Review

Harnessing Plant-Derived Tryptophan: Bridging the Gap Between Neurobiology and Psychiatry in Depression Management

Amanda Chabrour Chehadi , Enzo Pereira Lopes , Claudia Rucco P. Detregiachi , Rafael Santos de Argolo Haber , Virgínia Maria Cavallari Strozze Catharin , Lucas Fornari Laurindo , Vitor E. Valenti , Cristiano Machado Galhardi , Masaru Tanaka * , Sandra Maria Barbalho *

Posted Date: 29 September 2025

doi: 10.20944/preprints202509.2303.v1

Keywords: major depressive disorder (MDD); tryptophan metabolism; kynurenine pathway; phytochemicals; dietary supplements; 5-hydroxytryptophan; gut–brain axis; neuroinflammation; plant extracts; precision nutrition

 doi:10.20944/preprints202509.2303.v1

Review

Harnessing Plant-Derived Tryptophan: Bridging the Gap Between Neurobiology and Psychiatry in Depression Management

Amanda Chabrour Chehadi [1], Enzo Pereira Lopes [1], Claudia Rucco P. Detregiachi [2,3], Rafael Santos de Argolo Haber [4], Virgínia Maria Cavallari Strozze Catharin [2], Lucas Fornari Laurindo [5], Vitor E. Valenti [6], Cristiano Machado Galhardi [1], Masaru Tanaka [7,*,†] and Sandra Maria Barbalho [1,2,8,9,10,*,†]

[1] Department of Biochemistry and Pharmacology, School of Medicine, University of Marília (UNIMAR), Avenida Higino Muzzi Filho, 1001, Marília, São Paulo, Brazil

[2] Postgraduate Program in Structural and Functional Interactions in Rehabilitation, UNIMAR, Marília, SP, Brazil

[3] Bolsista de Produtividade Desenvolvimento Tecnológico e Extensão Inovadora C do CNPq, São Paulo, Brazil

[4] Division of Cellular Growth, Hemodynamic, and Homeostasis Disorders, Graduate Program in Medical Sciences, Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, SP 05403-000, Brazil

[5] Systematic Reviews Center for Cardiovascular and Metabolic Health, São Paulo State University, School of Philosophy and Sciences, Marília, SP, Brazil

[6] Systematic Reviews Center for Cardiovascular and Metabolic Health, São Paulo State University, School of Philosophy and Sciences, Marília, SP, Brazil

[7] Danube Neuroscience Research Laboratory, HUN-REN-SZTE Neuroscience Research Group, Hungarian Research Network, University of Szeged (HUN-REN-SZTE), Tisza Lajos krt. 113, H-6725 Szeged, Hungary

[8] Faculdade de Tecnologia em Alimentos, Marília, São Paulo, Brazil

[9] Researh Coordinator at UNIMAR Charitable Hospital, Marília, São Paulo, Brazil

[10] Bolsista de Produtividade em Pesquisa B do CNPq, PR, 86038-350, Brazil

* Correspondence: tanaka.masaru.1@med.u-szeged.hu (M.T.); smbarbalho@gmail.com (S.M.B.); Tel.: +36-62-342-847 (M.T.); +55-14-99655-3190 (S.M.B.)

† These authors contributed equally to this work.

Abstract

Major depressive disorder (MDD) remains a leading cause of disability worldwide, with conventional antidepressants offering incomplete and often transient relief. Mounting evidence highlights disturbances in tryptophan (Trp) metabolism as a key biological axis linking inflammation, neuroplasticity, and mood regulation. Plant-derived compounds that modulate this pathway, including 5-hydroxytryptophan, isoflavones, berberine, and polyphenols, have emerged as promising candidates for integrative treatment strategies. Yet, despite encouraging preclinical and clinical findings, knowledge gaps persist regarding long-term efficacy, mechanistic specificity, and standardized therapeutic protocols. This narrative review explores how plant-derived Trp modulators influence central and peripheral mechanisms relevant to depression, from serotonergic synthesis and kynurenine shunting to gut–brain–immune interactions. Evidence from animal models and randomized clinical trials is critically synthesized, with particular attention to outcomes on mood stabilization, anxiety reduction, cognitive function, and sleep regulation. Special emphasis is placed on translational potential, methodological limitations, and the need for harmonized research frameworks. Here we highlight that phytochemical interventions represent a mechanistically informed and biocompatible strategy for advancing depression management. By bridging neurobiology and clinical psychiatry, these insights may pave the way for next-generation therapeutics that integrate dietary, microbiota-targeted, and anti-inflammatory approaches. Broader

 doi:10.20944/preprints202509.2303.v1

application of this research could ultimately refine personalized psychiatry, expand therapeutic horizons, and contribute to global mental health resilience.

Keywords: major depressive disorder (MDD); tryptophan metabolism; kynurenine pathway; phytochemicals; dietary supplements; 5-hydroxytryptophan; gut–brain axis; neuroinflammation; plant extracts; precision nutrition

1. Introduction

Major depressive disorder (MDD) surpasses most chronic diseases in human toll, ranking consistently among the top causes of years lived with disability [1,2]. More than 300 million people currently experience the condition, and its relapsing course relentlessly erodes well-being, productivity, and social cohesion [2,3]. Annual indirect and direct costs already exceed one trillion United States dollars, weakening national economies while stigma quietly erodes family networks, impairs educational attainment, and narrows life opportunities [4,5]. Conventional monoamine-reuptake-based antidepressants, though invaluable, leave a sizeable fraction of patients with partial or transient relief, highlighting an unmet therapeutic horizon [2,6]. Recent neurobiological work has illuminated Trp metabolism as a convergent node linking serotonergic tone, kynurenine (KYN)-driven neuroinflammation, and gut-brain communication [7,8]. Consequently, nutritional psychiatry is moving center stage, exploring dietary enrichment, phytochemical extracts, and complex plant polysaccharides capable of steering Trp flux toward antidepressant pathways [3,8]. These multitarget, biocompatible candidates warrant rapid, translational exploration to transform MDD management [3,9].

Serotonin (5-HT) occupies the fulcrum of affective neurocircuitry, yet its synthesis depends on a single dietary precursor, tryptophan [10,11]. When circulating 5-HT dwindles—whether through genetic polymorphisms, persistent inflammation, or inadequate intake—clinical and pre-clinical data reveal cascades of anhedonia, low mood, and suicidality [10,11]. Supplementation with Trp, and more recently nanozyme-accelerated biosynthesis, swiftly restores synaptic stores, underscoring causality [12,13]. Because no alternative substrate can replenish this indoleamine, strategies that enrich Trp availability or steer its fate toward the serotonergic branch merit priority; they simultaneously quell microglial inflammation and normalize behavior in rodents and humans [11,13]. The problem deepens when pro-inflammatory cytokines activate indoleamine 2,3-dioxygenases (IDOs), shunting Trp down the KYN track, exhausting serotonin and generating neurotoxic quinolinic acid (QA) [11,14]. Meta-analytic biomarker work links this detour to melancholic features, treatment resistance, and suicidal intent, framing KYN dysregulation as a mechanistic bottleneck [10,11]. Encouragingly, plant-derived agents—ginsenoside Rk3, Pulsatilla saponins, Hypericum extracts, diverse polysaccharides, and indole alkaloids—re-calibrate this junction [13,15,16]. By activating tryptophan hydroxylase, repressing IDO1, re-shaping gut microbiota, and enriching anti-inflammatory indoles, they restore serotonergic dominance and offer a multimodal, biocompatible blueprint for next-generation antidepressant therapy [11,15].

Selective 5-HT and 5-HT-norepinephrine reuptake inhibitors still headline pharmacological guidelines for MDD, yet their benefit remains modest [17,18]. Effect sizes rarely exceed placebo by a single point on standardized mood scales, and clinical relief often arrives only after a fortnight—an eternity for suicidal or severely impaired individuals [17,19]. Adverse events accumulate in the interim: up to four patients in five experience sexual dysfunction that may persist beyond discontinuation; progressive weight gain and hyponatremia threaten metabolic and electrolyte balance; emotional blunting, apathy, and cognitive fog sap motivation and adherence, especially in adolescents and older adults vulnerable to withdrawal syndromes [17,19–21]. One patient in three becomes treatment-resistant after two adequate trials, and relapse still strikes forty percent of apparent responders within a year, each episode deepening psychosocial impairment and economic burden [19,20,22]. These intertwined shortcomings have energized the search for nutraceutical,

 doi:10.20944/preprints202509.2303.v1

phytochemical, and mind-body interventions [19,23–25]. Omega-3 fatty acids, flavonoid-rich extracts, acupuncture, mindfulness practice, and guided psilocybin sessions already display encouraging efficacy with fewer liabilities, earning cautious endorsement in emerging guidelines and stimulating expansive translational research [23–26]. Together, these trends justify systematic appraisal of plant-derived Trp as the next therapeutic frontier [19,23,27].

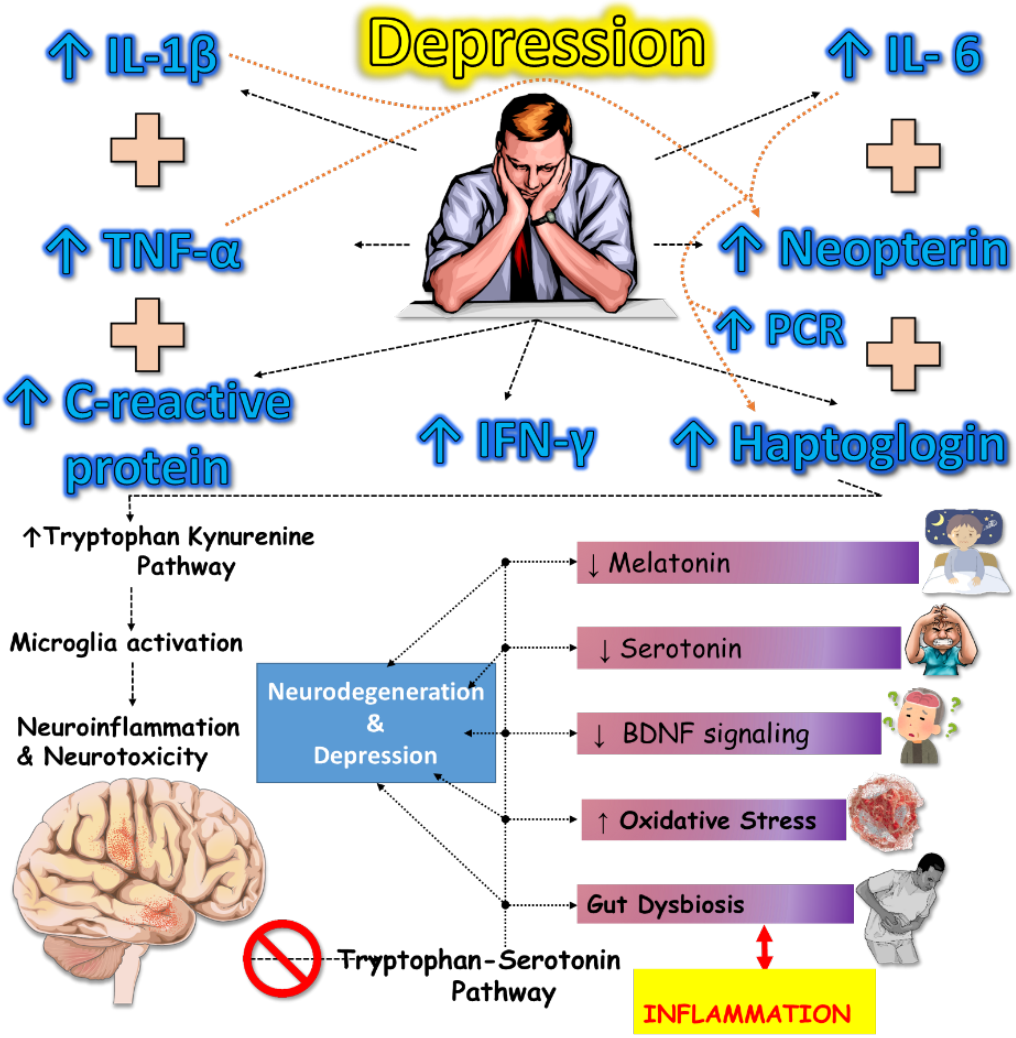

Figure 1. Inflammation-driven neurobiological alterations in depression. Pro-inflammatory cytokines [interleukin (IL)-1 beta (β), tumor necrosis factor-alpha (TNF-α), IL-6] and acute-phase proteins (C-reactive protein, haptoglobin, neopterin) are elevated in depression, reflecting systemic immune activation. These inflammatory mediators cross the blood-brain barrier, inducing neuroinflammation, oxidative stress, and microglial activation. Consequently, neurotrophic and neurotransmitter systems are impaired, including reduced melatonin, serotonin (5-HT), and brain-derived neurotrophic factor (BDNF), alongside increased oxidative stress and gut dysbiosis. Together, these changes contribute to neurotoxicity, synaptic dysfunction, and the pathophysiology of depressive disorders.

Plant-derived modulators of Trp metabolism have moved from folklore to the laboratory, carrying a mechanistic sophistication once reserved for synthetics [28–30]. Oligosaccharides from Morinda officinalis boost gut 5-hydroxy-L-tryptophan, elevating brain 5-HT and reversing stress-induced anhedonia [15,28,29]. Ginsenoside Rk3 and Pulsatilla saponins suppress IDOs, redirect KYN flux, and calm neuroinflammation, while Hypericum fractions, probiotic indoles, and alkaloid derivatives further polish gut-brain signaling with striking behavioral gains [29–31]. These findings echo an ethnopharmacological legacy: lavender, turmeric, bacopa, the Chinese formula Xiaoyao-san,

 doi:10.20944/preprints202509.2303.v1

and Ayurvedic rasayanas have eased melancholy for centuries, with more than 140 mood-modulating plants catalogued across ancient pharmacopoeias [28,29,31]. Their renaissance coincides with nutritional psychiatry, a field treating diet as neuronal software by integrating microbiome science, polyphenol chemistry, and amino-acid neuroscience [15,28,29]. Global guidelines now acknowledge nutraceuticals and phytoceuticals, and bibliometric analyses chart exponential growth in phytotherapeutic trials [28–30]. Moreover, xylopic acid, sclareol-quercetin blends, capsaicin, and Chaihu-Shugan-San enhance selective serotonin reuptake inhibitor (SSRI) efficacy while tempering metabolic and cognitive liabilities, underscoring the promise of safer, synergistic, multicomponent antidepressant strategies [28–30].

The primary objective of this review is to systematically examine the efficacy and neurobiological mechanisms of plant-derived Trp in the treatment of depression. By addressing both experimental and clinical evidence, the review seeks to clarify how dietary and phytochemical interventions targeting Trp metabolism may influence mood regulation and therapeutic outcomes [32–34]. A central aim is to bridge the gap between fundamental neurobiology and clinical psychiatry, offering an integrated perspective that connects molecular mechanisms with patient-centered applications. Specifically, the review focuses on delineating the pathways through which Trp and its metabolites modulate the serotonergic and KYN systems, evaluating preclinical and clinical trial data, and identifying limitations that must be overcome to enhance translational relevance. Attention is given to unresolved issues in bioavailability, pharmacokinetics, and long-term safety. Ultimately, this review highlights future therapeutic prospects and emphasizes the importance of integrating mechanistic insights with clinical practice to guide precision-based strategies for depression management.

This review carries significant implications for psychiatry, nutritional sciences, and integrative medicine by advancing understanding of plant-derived Trp as a therapeutic option for depression. Its contributions extend beyond cataloguing current evidence, offering a critical synthesis that highlights both mechanistic insights and clinical applications. By evaluating how dietary and phytochemical interventions influence Trp metabolism and related neurobiological pathways, the review provides an innovative framework with direct translational relevance. The discussion emphasizes how such approaches may complement existing pharmacological treatments, reduce side effect burden, and support individualized, nutrition-based strategies in mental health care. Importantly, the review underscores the potential of integrating dietary science with neuropsychiatric research to broaden treatment paradigms and improve patient outcomes. Here we highlight the necessity of sustained interdisciplinary collaboration, uniting psychiatry, molecular biology, nutrition, and clinical practice. Only through such efforts can the full therapeutic potential of Trp-related interventions be realized in depression management.

2. Neurobiology of Depression: Beyond Serotonin (5-HT)

For much of the twentieth century, textbooks portrayed depression as a straightforward consequence of diminished synaptic 5-HT, a view seemingly vindicated by selective-5-HT reuptake inhibitor success and reinforced through neat biochemical cartoons [35–37]. Accumulating evidence now unpicks that narrative. An umbrella analysis fails to locate a reliable serotonergic deficit signature in MDD (9), while parallel studies reveal stress-evoked glutamatergic drift at AMPA receptors, a shift that disrupts excitatory balance and long-term potentiation [35,38,39]. Cytokine surges further interweave immune and neural realms, diverting Trp toward KYN metabolites with neurotoxic or neuroprotective potential, and tuning mitochondrial resilience in vulnerable circuits [40–42]. Animal paradigms of chronic unpredictable stress echo these molecular fingerprints, exposing dendritic retraction and synaptic pruning that compromise mood-regulating networks [35,41,42]. Against this backdrop, neuroplastic frameworks embrace receptor heterocomplexes, neurotrophic signals, and dynamic gliovascular interactions, weaving a tapestry that better captures the disorder's heterogeneity [35,36,40]. Such multi-layered models do more than widen mechanistic horizons; they steer translational efforts toward modulators of plasticity, inflammation, and

 doi:10.20944/preprints202509.2303.v1

metabolism, promising interventions that transcend the monoaminergic lens and address the complex biology underlying depressive illness [40,43–45].

2.1. Microglia Activation and Neuroinflammation

Microglial cells act as vigilant guardians of the central nervous system, continuously scanning for threats, pruning synapses, and supplying neurotrophic support to preserve metabolic balance and neural circuitry under resting conditions [46–48]. Chronic psychosocial stress, however, propels these sentinels into a hyperactive state, marked by rapid proliferation, metabolic reprogramming, and elevated expression of pro-inflammatory markers that erode excitatory synapses [46,47,49]. Glucocorticoids and catecholamines coursing through hypothalamic-pituitary-adrenal (HPA) and sympathetic pathways reinforce this shift, entrenching microglia in maladaptive, inflammatory phenotypes [46,50,51]. A spectrum of reactive states emerges: some microglia secrete cytokines and reactive metabolites that fracture neuronal integrity, while others attempt repair through anti-inflammatory mediators [48,52,53]. Early-life immune challenges further dysregulate microglial surveillance, triggering excessive dendritic spine engulfment and predisposing adolescents to mood disturbances [54–56]. In adulthood, sustained IL-6 release drives hippocampal astrocyte apoptosis, and prostaglandin signaling in striatal regions amplifies negative affect [49,57,58]. Crucially, pharmacological or genetic dampening of microglial activation reduces cytokine burden and restores synaptic function, alleviating depressive-like behaviors in animal models [48,49,57]. Such findings underscore microglia's dual capacity for neuroprotection and neurotoxicity, and highlight inflammatory modulation as a promising axis for next-generation antidepressant development [46,48,49].

Converging evidence positions interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and Interferon gamma (IFN-γ) at the core of a neuroinflammatory blueprint for depression [59–61]. Meta-analytic syntheses, large observational cohorts, and translational models consistently show that concentrations of these cytokines rise in parallel with symptom load, forecast relapse, and differentiate treatment-resistant cases from treatment-responsive patients [62–64]. Stress priming activates NLRP3 inflammasomes, unleashing bursts of IL-1β that propagate glial crosstalk, while epigenetic regulators such as EZH2 intensify IL-6 and tumor necrosis factor-alpha (TNF-α) transcription, accelerating synaptic attrition and anhedonia [65–67]. Longitudinal work in adolescents demonstrates that elevated baseline TNF-α or IL-6 anticipates chronic anhedonia and white-matter dysconnectivity years later, underscoring a trajectory of immune-driven neuroprogression [68–70]. Complementary primate and lipopolysaccharide paradigms replicate the cytokine surge and its behavioral sequelae, bolstering causality [71–73]. Crucially, immunomodulatory interventions can reverse this profile: ketamine lowers IL-6 and TNF-α in treatment-resistant depression in tandem with rapid affective recovery, and targeted anti-cytokine therapies normalize peripheral markers while lifting mood in case studies and pilot trials [74–76]. Together, these findings portray a feed-forward inflammatory circuit that not only marks depressive severity and chronicity but also delineates mechanistic targets for next-generation precision antidepressants, with potential for biomarker-guided stratification in clinical practice worldwide [71,72,77].

2.2. Neurogenesis Impairment and Hippocampal Atrophy in Depressive Pathology

Adult hippocampal neurogenesis generates a steady stream of granule cells that weave into mnemonic and affective circuits, granting cognitive flexibility and insulating mood. Rodent, primate, and human proxy experiments reveal that boosting this renewal before stress inoculates against anhedonia and cognitive drift, whereas blocking it magnifies vulnerability and depressive phenotypes [78–80]. Mitochondrial fitness, autophagic clearance, and neuroimmune balance calibrate neurogenic yield, linking cellular housekeeping to psychological health and nominating the neurogenic niche as a tractable antidepressant target [81–83]. Chronic stress disrupts this equilibrium: sustained corticosterone primes microglia, activates NFκB, and floods the hippocampus with IL-1β,

 doi:10.20944/preprints202509.2303.v1

IL-6, TNF-α, and IFN-γ. These cytokines halt progenitor proliferation, misroute BDNF via CDK5-phosphorylated huntingtin, and push precursors toward apoptosis while astrocytic VEGF support wanes [84–86]. Glial activation amplifies oxidative damage, ADAM17/TNF-α signaling, and aberrant pruning, cementing a neurogenic standstill that melatonin or ginsenoside Rg1 can dismantle [87–89]. Structural imaging corroborates the cellular narrative: meta-analyses and cross-diagnostic cohorts consistently report bilateral, often left-dominant, hippocampal atrophy in depression [86,89,90]. Seven-Tesla datasets pinpoint shrinkage to dentate gyrus and tail subfields, especially in treatment-resistant illness [88,90,91]. Interventions that rekindle plasticity, including electroconvulsive therapy and aerobic exercise, partially restore volume, implying that suppressed neurogenesis and dendritic retraction are reversible contributors to mood recovery [88,92,93]. Such structural reversibility converges with behavioral improvements, reinforcing adult neurogenesis as both biomarker and mediator of durable resilience [94,95].

Chronic neuroinflammation progressively dismantles the hippocampal neurogenic niche. Activated microglia, astrocytes, and infiltrating immune cells inundate progenitor zones with IL-1β, caspases, reactive oxygen species, and other cytotoxic mediators, stalling cell-cycle progression and truncating dendritic maturation [96–98]. Sustained IL-10 exposure or traumatic injury reprograms microglia toward a phagocytic, synapse-stripping phenotype that disrupts neuron–glia crosstalk and shortens the lifespan of newborn neurons [99–101]. Intrinsic genetic vulnerabilities intensify the problem: loss of the transcription factor Tcf4 unleashes latent inflammatory pathways inside neural stem cells, extinguishing their regenerative capacity [96,97,102]. Systemic infections or chronic gut inflammation widen this suppression, propagating cytokine waves that reverberate into cognitive decline and depressive affect [103–105]. Compounding these injuries, elevations in IL-6 and tumor necrosis factor-α draw down brain-derived neurotrophic factor (BDNF), a molecule essential for synaptic refinement and mood stability, thereby tightening the grip of inflammation on neuroplasticity [106–108]. Clinical imaging and behavioral studies mirror these molecular events: higher cytokine loads predict smaller hippocampi, poorer memory, and deeper anhedonia, while agents that either quiet neuroimmune signaling or re-energize neurogenesis—such as Akebia saponin D, liraglutide, naringenin, or KYN-pathway modulators—restore plasticity and relieve symptoms [106,109–112].

2.3. The Link between Inflammation, Triptophan (Trp) metabolism, and Depressive Symptoms

Innate and adaptive immune signals divert Trp away from serotonergic fate, engaging IDOs and tryptophan 2,3-dioxygenase (TDO) that accelerate the KYN cascade of neuroactive compounds [113,114]. IFN-γ, IL-6, and tumor necrosis factor-α boost these enzymes across gut and brain, shrinking 5-HT stores while raising KYN and its downstream quinolinate products [114,115]. Chronic stress or intestinal inflammation magnifies the shift, elevating KYN-to-5-HT ratios in rodents and paralleling anhedonia in patients [114,116]. This metabolic rerouting therefore binds immune activation to depressed mood and cognitive decline [114,116–118] (Figure 2). Yet the pathway's end stage proves most damaging. QA overstimulates NMDA receptors, drives calcium overload, and sparks oxidative stress [114,115,119–121]. Traumatic brain injury or systemic inflammation upregulates KYN monooxygenase, intensifying quinolinate build-up, halting progenitor proliferation, and eroding hippocampal circuits [113,114,119]. Microplastic exposure yields similar DNA fragmentation and microglial activation [113,114,122]. Therapeutic blockade with ketamine or selective enzyme inhibitors lowers quinolinate, restores neurogenesis, and rescues behavior [113–115]. Reviews across neurodegenerative contexts confirm that balancing toxic and protective KYNs is critical for hippocampal integrity and mood regulation [113,114,116]. Collectively, these findings reposition the KYN axis as both biomarker and mechanistic driver, inviting precision anti-inflammatory or metabolic interventions that could recalibrate Trp flux, preserve plasticity, and alleviate depressive illness.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 September 2025 doi:10.20944/preprints202509.2303.v1

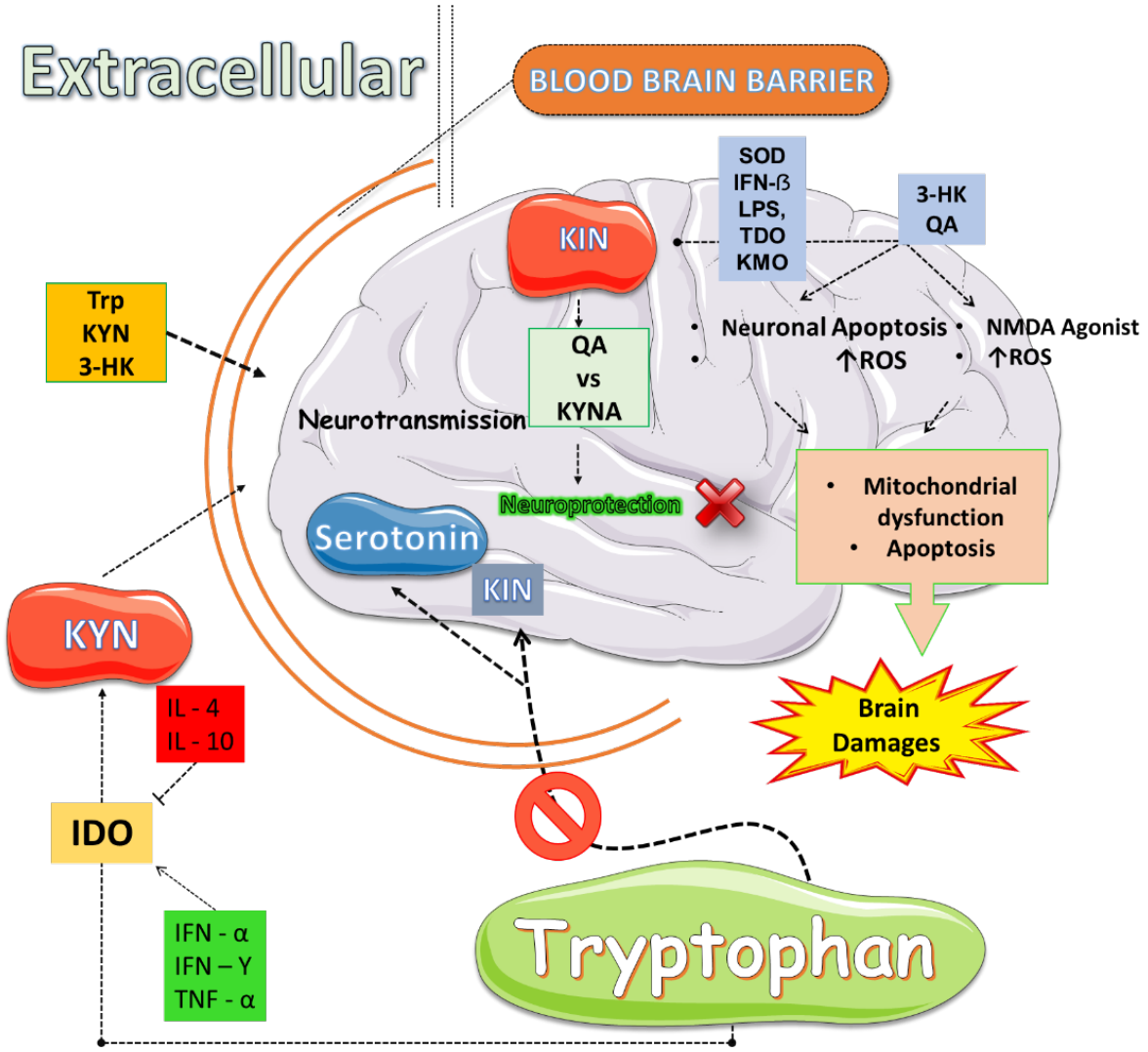

Figure 2. Tryptophan (Trp) metabolism through the kynurenine (KYN) pathway: Balancing neuroprotection and neurotoxicity in depression. This figure illustrates how immune-mediated activation of the KYN pathway disrupts Trp metabolism, linking inflammation with depression-related neuropathology. Stress hormone, cortisol stimulates tryptophan 2,3-dioxygenase (TDO). Pro-inflammatory cytokines [interferon (IFN)-alpha (α), IFN-beta (ß), IFN-gamma (γ), tumor necrosis factor (TNF)-α] and lipopolysaccharide (LPS) induce indoleamine 2,3-dioxygenases (IDOs), diverting Trp away from serotonin (5-HT) synthesis toward KYN production. In contrast, anti-inflammatory cytokines [interleukin (IL)-4, IL-10] and superoxide dismutase (SOD) counteract this process. Oxygen molecule (0_2), IFN-ß, IFN-γ, TNF-α stimulate and IL-4, IL-10, SOD suppress kynurenine 3-monooxydase (KMO). Furthermore, IDOs, TDO, and KMO activities are influenced by positive and negative feedback loops. Peripheral KYN crosses the blood-brain barrier, where it undergoes two competing fates: (i) conversion into kynurenic acid (KYNA), a putative neuroprotective N-Methyl-D-Aspartate (NMDA) receptor antagonist with putative antioxidant properties, or (ii) metabolism into 3-hydroxykynurenine (3-HK) and quinolinic acid (QA), which promotes reactive oxygen species (ROS), NMDA receptor overstimulation, mitochondrial dysfunction, and neuronal apoptosis, ultimately leading to neurodegeneration. The dashed inhibitory arrow indicates that enhanced KYN metabolism reduces 5-HT and melatonin synthesis, impairing neurotransmission and neuroprotection. The balance between KYNA and QA determines whether the KYN pathway promotes resilience or vulnerability to depression.

Chronic immune activation diverts Trp metabolism by up-regulating IDOs and TDO, drawing substrate from 5-HT synthesis and inflating production of neuroactive KYNs such as QA [114,123,124]. Quinolinic excess overstimulates N-methyl-D-aspartate (NMDA) receptors, kindles oxidative stress, and arrests hippocampal neurogenesis, thereby reducing BDNF, pruning synapses,

 doi:10.20944/preprints202509.2303.v1

and disturbing gut–brain communication essential for mood and memory [123,125]. These pathophysiological threads recast depression as a metabolic-immune-plasticity disorder that demands therapies surpassing monoaminergic repair [114,123,124]. Evidence now endorses blended strategies that curb inflammation, recalibrate microbiota signaling, temper glutamatergic drive, and reignite neurogenesis [126,127]. Phytochemicals illustrate this integrative ethos: polyphenols, soy isoflavones, berberine, albiflorin, Pulsatilla saponins, and naringenin jointly silence microglial cytokine release, inhibit IDO1, activate tryptophan hydroxylase, and foster survival of newborn neurons, collectively improving affective and cognitive outcomes in stress-resistant models [128–130]. Such multi-layered modulation repairs molecular circuitry while offering a blueprint for precision nutrition and pharmacology that mirrors depression's multifactorial biology, promising durable relief in clinical practice [131–133].

3. Tryptophan (Trp) Metabolism: Central Pathways and Peripheral Influences

Trp metabolism lies at the heart of neuropsychiatric research, serving as a biochemical crossroad between neurotransmission, immune regulation, and circadian control [134,135]. Among its metabolic fates, the 5-HT and KYN pathways represent fundamental routes with profound implications for mood and cognition [136,137]. The 5-HT branch underpins neurotransmitter synthesis and neuroplasticity, while the KYN branch generates a spectrum of neuroactive metabolites that shape neuroinflammation and excitotoxicity [138,139]. Dysregulation of this delicate balance has been repeatedly implicated in depression, schizophrenia, and neurodegenerative disorders [14,140]. This section introduces these dual metabolic routes, emphasizing their molecular complexity, clinical relevance, and potential as therapeutic targets for precision psychiatry.

