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Recent advances in polyphenolic compounds: Mechanisms underlying anti-anxiety, antidepressant, and anti-PTSD effects

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Abstract

Polyphenols are ubiquitous natural bioactive compounds with potent antioxidant and anti-inflammatory activities, emerging as promising candidates for intervening in psychiatric diseases. Emotional disorders, including anxiety, depression, and post-traumatic stress disorder, are highly prevalent, debilitating conditions that severely compromise patients' quality of life and pose substantial challenges to clinical management due to their multifactorial pathogenesis. This review comprehensively summarizes the therapeutic efficacy and multi-mechanistic actions of polyphenols against emotional disorders, focusing on five core regulatory pathways: neurotransmitter and receptor modulation, regulation of neurotrophic factors and neuroplasticity, anti-inflammatory and antioxidant effects, modulation of hypothalamic–pituitary–adrenal axis homeostasis, and gut–brain axis regulation. By integrating the latest findings from animal models and clinical studies, this article aims to provide a comprehensive theoretical framework and outline future research directions for the application of polyphenolic compounds in the prevention and treatment of psychiatric disorders.

Keywords: Polyphenolic compounds; Emotional disorders, Intervention strategies, Mechanisms

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1. Introduction

Anxiety disorders and depressive disorders accounted for approximately 301 million and 280 million cases worldwide, respectively, in 2019, and both contribute substantially to years lived with disability. In the World Mental Health Surveys, lifetime post-traumatic stress disorder (PTSD) prevalence was 3.9% in the total population and 5.6% among trauma-exposed respondents.[1,2] Anxiety disorders, depressive disorders, and PTSD share stress-linked neurobiological perturbations, compromised emotion regulation, and substantial disability burden.

Polyphenols represent a vast and structurally diverse class of plant secondary metabolites widely found in various dietary sources, including fruits, vegetables, tea, and coffee. Accumulating evidence indicates that polyphenols ameliorate anxiety, depression,

and PTSD through diverse mechanistic pathways. Several recent reviews have summarized antioxidant, anti-inflammatory, and neurotransmitter mechanisms of polyphenols in psychiatric or stress-related conditions.[3-5] The present review is deliberately differentiated in three ways. First, it links structural features to target preference rather than treating all polyphenols as one pharmacological class. Second, it dissects common molecular pathways in the neural circuits and endocrine phenotypes specific to anxiety, depression, and PTSD. Third, it analyzes human-derived evidence from both preventive and therapeutic perspectives to generate supporting evidence for translational trial design. Accordingly, polyphenols are assessed as potential adjunctive agents or nutritional interventions, rather than alternatives to evidence-based psychotherapy and pharmacotherapy.

This article is a structured narrative review. A reproducible literature search was conducted on June 30, 2026, in PubMed/MEDLINE, and ClinicalTrials.gov was searched to identify relevant human interventional studies. The search focused primarily on publications from the past 5–6 years. Search blocks combined polyphenol-related terms (polyphenol, flavonoid, phenolic acid, curcumin, quercetin, catechin, epigallocatechin gallate, resveratrol, tannin, anthocyanin) with disorder-related terms (anxiety, depression, post-traumatic stress, PTSD) and evidence-focused terms (mechanism, neurotransmitter, BDNF, neuroinflammation, oxidative stress, hypothalamic–pituitary–adrenal axis, microbiota, pharmacokinetic, trial).

