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TURMERIC (CURCUMA LONGA) AND MAJOR DEPRESSION BEYOND THE ANTI-INFLAMMATORY EFFECT: AN UPDATED JOURNALS REVIEW

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ABSTRACT Despite notable advances in modern pharmacotherapy, a considerable proportion of patients with Major Depressive Disorder continue to experience inadequate responses, residual symptoms, or treatment resistance. These limitations highlight the need for novel, safe, and mechanistically relevant adjunctive strategies. Turmeric (Curcuma longa) and its active polyphenol curcumin have gained increasing attention as nutraceutical candidates with antidepressant potential. Traditionally valued for its anti-inflammatory effects, curcumin is now recognized for its broader biological actions, including modulation of neurotrophic signaling, oxidative balance, and neuroplasticity, all of which are implicated in the pathophysiology of depression. A structured literature search was conducted across PubMed, Semantic Scholar, and OpenAlex, using the PRISMA-like methodology. Eligibility was restricted to English-language studies published between 2005 and August 2025 in Q1–Q2 journals, focusing on randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Of the 980 records screened, 14 high-quality studies met the inclusion criteria and were analyzed. The findings of these studies indicate that curcumin supplementation, either as monotherapy or adjunctive to standard antidepressants, is associated with modest but statistically significant improvements in depressive symptom severity compared with placebo. Safety outcomes were consistently favorable, with mild adverse events comparable to those of the placebo. However, its long-term safety, optimal dosing strategies, and effects in treatment-resistant populations remain poorly characterized. Current evidence is also limited by small sample sizes, short trial durations, and formulation heterogeneity.

KEYWORDS : curcuma longa, major depression, MDD, nutraceutical, antidepressant potential, adjunctive strategies

INTRODUCTION

Turmeric (*Curcuma Longa L., 1753* according to binomial nomenclature), also known as *haldi* in India and often referred to as the "golden spice" or "Indian saffron," has been cultivated for centuries in South Asia. India is the world's largest producer of turmeric, with key cultivation areas such as the Erode District in Tamil Nadu, underscoring its long-standing cultural and economic relevance (Sumathi & Gayathri, 2016). Beyond its widespread culinary use in Indian cuisine, turmeric plays a central role in Ayurvedic medicine, where it has traditionally been employed to treat digestive, inflammatory, and "mind–body" disorders. More recently, its therapeutic spectrum has expanded into areas such as immunomodulation and antiviral potential; for instance, investigations into its efficacy in COVID-19 prevention and treatment have underscored its broad pharmacological relevance and stimulated renewed clinical interest (Kothadia, & Parulkar, 2020).

In recent decades, modern research has extended this interest to neuropsychiatric conditions, including depression and anxiety. Major Depressive Disorder (MDD) is a highly prevalent psychiatric condition and a leading cause of disability worldwide, affecting over 300 million people and contributing substantially to the global burden of disease (World Health Organization, 2017). Despite the availability of multiple pharmacological options, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants, a considerable proportion of patients remain partially responsive or develop treatment-resistant depression (Rush et al., 2006). Furthermore, the delayed onset of action, adverse side effects, and residual functional impairment limit the effectiveness of current treatments and highlight the need for novel therapeutic strategies (Al-Karawi, Al Mamoori, & Tayyar, 2016; Wang, Zhang, Huang, & Liu, 2020).

In recent years, nutraceuticals have attracted growing interest in psychiatry as adjunctive or alternative treatment options. Turmeric and its primary bioactive constituent, curcumin, have emerged as promising candidates in this field. Turmeric has long been recognized for its anti-inflammatory and antioxidant properties and is traditionally employed in Ayurvedic and other systems of medicine for a wide range of ailments. Increasingly, modern pharmacological research has suggested that these pleiotropic effects may extend to neuropsychiatric disorders, particularly MDD (Lopresti & Drummond, 2017; Fusar-Poli, Vozza, Gabbiadini et al., 2020).

Notably, depression is no longer viewed solely as a disorder involving monoaminergic dysregulation. A growing body of evidence implicates chronic low-grade inflammation, oxidative and nitrosative stress, impaired neuroplasticity, and deficits in neurotrophic signaling, particularly involving brain-derived neurotrophic factor (BDNF), as key pathophysiological processes (Ng, Koh, Chan, & Ho, 2017; Yu, Pei, Zhang, Wen, & Yang, 2015; Guo, Fang, Xiong, Zhou, & Zeng, 2023). Curcumin has demonstrated modulatory effects across these domains, including the suppression of pro-inflammatory cytokines (e.g., interleukin IL, tumor necrosis factor TNF-), upregulation of BDNF, attenuation of oxidative stress, and possible regulation of monoaminergic neurotransmission (Zhang, Guo, Han et al., 2019; Wu, Sun, Guoet al., 2021).

Taken together, this convergence of ethnomedicine and contemporary neuroscience underscores the importance of re-examining the potential role of turmeric in psychiatry. This review aims to synthesize current preclinical and clinical evidence regarding the use of curcumin in MDD, with particular emphasis on its mechanistic actions that extend beyond its traditional characterization as an anti-inflammatory compound.

