



# The Role of Alpha Linolenic Acid on Neuroinflammation: A Systemic Review

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**Abstract:** Neuroinflammation, an inflammatory response within the central nervous system (CNS), plays a critical role in various neurological disorders, including neurodegenerative diseases. Alpha linolenic acid (ALA), an essential omega-3 polyunsaturated fatty acid, has shown promising health benefits due to its antioxidant and anti-inflammatory properties. This article aims to thoroughly examine the potential effects of ALA in reducing neuroinflammation, emphasizing its roles as an anti-inflammatory and antioxidant agent. The review focuses on studies published between 2018 and 2023, sourced from reputable academic databases such as PubMed, Semantic Scholar, Google Scholar, and ScienceDirect, with nine key papers selected. The findings indicate that ALA significantly mitigates neuroinflammation by decreasing reactive oxygen species (ROS) via the Nrf-2/HO-1/JNK signaling pathway. Additionally, ALA reduces inflammatory cytokines by inhibiting p-JNK activation, disrupting lipid rafts, blocking the pro-inflammatory transcription factor NF- $\kappa$ B, and altering cell membrane phospholipid composition. The review concludes that ALA may have potential therapeutic effects in reducing neuroinflammation through its antioxidant and anti-inflammatory actions, offering possible benefits for various neurological conditions, including Alzheimer's and Parkinson's diseases.

**Keywords:** Alpha linolenic acid; Antiinflammation; Antioxidant; Neuroinflammation

## Introduction

Neuroinflammation refers to the presence of inflammatory responses inside the central nervous system, encompassing both the brain and spinal cord (Kölliker-Frers et al., 2021). This process involves the synthesis of cytokines, chemokines, reactive oxygen species, and secondary messengers. Neuroinflammation is widely recognized as a significant contributing factor in various central nervous system disorders, both acute and chronic (Gorji, 2022). Mitigating neuroinflammation could potentially reduce disease severity and improve patient outcomes. In acute cases, neuroinflammation helps eliminate harmful stimuli and initiate healing to protect brain cells and functionality. However,

unresolved neuroinflammation with increased secretion of inflammatory agents can lead to maladaptive neuroinflammation, which is implicated in the development of various neurological disorders, including neurodegenerative conditions like Alzheimer's and Parkinson's diseases, mental ailments, stroke, and traumatic brain injury (DiSabato et al., 2016; Guzman-Martinez et al., 2019; Kip et al., 2023; Mukhara et al., 2020).

Alpha linolenic acid (ALA) is an essential omega-3 polyunsaturated fatty acid derived from plant sources such as flaxseed, walnut, chia seed, sacha inchi, and soybeans, as well as their oils. ALA has demonstrated several beneficial effects, including its potential role in modulating neuroinflammation through anti-

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inflammatory and antioxidant effects (Desai et al., 2016; Kim et al., 2024; Pandohee, 2022; Tofighi et al., 2021; Yan et al., 2013; Yuan et al., 2022).

While numerous studies highlight ALA's positive impact on neuroinflammation, some research presents contrasting findings. This discrepancy underscores the need for a comprehensive review to clarify ALA's potential in mitigating neuroinflammation through its anti-inflammatory and antioxidant properties. This literature review aims to address this gap by evaluating the existing evidence on ALA's role in neuroinflammation.

