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Protective Effects of Salvianolic Acid A on Ischemic Stroke: A Meta-Analysis of Preclinical Studies

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Liu, A; Li, P.

Corresponding author:
An Liu

liuandyx11@163.com

Author Affiliation:
The First Affiliated Hospital of Henan University of Chinese Medicine.

ADMINISTRATIVE INFORMATION

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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 November 2025 and was last updated on 13 November 2025.

INTRODUCTION

Review question / Objective The aim of this study was to investigate the protective effects of salvianolic acid A (SalA) on cerebral ischemic injury following ischemic stroke (IS) and its possible mechanisms, providing a scientific basis for future clinical research on IS. A preclinical studies.

Condition being studied According to the Global Burden of Disease (GBD) 2023 study, stroke is the second leading cause of death and the third leading cause of death and disability combined worldwide. From 2010 to 2023, the absolute burden of stroke increased substantially, with incident cases increasing by 70.0%, prevalent cases by 86.0%, deaths by 44.0%, and disability-adjusted life years (DALYs) by 32.0%. Ischemic stroke (IS) is the most common subtype, accounting for approximately 65.3% of all new strokes in 2023 . The pathophysiology of IS is initiated by the interruption of cerebral blood flow, typically due to thrombosis or embolism, leading to a cascade of detrimental events, including energy failure, excitotoxicity, oxidative stress, inflammation, and apoptosis, which ultimately cause irreversible neuronal damage.

METHODS

Participant or population This is a preclinical studies. The animal species included SD rats. Wistar rats, C57BL/6 mice , and ICR mice.

Intervention Salvianolic acid A (SalA) Dosage: The doses of SalA used in the included studies ranged from 2 mg/kg to 40 mg/kg, with the most commonly tested doses being 10 mg/kg and 20 mg/kg. Administration routes: The drug was administered via different routes including intravenous injection, intragastric gavage, tail vein injection, and intraperitoneal injection.

Comparator The comparator groups in the included studies were classified as follows:
1. Normal Group (no treatment or healthy control group)
2. MCAO Model Group (animals subjected to Middle Cerebral Artery Occlusion without treatment)
3. Sham Surgery Group (animals that underwent the same surgical procedure but without the ischemic event, serving as a control for surgical procedures)
4. Intervention Group (receiving different doses of SalA, ranging from 20 mg/kg to 40 mg/kg).

Study designs to be included The studies included in this systematic review are preclinical animal studies, primarily using rodent models (mice or rats). These studies employed different animal models to assess the therapeutic effects of Salvianolic Acid A (SalA), including:Middle Cerebral Artery Occlusion (MCAO) model,Transient MCAO (tMCAO) model,Ischemia/Reperfusion (I/R) model.These studies evaluated the effects of SalA on neurological function scores, cerebral infarct area, and brain edema to determine its neuroprotective potential.

Eligibility criteria The inclusion criteria are as follows: (1) studies involving rats or mice as subjects, with the establishment of MCAO or I/R models; (2) the experimental group receives SalA intervention post-surgery (selecting the group with the best therapeutic effect if different concentrations are used; (3) the model group receives a placebo or no treatment; (4) no restrictions on animal species, gender, age, weight, or sample size; (5) the primary outcome measures include neurological function scores, infarct area or proportion, and all biomarkers indicating IS.
The exclusion criteria for the literature are strictly defined as follows: (1) animal models of non-cerebral ischemia or global cerebral ischemia; (2) reviews, in vitro studies, and trials; (3) studies in which SalA was used to intervene in other diseases or was not used at all; (4) studies with insufficient data, including unpublished data; and (5) duplicated studies.

Information sources A comprehensive and systematic literature search was conducted across eight electronic databases: PubMed, Embase, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, and the China Biomedical Literature Database (CBM).

Main outcome(s) A total of 15 studies involving 564 animals were included. The analysis showed that compared to the control group, SalA significantly reduced the infarct volume [SMD = −4.67, 95% CI = (−5.98, −3.36), and $p < 0.001$] and brain edema area [SMD = −5.291, 95% CI = (−7.607, −2.975), and $p < 0.001$] and improved neurological deficits [SMD = −6.39, 95% CI = (−9.091, −3.688), and $p < 0.001$]. SalA also significantly inhibited interleukin 6 (IL-6), tumor necrosis factor-a (TNF- α), IL-1β, and other indicators, such as Bcl-2-associated X protein (Bax) and Caspase-3 index, while showing a positive effect on B-cell lymphoma-2 (Bcl-2), Bcl-2/Bax, and other indicators.

Quality assessment / Risk of bias analysis Two research workers independently assessed the quality of the literature using the SYRCLE animal experiment bias risk assessment tool within Review Manager 5.4 software, evaluating 10 criteria: selection bias (sequence generation, baseline characteristics, and allocation concealment), performance bias (random housing and blinding), detection bias (random outcome assessment and blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias. Each criterion was rated as follows: low risk (method correctly applied), unclear risk (method application unclear), or high risk (method incorrectly applied or not applied). The assessments were carried out independently by both research workers and crosschecked. In case of disagreements, the research workers discussed and reached a consensus; if no consensus was achieved, a third research worker was consulted to make the final decision. Each item was scored one point if it was met, for a maximum quality score of 10. Discrepancies in scoring were resolved through discussion. We generally consider a score above 6 to be the average score. Importantly, no studies were excluded based on their quality score. The risk-of-bias assessment was instead used to evaluate the overall quality of the evidence base

and to inform subsequent sensitivity analyses to investigate potential sources of heterogeneity.

Strategy of data synthesis Given that the outcome measurements in this study are continuous variables, the standardized mean difference (SMD) with a 95% confidence interval (95% CI) was used to combine the effect size. When $p < 0.05$, it indicates a significant difference between the intervention and control groups. The heterogeneity evaluation metric used is I-squared (I 2). When I 2 50%, it indicates that the quality of the studies retrieved is heterogeneous, and a randomeffects model is applied to combine the effect size. To identify potential causes of heterogeneity, subgroup analyses were performed based on animal species, methods, and stages of administration. To assess potential publication bias, the Egger test was used. Additionally, Origin 2021 was used for dose–response interval analysis.

Subgroup analysis Subgroup analyses were performed based on the following factors:
1. Different doses of Salvianolic Acid A (SalA): The studies were grouped according to the varying doses of SalA, ranging from 20 mg/kg to 40 mg/kg, to assess the dose-dependent effects.
2.Different administration routes: Subgroups were created based on the administration methods of SalA, which included intravenous injection, intragastric gavage, tail vein injection, and intraperitoneal injection, to evaluate how different delivery routes influenced the therapeutic outcomes.
3.Different animal species: The studies were also categorized based on the animal species used, including mice and rats, to examine potential species-specific differences in response to SalA treatment.
This will help to better understand how these variables influence the effectiveness of SalA in treating ischemic stroke.

Sensitivity analysis To evaluate the stability of the primary outcome measures (including cerebral infarction area, NDS, and cerebral edema volume), a sensitivity analysis was conducted. The analysis showed no significant differences in the results, indicating the robustness of the study findings.

Country(ies) involved China.

Keywords salvianolic acid A; ischemic stroke; ischemia injury; preclinical evidence; meta.

Contributions of each author

Author 1 - An Liu - Visualization, Writing – original draft, Writing – review and editing, Software.
Email: liuandyx11@163.com
Author 2 - Pin Li - Data curation, Formal analysis, Writing – review and editing.
Email: 17837767869@163.com