2. Classification and chemical properties of polyphenolic compounds

2.1. Flavonoids

Flavonoids constitute the major subclass of dietary polyphenols. They feature a conserved C6–C3–C6 backbone, with two aromatic moieties connected by a three-carbon heterocyclic pyran ring. Variations in ring oxidation states and hydroxylation patterns serve as the primary criteria for categorizing these compounds into six principal subclasses. Representative members include apigenin and luteolin for flavones, quercetin and kaempferol for flavonols, genistein and daidzein for isoflavones, naringenin and hesperetin for flavanones, catechin and epigallocatechin gallate (EGCG) for flavanols, as well as cyanidin and delphinidin for anthocyanidins.[6,7]

Flavonoids exhibit distinct target preferences primarily centered on key enzymes and transcription factors involved in redox signaling and inflammatory pathways. Chrysin can engage benzodiazepine-sensitive gamma-aminobutyric acid type A (GABA-A) receptor signaling in rodents. Catechins such as EGCG more consistently suppress nuclear factor kappa B (NF-κB), NLR family pyrin domain containing 3 (NLRP3), and oxidative signaling. Quercetin and myricetin affect redox, inflammatory, and brain-derived neurotrophic factor (BDNF)–extracellular signal-regulated kinase (ERK) pathways in stress models.[8-12]

2.2. Phenolic acids

Phenolic acids represent another pivotal subclass of polyphenols, structurally defined by a benzene ring conjugated with a carboxyl group. They are taxonomically divided into hydroxybenzoic acids and hydroxycinnamic acids based on the side-chain structure of the aromatic ring. Their smaller size and polar functional groups favor redox and inflammatory targets, although conjugation and microbial metabolism again reshape exposure. Chlorogenic, ferulic, caffeic, and protocatechuic acids converge on nuclear factor erythroid 2-related factor 2 (Nrf2), NF-κB, inflammasome, monoamine, and N-methyl-D-aspartate (NMDA) receptor-related glutamatergic pathways.[13-15] In single prolonged stress models, chlorogenic acid improved PTSD-like behavior through Nrf2–NF-κB crosstalk, whereas protocatechuic acid reduced anxiety-like behavior while restoring corticosterone, monoamines, and hippocampal BDNF.[16,17]

Despite phenolic acids possessing relatively simple structures, their brain exposure is difficult to predict.[18] As a representative phenolic acid, chlorogenic acid is partially absorbed in the small intestine, while most travels to the colon where gut microbiota convert it into secondary metabolites including caffeic acid and ferulic acid.[19] Such microbial metabolism confounds the assignment of biological functions.

2.3. Other polyphenols

Resveratrol and tannins are representative bioactive polyphenols with distinct structural characteristics and potent neuropharmacological properties, serving as promising natural regulators for stress-related neuropsychiatric disorders. Resveratrol is a stilbene whose planar, moderately lipophilic structure permits membrane passage and preclinical brain distribution. It has been linked to sirtuin 1 (SIRT1), AMP-activated protein kinase (AMPK), monoamine oxidase (MAO), glutamatergic signaling, inflammatory control, and glucocorticoid metabolism.[20,21] However, oral absorption does not equal parent-compound bioavailability: approximately three-quarters of an oral dose may be absorbed, while rapid sulfate and glucuronide formation leaves very low circulating free resveratrol.[22]

Tannins are high-molecular-weight polyphenols with limited intact absorption. Colonic metabolism generates

smaller phenolic acids and, from ellagitannins, urolithins. Urolithin metabotypes vary among individuals, creating biologically meaningful exposure heterogeneity.[23] Tannic acid has antidepressant-like effects in mice through serotonergic, MAO-A, inflammatory, and redox mechanisms, but no therapeutic psychiatric randomized controlled trial (RCT) establishes efficacy of intact tannic acid.[24,25]

3. Mechanisms of polyphenolic compounds against anxiety, depression, and PTSD

3.1. Neurotransmitter and receptor regulation

Polyphenols can influence serotonin (5-hydroxytryptamine [5-HT]), dopamine, norepinephrine, GABA, and glutamate signaling through receptor modulation, MAO inhibition, transmitter synthesis or transport, and indirect protection of neurons and astrocytes.[26,27] The same molecular event does not imply the same clinical effect: GABAergic and serotonergic regulation may be most relevant to threat responses in anxiety; monoamine effects in depression interact with glutamate homeostasis, reward processing, and plasticity; and PTSD additionally involves noradrenergic arousal and context-dependent fear learning in amygdala–hippocampus–medial prefrontal circuits.[28]

