

RESEARCH ARTICLE

Anti-inflammatory pharmacotherapy for depressive disorders: A network meta-analysis of double-blind, randomised, controlled, parallel-group clinical trials

Yan Bo^{1*}  and Youwei Wang²¹Department of Medicine, Northwest Minzu University, Lanzhou, Gansu, China²School of Medicine, Beihua University, Jilin City, Jilin, China

Abstract

Background: Neuroinflammation has emerged as a potential biological mechanism underlying depressive disorders and represents an increasingly investigated target for therapeutic intervention.

Objective: To compare the effects of pharmacological interventions evaluated within an inflammation-related framework on depressive symptom severity and inflammatory biomarker outcomes.

Methods: Randomised controlled trials reporting pharmacological interventions for depressive disorders were included. A frequentist fixed-effects network meta-analysis was conducted for depressive symptom severity at the end of randomised treatment. Treatments were ranked using surface under the cumulative ranking curve values. Exploratory pairwise meta-analyses were performed separately for tumour necrosis factor- α , interleukin-6, interferon- γ , C-reactive protein, and interleukin-2.

Results: Eleven randomised controlled trial reports contributed to a sparse network of 10 active interventions. Using a frequentist fixed-effect network meta-analysis, escitalopram oxalate showed the largest estimated reduction in depressive symptom severity relative to the reference control node (mean difference [MD]: -13.03; 95% confidence interval [CI]: -24.54 to -1.52). Ketamine 0.5 mg/kg (MD: -5.16; 95% CI: -8.81 to -1.51) and selective serotonin reuptake inhibitor plus glycyrrhizic acid (MD: -4.35; 95% CI: -7.16 to -1.55) also showed estimates favouring intervention. Fluoxetine, fluoxetine plus triiodothyronine, infliximab, ketamine 0.2 mg/kg, minocycline, sumac, and vortioxetine plus celecoxib did not show statistically precise differences from the reference control node. Exploratory biomarker analyses showed no consistent pooled differences in inflammatory markers and substantial heterogeneity for several biomarkers.

Conclusion: Current evidence does not support a consistent class-wide benefit of inflammation-informed pharmacotherapy for depressive disorders. Although several interventions showed potentially favourable effects on depressive symptom severity, the evidence network was sparse, and most comparisons were based on single trials. Future trials should enrol biologically defined patient subgroups and use standardised clinical and biomarker outcomes.

Keywords: Depression disorders; Anti-inflammatory strategy; Randomised controlled trials; Pharmaceutical treatment; Network meta-analysis

***Corresponding author:**

Yan Bo
(thoseformylovedpeople@outlook.com)

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1. Introduction

1.1. Overview

Neuroinflammation refers to immune-mediated processes within the central nervous system that involve interactions among neurons, glial cells, vascular structures, and peripheral immune signals. In depressive disorders, inflammatory processes may contribute to symptom development, persistence, or treatment response in a subgroup of patients rather than providing a universal explanation for depression. Proposed mechanisms include altered monoaminergic and glutamatergic neurotransmission, impaired neuroplasticity, dysregulated stress-related neuroendocrine signalling, and dysfunction of reward-related neural circuits. Genetic vulnerability, chronic stress, sleep disruption, metabolic disturbance, inflammatory illness, and environmental adversity may influence peripheral and central immune signalling. Peripheral inflammatory mediators may affect the brain through circulating immune signals, neural pathways, altered blood–brain barrier function, and context-dependent cellular responses.^{1–3}

At the molecular level, inflammatory pathways involving nuclear factor kappa B (NF- κ B), the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, caspase-1, interleukin (IL)-1 β , IL-18, and the purinergic P2X7 receptor (P2X7R) have been implicated in experimental models of depressive-like behaviour. Glial activation and inflammatory mediators may further influence synaptic function, glutamate regulation, and neurotrophic support. These findings provide a biological rationale for inflammation-informed interventions. However, mechanistic and preclinical evidence cannot establish clinical efficacy, safety, or appropriate patient-selection criteria. Human randomised controlled trials are therefore needed to assess their clinical relevance.

1.2. Development of the inflammatory hypothesis of depression

Early biological models of depression were largely centred on alterations in monoaminergic neurotransmission. Although these models remain clinically influential, they do not fully explain the heterogeneity of depressive disorders or the variable response to antidepressant treatment. Increasing evidence has subsequently linked depressive symptoms with immune and inflammatory processes, initially through observational findings involving peripheral inflammatory markers and later through mechanistic studies of neuroimmune signalling.⁴

More recent preclinical research has examined inflammatory pathways that may connect stress exposure

with depression-related behavioural phenotypes. In particular, the NLRP3 inflammasome, NF- κ B, and P2X7R have been investigated as potential mediators of stress-related neuroinflammation.^{5–7} Experimental studies suggest that pharmacological and non-pharmacological interventions can modulate these pathways and may attenuate neuroinflammatory changes and depressive-like behaviours in selected animal models. However, these findings remain predominantly preclinical.

The translation of neuroimmune targets from animal models to clinical depression remains uncertain. Animal models differ in stress paradigms, inflammatory stimuli, behavioural outcomes, and the timing of intervention, while human depressive disorders are characterised by substantial biological and clinical heterogeneity. Therefore, preclinical evidence provides a rationale for testing inflammation-informed interventions in humans but cannot establish clinical efficacy, long-term safety, or biomarker-guided treatment selection. This translational gap underpins the need to examine how anti-inflammatory pharmacological strategies have been evaluated in randomised controlled trials of depressive disorders.

1.3. Current preclinical evidence

A broad range of pharmacological and non-pharmacological strategies has been investigated in animal models of depression-like behaviour. These studies suggest that inflammation, oxidative stress, metabolic disturbance, impaired neuroplasticity, and gut–brain dysregulation may interact in selected experimental models. However, such findings provide mechanistic rationale rather than evidence of clinical efficacy in humans.

Among pharmacological approaches, repurposed metabolic agents, psychotropic augmentation strategies, immune-modulating compounds, hormonal interventions, nutritional supplements, and natural products have been evaluated. In a reserpine-induced rat model, empagliflozin was associated with improved depression-like behaviour, restoration of hippocampal monoaminergic alterations, and modulation of AMP-activated protein kinase-related autophagy, NLRP3 inflammasome signalling, and hippocampal neurogenesis.⁸ These findings suggest that metabolic interventions may influence both neuroimmune and neuroplasticity-related pathways, although their long-term effects and clinical relevance remain uncertain.

Established psychotropic agents have also been examined in inflammatory models. Brexpiprazole combined with fluoxetine improved behavioural and neuroplasticity-related changes in lipopolysaccharide-exposed mice, including alterations in brain-derived neurotrophic factor–tropomyosin receptor kinase B signalling and dendritic

spine density.⁹ This finding supports the hypothesis that pharmacological augmentation may influence inflammation-associated neuroplasticity; however, it does not establish a rapid or inflammation-specific clinical benefit in people with depressive disorders.