MATERIALS AND METHODS

Search Strategy

A structured literature search was conducted to identify clinical and mechanistic studies on turmeric and its main bioactive compound, curcumin, in the treatment of Major Depressive Disorder. A search string consisting of the main substring and an alternation of secondary substrings was used to broaden the search range in the various databases: main string: ("Curcuma longa" OR curcumin OR turmeric) AND ("depressive disorder" OR depression); substring: (adjunctive therapy OR add-on OR "combined with antidepressants" OR SSRI OR SNRI); substring: (remission OR response OR "treatment resistance" OR "symptom reduction")

Searches were performed across multiple open-access and widely used scientific databases, including PubMed, Semantic Scholar, and OpenAlex.

Eligibility Criteria

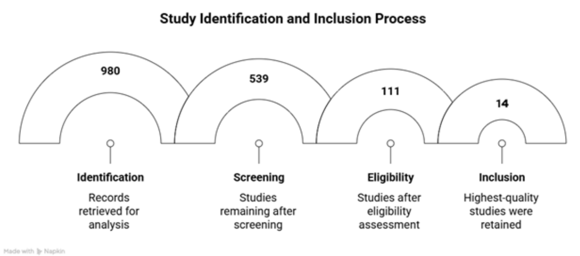
The review was restricted to the following:

- Language: English publications only.
- Date: Studies published between 2005 and August 2025 were included.
- Journal quality: Only studies published in Q1 and Q2 journals (based on Scimago Journal Rank and Clarivate Journal Citation Reports) were included.
- Study design: Randomized double-blind clinical trials (RCTs), systematic reviews, and meta-analyses. Narrative reviews, case series, and non-peer-reviewed materials were excluded from the analysis.
- Population and outcomes: Studies involving patients with MDD or depressive symptoms as primary outcomes. Subgroup analyses of atypical or treatment-resistant depression were performed when available.

Selection Process

The study identification and inclusion process followed a PRISMA-like framework.

- Identification: A total of *n = 980* records were retrieved for analysis.
- Screening: After removing duplicates and records without abstracts, *539* studies remained.
- Eligibility: Of these, 428 were excluded due to low semantic relevance based on title and abstract screenings.
- Inclusion: After the final quality appraisal, the top 14 highest-quality studies (eight RCTs and six systematic reviews and meta-analyses) were retained for the synthesis.



Data Extraction And Synthesis

The following information was extracted from the included studies: study design, population characteristics, intervention details (formulation, dose, and duration), comparator group, outcome measures (depressive symptom severity, response, remission, biomarker changes), and safety profile. Data were narratively synthesized according to the clinical, mechanistic, and adjunctive therapy evidence. Special attention was given to biomarker-guided outcomes, such as changes in BDNF, cytokines, oxidative stress markers, monoamines, and cortisol.

Phytochemistry And Pharmacology Of *Curcuma Longa*

Turmeric is a perennial herb of the Zingiberaceae family, contains more than 100 identified compounds, among which curcuminoids are the primary bioactive constituents. The three principal curcuminoids are curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the most extensively studied for its pharmacological activity (Hatamipour, Sahebkar, Alavizadeh et al., 2019; Lopresti, 2017). These polyphenolic compounds are responsible for the characteristic yellow pigment of turmeric and have been implicated in antioxidant, anti-inflammatory, and neuroprotective effects relevant to psychiatric disorders.

Despite its promising pharmacodynamic properties, curcumin has notoriously poor oral bioavailability. However, their clinical application is limited by low aqueous solubility, rapid intestinal metabolism, and systemic elimination (Anand, Kunnumakkara, Newman, & Aggarwal, 2007). Consequently, plasma and tissue concentrations following conventional oral administration are often insufficient to achieve robust central nervous system (CNS) effects in the target population. Several formulation strategies have been developed to overcome these challenges. These include co-administration with piperine, an alkaloid from black pepper that inhibits hepatic and intestinal glucuronidation and enhances curcumin bioavailability by up to 2000% (Shoba, Joy, Joseph et al., 1998), nanoparticle and liposomal encapsulations designed to improve stability and gastrointestinal absorption (Wang, Zhang, Huang, & Liu, 2020), and phytosomal preparations, which conjugate curcumin to phospholipids, increasing its systemic bioavailability (Deniz, Demiroz, Ulutas et al., 2025).

Preclinical studies have further suggested that curcumin can cross the blood-brain barrier, thereby directly exerting neuroprotective effects (Zhang, Guo, Han et al., 2019; Wu, Sun, Guoet al., 2021). Within the CNS, curcumin demonstrates pleiotropic activity, including the regulation of oxidative stress, modulation of pro-inflammatory cytokines, enhancement of brain-derived neurotrophic factor (BDNF), and facilitation of synaptic plasticity—all of which are critical targets in the pathophysiology of depression (Yu, Pei, Zhang et al., 2015; Guo, Fang, Xiong, Zhou, & Zeng, 2023).

Pathophysiological Basis For Curcumin In Depression

A growing body of pharmacological research has highlighted the multifaceted biological activities of curcumin, including its anti-inflammatory, antioxidant, neurotrophic, and monoaminergic effects (Baluja & Rehman, 2019). These mechanisms overlap with the key pathophysiological processes implicated in Major Depressive Disorder, suggesting that curcumin may influence several disease-relevant pathways simultaneously. Rather than acting through a single target, curcumin appears to exert system-level modulation of neuroimmune and neuroendocrine functions, which could explain its potential utility as an adjunctive antidepressant.

