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Antidepressant Effects of Artemisinin and Its Derivatives: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 August 2026 and was last updated on 16 August 2026.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis, framed by the PICOS approach, addresses the following research question: in rodent models of depression (Population), does artemisinin administration (Intervention), compared with placebo, vehicle, or no treatment (Comparison), effectively reduce depressive-like behaviors (immobility in the tail suspension and forced swimming tests, and anhedonia measured by sucrose preference), anxiety-like behaviors (parameters in the open field and elevated plus maze tests), and cognitive impairments (performance in the Morris water maze, Y-maze, and novel object recognition test) (Outcomes), as assessed in randomized controlled animal trials (Study Design)? Moreover, what study-level characteristics—such as rodent species, depression induction methods, intervention timing (preventive vs. therapeutic), total treatment duration, and dosing frequency—moderate the observed effect sizes? To answer this question, the present study has four specific objectives. First, to quantitatively synthesise the overall antidepressant efficacy of artemisinin by pooling standardized mean differences (SMDs) using a random-effects model, thereby providing the first meta-analytic estimate of its preclinical effects on each behavioural outcome. Second, to explore potential sources of heterogeneity through subgroup analyses that examine whether the treatment effect varies by animal species (mouse vs. rat), depression-inducing strategy (e.g., chronic stress, pharmacological induction, genetic models), intervention timing (preventive versus therapeutic administration), treatment duration (short-term vs. long-term), and dosing frequency (once vs. multiple times daily) – these analyses are crucial for identifying the experimental conditions under which artemisinin exerts its strongest effects. Third, to critically appraise the methodological quality and robustness of the included evidence by assessing risk of bias with the SYRCLE tool, performing sensitivity analyses to test the stability of the pooled estimates, and quantitatively evaluating publication bias using Egger's

regression test, which together will determine the reliability of the current preclinical database. Fourth, to translate these preclinical findings into future research directions by summarising the existing evidence, highlighting important gaps (such as the absence of direct comparisons with standard antidepressants), and providing a rationale for designing subsequent clinical trials that might explore artemisinin as an adjunctive therapy for depression in humans. By achieving these objectives, this review will offer a comprehensive, transparent, and PICOS-guided synthesis of artemisinin's antidepressant potential in animal models, while also critically appraising the strength and limitations of the available evidence, ultimately laying a solid foundation for future translational investigations.

Rationale Depression imposes a substantial global disease burden, and current pharmacotherapies are limited by delayed onset, significant adverse effects, and high costs. Preclinical studies suggest that artemisinin possesses neuroprotective and anti-inflammatory properties and exhibits antidepressant-like effects in rodent models. However, no meta-analysis has yet synthesized these preclinical data. Therefore, a systematic review and meta-analysis is warranted to quantitatively evaluate artemisinin's antidepressant efficacy in animal models and to identify factors that may influence treatment effect variability, thereby providing an evidence base for future clinical translation.

Condition being studied Depression (including depressive-like behaviors, anxiety-like behaviors, and cognitive impairments) modelled in rodents through various induction methods (e.g., chronic stress, pharmacological agents, genetic models).

METHODS

Search strategy A systematic search will be performed in four electronic databases: PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI), covering all randomized controlled animal trials published up to May 2026, without language restrictions. The search strategy will combine MeSH terms and free-text words such as "artemisinin", "depression", "depressive disorder", "rodent", "animal model", and "randomized controlled trial", adapted to each database. Additionally, reference lists of included studies will be hand-searched for supplementary records.

Participant or population The participants in this meta-analysis are rodent models of depression, specifically mice and rats, induced by various methods (e.g., chronic unpredictable stress, corticosterone injection, genetic susceptibility). Studies must clearly report the species and the modelling procedure.

Intervention Artemisinin administered at any dose, route (e.g., intraperitoneal, oral gavage), timing (preventive or therapeutic), frequency (single or multiple daily doses), and total duration of treatment, as reported in the primary studies.