Other experimental studies have identified potential immune-related targets beyond conventional antidepressant pharmacology. In chronically stressed mice, endogenous retrovirus activation was associated with microglial immune activation, cyclic GMP-AMP synthase–interferon-gamma inducible protein 16–STING signalling, NF- κ B priming, NLRP3 inflammasome activation, and negative emotional behaviours.¹⁰ Similarly, calcitriol reduced neuroinflammatory changes and depression-like behaviour in lipopolysaccharide-induced models while suppressing P2X7R/NLRP3/caspase-1 signalling.¹¹ Leukotriene-related pathways, gut–brain interactions, progesterone, and selenium-containing compounds have also been linked to behavioural and inflammatory changes in rodent models.^{12–15}

Nutritional supplements and natural products further illustrate the breadth of proposed mechanisms underlying inflammation. Propolis, n-3 polyunsaturated fatty acids, skeletal muscle-derived glycine, fustin, berberine, cinnamic acid, and other plant-derived compounds have been reported to improve behavioural outcomes while modifying inflammatory cytokines, oxidative stress, glial activity, or related signalling pathways.^{16–29} Although these studies broaden the range of candidate interventions, their findings remain dependent on the species, depression model, inflammatory stimulus, treatment dose, timing, target tissue, biomarker panel, and selected behavioural outcomes.

Non-pharmacological interventions have also been investigated in preclinical models. Acupuncture, electroacupuncture, and Du-moxibustion were associated with improvements in depressive-like behaviour and cognitive outcomes, accompanied by changes in oxidative stress, neuroinflammatory signalling, glial activation, ferroptosis-related pathways, and inflammatory cytokine expression.^{30–33} Exercise may also influence neuroimmune processes: swimming reduced depression-like behaviour and neuroinflammatory changes while improving hippocampal neuroplasticity-related protein expression in mice exposed to chronic unpredictable mild stress.³⁴ Brain–gut photobiomodulation has likewise been associated with improved cognitive performance, altered gut microbiota, restoration of hippocampal Sirt1 expression, and reduced neuroinflammation in chronically stressed mice.³⁵

1.4. Rationale, question, and objectives

Preclinical studies support inflammation-related mechanisms in depression, but the comparative clinical effects of inflammation pharmacotherapy remain unclear. We therefore conducted a network meta-analysis of randomised controlled trials.

The primary objective was to compare the effects of eligible pharmacological interventions on depressive symptom severity. Secondary objectives were to summarise inflammatory biomarker outcomes.

2. Methods

2.1. Design, protocol, and reporting

This study was conducted as a network meta-analysis of randomised controlled trials evaluating pharmacological interventions for depressive disorders. It represents the focused clinical trial component of a broader published protocol examining the role of inflammation in depression across mechanistic, preclinical, translational, and clinical evidence.³⁶

The broader protocol was published in *Research Connections*.³⁶ Following publication of the protocol, the clinical randomised controlled trial component was refined to permit quantitative comparative synthesis. This amendment specified depressive symptom severity as the primary outcome, defined treatment nodes, and introduced a frequentist network meta-analysis framework. The preclinical literature was retained as narrative background in the Introduction and was not included in the systematic study selection, risk-of-bias assessment, or quantitative analyses.

The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analysis.³⁷ The primary objective was to compare the relative effects of eligible pharmacological interventions on depressive symptom severity using direct and indirect evidence from randomised controlled trials. Secondary objectives were to summarise inflammatory biomarker outcomes.

2.2. Eligibility criteria

Eligibility criteria were developed using the Population, Concept, Context and framework.³⁸

2.2.1. Population

We included studies enrolling adults aged 18 years or older with a clinically diagnosed depressive disorder, including major depressive disorder, depressive episode, or

treatment-resistant depression. Diagnosis was required to be established using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, the International Classification of Diseases (ICD) criteria, a structured diagnostic interview, or another clearly reported clinical diagnostic procedure. Studies involving participants with comorbid physical or psychiatric conditions were eligible when depression was a prespecified treatment target and depressive symptoms were assessed as a clinical outcome.

2.2.2. Concept

Eligible interventions were pharmacological agents administered as monotherapy or adjunctive therapy when evaluated on an explicit anti-inflammatory or immunomodulatory rationale. This included, but was not limited to, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, cytokine-targeted biologics, tetracycline-derived anti-inflammatory agents, omega-3 fatty-acid formulations, and other pharmacological interventions targeting inflammatory or immune-related pathways. Conventional antidepressants were included only when the original trial explicitly evaluated an inflammation-related mechanism, biomarker, or anti-inflammatory treatment rationale.

2.2.3. Context and study design

We included parallel-group randomised controlled trials. Eligible comparators included placebo, usual care, no additional treatment, another pharmacological treatment, or an active control. Studies were required to report at least one clinical depression outcome, such as change in depressive symptom severity, response, remission, or relapse. Measurement of inflammatory biomarkers was mandatory for inclusion because one objective of the research was to determine whether, and how, trials incorporated inflammatory assessment into their design and outcome evaluation.

We excluded animal studies; cellular or *ex vivo* studies; observational studies; non-randomised interventional studies; qualitative studies; protocols without results; conference abstracts without full reports; narrative reviews; systematic reviews; editorials; letters without primary trial data; and studies in which depression was not a prespecified clinical target. We also excluded non-pharmacological interventions, including exercise, psychotherapy, dietary interventions without a defined pharmacological product, acupuncture, and neuromodulation, as they were outside the scope of this research.

2.3. Information sources and search strategy

We searched PubMed, Google Scholar, Web of Science, and medRxiv databases until June 21, 2026. A professional evidence-based medicine researcher (Yan Bo) developed a search strategy based on the study's purpose and eligibility criteria, using terms and free words in PubMed.

To fulfil the public participation requirements, one member of the research team (Yan Bo) and two public participants (Member A and Member B) were selected to participate in the literature screening and downloading. The specific identifying information of the public participants is not disclosed here because they requested anonymity.

Two independent reviewers (Yan Bo and Member A) screened articles by title/abstract and then by full text. The reviewers piloted the screening process using the first 50 records to refine the screening questions and to ensure that the eligibility criteria were correctly understood and interpreted by the reviewers. Discrepancies between reviewers were resolved through discussion or by a senior team member. Reasons for exclusions were documented at the full-text stage. Detailed screening procedures are reported in the previously published protocol.³⁶

A number of challenges were encountered during the screening process. For example, the titles and abstracts of some articles were ambiguous, making it difficult to determine directly whether they met the inclusion criteria for studies on anti-inflammatory strategies for treating depression. To address these challenges, we conducted a further review of the full text of the articles, focusing on the study objectives, methods, and results sections to determine their relevance to the use of anti-inflammatory strategies in the treatment of depression. In cases where the definition and mechanism of action of novel anti-inflammatory drugs or therapies used in certain studies were unclear, an in-depth understanding was gained by reviewing the relevant professional literature and consulting with experts in the field to ensure accurate judgement of the study content.

