2023

Fatty Acid therapy and Implications for Spinal Cord Injury Treatment: A Literature Review

Philippe J. Dentino
The University of Texas Rio Grande Valley, philippe.dentino01@utrgv.edu

MEDI-9331

Fatty Acid therapy and Implications for Spinal Cord Injury Treatment: A Literature Review

Philippe Dentino, PT, DPT
UTRGV School of Medicine

Abstract

Introduction: Spinal Cord Injuries (SCI) are catastrophic injury to spinal neurons that cause a tremendous socioeconomic and public health burden on individuals globally. The role of fatty acids in treatment of SCI is not well understood and poorly standardized across treatment provision. This review seeks to explore the role of fatty acids in neurorecovery and propose emerging themes in SCI treatment with fatty acids.

Methods: A PICO was designed and online databases were searched for relevant articles. A total of 55 studies were deemed appropriate for the review and summarized into thematic elements including) Cellular Transport 2) Neuroprotection 3) SCI Treatment.

Results: Polyunsaturated Fatty Acids (PUFAs) were the primary treatment of interest and demonstrated overall beneficial effect on neuroregeneration and SCI recovery. No consensus was found between selection, dosing, and measurement of SCI treatment outcomes in studies between 1982 and 2023.

Discussion: Publication biases were substantiated in systematic review of studies pertaining to PUFAs and SCI; further research is needed to understand the role of fatty acids and SCI treatment.

Introduction

Spinal Cord Injury (SCI) is defined as debilitating injury to spinal neurons causing sensation and motor impairment at and below the level of injury[1]. SCI remains a prominent cause of severe economic and social debility, with a prevalence ranging from 15 per 1,000,000 cases in Western Europe to 39 per 1,000,000 cases in North America[2]. SCI are estimated to cost between $1 million to $5 million USD per case over the lifetime of the individual. Deficits may range from mild motor or sensory impairment to profound loss of all neurological function based upon the extent of the neuronal loss. Considerably, every SCI is unique in clinical presentation and approach to rehabilitation, thus necessitating a broad range of treatment strategies. Administration of various fatty acids in setting of SCI in rodent studies have demonstrated promising findings in neuronal regeneration, return to ambulation, and functional improvements[3]; however, comprehensive review of current literature shows inconsistency in type of fatty acid administration, dosing, and length of treatment optimal for recovery parameters after SCI. This review aims to disseminate current literature exploring the usage of fatty acids in treatment of SCI and implications for clinical practice.

Methods

The research question, “What are the current pharmacological treatments for SCI?” was formulated via the PICO (Population, Intervention, Comparison, Outcome) method[4] as follows: 1) Human and animal subjects with acute and chronic SCI 2) Fatty acid administration 3) No treatment 4) Neurological function. Online databases were searched based upon access key words derived from PICO. The databases selected, terms queried, and results utilized from each search are seen in Table 1.

Table 1. Overview of Identified and Screened Articles

Search Terms	Results	Database
Oleic Acid and Albumin	1338	PubMed
Oleic Acid and Neuron	337	PubMed
Oleic Acid and Spinal Cord Injury	2	PubMed
2-hydroxyoleic Acid	33	PubMed
Fatty Acid and Spinal Cord Injury	898	PubMed
Omega 3 and Spinal Cord Injury	84	PubMed
Omega 9 and Spinal Cord Injury	17	PubMed
Alpha-linoleic Acid and Spinal Cord Injury	7	PubMed
Palmitoylethanolamide and Spinal Cord Injury	31	PubMed
Fatty Acid and Spinal Cord Injury	49	CINAHL
Fatty Acid and Spinal Cord Injury	0	PEDro

Results

55 studies were selected after final filtering based upon relevance to PICO and grouped in to the following thematic analysis categories: 1) Cellular Transport 2) Neuroprotection 3) SCI Treatment.

Fatty Acids and Cellular Transport

Rhoads et al. (1982) presented the earliest recorded evidence uncovering the role of albumin in cellular synaptosomal uptake of polar amino acids in the presence of unsaturated fatty acids[5]. Albumin was later shown to be a promising, multi-modular protein capable of delivering complex drug moieties via crystallography performed by Bhattacharya et al. in 2000. The study analyzed the extent of albumin’s binding affinity for fatty acids, notably supporting the discovery of drug-binding domain IIIA, showing high-affinity preference for long-chain fatty acids[6]. In 1992, DeWille et al. demonstrated in rodents that immediate post-natal ingestion of coconut oil (30% oleic acid by weight) increased the proteolipid protein and myeline basic protein mRNA synthesis in myelin; within the same year, Thiés et al. reported esterification of unsaturated 2-acyl-lysophosphatidylcholine was more efficiently incorporated in central