Neuroinflammation -

Chronic low-grade inflammation is increasingly recognized as a core contributor to the pathophysiology of major depressive disorder (Kouba, De Araujo Borba, Borges De Souza et al., 2024). Elevated circulating levels of pro-inflammatory cytokines, such as interleukin IL-1 , IL-6, and tumor necrosis factor-alpha (TNF-), are frequently observed in patients with depression, contributing to neuroimmune dysregulation, neurotransmitter metabolism alterations, and glucocorticoid resistance (Matias, Achete, Campanari et al., 2021). Curcumin has consistently demonstrated anti-inflammatory properties, including suppression of NF- B activation and inhibition of the NLRP3 inflammasome, leading to a reduction in cytokine production (Zhang, Guo, Han et al., 2019). Clinical studies have confirmed that curcumin supplementation lowers pro-inflammatory cytokines in MDD populations (Yaikwawong, Jansarikit, Jirawatnotai, & Chuengsamarn, 2024; Yu, Pei, Zhang, Wen, & Yang, 2015).

Neurotrophic And Neuroplastic Pathways -

Deficits in brain-derived neurotrophic factor (BDNF) signaling and impaired neuroplasticity are hallmarks of depression and predictors of poor treatment responses. Both preclinical and clinical studies have shown that curcumin enhances BDNF levels, particularly in the hippocampus and amygdala, thereby promoting neuronal survival, synaptic plasticity, and cognitive resilience (Hurley, Akinfiresoye, Nwulia et al., 2013; Zhang, Xu, Wanget al., 2012). This mechanism is partly mediated by the activation of the MAPK/ERK and CREB pathways, which regulate the transcription of neuroplasticity-related genes (Guo, Fang, Xiong, Zhou, & Zeng, 2023). Clinical trials have further demonstrated that curcumin supplementation is associated with increased serum BDNF levels, which correlate with reductionns in the severity of depressive symptoms (Yu, Pei, Zhang et al., 2015).

Oxidative And Nitrosative Stress -
MDD is characterized by increased oxidative and nitrosative stress, which damages neuronal structures and exacerbates mood dysregulation. Curcumin exerts antioxidant effects by upregulating endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, while simultaneously reducing malondialdehyde (MDA), a marker of lipid peroxidation (Hussain, Ahmad, Shah et al., 2022; Liao, Lv, Caoet al., 2020; Da Silva Marques, Antunes, Brum et al., 2020). In animal models of chronic stress, curcumin restores redox balance and activates the Nrf2 pathway, thereby reducing oxidative damage to neural tissues (Liao, Lv, Cao et al., 2020).

Monoaminergic Transmission and HPA Axis Regulation -
Although the monoamine hypothesis alone does not fully explain depression, serotonergic, dopaminergic, and noradrenergic systems remain central to the pharmacology of antidepressants. Curcumin has been shown to increase serotonin and dopamine levels in animal models, partly by inhibiting monoamine oxidase activity (Kulkarni, Bhutani, & Bishnoi, 2008; Li, Wang, Pan et al., 2009). These actions mirror the effects of conventional antidepressants, suggesting potential synergy when curcumin is combined with SSRIs or SNRIs (Lopresti, Hood, & Drummond, 2012). Additionally, curcumin supplementation has been associated with reduced salivary cortisol levels, reflecting partial normalization of hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, a common finding in MDD (Yu, Pei, Zhang et al., 2015; Matias, Achete, Campanari et al., 2021).

Clinical Evidence in Major Depressive Disorder
Randomized Controlled Trials (RCTs)
Across randomized controlled trials, curcumin consistently showed antidepressant signals—most clearly after several weeks of treatment—and a favorable tolerability profile, although effect sizes and designs varied.

Timing And Magnitude Of Symptom Changes.
In an 8-week double-blind RCT, curcumin (500 mg b.i.d.) and placebo both reduced IDS-SR30 (Inventory of Depressive Symptomatology) scores through week 4, but from weeks 4–8, curcumin was separated from placebo on total IDS-SR30 and the mood factor, indicating a delayed onset of superiority (Lopresti, Maes, Maker et al., 2014). A larger 12-week trial comparing low-dose curcumin, high-dose curcumin, and a curcumin-saffron combination to placebo replicated the superiority of active arms on IDS-SR30 and state/trait anxiety, again favoring active treatment over placebo across the treatment window (Lopresti & Drummond, 2017). In contrast, a three-arm pilot without a placebo (fluoxetine, curcumin, or their combination) found comparable HAM-D17 (Hamilton Depression Rating Scale) changes across groups over 6 weeks, with a numerically higher-but non-significant-response in the combination arm, underscoring the need for adequate control conditions and power (Sanmukhani, Satodia, Trivedi et al., 2014).