Compound-specific examples illustrate both the promise and the limits of this evidence. Chrysin's anxiolytic-like effects partly depend on GABA-A receptors.[8,9] Selected resveratrol and silibinin studies report monoaminergic changes, whereas a resveratrol–rufinamide combination affected GABAergic readouts in a neuropathic-pain model.[20,29-31]

Curcumin and resveratrol have also been linked to glutamatergic homeostasis, and tannic acid to serotonergic receptors and MAO-A activity.[24,25,32,33] Protocatechuic acid increased serum serotonin in mice, but a peripheral serotonin measure does not establish central serotonergic target engagement.[34]

3.2. Regulation of neurotrophic factors and neuroplasticity

Tropomyosin receptor kinase B (TrkB)–BDNF, ERK, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and cyclic AMP response element-binding protein (CREB) form a key signaling network mediating neural plasticity. Polyphenols upregulate BDNF expression and activate its downstream signaling cascades, enhance neuronal survival, neurogenesis, and synaptic plasticity, and reverse neuroplastic damage. Multiple polyphenols, including curcumin, resveratrol, quercetin, EGCG, and hydroxytyrosol, significantly increase BDNF expression.[35-38] Resveratrol activates SIRT1, AMPK, PI3K/Akt, and CREB pathways to promote BDNF transcription.[20] Polyphenols' antioxidant and anti-inflammatory effects synergize with BDNF modulation to alleviate anxiety.[39,40] Walnut polyphenols alleviate oxidative injury and enhance synaptic plasticity via activating the PKA/CREB/BDNF cascade, while modulating epigenetic regulators including DNA methylation and histone modification to govern BDNF transcription.[41]

Curcumin increases BDNF levels to improve synaptic function and cognitive resilience.[36,37] Polyphenol-rich nutraceuticals can raise plasma BDNF and CREB levels in humans, corresponding to improved cognitive performance.[38] Polyphenol derivatives such as chalcones elevate BDNF, insulin-like growth factor 1 receptor, and phosphorylated Akt to exert neuroprotective and anti-apoptotic effects.[42,43] The combination of polyphenols and exercise produces a synergistic effect to further amplify BDNF expression and neuroplasticity.[44] Tea polyphenols increase hippocampal *BDNF* messenger RNA (mRNA) expression in depression models.[45] Polyphenols activate Nrf2 and inhibit the NF-κB pathway to improve the microenvironment for BDNF signaling, thereby facilitating neuronal repair.[46-48]

Persistent downregulation of BDNF is closely associated with fear memory consolidation and emotional disorders in PTSD.[49] Protocatechuic acid effectively prevents the reduction of BDNF mRNA in the hippocampus of PTSD model animals, facilitates fear extinction, and relieves anxiety and depressive symptoms.[17] Resveratrol restores hippocampal neuroplasticity via the *ELAVL4–BDNF* mRNA pathway.[50] Cocoa flavanols increase hippocampal BDNF and adult neurogenesis to improve cognitive function.[51]

3.3. Anti-inflammatory and antioxidant mechanisms

Oxidative stress and neuroimmune activation connect chronic stress to synaptic dysfunction. Polyphenols exert dual anti-inflammatory and antioxidant activities, regulate key signaling pathways, eliminate reactive oxygen species, suppress inflammatory responses, and protect neurons from damage. Polyphenols inhibit the production of pro-inflammatory factors, including tumor necrosis factor-α, interleukin-1β, and interleukin-6, and suppress the expression of inducible nitric oxide synthase and cyclooxygenase-2 to reduce neuroinflammation.[52,53] They scavenge reactive oxygen species and reactive nitrogen species, mitigate lipid peroxidation, and increase the activity of endogenous antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase.[54,55] Polyphenols regulate NF-κB, mitogen-activated protein kinase (MAPK), and Nrf2 pathways: inhibiting NF-κB

and MAPK to block inflammatory cascades, and activating Nrf2 to enhance cytoprotective antioxidant gene expression.[56,57] They also suppress microglial activation, inhibit lipoxygenase activity, improve mitochondrial function, and reduce mitochondrial reactive oxygen species production.[58-61]