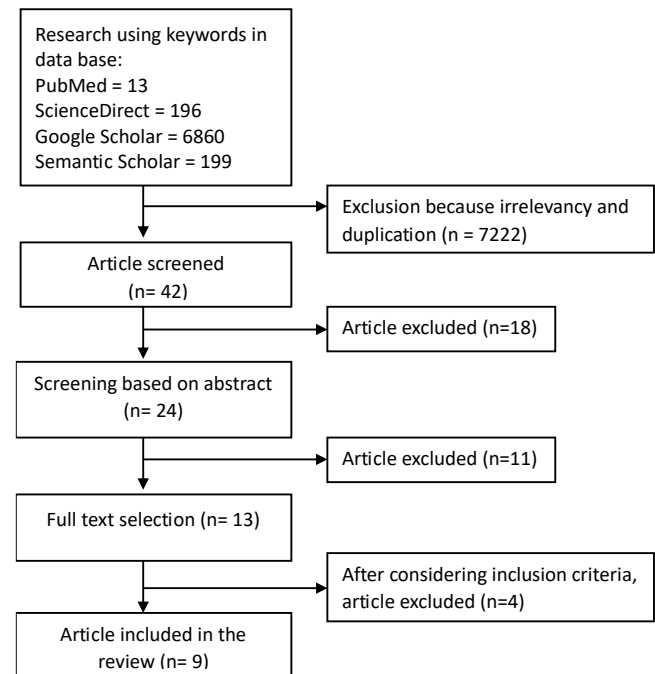
**Method**

This narrative review aims to analyze and outline the effects of alpha-linolenic acid in mitigating neuroinflammation. The publications utilized in this review were derived from prior experimental investigations sourced from reputable databases such as PubMed, Semantic Scholar, Google Scholar, and ScienceDirect.

The PICO framework is employed for the purpose of identifying, categorizing, and selecting articles. The study employed experimental animal models or cell cultures as participants. The intervention consisted of administering either ALA or an ALA-rich product to the experimental animals. The comparison groups were comprised of animals that did not receive the ALA treatment or were given alternative treatments instead of ALA. The outcome of interest pertained to the research findings that demonstrated enhancements in parameters associated with neuroinflammation.

The review employed a retrospective methodology, encompassing publications published within the timeframe of 2018 to 2023. The search terms employed include "alpha-linolenic acid AND neuroinflammation," "alpha-linolenic acid AND inflammation AND neuroprotective," and "alpha-linolenic acid AND anti-inflammation AND neuroprotection." The article's inclusion criteria encompassed several key factors:

publishing within a specified range, investigations conducted either in vitro or in vivo, subjects including animals or cells, papers written in English, full-length papers, and relevance to the purpose of the article. The publications that were excluded from consideration in this study included those that were inaccessible, as well as review or case report articles. Additionally, articles that were not related to the purpose of the review were also excluded. The preliminary investigation yielded a total of 7,222 articles, and subsequent screening procedures resulted in the selection of 9 articles that are pertinent to the subject matter.



**Figure 1.** PRISMA diagram article selection scheme

Data extraction was conducted for all articles that met the predetermined inclusion criteria. The extracted data encompassed many elements, including the author's name, publication year, study type, subject type, administered intervention, and study outcomes. (Table 1).

**Table 1.** Neuroprotective Role of Alpha Linolenic Acid

Authors	Study types	Subject	Intervention	Conclusions
Alam et al. (2021)	In vivo	Cadmium-Induced damage to mice brain in male C57BL/6N mice 8 weeks old	ALA 60 mg/kg per oral for 6 weeks	ALA may significantly counteract CdCl <sub>2</sub> -induced oxidative stress, neuroinflammation, and neurodegeneration in the cortex of the mouse brain
Lee et al. (2018)	In vitro	C6 glial cells	ALA (1, 2.5, 5, and 25 µg/mL) for 2 h, followed by Aβ <sub>25–35</sub> (50 µM) for 24 h.	ALA able to degrade Aβ by mediating the inhibition of inflammatory responses and activating the antioxidative system

Authors	Study types	Subject	Intervention	Conclusions
Wang et al. (2021)	In vivo	C57BL/6 mice with scopolamine injection	Diet high in ALA or deficient ALA in 2 consecutive mice generation	The reduction of dietary omega 3 has a notable impact on brain DHA levels and enhances susceptibility to scopolamine-induced cognitive decline in male C57BL/6 mice.
Livingston et al. (2023)	In vivo	5-week-old male C57BL/6 mice with LPS-injection	dietary supplement with flaxseed or flaxseed oil	There potential for flaxseed to attenuate LPS-induced inflammation in mice
Rui et al. (2018)	In vivo	SAMP8 mice and SAMR1 mice high fat diet	Chia seed (10%) supplementation for 18 weeks	Chia seed supplementation cause an elevation in neuroinflammation via activation of GFAP and Iba-1.
Gao et al. (2021)	In vivo	PS cDKO mice	Peony seed oil	PSO effectively inhibits the activation of microglial cells and reduces neuroinflammation by suppressing the expression of proinflammatory mediators.
Lowry et al. (2020)	In vitro	BV-2 mouse microglia and THP-1 human monocytic cells exposed to LPS and INF- $\gamma$	ALA or LA (25,100,250 $\mu$ M) for 24 hours	ALA and LA reduce NO release from microglia. ALA and LA do not affect the MCP-1 concentration
Ali et al. (2020)	In vivo	Male C57BL/6N mice injected with d A $\beta$ 1-42	ALA 60 mg/kg per oral for 6 weeks	ALA can serve as an effective intervention in amyloidogenesis, neuroinflammation, apoptotic cell loss, and memory impairment by suppressing TLR4 and its subsequent downstream targets inside the brain of mice.
Kim et al. (2020)	In vivo	4 weeks old male mice injected with A $\beta$ 1-42	walnut extract 10 and 20mg/kgBW for 3 weeks	Walnut extract can reduce oxidative stress and inflammatory response in brain tissue