Clinical studies were included if (i) the study population was human; (ii) participants had a confirmed diagnosis of depression, not limited to the type of depression; (iii) participants had a concomitant inflammatory or hyperinflammatory response; (iv) the study methodology employed random allocation and a control group; (v) the study objective was to evaluate the effectiveness of "medications based on anti-inflammatory therapeutic

strategies” in the treatment of inflammation related to depression; (vi) the outcome measured included at least one depression scale score and also included measurement of at least one inflammatory factor concentration; and (vii) there were sufficient details of the study. The complete PubMed search strategy was as follows:

- #1: (((((((((((((((((((((((((Depressive Disorder) OR (Depressive Disorders)) OR (Disorder, Depressive)) OR (Disorders, Depressive)) OR (Neurosis, Depressive)) OR (Depressive Neuroses)) OR (Depressive Neurosis)) OR (Neuroses, Depressive)) OR (Depression, Endogenous)) OR (Depressions, Endogenous)) OR (Endogenous Depression)) OR (Endogenous Depressions)) OR (Melancholia)) OR (Melancholias)) OR (Unipolar Depression)) OR (Depression, Unipolar)) OR (Depressions, Unipolar)) OR (Unipolar Depressions)) OR (Depressive Syndrome)) OR (Depressive Syndromes)) OR (Syndrome, Depressive)) OR (Syndromes, Depressive)) OR (Depression, Neurotic)) OR (Depressions, Neurotic)) OR (Neurotic Depression)) OR (Neurotic Depressions)) OR (“Depressive Disorder”[Mesh])) OR (((((Depression) OR (Depressive Symptoms)) OR (Depressive Symptom)) OR (Symptom, Depressive)) OR (Emotional Depression)) OR (Depression, Emotional))) OR (“Depression”[Mesh])
- #2: (((“Inflammation”[Mesh]) OR (((((Inflammation) OR (Inflammations)) OR (Innate Inflammatory Response)) OR (Inflammatory Response, Innate)) OR (Innate Inflammatory Responses))) OR (“Neurogenic Inflammation”[Mesh])) OR (((((Neurogenic Inflammation) OR (Inflammation, Neurogenic)) OR (Inflammations, Neurogenic)) OR (Neurogenic Inflammations))
- #3: “Randomized Controlled Trials as Topic”[MeSH Terms] OR “Randomized Controlled Trial”[Publication Type] OR “Equivalence Trial”[Publication Type] OR “Pragmatic Clinical Trial”[Publication Type] OR “Equivalence Trials as Topic”[MeSH Terms] OR “Intention to Treat Analysis”[MeSH Terms] OR “Pragmatic Clinical Trials as Topic”[MeSH Terms] OR “Single-Blind Method”[MeSH Terms] OR “Random Allocation”[MeSH Terms] OR “Double-Blind Method”[MeSH Terms] OR “Random Allocation”[MeSH Terms] OR “Adaptive Clinical Trial”[Publication Type] OR “Adaptive Clinical Trials as Topic”[MeSH Terms] OR “clinical trials, phase ii as topic”[MeSH Terms] OR “clinical trials, phase iii as topic”[MeSH Terms] OR “clinical trials, phase iv as topic”[MeSH Terms] OR “random*”[Title/Abstract] OR “Equivalence Trial”[Title/Abstract]

OR “equivalence clinical trial”[Title/Abstract] OR “equivalence design”[Title/Abstract] OR “non inferiority trial”[Title/Abstract] OR “noninferiority trial”[Title/Abstract] OR “pragmatic trial”[Title/Abstract] OR “non inferiority clinical trial”[Title/Abstract] OR “non inferiority design”[Title/Abstract] OR “practical clinical trial”[Title/Abstract] OR “Pragmatic Clinical Trial”[Title/Abstract] OR “superiority clinical trial”[Title/Abstract] OR “superiority design”[Title/Abstract] OR (“superior”[All Fields] OR “superior s”[All Fields] OR “superiorities”[All Fields] OR “superiority”[All Fields] OR “superiors”[All Fields]) AND “tria”[Title/Abstract] OR “single masked”[Title/Abstract] OR “single blind”[Title/Abstract] OR “single blind”[Title/Abstract] OR “double masked”[Title/Abstract] OR “double blind”[Title/Abstract] OR “double blind”[Title/Abstract] OR “triple masked”[Title/Abstract] OR “triple blind”[Title/Abstract] OR “triple blind”[Title/Abstract] OR “singleblind*”[Title/Abstract] OR “doubleblind*”[Title/Abstract] OR “tripleblind*”[Title/Abstract] OR “intent to treat”[Title/Abstract] OR “intention to treat”[Title/Abstract] OR “adaptive design”[Title/Abstract] OR “adaptive trial”[Title/Abstract]

- #4: ((“animals”[mesh] not(“animals”[mesh] AND “humans”[mesh])) or rat[ti] or rats[ti] or mice[ti] or mouse[ti] or rodent*[ti] or rabbit*[ti] or baboon*[ti] or cat[ti] or cats[ti] or cow[ti] or cows[ti] or dog[ti] or dogs[ti] or canine*[ti] or ferret*[ti] or fish[ti] or frog[ti] or guineapig*[ti] or hamster*[ti] or monkey*[ti] or pig[ti] or pigs[ti] or sheep[ti] or cattle*[ti] or horse*[ti] or bat[ti] or bats[ti] or “Review”[Publication Type] or “Editorial”[Publication Type] or “Letter”[Publication Type] or review*[ti] or “meta-analysis”[ti] or “meta-analyses”[ti] or “diagnostic stud*”[ti] or “diagnostic trial*”[ti] or “retrospective stud*”[ti] or “crosssectional stud*”[ti] or “observational stud*”[ti] or survey*[ti] or simulat*[ti])
- #5: #1 AND #2 AND #3 NOT #4
- #6: (((((((trials[Title]) OR (randomized controlled trials[Title])) OR (reviews[Title])) OR (trials[Title])) OR (meta-analysis[Title])) OR (systematic review[Title])) OR (this review[Title])) OR (literature review[Title])) OR (randomised controlled trials[Title])
- #7: (((((((((((((((((((((((survey[Title]) OR (prevalence[Title])) OR (observational[Title])) OR (non-randomized[Title])) OR (healthy controls[Title])) OR (regression analysis[Title])) OR (cohort[Title])) OR (equine[Title])) OR

(transgenic[Title])) OR (single arm[Title])) OR (age-matched[Title])) OR (case report[Title])) OR (case control[Title])) OR (case reports[Title])) OR (longitudinal[Title])) OR (nonrandomised[Title])) OR (nonrandomized[Title])) OR (non-randomised[Title])) OR (cross-sectional[Title])) OR (healthy control[Title])) OR (retrospectively[Title])) OR (regression analyses[Title])) OR (retrospective study[Title])) OR (retrospective cohort[Title])) OR (sensitivity[Title] AND specificity[Title])

- #8: NOT #6 NOT #7

2.4. Data charting process and data items

The following data were charted from each included randomised controlled trial.³⁶ The information extracted from each eligible report includes: study characteristics, country, diagnostic criteria, participant characteristics, baseline inflammatory status, intervention and comparator details, treatment duration, depression rating scales, inflammatory biomarkers, outcome assessment time points, adverse events, and withdrawals.

For depressive symptom severity, the outcome prespecified as primary by the original trial was selected whenever available. If no primary outcome was specified, the most commonly reported validated clinician-rated depression scale at the end of the randomised treatment period was used. Change-from-baseline scores were preferred when reported for both groups; otherwise, endpoint scores were extracted.

Biomarker values were recorded in their original units. No unit conversions were undertaken. Biomarker meta-analyses were performed only when at least two reports provided comparable data for the same marker using consistent units and assessment time points.

2.5. Risk of bias assessment

Because this review was restricted to randomised controlled trials and included interpretation of clinical and biomarker outcomes, methodological limitations were assessed using the Cochrane Risk of Bias 1 tool.³⁹ Assessments focused on the primary depressive symptom outcome and considered the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias.

