An et al. INPLASY protocol 202540083. doi:10.37766/inplasy2025.4.0083 Downloaded from https://inplasy.com/inplasy-2025-4-0083/

INPLASY

The efficacy of Z-ligustilide in experimental models of ischemic stroke: a systematic review and meta-analysis

INPLASY202540083
doi: 10.37766/inplasy2025.4.0083
Received: 24 April 2025
Published: 24 April 2025

Corresponding author:
Hengtong An

13785239077@163.com

Author Affiliation:
The Hebei University of chinese medicine.

An, HT; Zheng, TG; Gao, WJ.

ADMINISTRATIVE INFORMATION

Support - The Hebei University of chinese medicine.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202540083

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2025 and was last updated on 24 April 2025.

INTRODUCTION

Review question / Objective Population: Animal models of ischemic stroke (e.g., MCAO, photothrombotic model), any species
Intervention: Z-ligustilide (any dosage, form, and route of administration)
Comparator: Vehicle, placebo, or blank control
Outcomes: Primary: infarct volume, neurological deficit scores. Secondary: levels of inflammatory cytokines, oxidative stress markers
Study type: Controlled animal studies (randomized or non-randomized); excluding in vitro, clinical, or case reports.

Condition being studied Ischemic stroke is a leading cause of death and long-term disability worldwide, resulting from an interruption of blood flow to the brain, typically due to thrombotic or embolic occlusion of cerebral arteries. The consequent deprivation of oxygen and glucose leads to neuronal injury, blood-brain barrier disruption, and activation of inflammatory cascades, ultimately causing extensive brain tissue damage. Despite advances in thrombolytic and endovascular therapies, many patients remain ineligible for these treatments due to narrow therapeutic windows or contraindications. Moreover, there are currently no widely effective neuroprotective agents available in clinical practice, underscoring the urgent need for new therapeutic strategies.

METHODS

Participant or population This review will include animal models of ischemic stroke, regardless of species, strain, sex, or age. Commonly used models include the middle cerebral artery occlusion (MCAO) model, photothrombotic stroke model, and global cerebral ischemia models in rodents (rats and mice). Studies must involve live, intact animals subjected to experimental cerebral ischemia followed by treatment with Z-ligustilide. In vitro studies, clinical trials, and case reports will be excluded.

Intervention The intervention of interest is Z-ligustilide, a natural phthalide compound isolated from Ligusticum chuanxiong and other traditional Chinese medicinal herbs. All forms of Z-ligustilide administration will be considered, including purified compounds or extracts where Z-ligustilide is the major active component. The route of administration (e.g., intraperitoneal, intravenous, oral), dosage, frequency, and timing relative to ischemic onset will not be restricted.

Comparator The comparator group will include animals subjected to ischemic stroke induction and treated with vehicle, placebo, or no treatment. These control groups are essential for evaluating the independent effects of Z-ligustilide.

Study designs to be included Animal Experiments.

Eligibility criteria Additional Inclusion Criteria: 1.Full-text articles published in peer-reviewed journals. 2. Studies reporting sufficient quantitative data (mean, standard deviation or error, and sample size) for at least one primary or secondary outcome. 3. Studies that clearly describe the stroke induction method and Z-ligustilide administration protocol. 4. Articles published in English or Chinese.
Exclusion Criteria: 1. In vitro studies, case reports, reviews, conference abstracts without full data, and clinical trials. 2. Studies using herbal mixtures or formulas containing Z-ligustilide without isolating its independent effects. 3. Studies with unclear or missing outcome data that cannot be retrieved after contacting authors. 4. Duplicate publications (only the most complete or latest version will be included).

Information sources A comprehensive literature search will be conducted using the following electronic databases: PubMed, Web of Science, Embase, CNKI (China National Knowledge Infrastructure), Wanfang Data, SinoMed (Sinomedicine database). All databases will be searched from their inception to April 2025.

Main outcome(s) Infarct volume, Neurological deficit scores.

Additional outcome(s) Blood-brain barrier (BBB) permeability, Oxidative stress indicators, Inflammatory cytokines, Apoptosis-related markers.

Quality assessment / Risk of bias analysis The risk of bias of the included studies will be assessed using the SYRCLE's Risk of Bias (RoB) tool, which is specifically adapted for animal intervention studies. This tool is based on the Cochrane RoB tool and evaluates 10 domains, including: 1. Sequence generation 2. Baseline characteristics 3. Allocation concealment 4. Random housing 5. Blinding of caregivers and investigators 6. Random outcome assessment 7. Blinding of outcome assessment 8. Incomplete outcome data 9. Selective outcome reporting 10. Other sources of bias. Two reviewers will independently evaluate each study. Disagreements will be resolved through discussion or by consultation with a third reviewer.

Strategy of data synthesis Quantitative data synthesis will be conducted using Review Manager (RevMan) and/or R software (meta and metafor packages).The effect size for continuous outcomes (e.g., infarct volume, neurological scores) will be calculated using standardized mean difference (SMD) with 95% confidence intervals (CI) due to expected variability in measurement scales across studies.A random-effects model (DerSimonian and Laird method) will be used to account for heterogeneity between studies. Statistical heterogeneity will be assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively.

Subgroup analysis Animal species (rat vs. mouse), Dosage of Z-ligustilide, Time of administration post-ischemia, Route of administration (e.g., intraperitoneal, oral, intravenous).

Sensitivity analysis Sensitivity analyses will be conducted by excluding studies with high risk of bias, small sample size, or methodological outliers.

Country(ies) involved China.

Keywords Z-ligustilide; ischemic stroke; animal model; meta-analysis.

Contributions of each author

Author 1 - An Hengtong.
Email: 13785239077@163.com
Author 2 - Tiangang Zheng.
Email: 2068837515@qq.com
Author 3 - Weijuan Gao.
Email: gaoweijuan@hebcm.edu.cn

An et al. INPLASY protocol 202540083. doi:10.37766/inplasy2025.4.0083 Downloaded from https://inplasy.com/inplasy-2025-4-0083/