3.1. Serotonin (5HT) and Kynurenine (KYN) Metabolic Pathways: Fundamental Metabolic Routes

The 5-HT pathway begins when Trp undergoes hydroxylation by tryptophan hydroxylase (TPH1 and TPH2), producing 5-hydroxytryptophan (5-HTP), which is then decarboxylated to generate 5-HT [141,142]. This neurotransmitter engages multiple receptor families, including 5-HT1A, 5-HT2A, 5-HT4, and 5-HT6, each exerting distinct influences on mood regulation, neurogenesis, and synaptic plasticity [134,141]. Antidepressants such as SSRIs not only increase synaptic 5-HT but also enhance structural remodeling and circuit flexibility, shifting the focus from a deficit model to a neuroplasticity framework [142,143]. Receptor-receptor interactions, like 5-HT2A–TrkB heterodimerization, and receptor-specific mechanisms, such as biased 5-HT1A signaling or 5-HT4-mediated memory modulation, highlight the pathway's molecular sophistication [14,143]. Psychedelic compounds further reveal how 5-HT2A activation may promote cortical plasticity, though 5-HT itself may not be the primary ligand driving such effects [134,142]. Yet, pressing gaps persist. The precise endogenous mechanisms underlying receptor-driven plasticity remain unclear, while phase-specific roles of 5-HT in declarative memory are insufficiently mapped. Translational barriers hinder the movement of receptor-targeted and psychedelic-based therapies into clinical use, particularly regarding long-term safety. Moreover, the interplay of diet, stress, and genetic variability complicates predictions of therapeutic response [134,143]. Clarifying these complexities is critical for developing precise, individualized treatments for mood and cognitive disorders.

 doi:10.20944/preprints202509.2303.v1

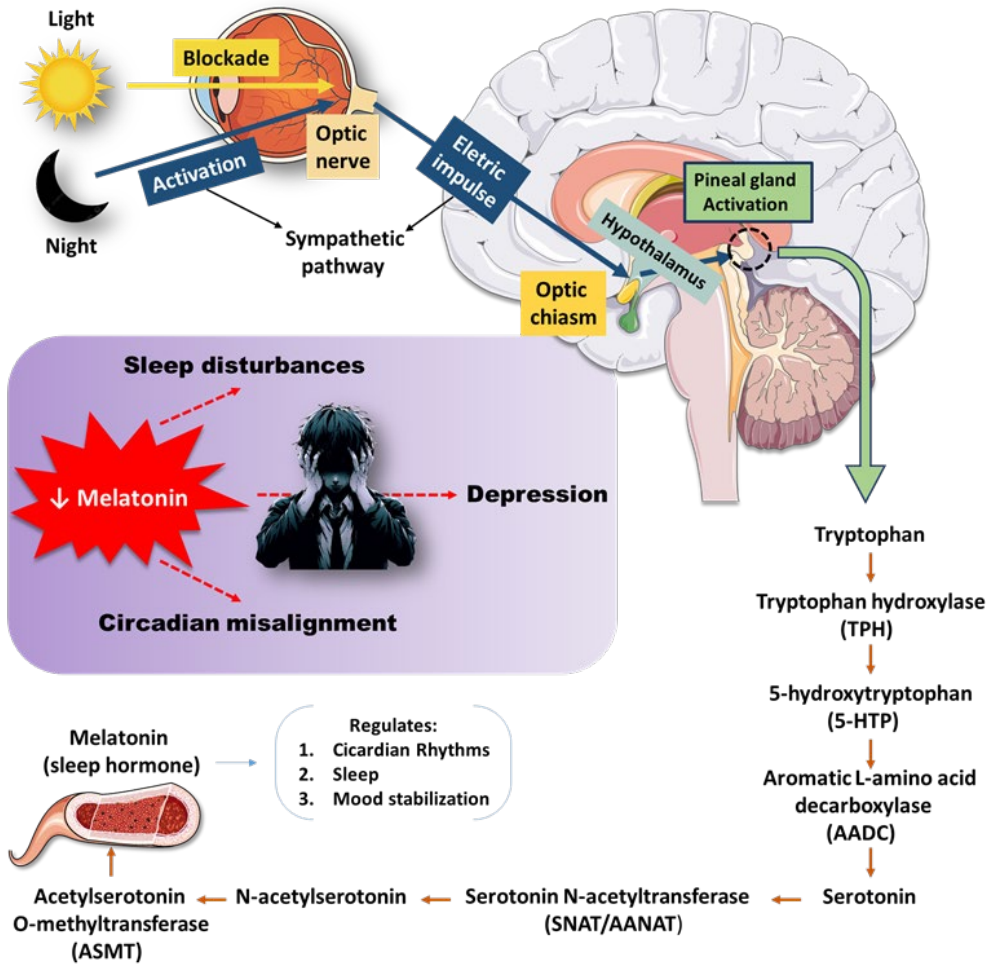

Figure 3. Light– suprachiasmatic nucleus (SCN)–pineal pathway regulating melatonin biosynthesis. Light information from the retina reaches the suprachiasmatic nucleus (SCN), the master circadian pacemaker, via the retinohypothalamic tract. The SCN projects to the paraventricular nucleus and modulates sympathetic innervation of the pineal gland. In darkness, SCN activity stimulates pineal metabolism of Trp through a sequential enzymatic cascade: tryptophan hydroxylase (TPH) converts Trp into 5-hydroxytryptophan (5-HTP), aromatic L-amino acid decarboxylase (AADC) generates serotonin (5-HT), serotonin N-acetyltransferase (SNAT) produces N-acetylserotonin, and acetylserotonin O-methyltransferase (ASMT) catalyzes the final step to melatonin. Light exposure suppresses this pathway, reducing melatonin output. Melatonin acts as a key circadian regulator, influencing sleep, neuroendocrine rhythms, and mood regulation.

The KYN metabolic pathway represents the primary route of Trp degradation, initiated by the rate-limiting enzymes IDOs and TDO, leading to the production of KYN [144,145]. This intermediate can be further metabolized into neuroactive derivatives with contrasting effects KYNA, which acts as an NMDA receptor antagonist with neuroprotective properties, and QA, an NMDA receptor agonist with excitotoxic and pro-inflammatory actions [146,147]. Additional metabolites such as 3-hydroxykynurenine (3-HK) contribute to oxidative stress, linking the pathway to neurodegenerative and psychiatric disorders [144,146]. Meta-analyses and experimental studies consistently show a pathological shift toward neurotoxic metabolites in depression, schizophrenia, Alzheimer's disease, and neurodegeneration [14,148]. Yet significant challenges persist. The dichotomy of KYNA as purely protective and QA as strictly harmful is now recognized as overly simplistic, since their impact varies with concentration, brain region, and disease context [149,150]. Furthermore, the spatial distribution and regulation of key enzymes such as kynurenine 3-monooxydase (KMO), kynurenine aminotransferases (KATs), and quinolinate phosphoribosyltransferase (QPRT) remain insufficiently characterized in both central and peripheral systems [151,152]. Peripheral metabolite measures often

 doi:10.20944/preprints202509.2303.v1

fail to accurately represent brain activity, limiting their use as biomarkers [152,153]. Finally, although enzyme inhibitors and analogues are under clinical investigation, their long-term efficacy and safety are far from established [151,154].

3.2. Oxidative Stress and Inflammation: Drivers of Kynurenine (KYN) Pathway Activation

Trp is an essential amino acid indispensable for neurochemical homeostasis, mood regulation, and cognitive integrity [14,123,135]. While a minor fraction enters the serotonin pathway to support neurotransmission and neuroplasticity, the vast majority is shunted into the KYN pathway, generating metabolites with neuroactive and immunomodulatory properties [11,114,135]. This balance is highly sensitive to oxidative stress and proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and IFN-γ, which divert metabolism away from 5-HT toward KYN derivatives, a shift consistently observed in depression, schizophrenia, and neurodegenerative disorders [14,114,155]. Accumulation of neurotoxic metabolites like QA exacerbates excitotoxicity and oxidative stress, whereas kynurenic acid (KYNA) may provide neuroprotection in a context-dependent manner [156–158]. Despite clear links between immune activation, oxidative stress, and altered Trp metabolism, major questions remain unresolved [14,114,156]. The molecular crosstalk between cytokine signaling, mitochondrial dysfunction, and metabolic reprogramming requires clarification [14,156,159]. Similarly, the role of gut microbiota and platelets as peripheral modulators of Trp fate is incompletely defined [110,116,136,160]. Translational gaps persist in developing reliable biomarkers and effective therapeutic strategies, particularly antioxidants, pathway modulators, and microbiota-targeted interventions [14,156,159]. Addressing these challenges will be crucial for precision approaches to neuropsychiatric and neurodegenerative diseases [161].

IDOs and TDO catalyze the first, rate-limiting step of the KYN pathway, thereby functioning as pivotal gatekeepers of Trp metabolism [162–164]. Under conditions of inflammation and oxidative stress, these enzymes are strongly upregulated: TDO, primarily expressed in the liver and regulated by systemic Trp levels and glucocorticoids, and IDO, widely induced in immune cells by cytokines such as IFN-γ and TNF-α [163,165,166]. Their activation diverts Trp away from 5-HT synthesis and channels it toward KYN, which in turn generates metabolites like QA with excitotoxic and pro-inflammatory effects, and KYNA with context-dependent neuroprotection [163–165]. Beyond enzymatic activity, KYN itself acts as a ligand for the aryl hydrocarbon receptor (AhR), modulating immune tolerance and tumor progression [162,167,168]. Despite these advances, substantial gaps remain. The tissue-specific regulation of IDO and TDO under stress conditions is not fully mapped, and their non-enzymatic roles in shaping the immune microenvironment remain underexplored [163–165]. Clinical trials with IDO inhibitors have yielded disappointing results, highlighting the need for dual IDO/TDO inhibition or combined targeting of downstream receptors[164,167,169]. Moreover, reliable biomarkers of enzyme activity and patient stratification strategies are lacking, while the dynamic regulation of heme incorporation and post-translational modifications introduces further complexity [162–164].

Elevated activity of the KYN pathway, particularly the accumulation of QA, has been strongly associated with depressive symptoms, impaired neurogenesis, and deficits in cognitive domains such as memory and executive function [170–172]. Neuroimaging and postmortem studies reveal that increased KYN metabolite ratios correlate with structural and functional brain abnormalities in depression, while animal models show that IDO-mediated pathway activation drives both neuroinflammation and cognitive decline [171–173]. Evidence also suggests that reduced kynurenic acid, a putative neuroprotective metabolite, exacerbates cognitive impairment, especially in mood disorders [148,174,175]. These findings have stimulated interest in KYN-targeted therapies, ranging from small molecules to microbiota-based interventions [116,136,150,176,177]. Yet, major questions remain unresolved. Central and peripheral measures of pathway activity often diverge complicating biomarker development [148,175,178,179]. The causal links between specific metabolites and clinical symptoms require more mechanistic studies [124,170,173]. Translational efforts remain limited, with few robust clinical trials validating efficacy [148,176,178]. Furthermore, the role of gut microbiota in

 doi:10.20944/preprints202509.2303.v1

modulating KYN metabolism and cognitive outcomes is only beginning to be understood [136,180,181]. Longitudinal studies are essential to map disease trajectories and clarify whether metabolite alterations differ across depression subtypes and cognitive phenotypes [148,173,178].

3.3. Gut-Brain Axis and Intestinal Microbiota: Peripheral Modulators of Tryptophan (Trp) Metabolism

The gut-brain axis is a dynamic bidirectional communication network linking the gastrointestinal tract with the central nervous system through neural, immune, endocrine, and metabolic pathways [182–184]. This system orchestrates critical processes that regulate neuroinflammation, energy metabolism, and psychiatric outcomes, with mounting evidence implicating gut microbiota and their metabolites as central mediators [160,185,186]. Dysbiosis has been consistently associated with depression, anxiety, schizophrenia, and neurodegenerative disorders, largely through altered signaling across the vagus nerve, HPA axis, and immune-inflammatory cascades [187–189]. At the same time, microbial metabolites such as short-chain fatty acids and Trp derivatives modulate neurotransmission and glial function, further linking gut health to brain plasticity and cognition [182,187,190]. Yet, despite compelling evidence, substantial gaps remain. The precise molecular and cellular mechanisms underlying gut-brain interactions are incompletely defined, particularly regarding causal links [191,192]. Translation of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation into reliable therapeutic strategies is hindered by inconsistent clinical results [184,191,193]. Biomarker development for diagnosis and treatment monitoring is still in its infancy, while most studies are restricted to narrow cohorts, limiting generalizability [184,191,194]. Longitudinal and mechanistic trials are urgently needed to clarify causality and optimize intervention strategies in psychiatric and neurodegenerative disorders [182,191,194].

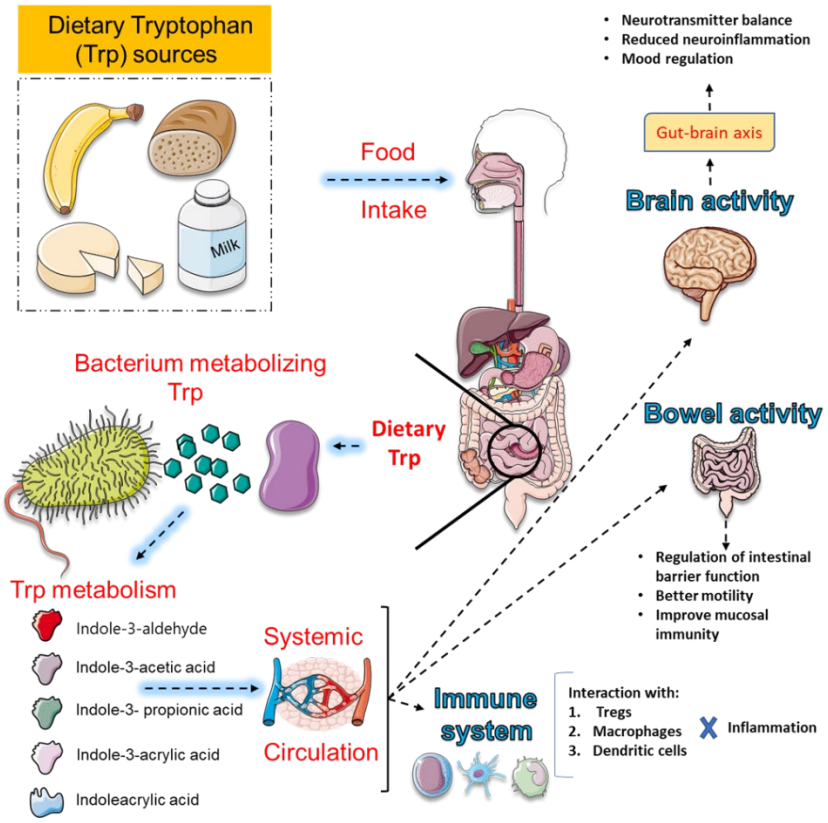

Figure 4. Dietary tryptophan (Trp) metabolism by gut microbiota and its systemic effects. Exogenous dietary Trp, derived from protein-rich foods, is metabolized by intestinal microbiota into indole derivatives including indole-3-aldehyde (IAld), indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and indoleacrylic acid. These metabolites enter the systemic circulation and exert pleiotropic effects on host physiology. IAld activates the aryl hydrocarbon receptor (AhR), modulating mucosal immunity, while IPA provides neuroprotection through

 doi:10.20944/preprints202509.2303.v1

antioxidant activity. IAA regulates intestinal motility and epithelial function, whereas indoleacrylic acid strengthens gut barrier integrity. Collectively, these microbial metabolites influence **brain activity** (neurotransmission, neuroinflammation, mood), **bowel function** (motility, barrier homeostasis), and the **immune system** (immune tolerance, inflammation). This highlights the central role of gut microbiota–Trp metabolism in the gut–brain–immune axis.

Gut microbiota profoundly influence Trp metabolism, shaping central nervous system function and mood through multiple converging pathways [136,160,195]. By modulating local inflammation, they alter the activity of enzymes that govern Trp's diversion into 5-HT and KYN branches, thereby influencing neurotransmission, neuroplasticity, and immune signaling [136,196,197]. Microbial metabolites also act directly: some species enhance 5-HT synthesis in the gut, while others promote KYN production or generate indole derivatives that engage the aryl hydrocarbon receptor to regulate neuroinflammation [198,199]. These interactions extend beyond the periphery, with microbial-driven metabolic shifts linked to depression, anxiety, and cognitive dysfunction in both preclinical models and clinical cohorts [136,160,195,197]. Yet, despite compelling evidence, important uncertainties remain. The identity of key microbial species responsible for shaping Trp metabolism is incompletely defined, and the molecular mechanisms orchestrating the balance between 5-HT, KYN, and indole pathways require clarification [197,200,201]. Translational progress is limited, as most findings derive from animal studies rather than large-scale human trials [197,202,203]. Therapeutic strategies such as probiotics, synbiotics, and dietary modulation hold promise, but their efficacy, safety, and mechanistic specificity need systematic evaluation [203–205]. Finally, reliable biomarkers to monitor microbiota-driven tryptophan metabolism and predict psychiatric outcomes are lacking, hindering the development of personalized interventions [197,200,206].

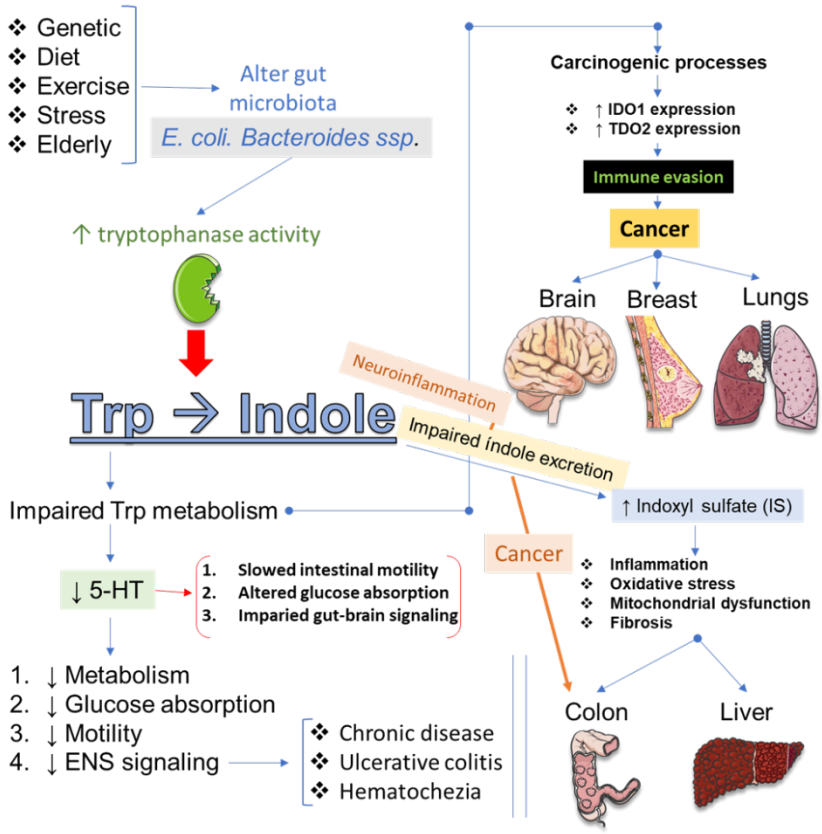

Figure 5. Tryptophan (Trp) –indole metabolism and its pathological consequences. Gut microbiota such as *Escherichia coli* and *Bacteroides spp.* metabolize dietary Trp via tryptophanase into indole. Host and environmental factors (genetics, diet, stress, aging, physical activity) modulate this pathway. Dysregulated Trp metabolism reduces serotonin (5-HT) availability, impairing enteric nervous system signaling, metabolism, glucose

 doi:10.20944/preprints202509.2303.v1

absorption, and intestinal motility, contributing to chronic gastrointestinal disorders such as ulcerative colitis and hematochezia. Indole derivatives, particularly indoxyl sulfate (IS), accumulate when excretion is impaired, leading to systemic inflammation, oxidative stress, and cell damage in the colon and liver. Overexpression of IDO1 and TDO2 further links altered Trp metabolism to carcinogenic processes in the brain, breast, and lungs. This highlights the central role of Trp–indole metabolism in the gut–brain–immune axis, cancer progression, and systemic disease.

Change: "Trp" → "Tryptophan"

Emerging preclinical and clinical evidence suggests that targeting gut microbiota through probiotics, prebiotics, dietary phytochemicals, or even fecal microbiota transplantation can restore Trp balance, reduce neuroinflammation, and alleviate depressive symptoms [194,197,207]. Probiotics such as Lactobacillus and Bifidobacterium strains have been shown to enhance 5-HT availability, while prebiotics and phytochemicals promote beneficial microbial shifts that dampen KYN-driven neurotoxicity [208–210]. In animal models, microbiota modulation improves stress-induced depressive behaviors by redirecting Trp metabolism toward 5-HT rather than neurotoxic KYN derivatives, findings now echoed in early human trials reporting improved mood outcomes [208,209,211]. Nevertheless, major gaps remain. Mechanistic clarity is limited, particularly regarding the molecular pathways by which specific microbial taxa regulate 5-HT and KYN branches [194,195,197]. Most clinical studies are small, short in duration, and heterogeneous in design, making efficacy and safety conclusions premature [211–213]. Inter-individual variability in microbiome composition complicates the development of standardized therapies, while long-term durability of benefits remains untested [194,197,212]. Finally, reliable microbial and metabolic biomarkers to guide patient stratification and therapeutic monitoring are lacking [194,197,212]. Addressing these gaps is essential for translating microbiota-based strategies into personalized, evidence-driven interventions for depression and related neuropsychiatric disorders.

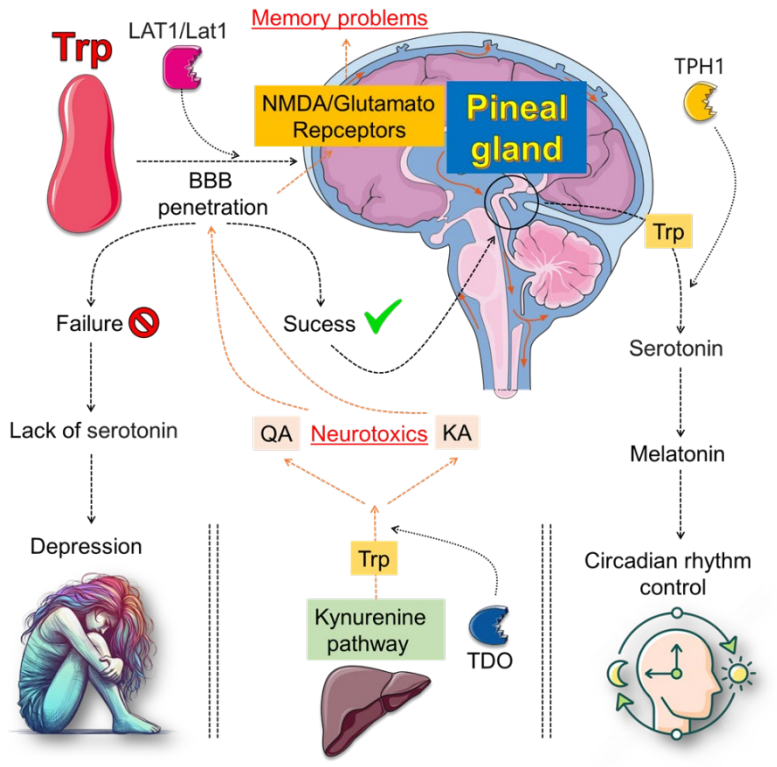

Figure 6. Dual pathways of tryptophan (Trp) metabolism and their neuropsychiatric implications. Trp crosses the blood-brain barrier via LAT1 transporters and follows two competing metabolic routes. One route converts

 doi:10.20944/preprints202509.2303.v1

Trp to serotonin (5-HT) through tryptophan hydroxylase (TPH1), which subsequently gives rise to melatonin, regulating circadian rhythms and mood. Impaired 5-HT synthesis contributes to depression and sleep disturbances. Alternatively, Trp is metabolized through the kynurenine (KYN) pathway, primarily via tryptophan 2,3-dioxygenase (TDO). This generates metabolites with opposing actions: quinolinic acid (QA), a neurotoxic NMDA receptor agonist that promotes excitotoxicity, oxidative stress, and cognitive dysfunction, and kynurenic acid (KYNA), a neuroprotective NMDA receptor antagonist that counterbalances QA's toxicity. Dysregulation of the Trp–5-HT–KYN axis disrupts neurotransmission, neuroprotection, and circadian control, ultimately contributing to depression, memory problems, and neurodegeneration.

4. Plant-Derived Compounds as Modulators of Tryptophan (Trp) Metabolism

Plant-derived compounds offer a versatile toolkit for modulating Trp metabolism at multiple biological levels, from enzyme activity to gut–brain signaling [32,134,214]. This section introduces how phytochemicals can rebalance flux between 5-HT and KYN pathways, thereby influencing mood, sleep, cognition, and neuroinflammation [32,134,215]. We integrate mechanistic insights with clinical observations, highlighting candidates such as 5-HTP, isoflavones, berberine, polyphenols, and Trp-rich dietary proteins [32,215,216]. Particular attention is given to bioavailability, pharmacokinetics, and microbiome interactions that shape therapeutic response [32,134,217]. By linking molecular targets to patient outcomes, this section frames an evidence-informed path toward translational strategies and sets the stage for a critical appraisal of clinical trials in the subsections that follow.

4.1. Clinical Evidence for Plant-Derived Modulators of Tryptophan (Trp) Metabolism

Clinical trials investigating phytochemicals that target Trp metabolism are driven by the hypothesis that plant-derived compounds can rebalance 5-HT and KYN pathways, thereby improving emotional regulation and sleep [32,138,215]. Among the most promising lines of inquiry, randomized controlled studies of L-Trp supplementation have recruited healthy adults and individuals with subclinical mood disturbances, reporting measurable effects on mood, anxiety, and affective stability [32,218,219]. Other interventions, such as Trp and magnesium-enriched Mediterranean diets tested in women with fibromyalgia, have explored the combined impact on sleep quality and anxiety, though results remain mixed due to small cohorts and gender-restricted samples [220–222]. Broader inclusion criteria have encompassed patients with MDD or fibromyalgia, while preclinical successes with compounds like albiflorin highlight the translational potential awaiting human validation [222–224]. Standard outcome measures include psychiatric rating scales, sleep quality indices, and neurochemical assays, allowing assessment of both symptomatic relief and mechanistic engagement [223,225,226]. The following table highlights the most relevant papers, summarizing their focus, inclusion criteria, outcomes, and patient populations, as well as identifying key research gaps in clinical trials of phytochemicals targeting Trp metabolism for neuropsychiatric outcomes.

Table 1. Summary of randomized controlled and clinical trials investigating dietary tryptophan (Trp), acute tryptophan depletion (ATD), and Trp-rich phytocompounds in depression and related disorders. The table outlines study design, patient populations, interventions, primary outcomes, and key observations.

Recovered / Remitted Depression				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
RCT, DB, 23 recovered depressed vs. 20 healthy controls (NL)	α-lactalbumin vs. casein	↑ TRP/LNAA, improved memory; no mood effect	Enhanced cognition, no mood change	[227]
RCT, DB, 29 stress-vulnerable vs. 29 stress-invulnerable adults (NL)	α-lactalbumin vs. casein	Slight mood improvement (POMS) in stress vulnerable	Small antidepressant-like effect under stress	[228]

 doi:10.20944/preprints202509.2303.v1

RCT, DB, 43 MDD in remission (UK)	[229]. TRP+	No mood change overall; ↑ thalamic/caudate activation in MDD	ATD altered neural responses to distractors	[230]
Clinically Depressed Patients				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
RCT, DB, 30 MDD (MY)	Talbinah (TRP-rich barley) vs. control	↓ depression & anxiety (DASS, POMS)	Multidomain improvement	[231]
RCT, DB, 70 MDD (IN)	5-HTP vs. fluoxetine (8 wks)	Both ↓ HDRS (by wk 2)	Comparable efficacy	[232]
RCT, DB, 25 Parkinson's disease (IT)	5-HTP (50 mg) vs. placebo (12 wks)	↓ depression (BDI-II, HDRS) ; no effect on apathy	5-HTP improved depressive symptoms but not apathy in PD	[233]
High-Risk / Vulnerable Groups				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
RCT, DB, 29 high vs. low stress vulnerability (NL)	α-lactalbumin (TRP-rich) vs. casein	TRP improved mood (POMS), ↓ cortisol in all; mood benefit only in vulnerable	Enhanced stress resilience in high-vulnerability group	[228]
RCT, DB, 38 high vs. low cognitive reactivity (NL)	TRP-rich hydrolysate vs. casein	TRP improved positive mood, ↓ cortisol after stress	Both groups benefited physiologically, mood benefit more pronounced in vulnerable	[234]
RCT, DB, 25 high-risk (family history) vs. low-risk (US)	ATD vs. control	High-risk: ↑ sad mood, slower RT to sad words after ATD	ATD amplified vulnerability markers; no effect in low-risk	[235]
Bulimia				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
RCT, DB, 64 26 ♂ bulimia ± 13 ♂ bulimia on SSRIs vs. healthy controls (CA)	ATD vs. control (balanced amino acids)	ATD ↓ mood in all; ↑ urge to binge eat in bulimia + SSRIs	Serotonin depletion linked to bulimic relapse, especially with SSRI use	[236]
Healthy Volunteers				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
RCT, DB, 38 healthy adults (UK)	TRP (1g, 3x/day, 14d) vs. placebo	TRP increased recognition of happy faces, reduced negative bias (females)	Positive emotional bias, effect stronger in women	[237]
RCT, DB, 20 healthy adults (CA/NL)	TRP (3g/day, 3wks) vs. placebo (crossover)	↑ plasma/urine kynurenine & indoles; no mood/GI changes	TRP activated immunomodulatory metabolic pathways	[238]
RCT, DB, 47 healthy adults (Netherlands)	TRP (2.8g/day, 6d) vs. placebo	No main effect on social fairness, but ↑ rejection of unfair offers	Prolonged TRP may affect social decision-making	[239]
RCT, DB, 18 healthy adults (NL)	TRP-rich hydrolyzed protein vs. ALAC, placebo, pure TRP, synthetic peptide	HPROT and pure TRP improved mood; HPROT fastest ↑ in plasma TRP/LNAA	Hydrolyzed TRP protein most effective for mood and serotonin	[240]
Elderly				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
RCT, SB, 35 elderly (ES)	TRP-enriched cereals vs. control	↑ sleep quality, ↓ anxiety & depression	Improved sleep efficiency, reduced fragmentation	[241]

 doi:10.20944/preprints202509.2303.v1

RCT, DB, 25 elderly with mild cognitive impairment (IT)	DHA-phospholipids + melatonin + TRP vs. placebo, 12 weeks	↑ cognitive function, ↑ nutrition, ↑ olfactory sensitivity	MMSE improved, positive trend for verbal fluency	[242]
RCT, DB, 14 elderly (NL)	TRP, nicotinic acid, nicotinamide vs. control, 32 days	No effect on mitochondrial or muscle function	↑ NAD+ metabolism, no functional benefit	[243]
RCT, SB, 40 elderly with depression/sleep disorders (PL)	TRP-rich diet (25 mg/kg/d) vs. usual diet, 12 weeks	↓ depression & insomnia scores, improved TRP metabolism	ISI and HAM-D scores halved post-intervention	[244]
Fibromyalgia				
Study Design & Population	Intervention / Control	Main Outcomes	Key Notes	Ref.
RCT, DB, 22 ♂ fibromyalgia (ES)	Mediterranean diet enriched with high-dose TRP (60 mg) and Mg (60 mg) vs. standard Mediterranean diet	↓ anxiety, ↓ mood disturbance, ↓ eating disorder symptoms, ↓ body image dissatisfaction; no improvement in sleep quality	Significant improvements in psychological variables; intervention was safe	[207][220]
Large-Scale Observational				
Study Design & Population	**Intervention / Control**	**Main Outcomes**	**Key Notes**	**Ref.**
Clinical trial, 29,687 adults (US) (NHANES 2001–2012)	Mean TRP intake: 826 mg/d (observational, no intervention)	Higher TRP intake associated with ↓ depression severity (PHQ-9), ↑ sleep duration	No adverse effects on liver, kidney, or metabolism; intake well above requirement	[229,245]

5-HTP, 5-Hydroxytryptophan; ↑, Increase; ↓, Decrease; ±, With or Without; ATD, Acute Tryptophan Depletion; BDI-II, Beck Depression Inventory-II; BMI, Body Mass Index; CA, Canada; CH, Switzerland; DASS, Depression Anxiety Stress Scales; DB, Double-Blind; DE, Germany; ES, Spain; HDRS, Hamilton Depression Rating Scale; IN, India; IT, Italy; LNAA, Large Neutral Amino Acids; MAOA, Monoamine Oxidase A; MAOB, Monoamine Oxidase B; Mg, Magnesium; MDD, Major Depressive Disorder; MY, Malaysia; NL, Netherlands; POMS, Profile of Mood States; RCT, Randomized Controlled Trial; RT, Reaction Time; SB, Single-Blind; SSRIs, Selective Serotonin Reuptake Inhibitors;.

TRP, Tryptophan; UK, United Kingdom; US, United States.