Plant polyphenols from *Rhamnus prinoides* and *Gynura procumbens* show strong free radical scavenging and nitric oxide inhibitory effects.[62,63] Tea polyphenols reduce pro-inflammatory cytokines and microglial activation and alleviate chronic unpredictable mild stress-induced depression via anti-inflammation and antioxidation.[12,64] Diosmin ameliorates depression-like behaviors in mice by inhibiting inflammation and oxidative stress in the prefrontal cortex.[65] Nano-formulated polyphenols further enhance bioavailability and continuously suppress inflammatory pathways and oxidative damage.[66]

Patients with PTSD have elevated peripheral and central pro-inflammatory cytokines and obvious oxidative damage in the hippocampus and prefrontal cortex.[67,68] Resveratrol reduces oxidative stress markers in the brain and liver, inhibits 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) and MAOs, and relieves neuroinflammation via the liver–brain axis.[21,69] Chlorogenic acid regulates crosstalk between the Nrf2 and NF-κB pathways: activating Nrf2 to enhance antioxidant defense, inhibiting NF-κB to cut off inflammatory signals, reducing hippocampal neuronal apoptosis, and improving synaptic plasticity.[16] Protocatechuic acid lowers corticosterone levels, improves monoamine imbalance, and counteracts neuronal dysfunction induced by inflammation and oxidative stress.[17] Coffee polyphenols also exert similar protective effects, but excessive caffeine will aggravate PTSD symptoms.[70]

3.4. Influence on the HPA axis

The hypothalamic–pituitary–adrenal (HPA) axis is not uniformly "hyperactive" across the three disorders. Many patients with major depression show impaired glucocorticoid feedback and elevated cortisol, whereas PTSD patients may show lower basal cortisol, enhanced glucocorticoid receptor sensitivity, or altered diurnal dynamics; anxiety phenotypes vary with chronicity and comorbidity. Polyphenols reduce the secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and corticosterone, and restore the negative feedback regulation of the HPA axis. They improve neuronal resilience in the hippocampus and hypothalamus by reducing inflammation and oxidative stress[71-73], and regulate serotonergic and noradrenergic systems to interact with the HPA axis, jointly stabilizing stress responses.[4]

High levels of circulating glucocorticoids are closely correlated with the severity of depressive symptoms. Apple polyphenol extracts reduce serum ACTH and corticosterone in depression models and restore gut–liver–brain axis balance.[74] EGCG decreases CRH, ACTH, and corticosterone to relieve HPA axis overactivation.[75] Polyphenols improve HPA axis dysfunction induced by high-fat diet and metabolic stress.[76] Curcumin alleviates liver oxidative damage caused by excessive corticosterone.[77]

Post-traumatic stress disorder is characterized by a blunted cortisol response and abnormal glucocorticoid receptor sensitivity.[78,79] Polyphenols modulate stress responses through multiple pathways: they transcriptionally regulate the expression of CRH and inflammatory cytokine genes [76,77], and remodel the gut microbiota to increase short-chain fatty acid production and tryptophan availability, thereby indirectly restraining HPA axis hyperactivity.[80-82] As a representative polyphenol, resveratrol modulates the hepatic metabolic enzymes 11β-HSD-1 and cytochrome P450 family 3, subfamily A (CYP3A) to maintain glucocorticoid homeostasis.[69] Consistently, trans-resveratrol exerts divergent effects in treatment-sensitive and treatment-resistant PTSD rats via differential regulation of these two hepatic glucocorticoid-metabolizing enzymes, whose activities are dysregulated under PTSD conditions.[69]

