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Neuroprotective Effects of Icariin in Animal Models of Depression and Anxiety: A Systematic Review of Preclinical Studies

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

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 13 May 2025 and was last updated on 13 May 2025.

INTRODUCTION

Review question / Objective This review aims to systematically evaluate the neuroprotective, antidepressant, and anxiolytic effects of Icariin or Epimedium extracts in rodent models of depression and anxiety. The review will assess behavioral, biochemical, and histological outcomes related to neuroprotection, including changes in depressive- or anxiety-like behaviors, neuroinflammation, oxidative stress, and neuronal apoptosis.

Rationale Icariin, a bioactive compound derived from Epimedium species, has demonstrated antidepressant and neuroprotective effects in preclinical models. This systematic review aims to synthesize existing animal evidence to clarify Icariin's therapeutic potential and mechanistic pathways for mood disorders, supporting future translational applications.

Condition being studied Depression and anxiety are among the most prevalent psychiatric disorders. Preclinical animal models such as chronic unpredictable mild stress (CUMS), forced swim test (FST), and elevated plus maze (EPM) are widely used to simulate depressive and anxious states. This review focuses on the neuroprotective effects of Icariin in such rodent models.

METHODS

Search strategy We will systematically search PubMed, Embase, and Scopus from inception to July 2025. The search will identify preclinical studies investigating the neuroprotective effects of Icariin or Epimedium extracts in animal models of depression or anxiety.

Example (PubMed):
(icariin OR "epimedium extract" OR "Herba Epimedii") AND (depression OR depressive OR "major depressive disorder" OR "chronic

unpredictable mild stress" OR anxiety OR anxious) AND (rat OR rats OR mice OR mouse OR animal OR "animal model") AND (neuroprotective OR brain OR hippocampus OR "prefrontal cortex")

The search strategy will be adapted for each database.

Participant or population This review will include preclinical in vivo animal studies using rodent models of depression and anxiety. Eligible models include chronic unpredictable mild stress (CUMS), forced swim test (FST), social defeat, restraint stress, and other validated paradigms. Studies must report behavioral and/or biochemical outcomes related to neuroprotection.

Intervention The interventions of interest are Icariin and Epimedium extracts containing Icariin as a primary active component. All routes of administration (oral, intraperitoneal, intranasal) and dosing regimens will be considered.

Comparator Comparators will include vehicle-treated, untreated, or placebo control groups, as well as positive control groups treated with standard antidepressant or anxiolytic agents where applicable. Studies without control groups will be excluded.

Study designs to be included This review will include in vivo preclinical animal studies using rodent models. In vitro studies, ex vivo experiments, case reports, reviews, and studies without a control group will be excluded.

Eligibility criteria Only full-text, peer-reviewed studies published in English or Chinese will be included. Conference abstracts, dissertations, reviews, and case reports will be excluded. Studies must involve in vivo rodent models and provide sufficient data for extraction (e.g., mean ± SD and sample size).

Information sources We will search PubMed, and Embase from inception to July 2025. Additional articles will be identified through manual reference checks of included studies and relevant reviews. Authors may be contacted for missing outcome data.

Main outcome(s) Primary outcomes include behavioral tests assessing depression/anxiety (e.g., forced swim test, tail suspension test, elevated plus maze, open field test, sucrose preference test), and biochemical outcomes such as levels of BDNF, IL-1β, TNF-α, oxidative stress markers, and histological changes in brain regions (e.g., hippocampus). Outcome timing will follow that reported by each study.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using the SYRCLE Risk of Bias tool for animal studies. Two reviewers will independently assess each study; discrepancies will be resolved through discussion or a third reviewer.

Strategy of data synthesis Data will be synthesized narratively and, if feasible, meta-analysis will be performed using RevMan or R. Standardized mean differences (SMD) with 95% CI will be calculated for continuous outcomes. Heterogeneity will be assessed using I^2 and Q statistics. A random-effects model will be used if $I^2 > 50\%$.

Subgroup analysis Subgroup analyses will be conducted based on animal species (rat vs. mouse), depression model type (CUMS, social defeat, etc.), route of administration (oral vs. i.p.), dose level, and treatment duration.

Sensitivity analysis Sensitivity analyses will exclude studies with high risk of bias, small sample size (e.g., <3 per group), or unclear methodology. Leave-one-out analysis and comparison of fixed vs. random effects models will be conducted to assess result stability.

Language restriction Yes – English and Chinese only.English, Chinese.

Country(ies) involved Taiwan.

Keywords Icariin; Epimedium; depression; anxiety; neuroprotection; animal model; systematic review.

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