Randomized controlled trials investigating phytochemicals with modulatory effects on Trp metabolism have yielded encouraging, though heterogeneous, findings across domains of mood, anxiety, sleep, and cognition. Rosemary extract demonstrated significant reductions in anxiety and depressive symptoms in university students, alongside measurable improvements in sleep quality and memory, suggesting a combined effect on mood regulation and cognitive processing [246–248]. Lavender oil (Silexan) consistently reduced generalized anxiety and restlessness while simultaneously enhancing sleep continuity, with benefits comparable to first-line anxiolytics but without sedative liabilities [249–251]. Trials with lemon balm further highlighted synergistic effects, showing improved psychological well-being, stress resilience, and sleep indices in adults with moderate emotional distress [249,252,253]. Beyond these botanicals, isoflavones and polyphenolic compounds have repeatedly been associated with improved affective stability and enhanced cognitive performance, likely mediated by their antioxidative and serotonergic interactions [254–256]. L-Trp supplementation and dietary enrichment strategies produced measurable anxiolytic and mood-stabilizing effects, particularly in fibromyalgia populations, although outcomes on sleep were inconsistent [255–257]. Berberine, while less frequently studied in formal RCTs, emerges from systematic analyses as a promising candidate due to its dual action on serotonergic pathways and neuroinflammation [16,256,258]. Collectively, these trials suggest that phytochemicals exert multi-dimensional benefits, though replication in larger, mechanistically informed studies remains essential.

 doi:10.20944/preprints202509.2303.v1

Clinical investigations of phytochemicals influencing Trp metabolism face several persistent limitations that restrict their translational power [259,260]. Variability in dosage and duration across trials complicates direct comparisons and limits the ability to establish optimal therapeutic regimens [259,261]. Intervention periods are often short, failing to capture long-term efficacy or safety profiles, particularly for compounds intended for chronic use in mood and anxiety disorders [259,261]. Patient populations are frequently homogeneous, with many studies confined to healthy adults or narrowly defined subgroups, reducing generalizability to clinically diverse cohorts [260,261]. Outcome measures further compound these issues, as trials employ a wide array of scales for mood, anxiety, and sleep, hindering reproducibility and meta-analytic synthesis [260,261]. Future research must prioritize methodological rigor by standardizing dosing protocols, harmonizing validated psychiatric and sleep measures, and extending trial durations [215,262]. Incorporating mechanistic endpoints through metabolomics, microbiome analysis, and neuroimaging would strengthen causal inference and bridge the translational gap [262,263].

4.2. Specific Tryptophan (Trp)-Rich Phytocompounds and Associated Clinical Outcomes

Griffonia simplicifolia seeds, a natural source of 5-HTP, have attracted considerable attention for their potential therapeutic effects on mood and anxiety disorders [264,265]. Clinical investigations, though often small in scale, consistently highlight improvements in depressive symptomatology, reductions in anxiety, and enhanced sleep quality following 5-HTP supplementation [265,266]. These outcomes are biologically plausible given that 5-HTP functions as the immediate precursor to 5-HT, bypassing the tightly regulated hydroxylation of Trp and directly fueling central serotonergic pathways [266,267]. Several narrative reviews underscore its promise in alleviating depression and insomnia, while preliminary trials report measurable gains in affective stability and reduced sleep latency [265,266]. Importantly, these findings align with mechanistic insights showing that oral 5-HTP elevates central 5-HT availability, thereby modulating emotional processing, stress resilience, and circadian regulation [266,268]. Although current evidence remains constrained by methodological limitations and the absence of large randomized controlled trials, the accumulating data suggest a clinically relevant role worth further exploration [242,269].

Soy isoflavones, particularly compounds such as genistein and S-equol, have emerged as promising candidates for mood regulation through their intertwined effects on neuroinflammation and Trp metabolism [270,271]. Clinical and preclinical findings suggest that these phytochemicals suppress pro-inflammatory signaling cascades, including TLR4/NF-κB activation, while simultaneously shifting Trp utilization away from the KYN pathway and toward 5-HT synthesis [254,271]. This dual action is highly relevant for psychiatric disorders, as chronic inflammation and altered Trp metabolism often converge to lower 5-HT availability and exacerbate depressive and anxiety symptoms [130,272]. Trials in animal models demonstrate that soy isoflavones normalize 5-HT levels, reduce KYN accumulation, and enhance synaptic plasticity, culminating in reduced depressive-like and anxiety-related behaviors [254,271]. Although direct human clinical trials remain scarce, pilot studies in related contexts indicate improvements in affective stability, sleep quality, and cognitive performance [273,274]. Together, these findings position soy isoflavones as a biologically grounded strategy with significant translational potential awaiting rigorous clinical validation.

Berberine and albiflorin have recently emerged as two of the most compelling phytochemicals targeting the gut–brain axis, with converging evidence pointing toward their ability to influence mood and cognition through microbiota-driven mechanisms [275,276]. Preclinical and early translational studies show that berberine exerts profound regulatory effects on gut microbial composition, enhancing the production of short-chain fatty acids and restoring gut barrier integrity, while simultaneously reducing peripheral and central inflammatory markers [275,277]. These changes translate into improved hippocampal 5-HT, dopamine, and BDNF signaling, resulting in alleviation of depressive-like behaviors and measurable gains in memory and learning in animal models of both depression and Alzheimer's disease [278,279]. Albiflorin, a bioactive monoterpene glycoside, demonstrates a complementary mode of action: gut microbes metabolize it into benzoic

 doi:10.20944/preprints202509.2303.v1

acid, which penetrates the blood–brain barrier and inhibits D-amino acid oxidase, ultimately fostering neurogenesis and reducing depressive symptoms [280,281]. Although direct human clinical trials remain sparse, small-scale investigations and mechanistic reviews highlight reductions in depression severity, relief from anxiety, and preliminary cognitive benefits consistent with these gut-brain interactions [282,283]. Together, the data suggest that berberine and albiflorin represent promising candidates for modulating Trp metabolism, suppressing neuroinflammation, and enhancing cognitive resilience, warranting rigorous clinical validation to confirm their therapeutic potential [284,285].

Polyphenols and flavonoids have gained significant attention as multi-targeted modulators of brain health, with a growing body of evidence supporting their roles in mood stabilization, neuroprotection, and anti-inflammatory activity [286–288]. Clinical studies involving polyphenol-rich extracts demonstrate improvements in depressive and anxiety symptoms, often accompanied by reductions in circulating inflammatory cytokines such as TNF-α and IL-6, and improved systemic redox balance [257,289,290]. Flavonoids like naringenin and quercetin show particular promise, as they not only suppress pro-inflammatory pathways including NF-κB and MAPK but also promote hippocampal neurogenesis and synaptic plasticity, thereby enhancing resilience against stress-related pathology [256,288,291]. A notable mechanistic insight involves their potential modulation of the KYN pathway: by restraining the diversion of Trp toward neurotoxic KYN metabolites, polyphenols may preserve 5-HT synthesis while fostering neuroprotective KYNA balance [256,292,293]. Preclinical studies reinforce these effects, highlighting synergistic actions between flavonoids and gut microbiota in maintaining metabolic and neurotransmitter homeostasis [292–294]. While large-scale psychiatric trials remain limited, smaller investigations and indirect clinical evidence suggest tangible benefits in mood stabilization, cognitive function, and anxiety reduction [256,293,295]. Collectively, these findings underscore the translational potential of polyphenols and flavonoids as pleiotropic agents targeting both immune and neurotransmitter pathways, yet demand well-designed trials to establish their clinical efficacy in psychiatric populations.

4.3. Concise Summaries: Key Outcomes from Clinical Trials

Concise visual summaries are provided in the form of tables and figures to synthesize key clinical trial outcomes on plant-derived Trp and related compounds. The rationale for these summaries is to facilitate rapid reference, enabling readers to compare study designs, interventions, and clinical endpoints in a clear and accessible format. Highlighted outcomes include mood improvement, modulation of stress responses, effects on cognitive reactivity, and sleep regulation, with interventions ranging from Trp-rich diets and hydrolyzed proteins to 5-HTP supplementation. Particularly promising applications, such as Talbinah-based interventions and L-5-HTP trials in depression, are emphasized for their translational relevance. These concise summaries provide a structured overview of therapeutic efficacy, tolerability, and mechanistic insights, supporting clinicians and researchers in evaluating the strengths and limitations of current evidence.

To distill complex findings into an accessible format, a summary table is presented highlighting the clinical efficacy of Trp-rich phytocompounds across diverse patient populations. This concise overview allows rapid comparison of trial designs, dosages, and key outcomes, providing clarity on the most promising applications. Studies included range from L-5-HTP supplementation in MDD to dietary interventions such as Talbinah or Trp-enriched cereals. Notably, consistent improvements were observed in mood, anxiety, and sleep regulation, while cognitive benefits appeared in select populations. By consolidating these findings, the table underscores both therapeutic potential and the need for further standardized, long-term clinical validation (Table 2).

 doi:10.20944/preprints202509.2303.v1

Table 2. Clinical efficacy of tryptophan (Trp)-rich phytocompounds in depression and related disorders.

Phytocompound	Dosage	Population	Duration	Primary Outcomes	Phytocompound
L-5-HTP	50 mg/day	Depression (n=70)	8 weeks	Comparable efficacy to fluoxetine; mood improvement	L-5-HTP
Talbinah (barley + milk + honey)	25 g/day	Depression (n=36)	7 weeks	Reduced depressive and anxiety scores	Talbinah (barley + milk + honey)
Trp-enriched cereals	60 mg/day	Elderly (n=35)	3 weeks	Improved sleep efficiency, reduced anxiety	Trp-enriched cereals
Alpha-lactalbumin	Trp-rich pro-tein diet	Recovered de-pressed (n=43)	4 weeks	Enhanced memory, modest mood effects	Alpha-lactalbumin
Egg protein hydroly-sate	Trp-rich sup-plement	High-stress vulnera-ble (n=35)	2 weeks	Reduced stress-related mood decline	Egg protein hydroly-sate

L-5-HTP, L-5-hydroxytryptophan: Trp, tryptophan.

A visual figure is provided to illustrate the mechanisms by which key phytochemicals such as 5-HTP, isoflavones, berberine, and polyphenols influence depression biology (Figure 7). The diagram highlights their capacity to enhance 5-HT synthesis, regulate KYN metabolism, reduce neuroinflammation, and promote neurogenesis. Arrows connect peripheral processes like gut microbial modulation and immune signaling with central effects in the brain, emphasizing the bidirectional nature of the gut–brain axis. By mapping these pathways together, the figure clarifies how dietary and phytotherapeutic interventions can complement pharmacological strategies. This visual summary strengthens understanding of mechanistic complexity while guiding translational applications in depression management.

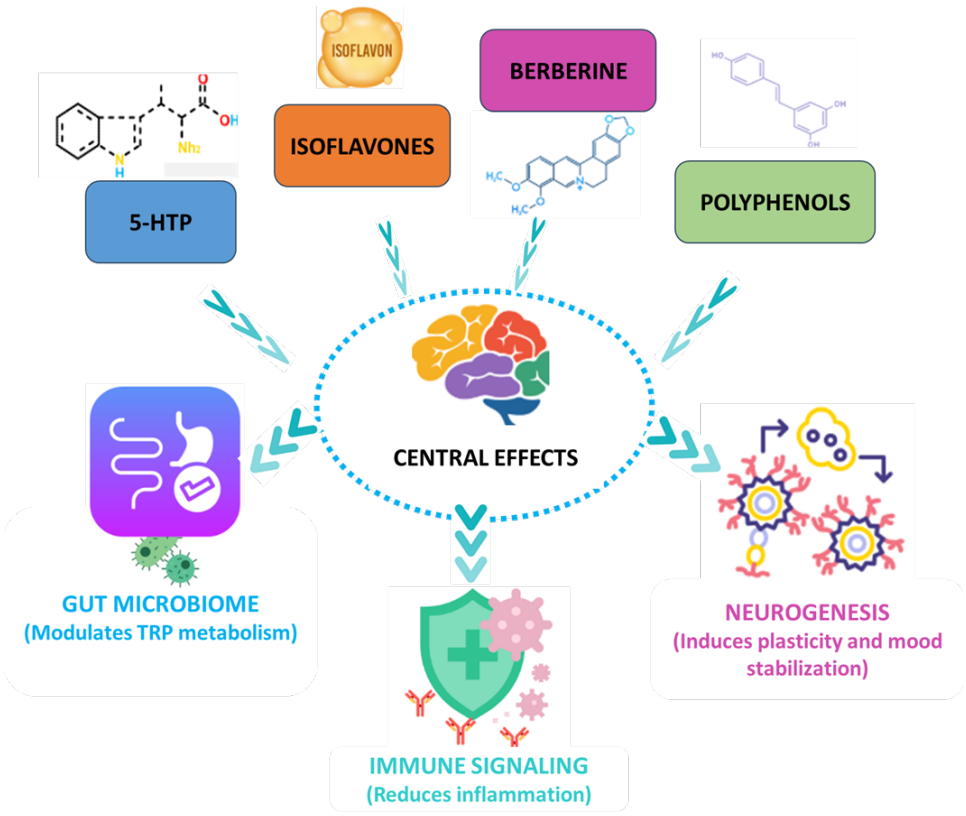

Figure 7. Mechanistic actions of phytochemicals in depression. Phytochemicals including 5-hydroxytryptophan (5-HTP), isoflavones, berberine, and polyphenols exert central effects through modulation of the gut microbiome (via tryptophan metabolism), regulation of immune signaling (attenuation of inflammation), and stimulation of

 doi:10.20944/preprints202509.2303.v1

neurogenesis (enhancement of plasticity and mood stabilization), collectively contributing to antidepressant outcomes. Created with Canva.com. Created with *Canva*.com.

5. Gaps and Controversies in Current Research

Despite growing enthusiasm for plant-derived Trp interventions, substantial uncertainties continue to challenge their clinical translation [296,297]. Research to date is marked by heterogeneity in trial design, inconsistency in dosing regimens, and insufficient mechanistic clarity, making it difficult to draw definitive conclusions about efficacy or safety [298,299]. Moreover, debates over bioavailability and the relative value of dietary versus supplemental sources remain unresolved [300,301]. This section critically examines the gaps and controversies that persist in the field, identifying key obstacles that must be addressed to advance evidence-based applications in psychiatry [297,300].

5.1. Identified Gaps in Current Research

Limited availability of long-term clinical trials on plant-derived Trp compounds represents a critical bottleneck in advancing depression therapeutics [302–304]. Most clinical investigations are confined to short durations, often between four and twelve weeks, providing valuable insights into initial symptom reduction but leaving long-term efficacy and safety largely unexplored [33,304,305]. For example, a randomized trial combining chamomile and saffron reported significant improvements in mood and inflammatory markers after just one month yet provided no information on whether these effects persist over extended treatment [33,304]. Historical work, such as Herrington's comparative trial of L-Trp and electroconvulsive therapy, included a six-month follow-up but involved a limited sample, offering only fragmentary evidence regarding durability of response [303]. This pattern highlights a broader issue: without longitudinal monitoring, it is impossible to determine whether early benefits represent genuine disease modification or transient relief [302,304,305]. Moreover, potential long-term risks, including serotonergic overstimulation, metabolic alterations, or shifts in gut–brain interactions, remain insufficiently characterized [13,304,306]. The absence of such data also obscures whether chronic administration leads to tolerance or adaptive physiological changes that diminish therapeutic value [303,304,306]. To truly assess the role of plant-derived Trp compounds in chronic depression management, carefully designed, multi-year randomized controlled trials with repeated follow-up assessments are urgently required.

Inconsistency in dosing regimens, variability in formulation purity, and absence of standardized protocols represent major obstacles to interpreting the therapeutic potential of phytochemical interventions for depression. Across clinical and preclinical studies, dosing practices vary widely, ranging from fixed low-dose supplementation to high-dose concentrated extracts, often administered at different frequencies . This lack of uniformity makes it nearly impossible to establish reliable dose–response relationships or determine optimal therapeutic windows. For example, the evaluation of Nayopayam Kwatha demonstrated striking inconsistencies, as the formulation was prepared in multiple ratios such as 3:2:1, 10:1:1, and 1:1:1, reflecting divergence between traditional and modern practices and complicating reproducibility. Equally problematic are variations in formulation purity, where batch-to-batch discrepancies in active compounds like berberine were revealed through quantitative analyses, with marketed products frequently failing to meet label claims. Differences in extraction methods, including choice of solvent, temperature, and processing time, further alter yield, bioavailability, and pharmacological activity. Clinical trials using saffron or chamomile extracts, while reporting short-term improvements in depressive symptoms, often employ heterogeneous extraction techniques and undefined purity standards, preventing direct comparison or meta-analytic synthesis. Without harmonized dosing protocols and rigorous phytochemical standardization, conclusions regarding the safety and efficacy of these promising compounds remain provisional, limiting translation into clinical guidelines.

Although the Trp–KYN pathway has been extensively linked to depression and neuroinflammation, mechanistic clarity regarding how plant-derived phytochemicals act upon this

 doi:10.20944/preprints202509.2303.v1

axis is strikingly underdeveloped. Most studies remain descriptive, emphasizing correlations between altered Trp metabolism and psychiatric outcomes, while offering little insight into whether phytochemicals exert direct enzymatic modulation or act indirectly through immune regulation and microbiome interactions. For instance, trials investigating saffron and chamomile supplementation demonstrate short-term clinical benefits, yet fail to examine whether these effects are mediated through IDO inhibition, KYN–5-HT balance, or shifts in neuroinflammatory markers. Similarly, preclinical studies employing Trp-rich diets in stress models suggest gut–brain axis involvement, but lack detailed mapping of metabolite flux or cell-type–specific enzyme regulation. Without such mechanistic endpoints, it remains speculative whether phytochemical interventions primarily restore serotonergic tone, rebalance KYN derivatives, or attenuate inflammatory cascades. The paucity of molecular and biochemical investigations severely limits translation into targeted therapies. To overcome this, future research must integrate omics-driven profiling, metabolite quantification, and longitudinal immune assays within both animal and human trials. Only through such rigor can we disentangle direct versus indirect pathways and fully clarify how plant-derived Trp interventions modulate the biochemical underpinnings of chronic depression.

5.2. Controversies Regarding Clinical Efficacy and Bioavailability

The debate surrounding dietary versus supplemental Trp remains unresolved, reflecting both biochemical complexity and methodological gaps in current research [138,307,308]. Isolated supplementation offers clear pharmacological advantages, including predictable dosing, rapid absorption, and more consistent increases in serum Trp and downstream metabolites [307,309,310]. Systematic reviews demonstrate modest but reproducible improvements in mood and sleep quality with supplementation, yet optimal dosing strategies are far from established [307,309,310]. In contrast, whole-food Trp intake introduces a range of variables: competition with other large neutral amino acids for transport across the blood–brain barrier, food matrix effects on absorption, and significant modulation by the gut microbiota [138,307,308]. Animal studies suggest that dietary Trp enhances intestinal barrier function and alters immune signaling pathways, implying potential systemic benefits distinct from supplementation, though mechanistic specificity remains elusive [311–313]. For example, interventions in piglet and rodent models show that dietary Trp influences gut–brain and immune interactions more strongly than supplementation alone, but human trials directly comparing the two approaches are absent [314–316]. The resulting uncertainty complicates translation into clinical practice [198,315,316]. While supplements provide pharmacological precision, dietary sources may confer broader metabolic resilience, albeit with unpredictable bioavailability [315–317]. Head-to-head, long-term trials are urgently required to determine whether whole-food Trp and supplementation exert complementary or divergent therapeutic effects in depression [203,317–319].

Bioavailability remains one of the most contentious issues in evaluating dietary Trp and plant-based supplements, as absorption and metabolic fate are strongly shaped by gut microbiota composition, digestive efficiency, and individual genetic differences. While isolated supplementation produces predictable rises in plasma Trp, dietary sources are subject to competition from other large neutral amino acids and modulation by the food matrix, making outcomes less consistent. Recent trials provide partial insights: a study using Trp-rich protein hydrolysates demonstrated acute improvements in mood and stress resilience in healthy adults, but these effects varied by sex and were not sustained beyond the intervention period. Animal data add another layer of complexity, showing that different formulations such as 60% biomass versus 98% crystalline Trp can yield bioequivalent outcomes in terms of absorption and metabolic effects, though translation to human physiology remains uncertain. Compounding these pharmacokinetic challenges is the unresolved question of whether enhanced bioavailability directly translates into clinically meaningful improvements in depression, since mood regulation involves downstream serotonergic, KYN, and immune pathways. Finally, safety concerns linked to supplement impurities, as highlighted by the eosinophilia–myalgia syndrome outbreak, emphasize the critical need for rigorous pharmacokinetic

 doi:10.20944/preprints202509.2303.v1

and pharmacodynamic studies. Only with such evidence can bioavailability be meaningfully tied to therapeutic outcomes.

6. Clinical Translation: From Bench to Bedside

Research into plant-derived Trp compounds has expanded rapidly, yet critical uncertainties continue to limit their clinical translation [14,32,143]. Evidence from preclinical and early clinical studies highlights promising effects on mood, sleep, and stress resilience, but methodological gaps and unresolved controversies persist [32,244,307]. Questions surrounding long-term efficacy, optimal dosing, and mechanistic pathways remain central obstacles [138,143,309]. Likewise, debates over dietary versus supplemental sources and challenges of bioavailability further complicate interpretation [134,244,307]. This section examines these gaps and controversies, outlining unresolved issues that must be addressed before phytochemical modulation of Trp metabolism can be reliably integrated into psychiatric practice.

6.1. Practical Considerations for Clinical Application

Determining the effective and safe dosage of plant-derived Trp remains a central challenge in translating experimental findings into clinical practice [32,320,321]. Current evidence suggests a relatively wide therapeutic window, yet precise dosing guidelines are lacking, particularly for chronic depression [32,304,320]. Human studies indicate that daily intakes of 1–5 g are generally well tolerated, with a proposed no-observed-adverse-effect level (NOAEL) of 4.5 g per day in young adults [309,321,322]. These findings are consistent with short-term supplementation trials in healthy women, where no safety concerns emerged after three weeks of use [304,310,322]. Animal studies further support this margin, showing no toxic effects at doses as high as 2000 mg/kg/day over 90 days, underscoring a substantial buffer between effective and harmful exposure [32,244,323]. However, dosage requirements appear to vary depending on formulation: free L-Trp, fermented products, and protein-bound dietary forms display distinct bioavailability profiles that may influence clinical outcomes [32,310,323]. Patient-specific factors, such as age, sex, metabolic status, and comorbid conditions, are rarely addressed in current trials, leaving critical gaps in personalized dosing [32,310,323]. Importantly, historical episodes of eosinophilia-myalgia syndrome highlight the need for strict quality control, as impurities rather than Trp itself caused adverse events [244,304,324]. Collectively, available evidence supports cautious short-term use within established limits, while long-term efficacy and safety require rigorous randomized controlled trials across diverse populations.

Plant-derived Trp supplements are widely regarded as safe when used within recommended limits, yet their safety profile warrants careful consideration given both historical precedents and documented adverse reactions [321,325,326]. The most serious concern remains eosinophilia–myalgia syndrome, a rare but debilitating condition that emerged in the late 1980s due to contaminated L-Trp supplements [326–328]. Although later investigations confirmed that impurities rather than the amino acid itself were responsible, this episode underscores the importance of rigorous quality control and sourcing from reliable manufacturers [325–327]. Beyond this, clinical evidence indicates that most individuals tolerate doses up to 5 g per day for short durations without metabolic or systemic disturbances [321,324,329]. Nevertheless, higher intakes or prolonged use have occasionally been associated with nausea, tremor, dizziness, or excessive drowsiness. Interactions with serotonergic medications raise the additional risk of 5-HT syndrome, marked by neuromuscular rigidity, confusion, and fever, highlighting the need for medical oversight in polypharmacy contexts. Related compounds such as 5-hydroxytryptophan show similarly favorable safety profiles, though isolated case reports suggest unresolved concerns that merit continued vigilance [324,329,330]. Practical guidance emphasizes regular monitoring for muscle pain, skin changes, and gastrointestinal symptoms, patient education on side effect recognition, and prompt discontinuation or dose reduction if adverse signs emerge, ensuring therapeutic benefit without undue risk [321,331,332].

 doi:10.20944/preprints202509.2303.v1

Plant-derived Trp supplements raise important considerations regarding potential interactions with commonly prescribed medications, particularly antidepressants and anxiolytics that influence serotonergic signaling [32,134,333]. The most clinically significant risk is 5-HT syndrome, a potentially life-threatening condition that can occur when Trp is combined with selective 5-HT reuptake inhibitors, 5-HT–norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or certain anxiolytics [32,134,333]. Characterized by agitation, hyperreflexia, autonomic instability, and in severe cases hyperthermia or coma, 5-HT syndrome underscores the need for clinicians to carefully review all concurrent serotonergic therapies before recommending Trp [142,334,335]. Beyond this, pharmacological overlap within the 5-HT and KYN pathways suggests that Trp supplementation could interfere with drugs targeting immune function or neuroinflammation, although robust clinical evidence remains sparse [32,134,336]. Pharmacokinetic interactions are less well defined but may involve competition for metabolic enzymes, potentially altering drug clearance and therapeutic effectiveness [142,335,337]. Contraindications include patients with a history of 5-HT syndrome, those taking multiple serotonergic agents, and individuals with unstable psychiatric or metabolic disorders [142,334,335]. Practical recommendations emphasize individualized assessment, use of the lowest effective dose, and structured patient education regarding early symptoms of adverse interactions [335,337,338]. Close monitoring and early discontinuation in the presence of concerning signs are essential to balance potential therapeutic benefits with safety in clinical application.

6.2. Personalized Medicine Approaches

Gut microbiota profiling is rapidly gaining attention as a tool for personalized depression management, with compelling evidence that microbial composition influences both Trp metabolism and therapeutic response to phytochemicals [195,197,339]. Altered microbiota profiles can shift the balance between 5-HT and KYN pathways, thereby modulating neuroinflammation and mood regulation [136,197,340]. Clinical studies now suggest that baseline microbiota signatures may predict antidepressant response: patients enriched in beneficial taxa such as *Faecalibacterium prausnitzii* or *Bifidobacterium* demonstrate greater remission rates, while depleted diversity often correlates with treatment resistance [339,341,342]. Early trials of Trp-rich dietary interventions and probiotics also reveal that therapeutic efficacy may hinge on an individual's microbial ecosystem, with some patients showing robust mood improvement and others little benefit despite identical regimens [339,341,343]. This variability highlights the potential of stool-based profiling to guide personalized strategies, matching patients to dietary, probiotic, or phytotherapeutic interventions most likely to be effective [211,341,344]. Emerging data also point to machine learning approaches that integrate microbial, metabolic, and cytokine biomarkers for predictive modeling of treatment outcomes [344–346]. Yet translation into practice is still nascent: large-scale, longitudinal trials and functional multi-omics studies are essential to confirm which microbial profiles drive therapeutic benefit [116,197,342]. Ultimately, microbiota-informed stratification could transform depression management into a more precise and individualized discipline.

Genetic polymorphisms in key enzymes regulating Trp metabolism, such as IDOs, TDO, and tryptophan hydroxylase (TPH), play a decisive role in shaping vulnerability to depression and responsiveness to therapeutic interventions [195,197,339]. Variants in these genes influence the metabolic fate of Trp, determining whether it is directed toward 5-HT synthesis or shunted into the KYN pathway, with downstream consequences for neuroinflammation and mood regulation [116,136,340]. Clinical data suggest that polymorphisms in TPH2 and 5-HT transporter-linked regions correlate with depression severity and treatment resistance, while IDO and IFN-γ gene variants are associated with enhanced KYN production, amplifying immune-driven depressive symptoms [114,347,348]. Postpartum depression studies also reveal IDO-related polymorphisms as predictors of higher risk, underscoring the clinical relevance of pathway-specific genetic variation [347,349,350]. These insights highlight the potential of genetic profiling to guide individualized treatment, where patients with high-risk alleles might benefit more from interventions targeting the KYN pathway or from plant-derived Trp formulations designed to enhance serotonergic flux [11,114,347]. Although

 doi:10.20944/preprints202509.2303.v1

current evidence remains fragmented, integrating genotyping into personalized medicine frameworks could enable stratification of patients, prediction of treatment outcomes, and rational selection of phytotherapeutic strategies [347,350,351]. Expanding multi-ethnic genetic studies and intervention trials is essential to validate these applications and move toward precision psychiatry [352].

7. Future Perspectives and Research Directions

Clinical translation represents the critical step of transforming mechanistic insights and preclinical discoveries into therapeutic strategies that can be safely and effectively applied in patient care [150,353,354]. For plant-derived tryptophan and related compounds, this bridge from bench to bedside demands careful attention to dosing, safety, interactions, and long-term monitoring [143,355,356]. Equally important is the integration of personalized medicine approaches, where genetic, metabolic, and microbiome profiles guide therapeutic choices [357–359]. By addressing these considerations, clinical application moves beyond experimental promise to evidence-based strategies capable of shaping future psychiatric treatments.

7.1. Advancing Clinical Evidence through Robust Study Designs

Large-scale, multi-center clinical trials represent the critical next step for validating plant-derived tryptophan therapies in depression [11,31,360]. While early-phase studies and small-scale trials suggest therapeutic promise, their limited sample sizes, short durations, and restricted demographic scope constrain clinical interpretation [116,360,361]. Multi-center designs allow for the inclusion of diverse populations across ethnic, geographic, and socioeconomic backgrounds, thereby addressing genetic polymorphisms in enzymes such as IDO, TDO, and TPH that influence Trp metabolism and treatment responsiveness [11,31,361]. Such diversity is essential to move beyond narrow, context-specific findings and toward results with broad clinical applicability. Equally important, multi-center collaborations enhance statistical power, enabling the detection of subtle treatment effects and the evaluation of subgroup responses [362–364]. Coordinated protocols across research networks also promote methodological consistency, ensuring that differences in formulation, dosing, and biomarker assessments do not confound outcomes [365–367]. Promising applications include testing whether specific genotypic or microbiota-defined subgroups derive greater benefit from phytotherapeutic interventions, a question only adequately addressed through large, well-controlled trials [368–370]. Beyond efficacy, safety monitoring on a global scale provides crucial insight into rare adverse events and long-term tolerability [366,367,370]. Ultimately, multi-center trials create the foundation for standardized guidelines, ensuring that plant-derived Trp interventions are evaluated with the rigor required for integration into precision psychiatry [371–375].

Standardization of methodologies and outcome measures is indispensable for advancing plant-derived Trp therapies from promising pilot studies to clinically actionable interventions [376,377]. At present, heterogeneity in dosing protocols, extraction techniques, biomarker panels, and outcome assessments undermines comparability across trials and limits the ability to generate robust meta-analyses [378,379]. For instance, differences in extraction solvents and processing conditions can yield markedly divergent metabolite profiles, complicating interpretation of therapeutic efficacy [246,378,379]. Similarly, clinical studies often apply variable dosing schedules—ranging from milligram-scale supplementation to multi-gram intakes—without harmonized reference points, making it difficult to establish optimal therapeutic windows [380–382]. Biomarker selection presents another challenge: while some studies emphasize 5-HT and KYN metabolites, others focus on inflammatory cytokines or gut microbiota-derived indoles, creating fragmented datasets that resist synthesis [383–385]. Outcome assessment tools are equally inconsistent, with trials variously employing clinician-rated depression scales, patient self-reports, or biochemical endpoints [381,382,385]. A shift toward standardized protocols—including consensus dosing frameworks, validated extraction procedures, and a unified “indolome” biomarker panel—would significantly

 doi:10.20944/preprints202509.2303.v1

enhance reproducibility and clinical interpretability [386–388]. Such consistency is particularly critical for large-scale, multi-center trials, where methodological alignment ensures that findings are both statistically reliable and generalizable [365,386,389]. Ultimately, methodological standardization is not a technical detail but the foundation for transforming plant-derived Trp research into credible, guideline-ready therapies.

Long-term follow-up studies are indispensable for establishing the true clinical value of plant-derived Trp therapies in depression management [11,32,390]. While short-term trials consistently report symptomatic improvements, they cannot determine whether these benefits persist over months or years, nor can they capture delayed adverse effects that may only emerge with prolonged use [303,304,390]. Longitudinal research is therefore essential to assess durability of mood stabilization, sustained neurobiological changes, and overall psychiatric outcomes [11,33,391]. Equally important is the evaluation of patient adherence, as real-world compliance often declines over time and directly influences therapeutic success [33,304,392]. Early evidence from nutritional and probiotic interventions suggests that Trp supplementation can modulate 5-HT and KYN pathways in ways that might yield lasting benefit, yet without systematic long-term monitoring, such effects remain speculative [13,305,393]. Furthermore, the safety profile of chronic use is not fully characterized, particularly in populations with comorbidities or concurrent pharmacotherapies [245,390,391]. Long-term follow-up would also clarify whether plant-derived formulations maintain efficacy or whether tolerance, metabolic adaptation, or microbiota shifts reduce their impact over time [32,390,394]. Only through rigorous, multi-year studies with repeated biochemical, clinical, and functional assessments can the field move from preliminary promise to evidence-based recommendations that ensure both efficacy and safety in chronic depression care.

7.2. Combined Pharmacological and Dietary Intervention Strategies

Integrating dietary interventions with standard pharmacological treatments offers a compelling strategy for enhancing depression management [395–397]. Evidence from randomized controlled trials, such as the SMILES study, demonstrates that improving diet alongside usual care leads to significantly greater reductions in depressive symptoms and higher remission rates compared with control conditions [397–399]. Meta-analyses further support these findings, showing that dietary modifications consistently improve mood outcomes, even when participants are already receiving antidepressants [400–403]. Nutrient-focused approaches, including supplementation with omega-3 fatty acids, vitamin D, and probiotics, have shown additive benefits, with effects on neurotransmitter synthesis, immune regulation, and gut–brain communication that complement pharmacological mechanisms [395,403,404]. Together, these findings highlight the rationale for combined strategies that address both biological and lifestyle determinants of mental health.

