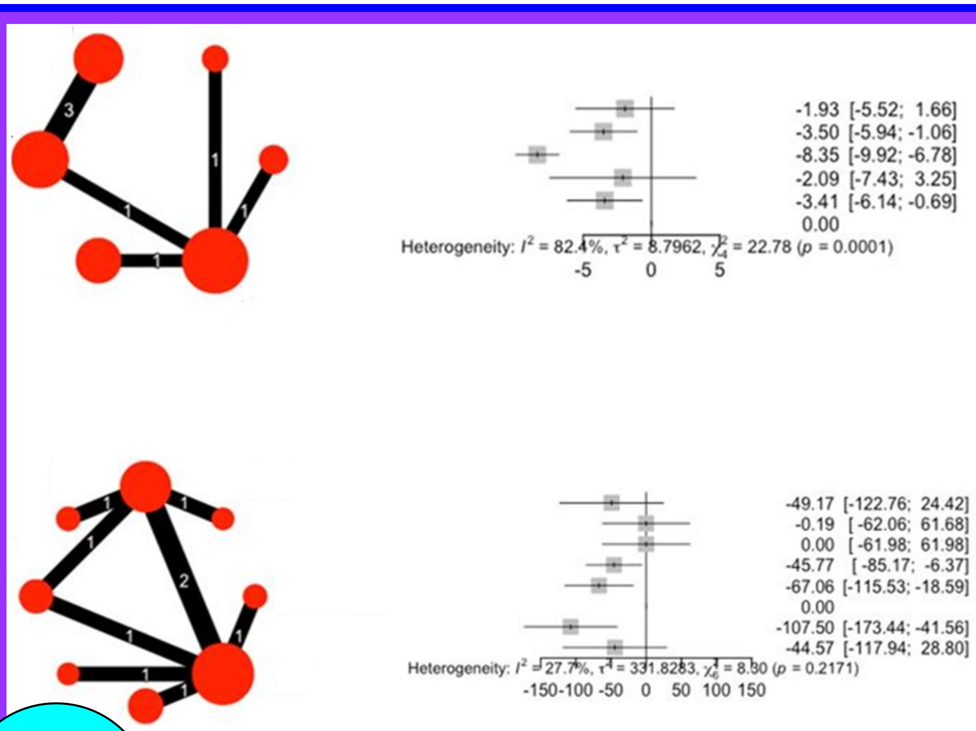

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Meta-Analysis

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Meta-analysis

Efficacy of herbal medicines and standard antidepressants on neurotransmitter and behavioral outcomes in animal models of depression

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Abstract

Herbal-based therapies show potential as antidepressants, though comparative efficacy remains uncertain. This study employed a meta-analysis to evaluate the efficacy of herbal interventions against standard antidepressants in animal depression models. A systematic search of PubMed, ScienceDirect, Cochrane, and Google Scholar (up to January 2025) identified 20 eligible studies. The behavior (open field test, tail suspension test) and neurotransmitters (serotonin, dopamine, noradrenaline) were analyzed as outcomes. Random-effects models were used, and risk of bias was assessed via SYRCLE. Curcumin improved open field test scores and increased serotonin and noradrenaline levels. Rosemary essential oil showed the strongest effect in the tail suspension test. Anthocyanins enhanced dopamine levels while zinc oxide nanoparticles exhibited effects comparable to curcumin. This finding supports the antidepressant potential of specific herbal, particularly curcumin, rosemary essential oil, and anthocyanins. Further standard research is necessary to confirm clinical relevance.

Introduction

Depression is a prevalent and debilitating psychiatric disorder characterized by low mood, loss of interest (anhedonia), cognitive dysfunction, and behavioral disturbances. Individuals with depression often struggle with daily activities, experiencing reduced productivity and diminished quality of life due to persistent sadness and lack of motivation (Almaghrabi et al., 2023). The global burden of depression estimating that approximately 280 million people worldwide are affected (World Health Organization, 2023). Moreover, depression is ranked as the second major cause of years lived with disability and is a major contributor to suicide-related death and physical health complications (Yan et al., 2024). Given these severe implications, enhancing treatment strategies for depression remains a critical research priority (Kupferberg and Hasler, 2023).

The pharmacological management of depression primarily targets neurotransmitter imbalances, with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase-A inhibitors (MAOIs) being the most prescribed classes of antidepressants. However, long-term administration of these drugs faces treatment challenges such as reduced receptor sensitivity and higher therapy costs (Chen et al., 2024). While these medications can be effective, they are often associated with significant limitations, including reduced long-term efficacy due to receptor desensitization and adaptive neuroplasticity changes, adverse side effects such as gastrointestinal distress, sexual dysfunction, and weight gain that impact treatment adherence, and withdrawal symptoms upon discontinuation. Furthermore, treatment resistance affects up to 30% of patients, substantially limiting therapeutic options for many individuals (Kolasa and Faron-Gorecka, 2023).

Depression is increasingly recognized as a multifactorial disorder, involving not only monoaminergic dysfunction but also neuroinflammation, oxidative stress, hypothalamic-pituitary-adrenal axis dysregulation, and neuronal remodelling (Cui et al., 2024). These complex neurobiological underpinnings highlight the urgent need for alternative and complementary therapeutic approaches that target multiple pathophysiological mechanisms

Growing evidence suggests that herbal-based interventions may offer antidepressant effects through multimodal mechanisms, including neurotransmitter modulation, anti-inflammatory and antioxidant properties, and enhancement of neurogenesis and synaptic plasticity. Several herbal compounds have been extensively investigated for their antidepressant potential in preclinical studies. Curcumin, a bioactive compound from turmeric, has been shown to enhance neurotrophic factors, regulate hypothalamic-pituitary-adrenal axis activity, and improve neurotransmitter balance (Zhang et al., 2020). Anthocyanins, found in purple sweet potatoes and berries, have been shown to modulate dopamine-related and gamma-aminobutyric acid-related neurotransmission, suggesting potential mood-stabilizing effects (Kurnianingsih et al., 2024). Tea polyphenols, particularly L-theanine and catechins from green tea extracts, exhibit neuroprotective and anxiolytic properties (Rothenberg and Zhang, 2019). Additionally, *Aegle marmelos* has been reported to modulate monoamine neurotransmitters, showing potential antidepressant effects in animal models (Pojala and Sayeli, 2023).

