

Neuroprotective effects of curcumin against ischemia-reperfusion injury: A meta-analysis of Animal Model Studies

INPLASY202480113

doi: 10.37766/inplasy2024.8.0113

Received: 24 August 2024

Published: 24 August 2024

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ADMINISTRATIVE INFORMATION**Support -** No.**Review Stage at time of this submission -** Preliminary searches.**Conflicts of interest -** None declared.**INPLASY registration number:** INPLASY202480113**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 August 2024 and was last updated on 24 August 2024.**INTRODUCTION**

Review question / Objective What is the therapeutic effect of curcumin in animal models of ischemia-reperfusion injury?

Condition being studied Acute ischemic stroke (AIS) is primarily caused by cerebrovascular embolism or thrombus formation and leads to the interruption of blood supply to the relevant cerebral regions. AIS, which accounts for 85 % of strokes, is the second highest cause of death globally and a leading cause of disability, with an increasing incidence in developing countries. The prompt application of reperfusion therapy for the ischemic region is crucial for alleviating the neurological damage induced by AIS. Endovascular thrombectomy (EVT), alone or combined with iv thrombolysis, is currently the most effective therapy for patients with acute ischemic stroke (AIS). Although adequate and timely blood flow restoration can help reduce severe neurological defects and deaths, cerebral ischemia reperfusion injury (CIRI) may result in excessive reactive

oxygen species (ROS) production, inflammatory cell recruitment, the increased release of pro-inflammatory cytokines, cell apoptosis, mitochondrial dysfunction, disruption of the blood-brain barrier (BBB), and hemorrhagic transformation. Moreover, the activation of these systems will further intensify brain tissue damage, eventually affecting the recovery of neurological functions. Currently, it has led researchers to look for effective therapies to improve CIRI. Curcumin is a natural polyphenolic compound, which is the main bioactive ingredient extracted from the roots and stems of turmeric plants. Curcumin is a natural antioxidant isolated from turmeric endowed with the merits of being easy to obtain and having strong antioxidant activity and low toxicity. Recently, an increasing body of evidence has revealed the advantageous role of curcumin in the recovery of CIRI. Additionally, multiple in vivo experiments have been designed to explore the mechanism of curcumin's neuroprotective effects for CIRI. Therefore, we use this scientific research method to determine whether animal evidence is beneficial for the efficacy of curcumin and its novel

formulations in CIRI, providing scientific basis for clinical trials.

METHODS

Participant or population Using an animal model of ischemia-reperfusion injury. There are no restrictions on the types of animals.

Intervention It must evaluate the therapeutic effect of curcumin on animal models of ischemia-reperfusion injury and compare it with the control group. There are no restrictions on dosage, administration mode and duration.

Comparator Physiological saline or other placebo.

Study designs to be included (1) controlled studies included laboratory rats as subjects; (2) in vivo animal studies; (3) rat models of CIRI; (4) curcumin compared with placebo control; (5) the reported outcomes and/or mechanisms included at least 1 of the following items: neurological deficit evaluation (NDE), infarct volume (IV), brain water content (BWC), biochemical analyses related to antioxidant activity (expressed as superoxide dismutase [SOD], glutathione [GSH], glutathione peroxidase [GPX], ROS, and malondialdehyde [MDA]), and/or anti-inflammatory effects of curcumin (indicated by interleukin-1 β (IL-1 β), IL-6).

Eligibility criteria Need to exclude cell trials, reviews, abstracts, letters, proposals, conference abstracts, etc.

Information sources The researchers in this paper will search four electronic databases (Pubmed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science) from their creation to May 2024. The search strategy will construct around the PICOS tool: (P) Animals/Population: animals with acute CIRI; (I) Intervention: curcumin; (C) Comparator: physiological saline or other placebo; (O) Outcomes: functional evaluation and biochemical analysis. (S) Study type: controlled studies assessing the in vivo administration of curcumin to rats with CIRI will be searched.

Main outcome(s) Measurement of changes in neurological deficit evaluation (NDE), infarct volume (IV), biochemical analyses related to antioxidant activity, anti-inflammatory effects.

Quality assessment / Risk of bias analysis Two researchers will use the SYRCLE Animal Studies Bias Risk Tool for bias risk assessment. SYRCLE's Risk of Bias tool is an adapted version of the Cochran Risk of Bias used in animal intervention

studies. Six areas of bias are covered: selection bias, implementation bias, measurement bias, loss of access bias, reporting bias, and other biases. In each area, the risk of bias was judged as low, unclear, or high. The risk of bias has not been assessed for in vitro studies because there are no validation tools available. The two researchers will independently assess the risk of bias in the included studies, and any disagreements will be resolved through discussion.

Strategy of data synthesis Data will be synthesized using Stata 15.0 for the results reported in 20 or more articles for network meta-analysis. We will test for heterogeneity. We will conduct a quantitative synthesis using meta-analysis if we identify at least five studies that meet our inclusion criteria. This threshold ensures sufficient data to estimate the effect size with reasonable precision. Studies will be included in the meta-analysis if they provide sufficient data to calculate the standardized mean difference (SMD).

Subgroup analysis The effect of different dosages, routes and courses on NDE or IV was analyzed by subgroup analysis. To explore the potential changes of drug-related factors in the therapeutic efficacy of IR models.

Sensitivity analysis Sensitivity analyses will be performed to determine the robustness of the meta-analysis findings. Studies may be excluded based on factors such as study quality, small sample size, or high risk of bias. The exclusion criteria will be predefined, and the impact of excluding these studies will be assessed to ensure the integrity and stability of the meta-analysis results.

Country(ies) involved China.

Keywords curcumin; meta-analysis; Cerebral ischemia/reperfusion (I/R) injury.

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