Adjunctive Use And Mechanistic Alignment Of The Treatment.
As an add-on therapy to ongoing escitalopram, curcumin (1,000 mg/day, 6 weeks) significantly reduced HDRS-17 and MADRS (Montgomery-Asberg Depression Rating Scale) scores compared to placebo and concurrently shifted mechanistic biomarkers-lower IL-1β and TNF-α, higher plasma BDNF, and reduced salivary cortisol-supporting anti-inflammatory and neurotrophic pathways of benefit (Yu, Pei, Zhang et al., 2015). In a biomarker-focused RCT of curcumin vs placebo, exploratory analyses linked greater symptom improvement to higher baseline endothelin-1 and leptin levels in the curcumin group and documented treatment-related changes across urinary and salivary neuroendocrine markers, suggesting biological engagement even when multiple comparisons and small samples limit firm inference (Lopresti, Maes, Maker et al., 2014). A longer, 12-month RCT in obese adults with type 2 diabetes showed robust improvement in PHQ-9 (Patient Health Questionnaire) alongside increases in serum serotonin, broad anti-inflammatory and antioxidant shifts, and metabolic benefits (lower HbA1c, FPG, and HOMA-IR), indicating that mood improvement may track with systemic immunometabolic modulation in comorbid populations (Yaikwawong, Jansarikit, Jirawatnotai et al., 2024).

Subgroup And Moderator Analyses
Subgroup analyses provided preliminary insights into the potential role of curcumin in patients with atypical or treatment-resistant depression. In one trial, a subgroup of 18 participants meeting the criteria for atypical depression demonstrated superior clinical improvements when treated with curcumin compared to placebo, suggesting that specific depressive phenotypes may be particularly responsive to its pharmacological properties (Lopresti, Maes, Maker et al, 2014). Similarly, in a 12-week multi-arm trial, response rates were higher among individuals with atypical presentations than among those with other forms of depression, reinforcing the relevance of stratified analyses (Lopresti & Drummond, 2017). Beyond atypical depression, additional exploratory findings indicated that curcumin supplementation yielded partial benefits in treatment-resistant populations, highlighting its potential role as an adjunctive strategy in difficult-to-treat cases (Lopresti, Maes, Meddens et al., 2015). Moderator analyses have also suggested sex-specific effects: in an add-on study, males receiving curcumin exhibited clearer improvements in depressive symptoms on the MADRS than females, whereas the impact on anxiety outcomes measured by the HAM-A was less consistent (Kanchanatawan, Tangwongchai, Sughondhabhirom et al., 2017). Collectively, these findings suggest that curcumin's efficacy may be moderated by depression subtypes and patient characteristics.

Dose, Formulation, And Duration Of Treatment.
Head-to-head dosing within a 12-week trial found no significant differences between low- and high-dose curcumin or curcumin–saffron combinations on primary mood or anxiety outcomes, leaving the dose–response unresolved (Lopresti & Drummond, 2016). Notably, across trials, the clearest separation from placebo often emerged after week 4, implying that curcumin may require sustained administration to manifest clinical advantages (Lopresti, Maes, Maker et al., 2014; Lopresti & Drummond, 2016). Longer courses (e.g., 12 months) may potentiate both mood and biological benefits in metabolically vulnerable groups (Yaikwawong, Jansarikit, Jirawatnotai, et al. 2024).

Reference & Country	Study Design	Patients, Age, Diagnosis	Intervention	Outcomes
Panahi & al. - 2014 (Iran)	OLT, 6w	61 curcuminoid group, 50 control group, ♂♀18-65 years, DSM-IV Major Depressive	Standard antidepressant therapy plus a curcuminoids-piperine combination (1000–10 mg/day), vs standard antidepressant therapy alone (control group); HADS and BDI-II scores	Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory II (BDI-II)

Lopresti & al. - 2014 (Australia)	RCT, DB, PC, 8w	28 in the curcumin group, 28 placebo group, ♂♀18-65, DSM-IV Major Depressive (18 atypical depression subgroup)	Curcumin (500 mg twice daily) vs placebo (cellulose)	Inventory of Depressive Symptomatology self-rated version (IDS-SR30) and Spielberger State-Trait Anxiety Inventory (STAI)
Yu & al. - 2015 (China)	RCT, DB, PC, 6w	50 in curcumin group, 50 in placebo, ♂♀31-59, DSM-IV Major Depressive	1000 mg of curcumin daily vs 1000 mg of placebo (soybean powder), both with antidepressant medications (escitalopram)	17-item Hamilton Depression Rating Scale (HDRS-17) and the Montgomery-Asberg Depression Rating Scale (MADRS)
Yaikwawong & al. - 2024 (Thailand)	RCT, DB, PC, 52w	113 curcumin group, 114 placebo, ♂♀ ≥35 years, DSM-IV Major Depressive and T2DM	Three 250 mg capsules of curcumin twice daily vs three capsules of placebo twice daily	Thai version of the nine-item Patient Health Questionnaire (PHQ-9)
Sanmukhani % al. - 2014 (India)	RCT, MB, 6w	20 fluoxetine, 20 curcumin, and 20 fluoxetine + curcumin group, ♂♀ ≥18,, DSM-IV Major Depressive	Fluoxetine 20 mg daily, curcumin 1000 mg daily or a combination of both	17-item Hamilton Depression Rating Scale (HDRS-17) and Clinical global impression-improvement (CGI-I) assessment scale, Clinical global impression-severity of illness (CGI-S)
Lopresti & Drummond - 2017 (Australia)	RCT, DB, PC, 12w	36 in placebo, 33 in high-dose curcumin (HDC), 28 in low-dose curcumin (LDC), and 26 in low-dose curcumin plus saffron (LDC+S), ♂♀ 18-65, DSM-IV Major Depressive (34 atypical depression and 46 other depression subgroup)	Low-dose curcumin extract (250mg twice daily), high-dose curcumin extract (500mg twice daily), and combined low-dose curcumin extract plus saffron (15mg twice daily) vs placebo; HDC vs LDC; LDC vs LDC+S	Depressive Symptomatology self-rated version (IDS-SR30), The Spielberger State-Trait Anxiety Inventory (STAI)
Lopresti & al. - 2015 (Australia)	RCT, DB, PC, 8w	22 curcumin group, 25 place group, ♂♀ 18-65, DSM-IV Major Depressive (19 high baseline Endothelin-1 (ET-1) levels subgroup)	Curcumin 500 mg capsule twice daily vs placebo cellulose capsules twice daily	Inventory of Depressive Symptomatology self-rated version (IDS-SR30)
Kanchanatawan & al. - 2018 (Thailand)	RCT, DB, PC, 12w	30 curcumin group, 31 placebo group, ♂♀ 18-63, DSM-IV-TR Major Depressive	Curcumin from 500 to 1500 mg daily over four weeks + CAU vs Placebo + CAU	Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A)