Despite the promising potential of herbal interventions, the existing literature presents methodological inconsistencies and variable efficacy results. For instance, curcumin's antidepressant effects vary across studies, influenced by dosage, administration route, and bioavailability challenges (Ramaholimihaso et al., 2020). Anthocyanins demonstrate significant antidepressant-like effects in some models, but their efficacy is inconsistent in others, potentially due to differences in experimental design and pharmacokinetics (Zaa et al., 2023). Many studies assess individual herbal treatments in isolation, comparing them only to placebo or standard medications without direct comparisons between different herbal interventions. These methodological disparities limit our understanding of which herbal compounds offer the most robust antidepressant effects. Furthermore, using various animal models, behavioral paradigms, and neurochemical assays complicates direct comparisons between studies.

The limitations of conventional antidepressants, coupled with the promising but fragmented evidence for herbal interventions, underscore the pressing need for a comprehensive evaluation of alternative treatment strategies. The high prevalence of treatment-resistant depression and medication side effects creates an urgent clinical imperative to identify effective complementary approaches. Given the methodological variations across existing studies, a systematic and quantitative approach that enables direct and indirect comparisons across multiple interventions would provide a more comprehensive and unbiased evaluation of their relative efficacy.

Therefore, this study aimed to systematically evaluate and compare the antidepressant efficacy of various herbal interventions using a network meta-analysis approach. Specifically, it seeks to assess behavioral outcomes (open field test, tail suspension test) to determine antidepressant-like effects, analyze neurotransmitter levels (serotonin, dopamine, noradrenaline) to elucidate potential mechanisms of action, and compare the efficacy of herbal interventions against standard antidepressants to explore their clinical relevance. By synthesizing preclinical evidence and accounting for methodological variations across studies, this meta-analysis provides a more comprehensive and balanced understanding of herbal treatments in depression management.

Materials and Methods

The study was performed by using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Page et al., 2021). The study protocol was registered in PROSPERO (registration number: CRD420251016020), ensuring the methodological transparency and reproducibility.

Search strategy

A comprehensive search of four major scientific databases- PubMed, ScienceDirect, Cochrane, and Google Scholar- was conducted up to January 2025 to identify relevant studies on the efficacy of herbal interventions in animal models of depression. The search strategy incorporated Boolean operators (AND, OR) to maximize the retrieval of relevant literature. The literature search was structured around three core domains: 1) depression models in animals, 2) herbal and standard antidepressant interventions, and 3) behavioral and neurotransmitter outcomes. The specific search strings used in each database are detailed in Table I.

Study eligibility criteria

The study eligibility criteria were determined to ensure the homogeneity of the studies. The inclusion in this study were as follows: 1) studies that involve depression model animals as their sample, 2) studies comparing outcomes between various herbal and

Table I

Literature search terms for included studies

Database	Keywords
PubMed	#1 "depression" [MeSH Terms] #2 (("depression" [Title/Abstract]) OR ("depressive behaviour" [Title/Abstract])) #3 #1 OR #2 #4 (("herbal" [Title/Abstract]) OR ("curcumin" [Title/Abstract]) OR ("anthocyanin" [Title/Abstract]) OR ("medication" [Title/Abstract]) OR ("antidepressant treatment" [Title/Abstract])) #5 #3 OR #4 #6 (("outcome" [Title/Abstract]) OR ("serotonin" [Title/Abstract]) OR ("dopamine" [Title/Abstract]) OR ("medication" [Title/Abstract]) OR ("noradrenaline" [Title/Abstract]) OR ("open field test" [Title/Abstract]) OR ("tail suspension test" [Title/Abstract])) #7 #6 AND #5 #8 #7, Filter : Trial
ScienceDirect	("Rodent" OR "Rabbit OR "Animal model" OR "Experimental animal") AND ("Herbal" OR "Curcumin" OR "Anthocyanin" OR "Herbal substances" OR "Medication" OR "Antidepressant treatment") AND ("Serotonin" OR "Dopamine" OR "Noradrenaline" OR "Neurotransmitters" OR "Open field test" OR "Tail suspension test")
Cochrane	("Rodent" OR "Rabbit OR "Animal model" OR "Experimental animal") AND ("Herbal" OR "Curcumin" OR "Anthocyanin" OR "Herbal substances" OR "Medication" OR "Antidepressant treatment") AND ("Serotonin" OR "Dopamine" OR "Noradrenaline" OR "Neurotransmitters" OR "Open field test" OR "Tail suspension test")
Google Scholar	(rodent animal AND (depression OR depressive)) AND (SSRI OR SNRI OR antidepressant OR herbal OR plant) AND (behavioral outcome OR neurotransmitter)

medication interventions regarding depression, and 3) studies involving at least one of these parameters, namely open field test, tail suspension test, serotonin level, dopamine level, and noradrenaline level. On the contrary, the criteria for exclusion in this study were 1) human sampling, 2) irretrievable articles, 3) articles with incompatible language, and 4) non-peer-reviewed articles. The researchers individually assessed each study to decide if it met the criteria, after which they deliberated on any disagreements until reaching a consensus.

Outcome measures

This paper examined five outcome parameters to assess the efficacy of herbal and medication interventions in animal model of depression. The analysis included efficacy parameters such as the open field test, tail suspension test, and levels of serotonin, dopamine, and noradrenaline. Differences in interpretation were resolved through discussion.

Quality assessment

Two reviewers used the critical appraisal tool to independently determine whether each study has a low, moderate, or high risk of bias using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool for animal studies (Hooijmans et al., 2014). The SYRCLE has ten domains of study quality, which were analyzed and summed up for the overall results. Subsequently, the assessment result for SYRCLE was extracted into a Microsoft Excel 2021 spreadsheet and then uploaded to the ROBVIS website to be visually presented using the traffic light system (McGuinness and Higgins, 2021)

Statistical analysis

RStudio was used for the network meta-analysis because all studies mentioned variable interventions and outcomes. Network meta-analysis was chosen to compare the direct and indirect effects of these strategies with placebo as the control group using the package "netmeta" in RStudio 2020 (RStudio Team 2020). The network graph was generated using the "netgraph" function, visually connecting and comparing all intervention strategies with the control group.