The integration of diet with pharmacotherapy also has practical advantages. Nutritional interventions may mitigate side effects commonly associated with antidepressant use, such as weight gain, fatigue, and gastrointestinal disturbances, thereby improving tolerability and adherence [403–405]. Patients often perceive dietary changes as more holistic and less stigmatizing than medication alone, which can enhance engagement and long-term treatment compliance [406–408]. From a mechanistic perspective, dietary modulation of inflammation, oxidative stress, and Trp metabolism provides synergistic support to monoamine-based drug action [396,401,409]. Thus, combining dietary and pharmacological approaches is not merely additive but has the potential to produce synergistic effects, optimizing both symptom relief and overall health outcomes [396,406,410]. This integrated model represents one of the most promising directions for personalized, sustainable depression care.

Future research on combined dietary Trp and antidepressant interventions requires rigorously designed clinical trials that address both short- and long-term outcomes. The most promising model is a randomized, double-blind, placebo-controlled design with multiple parallel arms: antidepressant plus Trp, antidepressant plus placebo, Trp alone, and full placebo [302,392,411]. Such structure allows investigators to disentangle additive and synergistic effects while also clarifying the standalone

 doi:10.20944/preprints202509.2303.v1

impact of dietary supplementation [33,392,411]. Control conditions should be carefully balanced to avoid expectancy bias, and stratification by baseline nutritional status or genetic polymorphisms in Trp metabolism (e.g., IDO, TDO, TPH variants) would enhance precision in interpreting outcomes [33,213,412].

Biomarker monitoring should be a central feature of these trials. Serial assessments of plasma Trp, KYN metabolites, 5-HT levels, inflammatory cytokines, and sleep parameters would help map mechanistic pathways linking supplementation to clinical response [413–415]. Alongside these biological endpoints, standardized psychiatric outcome measures—such as HDRS and BDI scores—should be collected, complemented by cognitive and emotional processing tasks to capture subtle shifts in mood regulation [416–418]. Adherence can be monitored with digital tracking tools and serum metabolite checks [419–421]. Duration of at least 8–12 weeks is needed to capture short-term efficacy, but follow-up at 6 to 12 months will be critical to assess durability, safety, and adherence in real-world contexts [422–424]. These models would not only clarify the therapeutic potential of combined interventions but also provide insight into patient subgroups most likely to benefit. By integrating dietary, pharmacological, and mechanistic perspectives, such studies could generate the evidence base necessary for translating plant-derived Trp strategies into precision-guided clinical practice.

7.3. Leveraging Biotechnological Innovations for Personalized Depression Management

Precision nutrition is redefining how dietary strategies are applied in depression care by emphasizing individualized interventions informed by genetic and metabolic profiling [425–427]. Nutritional genomics has revealed that polymorphisms in genes such as SLC6A4 and BDNF can influence how individuals respond to nutrient-based therapies, including plant-derived Trp [425,428,429]. For example, certain 5-HT transporter variants may determine whether Trp is preferentially metabolized into 5-HT or diverted into the KYN pathway, directly affecting mood outcomes [338,430,431]. Integrating this genetic information into clinical planning could enable targeted dietary prescriptions that align with a patient's unique metabolic capacity, thereby improving the precision and efficacy of treatment.

Beyond genomics, advanced biomarker analyses provide powerful tools to individualize dietary interventions [432–434]. Profiling gut microbiota, serum metabolites, and inflammatory markers allows clinicians to predict and monitor how patients metabolize Trp-rich foods or supplements [435–437]. Emerging evidence shows that personalized diets can reduce depressive symptoms, alter microbial composition, and improve quality of life in both older adults and adolescents [400,406,435]. These findings suggest that combining biomarker-driven monitoring with dietary tailoring may optimize long-term outcomes [433,434,438]. Importantly, precision nutrition also considers comorbidities: in patients with obesity or diabetes, individualized dietary plans have demonstrated benefits not only for metabolic regulation but also for mood stabilization [269,436,438]. Together, these insights support a move away from generic dietary recommendations toward integrative, personalized protocols. When fully developed, such strategies could complement pharmacological treatments and establish plant-based Trp interventions as a cornerstone of personalized psychiatry.

Microbiome-targeted therapeutic approaches are emerging as innovative strategies for addressing depression by modulating gut–brain communication and regulating Trp metabolism [390,439,440]. Probiotics and prebiotics are the most extensively studied, with randomized controlled trials showing that probiotic supplementation can alleviate depressive symptoms, maintain microbial diversity, and enhance serotonergic signaling [393,441,442]. Specific strains, such as *Lactobacillus* and *Bifidobacterium*, have been linked to improved mood outcomes and altered brain activation patterns, suggesting that targeted microbial interventions may complement conventional pharmacotherapy [343,443,444]. Prebiotics, by selectively stimulating beneficial gut bacteria, also influence the production of neuroactive metabolites, offering an indirect yet powerful means of modulating the Trp–KYN pathway [32,439,445].

 doi:10.20944/preprints202509.2303.v1

Fecal microbiota transplantation (FMT) represents a more radical but promising intervention [207,446,447]. Preclinical studies in rodent models demonstrate that transplantation from healthy donors reduces depressive behaviors, restores neurotransmitter balance, and dampens neuroinflammatory processes [448–450]. Early clinical findings echo these benefits, although long-term safety and efficacy remain insufficiently studied [451–453]. Beyond these approaches, engineered microbial therapies are on the horizon, with genetically modified strains designed to produce specific neuroactive compounds or regulate metabolic flux through Trp-related pathways [197,203,339]. When combined with multi-omics profiling, these advanced strategies could allow for precision-guided microbial interventions tailored to an individual's baseline microbiome and metabolic profile [197,207,339]. Collectively, probiotics, prebiotics, FMT, and engineered microbes hold strong potential to enhance therapeutic outcomes, particularly when integrated into holistic models of depression care that also consider diet, pharmacology, and genetics.

8. Conclusions

This review underscores the growing recognition of plant-derived Trp as a mechanistic bridge between neurobiology and psychiatry, offering innovative strategies to address the unmet needs in depression management. By weaving together evidence from neuroinflammation, KYN metabolism, gut–brain interactions, and phytochemical modulation, the authors provide a comprehensive framework that highlights both theoretical insights and translational promise. Importantly, the findings stress that phytocompounds can recalibrate serotonergic balance, temper neurotoxic cascades, and enhance resilience through multimodal pathways, supporting their integration alongside conventional antidepressants. At the same time, methodological limitations—heterogeneous dosing protocols, brief intervention periods, and insufficient long-term safety data—demand carefully designed clinical trials. Future research should prioritize precision nutrition strategies, biomarker-guided interventions, and longitudinal monitoring to fully elucidate the sustained impact of these therapies. Advancing this field will require interdisciplinary collaboration spanning psychiatry, neuroscience, nutrition, and pharmacology. Collectively, the evidence positions plant-derived Trp therapies as promising candidates to enrich depression care and move the field toward safer, more effective, and biologically informed treatment paradigms.

Author Contributions: Conceptualization, S.M.B., A.C., M.T. and L.F.L.; methodology, C.R.P.D.; investigation, A.C.C., E.P.L., V.E.V., C.R.P.D. and V..M.C.S..C.,. and L.F.L.; writing—original draft preparation, S.M.B., L.F.L, R.S.A.H.., and M.T.; writing—review and editing, S.M.B., L.F.L.., V.E.V., C.M.G., E.d.S.B.M.P. and R.S.A.H.; visualization, S.M.B., M.T. and C.M.G.; supervision, S.M.B. and M.T.; project administration, S.M.B.; funding acquisition, S.M.B. and M.T. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the HUN-REN Hungarian Research Network to M.T.

Acknowledgments: Images were built with biorender.com, Free.Pick.com, Canva Free, and pixabay.com. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

3-HK	3-hydroxykynurenine
5-HT	serotonin
5-HTP	5-hydroxytryptophan
AhR	aryl hydrocarbon receptor
ASMT	acetylserotonin O-methyltransferase
ATD	acute tryptophan depletion
BDNF	brain-derived neurotrophic factor
DOAJ	directory of open access journals

 doi:10.20944/preprints202509.2303.v1

HPA hypothalamic–pituitary–adrenal
IAld indole-3-aldehyde
IAA indole-3-acetic acid
IPA indole-3-propionic acid
IDO indoleamine 2,3-dioxygenase
IFN-γ interferon-gamma
IL interleukin
IS indoxyl sulfate
KYN kynurenine
KYNAkynurenic acid
LAT1 large neutral amino acid transporter 1
LD linear dichroism
LNAA large neutral amino acid
MDD major depressive disorder
QA quinolinic acid
RCT randomized controlled trial
ROS reactive oxygen species
SCN suprachiasmatic nucleus
SNAT serotonin N-acetyltransferase
SSRI selective serotonin reuptake inhibitor
TDO tryptophan 2,3-dioxygenase
TLA three letter acronym
TNF-αtumor necrosis factor-alpha
Trp tryptophan
TPH tryptophan hydroxylase
TPH1 tryptophan hydroxylase 1
TPH2 tryptophan hydroxylase 2

References

1. Filatova, E.V.; Shadrina, M.I.; Slominsky, P.A. Major Depression: One Brain, One Disease, One Set of Intertwined Processes. *Cells* **2021**, *10*. https://doi.org/10.3390/cells10061283.
2. Fries, G.R.; Saldana, V.A.; Finnstein, J.; Rein, T. Molecular pathways of major depressive disorder converge on the synapse. *Mol. Psychiatry* **2023**, *28*, 284–297. https://doi.org/10.1038/s41380-022-01806-1.
3. Cui, L.; Li, S.; Wang, S.; Wu, X.; Liu, Y.; Yu, W.; Wang, Y.; Tang, Y.; Xia, M.; Li, B. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduct. Target. Ther.* **2024**, *9*, 30. https://doi.org/10.1038/s41392-024-01738-y.
4. Proudman, D.; Greenberg, P.; Nellesen, D. The Growing Burden of Major Depressive Disorders (MDD): Implications for Researchers and Policy Makers. *Pharmacoeconomics* **2021**, *39*, 619–625. https://doi.org/10.1007/s40273-021-01040-7.
5. Greenberg, P.E.; Fournier, A.A.; Sisitsky, T.; Simes, M.; Berman, R.; Koenigsberg, S.H.; Kessler, R.C. The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018). *Pharmacoeconomics* **2021**, *39*, 653–665. https://doi.org/10.1007/s40273-021-01019-4.
6. Li, Z.; Ruan, M.; Chen, J.; Fang, Y. Major Depressive Disorder: Advances in Neuroscience Research and Translational Applications. *Neurosci. Bull.* **2021**, *37*, 863–880. https://doi.org/10.1007/s12264-021-00638-3.
7. Pu, J.; Liu, Y.; Zhang, H.; Tian, L.; Gui, S.; Yu, Y.; Chen, X.; Chen, Y.; Yang, L.; Ran, Y.; et al. An integrated meta-analysis of peripheral blood metabolites and biological functions in major depressive disorder. *Mol. Psychiatry* **2021**, *26*, 4265–4276. https://doi.org/10.1038/s41380-020-0645-4.
8. Kouba, B.R.; de Araujo Borba, L.; Borges de Souza, P.; Gil-Mohapel, J.; Rodrigues, A.L.S. Role of Inflammatory Mechanisms in Major Depressive Disorder: From Etiology to Potential Pharmacological Targets. *Cells* **2024**, *13*. https://doi.org/10.3390/cells13050423.
9. Athira, K.V.; Bandopadhyay, S.; Samudrala, P.K.; Naidu, V.G.M.; Lahkar, M.; Chakravarty, S. An Overview of the Heterogeneity of Major Depressive Disorder: Current Knowledge and Future Prospective. *Curr. Neuropharmacol.* **2020**, *18*, 168–187. https://doi.org/10.2174/1570159x17666191001142934.

10. Ilavská, L.; Morvová, M., Jr.; Paduchová, Z.; Muchová, J.; Garaiova, I.; Ďuračková, Z.; Šikurová, L.; Trebatická, J. The kynurenine and serotonin pathway, neopterin and biopterin in depressed children and adolescents: an impact of omega-3 fatty acids, and association with markers related to depressive disorder. A randomized, blinded, prospective study. *Front. Psychiatry* **2024**, *15*, 1347178. https://doi.org/10.3389/fpsyt.2024.1347178.
11. Correia, A.S.; Vale, N. Tryptophan Metabolism in Depression: A Narrative Review with a Focus on Serotonin and Kynurenine Pathways. *Int. J. Mol. Sci.* **2022**, *23*. https://doi.org/10.3390/ijms23158493.
12. Fang, X.; Wu, Y.; Dai, Y.; Xiao, H.; Li, S.; Chen, X.; Yuan, M.; Guo, Y.; Ma, L.; Lin, D.; et al. In Situ Recovery of Serotonin Synthesis by a Tryptophan Hydroxylase-Like Nanozyme for the Treatment of Depression. *J. Am. Chem. Soc.* **2025**, *147*, 9111–9121. https://doi.org/10.1021/jacs.4c10733.
13. Wang, D.; Wu, J.; Zhu, P.; Xie, H.; Lu, L.; Bai, W.; Pan, W.; Shi, R.; Ye, J.; Xia, B.; et al. Tryptophan-rich diet ameliorates chronic unpredictable mild stress induced depression- and anxiety-like behavior in mice: The potential involvement of gut-brain axis. *Food Res. Int.* **2022**, *157*, 111289. https://doi.org/10.1016/j.foodres.2022.111289.
14. Huang, Y.; Zhao, M.; Chen, X.; Zhang, R.; Le, A.; Hong, M.; Zhang, Y.; Jia, L.; Zang, W.; Jiang, C.; et al. Tryptophan Metabolism in Central Nervous System Diseases: Pathophysiology and Potential Therapeutic Strategies. *Aging Dis.* **2023**, *14*, 858–878. https://doi.org/10.14336/ad.2022.0916.
15. Zhang, Z.W.; Gao, C.S.; Zhang, H.; Yang, J.; Wang, Y.P.; Pan, L.B.; Yu, H.; He, C.Y.; Luo, H.B.; Zhao, Z.X.; et al. Morinda officinalis oligosaccharides increase serotonin in the brain and ameliorate depression via promoting 5-hydroxytryptophan production in the gut microbiota. *Acta Pharm. Sin. B* **2022**, *12*, 3298–3312. https://doi.org/10.1016/j.apsb.2022.02.032.
16. Figueiredo Godoy, A.C.; Frota, F.F.; Araújo, L.P.; Valenti, V.E.; Pereira, E.; Detregiachi, C.R.P.; Galhardi, C.M.; Caracio, F.C.; Haber, R.S.A.; Fornari Laurindo, L.; et al. Neuroinflammation and Natural Antidepressants: Balancing Fire with Flora. *Biomedicines* **2025**, *13*. https://doi.org/10.3390/biomedicines13051129.
17. Cowen, P.J. SSRIs in the Treatment of Depression: A Pharmacological CUL-DE-SAC? *Curr. Top. Behav. Neurosci.* **2024**, *66*, 1–19. https://doi.org/10.1007/7854_2023_447.
18. Gabriel, F.C.; de Melo, D.O.; Fráguas, R.; Leite-Santos, N.C.; Mantovani da Silva, R.A.; Ribeiro, E. Pharmacological treatment of depression: A systematic review comparing clinical practice guideline recommendations. *PLoS One* **2020**, *15*, e0231700. https://doi.org/10.1371/journal.pone.0231700.
19. Stachowicz, K.; Sowa-Kućma, M. The treatment of depression - searching for new ideas. *Front. Pharmacol.* **2022**, *13*, 988648. https://doi.org/10.3389/fphar.2022.988648.
20. Dudek, D.; Chrobak, A.A.; Krupa, A.J.; Gorostowicz, A.; Gerlich, A.; Juryk, A.; Siwek, M. TED-trazodone effectiveness in depression: a naturalistic study of the effeciveness of trazodone in extended release formulation compared to SSRIs in patients with a major depressive disorder. *Front. Pharmacol.* **2023**, *14*, 1296639. https://doi.org/10.3389/fphar.2023.1296639.
21. Srifuengfung, M.; Pennington, B.R.T.; Lenze, E.J. Optimizing treatment for older adults with depression. *Ther. Adv. Psychopharmacol.* **2023**, *13*, 20451253231212327. https://doi.org/10.1177/20451253231212327.
22. Zhao, Y.; Xu, D.; Wang, J.; Zhou, D.; Liu, A.; Sun, Y.; Yuan, Y.; Li, J.; Guo, W. The pharmacological mechanism of chaihu-jia-longgu-muli-tang for treating depression: integrated meta-analysis and network pharmacology analysis. *Front. Pharmacol.* **2023**, *14*, 1257617. https://doi.org/10.3389/fphar.2023.1257617.
23. Zhao, X.; Zhang, H.; Wu, Y.; Yu, C. The efficacy and safety of St. John's wort extract in depression therapy compared to SSRIs in adults: A meta-analysis of randomized clinical trials. *Adv. Clin. Exp. Med.* **2023**, *32*, 151–161. https://doi.org/10.17219/acem/152942.
24. Zhang, Z.; Cai, X.; Liang, Y.; Zhang, R.; Liu, X.; Lu, L.; Huang, Y. Electroacupuncture as a rapid-onset and safer complementary therapy for depression: A systematic review and meta-analysis. *Front. Psychiatry* **2022**, *13*, 1012606. https://doi.org/10.3389/fpsyt.2022.1012606.
25. Shafiee, A.; Jafarabady, K.; Seighali, N.; Mohammadi, I.; Rajai Firouz Abadi, S.; Abhari, F.S.; Bakhtiyari, M. Effect of Saffron Versus Selective Serotonin Reuptake Inhibitors (SSRIs) in Treatment of Depression and Anxiety: A Meta-analysis of Randomized Controlled Trials. *Nutr. Rev.* **2025**, *83*, e751–e761. https://doi.org/10.1093/nutrit/nuae076.

 doi:10.20944/preprints202509.2303.v1

26. Zhichao, H.; Ching, L.W.; Huijuan, L.; Liang, Y.; Zhiyu, W.; Weiyang, H.; Zhaoxiang, B.; Linda, Z.L.D. A network meta-analysis on the effectiveness and safety of acupuncture in treating patients with major depressive disorder. *Sci. Rep.* **2021**, *11*, 10384. https://doi.org/10.1038/s41598-021-88263-y.
27. Nitzan, K.; David, D.; Franko, M.; Toledano, R.; Fidelman, S.; Tenenbaum, Y.S.; Blonder, M.; Armoza-Eilat, S.; Shamir, A.; Rehavi, M.; et al. Anxiolytic and antidepressants' effect of Crataegus pinnatifida (Shan Zha): biochemical mechanisms. *Transl. Psychiatry* **2022**, *12*, 208. https://doi.org/10.1038/s41398-022-01970-6.
28. Di Sotto, A.; Vitalone, A.; Di Giacomo, S. Plant-Derived Nutraceuticals and Immune System Modulation: An Evidence-Based Overview. *Vaccines (Basel)* **2020**, *8*. https://doi.org/10.3390/vaccines8030468.
29. Vrânceanu, M.; Galimberti, D.; Banc, R.; Dragoş, O.; Cozma-Petruţ, A.; Hegheş, S.C.; Voştinaru, O.; Cuciureanu, M.; Stroia, C.M.; Miere, D.; et al. The Anticancer Potential of Plant-Derived Nutraceuticals via the Modulation of Gene Expression. *Plants (Basel)* **2022**, *11*. https://doi.org/10.3390/plants11192524.
30. Xiong, B.; Wang, H.; Song, Y.X.; Lan, W.Y.; Li, J.; Wang, F. Natural saponins and macrophage polarization: Mechanistic insights and therapeutic perspectives in disease management. *Front. Pharmacol.* **2025**, *16*, 1584035. https://doi.org/10.3389/fphar.2025.1584035.
31. Wang, T.; Song, Y.; Ai, Z.; Liu, Y.; Li, H.; Xu, W.; Chen, L.; Zhu, G.; Yang, M.; Su, D. Pulsatilla chinensis saponins ameliorated murine depression by inhibiting intestinal inflammation mediated IDO1 overexpression and rebalancing tryptophan metabolism. *Phytomedicine* **2023**, *116*, 154852. https://doi.org/10.1016/j.phymed.2023.154852.
32. Liaqat, H.; Parveen, A.; Kim, S.Y. Neuroprotective Natural Products' Regulatory Effects on Depression via Gut-Brain Axis Targeting Tryptophan. *Nutrients* **2022**, *14*. https://doi.org/10.3390/nu14163270.
33. Ahmad, S.; Azhar, A.; Tikmani, P.; Rafique, H.; Khan, A.; Mesiya, H.; Saeed, H. A randomized clinical trial to test efficacy of chamomile and saffron for neuroprotective and anti-inflammatory responses in depressive patients. *Heliyon* **2022**, *8*, e10774. https://doi.org/10.1016/j.heliyon.2022.e10774.
34. Yang, Y.H.; Li, C.X.; Zhang, R.B.; Shen, Y.; Xu, X.J.; Yu, Q.M. A review of the pharmacological action and mechanism of natural plant polysaccharides in depression. *Front. Pharmacol.* **2024**, *15*, 1348019. https://doi.org/10.3389/fphar.2024.1348019.
35. Tartt, A.N.; Mariani, M.B.; Hen, R.; Mann, J.J.; Boldrini, M. Dysregulation of adult hippocampal neuroplasticity in major depression: pathogenesis and therapeutic implications. *Mol. Psychiatry* **2022**, *27*, 2689–2699. https://doi.org/10.1038/s41380-022-01520-y.
36. Colucci-D'Amato, L.; Speranza, L.; Volpicelli, F. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. *Int. J. Mol. Sci.* **2020**, *21*. https://doi.org/10.3390/ijms21207777.
37. Sun, X.; Zu, Y.; Li, X.; Zhao, S.; Sun, X.; Li, L.; Zhang, X.; Wang, W.; Liang, Y.; Wang, W.; et al. Corticosterone-induced Hippocampal 5-HT Responses were Muted in Depressive-like State. *ACS Chem. Neurosci.* **2021**, *12*, 845–856. https://doi.org/10.1021/acschemneuro.0c00334.
38. Lee, M.T.; Peng, W.H.; Kan, H.W.; Wu, C.C.; Wang, D.W.; Ho, Y.C. Neurobiology of Depression: Chronic Stress Alters the Glutamatergic System in the Brain-Focusing on AMPA Receptor. *Biomedicines* **2022**, *10*. https://doi.org/10.3390/biomedicines10051005.
39. He, J.G.; Zhou, H.Y.; Wang, F.; Chen, J.G. Dysfunction of Glutamatergic Synaptic Transmission in Depression: Focus on AMPA Receptor Trafficking. *Biol. Psychiatry Glob. Open Sci.* **2023**, *3*, 187–196. https://doi.org/10.1016/j.bpsgos.2022.02.007.
40. Correia, A.S.; Cardoso, A.; Vale, N. Oxidative Stress in Depression: The Link with the Stress Response, Neuroinflammation, Serotonin, Neurogenesis and Synaptic Plasticity. *Antioxidants (Basel)* **2023**, *12*. https://doi.org/10.3390/antiox12020470.
41. Cui, Y.; Cao, K.; Lin, H.; Cui, S.; Shen, C.; Wen, W.; Mo, H.; Dong, Z.; Bai, S.; Yang, L.; et al. Early-Life Stress Induces Depression-Like Behavior and Synaptic-Plasticity Changes in a Maternal Separation Rat Model: Gender Difference and Metabolomics Study. *Front. Pharmacol.* **2020**, *11*, 102. https://doi.org/10.3389/fphar.2020.00102.
42. Yan, Y.; Xu, X.; Chen, R.; Wu, S.; Yang, Z.; Wang, H.; Zhang, T. Down-regulation of MST1 in hippocampus protects against stress-induced depression-like behaviours and synaptic plasticity impairments. *Brain Behav. Immun.* **2021**, *94*, 196–209. https://doi.org/10.1016/j.bbi.2021.02.007.

 doi:10.20944/preprints202509.2303.v1

43. Aleksandrova, L.R.; Phillips, A.G. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. *Trends Pharmacol. Sci.* **2021**, *42*, 929–942. https://doi.org/10.1016/j.tips.2021.08.003.
44. Brown, K.A.; Gould, T.D. Targeting metaplasticity mechanisms to promote sustained antidepressant actions. *Mol. Psychiatry* **2024**, *29*, 1114–1127. https://doi.org/10.1038/s41380-023-02397-1.
45. Tanaka, M.; Battaglia, S. Dualistic Dynamics in Neuropsychiatry: From Monoaminergic Modulators to Multiscale Biomarker Maps. *Biomedicines* **2025**, *13*. https://doi.org/10.3390/biomedicines13061456.
46. Li, B.; Yang, W.; Ge, T.; Wang, Y.; Cui, R. Stress induced microglial activation contributes to depression. *Pharmacol. Res.* **2022**, *179*, 106145. https://doi.org/10.1016/j.phrs.2022.106145.
47. Woodburn, S.C.; Bollinger, J.L.; Wohleb, E.S. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. *J. Neuroinflammation* **2021**, *18*, 258. https://doi.org/10.1186/s12974-021-02309-6.
48. Wang, H.; He, Y.; Sun, Z.; Ren, S.; Liu, M.; Wang, G.; Yang, J. Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. *J. Neuroinflammation* **2022**, *19*, 132. https://doi.org/10.1186/s12974-022-02492-0.
49. Kokkosis, A.G.; Madeira, M.M.; Hage, Z.; Valais, K.; Koliatsis, D.; Resutov, E.; Tsirka, S.E. Chronic psychosocial stress triggers microglial-/macrophage-induced inflammatory responses leading to neuronal dysfunction and depressive-related behavior. *Glia* **2024**, *72*, 111–132. https://doi.org/10.1002/glia.24464.
50. Sugama, S.; Kakinuma, Y. Stress and brain immunity: Microglial homeostasis through hypothalamus-pituitary-adrenal gland axis and sympathetic nervous system. *Brain Behav. Immun. Health* **2020**, *7*, 100111. https://doi.org/10.1016/j.bbih.2020.100111.
51. Picard, K.; Bisht, K.; Poggini, S.; Garofalo, S.; Golia, M.T.; Basilico, B.; Abdallah, F.; Ciano Albanese, N.; Amrein, I.; Vernoux, N.; et al. Microglial-glucocorticoid receptor depletion alters the response of hippocampal microglia and neurons in a chronic unpredictable mild stress paradigm in female mice. *Brain Behav. Immun.* **2021**, *97*, 423–439. https://doi.org/10.1016/j.bbi.2021.07.022.
52. Asveda, T.; Talwar, P.; Ravanan, P. Exploring microglia and their phenomenal concatenation of stress responses in neurodegenerative disorders. *Life Sci.* **2023**, *328*, 121920. https://doi.org/10.1016/j.lfs.2023.121920.
53. Biswas, K. Microglia mediated neuroinflammation in neurodegenerative diseases: A review on the cell signaling pathways involved in microglial activation. *J. Neuroimmunol.* **2023**, *383*, 578180. https://doi.org/10.1016/j.jneuroim.2023.578180.
54. Bolton, J.L.; Short, A.K.; Othy, S.; Kooiker, C.L.; Shao, M.; Gunn, B.G.; Beck, J.; Bai, X.; Law, S.M.; Savage, J.C.; et al. Early stress-induced impaired microglial pruning of excitatory synapses on immature CRH-expressing neurons provokes aberrant adult stress responses. *Cell Rep.* **2022**, *38*, 110600. https://doi.org/10.1016/j.celrep.2022.110600.
55. Reemst, K.; Kracht, L.; Kotah, J.M.; Rahimian, R.; van Irsen, A.A.; Congrains Sotomayor, G.; Verboon, L.N.; Brouwer, N.; Simard, S.; Turecki, G. Early-life stress lastingly impacts microglial transcriptome and function under basal and immune-challenged conditions. *Translational psychiatry* **2022**, *12*, 507.
56. Smail, M.A.; Lenz, K.M. Developmental functions of microglia: Impact of psychosocial and physiological early life stress. *Neuropharmacology* **2024**, *258*, 110084. https://doi.org/10.1016/j.neuropharm.2024.110084.
57. Shen, S.Y.; Liang, L.F.; Shi, T.L.; Shen, Z.Q.; Yin, S.Y.; Zhang, J.R.; Li, W.; Mi, W.L.; Wang, Y.Q.; Zhang, Y.Q.; et al. Microglia-Derived Interleukin-6 Triggers Astrocyte Apoptosis in the Hippocampus and Mediates Depression-Like Behavior. *Adv Sci (Weinh)* **2025**, *12*, e2412556. https://doi.org/10.1002/advs.202412556.
58. Klawonn, A.M.; Fritz, M.; Castany, S.; Pignatelli, M.; Canal, C.; Similä, F.; Tejeda, H.A.; Levinsson, J.; Jaarola, M.; Jakobsson, J.; et al. Microglial activation elicits a negative affective state through prostaglandin-mediated modulation of striatal neurons. *Immunity* **2021**, *54*, 225–234.e226. https://doi.org/10.1016/j.immuni.2020.12.016.
59. Wang, Y.L.; Wu, H.R.; Zhang, S.S.; Xiao, H.L.; Yu, J.; Ma, Y.Y.; Zhang, Y.D.; Liu, Q. Catalpol ameliorates depressive-like behaviors in CUMS mice via oxidative stress-mediated NLRP3 inflammasome and neuroinflammation. *Transl. Psychiatry* **2021**, *11*, 353. https://doi.org/10.1038/s41398-021-01468-7.
60. Xia, C.Y.; Guo, Y.X.; Lian, W.W.; Yan, Y.; Ma, B.Z.; Cheng, Y.C.; Xu, J.K.; He, J.; Zhang, W.K. The NLRP3 inflammasome in depression: Potential mechanisms and therapies. *Pharmacol. Res.* **2023**, *187*, 106625. https://doi.org/10.1016/j.phrs.2022.106625.

 doi:10.20944/preprints202509.2303.v1

61. Wang, L.; Hauenstein, A.V. The NLRP3 inflammasome: Mechanism of action, role in disease and therapies. *Mol. Aspects Med.* **2020**, *76*, 100889. https://doi.org/10.1016/j.mam.2020.100889.
62. Cattaneo, A.; Ferrari, C.; Turner, L.; Mariani, N.; Enache, D.; Hastings, C.; Kose, M.; Lombardo, G.; McLaughlin, A.P.; Nettis, M.A.; et al. Whole-blood expression of inflammasome- and glucocorticoid-related mRNAs correctly separates treatment-resistant depressed patients from drug-free and responsive patients in the BIODEP study. *Transl. Psychiatry* **2020**, *10*, 232. https://doi.org/10.1038/s41398-020-00874-7.
63. Xu, Y.; Liang, J.; Sun, Y.; Zhang, Y.; Shan, F.; Ge, J.; Xia, Q. Serum cytokines-based biomarkers in the diagnosis and monitoring of therapeutic response in patients with major depressive disorder. *Int. Immunopharmacol.* **2023**, *118*, 110108. https://doi.org/10.1016/j.intimp.2023.110108.
64. Bodnár, K.; Hermán, L.; Zsigmond, R.; Réthelyi, J. Investigation of cytokine imbalance in schizophrenia, assessment of the possible role of serum cytokine levels in predicting treatment response, prognosis and psychotic relapses. *European Psychiatry* **2024**, *67*, S685–S685.
65. Zhao, Z.; Wang, Y.; Zhou, R.; Li, Y.; Gao, Y.; Tu, D.; Wilson, B.; Song, S.; Feng, J.; Hong, J.S.; et al. A novel role of NLRP3-generated IL-1β in the acute-chronic transition of peripheral lipopolysaccharide-elicited neuroinflammation: implications for sepsis-associated neurodegeneration. *J. Neuroinflammation* **2020**, *17*, 64. https://doi.org/10.1186/s12974-020-1728-5.
66. Moraes, C.A.; Hottz, E.D.; Dos Santos Ornellas, D.; Adesse, D.; de Azevedo, C.T.; d'Avila, J.C.; Zaverucha-do-Valle, C.; Maron-Gutierrez, T.; Barbosa, H.S.; Bozza, P.T.; et al. Microglial NLRP3 Inflammasome Induces Excitatory Synaptic Loss Through IL-1β-Enriched Microvesicle Release: Implications for Sepsis-Associated Encephalopathy. *Mol. Neurobiol.* **2023**, *60*, 481–494. https://doi.org/10.1007/s12035-022-03067-z.
67. Xu, W.; Huang, Y.; Zhou, R. NLRP3 inflammasome in neuroinflammation and central nervous system diseases. *Cell Mol. Immunol.* **2025**, *22*, 341–355. https://doi.org/10.1038/s41423-025-01275-w.
68. Lu, S.; Wu, C.; Jia, L.; Fang, Z.; Lu, J.; Mou, T.; Hu, S.; He, H.; Huang, M.; Xu, Y. Increased plasma levels of IL-6 are associated with striatal structural atrophy in major depressive disorder patients with anhedonia. *Front. Psychiatry* **2022**, *13*, 1016735. https://doi.org/10.3389/fpsyt.2022.1016735.
69. Sanders, A.F.P.; Tirado, B.; Seider, N.A.; Triplett, R.L.; Lean, R.E.; Neil, J.J.; Miller, J.P.; Tillman, R.; Smyser, T.A.; Barch, D.M.; et al. Prenatal exposure to maternal disadvantage-related inflammatory biomarkers: associations with neonatal white matter microstructure. *Transl. Psychiatry* **2024**, *14*, 72. https://doi.org/10.1038/s41398-024-02782-6.
70. Lim, J.; Sohn, H.; Kwon, M.S.; Kim, B. White Matter Alterations Associated with Pro-inflammatory Cytokines in Patients with Major Depressive Disorder. *Clin. Psychopharmacol. Neurosci.* **2021**, *19*, 449–458. https://doi.org/10.9758/cpn.2021.19.3.449.
71. Yin, R.; Zhang, K.; Li, Y.; Tang, Z.; Zheng, R.; Ma, Y.; Chen, Z.; Lei, N.; Xiong, L.; Guo, P.; et al. Lipopolysaccharide-induced depression-like model in mice: meta-analysis and systematic evaluation. *Front. Immunol.* **2023**, *14*, 1181973. https://doi.org/10.3389/fimmu.2023.1181973.
72. Lasselin, J.; Schedlowski, M.; Karshikoff, B.; Engler, H.; Lekander, M.; Konsman, J.P. Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: Relevance for symptoms of anxiety and depression. *Neurosci. Biobehav. Rev.* **2020**, *115*, 15–24. https://doi.org/10.1016/j.neubiorev.2020.05.001.
73. Su, J.; Pan, Y.W.; Wang, S.Q.; Li, X.Z.; Huang, F.; Ma, S.P. Saikosaponin-d attenuated lipopolysaccharide-induced depressive-like behaviors via inhibiting microglia activation and neuroinflammation. *Int. Immunopharmacol.* **2020**, *80*, 106181. https://doi.org/10.1016/j.intimp.2019.106181.
74. Tomaz, V.S.; Chaves Filho, A.J.M.; Cordeiro, R.C.; Jucá, P.M.; Soares, M.V.R.; Barroso, P.N.; Cristino, L.M.F.; Jiang, W.; Teixeira, A.L.; de Lucena, D.F.; et al. Antidepressants of different classes cause distinct behavioral and brain pro- and anti-inflammatory changes in mice submitted to an inflammatory model of depression. *J. Affect. Disord.* **2020**, *268*, 188–200. https://doi.org/10.1016/j.jad.2020.03.022.
75. Yi, S.S.; Zou, J.J.; Meng, L.; Chen, H.M.; Hong, Z.Q.; Liu, X.F.; Farooq, U.; Chen, M.X.; Lin, Z.R.; Zhou, W.; et al. Ultrasound Stimulation of Prefrontal Cortex Improves Lipopolysaccharide-Induced Depressive-Like Behaviors in Mice. *Front. Psychiatry* **2022**, *13*, 864481. https://doi.org/10.3389/fpsyt.2022.864481.