nervous system (CNS) neurons when bound to albumin in the newborn rat[7,8]. Together, these studies indicated that albumin may be a key component of the delivery of fatty acids into the developing CNS neuron. Oleic acid and arachidonic acid were shown to inhibit gap junction permeability in astrocytes, leading to increased astrocyte glucose uptake, while albumin was linked to oleic acid production in the CNS[9,10]. These findings began establishing the role of oleic acid as a neurotrophic factor. Further support was demonstrated by electron microscopy of albumin endocytosis through a megalin and caveolin-mediated uptake mechanism in astrocytes[11], inhibition of fatty acid transport proteins in blood-brain barrier microvessel endothelial cells[12], and induction of axonal growth marker growth-associated protein 43 (GAP-43)[13]. Oleic acid has also been shown to induce synaptogenesis and synapse arrangement via interaction with synapse-associated proteins synaptotgamin and postsynaptic density protein (PDS-95) in astrocytes[14].

Fatty Acids and Neuroprotection

With growing evidence of the role of albumin-fatty acid binding in neurons, the neuro-protective effects of polyunsaturated acids (PUFAs) became more evident through observation of GAP-43 induction in rodent astrocytes through synergistic protein kinase c and neurotrophin 3-4/5-dependent mechanisms[15-17]. Later studies indicated neuron preservation was mediated by PUFAs through their effects on terminal synaptic differentiation via transcription factor NeuroD2, inhibition of pro-apoptotic factor S100B in setting of cellular ischemia, and exposure to recombinant human erythropoietin (rhEPO)[18-21].

Systemic and localized cellular inflammation is a known contributor to neuron dysfunction in SCI[1]. The molecular mechanisms of inflammation and their interaction with fatty acids is complex and thought to be mediated by a number of known markers of inflammation, including reactive oxygen species (ROS), p38 MAPK, and Akt/IKK/NF-kappaB signaling pathways in LPS-stimulated BV2 microglia[22,52]. Hirakawa et al. exposed medium-chain fatty acids (MCFA) to 2-decenoic acid ethyl ester (DAEE) after spinal neuron hemisection and observed improved functional recovery, decreased lesion size, increased activation of ERK1/2, and enhanced expression of bcl-2 and brain-derived neurotrophic factor (BDNF) mRNA in the injury site of the spinal cord[23]. Metabolically-active transcription factors PPARα and LXRβ have also been observed in injured white matter neurons, with decreased levels of PPARα noted in ependymal cells treated with oleic acid[24].

The neurolipidome was first discussed by Han et al. in 2007 as mass spectrometry was applied to the experimental observation of lipid movement[25]. The neurolipidome concept was expanded for therapeutic interventions in SCI with the dietary application of omega-3 PUFAs, primarily docosahexaenoic acid (DHA) and omega-6 PUFAs; the former of which was thought to partially confer metabolic neuronal resilience in SCI[26]. Later studies demonstrated significant benefits of metabolic homeostasis and increased antioxidant defenses after administration of omega-3 PUFAs, including influence upon neuron apoptosis after SCI, inflammasome mediation via NLRP3 modulation, and oxidative stress reduction in ischemic SCI[27-30]. Notably, the administration of omega-6 PUFAs were shown to be detrimental in the return to ambulatory

function after SCI and the ratio of omega-3 to omega-6 PUFAs was crucial in synaptogenesis and neurolipidomic composition[31].

SCI Treatment

Omega-3 fatty acids were amongst the first PUFAs to be studied and have been shown to significantly improve a number of functional and biochemical markers of SCI recovery, including increased locomotor performance, decreased neural lipid, protein, and mRNA oxidization, and increased neuroplasticity[32-41]. Of the known PUFAs benefitting neuron recovery in SCI, DHA is the most well-studied, with results supporting role of DHA administration in acute SCI and a significant white matter neuroprotective effect[42-44]. Arima et al. demonstrated administration of IL-6 inhibitor MR16-1in acute SCI reduced blockade of phosphatidylcholine binding to DHA in glial fibrillary acidic protein (GFAP) positive neurons, suggesting DHA's role in modulation of neuroregeneration after acute SCI and interaction with astrocytes[45]. Fatty acid binding protein 5 (FABP5) is another important neural protein thought to mediate cellular transport, uptake, and metabolism of DHA in GFAP positive neurons when genetically upregulated in the presence of PUFAs[46]. Eicosapentanoic acid, alpha-lipoic acid, and alpha-linoleic acid were other PUFAs observed to play a role in prevention of axonal disruption and neuron survival after SCI, with eicosapentanoic acid administered in conjunction with DHA to measure outcomes of SCI recovery in two studies reviewed[47-50]. Hydroxylinoleic acid-albumin treatment in rodents with experimentally-inflicted T9 SCI showed significant recovery in locomotor function and significant overexpression of growth factors with reduced prostaglandin and phospholipase expression[51]. Ingestion of safflower seed oil, containing primarily oleic and palmitic acids, was shown to increase embryonic stem cell proliferation and differentiation in the presence of significant upregulation of signaling factor mRNAs of notch1, hes1, and Ki-67, while increasing the number of oligodendrocytes, astrocytes, and β-III tubulin-positive neurons[53].