Statistical estimation was performed using a 95% confidence interval (CI) to assess continuous data. Random effect models were used due to the heterogeneity of the interventions included. Using cutoff criteria of 0%, 25%, 50%, and 75% to indicate insignificant, low, moderate, and high levels of heterogeneity, respectively, I2 statistics were used to assess heterogeneity. Closed loops were formed and verified to ensure the consistency of the network. Forest plots were utilized to summarize the pooled strategy comparisons for all outcome measures, with the control group as the reference.

Results

Study selection and identification

A total of 22 studies underwent a comprehensive evaluation after eliminating the duplicate studies. Ultimately, 20 studies were chosen for inclusion in the meta

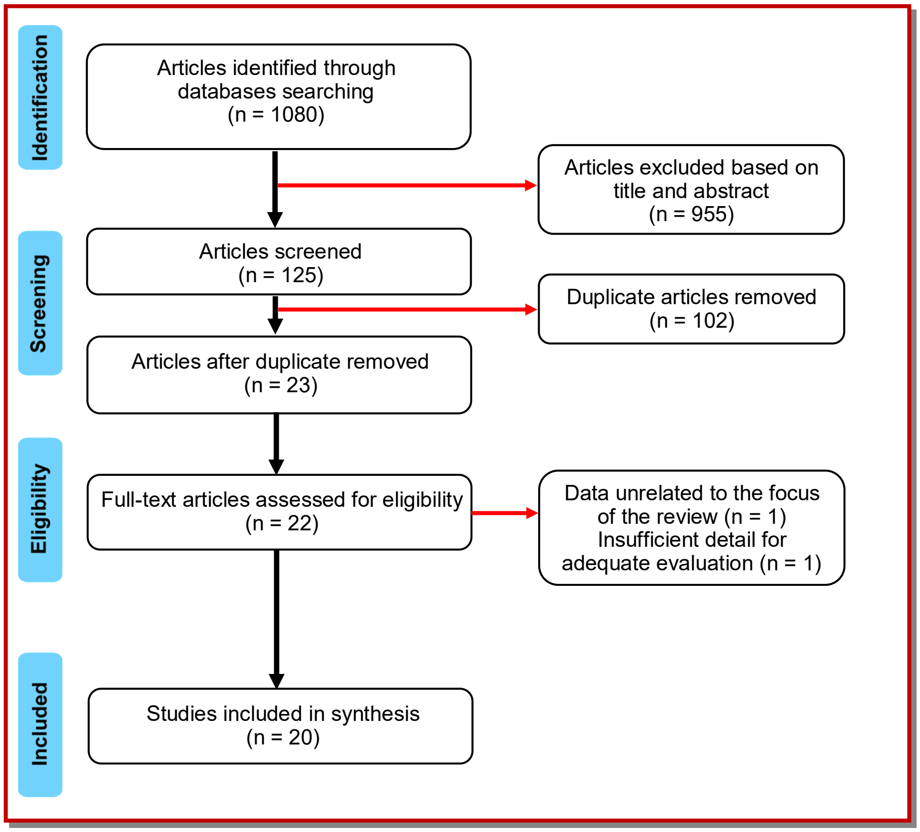

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart for study identification and selection

-analysis (Amoateng et al. 2015; Arora et al. 2011; Bhatt et al. 2022; Chang et al. 2016; Chi et al. 2022; Dudau et al. 2023; Fahmy et al. 2024; Gazal et al. 2014; Kurnianingsih et al., 2024; Madiha and Haider, 2019; Moorkoth et al., 2021; Pan et al., 2021; Sartim et al., 2021; Sasaki et al., 2021, 2022a, 2022b; Sharma et al., 2022; Zhai et al., 2024; Zhao et al., 2014), as depicted in Figure 1. The original database search resulted in 1,080 studies from eight databases searched, namely PubMed, ScienceDirect, Cochrane, and Google Scholar. Through title and abstract screening, 955 articles were removed, and 125 were screened for duplication. Duplicate screening resulted in 102 removed articles. Twenty-two were further assessed for eligibility, and two articles were removed due to unrelated or insufficient data. The final step resulted in 20 animal experimental studies included in the qualitative synthesis.

Characteristics of the included studies

Each study's demography and clinical characteristics were examined and listed in Supplementary Table I.

Risk of bias assessment of the included studies

Twenty studies were assessed using the SYRCLE. The overall assessment of all studies shows that 16 included studies were of low risk of bias, however, 4 studies showed moderate risk of bias. The overall risk of bias, as shown in the summary plot, is reported to be about 80% low risk, which indicates that most of the included studies were objected to good quality (Figure 2).

Behaviors

Open field test

Seven studies reported open field test results were analyzed through network meta-analysis. The graph plot in Figure 3A shows a direct comparison/relationship between all herbal and medication results regarding depression. The nodes denote the number of studies included in each arm of treatment. Curcumin has the second biggest node, next to placebo, indicating it has the second highest number of animals (24). Followed by medication, including reserpine, fluoxetine, imipramine, and bupropion (18), ethanol extract from *Gynura procumbens* stems (EEGS) (15), hydro-ethanolic extract of *Aegle marmelos* (EAM) (6), and lastly anthocyanin (5). Numbers in the line between each node indicate the number of studies comparing each intervention. Forest plot of network meta-analysis using a random effect model of the plot. Figure 3B shows a significant result with high heterogeneity (p=0.0001; I2=82.4%) favoring EAM with mean difference (MD) of -8.35 [95% CI: -9.92 — -6.78] compared to placebo, followed by curcumin -3.50 [95% CI: -5.94 — -1.06], medication -3.41 [95% CI: -6.14 — -0.69], EEGS -2.09 [95% CI: -7.43 — 3.25], and anthocyanin -

