporting improved mood and cognitive performance [112]. Collectively, this evidence reinforces the concept that exercise not only modulates peripheral TRP

Table 3
Exercise effects on serotonin metabolism in humans. Overview of clinical findings describing exercise-driven changes in circulating and central serotonin (5-HT) and related metabolites, with implications for mood, cognition, and overall health.

Population Type	Exercise Intervention	Sample type	Main findings (5-HT/5HIAA)	Reference
18–60 yrs old women with Fibromyalgia	Aerobics and stretching	Serum	Aerobic ex. causes increase in 5HIAA levels vs stretching	[113]
MS patients	Moderate intensity Aerobics and home exercise	Blood	5-HT inc. in moderate group vs home group	[114]
M & F with secondary progressive and relapsing recruiting multiple sclerosis (SPMS and RRMS)	Acute aerobic exercise	Blood	5-HT increased after training in both conditions	[115]
Young adults	Low, moderate and HI aerobic	Serum	5-HT levels inc. with intense exercise	[109]
Poststroke depression patients	Baduanjin aerobic exercise + behavior therapy	Serum, Sleep levels	5-HT levels inc. in exercise combined with rational behavior therapy	[110]
65yrs and above M & F with neurological disorders	Qigong exercise	Serum, saliva	Serum 5-HT dec.	[111]
Obese postmenopausal women	Taekwando	Plasma	5-HT inc. in exercise group	[116]
32 ± 5 yrs male	Cycling	Serum	Dec. 5-HT levels after exercise	[108]
Old women	Tai-Chi	Serum	Higher 5-HT levels in the exercise vs to the control	[117]
Healthy M & F	Tooth-clenching exercises	Muscle	5-HT levels did not change overtime in both test vs control	[132]
Untrained Young males	Resistance + saffron supplementation	Serum	5-HT levels inc. in exercise + saffron and exercise + placebo group	[133]

metabolism but also enhances central serotonergic signaling, providing a mechanistic link between physical activity, mood regulation, and neurological health in older adults.

Clinical trials further highlight the therapeutic potential of aerobic exercise. Valim et al. (2013) evaluated the impact of aerobic versus stretching exercise on serum 5-HT and its primary metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in women with fibromyalgia [113]. Participants were involved either in aerobic walking or stretching exercises three times per week for 20 weeks. The data revealed significant increases in both 5-HT and 5-HIAA in the aerobic group, while no significant changes were observed in the stretching group [113]. Most importantly, aerobic exercise was also associated with marked improvements in emotional and psychological well-being, outcomes that were not observed in the stretching group. These results indicate that aerobic exercise enhances serotonergic activity, potentially underlying its superior symptomatic benefits in fibromyalgia compared with stretching interventions. Similarly, a randomized controlled trial, performed by Al-Sharman et al. (2019) investigated the effects of a six-week moderate-intensity aerobic exercise program on sleep quality and sleep-related biomarkers, including serotonin, melatonin, and cortisol, in people with multiple sclerosis (MS) [114]. Participants were randomly assigned to either the aerobic exercise group (MAE) or a home exercise program (HEP). Sleep was assessed subjectively using the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI), and objectively via actigraphy [114]. Compared with HEP, MAE participants demonstrated significant improvements in PSQI, ISI, and sleep parameters. Only serotonin levels increased significantly in the MAE group, and changes in serotonin were strongly correlated with improvements in PSQI and ISI [114]. Additional studies in MS confirm this pattern. Bansi et al. (2018) investigated the effects of acute aerobic exercise on the tryptophan pathway in people with subtypes of Multiple Sclerosis (**S**econdary **P**rogressive **M**ultiple **S**clerosis (SPMS) and **R**elapsing **R**emitting **M**ultiple **S**clerosis (RRMS) [115]. Twenty-four patients with SPMS were compared with 33 patients with RRMS. They were each divided using stratified block randomization into a high-intensity training group and a standard training group. Serotonin levels were elevated after exercise therapy in both groups. They found out that KYN levels were indirectly proportional to serotonin levels, suggesting that TRP is rerouted more towards the serotonin pathway than the KYN pathway [115].