## Result and Discussion

### *Alpha Linolenic Acid*

Alpha-linolenic acid (ALA) is an omega 3 polyunsaturated fatty acid which can be found from plant sources, such as flaxseeds, flaxseed oil, canola oil, soybeans, walnuts, and perilla oil (Yuan et al., 2022) and obtaining this fatty acid is essential from dietary sources, as the human body lacks the ability to manufacture it. Alpha-linolenic acid (ALA) serves as a precursor to other polyunsaturated fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Cholewski et al., 2018). However, the conversion of ALA to EPA and DHA is limited. Nevertheless, there exists a hypothesis suggesting that ALA might possess the ability to exert an effect independent of its conversion to EPA or DHA (Pandohee, 2022; Punia et al., 2019; Takic et al., 2022). ALA is proposed to have a beneficial effect as an anti-metabolic syndrome, anti-inflammation, anti-cancer, neuroprotective properties, anti-oxidant, regulating intestinal flora, treating bone related disease and antibacterial effect (Amiri et al., 2020; Bertoni et al., 2023; Desale et al., 2021; Moura-Assis et al., 2018; Yuan et al., 2022). The recommended ALA intake in adult is 1.6g/day for male and 1.2g/day for female

(NIH, 2023), study by Naghshi et al. (2021), shows that ALA intake is associated with decrease risk of mortality from all causes, cardiovascular disease and chronic heart disease.

### *Neuroinflammation*

Neuroinflammation is now recognized as a significant factor in the development and underlying causes of neurodegenerative diseases (Kwon et al., 2020; Ransohoff, 2016). Neuroinflammation refers to the state characterized by an inflammatory reaction occurring inside the central nervous system. The observed inflammation can be attributed to the synthesis of pro-inflammatory cytokines (such as IL-1B, IL-6, and TNF- $\alpha$ ), chemokines (including CCL2, CCL5, and CXCL1), secondary messengers (such as nitric oxide and prostaglandin), and reactive oxygen species (ROS). The mediators mentioned in the statement are generated by various types of glial cells in the central nervous system (namely microglia and astrocytes), as well as endothelial cells and immune cells originating from outside the central nervous system (Chitnis et al., 2017; Guzman-Martinez et al., 2019; Moyse et al., 2022; Zhang et al., 2023).

Neuroinflammation can have both beneficial and detrimental effects on the central nervous system (CNS). On the positive side, neuroinflammation can enhance plasticity, aid in tissue repair, promote neuroprotection, and help rearrange host priorities to combat injuries or infections. However, prolonged or excessive neuroinflammation can lead to collateral damage, anxiety, depression, cognitive impairment, and neuronal damage. The impact of neuroinflammation is highly dependent on factors such as context, duration, and progression. For instance, a short-term inflammatory response might protect the CNS by removing harmful stimuli and initiating repair. Conversely, chronic inflammation can disrupt neuronal function and contribute to the pathology of neurodegenerative diseases like Alzheimer's and Parkinson's. To delve deeper into these effects, it is crucial to consider the balance and timing of neuroinflammatory responses, as they determine whether the outcomes will be protective or harmful to the CNS (DiSabato et al., 2016; Hong et al., 2018; Jayaraj et al., 2019).

Neuroinflammation encompasses four distinct stereotypic mechanisms: elevated levels of chemical mediators within the tissue, activation and proliferation of microglial and astrocytes within specific regions of the central nervous system (CNS), infiltration of peripheral immune cells from the systemic circulation, which is linked to blood-brain barrier permeability, and neuronal cell death resulting from neurotoxic conditions (Bersano et al., 2023; Moyses et al., 2022). Pathological neuroinflammation involves the activation of central nervous system (CNS) glial cells, leading to an excessive production of cytokines and chemokines, which results in a significant inflammatory response. This activation and the ensuing inflammatory cascade can lead to primary and secondary cellular damage, exacerbating the pathogenic nature of the process. This harmful state not only causes immediate and subsequent harm but can also establish a chronic neuroinflammatory response with long-lasting or even permanent effects. Chronic neuroinflammation is commonly associated with autoimmune disorders such as multiple sclerosis and Alzheimer's disease. These conditions are marked by sustained glial activation and an overproduction of inflammatory molecules, which can contribute to ongoing neuronal damage and disease progression (Amoriello et al., 2024; DiSabato et al., 2016; Matsuda et al., 2019; Streit et al., 2004).