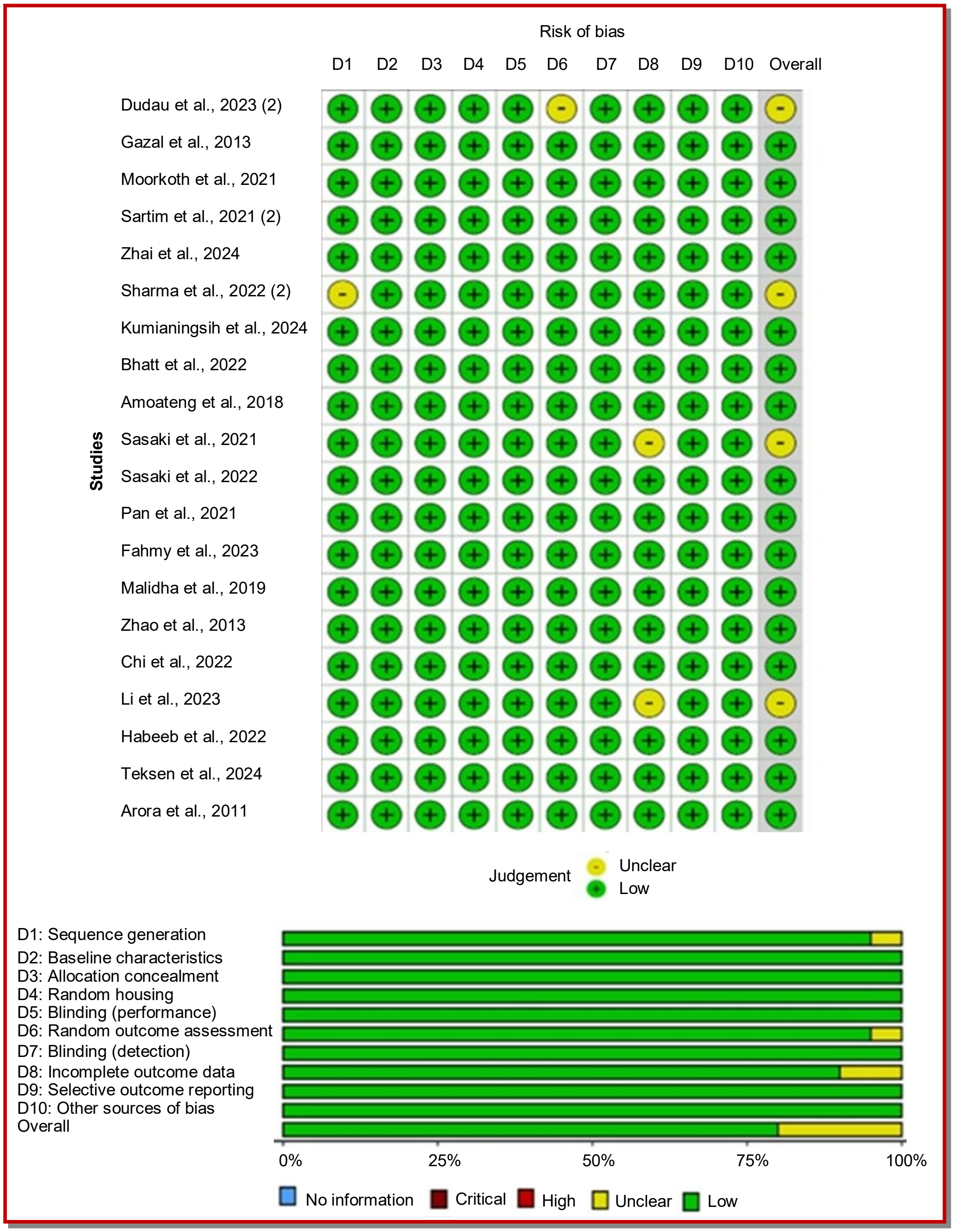

Figure 2: Risk of bias summary using the SYRCLE tool for animal trials. The green region represents studies with a low risk of bias, the yellow area shows studies with 'some concerns' risk of bias, the red area shows studies with a high risk of bias

1.93 [95% CI: -5.52 — 1.66].

Tail suspension test

Nine studies reported that tail suspension test results were analyzed using network meta-analysis. In Figure 3C, the graph plot depicts the direct comparisons and relationships between various herbal and medication-based interventions for the tail suspension test as depressive-like behavior. The node sizes correspond to the number of studies in each treatment arm, with medication having the second-largest node (32 animals), following placebo (47 animals). Other interventions include EEGS (15 animals), microalgae (14 animals), rosemary essential oil (7 animals), *Synedrella nodiflora* (SNE) (7 animals), *Cochlospermum religiosum* (CSR) leaf (6 animals), and curcumin (6 animals). The