Two assessors independently evaluated the included reports, and disagreements were resolved through discussion. For trials reported in multiple publications, information was collated across all linked reports and a single trial-level judgment was assigned.

Each domain was classified as low, unclear, or high risk of bias. Overall risk of bias was judged as low when all domains were rated low risk, unclear when at least one domain was unclear but none was high risk, and high when one or more domains were rated high risk. Risk-of-bias assessments were not used as exclusion criteria but were considered when interpreting the network meta-analysis and exploratory biomarker findings.

2.6. Data analysis

The primary outcome was depressive symptom severity at the end of the randomised treatment period. Change-from-baseline scores were preferred when reported, and endpoint scores were used otherwise. When more than one depression scale was available, the outcome prespecified as primary by the original trial was selected. For ketamine studies, the most recent planned assessment during the acute randomised treatment period was used.

To enable comparison across studies, depressive symptom scores were converted to a common metric prior to network meta-analysis. When different rating scales were used, scores were transformed according to the reported scale range and direction so that all outcomes reflected depressive symptom severity on the same scale, with lower values indicating less severe depressive symptoms. Treatment effects were expressed as mean differences (MDs) with 95% confidence intervals (CIs). Negative MDs indicated lower depressive symptom severity and favoured the first-listed intervention.

A frequentist fixed-effects network meta-analysis was conducted. Treatment nodes were defined by pharmacological regimen and dose; ketamine 0.2 mg/kg and ketamine 0.5 mg/kg were analysed as separate nodes. Combination therapies, including selective serotonin reuptake inhibitor (SSRI) plus glycyrrhizic acid and vortioxetine plus celecoxib, were treated as distinct interventions. Placebo or saline control arms were combined as a common control condition only when background treatment and treatment context were judged clinically comparable.

Multi-arm trials were analysed jointly to account for correlations among comparisons that share the same participants. Study-defined placebo, saline, usual care, and background treatment control arms were combined into a reference control node for the primary network model. Because the specific control conditions and background treatments differed across studies, estimates relative to the reference control node were interpreted as exploratory.

The transitivity assumption was assessed descriptively by comparing potential effect modifiers across treatment comparisons, including depression diagnosis, treatment-

resistant status, baseline symptom severity, baseline inflammatory status, concurrent antidepressant treatment, treatment duration, and outcome assessment time point. Owing to the sparse network structure and insufficient independent evidence loops, between-study heterogeneity, global inconsistency, and local inconsistency could not be evaluated reliably. Direct, indirect, and network estimates were compared descriptively for contrasts with available evidence from more than one route.

Treatment ranking was summarised using surface under the cumulative ranking curve (SUCRA) values derived from cumulative ranking probabilities. Higher SUCRA values indicate a greater probability of a more favourable relative rank for lower depressive symptom severity.

Inflammatory biomarkers were analysed separately by marker. Exploratory random-effects pairwise meta-analyses were conducted for tumour necrosis factor- α (TNF- α), IL-6, interferon- γ (IFN- γ), C-reactive protein (CRP), and IL-2 when at least two reports provided comparable data for the same marker, biological specimen, outcome time point, and measurement unit. Mean differences with 95% CIs were calculated when units were consistent. Biomarkers were not pooled across different cytokines or inflammatory pathways. All analyses were two-sided, and p -values below 0.05 were considered statistically significant.

3. Results

3.1. Selection of sources of evidence

Electronic literature searching was conducted until June 21, 2026, across four databases: PubMed, Web of Science, Google Scholar, and the medRxiv preprint platform. In total, 2,383 original records were retrieved, consisting of 647 from PubMed, 1,688 from Web of Science, 12 from Google Scholar, and 36 preprint records from medRxiv.

All retrieved citations underwent title and abstract screening after preliminary deduplication. A total of 293 duplicate records were removed at this stage, along with 42 records without inflammatory-related outcomes, 644 non-trial publications, and another 1,337 irrelevant records on mismatched topics. After initial screening, 67 full-text articles were obtained for complete eligibility assessment.

During full-text evaluation, 56 publications were excluded according to pre-defined criteria, including 1 research protocol, 4 non-randomised controlled trials, 45 studies failing to report inflammatory biomarkers, 1 article unrelated to depressive disorders, 1 study without pharmacological agents, 2 papers lacking therapeutic intervention arms, and 2 investigations with insufficient study and data details. Finally, 11 randomised controlled

trials fully satisfying all inclusion criteria were incorporated into this systematic review and network meta-analysis. The study-selection process is summarised in the PRISMA flow diagram (Figure 1).⁴⁰⁻⁵⁰

3.2. Characteristics of included randomised controlled trials

The characteristics of the included trials are presented in Table 1. The 11 studies included in this review collectively encompassed 763 patients diagnosed with depression, with major depression being the most prevalent form of depression ($n = 8$). The primary diagnostic criterion employed for depression was the DSM-IV ($n = 7$). The majority of the depressed populations studied were middle-aged. The anti-inflammatory drugs used to treat these patients included fluoxetine ($n = 1$), infliximab ($n = 2$), ketamine ($n = 1$), minocycline ($n = 2$), vortioxetine + celecoxib ($n = 2$), SSRI ($n = 1$), and sumac (*Rhus coriaria* L.) ($n = 1$).

Most trials enrolled adults with major depressive disorder or treatment-resistant depression. Diagnostic criteria included DSM-IV, DSM-5, ICD-based diagnoses, structured diagnostic interviews, or clearly reported clinician-confirmed diagnoses. Trials differed in baseline depressive symptom severity, previous antidepressant exposure, treatment-resistance definitions, and inflammatory enrichment criteria.

3.3. Risk of bias within studies

The risk of bias assessment is presented in Table 2. Four reports were judged to have a low risk of bias, five to have an unclear risk of bias, and two to have a high risk of bias.

The main concerns were incomplete reporting of outcome data and unclear blinding procedures. Mackay *et al.*⁴⁰ and Zhang *et al.*⁴³ were reported to be at high risk of bias, primarily due to limited blinding and incomplete methodological reporting. The remaining reports were generally judged to have low or unclear risk of bias across the assessed domains.

3.4. Network meta-analysis

The treatment network comprised 11 nodes and 12 direct pairwise comparisons (Figure 2). The control condition node was the principal connector within the network. Fluoxetine plus triiodothyronine and the two ketamine dose groups formed the only multi-arm trial structures, whereas most other treatment contrasts were informed by a single randomised controlled trial.