Studies focusing on women further highlight exercise-induced serotonergic modulation in specific populations. Lee et al. (2021) investigated the effects of Taekwondo training in obese postmenopausal women and observed a significant increase in the plasma serotonin levels and a decrease in their weight, BMI, percentage of body fat, and total cholesterol [116]. These findings indicate that exercise can be used to manage obesity and enhance the circulation of neurotransmitters such as serotonin in obese postmenopausal women. In older women, Chang et al. (2024), reported a significant increase in 5HT levels in groups that had been exposed to 24 weeks of Tai Chi training, with concomitant in depressive symptoms and sleep quality after the training [117]. Taken together, these studies suggest that exercise can modulate serotonergic activity across diverse populations, with the magnitude of response largely determined by exercise intensity, duration, and type, as well as participant-specific factors. Notably, interventions combining exercise with psychological or nutritional strategies may further enhance serotonin-related benefits, offering promising avenues for managing mood disorders and improving overall health.

6.2. Preclinical evidence for exercise-mediated regulation of serotonin in brain health

Human studies successfully demonstrated that exercise reduces depressive and anxiety-like behaviors through the serotonin pathway [118,119]. Animal studies provide important mechanistic insights into the effects of exercise on serotonergic signaling in the context of neurological and brain health (Table .4). A study by Lee et al. (2013) investigated the interaction between dietary tryptophan availability, stress, and exercise in male mice [120]. Animals were subjected to a tryptophan-deficient diet and exposed to chronic unpredictable stress for four weeks, with or without concurrent moderate or intense treadmill exercise [120]. In their findings, mice on the tryptophan deficient diet showed significantly lower levels of 5-HT when compared with control. Treadmill exercise failed to elevate the levels of 5-HT in the hippocampus as compared to the control [120].

Sajedi et al. (2021) explored the combined effects of aerobic exercise and probiotic supplementation on serotonin, leptin, and cortisol in a mouse model of multiple sclerosis (MS) [121]. The exercise was 5 days a week, including 10 min in the first week,

Table 4
Rodent evidence for exercise-driven regulation of serotonin pathways. Preclinical data illustrating how distinct exercise modalities modulate serotonin signaling and metabolism in the brain, supporting neuroprotection and behavioral benefits.

Population Type	Exercise intervention	Sample type	Main findings (5-HT/5HIAA)	Reference
Pregnant female Sprague-Dawley rats with postpartum depression (PD)	Treadmill, Forced swimming (FST)	Brain	Inc. in 5-HT positive cells in PD mice	[126]
Adult male C57BL/6 mice	Aerobics (VWR)	Brain	Exercise releases 5-HT and relieves pain by regulating 5-HT to act on 5-HT1A receptor and the 5-HT7 receptor.	[125]
6wks mice, 3months old and 1yr old female $Tph2^{-/-}$ mice, $Tph2^{+/+}$ littermates, C57BL/6 N mice	VWR	Brain	5-HT is required for exercise-induced neurogenesis.	[128]
M & F homozygous knock-in (KI) & homozygous wild-type (WT) Tph2R439H mice	VWR	Brain	Low 5-HT impacts behavioral effects of exercise in females but did not impact exercise-induced cellular alterations in either sex.	[129]
C57BL/6 male mice	Treadmill + bleomycin administration	Serum	Exercise blocks bleomycin-induced 5-HT signaling	[122]
Male mice	Treadmill at 6–8wks followed by VWR at 8–11wks	Whole body assessment	5-HT receptors are influenced by different pharmacological interventions impacted by exercise	[124]
Pregnant female NMRI & C57BL/6 mice	Swimming	Serum, brain	Swimming dec. 5-HT in brain. Strain type impacted the level of brain 5-HT	[127]
C57BL/6 female with MS	Treadmill	Brain	5-HT inc. in all groups in combination with exercise	[121]
TRP deficient and stressed 7wks C57BL/6 male	Treadmill + FST	Brain	Regular exercise prevents depression-like outcomes with and without 5-HT	[120]
7wks C57BL/6J male mice	Treadmill + alcohol vapor exposure	Hippocampus	Exercise reduces 5-HT in the hippocampus regardless of exposure to alcohol.	[123]
Mck-PGC-1α1 and MKO-PGC-1α	**Chronic mild stress**	**Vastus lateralis muscle**	**No change in 5-HT/5HIAA levels**	[95]