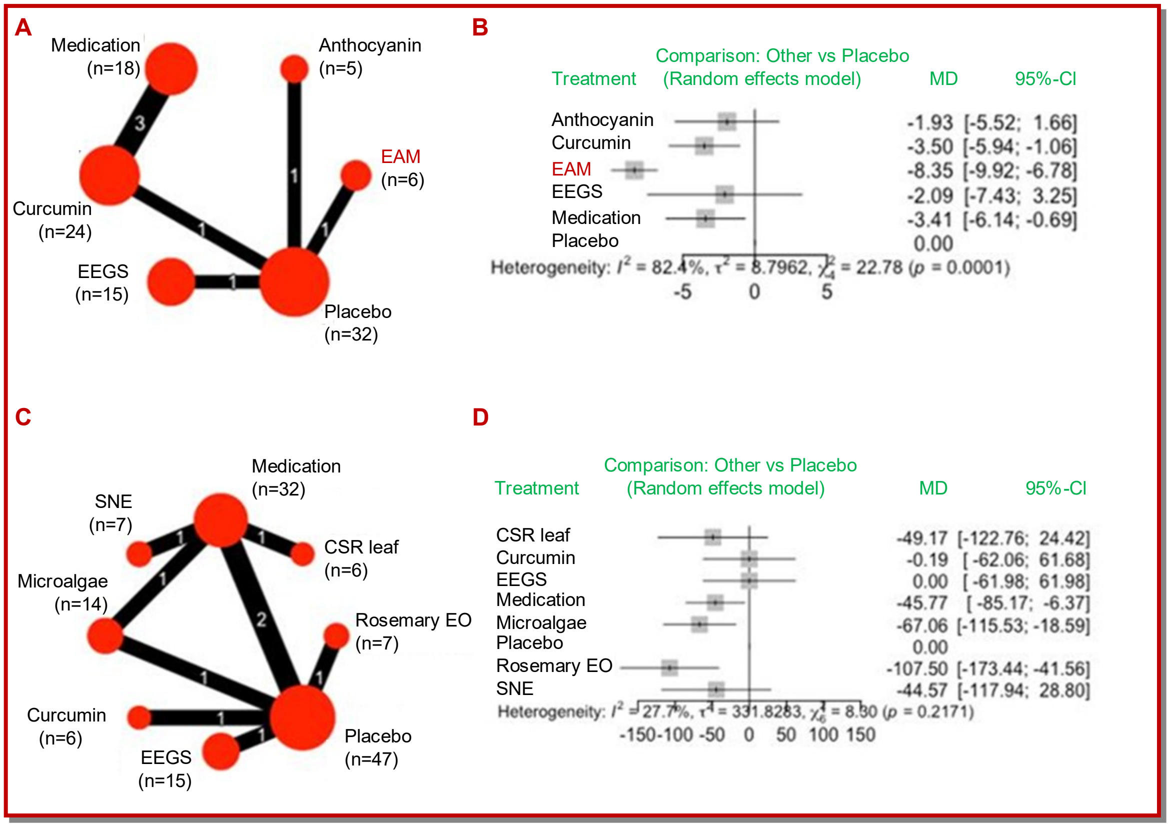

Figure 3: Network meta-analysis graph plot (left panel) and network meta-analysis random effect model forest plot (right panel) for behavioral outcomes. Analysis for open filed test behavior from six studies (A-B). Analysis for tail suspension test behavior from nine studies (C-D)

numbers on the connecting lines indicate the number of studies comparing each intervention pair.

Meanwhile, the forest plot, as depicted in Figure 3D, demonstrates the results of the random effects model analysis, showing significant findings with low heterogeneity (p=0.0001; I²=27.7%). Rosemary essential oil was favored with an MD of -107.5 [95% CI: -174.44 to -41.56] compared to placebo, followed by microalgae (-67.06 [95% CI: -115.53 to -18.59]), CSR leaf (-49.17 [95% CI: -122.76 to -24.42]), medication (-45.77 [95% CI: -85.17 to -6.37]), SNE (-44.57 [95% CI: -117.94 to 28.80]), curcumin (-0.19 [95% CI: -62.06 to 61.68]), and EEGS (0.00 [95% CI: -61.98 to -61.68]).

Neurotransmitter

Serotonin level

Ten studies assessing field suspension test results were analyzed through a network meta-analysis. Figure 4A presents a graph plot illustrating the direct comparisons and relationships between different herbal and medication-based interventions for depression. The node sizes reflect the number of participants in each treatment group, with placebo having the largest node (44 animals), followed by medication (29 animals), curcumin (21 animals), and curcumin combination (21 animals). Other interventions include curcumin-conjugated zinc oxide nanoparticle/ZnO NP (7 animals), rotenone (6 animals), and *Rehmannia glutinosa* decoction/LBRD (6 animals). The numbers on the connecting lines represent the number of studies comparing each intervention pair.

Meanwhile, the forest plot as depicted in Figure 4B, demonstrates the results of the random effects model analysis, showing significant findings with high heterogeneity (p=0.0006; I²=76.9%). Curcumin was favored with an MD of 66.35 [95% CI: -5.15 to 137.85] compared to placebo, followed by ZnO NP (65.04 [95% CI: -51.87 to 181.94]), and medication (35.77 [95% CI: -16.64 to 88.18]), while reverse results was found in curcumin combination (-16.14 [95% CI: -73.10 to 40.82]), LBRD (-36.00 [95% CI: -129.47 to 57.47]), and rotenone (-179.47 [95% CI: -271.96 to 86.98]).

Dopamine level

Ten studies evaluating dopamine levels were analyzed using network meta-analysis. Figure 4C displays a graph plot depicting the direct comparisons and relationships between various herbal and medication-based interventions for depression. The node sizes indicate the number of participants in each treatment