 doi:10.20944/preprints202509.2303.v1

76. Kappelmann, N.; Lewis, G.; Dantzer, R.; Jones, P.B.; Khandaker, G.M. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatry* **2018**, *23*, 335–343. https://doi.org/10.1038/mp.2016.167.
77. Zhang, M.; Wang, X.L.; Shi, H.; Meng, L.Q.; Quan, H.F.; Yan, L.; Yang, H.F.; Peng, X.D. Betaine Inhibits NLRP3 Inflammasome Hyperactivation and Regulates Microglial M1/M2 Phenotypic Differentiation, Thereby Attenuating Lipopolysaccharide-Induced Depression-Like Behavior. *J. Immunol. Res.* **2022**, *2022*, 9313436. https://doi.org/10.1155/2022/9313436.
78. Planchez, B.; Lagunas, N.; Le Guisquet, A.M.; Legrand, M.; Surget, A.; Hen, R.; Belzung, C. Increasing Adult Hippocampal Neurogenesis Promotes Resilience in a Mouse Model of Depression. *Cells* **2021**, *10*. https://doi.org/10.3390/cells10050972.
79. Jones, K.L.; Zhou, M.; Jhaveri, D.J. Dissecting the role of adult hippocampal neurogenesis towards resilience versus susceptibility to stress-related mood disorders. *NPJ Sci. Learn.* **2022**, *7*, 16. https://doi.org/10.1038/s41539-022-00133-y.
80. Fang, S.; Wu, Z.; Guo, Y.; Zhu, W.; Wan, C.; Yuan, N.; Chen, J.; Hao, W.; Mo, X.; Guo, X.; et al. Roles of microglia in adult hippocampal neurogenesis in depression and their therapeutics. *Front. Immunol.* **2023**, *14*, 1193053. https://doi.org/10.3389/fimmu.2023.1193053.
81. Tang, C.; Wang, Q.; Shen, J.; Wang, C.; Ding, H.; Wen, S.; Yang, F.; Jiao, R.; Wu, X.; Li, J.; et al. Neuron stem cell NLRP6 sustains hippocampal neurogenesis to resist stress-induced depression. *Acta Pharm. Sin. B* **2023**, *13*, 2017–2038. https://doi.org/10.1016/j.apsb.2023.03.010.
82. Zhang, S.Q.; Deng, Q.; Zhu, Q.; Hu, Z.L.; Long, L.H.; Wu, P.F.; He, J.G.; Chen, H.S.; Yue, Z.; Lu, J.H.; et al. Cell type-specific NRBF2 orchestrates autophagic flux and adult hippocampal neurogenesis in chronic stress-induced depression. *Cell Discov.* **2023**, *9*, 90. https://doi.org/10.1038/s41421-023-00583-7.
83. Zhang, K.; Wang, F.; Zhai, M.; He, M.; Hu, Y.; Feng, L.; Li, Y.; Yang, J.; Wu, C. Hyperactive neuronal autophagy depletes BDNF and impairs adult hippocampal neurogenesis in a corticosterone-induced mouse model of depression. *Theranostics* **2023**, *13*, 1059.
84. Du Preez, A.; Onorato, D.; Eiben, I.; Musaelyan, K.; Egeland, M.; Zunszain, P.A.; Fernandes, C.; Thuret, S.; Pariante, C.M. Chronic stress followed by social isolation promotes depressive-like behaviour, alters microglial and astrocyte biology and reduces hippocampal neurogenesis in male mice. *Brain Behav. Immun.* **2021**, *91*, 24–47. https://doi.org/10.1016/j.bbi.2020.07.015.
85. Parul; Mishra, A.; Singh, S.; Singh, S.; Tiwari, V.; Chaturvedi, S.; Wahajuddin, M.; Palit, G.; Shukla, S. Chronic unpredictable stress negatively regulates hippocampal neurogenesis and promote anxious depression-like behavior via upregulating apoptosis and inflammatory signals in adult rats. *Brain Res. Bull.* **2021**, *172*, 164–179. https://doi.org/10.1016/j.brainresbull.2021.04.017.
86. Zhang, J.; Rong, P.; Zhang, L.; He, H.; Zhou, T.; Fan, Y.; Mo, L.; Zhao, Q.; Han, Y.; Li, S.; et al. IL4-driven microglia modulate stress resilience through BDNF-dependent neurogenesis. *Sci. Adv.* **2021**, *7*. https://doi.org/10.1126/sciadv.abb9888.
87. Zhang, H.; Wei, M.; Sun, N.; Wang, H.; Fan, H. Melatonin attenuates chronic stress-induced hippocampal inflammatory response and apoptosis by inhibiting ADAM17/TNF-α axis. *Food Chem. Toxicol.* **2022**, *169*, 113441. https://doi.org/10.1016/j.fct.2022.113441.
88. Li, Y.; Wang, L.; Wang, P.; Fan, C.; Zhang, P.; Shen, J.; Yu, S.Y. Ginsenoside-Rg1 Rescues Stress-Induced Depression-Like Behaviors via Suppression of Oxidative Stress and Neural Inflammation in Rats. *Oxid. Med. Cell Longev.* **2020**, *2020*, 2325391. https://doi.org/10.1155/2020/2325391.
89. Li, J.; Gao, W.; Zhao, Z.; Li, Y.; Yang, L.; Wei, W.; Ren, F.; Li, Y.; Yu, Y.; Duan, W.; et al. Ginsenoside Rg1 Reduced Microglial Activation and Mitochondrial Dysfunction to Alleviate Depression-Like Behaviour Via the GAS5/EZH2/SOCS3/NRF2 Axis. *Mol. Neurobiol.* **2022**, *59*, 2855–2873. https://doi.org/10.1007/s12035-022-02740-7.
90. Amanollahi, M.; Jameie, M.; Heidari, A.; Rezaei, N. The Dialogue Between Neuroinflammation and Adult Neurogenesis: Mechanisms Involved and Alterations in Neurological Diseases. *Mol. Neurobiol.* **2023**, *60*, 923–959. https://doi.org/10.1007/s12035-022-03102-z.

 doi:10.20944/preprints202509.2303.v1

91. Zhang, J.; He, H.; Qiao, Y.; Zhou, T.; He, H.; Yi, S.; Zhang, L.; Mo, L.; Li, Y.; Jiang, W.; et al. Priming of microglia with IFN-γ impairs adult hippocampal neurogenesis and leads to depression-like behaviors and cognitive defects. *Glia* **2020**, *68*, 2674–2692. https://doi.org/10.1002/glia.23878.
92. Zhao, R.; Tian, X.; Xu, H.; Wang, Y.; Lin, J.; Wang, B. Aerobic Exercise Restores Hippocampal Neurogenesis and Cognitive Function by Decreasing Microglia Inflammasome Formation Through Irisin/NLRP3 Pathway. *Aging Cell* **2025**, *24*, e70061. https://doi.org/10.1111/acel.70061.
93. Wang, W.; Wang, L.; Wang, L.; Li, Y.; Lan, T.; Wang, C.; Chen, X.; Chen, S.; Yu, S. Ginsenoside-Rg1 synergized with voluntary running exercise protects against glial activation and dysregulation of neuronal plasticity in depression. *Food Funct.* **2023**, *14*, 7222–7239. https://doi.org/10.1039/d3fo00496a.
94. de Lima, E.P.; Tanaka, M.; Lamas, C.B.; Quesada, K.; Detregiachi, C.R.P.; Araújo, A.C.; Guiguer, E.L.; Catharin, V.; de Castro, M.V.M.; Junior, E.B.; et al. Vascular Impairment, Muscle Atrophy, and Cognitive Decline: Critical Age-Related Conditions. *Biomedicines* **2024**, *12*. https://doi.org/10.3390/biomedicines12092096.
95. Liloia, D.; Zamfira, D.A.; Tanaka, M.; Manuello, J.; Crocetta, A.; Keller, R.; Cozzolino, M.; Duca, S.; Cauda, F.; Costa, T. Disentangling the role of gray matter volume and concentration in autism spectrum disorder: A meta-analytic investigation of 25 years of voxel-based morphometry research. *Neurosci. Biobehav. Rev.* **2024**, *164*, 105791. https://doi.org/10.1016/j.neubiorev.2024.105791.
96. Müller, L.; Di Benedetto, S. Neuroimmune crosstalk in chronic neuroinflammation: microglial interactions and immune modulation. *Front. Cell Neurosci.* **2025**, *19*, 1575022. https://doi.org/10.3389/fncel.2025.1575022.
97. Navabi, S.P.; Badreh, F.; Khombi Shooshtari, M.; Hajipour, S.; Moradi Vastegani, S.; Khoshnam, S.E. Microglia-induced neuroinflammation in hippocampal neurogenesis following traumatic brain injury. *Heliyon* **2024**, *10*, e35869. https://doi.org/10.1016/j.heliyon.2024.e35869.
98. Kwon, H.S.; Koh, S.H. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl. Neurodegener.* **2020**, *9*, 42. https://doi.org/10.1186/s40035-020-00221-2.
99. Sanchez-Molina, P.; Almolda, B.; Giménez-Llort, L.; González, B.; Castellano, B. Chronic IL-10 overproduction disrupts microglia-neuron dialogue similar to aging, resulting in impaired hippocampal neurogenesis and spatial memory. *Brain Behav. Immun.* **2022**, *101*, 231–245. https://doi.org/10.1016/j.bbi.2021.12.026.
100. Izzy, S.; Yahya, T.; Albastaki, O.; Abou-El-Hassan, H.; Aronchik, M.; Cao, T.; De Oliveira, M.G.; Lu, K.J.; Moreira, T.G.; da Silva, P.; et al. Nasal anti-CD3 monoclonal antibody ameliorates traumatic brain injury, enhances microglial phagocytosis and reduces neuroinflammation via IL-10-dependent T(reg)-microglia crosstalk. *Nat. Neurosci.* **2025**, *28*, 499–516. https://doi.org/10.1038/s41593-025-01877-7.
101. Witcher, K.G.; Bray, C.E.; Chunchai, T.; Zhao, F.; O'Neil, S.M.; Gordillo, A.J.; Campbell, W.A.; McKim, D.B.; Liu, X.; Dziabis, J.E.; et al. Traumatic Brain Injury Causes Chronic Cortical Inflammation and Neuronal Dysfunction Mediated by Microglia. *J. Neurosci.* **2021**, *41*, 1597–1616. https://doi.org/10.1523/jneurosci.2469-20.2020.
102. Lawrence, J.M.; Schardien, K.; Wigdahl, B.; Nonnemacher, M.R. Roles of neuropathology-associated reactive astrocytes: a systematic review. *Acta Neuropathol. Commun.* **2023**, *11*, 42. https://doi.org/10.1186/s40478-023-01526-9.
103. Gao, Y.; Liu, X.; Gu, Y. Evaluation of serum brain-derived neurotrophic factor, IL-6, IL-10, and TNF-a cognitive function, and sleep quality in elderly patients with major depressive disorder and somatic symptoms. *J. Med. Biochem.* **2025**, *44*, 568–575. https://doi.org/10.5937/jomb0-53387.
104. Skelly, D.T.; Griffin É, W.; Murray, C.L.; Harney, S.; O'Boyle, C.; Hennessy, E.; Dansereau, M.A.; Nazmi, A.; Tortorelli, L.; Rawlins, J.N.; et al. Acute transient cognitive dysfunction and acute brain injury induced by systemic inflammation occur by dissociable IL-1-dependent mechanisms. *Mol. Psychiatry* **2019**, *24*, 1533–1548. https://doi.org/10.1038/s41380-018-0075-8.
105. Pan, X.; Guo, A.; Guan, K.; Chen, C.; Xu, S.; Tang, Y.; Li, X.; Huang, Z. Lactobacillus rhamnosus GG attenuates depression-like behaviour and cognitive deficits in chronic ethanol exposure mice by down-regulating systemic inflammatory factors. *Addict. Biol.* **2024**, *29*, e13445. https://doi.org/10.1111/adb.13445.

 doi:10.20944/preprints202509.2303.v1

106. Zhang, J.C.; Yao, W.; Hashimoto, K. Brain-derived Neurotrophic Factor (BDNF)-TrkB Signaling in Inflammation-related Depression and Potential Therapeutic Targets. *Curr. Neuropharmacol.* **2016**, *14*, 721–731. https://doi.org/10.2174/1570159x14666160119094646.
107. Calabrese, F.; Rossetti, A.C.; Racagni, G.; Gass, P.; Riva, M.A.; Molteni, R. Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. *Front. Cell Neurosci.* **2014**, *8*, 430. https://doi.org/10.3389/fncel.2014.00430.
108. Carniel, B.P.; da Rocha, N.S. Brain-derived neurotrophic factor (BDNF) and inflammatory markers: Perspectives for the management of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *108*, 110151. https://doi.org/10.1016/j.pnpbp.2020.110151.
109. Liu, Q.; Zhang, J.; Xiao, C.; Su, D.; Li, L.; Yang, C.; Zhao, Z.; Jiang, W.; You, Z.; Zhou, T. Akebia saponin D protects hippocampal neurogenesis from microglia-mediated inflammation and ameliorates depressive-like behaviors and cognitive impairment in mice through the PI3K-Akt pathway. *Front. Pharmacol.* **2022**, *13*, 927419. https://doi.org/10.3389/fphar.2022.927419.
110. Zhang, Q.; Zhao, W.; Yun, Y.; Ma, T.; An, H.; Fan, N.; Wang, J.; Wang, Z.; Yang, F. Multiomics analysis reveals aberrant tryptophan-kynurenine metabolism and immunity linked gut microbiota with cognitive impairment in major depressive disorder. *J. Affect. Disord.* **2025**, *373*, 273–283. https://doi.org/10.1016/j.jad.2024.12.070.
111. de Lima, E.P.; Laurindo, L.F.; Catharin, V.C.S.; Direito, R.; Tanaka, M.; Jasmin Santos German, I.; Lamas, C.B.; Guiguer, E.L.; Araújo, A.C.; Fiorini, A.M.R.; et al. Polyphenols, Alkaloids, and Terpenoids Against Neurodegeneration: Evaluating the Neuroprotective Effects of Phytocompounds Through a Comprehensive Review of the Current Evidence. *Metabolites* **2025**, *15*. https://doi.org/10.3390/metabo15020124.
112. Barbalho, S.M.; Laurindo, L.F.; de Oliveira Zanuso, B.; da Silva, R.M.S.; Gallerani Caglioni, L.; Nunes Junqueira de Moraes, V.B.F.; Fornari Laurindo, L.; Dogani Rodrigues, V.; da Silva Camarinha Oliveira, J.; Beluce, M.E.; et al. AdipoRon's Impact on Alzheimer's Disease-A Systematic Review and Meta-Analysis. *Int. J. Mol. Sci.* **2025**, *26*. https://doi.org/10.3390/ijms26020484.
113. Salminen, A. Role of indoleamine 2,3-dioxygenase 1 (IDO1) and kynurenine pathway in the regulation of the aging process. *Ageing Res. Rev.* **2022**, *75*, 101573. https://doi.org/10.1016/j.arr.2022.101573.
114. Tanaka, M.; Tóth, F.; Polyák, H.; Szabó, Á.; Mándi, Y.; Vécsei, L. Immune Influencers in Action: Metabolites and Enzymes of the Tryptophan-Kynurenine Metabolic Pathway. *Biomedicines* **2021**, *9*. https://doi.org/10.3390/biomedicines9070734.
115. Dawood, S.; Bano, S.; Badawy, A.A. Inflammation and serotonin deficiency in major depressive disorder: molecular docking of antidepressant and anti-inflammatory drugs to tryptophan and indoleamine 2,3-dioxygenases. *Biosci. Rep.* **2022**, *42*. https://doi.org/10.1042/bsr20220426.
116. Tiwari, S.; Paramanik, V. Role of Probiotics in Depression: Connecting Dots of Gut-Brain-Axis Through Hypothalamic-Pituitary Adrenal Axis and Tryptophan/Kynurenic Pathway involving Indoleamine-2,3-dioxygenase. *Mol. Neurobiol.* **2025**, *62*, 7230–7241. https://doi.org/10.1007/s12035-025-04708-9.
117. Sublette, M.E.; Postolache, T.T. Neuroinflammation and depression: the role of indoleamine 2,3-dioxygenase (IDO) as a molecular pathway. *Psychosom. Med.* **2012**, *74*, 668–672. https://doi.org/10.1097/PSY.0b013e318268de9f.
118. Tanaka, M.; Battaglia, S. From Biomarkers to Behavior: Mapping the Neuroimmune Web of Pain, Mood, and Memory. **2025**, *13*, 2226.
119. Stone, T.W.; Williams, R.O. Tryptophan metabolism as a 'reflex' feature of neuroimmune communication: Sensor and effector functions for the indoleamine-2, 3-dioxygenase kynurenine pathway. *J. Neurochem.* **2024**, *168*, 3333–3357. https://doi.org/10.1111/jnc.16015.
120. Juhász, L.; Spisák, K.; Szolnoki, B.Z.; Nászai, A.; Szabó, Á.; Rutai, A.; Tallósy, S.P.; Szabó, A.; Toldi, J.; Tanaka, M.; et al. The Power Struggle: Kynurenine Pathway Enzyme Knockouts and Brain Mitochondrial Respiration. *J. Neurochem.* **2025**, *169*, e70075. https://doi.org/10.1111/jnc.70075.
121. Szabó, Á.; Galla, Z.; Spekker, E.; Szűcs, M.; Martos, D.; Takeda, K.; Ozaki, K.; Inoue, H.; Yamamoto, S.; Toldi, J.; et al. Oxidative and Excitatory Neurotoxic Stresses in CRISPR/Cas9-Induced Kynurenine

 doi:10.20944/preprints202509.2303.v1

Aminotransferase Knockout Mice: A Novel Model for Despair-Based Depression and Post-Traumatic Stress Disorder. *Front Biosci (Landmark Ed)* **2025**, *30*, 25706. https://doi.org/10.31083/fbl25706.

122. Fiore, A.; Murray, P.J. Tryptophan and indole metabolism in immune regulation. *Curr. Opin. Immunol.* **2021**, *70*, 7–14. https://doi.org/10.1016/j.coi.2020.12.001.
123. Alfaro-Rodríguez, A.; Reyes-Long, S.; Roldan-Valadez, E.; González-Torres, M.; Bonilla-Jaime, H.; Bandala, C.; Avila-Luna, A.; Bueno-Nava, A.; Cabrera-Ruiz, E.; Sanchez-Aparicio, P.; et al. Association of the Serotonin and Kynurenine Pathways as Possible Therapeutic Targets to Modulate Pain in Patients with Fibromyalgia. *Pharmaceuticals (Basel)* **2024**, *17*. https://doi.org/10.3390/ph17091205.
124. Hunt, C.; Macedo, E.C.T.; Suchting, R.; de Dios, C.; Cuellar Leal, V.A.; Soares, J.C.; Dantzer, R.; Teixeira, A.L.; Selvaraj, S. Effect of immune activation on the kynurenine pathway and depression symptoms - A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **2020**, *118*, 514–523. https://doi.org/10.1016/j.neubiorev.2020.08.010.
125. Almulla, A.F.; Supasitthumrong, T.; Tunvirachaisakul, C.; Algon, A.A.A.; Al-Hakeim, H.K.; Maes, M. The tryptophan catabolite or kynurenine pathway in COVID-19 and critical COVID-19: a systematic review and meta-analysis. *BMC Infect. Dis.* **2022**, *22*, 615. https://doi.org/10.1186/s12879-022-07582-1.
126. Li, Y.; Peng, Y.; Shen, Y.; Zhang, Y.; Liu, L.; Yang, X. Dietary polyphenols: regulate the advanced glycation end products-RAGE axis and the microbiota-gut-brain axis to prevent neurodegenerative diseases. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 9816–9842. https://doi.org/10.1080/10408398.2022.2076064.
127. Ghimire, S.; Cady, N.M.; Lehman, P.; Peterson, S.R.; Shahi, S.K.; Rashid, F.; Giri, S.; Mangalam, A.K. Dietary Isoflavones Alter Gut Microbiota and Lipopolysaccharide Biosynthesis to Reduce Inflammation. *Gut Microbes* **2022**, *14*, 2127446. https://doi.org/10.1080/19490976.2022.2127446.
128. Winiarska-Mieczan, A.; Kwiecień, M.; Jachimowicz-Rogowska, K.; Donaldson, J.; Tomaszewska, E.; Baranowska-Wójcik, E. Anti-Inflammatory, Antioxidant, and Neuroprotective Effects of Polyphenols-Polyphenols as an Element of Diet Therapy in Depressive Disorders. *Int. J. Mol. Sci.* **2023**, *24*. https://doi.org/10.3390/ijms24032258.
129. Tian, E.; Sharma, G.; Dai, C. Neuroprotective Properties of Berberine: Molecular Mechanisms and Clinical Implications. *Antioxidants (Basel)* **2023**, *12*. https://doi.org/10.3390/antiox12101883.
130. Wang, L.; Wu, X.; Ma, Y.; Li, X.; Zhang, J.; Zhao, L. Supplementation with soy isoflavones alleviates depression-like behaviour via reshaping the gut microbiota structure. *Food Funct.* **2021**, *12*, 4995–5006. https://doi.org/10.1039/d0fo03254a.
131. Chatterjee, A.; Kumar, S.; Roy Sarkar, S.; Halder, R.; Kumari, R.; Banerjee, S.; Sarkar, B. Dietary polyphenols represent a phytotherapeutic alternative for gut dysbiosis associated neurodegeneration: A systematic review. *J. Nutr. Biochem.* **2024**, *129*, 109622. https://doi.org/10.1016/j.jnutbio.2024.109622.
132. Tayab, M.A.; Islam, M.N.; Chowdhury, K.A.A.; Tasnim, F.M. Targeting neuroinflammation by polyphenols: A promising therapeutic approach against inflammation-associated depression. *Biomed. Pharmacother.* **2022**, *147*, 112668. https://doi.org/10.1016/j.biopha.2022.112668.
133. Abbaszadeh, F.; Fakhri, S.; Khan, H. Targeting apoptosis and autophagy following spinal cord injury: Therapeutic approaches to polyphenols and candidate phytochemicals. *Pharmacol. Res.* **2020**, *160*, 105069. https://doi.org/10.1016/j.phrs.2020.105069.
134. Grifka-Walk, H.M.; Jenkins, B.R.; Kominsky, D.J. Amino Acid Trp: The Far Out Impacts of Host and Commensal Tryptophan Metabolism. *Front. Immunol.* **2021**, *12*, 653208. https://doi.org/10.3389/fimmu.2021.653208.
135. Comai, S.; Bertazzo, A.; Brughera, M.; Crotti, S. Tryptophan in health and disease. *Adv. Clin. Chem.* **2020**, *95*, 165–218. https://doi.org/10.1016/bs.acc.2019.08.005.
136. Deng, Y.; Zhou, M.; Wang, J.; Yao, J.; Yu, J.; Liu, W.; Wu, L.; Wang, J.; Gao, R. Involvement of the microbiota-gut-brain axis in chronic restraint stress: disturbances of the kynurenine metabolic pathway in both the gut and brain. *Gut Microbes* **2021**, *13*, 1–16. https://doi.org/10.1080/19490976.2020.1869501.
137. Tutakhail, A.; Boulet, L.; Khabil, S.; Nazari, Q.A.; Hamid, H.; Coudoré, F. Neuropathology of kynurenine pathway of tryptophan metabolism. *Current pharmacology reports* **2020**, *6*, 8–23.
138. Höglund, E.; Øverli, Ø.; Winberg, S. Tryptophan Metabolic Pathways and Brain Serotonergic Activity: A Comparative Review. *Front Endocrinol (Lausanne)* **2019**, *10*, 158. https://doi.org/10.3389/fendo.2019.00158.

 doi:10.20944/preprints202509.2303.v1

139. Fujigaki, H.; Yamamoto, Y.; Saito, K. L-Tryptophan-kynurenine pathway enzymes are therapeutic target for neuropsychiatric diseases: Focus on cell type differences. *Neuropharmacology* **2017**, *112*, 264–274. https://doi.org/10.1016/j.neuropharm.2016.01.011.
140. Messaoud, A.; Mensi, R.; Douki, W.; Neffati, F.; Najjar, M.F.; Gobbi, G.; Valtorta, F.; Gaha, L.; Comai, S. Reduced peripheral availability of tryptophan and increased activation of the kynurenine pathway and cortisol correlate with major depression and suicide. *World J. Biol. Psychiatry* **2019**, *20*, 703–711. https://doi.org/10.1080/15622975.2018.1468031.
141. Chivite, M.; Leal, E.; Míguez, J.M.; Cerdá-Reverter, J.M. Distribution of two isoforms of tryptophan hydroxylase in the brain of rainbow trout (Oncorhynchus mykiss). An in situ hybridization study. *Brain Struct. Funct.* **2021**, *226*, 2265–2278. https://doi.org/10.1007/s00429-021-02322-8.
142. Maffei, M.E. 5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology. *Int. J. Mol. Sci.* **2020**, *22*. https://doi.org/10.3390/ijms22010181.
143. Xue, C.; Li, G.; Zheng, Q.; Gu, X.; Shi, Q.; Su, Y.; Chu, Q.; Yuan, X.; Bao, Z.; Lu, J.; et al. Tryptophan metabolism in health and disease. *Cell Metab.* **2023**, *35*, 1304–1326. https://doi.org/10.1016/j.cmet.2023.06.004.
144. Zakrocka, I.; Urbańska, E.M.; Załuska, W.; Kronbichler, A. Kynurenine Pathway after Kidney Transplantation: Friend or Foe? *International Journal of Molecular Sciences* **2024**, *25*, 9940.
145. Perez--Castro, L.; Garcia, R.; Venkateswaran, N.; Barnes, S.; Conacci--Sorrell, M. Tryptophan and its metabolites in normal physiology and cancer etiology. *The FEBS journal* **2023**, *290*, 7–27.
146. Tanaka, M.; Bohár, Z.; Vécsei, L. Are Kynurenines Accomplices or Principal Villains in Dementia? Maintenance of Kynurenine Metabolism. *Molecules* **2020**, *25*. https://doi.org/10.3390/molecules25030564.
147. Fathi, M.; Vakili, K.; Yaghoobpoor, S.; Tavasol, A.; Jazi, K.; Mohamadkhani, A.; Klegeris, A.; McElhinney, A.; Mafi, Z.; Hajiesmaeili, M.; et al. Dynamic changes in kynurenine pathway metabolites in multiple sclerosis: A systematic review. *Front. Immunol.* **2022**, *13*, 1013784. https://doi.org/10.3389/fimmu.2022.1013784.
148. Ou, W.; Chen, Y.; Ju, Y.; Ma, M.; Qin, Y.; Bi, Y.; Liao, M.; Liu, B.; Liu, J.; Zhang, Y.; et al. The kynurenine pathway in major depressive disorder under different disease states: A systematic review and meta-analysis. *J. Affect. Disord.* **2023**, *339*, 624–632. https://doi.org/10.1016/j.jad.2023.07.078.
149. Kozieł, K.; Urbanska, E.M. Kynurenine Pathway in Diabetes Mellitus-Novel Pharmacological Target? *Cells* **2023**, *12*. https://doi.org/10.3390/cells12030460.
150. Tanaka, M.; Szabó, Á.; Vécsei, L. Redefining Roles: A Paradigm Shift in Tryptophan-Kynurenine Metabolism for Innovative Clinical Applications. *Int. J. Mol. Sci.* **2024**, *25*. https://doi.org/10.3390/ijms252312767.
151. Skorobogatov, K.; De Picker, L.; Verkerk, R.; Coppens, V.; Leboyer, M.; Müller, N.; Morrens, M. Brain Versus Blood: A Systematic Review on the Concordance Between Peripheral and Central Kynurenine Pathway Measures in Psychiatric Disorders. *Front. Immunol.* **2021**, *12*, 716980. https://doi.org/10.3389/fimmu.2021.716980.
152. Pocivavsek, A.; Schwarcz, R.; Erhardt, S. Neuroactive Kynurenines as Pharmacological Targets: New Experimental Tools and Exciting Therapeutic Opportunities. *Pharmacol. Rev.* **2024**, *76*, 978–1008. https://doi.org/10.1124/pharmrev.124.000239.
153. Zhang, S.; Sakuma, M.; Deora, G.S.; Levy, C.W.; Klausing, A.; Breda, C.; Read, K.D.; Edlin, C.D.; Ross, B.P.; Wright Muelas, M.; et al. A brain-permeable inhibitor of the neurodegenerative disease target kynurenine 3-monooxygenase prevents accumulation of neurotoxic metabolites. *Commun. Biol.* **2019**, *2*, 271. https://doi.org/10.1038/s42003-019-0520-5.
154. Jones, S.P.; Franco, N.F.; Varney, B.; Sundaram, G.; Brown, D.A.; de Bie, J.; Lim, C.K.; Guillemin, G.J.; Brew, B.J. Expression of the Kynurenine Pathway in Human Peripheral Blood Mononuclear Cells: Implications for Inflammatory and Neurodegenerative Disease. *PLoS One* **2015**, *10*, e0131389. https://doi.org/10.1371/journal.pone.0131389.
155. Sathyasaikumar, K.V.; Notarangelo, F.M.; Kelly, D.L.; Rowland, L.M.; Hare, S.M.; Chen, S.; Mo, C.; Buchanan, R.W.; Schwarcz, R. Tryptophan Challenge in Healthy Controls and People with Schizophrenia:

 doi:10.20944/preprints202509.2303.v1

Acute Effects on Plasma Levels of Kynurenine, Kynurenic Acid and 5-Hydroxyindoleacetic Acid. *Pharmaceuticals (Basel)* **2022**, *15*. https://doi.org/10.3390/ph15081003.