20 min in the second week and 30 min until completion. Exercise and/or probiotic treatment significantly increased serotonin levels and reduced leptin levels compared with MS mice, while cortisol levels showed a nonsignificant decrease [121]. These findings suggest that lifestyle interventions, including exercise and probiotics, may modulate key neuroendocrine and metabolic factors and hold potential for mitigating pathological changes in MS. Exercise has also been shown to modulate serotonin and inflammatory signaling in models of idiopathic pulmonary fibrosis (IPF). In a murine model of IPF, chronic aerobic training was shown to attenuate bleomycin-induced lung injury by dampening inflammatory responses and modulating serotonin (5-HT) and Akt signaling [122]. Specifically, exercise reduced immune cell infiltration, proinflammatory cytokines, collagen deposition, 5-HT levels, 5-HT2B receptor expression, and Akt phosphorylation, while enhancing IL-10 expression). These findings suggest that aerobic exercise confers antifibrotic and anti-inflammatory effects partly through serotonergic and Akt pathway regulation. Another important study investigated the importance of exercise on the brain impairment in alcohol use disorder after alcohol withdrawal [123]. An alcohol use disorder (AUD) mice model was established and used in this study. Male mice C57BL/6 were used in this study [123]. Exercise caused a reduction in the serotonin levels in the hippocampal region of mice and did not depend on whether they were exposed to alcohol or not.

The role of serotonin in mediating exercise endurance has been further explored pharmacologically. Claghorn et al. (2016) performed an interesting study to investigate the effect of 5-HT1A agonist and antagonist on forced and voluntary exercise in the mice model [124]. They hypothesized that drugs that target serotonin receptors would have unequal effects on the movement behavior in voluntary wheel running mice and control mice by injecting antagonist 5HT1A which is a combination of 5HT1A agonist and a 5HT1A/1B partial agonist [124]. Pharmacological manipulation of 5-HT1A receptors showed that the antagonist WAY-100635 reduced treadmill endurance in voluntary wheel running mice (HR) but not control mice, while the agonist/partial agonist combination (8-OH-DPAT + pindolol) reduced both treadmill endurance (dose-dependent) and wheel running at high doses in HR mice. These findings suggest that central 5-HT signaling contributes to exercise endurance, with enhanced endurance in HR mice linked to serotonergic modulation. Similarly, Zhou et al. (2022) showed that voluntary wheel running for 15 days increased 5-HT1A and 5-HT7 receptor expression [125]. These mice were placed on voluntary wheels for 30 min daily for 15 days. They were treated with 4f-chloro-DL-phenylalanine systemically to eliminate serotonin activity. It was shown that the pharmacological intervention and local delivery of serotonin to the Anterior Cingulate Cortex alleviates pain and anxiety moods by modulating synaptic plasticity [125]. These results reveal that aerobic exercise can mediate the increase in release of serotonin and improve anxiety behaviors through its receptors.

Exercise also improves depressive-like behaviors in models of postpartum depression. Ji et al. (2017) studied the therapeutic potential of treadmill exercise in a rodent model of postpartum depression (PPD) [126]. They demonstrated that postpartum rats exhibit reduced locomotor activity, increased immobility, and suppressed 5-HT and tryptophan hydroxylase (TPH) expression in the dorsal raphe [126]. Two weeks of treadmill running (30 min/day) reversed these deficits, restoring 5-HT/TPH expression and improving depressive-like behaviors. These findings support the role of exercise in alleviating postpartum depression via enhancement of serotonergic signaling [126]. Rodent studies suggest that the effects of exercise on serotonin and postpartum behaviors are both strain- and context-dependent. In a study examining the effects of swimming exercise before and during pregnancy, NMRI (outbred) and C57BL/6J dams exhibited markedly different outcomes [127]. They reported that in C57BL/6J dams, swimming increased gestational corticosterone, reduced maternal care and brain serotonin, and exacerbated all depression-related behaviors postpartum. In contrast, NMRI dams showed enhanced licking/grooming and social behavior, along with reduced anhedonia-like behaviors [127]. These findings highlight the critical role genetic background plays in shaping exercise outcomes and indicate that both the timing and type of physical activity can differentially influence maternal care and postpartum depression-related behaviors.