Treatment ranking based on SUCRA is shown in Figure 3. Escitalopram oxalate ranked first, followed by fluoxetine, ketamine 0.5 mg/kg, and SSRI plus glycyrrhizic

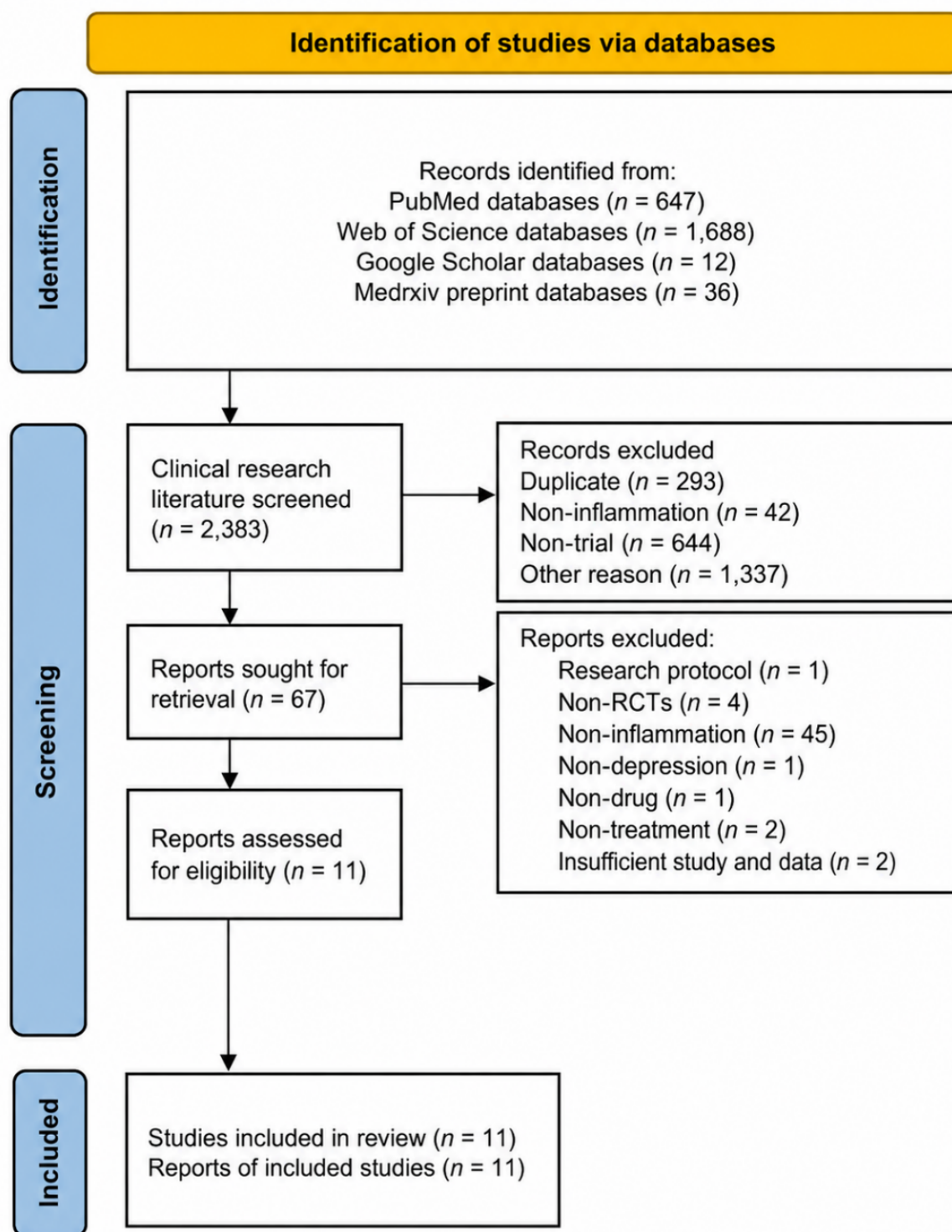


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection

Table 1. Characteristics of included randomised controlled trial reports

Study report	Country	Design and sample size	Population and diagnostic criteria	Intervention and comparator	Treatment duration	Depression outcome used for synthesis	Inflammatory biomarkers reported
Mackay <i>et al.</i> ⁴⁰	United Kingdom	Three-arm randomised controlled trial; <i>n</i> = 63	Moderate major depressive disorder; DSM-IV	Fluoxetine; fluoxetine + triiodothyronine (T3); psychological counselling	18 weeks	Depression symptom severity at week 18	CRP; IL-2
Raison <i>et al.</i> ⁴¹	United States	Double-blind, placebo-controlled randomised trial; <i>n</i> = 60	Treatment-resistant major depressive disorder; DSM-IV	Infliximab 5 mg/kg intravenously vs placebo	12 weeks	HAM-D-17 change from baseline at week 12	hs-CRP; TNF; sTNFR1; sTNFR2
Weinberger <i>et al.</i> ⁴²	United States	Randomised placebo-controlled trial report; <i>n</i> = 36	Treatment-resistant major depressive disorder; DSM-IV	Infliximab vs placebo	8 weeks	Sleep-related and depressive symptom outcomes	hs-CRP; sTNFR1; sTNFR2
Zhang <i>et al.</i> ⁴³	China	Two-arm randomised trial; <i>n</i> = 130	Depressive disorder; diagnostic criteria not clearly reported in the original table	Escitalopram oxalate vs fluoxetine hydrochloride	6 weeks	HAMD total score at week 6	IL-2; IL-6; TNF- α
Chen <i>et al.</i> ⁴⁴	Taiwan, China	Three-arm randomised, double-blind, saline-controlled trial; <i>n</i> = 71	Treatment-resistant depression; DSM-IV	Ketamine 0.5 mg/kg; ketamine 0.2 mg/kg; saline placebo	Single infusion; follow-up to day 7	MADRS change from baseline at day 7	CRP; IL-6; TNF- α
Cao <i>et al.</i> ⁴⁵	China	Randomised placebo-controlled adjunctive trial; <i>n</i> = 56	Major depressive disorder; DSM-5	SSRI + glycyrrhizic acid vs SSRI + placebo	4 weeks	Depression symptom severity, response, and remission at week 4	CRP; IL-6; TNF- α ; IL-1 β ; IFN- γ ; cortisol
Hariri <i>et al.</i> ⁴⁶	Iran	Double-blind randomised placebo-controlled trial; <i>n</i> = 62	Mild-to-moderate depression in overweight or obese women; DSM-IV	Sumac (<i>Rhus coriaria</i> L.) plus calorie-restricted diet vs placebo plus calorie-restricted diet	12 weeks	Depression symptom score at week 12	hs-CRP; IL-6; TNF- α ; oxidative-stress markers
Nettis <i>et al.</i> ⁴⁷	United Kingdom	Double-blind randomised placebo-controlled augmentation trial; <i>n</i> = 39	Treatment-resistant major depressive disorder; low-grade peripheral inflammation	Mino cycline 200 mg/day vs placebo	4 weeks	HAM-D-17 change from baseline at week 4	hs-CRP; IL-6; IFN- γ
Baune <i>et al.</i> ⁴⁸	Australia	Double-blind randomised placebo-controlled augmentation trial; <i>n</i> = 119	Major depressive disorder; most participants had treatment-resistant illness	Vortioxetine + celecoxib 400 mg/day vs vortioxetine + placebo	6 weeks	MADRS change from baseline at week 6	hs-CRP
Nettis <i>et al.</i> ⁴⁹	United Kingdom	Randomised controlled trial report; <i>n</i> = 39	Major depressive disorder; DSM-5	Mino cycline vs placebo	4 weeks	Depression symptom severity and biomarker-related outcomes	hs-CRP; kynurenine-pathway markers
Sampson <i>et al.</i> ⁵⁰	Australia/Germany	Randomised placebo-controlled trial report; <i>n</i> = 88	Major depressive disorder; DSM-IV	Vortioxetine + celecoxib vs vortioxetine + placebo	6 weeks	Cognitive or emotional-blunting outcomes alongside depressive symptoms	hs-CRP where available

Abbreviations: CRP: C-reactive protein; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAM-D-17: 17-item Hamilton Depression Rating Scale; HAM-D: Hamilton Depression Rating Scale; hs-CRP: High-sensitivity C-reactive protein; IFN- γ : Interferon gamma; IL: Interleukin; MADRS: Montgomery-Åsberg Depression Rating Scale; SSRI: Selective serotonin reuptake inhibitor; sTNFR: Soluble tumour necrosis factor receptor; TNF: Tumour necrosis factor.