3.5. Regulation of the gut–brain axis

The gut–brain axis is a critical indirect pathway through which polyphenols regulate mental disorders. Most ingested polyphenols reach the colon, where microbial enzymes produce smaller phenolic metabolites, which in turn reshape microbial ecology. Candidate mediators include short-chain fatty acids, tryptophan metabolites, bile-acid signaling, gut permeability, and systemic immune tone. Polyphenols reshape the structure of gut microbiota, promote the production of microbial metabolites that can pass through the blood–brain barrier, and use these metabolites as neurotransmitter precursors or regulators to indirectly increase central dopamine, 5-HT, and GABA levels.[83-85] The gut microbiota-mediated pathway is an important way for polyphenols to exert anxiolytic effects. Meanwhile, gut microbiota remodeling reduces systemic inflammation, further improving the anxiety-related neural circuit dysfunction.[86,87]

Polyphenols optimize gut microbiota composition, reduce anxiety levels and depression-related metabolites such as 4-ethylphenyl sulfate [88], and inhibit the high-mobility group box 1 (HMGB1)–receptor for advanced glycation end products (RAGE) inflammatory pathway in the brain. Gut microbiota metabolize polyphenols

into active derivatives to enhance central antioxidant and anti-inflammatory capacities.[89,90] The gut–brain axis also mediates polyphenol-mediated BDNF upregulation and synergizes with HPA-axis regulation to improve depressive behaviors.[91] The polyphenol-rich Mediterranean diet exerts antidepressant effects through bidirectional regulation of the gut–brain axis.[92] Treatment with hydroxytyrosol reduces neuroinflammation, enhances dentate gyrus neurogenesis, and modulates the microbiota–gut–brain axis in trauma-exposed mice, thereby alleviating anxiety-like behaviors.[93] Dietary polyphenols are promising modulators of the microbiota–gut–brain axis, underscoring their relevance for future nutritional strategies targeting mood-related disorders.[94] Mechanistic overlap and disease-specific interpretations are summarized in Table 1.

4. Clinical evidence of polyphenol interventions

4.1. Dietary exposure and food-based interventions

Food-based randomized trials recruiting participants with self-reported or clinically diagnosed mood disorders yield inconsistent results. Four-week wild-blueberry supplementation mitigated depressive rather than anxiety symptoms in adolescents. In 60 symptomatic young adults, blueberry elicited only transient positive mood, with superior long-term depressive outcomes in the placebo group.[96,97] Among 40 patients with major depressive disorder, eight-week flavonoid-rich orange juice and low-flavonoid control comparably reduced depression scores. Absence of intergroup symptom differences means concomitant BDNF and microbiome alterations cannot confirm antidepressant efficacy.[98] A two-phase 12-week crossover pilot using blueberry powder suggested mood improvements in depressed/anxious adults, yet these findings remain preliminary owing to 23 completers, pseudo-randomized matching, high attrition, and permitted adjustments to concurrent therapies.[99]

4.2. Supplement and purified-compound trials

Curcumin has the largest human evidence base among purified polyphenols studied for depression, but the trials are heterogeneous in diagnosis, formulation, dose, and background treatment. Nano-curcumin 80 mg/day produced small reductions in depression and anxiety scores in patients with diabetic neuropathy.[100] A larger 12-month trial of curcumin 1,500 mg/day improved Patient Health Questionnaire-9 (PHQ-9) scores in 227 adults with obesity and type 2 diabetes, but participants were not enrolled for a primary depressive disorder, so metabolic improvement and the comorbid population limit psychiatric generalization.[101] In a separate prevention trial, 96 primiparous women without baseline depression or psychiatric history had lower postpartum symptom