Genetic animal models provide valuable insights into loss and gain of function. Recent work using tryptophan hydroxylase (TPH) 2-deficient mice, which lack brain serotonin, demonstrated that while baseline hippocampal neurogenesis remains intact, activity-induced proliferation is impaired [128]. These findings indicate that central serotonin is essential for the proliferative effects of exercise in both young-adult and aged mice. Notably, the absence of brain serotonin altered Sox2-positive precursor cells, suggesting compensatory adaptations to maintain homeostasis in the neurogenic niche [128]. Recently, a similar study was performed by Warner and group (2024). They investigated the role of brain serotonin in exercise-induced antidepressant effects in male and female mice with reduced 5-HT synthesis, using a mouse model with reduced 5-HT synthesis (Tryptophan hydroxylase 2 knock-in mice) [129]. The study found that low 5-HT impaired the behavioral benefits of exercise in females, particularly in the forced swim and novelty-suppressed feeding tests, while exercise-induced hippocampal neurogenesis and immature neuron production were not significantly affected in either sex [129]. This study highlights a direct and acute role of serotonin in mediating exercise-induced hippocampal neurogenesis, providing mechanistic insight into how physical activity might confer preventive and therapeutic benefits for depression and age-related cognitive decline.

7. Exercise and indole pathway

Despite its growing relevance, the interaction between physical activity and the indole pathway remains relatively underexplored, with only limited studies investigating this co-relation (Table .5). Recent reports suggest that exercise-induced alterations in gut microbiota composition can significantly affect the production of indole derivatives such as IPA, IAA, and ILA metabolites known to exert anti-inflammatory, antioxidant, and neuroprotective effects.

In a recent study, Wang et al. (2025) investigated the combined effects of a tryptophan-enriched diet (TED) and high-intensity exercise (HIE) on liver injury, focusing on both endogenous and microbiota-derived tryptophan metabolites [58]. Using a C57BL/6 mouse model, they subjected animals in the HIE group to intensive swimming at a 30 cm water depth for 2.5 h daily over five consecutive days [58]. Metabolomic analyses revealed that HIE markedly elevated hepatic aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, indicating liver tissue damage. This was accompanied by a significant depletion of tryptophan and its downstream metabolites, including 3-hydroxyanthranilic acid, anthranilic acid, and L-kynurenine [58]. It was interesting to note that HIE-TED group rescued liver damage was indicated by a decrease in the ALTs and ASTs and an increase in the liver glycogen and glucose. Most importantly, microbiota derived Indoles metabolites ILA and IPA were elevated in this group and positively correlated with the liver aminotransferases except only IAA which was negatively correlated. mRNA levels of AhR and CYP1A1 were also significantly elevated in this group. Administration of an AhR inhibitor, CH223191 reversed all these positive changes as shown by an increase in ASTs and ALTs, increase in macrophage aggregation and ROS production [58]. In our previous work, we also demonstrated a close association between dietary tryptophan (TRP) levels, gut microbiome composition, and systemic inflammatory responses in an aged mouse model [60]. Aged mice were fed diets containing either low TRP (0.1 %), recommended TRP (0.2 %), or high TRP (1.25 %) concentrations for eight weeks to assess how dietary TRP availability influences microbial composition and immune activation [60]. 16S rRNA sequencing revealed that TRP deficiency markedly altered the gut microbial landscape, characterized by changes in the relative abundance of the *Coriobacteriia* class, *Acetatifactor* genus, *Lachnospiraceae* family, *Enterococcus faecalis*, *Clostridium* sp., and *Oscillibacter* genus [60]. Consistent with these microbiota shifts, cytokine profiling indicated that mice on the TRP-deficient diet exhibited significant elevations in pro-inflammatory cytokines including IL-6, IL-17A, and IL-1α accompanied by a reduction in the anti-inflammatory cytokine IL-27 [60]. These findings suggest that insufficient TRP intake disrupts gut microbial balance and promotes a systemic pro-inflammatory milieu in aged organisms. Collectively, these findings reveal that exercise combined with dietary tryptophan enrichment enhances microbiota-derived indole production, which in turn activates the AhR-CYP1A1 signaling axis to confer hepatoprotection and mitigate oxidative and inflammatory damage induced by exhaustive exercise [58,60].