RCT: Randomized Controlled Trial; **OLT**: Open Label Trial; **DB**: Double-Blind; **MB**: Mono-Blind; **PC**: Placebo-Controlled; **w**: weeks

Meta-analyses And Systematic Reviews

Across the evidence base, at least three traditional meta-analyses and two systematic reviews (one of which is a network meta-analysis) have evaluated curcumin for depressive symptoms. Early syntheses focusing on patients with major depressive disorder found curcumin to be more effective than placebo or control (Al-Karawi, Mamoori, & Tayyar, 2016; Ng, Koh, Chan,& Ho et al., 2017). A subsequent broader meta-analysis, including both diagnosed depression and subthreshold depressive symptoms, confirmed a statistically significant antidepressant effect but rated the overall quality of evidence as low (Wang, Zhang, Huang et al., 2020). A comprehensive systematic review highlighted heterogeneous findings likely driven by differences in the dose, formulation, and study populations (Matias, Achete, Campanari et al., 2021). Finally, a large network meta-analysis (NMA) comparing numerous nutraceuticals reported that curcumin, especially as an adjunct to antidepressant therapy (ADT), ranked above ADT alone for efficacy, although with very low to low certainty of evidence (Cheng, Huang, Chen et al., 2025). Another systematic review and meta-analysis reported sizeable effects on both depression and anxiety outcomes while cautioning about small samples and heterogeneity (Fusar-Poli, Vozza, Gabbiadini et al., 2020).

Consistency of Findings Across Reviews -

Despite methodological diversity, the direction of effect is broadly consistent: curcumin is associated with reductions in depressive symptoms compared with placebo or control conditions (Al-Karawi, Mamoori, & Tayyar, 2016; Ng, Koh, Chan,& Ho et al., 2017; Fusar-Poli, Vozza, Gabbiadini et al., 2020; Wang, Zhang, Huang et al., 2020). However, estimates vary, and certainty ranges from low to moderate, with some syntheses emphasizing considerable uncertainty, heterogeneity, and design limitations in the underlying trials (Matias, Achete, Campanari et al., 2021; Wang, Zhang, Huang et al., 2020). The NMA aligns with this pattern by ranking adjunctive curcumin favorably relative to ADT alone; however, it simultaneously flags inconsistency and very low overall confidence in many comparisons (Cheng, Huang, Chen et al., 2025).

Effect Size and Clinical Relevance -

Pooled standardized effects from traditional meta-analyses fell within the small-to-moderate range. Ng et al. (2017) reported Standardized Mean Difference (SMD) ≈ −0.34 on HAM-D, and Wang et al. (2020) found SMD = −0.32 (95% CI −0.50 to −0.13) when pooling depression and depressive-symptom studies, with a slightly larger effect confined to diagnosed depression (SMD = −0.35). Fusar-Poli et al. (2020) reported larger pooled effects (e.g., Hedges' g ≈ −0.75 for depression), and sizeable effects for anxiety (Hedges' g of -2.62), but urged caution because of small, heterogeneous trial samples. Al-Karawi et al. (2016) observed SMD = −0.34 with minimal statistical heterogeneity and exploratory indications that ≥ 6 weeks of treatment and ~1 g/day doses may be associated with stronger effects. In an NMA, adjunctive curcumin surpassed ADT alone in terms of depressive symptoms (SMD ≈ 1.03, 95% CI 0.55–1.51), with weaker and imprecise signals for curcumin monotherapy (Cheng, Huang, Chen et al., 2025).