Table 2. Risk of bias summary

Ref	D1	D2	D3	D4	D5	D6	D7	Overall risk of bias
Mackay <i>et al.</i> 40	Unclear	Unclear	High	Unclear	Low	Low	Unclear	High
Raison <i>et al.</i> 41	Low	Low	Low	Low	Low	Low	Low	Low
Weinberger <i>et al.</i> 42	Low	Low	Low	Low	Unclear	Low	Low	Unclear
Zhang <i>et al.</i> 43	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	High
Chen <i>et al.</i> 44	Low	Low	Low	Low	Low	Low	Low	Low
Cao <i>et al.</i> 45	Low	Low	Low	Low	Unclear	Low	Unclear	Unclear
Hariri <i>et al.</i> 46	Low	Low	Low	Low	Unclear	Low	Unclear	Unclear
Nettis <i>et al.</i> 47	Low	Low	Low	Low	Low	Low	Low	Low
Baune <i>et al.</i> 48	Low	Low	Low	Low	Low	Low	Low	Low
Nettis <i>et al.</i> 49	Low	Low	Low	Low	Unclear	Low	Low	Unclear
Sampson <i>et al.</i> 50	Low	Low	Low	Low	Unclear	Low	Low	Unclear

Note: D1: Random sequence generation; D2: Allocation concealment; D3: Blinding of participants and personnel; D4: Blinding of outcome assessment; D5: Incomplete outcome data; D6: Selective reporting; D7: Other bias.

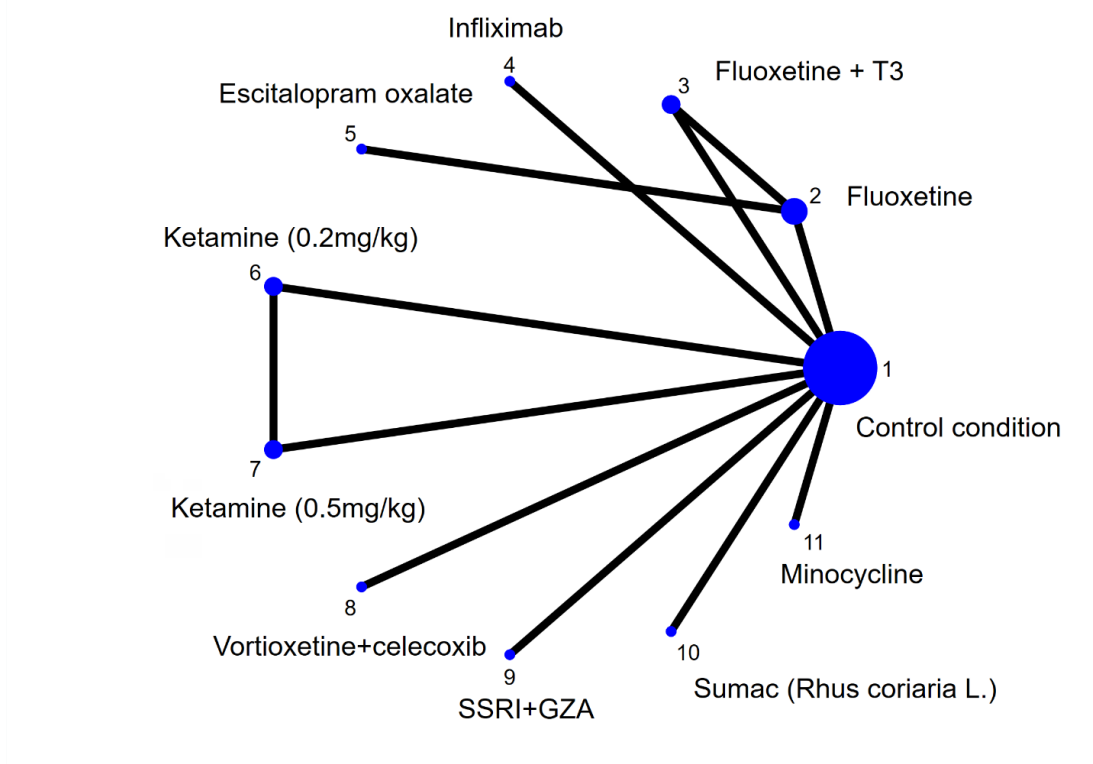


Figure 2. Network plot for anti-inflammatory pharmacotherapy for depression disorders. Each node represents an intervention or control condition, and each connecting line represents at least one direct randomised comparison between the two connected treatments. The number shown on each line indicates the number of direct study-level comparisons contributing to that treatment contrast. Node size and line thickness are not intended to represent treatment efficacy or study precision. Abbreviations: GZA: Glycyrrhizic acid; SSRI: Selective serotonin reuptake inhibitor.