Expanding our understanding of how physical activity reshapes host–microbiota interactions, Vázquez-Medina et al. (2024) examined the effects of prolonged voluntary running on the gut–microbiota–brain axis in a 20-week C57BL/6 mouse model (RUN group) [102]. Through a comprehensive multi-omics analysis, it was revealed that exercise caused alterations in TRP metabolism in the gut, hippocampus and blood. Exercise also modified gut microbial composition and diversity, with a pronounced increase in *Firmicutes* a phylum enriched in indole-producing species and a reduction in *Bacteroidota* abundance [102]. Moreover, the beneficial bacterium *Akkermansia muciniphila* was significantly elevated in the RUN group, contributing to improved mucosal integrity and metabolic regulation. A symbiotic relationship was also shown between *Romboutsia* and *A. muciniphila* in regulating TRP metabolism along the gut-microbiome brain axis associated with physical activity [102]. These findings underscore potential applications for developing microbiota-based approaches in relation to physical activity for neurological dysfunctions concerning mental health and overall wellbeing.

Recent human data also support the role of exercise in modulating the indole-tryptophan-microbiota axis. Tabone et al. (2021) investigated the effects of a single session of acute moderate-

Table 5
Impact of Exercise on Tryptophan Metabolism and Tryptophanase-Expressing Microbes in Human and Animal Studies. Collection of murine data on exercise-driven indole metabolism and how it impacts the gut microbiome and overall wellbeing.

Human Studies Population Type	Exercise intervention	Sample type	Main findings (Indole/IAA/IPA, Tryptophanase, microbes)	Reference
Cross-country endurance athletes (Healthy males-18-50yrs)	Treadmill	Serum. Stool	Inc. in ILA, Inc. in *(Romboutsia, Ruminococcocaceae UCG-005, Blautia, Ruminiclostridium 9 and Clostridium phoceensis*	[130]
Lean & obese subjects	6wks aerobic exercise	Serum, Stool	Inc. in ILA, Inc. in *Bifidobacterium* and *Lactobacillus* species	[131]
Mouse Studies				
7 wks old C57BL/6 male	HIE (swimming) + TRP diet	Liver, Serum	Inc. in IAA, ILA	[58]
20 wks old C57BL/6 male	VWR	Fecal matter, blood, brain	Inc. in tryptophanase, *Bacteroides, Muribaculaceae,* and *Turicibacter*	[102]

intensity exercise on the serum and fecal metabolomes, as well as the gut microbiota composition, in forty male cross-country endurance athletes [130]. Following a controlled bout of exercise to volitional exhaustion, metabolomic profiling revealed a decrease in serum tryptophan and an increase in kynurenic acid, alongside elevated levels of purine metabolism intermediates such as inosine, xanthine, hypoxanthine, and uric acid [130]. In contrast, fecal analyses demonstrated increased levels of tryptophan, tyrosine, and phenylalanine metabolites, suggesting enhanced microbial amino acid synthesis and turnover. Exercise also induced distinct microbial compositional changes, characterized by increased abundance of the *Romboutsia* genus, *Ruminococcaceae* UCG-005, *Escherichia coli* TOP498, and *Blautia*, accompanied by decreased *Ruminiclostridium* 9 and *Clostridium phoceensis* populations all taxa associated with indole and aromatic amino acid metabolism [130]. Collectively, these findings demonstrate that even a single bout of moderate-intensity exercise can induce rapid and coordinated changes in both systemic and gut-derived metabolites, highlighting the dynamic responsiveness of the indole pathway to physical activity and its potential role in mediating the health-promoting effects of exercise [130].