Subgroup Analyses and Moderators -

Subgroup and moderator analyses across trials and reviews provide important insights into the heterogeneity of treatment effects with curcumin. Several studies have indicated that the benefits of antidepressants are more pronounced in patients with major depressive disorder than in those with subclinical or nonspecific depressive symptoms, underscoring the relevance of baseline diagnostic status and severity as moderators of response (Wang, Zhang, Huang et al., 2020). Meta-analytic findings further suggest that treatment duration plays a critical role, with clearer efficacy emerging after six or more weeks of administration (Al-Karawi, Mamoori, & Tayyar, 2016). Evidence has also highlighted that patients with comcomorbidities, such as diabetes, obesity, or chronic inflammation, appear to benefit more strongly, potentially reflecting curcumin's anti-inflammatory and metabolic effects (Ng, Koh, Chan,& Ho et al., 2017). Additional analyses have pointed to sex- and age-related differences, with some studies indicating greater improvements in younger or male participants, although these findings remain inconsistent (Matias, Achete, Campanari et al., 2021). Formulation-related factors also emerged as potential moderators; bioavailability enhancers such as piperine, BCM-95, and nano-curcumin were associated with stronger signals, although comparative evidence remains limited (Al-Karawi, Mamoori, & Tayyar, 2016; Matias, Achete, Campanari et al., 2021). Furthermore, the distinctions between atypical and typical depression suggest that atypical presentations may be particularly responsive to curcumin (Fusar-Poli, Vozza, Gabbiadini et al., 2020). Finally, network meta-analysis indicated that curcumin used as an adjunct to standard antidepressant therapy produced stronger and more consistent improvements than antidepressant monotherapy, even across severity strata, although the certainty of evidence was rated low (Cheng, Huang, Chen et al., 2025; Al-Karawi, Mamoori, & Tayyar, 2016). Collectively, these findings highlight the importance of considering diagnostic subtypes, treatment duration, comorbid conditions, and formulations to optimize curcumin's antidepressant potential.

Methodological Strengths and Weaknesses of the Evidence Base -

Most reviews adhered to PRISMA standards, used Cochrane risk-of-bias tools, and, where feasible, assessed publication bias (Al-Karawi, Mamoori, & Tayyar, 2016; Fusar-Poli, Vozza, Gabbiadini et al., 2020; Ng, Koh, Chan,& Ho et al., 2017; Wang, Zhang, Huang et al., 2020). Strengths include prespecified protocols (e.g., PROSPERO registration in some cases), sensitivity and subgroup analyses, and attempts to harmonize the outcome metrics. Weaknesses include small and few primary trials, variable risk of bias (with only a minority judged low risk), short intervention periods, reliance on self-report scales, and substantial between-study heterogeneity in populations, dosing, and formulations (Matias, Achete, Campanari et al., 2021; Wang, Zhang, Huang et al., 2020). The NMA provides breadth (hundreds of RCTs across nutraceuticals) and modern comparative methods but also exhibits global inconsistency, moderate-to-high heterogeneity, and very low certainty for many comparisons (Cheng, Huang, Chen et al., 2025).

Comparisons With Other Interventions -

Within comparative frameworks, curcumin's effects are broadly in line with several nutraceuticals and can augment standard antidepressants. The NMA places adjunctive curcumin above ADT alone for symptom reduction and response/remission outcomes, with tolerability comparable to that of placebo across most nutraceuticals (Cheng, Huang, Chen et al., 2025). Traditional meta-analyses also note benefits on anxiety outcomes and comparability (or potential complementarity) with other add-on strategies, although direct head-to-head curcumin comparisons remain sparse (Fusar-Poli, Vozza, Gabbiadini et al., 2020). Earlier reviews pointed to plausible synergy with antidepressants and animal-model parallels with conventional agents, yet emphasized that definitive clinical non-inferiority or superiority trials versus standard pharmacotherapies are lacking (Ng, Koh, Chan,& Ho et al., 2017).

Safety And Tolerability

Across randomized controlled trials (RCTs), curcumin has consistently demonstrated a favorable safety profile, with adverse event rates comparable to those of the placebo. The most commonly reported side effects were mild gastrointestinal complaints, such as loose bowels or a transient spicy aftertaste, without evidence of clinically significant harm (Lopresti, Maes, Maker e al., 2014; Lopresti & Drummond, 2017). Importantly, no pharmacokinetic interactions were observed when curcumin was co-administered with escitalopram, supporting its safety for routine combination with antidepressants (Yu, Pei, Zhang et al., 2015). Similarly, Sanmukhani et al. (2014) reported no meaningful safety differences between curcumin, fluoxetine, and combination groups.

Meta-analyses and systematic reviews corroborate these findings, concluding that curcumin is both safe and well tolerated in patients with major depressive disorder. Pooled evidence indicates that treatment discontinuation rates and incidence of adverse events do not differ significantly from placebo (Ng, Koh, Chan,& Ho et al., 2017; Wang, Zhang, Huang et al., 2020). A mini meta-analysis confirmed minimal heterogeneity in adverse event reporting and no evidence of treatment withdrawal due to safety issues (Al-Karawi, Mamoori, & Tayyar, 2016). Broader syntheses also highlight the tolerability of curcumin as at least equivalent to, and in some cases superior to, other nutraceuticals (Matias, Achete, Campanari et al., 2021; Cheng, Huang, Chen et al., 2025).