156. Hestad, K.; Alexander, J.; Rootwelt, H.; Aaseth, J.O. The Role of Tryptophan Dysmetabolism and Quinolinic Acid in Depressive and Neurodegenerative Diseases. *Biomolecules* **2022**, *12*. https://doi.org/10.3390/biom12070998.
157. Martos, D.; Tuka, B.; Tanaka, M.; Vécsei, L.; Telegdy, G. Memory Enhancement with Kynurenic Acid and Its Mechanisms in Neurotransmission. *Biomedicines* **2022**, *10*. https://doi.org/10.3390/biomedicines10040849.
158. Tanaka, M.; Szatmári, I.; Vécsei, L. Quinoline Quest: Kynurenic Acid Strategies for Next-Generation Therapeutics via Rational Drug Design. *Pharmaceuticals (Basel)* **2025**, *18*. https://doi.org/10.3390/ph18050607.
159. Mor, A.; Tankiewicz-Kwedlo, A.; Krupa, A.; Pawlak, D. Role of Kynurenine Pathway in Oxidative Stress during Neurodegenerative Disorders. *Cells* **2021**, *10*. https://doi.org/10.3390/cells10071603.
160. Tanaka, M.; Vécsei, L. From Microbial Switches to Metabolic Sensors: Rewiring the Gut-Brain Kynurenine Circuit. *Biomedicines* **2025**, *13*. https://doi.org/10.3390/biomedicines13082020.
161. Tanaka, M.; Vécsei, L. Revolutionizing our understanding of Parkinson's disease: Dr. Heinz Reichmann's pioneering research and future research direction. *J Neural Transm (Vienna)* **2024**, *131*, 1367–1387. https://doi.org/10.1007/s00702-024-02812-z.
162. Cheong, J.E.; Sun, L. Targeting the IDO1/TDO2-KYN-AhR Pathway for Cancer Immunotherapy - Challenges and Opportunities. *Trends Pharmacol. Sci.* **2018**, *39*, 307–325. https://doi.org/10.1016/j.tips.2017.11.007.
163. Ye, Z.; Yue, L.; Shi, J.; Shao, M.; Wu, T. Role of IDO and TDO in Cancers and Related Diseases and the Therapeutic Implications. *J. Cancer* **2019**, *10*, 2771–2782. https://doi.org/10.7150/jca.31727.
164. Lu, Z.; Zhang, C.; Zhang, J.; Su, W.; Wang, G.; Wang, Z. The Kynurenine Pathway and Indole Pathway in Tryptophan Metabolism Influence Tumor Progression. *Cancer Med.* **2025**, *14*, e70703. https://doi.org/10.1002/cam4.70703.
165. Stone, T.W.; Williams, R.O. Interactions of IDO and the Kynurenine Pathway with Cell Transduction Systems and Metabolism at the Inflammation-Cancer Interface. *Cancers (Basel)* **2023**, *15*. https://doi.org/10.3390/cancers15112895.
166. Lashgari, N.A.; Roudsari, N.M.; Shayan, M.; Niazi Shahraki, F.; Hosseini, Y.; Momtaz, S.; Abdolghaffari, A.H. IDO/Kynurenine; novel insight for treatment of inflammatory diseases. *Cytokine* **2023**, *166*, 156206. https://doi.org/10.1016/j.cyto.2023.156206.
167. Labadie, B.W.; Bao, R.; Luke, J.J. Reimagining IDO Pathway Inhibition in Cancer Immunotherapy via Downstream Focus on the Tryptophan-Kynurenine-Aryl Hydrocarbon Axis. *Clin. Cancer Res.* **2019**, *25*, 1462–1471. https://doi.org/10.1158/1078-0432.Ccr-18-2882.
168. Campesato, L.F.; Budhu, S.; Tchaicha, J.; Weng, C.H.; Gigoux, M.; Cohen, I.J.; Redmond, D.; Mangarin, L.; Pourpe, S.; Liu, C.; et al. Blockade of the AHR restricts a Treg-macrophage suppressive axis induced by L-Kynurenine. *Nat. Commun.* **2020**, *11*, 4011. https://doi.org/10.1038/s41467-020-17750-z.
169. Fujiwara, Y.; Kato, S.; Nesline, M.K.; Conroy, J.M.; DePietro, P.; Pabla, S.; Kurzrock, R. Indoleamine 2,3-dioxygenase (IDO) inhibitors and cancer immunotherapy. *Cancer Treat. Rev.* **2022**, *110*, 102461. https://doi.org/10.1016/j.ctrv.2022.102461.
170. Bertollo, A.G.; Mingoti, M.E.D.; Ignácio, Z.M. Neurobiological mechanisms in the kynurenine pathway and major depressive disorder. *Rev. Neurosci.* **2025**, *36*, 169–187. https://doi.org/10.1515/revneuro-2024-0065.
171. Gong, X.; Chang, R.; Zou, J.; Tan, S.; Huang, Z. The role and mechanism of tryptophan - kynurenine metabolic pathway in depression. *Rev. Neurosci.* **2023**, *34*, 313–324. https://doi.org/10.1515/revneuro-2022-0047.
172. Anderson, E.W.; Fishbein, J.; Hong, J.; Roeser, J.; Furie, R.A.; Aranow, C.; Volpe, B.T.; Diamond, B.; Mackay, M. Quinolinic acid, a kynurenine/tryptophan pathway metabolite, associates with impaired cognitive test performance in systemic lupus erythematosus. *Lupus Sci. Med.* **2021**, *8*. https://doi.org/10.1136/lupus-2021-000559.
173. Wang, L.; Feng, Z.; Zheng, T.; Dai, G.; Wang, M.; Zhou, L.; Zheng, Y.; Chen, G. Associations between the kynurenine pathway and the brain in patients with major depressive disorder-A systematic review of

 doi:10.20944/preprints202509.2303.v1

neuroimaging studies. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2023**, *121*, 110675. https://doi.org/10.1016/j.pnpbp.2022.110675.

174. Ogyu, K.; Kubo, K.; Noda, Y.; Iwata, Y.; Tsugawa, S.; Omura, Y.; Wada, M.; Tarumi, R.; Plitman, E.; Moriguchi, S.; et al. Kynurenine pathway in depression: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **2018**, *90*, 16–25. https://doi.org/10.1016/j.neubiorev.2018.03.023.
175. Marx, W.; McGuinness, A.J.; Rocks, T.; Ruusunen, A.; Cleminson, J.; Walker, A.J.; Gomes-da-Costa, S.; Lane, M.; Sanches, M.; Diaz, A.P.; et al. The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a meta-analysis of 101 studies. *Mol. Psychiatry* **2021**, *26*, 4158–4178. https://doi.org/10.1038/s41380-020-00951-9.
176. Joisten, N.; Ruas, J.L.; Braidy, N.; Guillemin, G.J.; Zimmer, P. The kynurenine pathway in chronic diseases: a compensatory mechanism or a driving force? *Trends Mol. Med.* **2021**, *27*, 946–954. https://doi.org/10.1016/j.molmed.2021.07.006.
177. Martos, D.; Lőrinczi, B.; Szatmári, I.; Vécsei, L.; Tanaka, M. Decoupling Behavioral Domains via Kynurenic Acid Analog Optimization: Implications for Schizophrenia and Parkinson's Disease Therapeutics. *Cells* **2025**, *14*. https://doi.org/10.3390/cells14130973.
178. Inam, M.E.; Fernandes, B.S.; Salagre, E.; Grande, I.; Vieta, E.; Quevedo, J.; Zhao, Z. The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a systematic review and meta-analysis of cerebrospinal fluid studies. *Braz. J. Psychiatry* **2023**, *45*, 343–355. https://doi.org/10.47626/1516-4446-2022-2973.
179. Tanaka, M.; Battaglia, S.; Liloia, D. Navigating Neurodegeneration: Integrating Biomarkers, Neuroinflammation, and Imaging in Parkinson's, Alzheimer's, and Motor Neuron Disorders. *Biomedicines* **2025**, *13*. https://doi.org/10.3390/biomedicines13051045.
180. Więdłocha, M.; Marcinowicz, P.; Janoska-Jaździk, M.; Szulc, A. Gut microbiota, kynurenine pathway and mental disorders - Review. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *106*, 110145. https://doi.org/10.1016/j.pnpbp.2020.110145.
181. Chen, C.Y.; Wang, Y.F.; Lei, L.; Zhang, Y. Impacts of microbiota and its metabolites through gut-brain axis on pathophysiology of major depressive disorder. *Life Sci.* **2024**, *351*, 122815. https://doi.org/10.1016/j.lfs.2024.122815.
182. Cryan, J.F.; O'Riordan, K.J.; Cowan, C.S.M.; Sandhu, K.V.; Bastiaanssen, T.F.S.; Boehme, M.; Codagnone, M.G.; Cussotto, S.; Fulling, C.; Golubeva, A.V.; et al. The Microbiota-Gut-Brain Axis. *Physiol. Rev.* **2019**, *99*, 1877–2013. https://doi.org/10.1152/physrev.00018.2018.
183. Ohara, T.E.; Hsiao, E.Y. Microbiota-neuroepithelial signalling across the gut-brain axis. *Nat. Rev. Microbiol.* **2025**, *23*, 371–384. https://doi.org/10.1038/s41579-024-01136-9.
184. Zheng, Y.; Bonfili, L.; Wei, T.; Eleuteri, A.M. Understanding the Gut-Brain Axis and Its Therapeutic Implications for Neurodegenerative Disorders. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15214631.
185. Ullah, H.; Arbab, S.; Tian, Y.; Liu, C.Q.; Chen, Y.; Qijie, L.; Khan, M.I.U.; Hassan, I.U.; Li, K. The gut microbiota-brain axis in neurological disorder. *Front. Neurosci.* **2023**, *17*, 1225875. https://doi.org/10.3389/fnins.2023.1225875.
186. Ma, Q.; Xing, C.; Long, W.; Wang, H.Y.; Liu, Q.; Wang, R.F. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J. Neuroinflammation* **2019**, *16*, 53. https://doi.org/10.1186/s12974-019-1434-3.
187. Ashique, S.; Mohanto, S.; Ahmed, M.G.; Mishra, N.; Garg, A.; Chellappan, D.K.; Omara, T.; Iqbal, S.; Kahwa, I. Gut-brain axis: A cutting-edge approach to target neurological disorders and potential synbiotic application. *Heliyon* **2024**, *10*, e34092. https://doi.org/10.1016/j.heliyon.2024.e34092.
188. Góralczyk-Bińkowska, A.; Szmajda-Krygier, D.; Kozłowska, E. The Microbiota-Gut-Brain Axis in Psychiatric Disorders. *Int. J. Mol. Sci.* **2022**, *23*. https://doi.org/10.3390/ijms231911245.
189. Han, Y.; Wang, B.; Gao, H.; He, C.; Hua, R.; Liang, C.; Zhang, S.; Wang, Y.; Xin, S.; Xu, J. Vagus Nerve and Underlying Impact on the Gut Microbiota-Brain Axis in Behavior and Neurodegenerative Diseases. *J. Inflamm. Res.* **2022**, *15*, 6213–6230. https://doi.org/10.2147/jir.S384949.

 doi:10.20944/preprints202509.2303.v1

190. Naufel, M.F.; Truzzi, G.M.; Ferreira, C.M.; Coelho, F.M.S. The brain-gut-microbiota axis in the treatment of neurologic and psychiatric disorders. *Arq. Neuropsiquiatr.* **2023**, *81*, 670–684. https://doi.org/10.1055/s-0043-1767818.
191. Loh, J.S.; Mak, W.Q.; Tan, L.K.S.; Ng, C.X.; Chan, H.H.; Yeow, S.H.; Foo, J.B.; Ong, Y.S.; How, C.W.; Khaw, K.Y. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct. Target. Ther.* **2024**, *9*, 37. https://doi.org/10.1038/s41392-024-01743-1.
192. Rutsch, A.; Kantsjö, J.B.; Ronchi, F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. *Front. Immunol.* **2020**, *11*, 604179. https://doi.org/10.3389/fimmu.2020.604179.
193. Long-Smith, C.; O'Riordan, K.J.; Clarke, G.; Stanton, C.; Dinan, T.G.; Cryan, J.F. Microbiota-Gut-Brain Axis: New Therapeutic Opportunities. *Annu. Rev. Pharmacol. Toxicol.* **2020**, *60*, 477–502. https://doi.org/10.1146/annurev-pharmtox-010919-023628.
194. Lee, S.H.; Han, C.; Shin, C. IUPHAR review: Microbiota-gut-brain axis and its role in neuropsychiatric disorders. *Pharmacol. Res.* **2025**, *216*, 107749. https://doi.org/10.1016/j.phrs.2025.107749.
195. Zhou, M.; Fan, Y.; Xu, L.; Yu, Z.; Wang, S.; Xu, H.; Zhang, J.; Zhang, L.; Liu, W.; Wu, L.; et al. Microbiome and tryptophan metabolomics analysis in adolescent depression: roles of the gut microbiota in the regulation of tryptophan-derived neurotransmitters and behaviors in human and mice. *Microbiome* **2023**, *11*, 145. https://doi.org/10.1186/s40168-023-01589-9.
196. Zhao, H.; Qiu, X.; Wang, S.; Wang, Y.; Xie, L.; Xia, X.; Li, W. Multiple pathways through which the gut microbiota regulates neuronal mitochondria constitute another possible direction for depression. *Front. Microbiol.* **2025**, *16*, 1578155. https://doi.org/10.3389/fmicb.2025.1578155.
197. Liu, L.; Wang, H.; Chen, X.; Zhang, Y.; Zhang, H.; Xie, P. Gut microbiota and its metabolites in depression: from pathogenesis to treatment. *EBioMedicine* **2023**, *90*, 104527. https://doi.org/10.1016/j.ebiom.2023.104527.
198. Ma, N.; He, T.; Johnston, L.J.; Ma, X. Host-microbiome interactions: the aryl hydrocarbon receptor as a critical node in tryptophan metabolites to brain signaling. *Gut Microbes* **2020**, *11*, 1203–1219. https://doi.org/10.1080/19490976.2020.1758008.
199. Salminen, A. Activation of aryl hydrocarbon receptor (AhR) in Alzheimer's disease: role of tryptophan metabolites generated by gut host-microbiota. *J Mol Med (Berl)* **2023**, *101*, 201–222. https://doi.org/10.1007/s00109-023-02289-5.
200. Zhu, S.; Jiang, Y.; Xu, K.; Cui, M.; Ye, W.; Zhao, G.; Jin, L.; Chen, X. The progress of gut microbiome research related to brain disorders. *J. Neuroinflammation* **2020**, *17*, 25. https://doi.org/10.1186/s12974-020-1705-z.
201. You, M.; Chen, N.; Yang, Y.; Cheng, L.; He, H.; Cai, Y.; Liu, Y.; Liu, H.; Hong, G. The gut microbiota-brain axis in neurological disorders. *MedComm (2020)* **2024**, *5*, e656. https://doi.org/10.1002/mco2.656.
202. Zatorska, O. Impact of gut microbiota on the central nervous system relevance in neurodegenerative and psychiatric diseases. *Current Problems of Psychiatry* **2024**, *25*, 239–247.
203. Varesi, A.; Campagnoli, L.I.M.; Chirumbolo, S.; Candiano, B.; Carrara, A.; Ricevuti, G.; Esposito, C.; Pascale, A. The brain-gut-microbiota interplay in depression: A key to design innovative therapeutic approaches. *Pharmacol. Res.* **2023**, *192*, 106799. https://doi.org/10.1016/j.phrs.2023.106799.
204. Palepu, M.S.K.; Dandekar, M.P. Remodeling of microbiota gut-brain axis using psychobiotics in depression. *Eur. J. Pharmacol.* **2022**, *931*, 175171. https://doi.org/10.1016/j.ejphar.2022.175171.
205. Bhatt, S.; Kanoujia, J.; Mohana Lakshmi, S.; Patil, C.R.; Gupta, G.; Chellappan, D.K.; Dua, K. Role of Brain-Gut-Microbiota Axis in Depression: Emerging Therapeutic Avenues. *CNS Neurol. Disord. Drug Targets* **2023**, *22*, 276–288. https://doi.org/10.2174/1871527321666220329140804.
206. Generoso, J.S.; Giridharan, V.V.; Lee, J.; Macedo, D.; Barichello, T. The role of the microbiota-gut-brain axis in neuropsychiatric disorders. *Braz. J. Psychiatry* **2021**, *43*, 293–305. https://doi.org/10.1590/1516-4446-2020-0987.
207. Zhang, Q.; Bi, Y.; Zhang, B.; Jiang, Q.; Mou, C.K.; Lei, L.; Deng, Y.; Li, Y.; Yu, J.; Liu, W.; et al. Current landscape of fecal microbiota transplantation in treating depression. *Front. Immunol.* **2024**, *15*, 1416961. https://doi.org/10.3389/fimmu.2024.1416961.

 doi:10.20944/preprints202509.2303.v1

208. Qiao, Y.; Yu, J.; Zhang, Z.; Hou, Q.; Guo, Z.; Wang, Y. Regulatory effects of Lactobacillus zhachilii HBUAS52074(T) on depression-like behavior induced by chronic social defeat stress in mice: modulation of the gut microbiota. *Food Funct.* **2025**, *16*, 691–706. https://doi.org/10.1039/d4fo04542d.
209. Li, W.; Xu, M.; Liu, Y.; Zhang, S.; Wang, J.; Zhang, Z.; Xiao, G.; Wang, R.; Zhang, J.; Xue, H. Lactiplantibacillus plantarum GOLDGUT-HNU082 Alleviates CUMS-Induced Depressive-like Behaviors in Mice by Modulating the Gut Microbiota and Neurotransmitter Levels. *Foods* **2025**, *14*. https://doi.org/10.3390/foods14050813.
210. Xiong, R.G.; Li, J.; Cheng, J.; Zhou, D.D.; Wu, S.X.; Huang, S.Y.; Saimaiti, A.; Yang, Z.J.; Gan, R.Y.; Li, H.B. The Role of Gut Microbiota in Anxiety, Depression, and Other Mental Disorders as Well as the Protective Effects of Dietary Components. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15143258.
211. Sanada, K.; Nakajima, S.; Kurokawa, S.; Barceló-Soler, A.; Ikuse, D.; Hirata, A.; Yoshizawa, A.; Tomizawa, Y.; Salas-Valero, M.; Noda, Y.; et al. Gut microbiota and major depressive disorder: A systematic review and meta-analysis. *J. Affect. Disord.* **2020**, *266*, 1–13. https://doi.org/10.1016/j.jad.2020.01.102.
212. Ng, Q.X.; Lim, Y.L.; Yaow, C.Y.L.; Ng, W.K.; Thumboo, J.; Liew, T.M. Effect of Probiotic Supplementation on Gut Microbiota in Patients with Major Depressive Disorders: A Systematic Review. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15061351.
213. Hofmeister, M.; Clement, F.; Patten, S.; Li, J.; Dowsett, L.E.; Farkas, B.; Mastikhina, L.; Egunsola, O.; Diaz, R.; Cooke, N.C.A.; et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* **2021**, *9*, E1195–e1204. https://doi.org/10.9778/cmajo.20200283.
214. Esmeeta, A.; Adhikary, S.; Dharshnaa, V.; Swarnamughi, P.; Ummul Maqsummiya, Z.; Banerjee, A.; Pathak, S.; Duttaroy, A.K. Plant-derived bioactive compounds in colon cancer treatment: An updated review. *Biomed. Pharmacother.* **2022**, *153*, 113384. https://doi.org/10.1016/j.biopha.2022.113384.
215. Naoi, M.; Wu, Y.; Maruyama, W.; Shamoto-Nagai, M. Phytochemicals Modulate Biosynthesis and Function of Serotonin, Dopamine, and Norepinephrine for Treatment of Monoamine Neurotransmission-Related Psychiatric Diseases. *Int. J. Mol. Sci.* **2025**, *26*. https://doi.org/10.3390/ijms26072916.
216. Rahman, M.A.; Hannan, M.A.; Dash, R.; Rahman, M.H.; Islam, R.; Uddin, M.J.; Sohag, A.A.M.; Rahman, M.H.; Rhim, H. Phytochemicals as a Complement to Cancer Chemotherapy: Pharmacological Modulation of the Autophagy-Apoptosis Pathway. *Front. Pharmacol.* **2021**, *12*, 639628. https://doi.org/10.3389/fphar.2021.639628.
217. Phan, M.A.T.; Paterson, J.; Bucknall, M.; Arcot, J. Interactions between phytochemicals from fruits and vegetables: Effects on bioactivities and bioavailability. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 1310–1329. https://doi.org/10.1080/10408398.2016.1254595.
218. Zhao, Q.; Liu, J.; Chen, L.; Gao, Z.; Lin, M.; Wang, Y.; Xiao, Z.; Chen, Y.; Huang, X. Phytomedicine Fructus Aurantii-derived two absorbed compounds unlock antidepressant and prokinetic multi-functions via modulating 5-HT(3)/GHSR. *J. Ethnopharmacol.* **2024**, *323*, 117703. https://doi.org/10.1016/j.jep.2024.117703.
219. Cheng, S.; Zhu, Z.; Li, H.; Wang, W.; Jiang, Z.; Pan, F.; Liu, D.; Ho, R.C.M.; Ho, C.S.H. Rifaximin ameliorates depression-like behaviour in chronic unpredictable mild stress rats by regulating intestinal microbiota and hippocampal tryptophan metabolism. *J. Affect. Disord.* **2023**, *329*, 30–41. https://doi.org/10.1016/j.jad.2023.02.086.
220. Martínez-Rodríguez, A.; Rubio-Arias, J.; Ramos-Campo, D.J.; Reche-García, C.; Leyva-Vela, B.; Nadal-Nicolás, Y. Psychological and Sleep Effects of Tryptophan and Magnesium-Enriched Mediterranean Diet in Women with Fibromyalgia. *Int. J. Environ. Res. Public. Health* **2020**, *17*. https://doi.org/10.3390/ijerph17072227.
221. Patel, A.; Cheung, J. The effect of mediterranean diet and chrononutrition on sleep quality: a scoping review. *Nutr. J.* **2025**, *24*, 31. https://doi.org/10.1186/s12937-025-01095-8.
222. Scoditti, E.; Tumolo, M.R.; Garbarino, S. Mediterranean Diet on Sleep: A Health Alliance. *Nutrients* **2022**, *14*. https://doi.org/10.3390/nu14142998.
223. Godos, J.; Ferri, R.; Lanza, G.; Caraci, F.; Vistorte, A.O.R.; Yelamos Torres, V.; Grosso, G.; Castellano, S. Mediterranean Diet and Sleep Features: A Systematic Review of Current Evidence. *Nutrients* **2024**, *16*. https://doi.org/10.3390/nu16020282.

 doi:10.20944/preprints202509.2303.v1

224. Gantenbein, K.V.; Kanaka-Gantenbein, C. Mediterranean Diet as an Antioxidant: The Impact on Metabolic Health and Overall Wellbeing. *Nutrients* **2021**, *13*. https://doi.org/10.3390/nu13061951.
225. Godos, J.; Ferri, R.; Caraci, F.; Cosentino, F.I.I.; Castellano, S.; Galvano, F.; Grosso, G. Adherence to the Mediterranean Diet is Associated with Better Sleep Quality in Italian Adults. *Nutrients* **2019**, *11*. https://doi.org/10.3390/nu11050976.
226. Casas, I.; Nakaki, A.; Pascal, R.; Castro-Barquero, S.; Youssef, L.; Genero, M.; Benitez, L.; Larroya, M.; Boutet, M.L.; Casu, G.; et al. Effects of a Mediterranean Diet Intervention on Maternal Stress, Well-Being, and Sleep Quality throughout Gestation-The IMPACT-BCN Trial. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15102362.
227. Booij, L.; Merens, W.; Markus, C.R.; Van der Does, A.J. Diet rich in alpha-lactalbumin improves memory in unmedicated recovered depressed patients and matched controls. *J. Psychopharmacol.* **2006**, *20*, 526–535. https://doi.org/10.1177/0269881105057466.
228. Markus, C.R.; Olivier, B.; Panhuysen, G.E.; Van Der Gugten, J.; Alles, M.S.; Tuiten, A.; Westenberg, H.G.; Fekkes, D.; Koppeschaar, H.F.; de Haan, E.E. The bovine protein alpha-lactalbumin increases the plasma ratio of tryptophan to the other large neutral amino acids, and in vulnerable subjects raises brain serotonin activity, reduces cortisol concentration, and improves mood under stress. *Am. J. Clin. Nutr.* **2000**, *71*, 1536–1544. https://doi.org/10.1093/ajcn/71.6.1536.
229. Procópio Pinheiro, R.; Gaubeur, M.A.; Itezerote, A.M.; Saleh, S.O.; Hojaij, F.; Andrade, M.; Jacomo, A.L.; Akamatsu, F.E. Anatomical Study of the Innervation of the Masseter Muscle and Its Correlation with Myofascial Trigger Points. *J. Pain. Res.* **2020**, *13*, 3217–3226. https://doi.org/10.2147/jpr.S265717.
230. Porter, R.J.; Phipps, A.J.; Gallagher, P.; Scott, A.; Stevenson, P.S.; O'Brien, J.T. Effects of acute tryptophan depletion on mood and cognitive functioning in older recovered depressed subjects. *The American journal of geriatric psychiatry* **2005**, *13*, 607–615.
231. Badrasawi, M.M.; Shahar, S.; Abd Manaf, Z.; Haron, H. Effect of Talbinah food consumption on depressive symptoms among elderly individuals in long term care facilities, randomized clinical trial. *Clin. Interv. Aging* **2013**, *8*, 279–285. https://doi.org/10.2147/cia.S37586.
232. Jangid, P.; Malik, P.; Singh, P.; Sharma, M.; Gulia, A.K. Comparative study of efficacy of l-5-hydroxytryptophan and fluoxetine in patients presenting with first depressive episode. *Asian J. Psychiatr.* **2013**, *6*, 29–34. https://doi.org/10.1016/j.ajp.2012.05.011.
233. Meloni, M.; Puligheddu, M.; Carta, M.; Cannas, A.; Figorilli, M.; Defazio, G. Efficacy and safety of 5-hydroxytryptophan on depression and apathy in Parkinson's disease: a preliminary finding. *Eur. J. Neurol.* **2020**, *27*, 779–786. https://doi.org/10.1111/ene.14179.
234. Firk, C.; Markus, C.R. Mood and cortisol responses following tryptophan-rich hydrolyzed protein and acute stress in healthy subjects with high and low cognitive reactivity to depression. *Clin. Nutr.* **2009**, *28*, 266–271. https://doi.org/10.1016/j.clnu.2009.03.002.
235. Benkelfat, C.; Ellenbogen, M.A.; Dean, P.; Palmour, R.M.; Young, S.N. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. *Arch. Gen. Psychiatry* **1994**, *51*, 687–697. https://doi.org/10.1001/archpsyc.1994.03950090019003.
236. Bruce, K.R.; Steiger, H.; Young, S.N.; Kin, N.M.; Israël, M.; Lévesque, M. Impact of acute tryptophan depletion on mood and eating-related urges in bulimic and nonbulimic women. *J. Psychiatry Neurosci.* **2009**, *34*, 376–382.
237. Murphy, S.E.; Longhitano, C.; Ayres, R.E.; Cowen, P.J.; Harmer, C.J. Tryptophan supplementation induces a positive bias in the processing of emotional material in healthy female volunteers. *Psychopharmacology (Berl)* **2006**, *187*, 121–130. https://doi.org/10.1007/s00213-006-0401-8.
238. Rueda, G.H.; Causada-Calo, N.; Borojevic, R.; Nardelli, A.; Pinto-Sanchez, M.I.; Constante, M.; Libertucci, J.; Mohan, V.; Langella, P.; Loonen, L.M.P.; et al. Oral tryptophan activates duodenal aryl hydrocarbon receptor in healthy subjects: a crossover randomized controlled trial. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2024**, *326*, G687–g696. https://doi.org/10.1152/ajpgi.00306.2023.
239. Cerit, H.; Schuur, R.J.; de Bruijn, E.R.; Van der Does, W. Tryptophan supplementation and the response to unfairness in healthy volunteers. *Front. Psychol.* **2015**, *6*, 1012. https://doi.org/10.3389/fpsyg.2015.01012.

 doi:10.20944/preprints202509.2303.v1

240. Markus, C.R.; Firk, C.; Gerhardt, C.; Kloek, J.; Smolders, G.F. Effect of different tryptophan sources on amino acids availability to the brain and mood in healthy volunteers. *Psychopharmacology (Berl)* **2008**, *201*, 107–114. https://doi.org/10.1007/s00213-008-1254-0.
241. Bravo, R.; Matito, S.; Cubero, J.; Paredes, S.D.; Franco, L.; Rivero, M.; Rodríguez, A.B.; Barriga, C. Tryptophan-enriched cereal intake improves nocturnal sleep, melatonin, serotonin, and total antioxidant capacity levels and mood in elderly humans. *Age (Dordr)* **2013**, *35*, 1277–1285. https://doi.org/10.1007/s11357-012-9419-5.
242. Rondanelli, M.; Opizzi, A.; Faliva, M.; Mozzoni, M.; Antoniello, N.; Cazzola, R.; Savarè, R.; Cerutti, R.; Grossi, E.; Cestaro, B. Effects of a diet integration with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan in elderly patients suffering from mild cognitive impairment. *Nutr. Neurosci.* **2012**, *15*, 46–54. https://doi.org/10.1179/1476830511y.0000000032.
243. Connell, N.J.; Grevendonk, L.; Fealy, C.E.; Moonen-Kornips, E.; Bruls, Y.M.H.; Schrauwen-Hinderling, V.B.; de Vogel, J.; Hageman, R.; Geurts, J.; Zapata-Perez, R.; et al. NAD+-Precursor Supplementation With L-Tryptophan, Nicotinic Acid, and Nicotinamide Does Not Affect Mitochondrial Function or Skeletal Muscle Function in Physically Compromised Older Adults. *J. Nutr.* **2021**, *151*, 2917–2931. https://doi.org/10.1093/jn/nxab193.
244. Chojnacki, C.; Gąsiorowska, A.; Popławski, T.; Konrad, P.; Chojnacki, M.; Fila, M.; Blasiak, J. Beneficial Effect of Increased Tryptophan Intake on Its Metabolism and Mental State of the Elderly. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15040847.
245. Lieberman, H.R.; Agarwal, S.; Fulgoni, V.L., 3rd. Tryptophan Intake in the US Adult Population Is Not Related to Liver or Kidney Function but Is Associated with Depression and Sleep Outcomes. *J. Nutr.* **2016**, *146*, 2609s–2615s. https://doi.org/10.3945/jn.115.226969.
246. Nematolahi, P.; Mehrabani, M.; Karami-Mohajeri, S.; Dabaghzadeh, F. Effects of Rosmarinus officinalis L. on memory performance, anxiety, depression, and sleep quality in university students: A randomized clinical trial. *Complement. Ther. Clin. Pract.* **2018**, *30*, 24–28. https://doi.org/10.1016/j.ctcp.2017.11.004.
247. Ghasemzadeh Rahbardar, M.; Hosseinzadeh, H. Therapeutic effects of rosemary (Rosmarinus officinalis L.) and its active constituents on nervous system disorders. *Iran. J. Basic. Med. Sci.* **2020**, *23*, 1100–1112. https://doi.org/10.22038/ijbms.2020.45269.10541.
248. Li, T.; Wang, W.; Guo, Q.; Li, J.; Tang, T.; Wang, Y.; Liu, D.; Yang, K.; Li, J.; Deng, K.; et al. Rosemary (Rosmarinus officinalis L.) hydrosol based on serotonergic synapse for insomnia. *J. Ethnopharmacol.* **2024**, *318*, 116984. https://doi.org/10.1016/j.jep.2023.116984.
249. Kenda, M.; Kočevar Glavač, N.; Nagy, M.; Sollner Dolenc, M. Medicinal Plants Used for Anxiety, Depression, or Stress Treatment: An Update. *Molecules* **2022**, *27*. https://doi.org/10.3390/molecules27186021.
250. Can, S.; Yildirim Usta, Y.; Yildiz, S.; Tayfun, K. The effect of lavender and rosemary aromatherapy application on cognitive functions, anxiety, and sleep quality in the elderly with diabetes. *Explore (NY)* **2024**, *20*, 103033. https://doi.org/10.1016/j.explore.2024.103033.
251. Ghasemi, A.; Sharafabadi, F.M.; Marani, E. The Effect of Inhalation Aromatherapy with Essential Oils of Various Plants on Anxiety and Sleep Quality in Diabetic Patients: A Review Study. *Iranian journal of diabetes and obesity* **2025**.
252. Caballero-Gallardo, K.; Quintero-Rincón, P.; Olivero-Verbel, J. Aromatherapy and Essential Oils: Holistic Strategies in Complementary and Alternative Medicine for Integral Wellbeing. *Plants (Basel)* **2025**, *14*. https://doi.org/10.3390/plants14030400.
253. Mathews, I.M.; Eastwood, J.; Lamport, D.J.; Cozannet, R.L.; Fanca-Berthon, P.; Williams, C.M. Clinical Efficacy and Tolerability of Lemon Balm (Melissa officinalis L.) in Psychological Well-Being: A Review. *Nutrients* **2024**, *16*. https://doi.org/10.3390/nu16203545.
254. Lu, C.; Wei, Z.; Jiang, N.; Chen, Y.; Wang, Y.; Li, S.; Wang, Q.; Fan, B.; Liu, X.; Wang, F. Soy isoflavones protects against cognitive deficits induced by chronic sleep deprivation via alleviating oxidative stress and suppressing neuroinflammation. *Phytother. Res.* **2022**, *36*, 2072–2080. https://doi.org/10.1002/ptr.7354.
255. Mendonça, C.R.; Manhães-de-Castro, R.; de Santana, B.; Olegário da Silva, L.; Toscano, A.E.; Guzmán-Quevedo, O.; Galindo, L.C.M. Effects of flavonols on emotional behavior and compounds of the

 doi:10.20944/preprints202509.2303.v1

serotonergic system: A preclinical systematic review. *Eur. J. Pharmacol.* **2022**, *916*, 174697. https://doi.org/10.1016/j.ejphar.2021.174697.

