International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Potential Neuroprotective Effects of Docosahexaenoic Acid On Glutamate-Induced Neurotoxicity: A Systematic Review of Pre-clinical Studies

INPLASY202650047

doi: 10.37766/inplasy2026.5.0047

Received: 8 May 2026

Published: 8 May 2026

Corresponding author:
Nur Izzati Mansor

nurizzatimansor@ukm.edu.my

Author Affiliation:
Universiti Kebangsaan Malaysia.

Rusleen, MHR; Mansor, NI; A. Hamid, A; Mohd Nor, NH; Mohamed, Z.

ADMINISTRATIVE INFORMATION

Support - Universiti Kebangsaan Malaysia.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650047

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 May 2026 and was last updated on 8 May 2026.

INTRODUCTION

Review question / Objective How does docosahexaenoic acid (DHA) mitigate glutamate-induced neurotoxicity in pre-clinical studies? / This study will provide comprehensive information on the potential neuroprotective effects of DHA on glutamate-induced neurotoxicity in pre-clinical studies.

Condition being studied Glutamate excitotoxicity is a condition characterised by elevated extracellular glutamate levels in the brain, caused by dysregulation of glutamate signaling, which leads to excessive stimulation of glutamate receptors. This overstimulation interferes with calcium ion (Ca2+) homeostasis, impairs mitochondrial function, generates oxidative stress, initiates the apoptotic cascade, and eventually leads to neuronal death. Glutamate excitotoxicity has been associated with several neurological disorders. Therefore, a dietary supplement targeting mechanisms associated with dysregulation of glutamate signaling may offer substantial therapeutic potential.

METHODS

Search strategy This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. A comprehensive search was conducted using five primary databases: Cochrane Library, Scopus, Web of Science, PubMed and ScienceDirect. The following keywords were used: ("DHA" OR "docosahexaenoic acid") AND (Excitotoxicity OR "Glutamate-induced Excitotoxicity" OR "Glutamate-induced neurotoxicity"). A similar search was also performed on Google Scholar. To identify the most relevant studies, Harzing's Publish or Perish software was employed. The publication date and country were not restricted, however, only studies published in English would be considered.

Participant or population (1) In vivo studies include animal models of glutamate-induced

excitotoxicity, including those using monosodium glutamate, glutamate receptor agonists, or any CNS-related models that directly assess glutamate dysregulation or excitotoxicity, regardless of age, gender, weight, or species. (2) Neuronal cultures (in vitro or ex vivo) from any source, whether primary or commercially acquired and subjected to glutamate excitotoxicity, including those using L-glutamate and glutamate receptor agonists.

Intervention Studies that used docosahexaenoic acid (DHA) as an intervention in the experimental group in any form such as from fish oil, microalgal biomass or store-bought purified DHA, regardless of route of administration, formulation and duration of intervention.

Comparator The comparators groups received either no intervention or were treated with relevant conventional drug or other types of poly-unsaturated fatty acids (PUFA).

Study designs to be included The study design included in this review were in vivo, in vitro and ex vivo experiments. Other publications such as case reports, editorial, reviews and abstract/conference proceedings were excluded.

Eligibility criteria Any pre-clinical studies that reported the neuroprotective effects of DHA on glutamate-induced neurotoxicity. Combination dosing of DHA with other types of poly-unsaturated fatty acids (PUFA) such as in fish oil and microalgal biomass were included if the DHA concentration was specified.

Information sources A comprehensive literature search of electronic databases using Cochrane Library, Scopus, Web of Science, PubMed, ScienceDirect and Google Scholar, using the following set of keywords: ("DHA" OR "docosahexaenoic acid") AND (Excitotoxicity OR "Glutamate-induced Excitotoxicity" OR "Glutamate-induced neurotoxicity"). These databases were searched for findings until December 2025.

Main outcome(s) (1) Changes in neuronal cell viability and neuronal marker expression.
(2) Molecular and biochemical analyses related to antioxidant activity, anti-inflammatory and anti-apoptotic effects.
(3) Histological changes in brain regions.
(4) Neurobehavioral outcomes (including learning and memory performance, and motor function).

Additional outcome(s) Changes in neurotransmitter levels, signaling pathways, DHA content, mitochondrial function.

Data management Firstly, one reviewer (MHRR) screened the articles based on type, title, language, and abstract related to the effect of DHA on glutamate-induced neurotoxicity. During the second screening, two reviewers (MHRR and NIM) screened the articles according to a predefined, standardized data collection form. Any disagreements were resolved through discussion with a third reviewer (NHMN). A data spreadsheet was generated using Microsoft Excel to compile all relevant data and information. The following data were extracted: title, authors, publication year, journal, study design, intervention source, dosage, duration of treatment, and outcomes.

Quality assessment / Risk of bias analysis The risk of bias (RoB) was assessed independently by two reviewers (MHRR and NIM). Any disagreements were resolved through discussion with a third reviewer (NHMN). In vivo studies were assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool. The key components of this evaluation were: (1) Selection bias: random sequence generation, baseline characteristics, allocation concealment; (2) Detection bias: random housing, blinding, random outcome assessment; (3) Attrition bias: incomplete outcome data; 4) Reporting bias: selective reporting; and (5) Other bias. Meanwhile, for in vitro studies, a customised Joanna Briggs Institute (JBI) checklist for non-randomised experimental studies was used, consisting of: (1) Reporting bias: source of DHA, cell origin, treatment duration, and dosage; (2) Performance bias: positive or negative control, blinded investigator, reliable tool, and random assessor; (3) Detection bias: triplicate, more than one independent experiment, outcome assessor blinded; (4) Selection bias: missing data reported. Each domain was assessed to determine high, moderate, low, or unclear risk of bias. However, the RoB tool was not used as an indicator of study eligibility.

Strategy of data synthesis Study characteristics and outcomes were tabulated and described narratively. The risk of bias was summarised and reported narratively.

Subgroup analysis None.

Sensitivity analysis None.

Language restriction English.

Country(ies) involved Malaysia.

Keywords Docosahexaenoic acid; glutamate; excitotoxicity; neuroprotection.

Contributions of each author

Author 1 - Muhammad Hani Rahimi Rusleen.
Email: mhrahimi1301@gmail.com
Author 2 - Nur Izzati Mansor.
Email: nurizzatimansor@ukm.edu.my
Author 3 - Adila A. Hamid.
Email: adilahamid@ukm.edu.my
Author 4 - Nurul Hafizah Mohd Nor.
Email: nurulhafizah@ukm.edu.my
Author 5 - Zainah Mohamed.
Email: zainah_mohamed@ukm.edu.my