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The Effects of Berberine on Depressive Symptoms: A Systematic Review and Meta-Analysis of Preclinical Studies

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ADMINISTRATIVE INFORMATION

Support - No.

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 1 June 2025 and was last updated on 1 June 2025.

INTRODUCTION

Review question / Objective Synthesis of evidence from animal randomized controlled trials to assess the efficacy of berberine in depressed mice.

Rationale Depression has high morbidity and mortality. Available antidepressants include selective 5-hydroxytryptamine reuptake inhibitors (SSRIs), 5-hydroxytryptamine and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic and tetracyclic antidepressants. However, these drugs have the disadvantages of long treatment cycles, high drug side effects, and lack of effectiveness. A growing body of research points to natural botanicals for the treatment of depression. Although the available animal studies suggest that Flavopiridol has great potential in the treatment of depression, controversy still exists on its pharmacological effects. In particular, no meta-analysis based on preclinical studies has been performed to date to synthesize the role of berberine in depression. Therefore, the aim of this paper is to conduct a systematic evaluation and meta-analysis by integrating relevant animal studies in order to further comprehensively summarize the potential mechanism of action of berberine in DD and to provide systematic scientific support for further clinical studies.

Condition being studied Depressive Disorder (DD) is a common mental disorder that mainly includes symptoms such as depressed mood, cognitive impairment, sleep disturbance, avoidance of social interactions, and decreased motivation, and in severe cases, self-harming behavior. Available survey data show that the prevalence of depression is about 5% worldwide.

METHODS

Search strategy To obtain comprehensive information on preclinical studies of BBR for DD, we searched for relevant studies from five databases (PubMed, Embase, Web of Science, Cochrane Library, and OVID). The search was

conducted until March 20, 2025. Participating authors discussed search methods to minimize the loss of research literature. Finally, a combined disease and treatment approach was used based on the PICOS principle. In PubMed, a Mesh word search was used, with search terms including “Berberine”, “Coptis chinensis”, “Depression Depression”, ‘Depressive Disorder.

Participant or population Depressed mice/rat.

Intervention Intraperitoneal or oral berberine.

Comparator Model group given vector or blank control.

Study designs to be included Randomized controlled trials (RCTs), including parallel-group and cluster-randomized designs.

Eligibility criteria 1) Published findings.2) Studies with separate experimental and control groups.3) No restrictions on animal modeling methods, animal species, animal sex, size, or sample size.4) Experimental group given BBR treatment only, model group given vector treatment or used as a model control.5) Availability of experimental data.6) No restrictions on the language of the literature.

Information sources To obtain comprehensive information on preclinical studies of BBR for DD, we searched relevant studies from five databases (PubMed, Embase, Web of Science, Cochrane Library, and OVID).

Main outcome(s) ①weight②Number of crossing③total moving distance④Number of rearings⑤time duration of center square⑥Forced swimming test⑦Tail suspension test⑧Sucrose preference test⑨Novelty suppressed feeding test ⑩ BDNF⑪ DA⑫ 5-HT⑬ NA ⑭ TNF-α⑮ IL-1β⑯ IL-6.

Quality assessment / Risk of bias analysis Two authors independently evaluated the quality of the literature on BBR for DD using the 10-item risk of bias assessment tool of the Center for the Evaluation of Laboratory Animal Experiments (SYRCLE) . Quality assessment entries included: sequence generation, baseline characteristics, concealed grouping, randomization of animal placement, blinding of animal keepers and investigators, assessment of randomized outcomes, blinding of outcome assessors, incomplete data reporting, selective outcome reporting, and other sources of bias. Disagreements that arose during the quality assessment process were ultimately resolved through consultation with the corresponding author.

Strategy of data synthesis STATA 15.0 and Review Manager 5.4 software were used for statistical analysis. As the outcome indicators in this paper are continuous variable data, the results were assessed using standardized mean difference (SMD) and 95% confidence interval (CI). The p 50% indicated a high degree of heterogeneity, the random-effects model was used to combine the outcome effect sizes. Subgroup analyses were conducted on data with >10 included studies and high heterogeneity of outcomes to explore potential sources of heterogeneity. Predefined subgroups included: species, treatment period (≤10 days and >10 days), and dose administered (≤50 mg/kg and >50 mg/kg). When ≥10 datasets were included, publication bias was assessed using Egger's test and corrected using the cut-and-patch method if bias existed.

Subgroup analysis Due to the high degree of heterogeneity between studies, we performed the analysis of weight, number of crossings, total distance, number of rearings, time duration of center square, FST, TST, SFT , NSFT, BDNF, DA, 5-HT, NA, 5-HT , NA, TNF-α, IL-1β, and IL-6 16 metrics were subgroup analyzed.

Sensitivity analysis The stability of the meta-analysis results was tested through a one-by-one elimination method insensitivity analysis.

Language restriction No.

Country(ies) involved China.

Keywords berberine, depression, animal model, meta-analysis, systematic review.

Contributions of each author

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