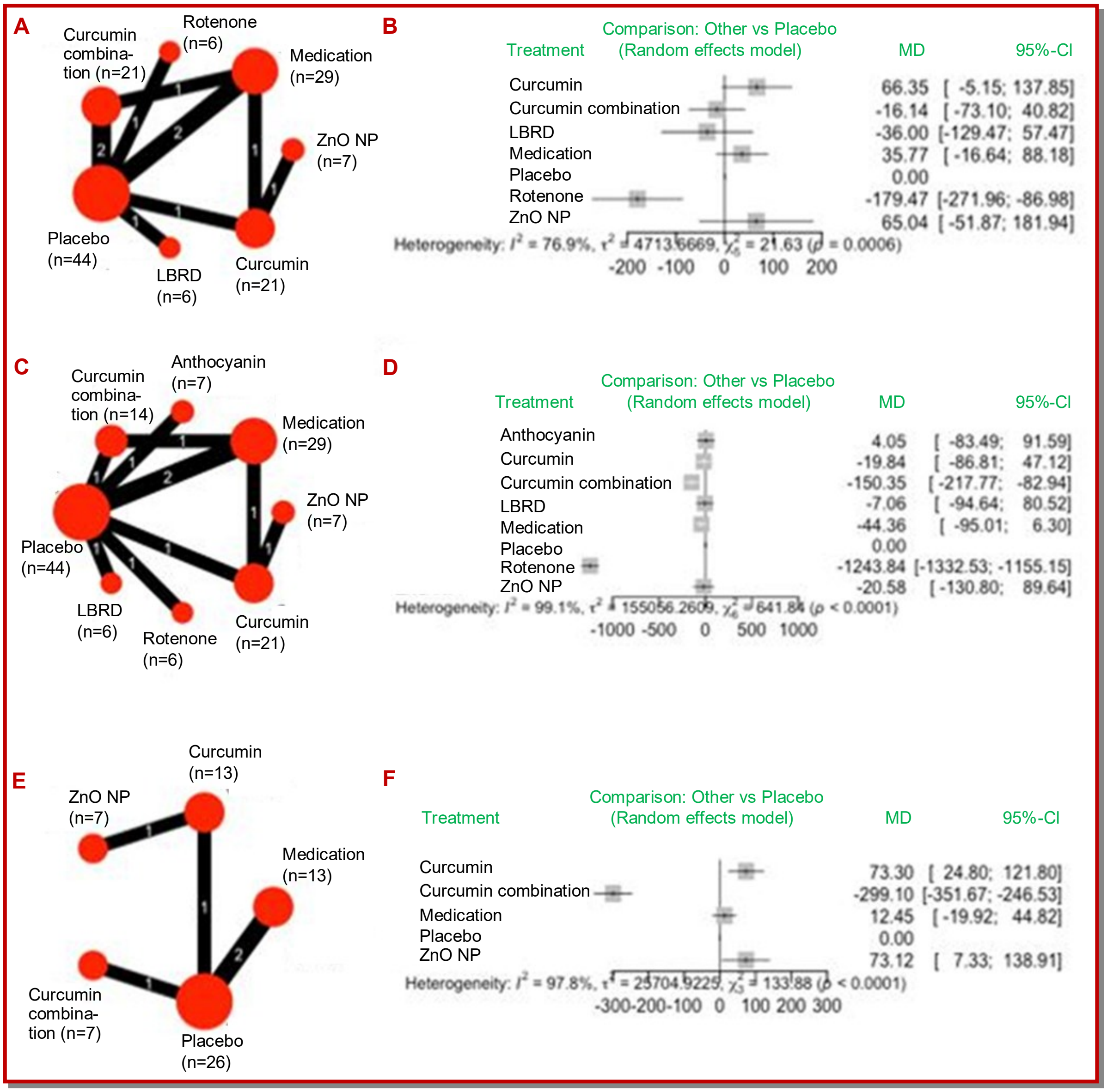

Figure 4: Network meta-analysis graph plot and network meta-analysis random effect model forest plot for neurotransmitter outcomes. The size of the node indicates the number of participants in each intervention. Analysis for serotonin level from eight interventions (A-B). Analysis for dopamine level from ten interventions (C-D). Analysis for noradrenaline level from five interventions (E-F)

group, with placebo having the largest node (44 animals), followed by medication (29 animals), curcumin (21 animals), curcumin combination (14 animals), ZnO NP (7 animals), anthocyanin (7 animals), LBRD (6 animals), and rotenone (6 animals). The numbers on the connecting lines represent the studies comparing each intervention pair.

Figure 4D presents the forest plot from the random effects model analysis, revealing significant findings with high heterogeneity ($p<0.0001$; $I^2=99.1\%$). Among the interventions, anthocyanin showed a significant positive effect with a mean difference (MD) of 4.05 [95% CI: -83.49 to 91.59] compared to placebo. Meanwhile, other interventions showed a negative effect, respectively, from the smallest to largest, LBRD (-7.06 [95% CI: -94.64 to 80.52]), curcumin (-19.84 [95% CI: -86.81 to 47.12]), ZnO NP (-20.58 [95% CI: -130.80 to 89.64]), medication (-44.36 [95% CI: -95.01 to 6.30]), curcumin combination (-150.35 [95% CI: -217.77 to -82.94]), and rotenone (-1243.84 [95% CI: -1332.53 to -1155.15]).

Noradrenaline level

Five studies of noradrenaline level results were analyzed through network meta-analysis. Figure 4E presents a graph plot that visualizes the direct comparisons and interactions between various herbal and medication-based treatments for depression. The size of each node corresponds to the number of participants in each treatment group, with placebo having the highest number (26 animals), followed by medication (13 animals), curcumin (13 animals), ZnO NP (7 animals), and curcumin combination (7 animals). The numbers along the connecting lines indicate the number of studies that compared each intervention pair.

The forest plot in Figure 4F illustrates the results of the random effects model analysis, highlighting significant findings with high heterogeneity (p=0.0001; I^2=97.8%). Curcumin demonstrated the most substantial effect, with a mean difference (MD) of 73.30 [95% CI: 24.80 to 121.80] compared to placebo. This was followed by ZnO NP (73.12 [95% CI: 7.33 to 138.91]), medication (12.45 [95% CI: -19.92 to 44.82]), while curcumin combination (-299.10 [95% CI: -351.67 to -246.53]) showed a reverse effect.

Discussion

This study systematically reviewed the different outcomes of behavioral test and neurotransmitter levels among various herbal interventions for depression in animal models. Through a comprehensive literature search, 20 studies using diverse herbal treatments were included. The open field and tail suspension tests were used as behavioral parameters, while serotonin, dopamine, and noradrenaline levels served as neurotransmitter outcome measures. This meta-analysis provides valuable insights into the comparative efficacy of herbal treatments, emphasizing the need for a nuanced approach to understanding their therapeutic potential in depression.

The behavioral analysis through the open field test revealed that curcumin demonstrated greater efficacy than other herbal treatments in the open field test of behavior analysis. This finding aligns with a previous study that identified multiple mechanisms of action for curcumin, including enhancement of neurotrophic factors, improvement of mitochondrial activity, normalization of inflammation, reduction of oxidative stress, regulation of the hypothalamic-pituitary-adrenal axis and restoration of neurotransmitter activity (Lopresti, 2022). Notably, curcumin also exhibited the highest effectiveness in increasing serotonin levels among herbal studies. Serotonin plays a crucial role in mood regulation, and this finding strengthens existing evidence that curcumin modulates the serotonergic pathway, possibly through the inhibition of monoamine oxidase enzymes or by increasing the availability of tryptophan for serotonin synthesis (Ramaholimihaso et al., 2020). Additionally, curcumin enhanced the brain-derived neurotrophic factor in the hippocampus (Hosseinzadeh et al., 2012)

In the tail suspension test, which precisely measures despair behavior in animal models of depression (Ueno et al., 2022), rosemary essential oil demonstrated the most pronounced effect in reducing immobility time. This supports its potential to alleviate depressive symptoms through anti-inflammatory properties and enhancement of neurotransmitter levels, such as serotonin and dopamine. Research has shown that rosemary essential oil significantly reduced the production of pro-inflammatory cytokines Interleukin-1β and tumor necrosis factor-α (Niu et al., 2025). Furthermore, rosemary contains rosmarinic acid, a key component of rosemary, appears to mitigate oxidative stress by reducing reactive oxygen species, lipid peroxidation, and malondialdehyde, while concurrently enhancing the antioxidant defense mechanism through increased activities of enzymes such as superoxide dismutase, catalase, and glutathione, as well as by upregulation of nuclear factor erythroid-2 expression (Abdel-Azeem et al., 2017; Dahchour, 2022).