Collectively, the evidence suggests that curcumin is safe when administered at doses ranging from 500 to 1,500 mg/day for up to 12 weeks and does not increase treatment discontinuation or clinically significant adverse events relative to placebo or antidepressant therapy (Fusar-Poli, Vozza, Gabbiadini et al., 2020; Wang, Zhang, Huang et al., 2020). Moreover, data from longer trials reinforce this conclusion: in a 12-month study of obese patients with comorbid type 2 diabetes, curcumin up to 1,500 mg/day was well tolerated, with no serious safety signals and additional metabolic benefits (Yaikwawong, Jansarikit, Jirawatnotai et al., 2024).

Taken together, these findings provide strong reassurance regarding the short-to medium-term tolerability of curcumin in MDD populations. Nonetheless, gaps remain concerning its long-term safety in psychiatric populations with polypharmacy, where cumulative drug–nutraceutical interactions may differ. Future large-scale multicenter RCTs with extended follow-up and systematic monitoring of adverse events are warranted to consolidate curcumin's safety profile and optimize its clinical integration.

Limitations Of Current Evidence

Despite encouraging signals, the evidence base on curcumin for Major Depressive Disorder is constrained by methodological and translational limitations spanning primary RCTs and evidence syntheses.

Small Sample Sizes And Short Durations -

Most randomized controlled trials enrolled small cohorts and used brief treatment windows (approximately 6–12 weeks), limiting precision, external validity, and inference about relapse prevention or maintenance of remission (Lopresti, Maes, Maker et al., 2014; Sanmukhani, Satodia, Trivediet al., 2014; Yu, Pei, Zhang et al., 2015). Several trials were pilot studies, some with multiple comparisons, and in one instance, no placebo arm, further reducing internal validity (Sanmukhani, Satodia, Trivediet al., 2014; Lopresti, Maes, Maker et al., 2014; Lopresti & Drummond, 2017). Meta-analyses corroborate modest pooled effects but emphasize that the paucity of large, multicenter studies restricts confidence in long-term efficacy estimates (Fusar-Poli, Vozza, Gabbiadini et al., 2020; Wang, Zhang, Huang et al., 2020).

Heterogeneity In Formulations And Dosing -
Curcumin preparations vary widely across studies (standard extracts vs. bioavailability-enhanced products with piperine, nanoformulations, or phytosomes), and the dosing spans ~500–1,500 mg/day (Panahi, Badeli, Karami et al., 2015). Such variability complicates cross-trial synthesis and may confound the attribution to curcumin per se when enhancers are co-administered (Wang, Zhang, Huang et al., 2020). Dose–response relationships remain unresolved, and within-trial contrasts do not consistently separate low doses from high doses or combinations (Lopresti & Drummond, 2017; Fusar-Poli, Vozza, Gabbiadini et al., 2020).

Patient Population Variability And Generalizability -
Most RCTs recruited individuals with mild-to-moderate MDD, with few trials in severe or treatment-resistant depression (TRD), limiting the conclusions for higher-acuity populations (Lopresti, 2022). Subgroup signals suggest greater benefits in atypical depression (Lopresti & Drummond, 2017), and heterogeneity in comorbid profiles (e.g., metabolic disease) further complicates the interpretation (Kanchanatawan, Tangwongchai, Sughondhabhirom et al., 2017). Evidence syntheses also note geographic concentration (many trials in Asian-Pacific settings), which may limit transportability to other dietary and healthcare contexts (Fusar-Poli, Vozza, Gabbiadini et al., 2020).

Outcomes And Measurement Issues Beyond Symptom Reduction -
Although symptom scales typically improve, remission, response durability, functioning, and quality of life outcomes are inconsistently captured (Wang, Zhang, Huang et al., 2020). Several trials relied primarily on self-report instruments (e.g., IDS-SR30, STAI) without parallel clinician-rated endpoints, constraining triangulation (Lopresti, Maes, Maker et al., 2014; Lopresti & Drummond, 2017). Biomarker integration is uneven across studies, limiting mechanistic inference despite promising shifts in inflammatory, neurotrophic, and stress axis markers in some trials (Yu, Pei, Zhang et al., 2015; Matias, Achete, Campanari et al., 2021). Acceptability and safety reporting are generally favorable but not uniformly assessed across all studies (Wang, Zhang, Huang et al., 2020).

Risk of Bias, Reporting Quality, and Publication Bias -
The risk-of-bias profiles were mixed, with only a minority of trials rated as low risk and frequent concerns about allocation concealment, blinding depth, selective reporting, and small-study effects (Wang, Zhang, Huang et al., 2020; Fusar-Poli, Vozza, Gabbiadini et al., 2020). Multiple comparisons within small trials also increase the risk of type I errors (Lopresti & Drummond, 2017).

Constraints Specific to Evidence Syntheses (Systematic Reviews and Meta-Analyses) -
Across meta-analyses, recurring limitations include dependence on small, short-duration RCTs, pronounced heterogeneity in populations, interventions, and measurements, unclear or variable risk of bias, and incomplete reporting (Al-Karawi, Mamoori, & Tayyar, 2016; Fusar-Poli, Vozza, Gabbiadini et al., 2020; Matias, Achete, Campanari et al., 2021; Ng, Koh, Chan et al., 2017; Wang, Zhang, Huang et al., 2020). Some syntheses did not register protocols and several pooled datasets mixed bioavailability-enhanced formulations and confounding attribution (Wang, Zhang, Huang et al., 2020). The network meta-analysis adds structural issues-transitivity assumptions, global inconsistency between direct and indirect evidence, and classification challenges for chemically similar nutraceuticals-yielding very low to low certainty despite favorable rankings for adjunctive curcumin over antidepressant therapy (Cheng, Huang, Chen et al., 2025).