Extending these insights to broader human populations, Kasperek et al. (2023) investigated the effects of long-term physical activity on the gut microbiome and metabolic function in lean and obese adults aged 20–45 years, classified by body mass index (BMI <25 kg/m^2 for lean and >30 kg/m^2 for obese participants) [131]. Participants engaged in moderate-to high-intensity exercise including cycling and treadmill training over a six-month intervention period [131]. KEGG pathway analysis revealed a significant upregulation of indole metabolites, particularly indole-3-lactic acid (ILA), following exercise. Although ILA concentrations were higher in obese individuals than in their lean counterparts, this difference did not reach statistical significance [131]. Fecal Metabolomic profiling further showed exercise-induced shifts in purine metabolism, tyrosine metabolism, and 5-hydroxyindoleacetic acid (5-HIAA) production, particularly in the obese group. Additionally, there was an increased relative abundance of *Bifidobacterium* and *Lactobacillus* species microbial taxa known for their roles in gut homeostasis and indole biosynthesis-after training [131]. These findings demonstrate that regular exercise modulates gut microbial composition and activates metabolic pathways linked to indole and aromatic amino acid metabolism, independent of body weight [131]. Such adaptations may enhance metabolic flexibility, intestinal integrity, and systemic homeostasis, reinforcing the role of exercise as a key modulator of the microbiota-indole-host signaling axis across different metabolic states.

Collectively, findings from both animal and human studies demonstrate that exercise acts as a potent modulator of the gut-microbiota-indole axis, influencing indole metabolite production, AhR signaling, and downstream metabolic and inflammatory processes. Whether through acute or long-term training, physical activity enhances microbiota-derived indole output, promotes intestinal and hepatic homeostasis, and supports gut-brain communication via the regulation of tryptophan metabolism. These insights highlight the indole pathway as a critical mediator linking exercise to systemic resilience, neuroprotection, and overall metabolic health, and point toward the development of microbiota and exercise-based therapeutic strategies for preventing inflammation-associated and age-related diseases.

8. Conclusion

Exercise is a potent regulator of tryptophan metabolism, modulating both the KYN and serotonergic pathways to attenuate inflammation, promote muscle and cognitive function, enhance neuroprotection, and improve systemic resilience (Fig. 2). Acute bouts of exercise elevate KYNA and lower the QUIN/KYNA ratio, while chronic training promotes skeletal muscle adaptations such as increased kynurenine aminotransferase (KAT) expression that enhances peripheral KYN clearance. Evidence from clinical populations, including individuals with multiple sclerosis, cancer, and chronic pain, demonstrates that both endurance and resistance training can lower circulating KYN levels, reduce neurodegeneration markers, and improve immune regulation.

The rodent studies provide strong mechanistic evidence that exercise modulates the IDO1-kynurenine pathway across multiple biological systems. Exercise not only counteracts age-related alterations in tryptophan metabolism and mitigates the accumulation of neurotoxic KYN metabolites in the context of dietary tryptophan overload but also protects against KYN-induced behavioral deficits and neurodegenerative disturbances associated with age-related neurodegeneration. Exercise in rodents has been shown to restore the KYNA/3-HK balance, prevent KYN-induced muscle atrophy, and reduce depressive-like behaviors through upregulation of kynurenine aminotransferases in skeletal muscle. Moreover, experimental models of Alzheimer's disease demonstrate that exercise lowers hippocampal IDO activity and restores tryptophan levels, highlighting a neuroprotective role that parallels human findings in multiple sclerosis and cognitive impairment. Importantly, genetic background and diet further influence the degree to which exercise can remodel the pathway, emphasizing the need for personalized approaches when considering exercise as a therapeutic strategy. Extending beyond tissue-specific effects, exercise also reshapes the gut microbiota and alters indole pathway dynamics, linking microbial diversity with tryptophan metabolism and systemic health. However, the effects of exercise on KYN metabolism are context-dependent, varying with disease state, exercise modality, and supervision, underscoring the need to tailor exercise prescriptions for maximal therapeutic benefit.