256. Hamsalakshmi; Alex, A.M.; Arehally Marappa, M.; Joghee, S.; Chidambaram, S.B. Therapeutic benefits of flavonoids against neuroinflammation: a systematic review. *Inflammopharmacology* **2022**, *30*, 111–136. https://doi.org/10.1007/s10787-021-00895-8.
257. Scuto, M.; Majzúnová, M.; Torcitto, G.; Antonuzzo, S.; Rampulla, F.; Di Fatta, E.; Trovato Salinaro, A. Functional Food Nutrients, Redox Resilience Signaling and Neurosteroids for Brain Health. *Int. J. Mol. Sci.* **2024**, *25*. https://doi.org/10.3390/ijms252212155.
258. Zhang, Z.; Li, X.; Li, F.; An, L. Berberine alleviates postoperative cognitive dysfunction by suppressing neuroinflammation in aged mice. *Int. Immunopharmacol.* **2016**, *38*, 426–433. https://doi.org/10.1016/j.intimp.2016.06.031.
259. Premkumar, L.S. Transient receptor potential channels as targets for phytochemicals. *ACS Chem. Neurosci.* **2014**, *5*, 1117–1130. https://doi.org/10.1021/cn500094a.
260. Pham, D.C.; Shibu, M.A.; Mahalakshmi, B.; Velmurugan, B.K. Effects of phytochemicals on cellular signaling: reviewing their recent usage approaches. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 3522–3546. https://doi.org/10.1080/10408398.2019.1699014.
261. Rao, P.P. Phytochemicals in Obesity Management: Mechanisms and Clinical Perspectives. *Curr. Nutr. Rep.* **2025**, *14*, 17. https://doi.org/10.1007/s13668-025-00611-w.
262. Sarris, J.; Ravindran, A.; Yatham, L.N.; Marx, W.; Rucklidge, J.J.; McIntyre, R.S.; Akhondzadeh, S.; Benedetti, F.; Caneo, C.; Cramer, H.; et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce. *World J. Biol. Psychiatry* **2022**, *23*, 424–455. https://doi.org/10.1080/15622975.2021.2013041.
263. Hao, W.Z.; Ma, Q.Y.; Tao, G.; Huang, J.Q.; Chen, J.X. Oral coniferyl ferulate attenuated depression symptoms in mice via reshaping gut microbiota and microbial metabolism. *Food Funct.* **2021**, *12*, 12550–12564. https://doi.org/10.1039/d1fo02655k.
264. Mannino, G.; Serio, G.; Gaglio, R.; Maffei, M.E.; Settanni, L.; Di Stefano, V.; Gentile, C. Biological Activity and Metabolomics of Griffonia simplicifolia Seeds Extracted with Different Methodologies. *Antioxidants (Basel)* **2023**, *12*. https://doi.org/10.3390/antiox12091709.
265. Ribas, R.; Oliveira, D.; Silva, P. The different roles of Griffonia simplicifolia in the treatment of depression: a narrative review. *Int. J. Complement. Alt. Med.* **2021**, *14*, 167–172.
266. Moharir, Y. 5-HTP for Improved Sleep, Mood and Weight Loss.
267. Fellows, L.E.; Bell, E.A. 5-Hydroxy-L-tryptophan, 5-hydroxytryptamine and L-tryptophan-5-hydroxylase in Griffonia simplicifolia. *Phytochemistry* **1970**, *9*, 2389–2396.
268. Vigliante, I.; Mannino, G.; Maffei, M.E. Chemical Characterization and DNA Fingerprinting of Griffonia simplicifolia Baill. *Molecules* **2019**, *24*. https://doi.org/10.3390/molecules24061032.
269. Fijałkowska, A.; Jędrejko, K.; Sułkowska-Ziaja, K.; Ziaja, M.; Kała, K.; Muszyńska, B. Edible Mushrooms as a Potential Component of Dietary Interventions for Major Depressive Disorder. *Foods* **2022**, *11*. https://doi.org/10.3390/foods11101489.
270. Lu, C.; Wei, Z.; Wang, Y.; Li, S.; Tong, L.; Liu, X.; Fan, B.; Wang, F. Soy isoflavones alleviate lipopolysaccharide-induced depressive-like behavior by suppressing neuroinflammation, mediating tryptophan metabolism and promoting synaptic plasticity. *Food Funct.* **2022**, *13*, 9513–9522. https://doi.org/10.1039/d2fo01437h.
271. Lu, C.; Gao, R.; Zhang, Y.; Jiang, N.; Chen, Y.; Sun, J.; Wang, Q.; Fan, B.; Liu, X.; Wang, F. S-equol, a metabolite of dietary soy isoflavones, alleviates lipopolysaccharide-induced depressive-like behavior in mice by inhibiting neuroinflammation and enhancing synaptic plasticity. *Food Funct.* **2021**, *12*, 5770–5778. https://doi.org/10.1039/d1fo00547b.
272. McLaren, S.; Seidler, K.; Neil, J. Investigating the Role of 17β-Estradiol on the Serotonergic System, Targeting Soy Isoflavones as a Strategy to Reduce Menopausal Depression: A Mechanistic Review. *J. Am. Nutr. Assoc.* **2024**, *43*, 221–235. https://doi.org/10.1080/27697061.2023.2255237.

 doi:10.20944/preprints202509.2303.v1

273. Sekikawa, A.; Wharton, W.; Butts, B.; Veliky, C.V.; Garfein, J.; Li, J.; Goon, S.; Fort, A.; Li, M.; Hughes, T.M. Potential Protective Mechanisms of S-equol, a Metabolite of Soy Isoflavone by the Gut Microbiome, on Cognitive Decline and Dementia. *Int. J. Mol. Sci.* **2022**, *23*. https://doi.org/10.3390/ijms231911921.
274. Cui, C.; Birru, R.; Snitz, B.E.; Ihara, M.; Lopresti, B.J.; Aizenstein, H.J.; Lopez, O.L.; Mathis, C.; Miyamoto, Y.; Kuller, L.H. P3--615: EFFECTS OF SOY ISOFLAVONES ON COGNITIVE FUNCTION: A SYSTEMATIC REVIEW AND META--ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *Alzheimer's & Dementia* **2018**, *14*, P1365–P1366.
275. Huang, M.; He, Y.; Tian, L.; Yu, L.; Cheng, Q.; Li, Z.; Gao, L.; Gao, S.; Yu, C. Gut microbiota-SCFAs-brain axis associated with the antidepressant activity of berberine in CUMS rats. *J. Affect. Disord.* **2023**, *325*, 141–150. https://doi.org/10.1016/j.jad.2022.12.166.
276. Lu, Y.; Yu, X.; Wang, Z.; Kong, L.; Jiang, Z.; Shang, R.; Zhong, X.; Lv, S.; Zhang, G.; Gao, H.; et al. Microbiota-gut-brain axis: Natural antidepressants molecular mechanism. *Phytomedicine* **2024**, *134*, 156012. https://doi.org/10.1016/j.phymed.2024.156012.
277. Xiao, W.; Su, J.; Gao, X.; Yang, H.; Weng, R.; Ni, W.; Gu, Y. The microbiota-gut-brain axis participates in chronic cerebral hypoperfusion by disrupting the metabolism of short-chain fatty acids. *Microbiome* **2022**, *10*, 62. https://doi.org/10.1186/s40168-022-01255-6.
278. Qian, X.H.; Xie, R.Y.; Liu, X.L.; Chen, S.D.; Tang, H.D. Mechanisms of Short-Chain Fatty Acids Derived from Gut Microbiota in Alzheimer's Disease. *Aging Dis.* **2022**, *13*, 1252–1266. https://doi.org/10.14336/ad.2021.1215.
279. Cheng, J.; Hu, H.; Ju, Y.; Liu, J.; Wang, M.; Liu, B.; Zhang, Y. Gut microbiota-derived short-chain fatty acids and depression: deep insight into biological mechanisms and potential applications. *Gen. Psychiatr.* **2024**, *37*, e101374. https://doi.org/10.1136/gpsych-2023-101374.
280. Zhao, Z.X.; Fu, J.; Ma, S.R.; Peng, R.; Yu, J.B.; Cong, L.; Pan, L.B.; Zhang, Z.G.; Tian, H.; Che, C.T.; et al. Gut-brain axis metabolic pathway regulates antidepressant efficacy of albiflorin. *Theranostics* **2018**, *8*, 5945–5959. https://doi.org/10.7150/thno.28068.
281. Wu, D.; Chen, Q.; Chen, X.; Han, F.; Chen, Z.; Wang, Y. The blood-brain barrier: structure, regulation, and drug delivery. *Signal Transduct. Target. Ther.* **2023**, *8*, 217. https://doi.org/10.1038/s41392-023-01481-w.
282. Qin, Z.; Shi, D.D.; Li, W.; Cheng, D.; Zhang, Y.D.; Zhang, S.; Tsoi, B.; Zhao, J.; Wang, Z.; Zhang, Z.J. Berberine ameliorates depression-like behaviors in mice via inhibiting NLRP3 inflammasome-mediated neuroinflammation and preventing neuroplasticity disruption. *J. Neuroinflammation* **2023**, *20*, 54. https://doi.org/10.1186/s12974-023-02744-7.
283. Tang, C.F.; Wang, C.Y.; Wang, J.H.; Wang, Q.N.; Li, S.J.; Wang, H.O.; Zhou, F.; Li, J.M. Short-Chain Fatty Acids Ameliorate Depressive-like Behaviors of High Fructose-Fed Mice by Rescuing Hippocampal Neurogenesis Decline and Blood-Brain Barrier Damage. *Nutrients* **2022**, *14*. https://doi.org/10.3390/nu14091882.
284. Dudek, K.A.; Dion-Albert, L.; Lebel, M.; LeClair, K.; Labrecque, S.; Tuck, E.; Ferrer Perez, C.; Golden, S.A.; Tamminga, C.; Turecki, G.; et al. Molecular adaptations of the blood-brain barrier promote stress resilience vs. depression. *Proc. Natl. Acad. Sci. U S A* **2020**, *117*, 3326–3336. https://doi.org/10.1073/pnas.1914655117.
285. Knox, E.G.; Aburto, M.R.; Clarke, G.; Cryan, J.F.; O'Driscoll, C.M. The blood-brain barrier in aging and neurodegeneration. *Mol. Psychiatry* **2022**, *27*, 2659–2673. https://doi.org/10.1038/s41380-022-01511-z.
286. Grabska-Kobyłecka, I.; Szpakowski, P.; Król, A.; Książek-Winiarek, D.; Kobyłecki, A.; Głąbiński, A.; Nowak, D. Polyphenols and Their Impact on the Prevention of Neurodegenerative Diseases and Development. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15153454.
287. Jaeger, B.N.; Parylak, S.L.; Gage, F.H. Mechanisms of dietary flavonoid action in neuronal function and neuroinflammation. *Mol. Aspects Med.* **2018**, *61*, 50–62. https://doi.org/10.1016/j.mam.2017.11.003.
288. Calderaro, A.; Patanè, G.T.; Tellone, E.; Barreca, D.; Ficarra, S.; Misiti, F.; Laganà, G. The Neuroprotective Potentiality of Flavonoids on Alzheimer's Disease. *Int. J. Mol. Sci.* **2022**, *23*. https://doi.org/10.3390/ijms232314835.
289. Pontifex, M.G.; Malik, M.; Connell, E.; Müller, M.; Vauzour, D. Citrus Polyphenols in Brain Health and Disease: Current Perspectives. *Front. Neurosci.* **2021**, *15*, 640648. https://doi.org/10.3389/fnins.2021.640648.

290. Martínez-Coria, H.; Arrieta-Cruz, I.; Gutiérrez-Juárez, R.; López-Valdés, H.E. Anti-Inflammatory Effects of Flavonoids in Common Neurological Disorders Associated with Aging. *Int. J. Mol. Sci.* **2023**, *24*. https://doi.org/10.3390/ijms24054297.
291. Bakoyiannis, I.; Daskalopoulou, A.; Pergialiotis, V.; Perrea, D. Phytochemicals and cognitive health: Are flavonoids doing the trick? *Biomed. Pharmacother.* **2019**, *109*, 1488–1497. https://doi.org/10.1016/j.biopha.2018.10.086.
292. Zagoskina, N.V.; Zubova, M.Y.; Nechaeva, T.L.; Kazantseva, V.V.; Goncharuk, E.A.; Katanskaya, V.M.; Baranova, E.N.; Aksenova, M.A. Polyphenols in Plants: Structure, Biosynthesis, Abiotic Stress Regulation, and Practical Applications (Review). *Int. J. Mol. Sci.* **2023**, *24*. https://doi.org/10.3390/ijms241813874.
293. Moosavi, F.; Hosseini, R.; Saso, L.; Firuzi, O. Modulation of neurotrophic signaling pathways by polyphenols. *Drug Des. Devel Ther.* **2016**, *10*, 23–42. https://doi.org/10.2147/dddt.S96936.
294. Sharma, A.; Shahzad, B.; Rehman, A.; Bhardwaj, R.; Landi, M.; Zheng, B. Response of Phenylpropanoid Pathway and the Role of Polyphenols in Plants under Abiotic Stress. *Molecules* **2019**, *24*. https://doi.org/10.3390/molecules24132452.
295. Carey, C.C.; Lucey, A.; Doyle, L. Flavonoid Containing Polyphenol Consumption and Recovery from Exercise-Induced Muscle Damage: A Systematic Review and Meta-Analysis. *Sports Med.* **2021**, *51*, 1293–1316. https://doi.org/10.1007/s40279-021-01440-x.
296. Shi, J.; Du, P.; Xie, Q.; Wang, N.; Li, H.; Smith, E.E.; Li, C.; Liu, F.; Huo, G.; Li, B. Protective effects of tryptophan-catabolizing Lactobacillus plantarum KLDS 1.0386 against dextran sodium sulfate-induced colitis in mice. *Food Funct.* **2020**, *11*, 10736–10747. https://doi.org/10.1039/d0fo02622k.
297. Friedman, M. Analysis, Nutrition, and Health Benefits of Tryptophan. *Int. J. Tryptophan Res.* **2018**, *11*, 1178646918802282. https://doi.org/10.1177/1178646918802282.
298. Ferrer, L.; Elsaraf, M.; Mindt, M.; Wendisch, V.F. l-Serine Biosensor-Controlled Fermentative Production of l-Tryptophan Derivatives by Corynebacterium glutamicum. *Biology (Basel)* **2022**, *11*. https://doi.org/10.3390/biology11050744.
299. Guo, Y.W.; Liu, X.J.; Yuan, J.; Li, H.J.; Mahmud, T.; Hong, M.J.; Yu, J.C.; Lan, W.J. l-Tryptophan Induces a Marine-Derived Fusarium sp. to Produce Indole Alkaloids with Activity against the Zika Virus. *J. Nat. Prod.* **2020**, *83*, 3372–3380. https://doi.org/10.1021/acs.jnatprod.0c00717.
300. Henarejos-Escudero, P.; Méndez-García, F.F.; Hernández-García, S.; Martínez-Rodríguez, P.; Gandía-Herrero, F. Design, Synthesis and Gene Modulation Insights into Pigments Derived from Tryptophan-Betaxanthin, Which Act against Tumor Development in Caenorhabditis elegans. *Int. J. Mol. Sci.* **2023**, *25*. https://doi.org/10.3390/ijms25010063.
301. Wang, Y.; Chen, X.; Chen, Q.; Zhou, N.; Wang, X.; Zhang, A.; Chen, K.; Ouyang, P. Construction of cell factory capable of efficiently converting L-tryptophan into 5-hydroxytryptamine. *Microb. Cell Fact.* **2022**, *21*, 47. https://doi.org/10.1186/s12934-022-01745-0.
302. Shaw, K.; Turner, J.; Del Mar, C. Tryptophan and 5-hydroxytryptophan for depression. *Cochrane Database Syst. Rev.* **2002**, Cd003198. https://doi.org/10.1002/14651858.Cd003198.
303. Herrington, R.N.; Bruce, A.; Johnstone, E.C. Comparative trial of L-tryptophan and E.C.T. in severe depressive illness. *Lancet* **1974**, *2*, 731–734. https://doi.org/10.1016/s0140-6736(74)90936-2.
304. Kikuchi, A.M.; Tanabe, A.; Iwahori, Y. A systematic review of the effect of L-tryptophan supplementation on mood and emotional functioning. *J. Diet. Suppl.* **2021**, *18*, 316–333. https://doi.org/10.1080/19390211.2020.1746725.
305. Tian, P.; Chen, Y.; Zhu, H.; Wang, L.; Qian, X.; Zou, R.; Zhao, J.; Zhang, H.; Qian, L.; Wang, Q.; et al. Bifidobacterium breve CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: A randomized clinical trial. *Brain Behav. Immun.* **2022**, *100*, 233–241. https://doi.org/10.1016/j.bbi.2021.11.023.
306. Liang, X.; Su, T.; Wu, P.; Dai, Y.; Chen, Y.; Wang, Q.; Cao, C.; Chen, F.; Wang, Q.; Wang, S. Identification of paeoniflorin from Paeonia lactiflora pall. As an inhibitor of tryptophan 2,3-dioxygenase and assessment of its pharmacological effects on depressive mice. *J. Ethnopharmacol.* **2023**, *317*, 116714. https://doi.org/10.1016/j.jep.2023.116714.

 doi:10.20944/preprints202509.2303.v1

307. Kałużna-Czaplińska, J.; Gątarek, P.; Chirumbolo, S.; Chartrand, M.S.; Bjørklund, G. How important is tryptophan in human health? *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 72–88. https://doi.org/10.1080/10408398.2017.1357534.
308. Sutanto, C.N.; Loh, W.W.; Toh, D.W.K.; Lee, D.P.S.; Kim, J.E. Association Between Dietary Protein Intake and Sleep Quality in Middle-Aged and Older Adults in Singapore. *Front. Nutr.* **2022**, *9*, 832341. https://doi.org/10.3389/fnut.2022.832341.
309. Sutanto, C.N.; Loh, W.W.; Kim, J.E. The impact of tryptophan supplementation on sleep quality: a systematic review, meta-analysis, and meta-regression. *Nutr. Rev.* **2022**, *80*, 306–316. https://doi.org/10.1093/nutrit/nuab027.
310. Mohajeri, M.H.; Wittwer, J.; Vargas, K.; Hogan, E.; Holmes, A.; Rogers, P.J.; Goralczyk, R.; Gibson, E.L. Chronic treatment with a tryptophan-rich protein hydrolysate improves emotional processing, mental energy levels and reaction time in middle-aged women. *Br. J. Nutr.* **2015**, *113*, 350–365. https://doi.org/10.1017/s0007114514003754.
311. Chen, M.; Liu, Y.; Xiong, S.; Wu, M.; Li, B.; Ruan, Z.; Hu, X. Dietary l-tryptophan alleviated LPS-induced intestinal barrier injury by regulating tight junctions in a Caco-2 cell monolayer model. *Food Funct.* **2019**, *10*, 2390–2398. https://doi.org/10.1039/c9fo00123a.
312. Scott, S.A.; Fu, J.; Chang, P.V. Microbial tryptophan metabolites regulate gut barrier function via the aryl hydrocarbon receptor. *Proc. Natl. Acad. Sci. U S A* **2020**, *117*, 19376–19387. https://doi.org/10.1073/pnas.2000047117.
313. Liu, W.; Mi, S.; Ruan, Z.; Li, J.; Shu, X.; Yao, K.; Jiang, M.; Deng, Z. Dietary Tryptophan Enhanced the Expression of Tight Junction Protein ZO-1 in Intestine. *J. Food Sci.* **2017**, *82*, 562–567. https://doi.org/10.1111/1750-3841.13603.
314. Liang, H.; Dai, Z.; Kou, J.; Sun, K.; Chen, J.; Yang, Y.; Wu, G.; Wu, Z. Dietary l-Tryptophan Supplementation Enhances the Intestinal Mucosal Barrier Function in Weaned Piglets: Implication of Tryptophan-Metabolizing Microbiota. *Int. J. Mol. Sci.* **2018**, *20*. https://doi.org/10.3390/ijms20010020.
315. Taleb, S. Tryptophan Dietary Impacts Gut Barrier and Metabolic Diseases. *Front. Immunol.* **2019**, *10*, 2113. https://doi.org/10.3389/fimmu.2019.02113.
316. Gao, J.; Xu, K.; Liu, H.; Liu, G.; Bai, M.; Peng, C.; Li, T.; Yin, Y. Impact of the Gut Microbiota on Intestinal Immunity Mediated by Tryptophan Metabolism. *Front. Cell Infect. Microbiol.* **2018**, *8*, 13. https://doi.org/10.3389/fcimb.2018.00013.
317. Dai, H.; Yang, H.; Wang, R.; Wang, X.; Zhang, X. Modulating Gut Microbiota with Dietary Components: A Novel Strategy for Cancer-Depression Comorbidity Management. *Nutrients* **2025**, *17*. https://doi.org/10.3390/nu17091505.
318. Trzeciak, P.; Herbet, M. Role of the Intestinal Microbiome, Intestinal Barrier and Psychobiotics in Depression. *Nutrients* **2021**, *13*. https://doi.org/10.3390/nu13030927.
319. Nunes, Y.C.; Mendes, N.M.; Pereira de Lima, E.; Chehadi, A.C.; Lamas, C.B.; Haber, J.F.S.; Dos Santos Bueno, M.; Araújo, A.C.; Catharin, V.C.S.; Detregiachi, C.R.P.; et al. Curcumin: A Golden Approach to Healthy Aging: A Systematic Review of the Evidence. *Nutrients* **2024**, *16*. https://doi.org/10.3390/nu16162721.
320. Nabavi, S.M.; Daglia, M.; Braidy, N.; Nabavi, S.F. Natural products, micronutrients, and nutraceuticals for the treatment of depression: A short review. *Nutr. Neurosci.* **2017**, *20*, 180–194. https://doi.org/10.1080/1028415x.2015.1103461.
321. Fernstrom, J.D. Effects and side effects associated with the non-nutritional use of tryptophan by humans. *J. Nutr.* **2012**, *142*, 2236s–2244s. https://doi.org/10.3945/jn.111.157065.
322. Hiratsuka, C.; Fukuwatari, T.; Sano, M.; Saito, K.; Sasaki, S.; Shibata, K. Supplementing healthy women with up to 5.0 g/d of L-tryptophan has no adverse effects. *J. Nutr.* **2013**, *143*, 859–866. https://doi.org/10.3945/jn.112.173823.
323. Zhu, X.; Tao, Q.; Sun-Waterhouse, D.; Li, W.; Liu, S.; Cui, C. γ-[Glu]n-Trp ameliorates anxiety/depression-like behaviors and its anti-inflammatory effect in an animal model of anxiety/depression. *Food Funct.* **2019**, *10*, 5544–5554. https://doi.org/10.1039/c9fo01467e.

 doi:10.20944/preprints202509.2303.v1

324. Medsger, T.A., Jr. Tryptophan-induced eosinophilia-myalgia syndrome. *N. Engl. J. Med.* **1990**, *322*, 926–928. https://doi.org/10.1056/nejm199003293221309.
325. Ko, S.M.; Park, J.E.; Heo, I.K.; Shin, Y.U.; Kim, Y.H.; Son, W.C. Safety concerns regarding impurities in L-Tryptophan associated with eosinophilia myalgia syndrome. *Food Chem. Toxicol.* **2023**, *179*, 113946. https://doi.org/10.1016/j.fct.2023.113946.
326. Mayeno, A.N.; Gleich, G.J. Eosinophilia-myalgia syndrome and tryptophan production: a cautionary tale. *Trends Biotechnol.* **1994**, *12*, 346–352. https://doi.org/10.1016/0167-7799(94)90035-3.
327. Hill, R.H., Jr.; Caudill, S.P.; Philen, R.M.; Bailey, S.L.; Flanders, W.D.; Driskell, W.J.; Kamb, M.L.; Needham, L.L.; Sampson, E.J. Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. *Arch. Environ. Contam. Toxicol.* **1993**, *25*, 134–142. https://doi.org/10.1007/bf00230724.
328. Eidson, M.; Philen, R.M.; Sewell, C.M.; Voorhees, R.; Kilbourne, E.M. L-tryptophan and eosinophilia-myalgia syndrome in New Mexico. *Lancet* **1990**, *335*, 645–648. https://doi.org/10.1016/0140-6736(90)90421-z.
329. Hertzman, P.A.; Blevins, W.L.; Mayer, J.; Greenfield, B.; Ting, M.; Gleich, G.J. Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. *N. Engl. J. Med.* **1990**, *322*, 869–873. https://doi.org/10.1056/nejm199003293221301.
330. Das, Y.T.; Bagchi, M.; Bagchi, D.; Preuss, H.G. Safety of 5-hydroxy-L-tryptophan. *Toxicol. Lett.* **2004**, *150*, 111–122. https://doi.org/10.1016/j.toxlet.2003.12.070.
331. Martin, R.W.; Duffy, J.; Engel, A.G.; Lie, J.T.; Bowles, C.A.; Moyer, T.P.; Gleich, G.J. The clinical spectrum of the eosinophilia-myalgia syndrome associated with L-tryptophan ingestion. Clinical features in 20 patients and aspects of pathophysiology. *Ann. Intern. Med.* **1990**, *113*, 124–134. https://doi.org/10.7326/0003-4819-113-2-124.
332. Verity, M.A.; Bulpitt, K.J.; Paulus, H.E. Neuromuscular manifestations of L-tryptophan-associated eosinophilia-myalgia syndrome: a histomorphologic analysis of 14 patients. *Hum. Pathol.* **1991**, *22*, 3–11. https://doi.org/10.1016/0046-8177(91)90054-s.
333. Munir, S.; Shahid, A.; Aslam, B.; Ashfaq, U.A.; Akash, M.S.H.; Ali, M.A.; Almatroudi, A.; Allemailem, K.S.; Rajoka, M.S.R.; Khurshid, M. The Therapeutic Prospects of Naturally Occurring and Synthetic Indole Alkaloids for Depression and Anxiety Disorders. *Evid. Based Complement. Alternat Med.* **2020**, *2020*, 8836983. https://doi.org/10.1155/2020/8836983.
334. Kanova, M.; Kohout, P. Serotonin-Its Synthesis and Roles in the Healthy and the Critically Ill. *Int. J. Mol. Sci.* **2021**, *22*. https://doi.org/10.3390/ijms22094837.
335. Guzel, T.; Mirowska-Guzel, D. The Role of Serotonin Neurotransmission in Gastrointestinal Tract and Pharmacotherapy. *Molecules* **2022**, *27*. https://doi.org/10.3390/molecules27051680.
336. Mokhtari, T. Targeting autophagy and neuroinflammation pathways with plant-derived natural compounds as potential antidepressant agents. *Phytother. Res.* **2022**, *36*, 3470–3489. https://doi.org/10.1002/ptr.7551.
337. Jamu, I.M.; Okamoto, H. Recent advances in understanding adverse effects associated with drugs targeting the serotonin receptor, 5-HT GPCR. *Front. Glob. Womens Health* **2022**, *3*, 1012463. https://doi.org/10.3389/fgwh.2022.1012463.
338. Gibson, E.L. Tryptophan supplementation and serotonin function: genetic variations in behavioural effects. *Proc. Nutr. Soc.* **2018**, *77*, 174–188. https://doi.org/10.1017/s0029665117004451.
339. Averina, O.V.; Poluektova, E.U.; Zorkina, Y.A.; Kovtun, A.S.; Danilenko, V.N. Human Gut Microbiota for Diagnosis and Treatment of Depression. *Int. J. Mol. Sci.* **2024**, *25*. https://doi.org/10.3390/ijms25115782.
340. Lin, P.; Li, D.; Shi, Y.; Li, Q.; Guo, X.; Dong, K.; Chen, Q.; Lou, X.; Li, Z.; Li, P.; et al. Dysbiosis of the Gut Microbiota and Kynurenine (Kyn) Pathway Activity as Potential Biomarkers in Patients with Major Depressive Disorder. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15071752.
341. Xie, Y.; Zhu, H.; Yuan, Y.; Guan, X.; Xie, Q.; Dong, Z. Baseline gut microbiota profiles affect treatment response in patients with depression. *Front. Microbiol.* **2024**, *15*, 1429116. https://doi.org/10.3389/fmicb.2024.1429116.

 doi:10.20944/preprints202509.2303.v1

342. Liu, L.; Wang, H.; Zhang, H.; Chen, X.; Zhang, Y.; Wu, J.; Zhao, L.; Wang, D.; Pu, J.; Ji, P.; et al. Toward a Deeper Understanding of Gut Microbiome in Depression: The Promise of Clinical Applicability. *Adv Sci (Weinh)* **2022**, *9*, e2203707. https://doi.org/10.1002/advs.202203707.
343. Tian, P.; Wang, G.; Zhao, J.; Zhang, H.; Chen, W. Bifidobacterium with the role of 5-hydroxytryptophan synthesis regulation alleviates the symptom of depression and related microbiota dysbiosis. *J. Nutr. Biochem.* **2019**, *66*, 43–51. https://doi.org/10.1016/j.jnutbio.2019.01.007.
344. Wang, M.; Song, Z.; Lai, S.; Tang, F.; Dou, L.; Yang, F. Depression-associated gut microbes, metabolites and clinical trials. *Front. Microbiol.* **2024**, *15*, 1292004. https://doi.org/10.3389/fmicb.2024.1292004.
345. Clerici, L.; Bottari, D.; Bottari, B. Gut Microbiome, Diet and Depression: Literature Review of Microbiological, Nutritional and Neuroscientific Aspects. *Curr. Nutr. Rep.* **2025**, *14*, 30. https://doi.org/10.1007/s13668-025-00619-2.
346. Jiang, Y.; Qu, Y.; Shi, L.; Ou, M.; Du, Z.; Zhou, Z.; Zhou, H.; Zhu, H. The role of gut microbiota and metabolomic pathways in modulating the efficacy of SSRIs for major depressive disorder. *Transl. Psychiatry* **2024**, *14*, 493. https://doi.org/10.1038/s41398-024-03208-z.
347. Pawlowski, T.; Malyszczak, K.; Pawlak, D.; Inglot, M.; Zalewska, M.; Grzywacz, A.; Radkowski, M.; Laskus, T.; Janocha-Litwin, J.; Frydecka, D. HTR1A, TPH2, and 5-HTTLPR Polymorphisms and Their Impact on the Severity of Depressive Symptoms and on the Concentration of Tryptophan Catabolites during Hepatitis C Treatment with Pegylated Interferon-α2a and Oral Ribavirin (PEG-IFN-α2a/RBV). *Cells* **2023**, *12*. https://doi.org/10.3390/cells12060970.
348. Duan, K.M.; Wang, S.Y.; Yin, J.Y.; Li, X.; Ma, J.H.; Huang, Z.D.; Zhou, Y.Y.; Yu, H.Y.; Yang, M.; Zhou, H.H.; et al. The IDO genetic polymorphisms and postpartum depressive symptoms: an association study in Chinese parturients who underwent cesarean section. *Arch. Womens Ment. Health* **2019**, *22*, 339–348. https://doi.org/10.1007/s00737-018-0898-y.
349. Fasching, P.A.; Faschingbauer, F.; Goecke, T.W.; Engel, A.; Häberle, L.; Seifert, A.; Voigt, F.; Amann, M.; Rebhan, D.; Burger, P.; et al. Genetic variants in the tryptophan hydroxylase 2 gene (TPH2) and depression during and after pregnancy. *J. Psychiatr. Res.* **2012**, *46*, 1109–1117. https://doi.org/10.1016/j.jpsychires.2012.05.011.
350. MUSHTAQ, R. TRYPTOPHAN HYDROXYLASE GENE POLYMORPHISM AND 5HT TRANSPORTER GENE PROMOTER REGION POLYMORPHISM IN ANXIETY AND DEPRESSIVE DISORDER-COMPREHENSIVE LITERATURE REVIEW. *INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES* **2024**, *12*, 3957–3961.
351. Ottenhof, K.W.; Sild, M.; Lévesque, M.L.; Ruhé, H.G.; Booij, L. TPH2 polymorphisms across the spectrum of psychiatric morbidity: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **2018**, *92*, 29–42. https://doi.org/10.1016/j.neubiorev.2018.05.018.
352. Tanaka, M.; Battaglia, S.; Giménez-Llort, L.; Chen, C.; Hepsomali, P.; Avenanti, A.; Vécsei, L. Innovation at the Intersection: Emerging Translational Research in Neurology and Psychiatry. *Cells* **2024**, *13*. https://doi.org/10.3390/cells13100790.
353. Platten, M.; Nollen, E.A.A.; Röhrig, U.F.; Fallarino, F.; Opitz, C.A. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. *Nat. Rev. Drug Discov.* **2019**, *18*, 379–401. https://doi.org/10.1038/s41573-019-0016-5.
354. Chen, X.; Xu, D.; Yu, J.; Song, X.J.; Li, X.; Cui, Y.L. Tryptophan Metabolism Disorder-Triggered Diseases, Mechanisms, and Therapeutic Strategies: A Scientometric Review. *Nutrients* **2024**, *16*. https://doi.org/10.3390/nu16193380.
355. Siddiqui, A.J.; Adnan, M.; Saxena, J.; Alam, M.J.; Abdelgadir, A.; Badraoui, R.; Singh, R. Therapeutic Potential of Plant- and Marine-Derived Bioactive Compounds in Prostate Cancer: Mechanistic Insights and Translational Applications. *Pharmaceuticals (Basel)* **2025**, *18*. https://doi.org/10.3390/ph18030286.
356. Modoux, M.; Rolhion, N.; Mani, S.; Sokol, H. Tryptophan Metabolism as a Pharmacological Target. *Trends Pharmacol. Sci.* **2021**, *42*, 60–73. https://doi.org/10.1016/j.tips.2020.11.006.
357. Sadee, W.; Wang, D.; Hartmann, K.; Toland, A.E. Pharmacogenomics: Driving Personalized Medicine. *Pharmacol. Rev.* **2023**, *75*, 789–814. https://doi.org/10.1124/pharmrev.122.000810.