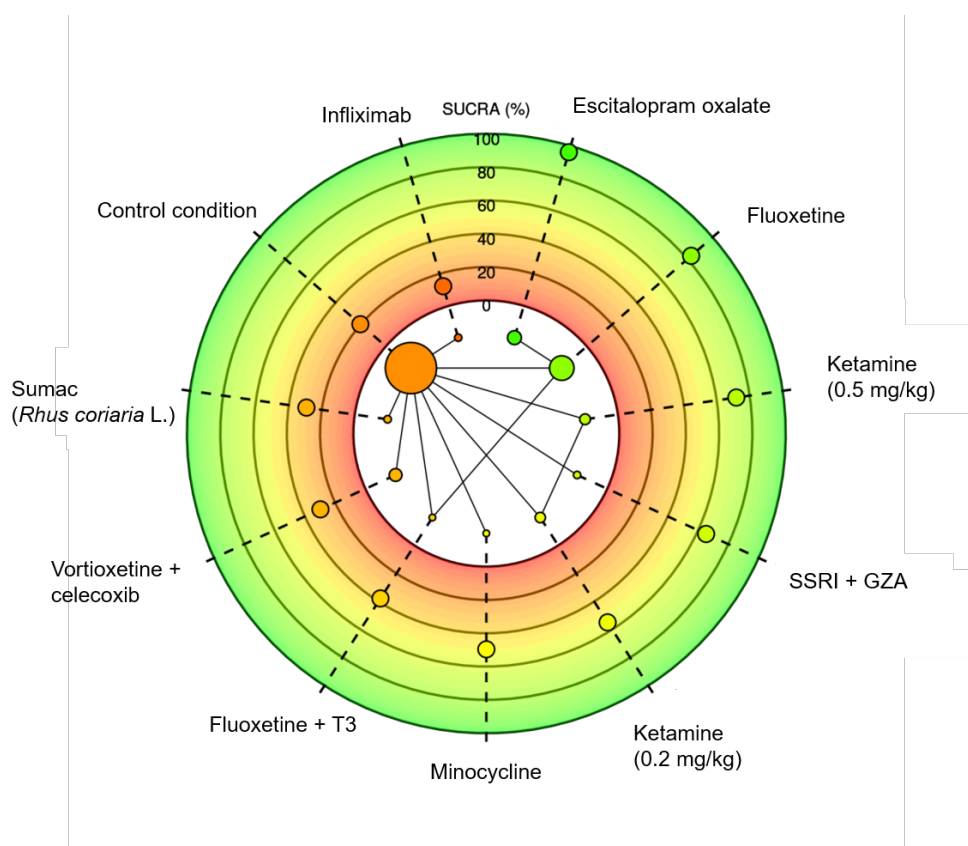


Figure 3. Treatment ranking and network structure for depressive symptom severity. The outer radial plot presents the exploratory surface under the cumulative ranking curve (SUCRA) values for each intervention, where higher values indicate a greater probability of achieving a more favourable rank for lower depressive symptom severity. The inner network displays the direct treatment comparisons available from the included randomised controlled trials. Each node represents an intervention or control condition, and each connecting line represents a direct comparison between two treatment nodes. In ranking analyses, escitalopram oxalate, ketamine 0.5 mg/kg, and SSRI plus glycyrrhizic acid showed relatively favourable positions. Abbreviations: GZA: Glycyrrhizic acid; SSRI: Selective serotonin reuptake inhibitor.

acid. Ketamine 0.2 mg/kg and minocycline occupied intermediate positions. Fluoxetine plus triiodothyronine, vortioxetine plus celecoxib, sumac (*Rhus coriaria* L.), the control condition, and infliximab ranked lower (Figure 3).

Fixed-effect network meta-analysis estimates relative to the reference control node are shown in Figure 4. Escitalopram oxalate was associated with lower depressive symptom severity than the control node (MD: -13.03, 95% CI: -24.54 to -1.52). Ketamine 0.5 mg/kg (MD: -5.16, 95% CI: -8.81 to -1.51) and SSRI plus glycyrrhizic acid (MD: -4.35, 95% CI: -7.16 to -1.55) also showed 95% CIs excluding the null value. Fluoxetine showed a numerically favourable estimate, although the CI crossed zero (MD: -11.11, 95% CI: -22.57 to 0.35). No statistically precise differences from the reference control node were observed for fluoxetine plus triiodothyronine, infliximab, ketamine 0.2 mg/kg, minocycline, sumac, or vortioxetine plus celecoxib.

3.5. Exploratory meta-analyses of inflammatory biomarkers

No pooled analysis demonstrated a statistically precise difference between intervention and comparator groups (Figure 5). For TNF- α , the pooled MD was 0.03 (95% CI: -0.53 to 0.58; $P = 71\%$). For IL-6, the pooled MD was 1.19 (95% CI: -1.93 to 4.32; $P = 94\%$). For IFN- γ , the pooled MD was 0.98 (95% CI: -0.23 to 2.18; $P = 0\%$). For CRP, the pooled MD was 2.03 (95% CI: -0.76 to 4.82; $P = 73\%$). For IL-2, the pooled MD was 2.04 (95% CI: -2.44 to 6.32; $P = 87\%$).

Individual study estimates varied in both direction and magnitude. Substantial heterogeneity was observed for TNF- α , IL-6, CRP, and IL-2, indicating important between-study differences in intervention type, clinical population, baseline inflammatory status, treatment duration, sample type, assay method, and timing of biomarker assessment.

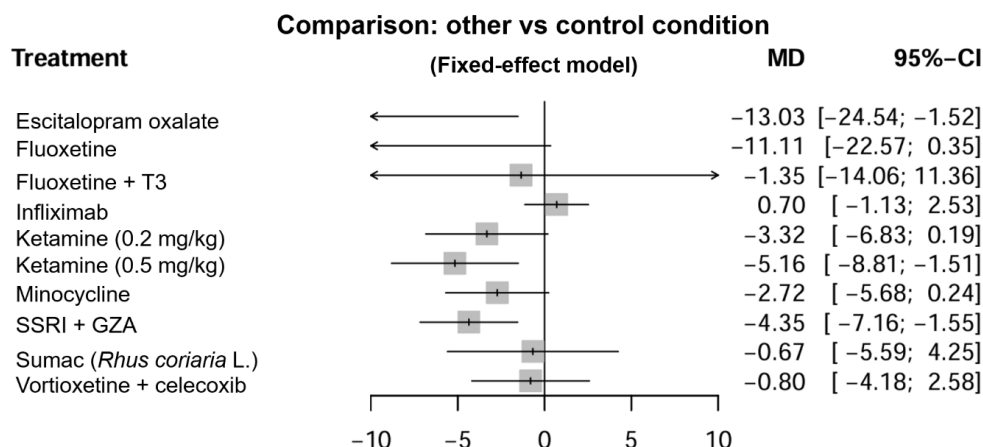


Figure 4. Fixed-effects network meta-analysis estimates for depressive symptom severity relative to the control node. Squares represent mean differences and horizontal lines represent 95% confidence intervals. Negative values indicate lower depressive symptom severity in the listed intervention relative to the control node. Compared with the control node, escitalopram oxalate (MD: -13.03, 95% CI: -24.54 to -1.52), ketamine 0.5 mg/kg (MD: -5.16, 95% CI: -8.81 to -1.51), and SSRI plus glycyrrhizic acid (MD: -4.35, 95% CI: -7.16 to -1.55) were associated with lower depressive symptom severity. Fluoxetine showed a numerically favourable estimate, but its 95% confidence interval crossed the null value (MD: -11.11, 95% CI: -22.57 to 0.35). No statistically precise differences from the control node were observed for fluoxetine plus triiodothyronine, infliximab, ketamine 0.2 mg/kg, minocycline, Sumac (*Rhus coriaria* L.), or vortioxetine plus celecoxib.

Abbreviations: CI: Confidence interval; GZA: Glycyrrhizic acid; MD: Mean difference; SSRI: Selective serotonin reuptake inhibitor.

By contrast, the IFN- γ analysis showed no statistical heterogeneity, although it was informed by only two reports and remained imprecise.

Overall, these exploratory analyses did not provide evidence of a consistent class-wide reduction or increase in circulating inflammatory biomarkers across the included interventions.

4. Discussion

4.1. Summary of evidence

The current network meta-analysis suggests that the available evidence does not support a consistent overall benefit of inflammation-informed pharmacological strategies for depressive disorders. From an evidence-based perspective, the included interventions did not show a uniform association with remission or improvement in depressive symptoms across studies.

The exploratory biomarker meta-analyses further indicated that these interventions did not consistently reduce systemic inflammation, as measured by TNF- α , IL-6, IFN- γ , CRP, and IL-2. Although some interventions showed potentially favourable effects on depressive symptom severity, the available clinical evidence was sparse and imprecise. No included study provided sufficient evidence to confirm a reproducible treatment benefit within a clearly defined inflammatory subgroup.

Therefore, conclusions regarding the clinical efficacy of inflammation-informed pharmacotherapy should remain cautious. Some original trial reports may have placed greater emphasis on exploratory subgroup findings or biomarker-associated effects than the overall comparative evidence supports.