Table 1. Mechanistic overlap and disease-specific interpretation

Mechanism	Anxiety emphasis	Depression emphasis	PTSD emphasis	Representative evidence
Neurotransmission	Amygdala–prefrontal threat regulation; GABA-A and 5-HT signaling.	Monoamines plus glutamate, reward, and cognitive-bias circuits.	Noradrenergic arousal and contextual fear in amygdala–hippocampus–medial prefrontal circuits.	Chrysin, caffeic acid, silibinin, and quercetin in preclinical models.[8-10,15,30]
Neuroplasticity	Extinction learning and top-down regulation.	Hippocampal/Prefrontal BDNF-TrkB-CREB signaling, anhedonia, and cognition.	Fear-memory updating and extinction; timing and brain region are critical.	Myricetin, EGCG, and protocatechuic acid alter BDNF-related signals in animals.[11,17,45]
Oxidative-inflammatory signaling	Stress-linked inflammatory amplification and threat sensitivity.	Inflammatory subgroups; microglia, NLRP3, and oxidative injury.	Trauma-related immune activation and oxidative signaling in fear circuits.	EGCG, diosmin, chlorogenic acid, and quercetin in animal models.[10,16,64,65,95]
HPA axis	Variable reactivity depending on chronicity and comorbidity.	Impaired feedback and elevated cortisol in a subgroup.	Often lower basal cortisol or enhanced receptor sensitivity; altered diurnal dynamics.	Resveratrol response heterogeneity tracks hepatic glucocorticoid metabolism in rats.[69,79]
Microbiota–gut–brain axis	Microbial metabolites and immune tone may affect arousal.	Short-chain fatty acids, tryptophan, bile acids, permeability, and inflammatory tone.	Trauma- or stress-related dysbiosis may influence resilience and extinction.	Stress and trauma models respond to selected polyphenols or hydroxytyrosol.[80,81,93,94]

Abbreviations: 5-HT: 5-hydroxytryptamine (serotonin); BDNF: Brain-derived neurotrophic factor; CREB: cAMP response element-binding protein; EGCG: Epigallocatechin gallate; GABA-A: Gamma-aminobutyric acid type A; HPA: Hypothalamic–pituitary–adrenal; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; PTSD: Post-traumatic stress disorder; TrkB: Tropomyosin receptor kinase B.

scores after curcumin 500 mg/day. This is not evidence for treatment of established postpartum depression.[102]

Nevertheless, recent null findings moderate these positive observations. In an open-label randomized pilot, 19 adults with major depressive disorder received escitalopram with or without 200 mg/day tetrahydrocurcumin for 29 days. Comparable Hamilton Depression Rating Scale-17 (HAMD-17) changes were observed between groups among 16 completers.[103] An eight-week trial in 64 adults with elevated depressive symptoms demonstrated no superiority of combined 1,330 mg/day curcumin and 350 mg/day EGCG over placebo regarding mood, anxiety, sleep, or serum BDNF.[104] One meta-analysis detected modest antidepressant effects of polyphenol supplementation, yet heterogeneity in compounds, populations, endpoints, intervention duration, and study quality constrains pooled inference.[105] Clinical anxiolytic evidence for polyphenols is restricted to subclinical or comorbid cohorts. Notably, no completed therapeutic RCT has evaluated purified polyphenols in clinically diagnosed PTSD. Their putative anti-PTSD effects remain preclinical and do not support clinical application. Representative human studies on polyphenols and mood/stress-related outcomes are summarized in Table 2.

Table 2. Representative human evidence for polyphenols and mood- or stress-related outcomes