Comparator Control groups receiving placebo, vehicle, or no treatment (untreated/sham-treated) in parallel with the intervention group.

Study designs to be included Randomized controlled trials (RCTs) conducted in vivo in rodents. Non-randomized studies, in vitro experiments, human clinical trials, reviews, and conference abstracts will be excluded.

Eligibility criteria Inclusion criteria: (1) rodent models of depression (mice or rats); (2) intervention with artemisinin (any dose, route, regimen); (3) comparator as placebo, vehicle, or no treatment; (4) reporting at least one behavioural outcome (TST, FST, SPT, OFT, EPM, MWM, Y-maze, or NOR); (5) random allocation to groups; (6) published up to May 2026.Exclusion criteria: (1) duplicate publications or overlapping data; (2) non-original studies (reviews, editorials, conference abstracts); (3) insufficient data to extract means and standard deviations; (4) unclear depression modelling or intervention details.

Information sources The four databases: PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI). In addition, reference lists of included articles and relevant reviews will be manually screened to identify any additional eligible studies.

Main outcome(s) Behavioural test results, including:
Depressive-like behaviours: immobility time in the tail suspension test (TST) and forced swimming test (FST); sucrose preference in the sucrose preference test (SPT) as a measure of anhedonia.
Anxiety-like behaviours: central zone activity in the open field test (OFT) and open-arm entries/time in the elevated plus maze (EPM).
Cognitive function: escape latency or target quadrant time in the Morris water maze (MWM); spontaneous alternation in the Y-maze; discrimination index in the novel object recognition (NOR) test.

Additional outcome(s) Methodological quality and risk of bias will be assessed using the SYRCLE's Risk of Bias tool for animal studies, covering selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain will be judged as "low risk", "high risk", or "unclear". Additionally, publication bias will be quantitatively examined using Egger's regression test.

Quality assessment / Risk of bias analysis Methodological quality and risk of bias will be assessed using the SYRCLE's Risk of Bias tool for animal studies, covering selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain will be judged as "low risk", "high risk", or "unclear". Additionally, publication bias will be quantitatively examined using Egger's regression test.A random-effects model will be used to pool the effect sizes across studies, given anticipated heterogeneity. The effect measure will be the standardized mean difference (SMD) with 95% confidence intervals (95% CI) for each behavioural outcome. Heterogeneity will be assessed using Cochran's Q test and the I^2 statistic (I^2 > 50% considered moderate to high heterogeneity). All statistical analyses will be performed using appropriate software (e.g., Stata or RevMan). Forest plots will be generated for visual presentation.

Strategy of data synthesis A random-effects model will be used to pool the effect sizes across studies, given anticipated heterogeneity. The effect measure will be the standardized mean difference (SMD) with 95% confidence intervals (95% CI) for each behavioural outcome. Heterogeneity will be assessed using Cochran's Q test and the I^2 statistic (I^2 > 50% considered moderate to high heterogeneity). All statistical analyses will be performed using appropriate software (e.g., Stata or RevMan). Forest plots will be generated for visual presentation.

Subgroup analysis To explore potential moderators of treatment effects, subgroup analyses will be performed based on the following study-level characteristics:
Rodent species: mice vs. rats;
Depression induction method: chronic stress, pharmacological induction, genetic models, etc.;
Intervention timing: preventive (before or during modelling) vs. therapeutic (after modelling);
Total treatment duration: short-term (≤7 days) vs. long-term (>7 days);
Dosing frequency: once daily vs. multiple times daily.

Sensitivity analysis Sensitivity analyses will be conducted by leave-one-out analysis (sequentially excluding each study) to assess the stability and robustness of the pooled results. Additionally, if studies with high risk of bias are identified, we will repeat the meta-analysis after excluding them to examine whether the overall conclusions change.

Country(ies) involved China.

Keywords animal experiment, artemisinin, meta-analysis, depressive symptoms, systematic review.

Contributions of each author
Author 1 - Xu Zhang - conceptualized and designed the study.
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