Interim Implications -
Taken together, limitations at both the trial and synthesis levels temper certainty about the magnitude, durability, and generalizability of the effects. Nevertheless, the convergence of clinical improvement with biologically plausible changes in inflammatory, neurotrophic, and HPA axis markers supports curcumin, particularly as an adjunct to antidepressants, as a candidate for larger, multicenter, longer-duration, and stratified RCTs incorporating standardized formulations/doses, clinician- and patient-reported outcomes, relapse/maintenance endpoints, and prespecified biomarker panels (Lopresti, Maes, Maker et al., 2014; Yu, Pei, Zhang et al., 2015; Yaikwawong, Jansarikit, Jirawatnotai et al., 2024).

Future Directions

While the current evidence supports curcumin as a promising adjunctive treatment for Major Depressive Disorder, several avenues for future research and clinical translation remain.

Larger, Standardized Clinical Trials -
Most available RCTs are small, single-center, and short-term studies. There is an urgent need for multicenter, adequately powered studies employing standardized bioavailability-enhanced formulations of curcumin. Such trials should use harmonized dosing regimens, treatment durations beyond 12 weeks, and clinically meaningful outcomes, including remission and relapse prevention (Fusar-Poli, Vozza, Gabbiadini et al., 2020; Wang, Zhang, Huang et al., 2020).

Biomarker-Guided Research -
The integration of mechanistic biomarkers, such as BDNF, pro-inflammatory cytokines (IL-1 , IL-6, TNF-), oxidative stress markers (MDA, SOD, catalase), and cortisol, may clarify the biological pathways underlying curcumin's antidepressant effects. Consistent biomarker measurements across trials could allow for mechanistic validation and identification of predictive markers of response (Hurley, Akinfiresoye, Nwulia et al., 2013; Yu, Pei, Zhanget al., 2015; Liao, Lv, Cao et al., 2020; Yaikwawong, Jansarikit, Jirawatnotai et al., 2024).

Personalized And Precision Psychiatry Approaches -
Future research should explore the inter-individual variability in treatment response. This includes investigating pharmacogenomic interactions (e.g., CYP450 metabolism), inflammatory phenotypes, and metabolic profiles to identify the subgroups most likely to benefit. Subtype-specific efficacy, particularly in atypical depression and partially treatment-resistant depression, warrants targeted exploration (Lopresti & Drummond, 2017; Lopresti, 2022).

Expansion To Comorbid Populations -
Given the broad anti-inflammatory and metabolic effects of curcumin, trials in patients with comorbid conditions, such as diabetes, obesity, and cardiovascular disease, may yield particularly relevant insights. Early evidence supports curcumin's efficacy in obese individuals with type 2 diabetes and comorbid depression (Yaikwawong, Jansarikit, Jirawatnotai et al., 2024), highlighting the potential for integrating psychiatric and metabolic care.

Integrative Psychiatry And Lifestyle-based Interventions -
Curcumin should be evaluated as part of a multimodal approach in integrative psychiatry, combined with established interventions such as exercise, mindfulness-based therapies, dietary modification, and other nutraceuticals (Ng, Koh, Chan et al., 2017). Positioning curcumin within a holistic, lifestyle-oriented model may maximize clinical and functional outcomes.

Bridging Traditional And Modern Medicine -

Turmeric has deep roots in Ayurvedic medicine, and bridging ethnopharmacological knowledge with contemporary clinical trials may enhance its acceptance and innovation. Exploring formulations and dosages derived from traditional practices validated through modern biomarker-driven methods could strengthen the evidence base and cultural relevance of curcumin in global psychiatry (Matias, Achete, Campanari et al., 2021).

CONCLUSION

Current evidence indicates that curcumin, the principal bioactive compound of turmeric (*Curcuma longa*), exerts consistent, albeit modest, benefits in the management of Major Depressive Disorder. Its therapeutic potential extends beyond the traditionally recognized anti-inflammatory effects and encompasses neurotrophic, neuroplastic, antioxidant, and monoaminergic mechanisms. Preclinical studies strongly support its multimodal activity, while randomized controlled trials and meta-analyses have demonstrated reductions in depressive symptom severity, particularly when curcumin is used as an adjunct to conventional antidepressants.

Its favorable safety and tolerability profiles further strengthen its candidacy as a low-risk nutraceutical option in integrative psychiatry. Subgroup analyses suggest that individuals with atypical depression, partial responders, or comorbid metabolic conditions may derive particular benefits. Nonetheless, methodological limitations, including small sample sizes, heterogeneous formulations, short treatment durations, and insufficient data on remission rates, temper the strength of the current conclusions.

In summary, curcumin holds promise as a complementary therapeutic agent for MDD, acting through multiple converging biological pathways. To move from promising adjunctive therapy to evidence-based clinical adoption, large, multicenter, biomarker-driven, and long-term trials are essential.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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Author Contribution

Dr. Federico Baranzini is the only author of this review

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