Study/Population	Exposure or intervention	Design/Duration	Main finding	Interpretation
Fisk *et al.*[96]; 64 adolescents	Wild blueberry	Randomized, placebo-controlled; 4 weeks	Lower depressive symptoms; no anxiety effect.	Subclinical sample and short duration; not treatment of a diagnosed disorder.
Velichkov *et al.*[97]; 60 emerging adults with self-reported depressive symptoms	Wild blueberry	Double-blind placebo RCT; 6 weeks	Placebo produced a 5.8-point greater reduction in BDI-II scores; an acute positive-affect signal followed blueberry intake.	Contradicts a simple benefit narrative; chronic and acute outcomes diverged.
Choi *et al.*[98]; 40 young adults with major depressive disorder	Flavonoid-rich orange juice, 190 mL three times/day	Single-blind controlled trial; 8 weeks	Depression scores declined in both the flavonoid-rich and low-flavonoid drink groups.	No demonstrated between-group symptom superiority; biomarker changes do not establish efficacy.
Venable *et al.*[99]; diagnosed depressive or anxiety disorder; 53 enrolled, 23 completed both periods	Whole freeze-dried blueberry powder, 24 g/day	Double-blind matched-pair crossover; two 12-week periods	Reported lower depression and anxiety symptoms; inflammatory markers were unchanged.	High attrition, pseudo-randomized allocation, and small completer sample make the result preliminary.
Asadi *et al.*[100]; 80 patients with diabetes and peripheral neuropathy	Nano-curcumin 80 mg/day	Double-blind placebo RCT; 8 weeks	Small reductions in depression and anxiety scores.	Comorbid metabolic population; does not establish efficacy in primary psychiatric disease.
Yaikwawong *et al.*[101]; 227 adults with obesity and type 2 diabetes	Curcuminoids 1,500 mg/day	Double-blind placebo RCT; 12 months	PHQ-9 scores and metabolic/inflammatory measures improved versus placebo.	Not enrolled for primary depression; metabolic change and comorbidity limit psychiatric generalization.
Hamlbar *et al.*[102]; 96 primiparous women without baseline depression	Curcumin 500 mg/day	Double-blind placebo RCT; 8 weeks	Postpartum depression and anxiety symptom scores were lower than placebo.	Prevention in a selected low-risk cohort, not treatment of established postpartum depression.
Guo *et al.*[103]; 19 adults with major depressive disorder; 16 completed	Escitalopram with or without tetrahydrocurcumin 200 mg/day	Open-label randomized pilot with blinded raters; 29 days	No between-group difference in total HAMD-17; gastrointestinal symptoms improved.	Very small, short, open-label augmentation study; mechanistic findings do not establish efficacy.
Cavanah *et al.*[104]; 64 adults with elevated depressive symptoms	Curcumin 1,330 mg/day plus EGCG 350 mg/day	Double-blind placebo RCT; 8 weeks	Mood, anxiety, sleep, and BDNF changes did not differ from placebo.	Well-controlled null result in a symptom-defined rather than diagnosed sample.

Abbreviations: BDI-II: Beck Depression Inventory-II; BDNF: Brain-derived neurotrophic factor; EGCG: Epigallocatechin gallate; HAMD-17: Hamilton Depression Rating Scale-17; PHQ-9: Patient Health Questionnaire-9; RCT: Randomized controlled trial.

5. Pharmacokinetics and brain delivery

Polyphenol pharmacokinetics vary by chemical class and formulation. In human studies, circulating metabolites generally differ from native dietary compounds. Total metabolite concentrations and urinary recovery show substantial inter-study variability.[106] Resveratrol exemplifies the pharmacological divergence between parent molecules and their metabolites. Quercetin demonstrates glycoside-dependent absorption. Chlorogenic acid and tannins highlight reliance on gut microbial metabolism. Repeated dosing or fasting elevates EGCG systemic exposure. Such exposure changes may augment biological activity while raising the risk of adverse events.[22,107-109]

Delivery strategies should be matched to the pharmacological bottleneck. Lipid, polymeric, phospholipid, and micellar formulations improve solubility or stability. Receptor-targeted nanoparticles enhance endothelial transport. Intranasal delivery exploits olfactory and trigeminal pathways. Transferrin-functionalized curcumin lipid nanoparticles, curcumin–lactoferrin nanoparticles, and intranasal resveratrol nanosuspension gel achieve better permeability or brain exposure in cellular and animal models.[110-112] These findings only validate delivery performance and do not confirm psychiatric efficacy. Clinical translation requires further verification of stability, release profiles, biodistribution, repeated-dose toxicology, immunogenicity, and device practicality, alongside proven advantages over chemically standardized oral preparations.[113]