Discussion

In the four decades during which PUFAs have been studied for their role in SCI treatment, no consensus has been drawn on the most effective singular fatty acid in light of a wealth of studies that support the benefits of PUFAs after neuronal insult. MacIntosh-Smith et al. discussed the relative efficacy of PUFAs in SCI treatment and found although administration of PUFAs significantly impacted gross locomotor function and neuroregeneration after SCI, no known secondary benefits (analgesia and lesion volume) were significantly different. Notably, a moderate publication bias was discovered, indicating many of the studies may not as strongly substantiate the claims of PUFA administration in light of primary neurorecovery parameters[54]. None of the articles reviewed strictly detail the most efficacious dosing and ratios of PUFAs in SCI treatment—in addition to all being rodent studies—leaving further questions of appropriate pharmacological utility in humans. As modern biotechnologies progress in their versatility of cellular manipulation, techniques such as membrane lipid therapy promise to continue a path forward in experimental validation of plausible treatments for SCI[55]. Given the enormous complexity of the human nervous system and the socioeconomic impact of SCI, future research

is warranted to understand the role of fatty acids in neuronal proliferation, differentiation, and regeneration.

References

1. Punjani N, Deska-Gauthier D, Hachem LD, Abramian M, Fehlings MG. Neuroplasticity and regeneration after spinal cord injury. *N Am Spine Soc J*. 2023;15:100235. doi:10.1016/j.xnsj.2023.100235
2. Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. *Nat Rev Dis Primers*. 2017;3(1):1-21. doi:10.1038/nrdp.2017.18
3. Ahuja CS, Nori S, Tetreault L, et al. Traumatic Spinal Cord Injury-Repair and Regeneration. *Neurosurgery*. 2017;80(3S):S9-S22. doi:10.1093/neuros/nyw080
4. Tawfik GM, Dila KAS, Mohamed MYF, et al. A step by step guide for conducting a systematic review and meta-analysis with simulation data. *Trop Med Health*. 2019;47:46. Published 2019 Aug 1. doi:10.1186/s41182-019-0165-6
5. Rhoads DE, Kaplan MA, Peterson NA, Raghupathy E. Effects of free fatty acids on synaptosomal amino acid uptake systems. *J Neurochem*. 1982;38(5):1255-1260. doi:10.1111/j.1471-4159.1982.tb07898.x
6. Bhattacharya AA, Grüne T, Curry S. Crystallographic analysis reveals common modes of binding of medium and long-chain fatty acids to human serum albumin. *J Mol Biol*. 2000;303(5):721-732. doi:10.1006/jmbi.2000.4158
7. DeWille JW, Farmer SJ. Postnatal dietary fat influences mRNAS involved in myelination. *Dev Neurosci*. 1992;14(1):61-68. doi:10.1159/000111648
8. Thiés F, Delachambre MC, Bentejac M, Lagarde M, Lecerf J. Unsaturated fatty acids esterified in 2-acyl-l-lysophosphatidylcholine bound to albumin are more efficiently taken up by the young rat brain than the unesterified form. *J Neurochem*. 1992;59(3):1110-1116. doi:10.1111/j.1471-4159.1992.tb08353.x
9. Lavado E, Sanchez-Abarca LI, Tabernero A, Bolaños JP, Medina JM. Oleic acid inhibits gap junction permeability and increases glucose uptake in cultured rat astrocytes. *J Neurochem*. 1997;69(2):721-728. doi:10.1046/j.1471-4159.1997.69020721.x
10. Tabernero A, Velasco A, Granda B, Lavado EM, Medina JM. Transcytosis of albumin in astrocytes activates the sterol regulatory element-binding protein-1, which promotes the synthesis of the neurotrophic factor oleic acid. *J Biol Chem*. 2002;277(6):4240-4246. doi:10.1074/jbc.M108760200
11. Bento-Abreu A, Velasco A, Polo-Hernández E, et al. Albumin endocytosis via megalin in astrocytes is caveola- and Dab-1 dependent and is required for the synthesis of the neurotrophic factor oleic acid. *J Neurochem*. 2009;111(1):49-60. doi:10.1111/j.1471-4159.2009.06304.x
12. Mitchell RW, Edmundson CL, Miller DW, Hatch GM. On the mechanism of oleate transport across human brain microvessel endothelial cells. *J Neurochem*. 2009;110(3):1049-1057. doi:10.1111/j.1471-4159.2009.06199.x
13. Polo-Hernández E, De Castro F, García-García AG, Tabernero A, Medina JM. Oleic acid synthesized in the periventricular zone promotes axonogenesis in the striatum during