Parallel to these metabolic adaptations of KYN pathways, exercise consistently enhances serotonergic signaling. Human and animal studies show that aerobic and high-intensity training elevates serotonin synthesis, receptor expression, and downstream activity, improving mood, cognition, sleep, and anxiety-like behaviors. Traditional mind-body exercises such as Tai Chi, Qigong, and Baduanjin also yield benefits, though outcomes are shaped by health status and adherence. Importantly, exercise may simultaneously redirect tryptophan metabolism away from the KYN pathway toward serotonin production, reinforcing its neuroprotective and antidepressant effects. Mechanistic insights from animal and genetic models highlight the critical role of serotonin in mediating behavioral adaptations to exercise. Pharmacological, dietary, and genetic manipulations of serotonin demonstrate its necessity for exercise-induced antidepressant- and anxiolytic-like effects, with outcomes influenced by sex, stress exposure, and genetic background. Notably, studies using TPH2-deficient mice reveal that while hippocampal neurogenesis can proceed independently of serotonin, the behavioral benefits of exercise particularly in females are abolished without intact serotonergic signaling. These findings establish serotonin as a key driver of exercise-induced mood regulation, resilience, and cognitive protection.

Beyond tissue-specific effects, exercise profoundly influences the gut-microbiota-indole axis, a third major branch of tryptophan metabolism. Both human and animal studies demonstrate that regular physical activity reshapes gut microbial diversity, promoting the growth of indole-producing bacteria such as *Clostridium sporogenes*, *Akkermansia muciniphila*, and *Romboutsia*.