 doi:10.20944/preprints202509.2303.v1

358. Heinken, A.; Basile, A.; Hertel, J.; Thinnes, C.; Thiele, I. Genome-Scale Metabolic Modeling of the Human Microbiome in the Era of Personalized Medicine. *Annu. Rev. Microbiol.* **2021**, *75*, 199–222. https://doi.org/10.1146/annurev-micro-060221-012134.
359. Nowicka, A.; Tomczak, H.; Szałek, E.; Karbownik, A.; Gil, L. Microbial Crosstalk with Therapy: Pharmacomicrobiomics in AML-One Step Closer to Personalized Medicine. *Biomedicines* **2025**, *13*. https://doi.org/10.3390/biomedicines13071761.
360. Li, D.; Yu, S.; Long, Y.; Shi, A.; Deng, J.; Ma, Y.; Wen, J.; Li, X.; Liu, S.; Zhang, Y.; et al. Tryptophan metabolism: Mechanism-oriented therapy for neurological and psychiatric disorders. *Front. Immunol.* **2022**, *13*, 985378. https://doi.org/10.3389/fimmu.2022.985378.
361. Ge, P.Y.; Qu, S.Y.; Ni, S.J.; Yao, Z.Y.; Qi, Y.Y.; Zhao, X.; Guo, R.; Yang, N.Y.; Zhang, Q.C.; Zhu, H.X. Berberine ameliorates depression-like behavior in CUMS mice by activating TPH1 and inhibiting IDO1-associated with tryptophan metabolism. *Phytother. Res.* **2023**, *37*, 342–357. https://doi.org/10.1002/ptr.7616.
362. Hu, M.; Shi, X.; Song, P.X. Collaborative inference for treatment effect with distributed data-sharing management in multicenter studies. *Stat. Med.* **2024**, *43*, 2263–2279. https://doi.org/10.1002/sim.10068.
363. Adhikari, B.M.; Jahanshad, N.; Shukla, D.; Turner, J.; Grotegerd, D.; Dannlowski, U.; Kugel, H.; Engelen, J.; Dietsche, B.; Krug, A.; et al. A resting state fMRI analysis pipeline for pooling inference across diverse cohorts: an ENIGMA rs-fMRI protocol. *Brain Imaging Behav.* **2019**, *13*, 1453–1467. https://doi.org/10.1007/s11682-018-9941-x.
364. Lu, B.; Chen, X.; Xavier Castellanos, F.; Thompson, P.M.; Zuo, X.N.; Zang, Y.F.; Yan, C.G. The power of many brains: Catalyzing neuropsychiatric discovery through open neuroimaging data and large-scale collaboration. *Sci Bull (Beijing)* **2024**, *69*, 1536–1555. https://doi.org/10.1016/j.scib.2024.03.006.
365. Llovera, G.; Langhauser, F.; Isla Cainzos, S.; Hoppen, M.; Abberger, H.; Mohamud Yusuf, A.; Mencl, S.; Heindl, S.; Ricci, A.; Haupeltshofer, S.; et al. Stroke of Consistency: Streamlining Multicenter Protocols for Enhanced Reproducibility of Infarct Volumes in Preclinical Stroke Research. *Stroke* **2024**, *55*, 2522–2527. https://doi.org/10.1161/strokeaha.124.047232.
366. Sheller, M.J.; Edwards, B.; Reina, G.A.; Martin, J.; Pati, S.; Kotrotsou, A.; Milchenko, M.; Xu, W.; Marcus, D.; Colen, R.R.; et al. Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. *Sci. Rep.* **2020**, *10*, 12598. https://doi.org/10.1038/s41598-020-69250-1.
367. Zhang, X.; Wang, N.; Zhang, L.; Cheng, C.W.; Liu, Z.; Liang, F.; Xiong, W.; Deng, J.; Shi, D.; Cui, W.; et al. Reporting assessment of multicenter clinical trial protocols: A cross-sectional study. *J. Evid. Based Med.* **2023**, *16*, 16–18. https://doi.org/10.1111/jebm.12519.
368. Chen, N.; Lee, J.J. Bayesian cluster hierarchical model for subgroup borrowing in the design and analysis of basket trials with binary endpoints. *Stat. Methods Med. Res.* **2020**, *29*, 2717–2732. https://doi.org/10.1177/0962280220910186.
369. Zhang, J.; Lin, R.; Chen, X.; Yan, F. Adaptive Bayesian information borrowing methods for finding and optimizing subgroup-specific doses. *Clin. Trials* **2024**, *21*, 308–321. https://doi.org/10.1177/17407745231212193.
370. Wang, G.; Levis, A.; Steingrimsson, J.; Dahabreh, I. Efficient estimation of subgroup treatment effects using multi-source data. *arXiv preprint arXiv:2402.02684* **2024**.
371. Tanaka, M. Parkinson's Disease: Bridging Gaps, Building Biomarkers, and Reimagining Clinical Translation. *Cells* **2025**, *14*. https://doi.org/10.3390/cells14151161.
372. Tanaka, M. From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care. *Biomedicines* **2025**, *13*. https://doi.org/10.3390/biomedicines13010167.
373. Tanaka, M. Beyond the boundaries: Transitioning from categorical to dimensional paradigms in mental health diagnostics. *Adv. Clin. Exp. Med.* **2024**, *33*, 1295–1301. https://doi.org/10.17219/acem/197425.
374. Pagotto, G.L.O.; Santos, L.; Osman, N.; Lamas, C.B.; Laurindo, L.F.; Pomini, K.T.; Guissoni, L.M.; Lima, E.P.; Goulart, R.A.; Catharin, V.; et al. Ginkgo biloba: A Leaf of Hope in the Fight against Alzheimer's Dementia: Clinical Trial Systematic Review. *Antioxidants (Basel)* **2024**, *13*. https://doi.org/10.3390/antiox13060651.
375. Tanaka, M.; Vécsei, L. A Decade of Dedication: Pioneering Perspectives on Neurological Diseases and Mental Illnesses. *Biomedicines* **2024**, *12*. https://doi.org/10.3390/biomedicines12051083.

 doi:10.20944/preprints202509.2303.v1

376. Chahla, J.; Cinque, M.E.; Piuzzi, N.S.; Mannava, S.; Geeslin, A.G.; Murray, I.R.; Dornan, G.J.; Muschler, G.F.; LaPrade, R.F. A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting: A Systematic Review of the Clinical Orthopaedic Literature. *J. Bone Joint Surg. Am.* **2017**, *99*, 1769–1779. https://doi.org/10.2106/jbjs.16.01374.
377. Nueraihemaiti, N.; Dilimulati, D.; Baishan, A.; Hailati, S.; Maihemuti, N.; Aikebaier, A.; Paerhati, Y.; Zhou, W. Advances in Plant-Derived Extracellular Vesicle Extraction Methods and Pharmacological Effects. *Biology (Basel)* **2025**, *14*. https://doi.org/10.3390/biology14040377.
378. Lezoul, N.E.H.; Belkadi, M.; Habibi, F.; Guillén, F. Extraction Processes with Several Solvents on Total Bioactive Compounds in Different Organs of Three Medicinal Plants. *Molecules* **2020**, *25*. https://doi.org/10.3390/molecules25204672.
379. Mew, E.J.; Monsour, A.; Saeed, L.; Santos, L.; Patel, S.; Courtney, D.B.; Watson, P.N.; Szatmari, P.; Offringa, M.; Monga, S.; et al. Systematic scoping review identifies heterogeneity in outcomes measured in adolescent depression clinical trials. *J. Clin. Epidemiol.* **2020**, *126*, 71–79. https://doi.org/10.1016/j.jclinepi.2020.06.013.
380. Centanni, M.; Friberg, L.E. Model-Based Biomarker Selection for Dose Individualization of Tyrosine-Kinase Inhibitors. *Front. Pharmacol.* **2020**, *11*, 316. https://doi.org/10.3389/fphar.2020.00316.
381. Yap, C.; Solovyeva, O.; de Bono, J.; Rekowski, J.; Patel, D.; Jaki, T.; Mander, A.; Evans, T.R.J.; Peck, R.; Hayward, K.S.; et al. Enhancing reporting quality and impact of early phase dose-finding clinical trials: CONSORT Dose-finding Extension (CONSORT-DEFINE) guidance. *Bmj* **2023**, *383*, e076387. https://doi.org/10.1136/bmj-2023-076387.
382. Schwarz, A.J. The Use, Standardization, and Interpretation of Brain Imaging Data in Clinical Trials of Neurodegenerative Disorders. *Neurotherapeutics* **2021**, *18*, 686–708. https://doi.org/10.1007/s13311-021-01027-4.
383. Carini, C.; Seyhan, A.A. Tribulations and future opportunities for artificial intelligence in precision medicine. *J. Transl. Med.* **2024**, *22*, 411. https://doi.org/10.1186/s12967-024-05067-0.
384. Chen, X.; He, R.; Chen, X.; Jiang, L.; Wang, F. Optimizing dose-schedule regimens with bayesian adaptive designs: opportunities and challenges. *Front. Pharmacol.* **2023**, *14*, 1261312. https://doi.org/10.3389/fphar.2023.1261312.
385. Cottrell, T.R.; Lotze, M.T.; Ali, A.; Bifulco, C.B.; Capitini, C.M.; Chow, L.Q.M.; Cillo, A.R.; Collyar, D.; Cope, L.; Deutsch, J.S.; et al. Society for Immunotherapy of Cancer (SITC) consensus statement on essential biomarkers for immunotherapy clinical protocols. *J. Immunother. Cancer* **2025**, *13*. https://doi.org/10.1136/jitc-2024-010928.
386. Ciobanu-Caraus, O.; Aicher, A.; Kernbach, J.M.; Regli, L.; Serra, C.; Staartjes, V.E. A critical moment in machine learning in medicine: on reproducible and interpretable learning. *Acta Neurochir (Wien)* **2024**, *166*, 14. https://doi.org/10.1007/s00701-024-05892-8.
387. Kim, J.W.; Choi, E.C.; Lee, K.J. Standardizing the approach to clinical-based human microbiome research: from clinical information collection to microbiome profiling and human resource utilization. *Osong Public. Health Res. Perspect.* **2025**, *16*, 300–307. https://doi.org/10.24171/j.phrp.2024.0319.
388. Sharifi, S.; Mahmoud, N.N.; Voke, E.; Landry, M.P.; Mahmoudi, M. Importance of Standardizing Analytical Characterization Methodology for Improved Reliability of the Nanomedicine Literature. *Nanomicro Lett.* **2022**, *14*, 172. https://doi.org/10.1007/s40820-022-00922-5.
389. Arroyo-Araujo, M.; Voelkl, B.; Laloux, C.; Novak, J.; Koopmans, B.; Waldron, A.M.; Seiffert, I.; Stirling, H.; Aulehner, K.; Janhunen, S.K.; et al. Systematic assessment of the replicability and generalizability of preclinical findings: Impact of protocol harmonization across laboratory sites. *PLoS Biol.* **2022**, *20*, e3001886. https://doi.org/10.1371/journal.pbio.3001886.
390. Lukić, I.; Ivković, S.; Mitić, M.; Adžić, M. Tryptophan metabolites in depression: Modulation by gut microbiota. *Front. Behav. Neurosci.* **2022**, *16*, 987697. https://doi.org/10.3389/fnbeh.2022.987697.
391. Hoepner, C.T.; McIntyre, R.S.; Papakostas, G.I. Impact of Supplementation and Nutritional Interventions on Pathogenic Processes of Mood Disorders: A Review of the Evidence. *Nutrients* **2021**, *13*. https://doi.org/10.3390/nu13030767.

 doi:10.20944/preprints202509.2303.v1

392. Thomson, J.; Rankin, H.; Ashcroft, G.W.; Yates, C.M.; McQueen, J.K.; Cummings, S.W. The treatment of depression in general practice: a comparison of L-tryptophan, amitriptyline, and a combination of L-tryptophan and amitriptyline with placebo. *Psychol. Med.* **1982**, *12*, 741–751. https://doi.org/10.1017/s0033291700049047.
393. Kazemi, A.; Noorbala, A.A.; Azam, K.; Eskandari, M.H.; Djafarian, K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin. Nutr.* **2019**, *38*, 522–528. https://doi.org/10.1016/j.clnu.2018.04.010.
394. Jia, L.; Xiao, L.; Fu, Y.; Shao, Z.; Jing, Z.; Yuan, J.; Xie, Y.; Guo, J.; Wang, Y.; Geng, W. Neuroprotective effects of probiotics on anxiety- and depression-like disorders in stressed mice by modulating tryptophan metabolism and the gut microbiota. *Food Funct.* **2024**, *15*, 2895–2905. https://doi.org/10.1039/d3fo03897a.
395. Donoso, F.; Cryan, J.F.; Olavarría-Ramírez, L.; Nolan, Y.M.; Clarke, G. Inflammation, Lifestyle Factors, and the Microbiome-Gut-Brain Axis: Relevance to Depression and Antidepressant Action. *Clin. Pharmacol. Ther.* **2023**, *113*, 246–259. https://doi.org/10.1002/cpt.2581.
396. Nikdasti, A.; Khodadadi, E.S.; Ferdosi, F.; Dadgostar, E.; Yahyazadeh, S.; Heidari, P.; Ehtiati, S.; Vakili, O.; Khatami, S.H. Nutritional Strategies in Major Depression Disorder: From Ketogenic Diet to Modulation of the Microbiota-Gut-Brain Axis. *Mol. Neurobiol.* **2025**, *62*, 2973–2994. https://doi.org/10.1007/s12035-024-04446-4.
397. Merino Del Portillo, M.; Clemente-Suárez, V.J.; Ruisoto, P.; Jimenez, M.; Ramos-Campo, D.J.; Beltran-Velasco, A.I.; Martínez-Guardado, I.; Rubio-Zarapuz, A.; Navarro-Jiménez, E.; Tornero-Aguilera, J.F. Nutritional Modulation of the Gut-Brain Axis: A Comprehensive Review of Dietary Interventions in Depression and Anxiety Management. *Metabolites* **2024**, *14*. https://doi.org/10.3390/metabo14100549.
398. Parletta, N.; Zarnowiecki, D.; Cho, J.; Wilson, A.; Bogomolova, S.; Villani, A.; Itsiopoulos, C.; Niyonsenga, T.; Blunden, S.; Meyer, B.; et al. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). *Nutr. Neurosci.* **2019**, *22*, 474–487. https://doi.org/10.1080/1028415x.2017.1411320.
399. Opie, R.S.; O'Neil, A.; Jacka, F.N.; Pizzinga, J.; Itsiopoulos, C. A modified Mediterranean dietary intervention for adults with major depression: Dietary protocol and feasibility data from the SMILES trial. *Nutr. Neurosci.* **2018**, *21*, 487–501. https://doi.org/10.1080/1028415x.2017.1312841.
400. Firth, J.; Marx, W.; Dash, S.; Carney, R.; Teasdale, S.B.; Solmi, M.; Stubbs, B.; Schuch, F.B.; Carvalho, A.F.; Jacka, F.; et al. The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials. *Psychosom. Med.* **2019**, *81*, 265–280. https://doi.org/10.1097/psy.0000000000000673.
401. Xu, Y.; Zeng, L.; Zou, K.; Shan, S.; Wang, X.; Xiong, J.; Zhao, L.; Zhang, L.; Cheng, G. Role of dietary factors in the prevention and treatment for depression: an umbrella review of meta-analyses of prospective studies. *Transl. Psychiatry* **2021**, *11*, 478. https://doi.org/10.1038/s41398-021-01590-6.
402. Schefft, C.; Kilarski, L.L.; Bschor, T.; Köhler, S. Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis. *Eur. Neuropsychopharmacol.* **2017**, *27*, 1090–1109. https://doi.org/10.1016/j.euroneuro.2017.07.004.
403. Thurfah, J.N.; Christine; Bagaskhara, P.P.; Alfian, S.D.; Puspitasari, I.M. Dietary Supplementations and Depression. *J. Multidiscip. Healthc.* **2022**, *15*, 1121–1141. https://doi.org/10.2147/jmdh.S360029.
404. Sarris, J.; Murphy, J.; Mischoulon, D.; Papakostas, G.I.; Fava, M.; Berk, M.; Ng, C.H. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. *Am. J. Psychiatry* **2016**, *173*, 575–587. https://doi.org/10.1176/appi.ajp.2016.15091228.
405. Mötteli, S.; Vetter, S.; Colla, M.; Hotzy, F. Are probiotics effective in reducing the metabolic side effects of psychiatric medication? A scoping review of evidence from clinical studies. *Transl. Psychiatry* **2024**, *14*, 26. https://doi.org/10.1038/s41398-024-02735-z.
406. Jacka, F.N.; O'Neil, A.; Opie, R.; Itsiopoulos, C.; Cotton, S.; Mohebbi, M.; Castle, D.; Dash, S.; Mihalopoulos, C.; Chatterton, M.L.; et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med.* **2017**, *15*, 23. https://doi.org/10.1186/s12916-017-0791-y.

 doi:10.20944/preprints202509.2303.v1

407. Swainson, J.; Reeson, M.; Malik, U.; Stefanuk, I.; Cummins, M.; Sivapalan, S. Diet and depression: A systematic review of whole dietary interventions as treatment in patients with depression. *J. Affect. Disord.* **2023**, *327*, 270–278. https://doi.org/10.1016/j.jad.2023.01.094.
408. Ljungberg, T.; Bondza, E.; Lethin, C. Evidence of the Importance of Dietary Habits Regarding Depressive Symptoms and Depression. *Int. J. Environ. Res. Public. Health* **2020**, *17*. https://doi.org/10.3390/ijerph17051616.
409. Marx, W.; Lane, M.; Hockey, M.; Aslam, H.; Berk, M.; Walder, K.; Borsini, A.; Firth, J.; Pariante, C.M.; Berding, K.; et al. Diet and depression: exploring the biological mechanisms of action. *Mol. Psychiatry* **2021**, *26*, 134–150. https://doi.org/10.1038/s41380-020-00925-x.
410. Marx, W.; Moseley, G.; Berk, M.; Jacka, F. Nutritional psychiatry: the present state of the evidence. *Proc. Nutr. Soc.* **2017**, *76*, 427–436. https://doi.org/10.1017/s0029665117002026.
411. Levitan, R.D.; Shen, J.H.; Jindal, R.; Driver, H.S.; Kennedy, S.H.; Shapiro, C.M. Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J. Psychiatry Neurosci.* **2000**, *25*, 337–346.
412. Frost, R.; Zamri, A.; Mathew, S.; Salame, A.; Bhanu, C.; Bhamra, S.K.; Bazo-Alvarez, J.C.; Heinrich, M.; Walters, K. Understanding the research landscape of over-the-counter herbal products, dietary supplements, and medications evaluated for depressive symptoms in adults: a scoping review. *Front. Pharmacol.* **2025**, *16*, 1609605. https://doi.org/10.3389/fphar.2025.1609605.
413. Simon, M.S.; Weidinger, E.; Burger, B.; Kisla, Y.; Niedeggen, J.; Thaler, P.; Zaudig, M.; Voderholzer, U.; Schwarz, M.; Müller, N. Tryptophan metabolites predict response after cognitive behavioral therapy for depression: A single-arm trial. *Journal of Affective Disorders Reports* **2023**, *11*, 100464.
414. Kuwano, N.; Kato, T.A.; Setoyama, D.; Sato-Kasai, M.; Shimokawa, N.; Hayakawa, K.; Ohgidani, M.; Sagata, N.; Kubo, H.; Kishimoto, J.; et al. Tryptophan-kynurenine and lipid related metabolites as blood biomarkers for first-episode drug-naïve patients with major depressive disorder: An exploratory pilot case-control study. *J. Affect. Disord.* **2018**, *231*, 74–82. https://doi.org/10.1016/j.jad.2018.01.014.
415. Sha, Q.; Madaj, Z.; Keaton, S.; Escobar Galvis, M.L.; Smart, L.; Krzyzanowski, S.; Fazleabas, A.T.; Leach, R.; Postolache, T.T.; Achtyes, E.D.; et al. Cytokines and tryptophan metabolites can predict depressive symptoms in pregnancy. *Transl. Psychiatry* **2022**, *12*, 35. https://doi.org/10.1038/s41398-022-01801-8.
416. von Glischinski, M.; von Brachel, R.; Thiele, C.; Hirschfeld, G. Not sad enough for a depression trial? A systematic review of depression measures and cut points in clinical trial registrations. *J. Affect. Disord.* **2021**, *292*, 36–44. https://doi.org/10.1016/j.jad.2021.05.041.
417. Dawson, G.R.; Post, A.; Smart, T.S.; Browning, M.; Harmer, C.J. Accuracy in recognising happy facial expressions is associated with antidepressant response to a NOP receptor antagonist but not placebo treatment. *J. Psychopharmacol.* **2021**, *35*, 1473–1478. https://doi.org/10.1177/02698811211044684.
418. Hershenberg, R.; McDonald, W.M.; Crowell, A.; Riva-Posse, P.; Craighead, W.E.; Mayberg, H.S.; Dunlop, B.W. Concordance between clinician-rated and patient reported outcome measures of depressive symptoms in treatment resistant depression. *J. Affect. Disord.* **2020**, *266*, 22–29. https://doi.org/10.1016/j.jad.2020.01.108.
419. Bain, E.E.; Shafner, L.; Walling, D.P.; Othman, A.A.; Chuang-Stein, C.; Hinkle, J.; Hanina, A. Use of a Novel Artificial Intelligence Platform on Mobile Devices to Assess Dosing Compliance in a Phase 2 Clinical Trial in Subjects With Schizophrenia. *JMIR Mhealth Uhealth* **2017**, *5*, e18. https://doi.org/10.2196/mhealth.7030.
420. Steinkamp, J.M.; Goldblatt, N.; Borodovsky, J.T.; LaVertu, A.; Kronish, I.M.; Marsch, L.A.; Schuman-Olivier, Z. Technological Interventions for Medication Adherence in Adult Mental Health and Substance Use Disorders: A Systematic Review. *JMIR Ment. Health* **2019**, *6*, e12493. https://doi.org/10.2196/12493.
421. Straczkiewicz, M.; Wisniewski, H.; Carlson, K.W.; Heidary, Z.; Knights, J.; Keshavan, M.; Onnela, J.P.; Torous, J. Combining digital pill and smartphone data to quantify medication adherence in an observational psychiatric pilot study. *Psychiatry Res.* **2022**, *315*, 114707. https://doi.org/10.1016/j.psychres.2022.114707.
422. Fava, M.; Pani, L.; De Martin, S.; Cutler, A.J.; Gorodetzky, C.W.; Vocci, F.J.; Sapienza, F.L.; Kosten, T.R.; Kröger, C.; Champasa, P.; et al. Long-Term Safety and Efficacy of Esmethadone in Patients With Major

 doi:10.20944/preprints202509.2303.v1

Depressive Disorder: Findings From a 12-Month Open-Label Study. *J. Clin. Psychiatry* **2025**, *86*. https://doi.org/10.4088/JCP.24m15438.

423. Rutherford, B.R.; Sneed, J.R.; Roose, S.P. Does study design influence outcome?. The effects of placebo control and treatment duration in antidepressant trials. *Psychother. Psychosom.* **2009**, *78*, 172–181. https://doi.org/10.1159/000209348.
424. Henssler, J.; Kurschus, M.; Franklin, J.; Bschor, T.; Baethge, C. Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. *J. Clin. Psychiatry* **2018**, *79*. https://doi.org/10.4088/JCP.15r10545.
425. Owoyemi, E.P.; Agwaza, K.P.; Doris, O.K.; Egwuatu, D.C.; Ogunye, R.O.; Anene, P.C.; Azubuike, E.O.; Ojobor, J.F.C.; Odanibeh, D.; Asenuga, O.O. Nutritional Genomics: The Use of Personalized Diets for Managing Depression. *Journal of Complementary and Alternative Medical Research* **2024**, *25*, 23–37.
426. Singar, S.; Nagpal, R.; Arjmandi, B.H.; Akhavan, N.S. Personalized Nutrition: Tailoring Dietary Recommendations through Genetic Insights. *Nutrients* **2024**, *16*. https://doi.org/10.3390/nu16162673.
427. Julian, C.; Shen, N.; Molusky, M.; Hu, L.; Gopu, V.; Gorakshakar, A.; Patridge, E.; Antoine, G.; Connell, J.; Keiser, H. The effectiveness of precision supplements on depression symptoms in a US population. *medRxiv* **2023**, 2023.2004. 2018.23288750.
428. Zelada, M.I.; Garrido, V.; Liberona, A.; Jones, N.; Zúñiga, K.; Silva, H.; Nieto, R.R. Brain-Derived Neurotrophic Factor (BDNF) as a Predictor of Treatment Response in Major Depressive Disorder (MDD): A Systematic Review. *Int. J. Mol. Sci.* **2023**, *24*. https://doi.org/10.3390/ijms241914810.
429. Suktas, A.; Ekalaksananan, T.; Aromseree, S.; Bumrungthai, S.; Songserm, N.; Pientong, C. Genetic polymorphism involved in major depressive disorder: a systemic review and meta-analysis. *BMC Psychiatry* **2024**, *24*, 716. https://doi.org/10.1186/s12888-024-06195-z.
430. Ugartemendia, L.; Bravo, R.; Reuter, M.; Castaño, M.Y.; Plieger, T.; Zamoscik, V.; Kirsch, P.; Rodríguez, A.B. SLC6A4 polymorphisms modulate the efficacy of a tryptophan-enriched diet on age-related depression and social cognition. *Clin. Nutr.* **2021**, *40*, 1487–1494. https://doi.org/10.1016/j.clnu.2021.02.023.
431. van Dalfsen, J.H.; Markus, C.R. The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and the sleep-promoting effects of tryptophan: A randomized placebo-controlled crossover study. *J. Psychopharmacol.* **2019**, *33*, 948–954. https://doi.org/10.1177/0269881119855978.
432. Nedic Erjavec, G.; Sagud, M.; Nikolac Perkovic, M.; Svob Strac, D.; Konjevod, M.; Tudor, L.; Uzun, S.; Pivac, N. Depression: Biological markers and treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *105*, 110139. https://doi.org/10.1016/j.pnpbp.2020.110139.
433. Milic, J.; Jovic, S.; Sapic, R. Advancing Depression Management Through Biomarker Discovery with a Focus on Genetic and Epigenetic Aspects: A Comprehensive Study on Neurobiological, Neuroendocrine, Metabolic, and Inflammatory Pathways. *Genes (Basel)* **2025**, *16*. https://doi.org/10.3390/genes16050487.
434. Beer, C.; Rae, F.; Semmler, A.; Voisey, J. Biomarkers in the Diagnosis and Prediction of Medication Response in Depression and the Role of Nutraceuticals. *Int. J. Mol. Sci.* **2024**, *25*. https://doi.org/10.3390/ijms25147992.
435. Magzal, F.; Turroni, S.; Fabbrini, M.; Barone, M.; Vitman Schorr, A.; Ofran, A.; Tamir, S. A personalized diet intervention improves depression symptoms and changes microbiota and metabolite profiles among community-dwelling older adults. *Front. Nutr.* **2023**, *10*, 1234549. https://doi.org/10.3389/fnut.2023.1234549.
436. Chen, L.; Liu, B.; Ren, L.; Du, H.; Fei, C.; Qian, C.; Li, B.; Zhang, R.; Liu, H.; Li, Z.; et al. High-fiber diet ameliorates gut microbiota, serum metabolism and emotional mood in type 2 diabetes patients. *Front. Cell Infect. Microbiol.* **2023**, *13*, 1069954. https://doi.org/10.3389/fcimb.2023.1069954.
437. Krishnan, S.; Ding, Y.; Saedi, N.; Choi, M.; Sridharan, G.V.; Sherr, D.H.; Yarmush, M.L.; Alaniz, R.C.; Jayaraman, A.; Lee, K. Gut Microbiota-Derived Tryptophan Metabolites Modulate Inflammatory Response in Hepatocytes and Macrophages. *Cell Rep.* **2018**, *23*, 1099–1111. https://doi.org/10.1016/j.celrep.2018.03.109.
438. Mugo Moses, H. The Impact of Personalized Dietary Interventions on Glycemic Control and Quality of Life in Middle-Aged Adults with Type 2 Diabetes and Co-occurring Depression.
439. Radford-Smith, D.E.; Anthony, D.C. Prebiotic and Probiotic Modulation of the Microbiota-Gut-Brain Axis in Depression. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15081880.

440. Gao, K.; Mu, C.L.; Farzi, A.; Zhu, W.Y. Tryptophan Metabolism: A Link Between the Gut Microbiota and Brain. *Adv. Nutr.* **2020**, *11*, 709–723. https://doi.org/10.1093/advances/nmz127.
441. Asad, A.; Kirk, M.; Zhu, S.; Dong, X.; Gao, M. Effects of Prebiotics and Probiotics on Symptoms of Depression and Anxiety in Clinically Diagnosed Samples: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Nutr. Rev.* **2025**, *83*, e1504–e1520. https://doi.org/10.1093/nutrit/nuae177.
442. Liu, R.T.; Walsh, R.F.L.; Sheehan, A.E. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neurosci. Biobehav. Rev.* **2019**, *102*, 13–23. https://doi.org/10.1016/j.neubiorev.2019.03.023.
443. Bankah, A.Z.; Tagoe, T.A.; Darko, E.; Agoha, R.; Ametefe, E.N.; Kukuia, K.K.E.; Adjei, S. Combined Administration of Lactobacillus or Bifidobacterium Offers Enhanced Antidepressant and Anxiolytic Activity in a Dose Dependent Manner. *Brain Behav.* **2025**, *15*, e70564. https://doi.org/10.1002/brb3.70564.
444. Dandekar, M.P.; Palepu, M.S.K.; Satti, S.; Jaiswal, Y.; Singh, A.A.; Dash, S.P.; Gajula, S.N.R.; Sonti, R. Multi-strain Probiotic Formulation Reverses Maternal Separation and Chronic Unpredictable Mild Stress-Generated Anxiety- and Depression-like Phenotypes by Modulating Gut Microbiome-Brain Activity in Rats. *ACS Chem. Neurosci.* **2022**, *13*, 1948–1965. https://doi.org/10.1021/acschemneuro.2c00143.
445. Kennedy, P.J.; Cryan, J.F.; Dinan, T.G.; Clarke, G. Kynurenine pathway metabolism and the microbiota-gut-brain axis. *Neuropharmacology* **2017**, *112*, 399–412. https://doi.org/10.1016/j.neuropharm.2016.07.002.
446. Fond, G.B.; Lagier, J.C.; Honore, S.; Lancon, C.; Korchia, T.; Sunhary De Verville, P.L.; Llorca, P.M.; Auquier, P.; Guedj, E.; Boyer, L. Microbiota-Orientated Treatments for Major Depression and Schizophrenia. *Nutrients* **2020**, *12*. https://doi.org/10.3390/nu12041024.
447. Chang, M.; Chang, K.T.; Chang, F. Just a gut feeling: Faecal microbiota transplant for treatment of depression - A mini-review. *J. Psychopharmacol.* **2024**, *38*, 353–361. https://doi.org/10.1177/02698811241240308.
448. Hu, B.; Das, P.; Lv, X.; Shi, M.; Aa, J.; Wang, K.; Duan, L.; Gilbert, J.A.; Nie, Y.; Wu, X.L. Effects of 'Healthy' Fecal Microbiota Transplantation against the Deterioration of Depression in Fawn-Hooded Rats. *mSystems* **2022**, *7*, e0021822. https://doi.org/10.1128/msystems.00218-22.
449. Rao, J.; Qiao, Y.; Xie, R.; Lin, L.; Jiang, J.; Wang, C.; Li, G. Fecal microbiota transplantation ameliorates stress-induced depression-like behaviors associated with the inhibition of glial and NLRP3 inflammasome in rat brain. *Journal of Psychiatric Research* **2021**, *137*, 147–157.
450. Rao, J.; Xie, R.; Lin, L.; Jiang, J.; Du, L.; Zeng, X.; Li, G.; Wang, C.; Qiao, Y. Fecal microbiota transplantation ameliorates gut microbiota imbalance and intestinal barrier damage in rats with stress-induced depressive-like behavior. *Eur. J. Neurosci.* **2021**, *53*, 3598–3611. https://doi.org/10.1111/ejn.15192.
451. Doll, J.P.K.; Vázquez-Castellanos, J.F.; Schaub, A.C.; Schweinfurth, N.; Kettelhack, C.; Schneider, E.; Yamanbaeva, G.; Mählmann, L.; Brand, S.; Beglinger, C.; et al. Fecal Microbiota Transplantation (FMT) as an Adjunctive Therapy for Depression-Case Report. *Front. Psychiatry* **2022**, *13*, 815422. https://doi.org/10.3389/fpsyt.2022.815422.
452. Chinna Meyyappan, A.; Forth, E.; Wallace, C.J.K.; Milev, R. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. *BMC Psychiatry* **2020**, *20*, 299. https://doi.org/10.1186/s12888-020-02654-5.
453. Cai, T.; Shi, X.; Yuan, L.Z.; Tang, D.; Wang, F. Fecal microbiota transplantation in an elderly patient with mental depression. *Int. Psychogeriatr.* **2019**, *31*, 1525–1526. https://doi.org/10.1017/s1041610219000115.