Neuroinflammation has been documented to be linked with acute lesions following trauma or vascular occlusion and/or rupture, resulting in ischemia and/or hemorrhage. Additionally, it is associated with chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease,

amyotrophic lateral sclerosis, and multiple sclerosis. Neuroinflammation is also observed in conjunction with systemic inflammatory illnesses, such as type II diabetes (Borlongan et al., 2015; Kaur et al., 2020; Moyses et al., 2022; Muzio et al., 2021).

#### *Neuroprotective Potential of Alpha Linolenic Acid*

Alpha-linolenic acid (ALA) exerts beneficial effects in attenuating neuroinflammation by demonstrating anti-inflammatory and antioxidant properties. These attributes enable ALA to protect brain cells from damage caused by proinflammatory cytokines and reactive oxygen species (ROS). ALA mitigates ROS levels by activating the Nrf-2/HO-1/JNK signaling pathway. Furthermore, it reduces the production of inflammatory cytokines by inhibiting excessive p-JNK activation, disrupting lipid rafts, suppressing the proinflammatory transcription factor NF- $\kappa$ B, and altering the composition of fatty acids in cell membrane phospholipids (Brown, 2016; Calder, 2017; Yuan et al., 2022). Besides that, ALA is also able to cross the blood brain barriers (BBB), thus it also plays a key role in protecting the brain (Bazinet et al., 2014; Brown, 2016; Pandohee, 2022).

According to Alam et al. (2021), the administration of ALA has been found to effectively mitigate inflammation and oxidative stress through the activation of the Nrf-2/HO-1/JNK signaling pathway. The study demonstrates that the group treated with ALA exhibits a notable elevation in the expression of heme-oxygenase-1 (HO-1) and nuclear factor-2 erythroid-2 (Nrf-2), along with a considerable reduction in reactive oxygen species (ROS) levels. These findings provide evidence for the antioxidant properties of ALA. In addition, ALA has the capacity to reduce the excessive activity of the c-Jun N-terminal kinase (JNK), so impeding the advancement of pro-inflammatory cytokines and the increase in neuronal death (Schunck et al., 2018). The levels of GFAP, NF-Kb, and IL-1B expression in the cortical region of the mice brain were shown to be significantly reduced in the group that received ALA treatment, indicating the anti-inflammatory properties of ALA. Hence, the findings of this study indicate that alpha-linolenic acid (ALA) possesses the ability to impede the advancement of neuroinflammation triggered by cadmium chloride (CdCl<sub>2</sub>) in the mice brain.

Lee et al. (2018) found that alpha linolenic acid (ALA) protects against neurotoxicity induced by A $\beta$ 25-35 in C6 glial cells. A $\beta$ 25-35 exposure causes cellular apoptosis, excessive nitric oxide (NO) production, and release of pro-inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ), contributing to neuroinflammation. ALA administration enhances cellular survival by reducing NO and cytokine production via down-regulating iNOS, cyclooxygenase-2, and mRNA expressions. ALA

treatment also lowers TNF- $\alpha$  and IL-6 levels and reduces reactive oxygen species (ROS) by upregulating Nrf-2 and inducing HO-1 expression. ALA-treated cells show increased neprilysin and insulin-digesting enzyme proteins, which degrade A $\beta$ .

Study by Kim et al. (2020) shows that by supplementation with walnut extract, which contain high ALA able to exert antioxidant and antiinflammation effect. The MDA level is significantly reduced by using walnut extract with dose of 20mg/kgBW, SOD level significantly increases at both dose (10mg/kgBW and 20 mg/kgBW). With walnut extract of 20mg/kgBW, the ROS production, MMP, and mitochondrial ATP content is significantly decreases and the antiinflammation benefit of the walnut extract is shown by the down-regulation of the expression of TNF- $\alpha$ , p-JNK, and IL-1 $\beta$  value. Besides that, the expression of p-Akt and HO-1 are restored significantly.