At the neurotransmitter level, anthocyanins exerted the most pronounced effect on dopamine levels. These findings corroborated previous research indicating that anthocyanins from purple sweet potatoes modulate neurotransmitter levels, specifically dopamine and gamma-aminobutyric acid, with predicted activity on dopamine receptors and inhibition monoamine oxidase enzyme activity (Kurnianingsih et al., 2021, 2024a). Anthocyanins have been shown to reduce microglial reactivity by inhibiting the pathway of nuclear factor kappa-light-chain-enhancer of activated B cells, thereby reducing inflammatory cytokine production and free radical formation and alleviating neuronal excitotoxicity (Zaa et al., 2023). Curcumin most significantly enhanced noradrenaline levels, like its effect on serotonin, further underscoring its pivotal role in the monoaminergic neurotransmitter system. Interestingly, conjugating curcumin with zinc oxide nanoparticles demonstrated efficacy comparable to curcumin alone in elevating noradrenaline levels. This effect may be attributed to the enhanced ability of nanoparticles to cross the blood–brain barrier due to their small size and high lipid solubility, facilitating targeted delivery to the brain (Hersh et al., 2022).

The current findings highlight the differential efficacy of herbal treatments for depression, reflected in the high score of heterogeneity observed across studies. Multiple factors contribute to this heterogeneity, including variations in study design, intervention protocols, dosage regimens, treatment duration, and outcome measures (Higgins et al., 2003). This study examined animal research by evaluating species diversity, experimental designs, and methodological approaches. While this heterogeneity presents challenges for direct comparison, it also offers opportunities for further exploration to identify specific therapeutic targets for depression and to assess the potential synergistic effects of combining various herbal treatments.

Several limitations must be acknowledged when interpreting these results. The high heterogeneity across studies limits the generalizability of the findings and necessitates careful consideration when translating these results to clinical applications. Additionally, the lack of standardized dosing protocols and variations in animal models used across studies present challenges for direct comparison. Despite these limitations, this research significantly contributes by bridging traditional herbal medicine with neuroscience, highlighting the potential effects of natural compounds on mental health.

The findings of this meta-analysis have important implications for depression treatment research. The differential effects of herbal interventions on behavioral and neurotransmitter parameters suggest that personalized approaches might be beneficial, with specific herbal compounds targeting aspects of depression symptomatology. The promising results with curcumin, rosemary essential oil, and anthocyanins provide a foundation for more focused investigations into their mechanisms of action and potential clinical applications. Moreover, the comparable efficacy of some herbal treatments to conventional antidepressants highlights their potential as complementary or alternative therapeutic options, particularly for patients who experience adverse effects from standard medications or have treatment-resistant depression.

Conclusion

This meta-analysis study highlights the diverse effects of herbal treatments on depression-like behavior in animal models. Curcumin, rosemary essential oil, and anthocyanins demonstrated distinct benefits on behavioral and neurotransmitter outcomes. Curcumin showed greater efficacy in the open field test and significantly increased serotonin and noradrenaline levels. Rosemary essential oil exhibited the most substantial antidepressant effect in the tail suspension test, while anthocyanins specifically enhanced dopamine levels. Additionally, zinc oxide nanoparticles combined with curcumin showed promising effects, suggesting potential benefits in improving bioavailability. The variability in efficacy across different herbal treatments underscores the complexity of their pharmacological mechanisms and the need for further research. Future studies should focus on clinical translation, detailed mechanistic investigations, standardization of experimental protocols, and exploration of potential synergistic effects. This research provides a foundation for more targeted investigations into the antidepressant potential of herbal compounds, poten-tially leading to novel therapeutic approaches for depression.

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Ethical Issue

Not applicable

Conflict of Interest

Authors declare no conflict of interest

References

Abdel-Azeem AS, Hegazy AM, Zeidan HM, Ibrahim KS, El-Sayed EM. Potential renoprotective effects of rosemary and thyme against gentamicin toxicity in rats. J Diet Suppl. 2017; 14: 380-94.

Almaghrabi SA, Clark SR, Baumert M. Bio-acoustic features of depression: A review. Biomed Signal Process Control. 2023; 85: 105020.

Amoateng P, Kukuia KKE, Mensah JA, Osei-Safo D, Adjei S, Eklemet AA, Vinyo, EA, Karikari TK. An extract of *Synedrella nodiflora (L)* Gaertn exhibits antidepressant properties through monoaminergic mechanisms. Metab Brain Dis. 2018; 33: 1359-68.

Arora V, Kuhad A, Tiwari V, Chopra K. Curcumin ameliorates reserpine-induced pain-depression dyad: Behavioural, biochemical, neurochemical and molecular evidence. Psychoneuroendocrinology 2011; 36: 1570-81.

Bhatt S, Behl T, Sehgal A, Singh S, Sharma N, Chigurupati S, Ahmed AS, Gari SBV. Investigation of *Cochlospermum religiosum* leaves for antidepressant and anxiolytic activities and its synergistic effect with imipramine and fluoxetine. Environ Sci Pollut Res. 2022; 29: 27172-81.

Chang XR, Wang L, Li J, Wu DS. Analysis of anti-depressant potential of curcumin against depression induced male albino wistar rats. Brain Res. 2016; 1642: 219-25.

Chen Y, Wang R, Li X, Wang Z, Cao B, Du J, Deng T, Han J, Yang M. Progress of research on the treatment of depression by traditional Chinese medicine prescriptions. Heliyon 2024; 10: e34970.

Chi X, Xue X, Pan J, Wu J, Shi H, Wang Y, Lu Y, Zhang Z, Ma K. Mechanism of lily bulb and *Rehmannia decoction* in the treatment of lipopolysaccharide-induced depression-like rats based on metabolomics study and network pharmacology. Pharm Biol. 2022; 60: 1850-64.

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.

Dahchour A. Anxiolytic and antidepressive potentials of rosmarinic acid: A review with a focus on antioxidant and anti-inflammatory effects. Pharmacol Res. 2022; 184: 106421.

Dudau LE, Moisa E, Sevastre-Berghian A, Moldovan R, Decea R, Donosa M, Filip GA, Stancu B. The effect of curcumin on reserpine-induced depression-like behaviour in rats. Psychiatry Res Neuroimaging. 2023; 334: 111682.

Fahmy HM, Aboalasaad FA, Mohamed AS, Elhusseiny FA, Khadrawy YA, Elmekawy A. Evaluation of the therapeutic effect of curcumin-conjugated zinc oxide nanoparticles on reserpine-induced depression in wistar rats. Biol Trace Elem Res. 2024; 202: 2630-44.

Gazal M, Valente MR, Acosta BA, Kaufmann FN, Braganhol E, Lencina CL, Stefanello FM, Ghisleni G, Kaster MP. Neuroprotective and antioxidant effects of curcumin in a ketamine-induced model of mania in rats. Eur J Pharmacol. 2014; 724: 132-39.