4.2. Implications for future clinical trials

Clinicians have observed in practice that anti-inflammatory strategies can address psychological and emotional symptoms; this experience has not yet been translated into a widely applicable clinical consensus. This requires psychologists, researchers, and clinicians to work together to explore a viable and scalable research approach.

On the other hand, if anti-inflammatory drug strategies offer clinical benefits to patients with depressive disorders characterised by high levels of inflammation, it is necessary to analyse whether this is attributable to the depressive disorder itself or to inflammation-related underlying conditions. Although inflammation may occasionally act as a triggering factor for psychological and emotional states, thereby leading to the development of a depressive disorder, such an observation is difficult to generalise to other countries or regions. Future clinical researchers could draw on these lessons by stratifying the included patients with depressive disorders and high levels of inflammation according to their accompanying underlying conditions,

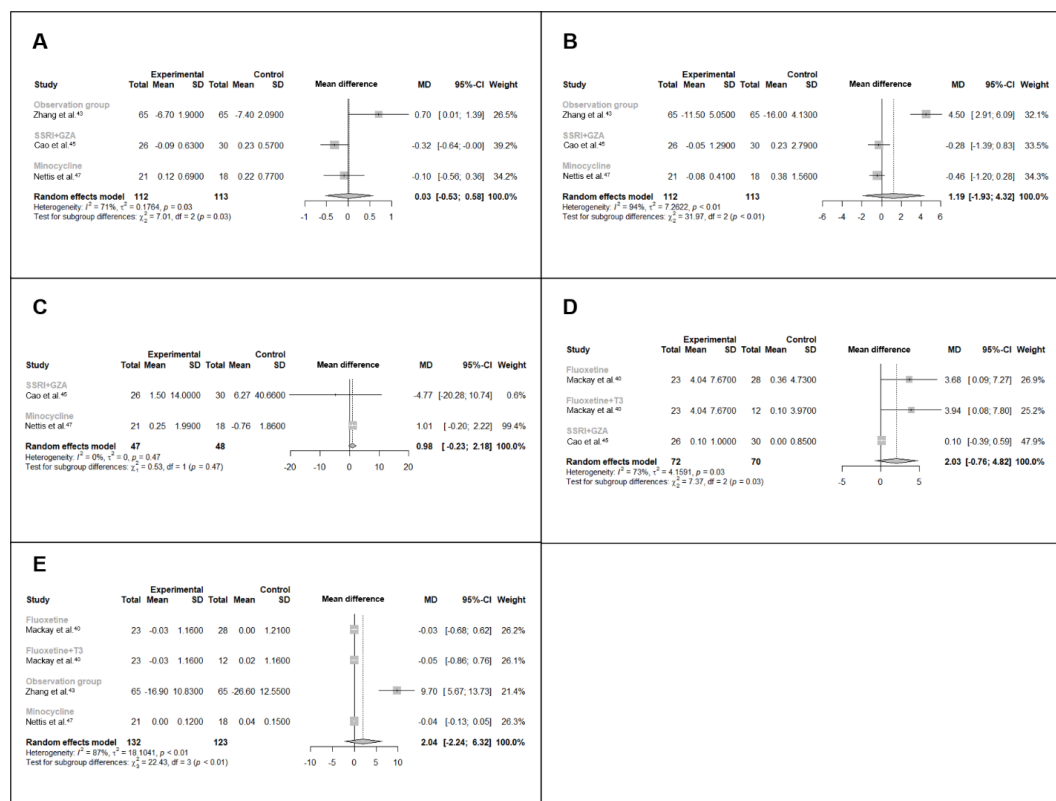


Figure 5. Exploratory random-effects meta-analyses of differences in inflammatory biomarkers between intervention and control groups. (A) TNF- α . (B) IL-6. (C) INF- γ . (D) CRP. (E) IL-2. The pooled MD was 0.03 (95% CI: -0.53 to 0.58) for TNF- α , 1.19 (95% CI: -1.93 to 4.32) for IL-6, 0.98 (95% CI: -0.23 to 2.18) for INF- γ , 2.03 (95% CI: -0.76 to 4.82) for CRP, and 2.04 (95% CI: -2.44 to 6.32) for IL-2. Heterogeneity was substantial for TNF- α ($I^2 = 71\%$), IL-6 ($I^2 = 94\%$), CRP ($I^2 = 73\%$), and IL-2 ($I^2 = 87\%$), whereas no heterogeneity was observed for INF- γ ($I^2 = 0\%$). Overall, these exploratory analyses do not show consistent evidence that the included interventions produce a uniform reduction or increase in circulating inflammatory biomarkers. The wide confidence intervals and substantial heterogeneity indicate that biomarker effects may vary by intervention class, baseline inflammatory status, laboratory assay, clinical population, and timing of outcome assessment. These pooled estimates should be regarded as hypothesis-generating rather than as evidence of a class-wide biological effect.

Abbreviations: CI: Confidence interval; CRP: C-reactive protein; GZA: Glycyrrhizic acid; IFN- γ : Interferon gamma; IL: Interleukin; MD: Mean difference; SSRI: Selective serotonin reuptake inhibitor; TNF- α : Tumour necrosis factor alpha.

and producing open and transparent reports. In other words, this anti-inflammatory drug strategy for treating depressive disorders may be ineffective for typical cases of the condition; rather, it may prove effective for patients with atypical forms of depressive disorder accompanied by underlying inflammation-related conditions.

4.3. Authors' perspective

This network meta-analysis highlights an important translational problem: inflammatory biomarkers were measured inconsistently across trials, with substantial variation in marker selection, assay methods, thresholds, sampling time points, comorbidities, and clinical

outcomes. Consequently, current evidence cannot yet define a reproducible inflammation-related phenotype of depressive disorders or identify patients most likely to benefit from inflammation-informed pharmacotherapy.

Future research should establish transparent and longitudinal frameworks that integrate depressive symptom measures, repeated blood-based inflammatory biomarkers, physical comorbidities, medication exposure, and treatment outcomes. Artificial intelligence may assist this process by identifying multivariable patterns, supporting biomarker selection, and developing testable prediction models for treatment response. Such systems could help researchers move from isolated cytokine measurements toward clinically interpretable inflammatory profiles.

4.4. Limitations

One limitation of this study is that we searched only four databases. Furthermore, we were unable to access the raw data from these clinical trials, so we could not further adjust the meta-analysis results to account for individual patients' comorbid inflammatory conditions. Our secondary analysis of the available evidence did not validate this view.

5. Conclusion

This network meta-analysis found no consistent class-wide benefit of inflammation-informed pharmacotherapy for depressive disorders. Although SSRI plus glycyrrhizic acid, escitalopram oxalate, and ketamine 0.5 mg/kg showed potentially favourable effects on depressive symptom severity, the evidence network was sparse, and most comparisons were based on single trials.

No consistent changes were observed across inflammatory biomarkers. Current evidence is therefore insufficient to support routine use of inflammation-informed pharmacotherapy for all patients with depressive disorders. Future trials should recruit biologically defined patient subgroups and use standardised clinical and biomarker outcomes.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization: Yan Bo

Formal analysis: Yan Bo

Investigation: Yan Bo

Methodology: Yan Bo

Writing—original draft: Yan Bo

Writing—review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The study has been registered on the Open Science Framework (OSF) platform. Supplementary materials have been deposited with the OSF Registry (doi: 10.17605/OSF.IO/A64GC).

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