Studies by Alam et al. (2021), Kim et al. (2020) and Lee et al. (2018) shows that ALA has an anti-inflammation and anti-oxidant effect in attenuating neuroinflammation. The study shows that the antioxidant property of ALA is by enhancing the nuclear factor-erythroid 2-related factor-2 (Nrf-2) protein levels and subsequent induction of heme-oxygenase-1 (HO-1) expression thus able to decrease the production of ROS. The anti-inflammation effect of ALA through inhibition of inflammatory responses that interfere with production of NO and the expressions of protein/mRNA of iNOS, COX-2, TNF- $\alpha$ , and IL-6.

Study by Ali et al. (2020), shows that ALA significantly reduce TLR4 and GFAP, and Iba-1 in mouse brain injected with A $\beta$ . ALA also able to significantly reduced inflammatory marker such as p-JNK, p-NF- $\kappa$ B, and TNF- $\alpha$  in the mouse brain (frontal cortex and hippocampus). The expression of PARP-1 in mouse brain was also markedly reduced in mouse treated with ALA. This study results are comparable to study done by Livingstone et al. (2023), where it shows that by giving dietary supplementation with flaxseed (high in ALA) able to partially attenuates the neuroinflammation in the hippocampus and medial prefrontal cortex IL-10, TNF- $\alpha$ , IL-1 $\beta$  mRNA expression. This result is also supported by Gao et al. (2021), by giving peony oil supplementation (high in ALA), able to suppressed the activation of microglial and neuroinflammation by down regulating the inflammatory mediators, such as iNOS, COX-2, IL-1 $\beta$ , and TNF- $\alpha$ , in the prefrontal cortex and hippocampus of PS cDKO mice. Study by Wang et al. (2021), shows that in mice with ALA deficiency and scopolamine-induced cognitive impairment model has significantly reduced brain antioxidant activity, lower GFAP and TNF- $\alpha$  protein expression, higher MDA concentration than the mice with sufficient ALA diet. Therefore, it shows that

ALA is important in attenuating neuroinflammation by its anti-inflammatory and antioxidant effect.

In contrast, the study by Lowry et al. (2020), shows that supplementation with ALA able to reduce NO released from microglial, but unable to significantly inhibit iNOS protein level with 100uM dose. This probably because ALA inhibitory activity could alter levels of thiols, like the glutathione. Besides that, ALA also unable to affect the concentration of MCP-1 or cytotoxins by microglia-like human THP-1 cells. Besides that, the study by Rui et al. (2018) demonstrated that supplementation with Chia seed, which is high in ALA shows that it is able to induced neuroinflammation. This study shows that by giving 10% supplementation of chia seed in HFD SAMP8-rats able to increase GFAP and Iba-1 protein expression significantly. This protein is considered a marker for reactive astrogliosis and microglia activation, which plays a role in neuroinflammation. GFAP activation was observed in both hippocampus and cortex of the brain. This study results are contradicting with the other studies, as the other study shows that supplementation with ALA should be able to decrease the GFAP and Iba-1 protein expression, thus able to attenuates neuroinflammation. Therefore, more studies need to be done to know the effect of ALA as neuroprotector to make sure that it is beneficial to be used as prevention or treatment for patient with neuroinflammation.

## Conclusion

Alpha linolenic acid (ALA) is an omega-3 fatty acid found mainly in plant sources such as nuts and their oils. ALA has a protective role in neuroinflammation due to its anti-inflammatory and antioxidant properties and a precursor to EPA and DHA. ALA's antioxidant effects are achieved by upregulating Nrf2 and Ho-1, reducing reactive oxygen species (ROS). Its anti-inflammatory activity involves inhibiting inflammatory responses, helping to alleviate neuroinflammation. Further research is needed to explore ALA's neuroprotective potential and its therapeutic or preventive applications in neuroinflammation.

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## Author Contributions

Investigation, DCW and NML; formal analysis DCW and NML; investigation, DCW; resources, DCW and NML; data curation, DCW and NML; writing – original draft preparation, DCW; writing – review and editing, DCW and NML; visualization, DCW and NML; supervision, DCW and NML; project administration, DCW; funding acquisition, DCW and

NML. All authors have read and agreed to the published version of the manuscript.

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### Conflicts of Interest

We certify that there is no conflict of interest with any financial, personal and other relationships with other peoples or organisation related to the material discussed in the manuscript.

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