brain development. *J Neurochem*. 2010;114(6):1756-1766. doi:10.1111/j.1471-4159.2010.06891.x

14. Polo-Hernández E, Tello V, Arroyo AA, et al. Oleic acid synthesized by stearoyl-CoA desaturase (SCD-1) in the lateral periventricular zone of the developing rat brain mediates neuronal growth, migration and the arrangement of prospective synapses. *Brain Res*. 2014;1570:13-25. doi:10.1016/j.brainres.2014.04.038
15. Tabernero A, Lavado EM, Granda B, Velasco A, Medina JM. Neuronal differentiation is triggered by oleic acid synthesized and released by astrocytes. *J Neurochem*. 2001;79(3):606-616. doi:10.1046/j.1471-4159.2001.00598.x
16. Medina JM, Tabernero A. Astrocyte-synthesized oleic acid behaves as a neurotrophic factor for neurons. *J Physiol Paris*. 2002;96(3-4):265-271. doi:10.1016/s0928-4257(02)00015-3
17. Granda B, Tabernero A, Tello V, Medina JM. Oleic acid induces GAP-43 expression through a protein kinase C-mediated mechanism that is independent of NGF but synergistic with NT-3 and NT-4/5. *Brain Res*. 2003;988(1-2):1-8. doi:10.1016/s0006-8993(03)03253-0
18. Velasco A, Tabernero A, Medina JM. Role of oleic acid as a neurotrophic factor is supported in vivo by the expression of GAP-43 subsequent to the activation of SREBP-1 and the up-regulation of stearoyl-CoA desaturase during postnatal development of the brain. *Brain Res*. 2003;977(1):103-111. doi:10.1016/s0006-8993(03)02772-0
19. Rodríguez-Rodríguez RA, Tabernero A, Velasco A, Lavado EM, Medina JM. The neurotrophic effect of oleic acid includes dendritic differentiation and the expression of the neuronal basic helix-loop-helix transcription factor NeuroD2. *J Neurochem*. 2004;88(5):1041-1051. doi:10.1046/j.1471-4159.2003.02262.x
20. Asano T, Mori T, Shimoda T, et al. Arundic acid (ONO-2506) ameliorates delayed ischemic brain damage by preventing astrocytic overproduction of S100B. *Curr Drug Targets CNS Neurol Disord*. 2005;4(2):127-142. doi:10.2174/1568007053544084
21. Vitellaro-Zuccarello L, Mazzetti S, Madaschi L, Bosisio P, Gorio A, De Biasi S. Erythropoietin-mediated preservation of the white matter in rat spinal cord injury. *Neuroscience*. 2007;144(3):865-877. doi:10.1016/j.neuroscience.2006.10.023
22. Oh YT, Lee JY, Lee J, et al. Oleic acid reduces lipopolysaccharide-induced expression of iNOS and COX-2 in BV2 murine microglial cells: possible involvement of reactive oxygen species, p38 MAPK, and IKK/NF-kappaB signaling pathways. *Neurosci Lett*. 2009;464(2):93-97. doi:10.1016/j.neulet.2009.08.040
23. Hirakawa A, Shimizu K, Fukumitsu H, Soumiya H, Iinuma M, Furukawa S. 2-Decenoic acid ethyl ester, a derivative of unsaturated medium-chain fatty acids, facilitates functional recovery of locomotor activity after spinal cord injury. *Neuroscience*. 2010;171(4):1377-1385. doi:10.1016/j.neuroscience.2010.10.004
24. Fandel D, Wasmuht D, Avila-Martín G, Taylor JS, Galán-Arriero I, Mey J. Spinal cord injury induced changes of nuclear receptors PPARα and LXRβ and modulation with oleic acid/albumin treatment. *Brain Res*. 2013;1535:89-105. doi:10.1016/j.brainres.2013.08.022
25. Han X. Neurolipidomics: challenges and developments. *Front Biosci*. 2007;12:2601-2615. doi:10.2741/2258