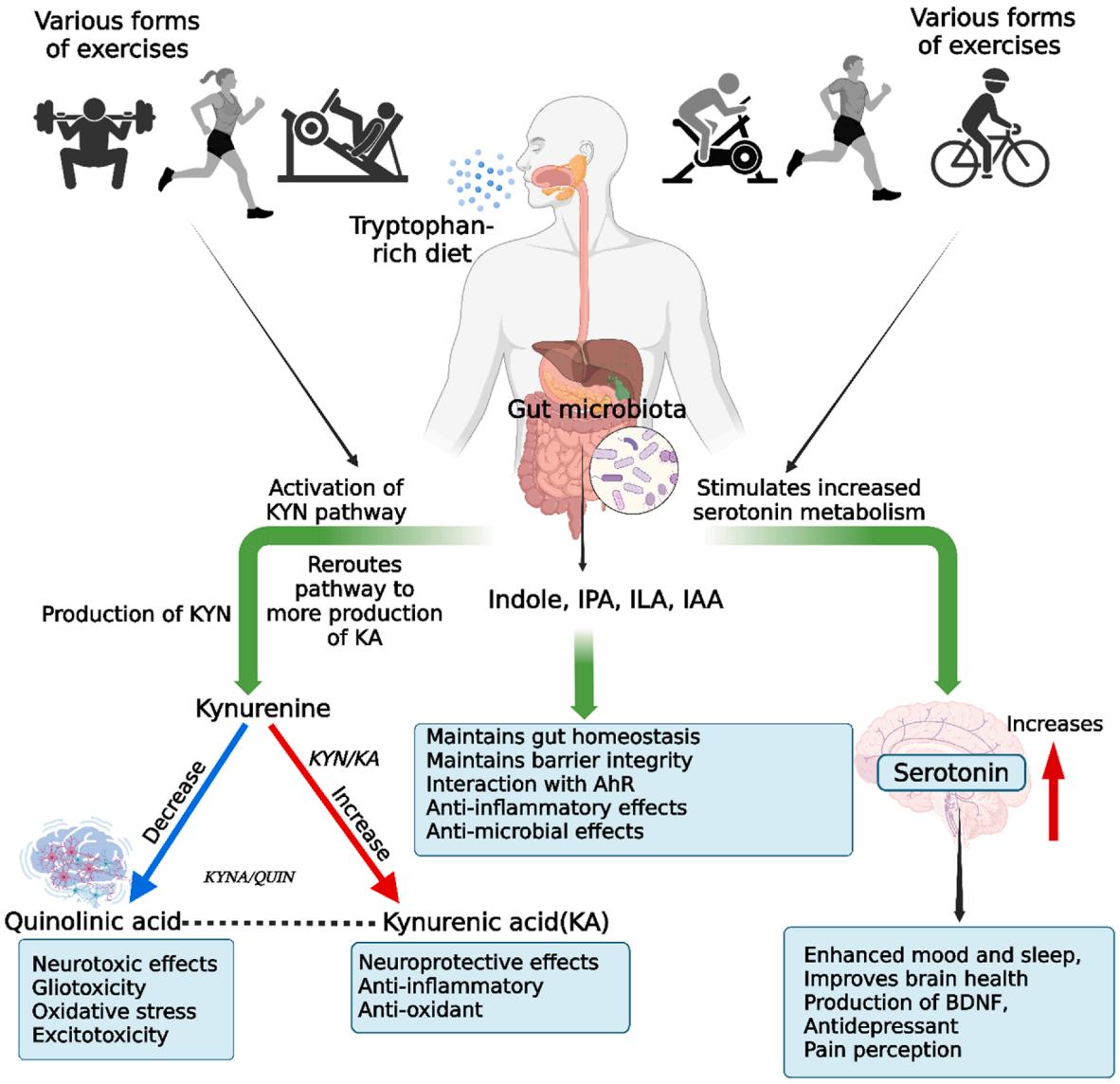

Fig. 2. Schematic illustration showing the effects of exercise on the kynurenine (KYN) and serotonin (5-HT) pathways (Created using https://BioRender.com).

These microbiota-derived indole metabolites particularly indole-3-propionic acid (IPA), indole-3-acetic acid (IAA), and indole-3-lactic acid (ILA) activate the AhR and its downstream target genes, thereby enhancing intestinal barrier integrity, mitigating inflammation, and improving metabolic and hepatic resilience. This microbiota-indole-AhR signaling cascade provides a mechanistic explanation for the systemic benefits of exercise extending to the gut-liver-brain axis, linking microbial metabolism with neuroprotection, cognitive health, and longevity.

Taken together, the integration of findings across human and animal studies underscores that exercise engages a dual mechanism: rerouting tryptophan metabolism toward both neuroprotective KYN derivatives and enhanced serotonin signaling. This bidirectional modulation provides a strong biological basis for exercise as a non-pharmacological intervention to prevent and treat mood disorders, support cognitive health, and promote resilience against age- and inflammation-related decline. Optimizing exercise type, intensity, and context will be critical for translating these insights into personalized therapeutic strategies.

9. Future directions

Despite major advances in defining the molecular links between exercise and tryptophan metabolism, the complex interplay among the kynurenine, serotonin, and indole pathways and their coordinated contribution to systemic health and function remains poorly understood. Future studies should adopt a systems-level approach, integrating metabolomics, transcriptomics, and microbiome analyses to reveal how exercise intensity, duration, and modality collectively shape metabolic flux through these pathways. Mechanistic investigations are also needed to define how different tissues (e.g., skeletal muscle, liver, adipose tissue, and brain) coordinate to maintain tryptophan homeostasis and respond to exercise-induced stress. Mounting evidence implicates the gut microbiota as a central mediator of these adaptations, yet the specific microbial taxa and metabolic routes responsible for producing beneficial indole derivatives (e.g., IPA, IAA, and ILA) remain unclear. Elucidating these microbial determinants and their role in modulating AhR signaling and systemic inflammation

could identify new therapeutic targets. Furthermore, sex hormones and aging profoundly influence tryptophan metabolism; therefore, exploring how these variables interact with exercise will be essential for developing precision exercise interventions tailored to individual metabolic and hormonal contexts. Combining structured exercise with dietary modulation or pharmacological approaches such as IDO1 inhibition may enhance outcomes in older adults and patients with chronic inflammation. Such integrated approaches hold promise for extending healthspan and mitigating neuroinflammation, metabolic dysfunction, and frailty.

CRediT authorship contribution statement

Diana M. Asante: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Sagar Vyavahare:** Writing – review & editing, Visualization, Formal analysis. **Mansi Shukla:** Visualization, Formal analysis. **Meghan E. McGee-Lawrence:** Writing – review & editing, Funding acquisition. **Carlos M. Isales:** Writing – review & editing, Funding acquisition. **Sadanand Fulzele:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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Data availability

The data from this study are available from the corresponding author upon reasonable request.

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