6. Discussion

Accumulating preclinical and preliminary clinical evidence demonstrates the robust neuroprotective, antioxidant, and anti-inflammatory efficacy of polyphenols in mitigating anxiety, depression, and PTSD. However, undefined optimal dosages, low bioavailability, unfavorable pharmacokinetic properties, and limited clinical validation substantially hinder their clinical translation.[114] Additionally, gut microbiota-driven individual variability greatly affects polyphenol metabolism and neuroactive effects.[115,116] The human record is encouraging but not definitive. Current clinical trials are limited by short durations and small sample sizes and do not clarify long-term cumulative toxicity or drug-interaction risks. Current data do not justify replacing established treatment or recommending a class-wide dose. Future large-scale, long-term clinical trials and standardized dose–response studies are therefore critical to establish safe, personalized dosing and reliable safety profiles for polyphenol intervention.

Poor oral absorption, rapid *in vivo* metabolism, and low central nervous system bioavailability markedly compromise the *in vivo* efficacy of polyphenols, despite their potent *in vitro* neuroprotective activities. To overcome these limitations, advanced delivery strategies including nanoformulations and metal–polyphenol networks have been developed to enhance polyphenol stability and brain-targeting efficiency.[117] Advanced encapsulation, nanoformulation, and controlled-release systems can increase delivery efficiency[113], while standardized quality control of polyphenol content is essential to ensure consistent functional food efficacy.[118]

7. Conclusion

Preclinical studies reveal compound-specific polyphenol regulation of neurotransmission, neuroplasticity, oxidative-inflammatory signaling, HPA-axis activity, and microbiota-derived metabolites, as illustrated in Figure 1. Nevertheless, human therapeutic evidence remains

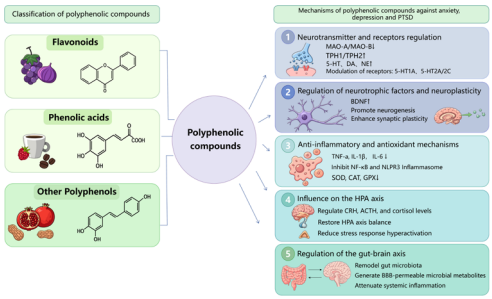


Figure 1. Classification of polyphenolic compounds and their potential mechanisms against anxiety, depression, and PTSD. The neuroprotective effects of polyphenols against stress-related mental disorders are mediated via five core pathways: neurotransmitter and receptor regulation, modulation of neurotrophic factors and neuroplasticity, anti-inflammatory and antioxidant activities, HPA-axis homeostasis, and gut–brain axis modulation.
Abbreviations: 5-HT: 5-hydroxytryptamine; 5-HT1A: 5-hydroxytryptamine receptor 1A; 5-HT2A: 5-hydroxytryptamine receptor 2A; 5-HT2C: 5-hydroxytryptamine receptor 2C; ACTH: Adrenocorticotropic hormone; BBB: Blood–brain barrier; BDNF: Brain-derived neurotrophic factor; CAT: Catalase; CRH: Corticotropin-releasing hormone; DA: Dopamine; GPX: Glutathione peroxidase; HPA: Hypothalamic–pituitary–adrenal; IL-1β: Interleukin-1 beta; MAO-A: Monoamine oxidase A; NE: Norepinephrine; NF-κB: Nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor alpha; TPH1: Tryptophan hydroxylase 1.

limited and inconsistent. Curcumin represents the most well-studied candidate, yet major-depression trials are small, formulation-dependent, and yield discordant results. Whole-food interventions likewise produce positive, null, and adverse outcomes. Clinical evidence for anxiolytic effects is largely restricted to subclinical, preventive, or comorbid cohorts. No completed therapeutic RCT has evaluated polyphenols in clinically diagnosed PTSD. Polyphenols cannot replace established psychotherapy or pharmacotherapy and are not recommended as a class-wide intervention. Robust clinical translation requires chemically standardized preparations, parent-metabolite pharmacokinetic profiles, validated target engagement, diagnosis-specific endpoints, adequately powered long-term randomized trials, and continuous monitoring for toxicity and supplement–drug interactions.

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