Hersh AM, Alomari S, Tyler BM. Crossing the blood-brain barrier: Advances in nanoparticle technology for drug delivery in neuro-oncology. Int J Mol Sci. 2022; 23: 1-28.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in knowledge bases. BMJ. 2003; 327: 557-60.

Hooijmans CR, Rovers MM, Vries RB, de Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014; 14: 1-9.

Hosseinzadeh S, Roshan VD, Mahjoub S. Continuous exercise training and curcumin attenuate changes in brain-derived neurotrophic factor and oxidative stress induced by lead acetate in the hippocampus of male rats. Pharm Biol. 2012; 51: 240-45.

Kolasa M, Faron-Gorecka A. Preclinical models of treatment-resistant depression: Challenges and perspectives. Pharmacol Rep. 2023; 75: 1326-40.

Kupferberg A, Hasler G. The social cost of depression: Investigating the impact of impaired social emotion regulation, social cognition, and interpersonal behavior on social functioning. J Affect Disord Rep. 2023; 14: 100631.

Kurnianingsih N, Hakim AR, Salsabila D, Fahanani AF, Harbiyanti NT, Ratnawati R. Anthocyanin extract from purple sweet potato improving neurotransmitter and locomotor in chronic stressed-mice. Iran J Vet Med. 2024; 18: 333-44.

Kurnianingsih N, Ratnawati R, Nazwar T, Ali M, Fatchiyah F. Purple sweet potatoes from east java of Indonesia revealed the macronutrient, anthocyanin compound and antidepressant activity candidate. Med Arch. 2021; 75: 94-100.

Lopresti AL. Potential role of curcumin for the treatment of major depressive disorder. CNS Drugs. 2022; 36: 123-41.

Madiha S, Haider S. Curcumin restores rotenone induced depressive-like symptoms in animal model of neurotoxicity: Assessment by social interaction test and sucrose preference test. Metab Brain Dis. 2019; 34: 297-308.

McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12: 55-61.

Moorkoth S, Prathyusha NS, Manandhar S, Xue Y, Sankhe R, Pai KSR, Kumar N. Antidepressant-like effect of dehydrozingerone from *Zingiber officinale* by elevating monoamines in brain: *In silico* and *in vivo* studies. Pharmacol Rep. 2021; 73: 1273-86.

Niu Y, Xu L, Qiao M, Wang Y. The anti-depression effect and mechanism of harmonious rosemary essential oil and its application in microcapsules. Mater Today Bio. 2025; 31: 101546.

Pan X, Chen L, Xu W, Bao S, Wang J, Cui X, Gao S, Liu K, Avasthi S, Zhang M, Chen R. Activation of monoaminergic system contributes to the antidepressant- and anxiolytic-like effects of J147. Behav Brain Res. 2021; 411: 113477.

Pojala K, Sayeli V. An experimental study evaluating antidepressant activity of methanolic leaf and fruit pulp extracts of *Aegle marmelos* in Wistar rats. Nat J Physiol Pharm Pharmacol. 2023; 13: 1456-60.

Ramaholimihaso T, Bouazzaoui F, Kaladjian A. Curcumin in depression: Potential mechanisms of action and current evidence- a narrative review. Front Psychiatry. 2020; 11: 572533.

Rothenberg DO, Zhang L. Mechanisms underlying the antidepressive effects of regular tea consumption. Nutrients 2019; 11: 1-38.

Sartim AG, Marques J, Silveira KM, Gobira PH, Guimarães FS, Wegener G, Joca SR. Co-administration of cannabidiol and ketamine induces antidepressant-like effects devoid of hyperlocomotor side-effects. Neuropharmacology 2021; 195: 108679.

Sasaki K, Ferdousi F, Fukumitsu S, Kuwata H, Isoda H. Antidepressant- and anxiolytic-like activities of *Rosmarinus officinalis* extract in rodent models: Involvement of oxytocinergic system. Biomed Pharmacother. 2021; 144: 112291.

Sasaki K, Linh TN, Hirano A, Tominaga K, Nukaga S, Nozaki H, Arimura T, Isoda H. Microalgae extract induces antidepressant-like activity via neuroinflammation regulation and enhances the neurotransmitter system. Food Chem Toxicol. 2022; 170: 113508.

Sharma A, Singh T, Pathak D, Virmani T, Kumar G, Alhalmi A. Antidepressive-like effect of *Aegle marmelos* leaf extract in chronic unpredictable mild stress-induced depression-like behaviour in rats. Biomed Res Int. 2022; 2022.

Ueno H. Takahashi Y, Murakami S, Wani K, Matsumoto Y, Okamoto M, Ishihara T. Effect of simultaneous testing of two mice in the tail suspension test and forced swim test. Sci Rep. 2022; 12: 1-14.

World Health Organization (WHO). Depressive disorder (depression). World Health Organization Key Facts. USA. World Health Organization [accessed 2025 March 10]. https://www.who.int/news-room/fact-sheets/detail/depression.

Yan G, Zhang Y, Wang S, Yan Y, Liu M, Tian M, Tian W. Global, regional, and national temporal trend in burden of major depressive disorder from 1990 to 2019: An analysis of the global burden of disease study. Psychiatry Res. 2024; 337: 115958.

Zaa CA, Marcelo AJ, An Z, Medina-Franco JL, Velasco-Velázquez MA. Anthocyanins: Molecular aspects on their neuroprotective activity. Biomolecules 2023; 13: 1-16.

Zhai SY, Gu HW, Wang C, Li YS, Tang H. *Gynura procumbens* and selected metabolites: Amelioration of depressive-like behaviors in mice and risperidone-induced hyperprolactinemia in rats. Biomed Pharmacother. 2024; 173: 116361.

Zhang Y, Li L, Zhang J. Curcumin in antidepressant treatments: An overview of potential mechanisms, pre-clinical/clinical trials and ongoing challenges. Basic Clin Pharmacol Toxicol. 2020; 127: 243-53.

Zhao X, Wang C, Zhang JF, Liu L, Liu AM, Ma Q, Zhou WH, Xu Y. Chronic curcumin treatment normalizes depression-like behaviors in mice with mononeuropathy: Involvement of supraspinal serotonergic system and GABAA receptor. Psychopharmacology 2014; 231: 2171-87.

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