INPLASY

INPLASY202660057

doi: 10.37766/inplasy2026.6.0057

Received: 12 June 2026

Published: 12 June 2026

Effect of Nrf2/HO-1 signaling pathway activation on neuropathic pain in experimental animal models: a systematic review protocol

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ADMINISTRATIVE INFORMATION

Support - No funding sources.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202660057

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 June 2026 and was last updated on 12 June 2026.

INTRODUCTION

Review question / Objective Does activation of the Nrf2/HO-1 signaling pathway reduce neuropathic pain-related behaviors in experimental animal models compared with untreated, vehicle-treated, or sham controls?

Objetive: To systematically evaluate the available preclinical evidence regarding the effects of Nrf2/HO-1 signaling pathway activation on neuropathic pain-related outcomes in experimental animal models.

Condition being studied Neuropathic pain is a chronic and debilitating condition resulting from lesions or diseases affecting the somatosensory nervous system. Despite advances in pharmacological management, current treatments often provide only partial symptom relief and may be associated with significant adverse effects. Increasing evidence suggests that oxidative stress and neuroinflammation play key roles in the development and maintenance of neuropathic pain.

The nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates cellular antioxidant defense mechanisms. Upon activation, Nrf2 promotes the expression of several cytoprotective genes, including heme oxygenase-1 (HO-1), which has demonstrated anti-inflammatory and antioxidant properties. Experimental studies have suggested that activation of the Nrf2/HO-1 signaling pathway may attenuate neuropathic pain behaviors and reduce molecular processes associated with neuronal injury and central sensitization.

This systematic review aims to synthesize and critically appraise the current preclinical evidence regarding the effects of Nrf2/HO-1 pathway

activation on neuropathic pain outcomes in animal models.

METHODS

Participant or population Experimental animal models of neuropathic pain.

Eligible populations will include:

Rats.
Mice.

Models may include:

Chronic constriction injury (CCI).
Spinal nerve ligation (SNL).
Partial sciatic nerve ligation (PSNL).
Diabetic neuropathy.
Chemotherapy-induced peripheral neuropathy.
Spinal cord injury-associated neuropathic pain.
Experimental autoimmune encephalomyelitis.
Other validated neuropathic pain models.

No restrictions regarding sex, strain, or age will be applied.

Intervention Any intervention aimed at activating the Nrf2/HO-1 signaling pathway.

Eligible interventions may include:

Pharmacological activators.
Natural compounds.
Nutraceuticals.
Genetic modulation strategies.
Molecular interventions.

Examples include, but are not limited to:

Sulforaphane.
Dexmedetomidine.
Isorhamnetin.
Astaxanthin.
Melatonin.
Oltipraz.
Other Nrf2/HO-1 activators.

Comparator Eligible comparators include:

Sham-operated animals.
Vehicle-treated animals.
Untreated neuropathic pain models.
Negative control groups.

Study designs to be included Controlled preclinical studies.Experimental animal studies.Original research articles published in peer-reviewed journals.

Eligibility criteria Inclusion criteria:

Controlled preclinical studies.
Experimental animal studies.
Original research articles published in peer-reviewed journals.

Exclusion criteria:

Human studies.
Narrative reviews.
Systematic reviews.
Meta-analyses.
Editorials.
Conference abstracts without full text.
Letters to the editor.
Case reports.
In vitro studies.

Information sources The following electronic databases will be searched from inception until the date of the final search:

PubMed/MEDLINE.
Scopus.
Web of Science Core Collection.
Embase.
Cochrane Library.

Additionally, reference lists of included studies and relevant reviews will be manually screened to identify potentially eligible studies.

Main outcome(s) The primary outcomes will include behavioral measures related to neuropathic pain, such as:

Mechanical allodynia.
Thermal allodynia.
Mechanical hyperalgesia.
Thermal hyperalgesia.
Paw withdrawal threshold.
Paw withdrawal latency.
Other validated nociceptive behavioral assessments.

Quality assessment / Risk of bias analysis Methodological quality and risk of bias will be assessed independently by two reviewers using the SYRCLE Risk of Bias Tool for animal studies.

The following domains will be evaluated:

Sequence generation.
Baseline characteristics.

Allocation concealment.
Random housing.
Blinding of investigators.
Blinding of outcome assessment.
Incomplete outcome data.
Selective outcome reporting.
Other sources of bias.

Disagreements will be resolved through consensus.

Strategy of data synthesis A narrative synthesis will be conducted to summarize the characteristics and findings of included studies.

Results will be organized according to:

Animal model.
Intervention type.
Neuropathic pain outcomes.
Molecular outcomes.

Where sufficient homogeneity exists in study design, outcome measures, and reported data, a quantitative meta-analysis may be considered.

Subgroup analysis Where data permit, subgroup analyses will be performed according to:

Animal species.
Sex.
Neuropathic pain model.
Type of Nrf2/HO-1 activator.
Duration of intervention.
Route of administration.

Sensitivity analysis If a meta-analysis is performed, sensitivity analyses will be conducted by excluding studies judged to have a high risk of bias to assess the robustness of the pooled estimates.

Language restriction No language restrictions will be applied.

Country(ies) involved Chile.

Keywords Neuropathic pain; Nrf2; HO-1; heme oxygenase-1; oxidative stress; neuroinflammation; animal model; experimental pain; preclinical research.

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