26. Figueroa JD, Cordero K, Llán MS, De Leon M. Dietary omega-3 polyunsaturated fatty acids improve the neurolipidome and restore the DHA status while promoting functional recovery after experimental spinal cord injury. *J Neurotrauma*. 2013;30(10):853-868. doi:10.1089/neu.2012.2718
27. Figueroa JD, De Leon M. Neurorestorative targets of dietary long-chain omega-3 fatty acids in neurological injury. *Mol Neurobiol*. 2014;50(1):197-213. doi:10.1007/s12035-014-8701-1
28. Galán-Arriero I, Serrano-Muñoz D, Gómez-Soriano J, et al. The role of Omega-3 and Omega-9 fatty acids for the treatment of neuropathic pain after neurotrauma. *Biochim Biophys Acta Biomembr*. 2017;1859(9 Pt B):1629-1635. doi:10.1016/j.bbamem.2017.05.003
29. Bi J, Chen C, Sun P, Tan H, Feng F, Shen J. Neuroprotective effect of omega-3 fatty acids on spinal cord injury induced rats. *Brain Behav*. 2019;9(8):e01339. doi:10.1002/brb3.1339
30. Baazm M, Behrens V, Beyer C, Nikoubashman O, Zendedel A. Regulation of Inflammasomes by Application of Omega-3 Polyunsaturated Fatty Acids in a Spinal Cord Injury Model. *Cells*. 2021;10(11):3147. doi:10.3390/cells10113147
31. Lim SN, Gladman SJ, Dyall SC, et al. Transgenic mice with high endogenous omega-3 fatty acids are protected from spinal cord injury. *Neurobiol Dis*. 2013;51:104-112. doi:10.1016/j.nbd.2012.10.021
32. Kakulas BA. Neuropathology: the foundation for new treatments in spinal cord injury. *Spinal Cord*. 2004;42(10):549-563. doi:10.1038/sj.sc.3101670
33. Javierre C, Vidal J, Segura R, Lizarraga MA, Medina J, Ventura JL. The effect of supplementation with n-3 fatty acids on the physical performance in subjects with spinal cord injury. *J Physiol Biochem*. 2006;62(4):271-279. doi:10.1007/BF03165756
34. King VR, Huang WL, Dyall SC, Curran OE, Priestley JV, Michael-Titus AT. Omega-3 fatty acids improve recovery, whereas omega-6 fatty acids worsen outcome, after spinal cord injury in the adult rat. *J Neurosci*. 2006;26(17):4672-4680. doi:10.1523/JNEUROSCI.5539-05.2006
35. Huang WL, King VR, Curran OE, et al. A combination of intravenous and dietary docosahexaenoic acid significantly improves outcome after spinal cord injury. *Brain*. 2007;130(Pt 11):3004-3019. doi:10.1093/brain/awm223
36. Michael-Titus AT. Omega-3 fatty acids and neurological injury. *Prostaglandins Leukot Essent Fatty Acids*. 2007;77(5-6):295-300. doi:10.1016/j.plefa.2007.10.021
37. Dyall SC, Michael-Titus AT. Neurological benefits of omega-3 fatty acids. *Neuromolecular Med*. 2008;10(4):219-235. doi:10.1007/s12017-008-8036-z
38. Kwon BK, Okon EB, Plunet W, et al. A systematic review of directly applied biologic therapies for acute spinal cord injury. *J Neurotrauma*. 2011;28(8):1589-1610. doi:10.1089/neu.2009.1150
39. Michael-Titus AT, Priestley JV. Omega-3 fatty acids and traumatic neurological injury: from neuroprotection to neuroplasticity? *Trends Neurosci*. 2014;37(1):30-38. doi:10.1016/j.tins.2013.10.005
40. Wojdasiewicz P, Poniatowski ŁA, Turczyn P, Frasuńska J, Paradowska-Gorycka A, Tarnacka B. Significance of Omega-3 Fatty Acids in the Prophylaxis and Treatment after Spinal Cord

Injury in Rodent Models. *Mediators Inflamm*. 2020;2020:3164260. doi:10.1155/2020/3164260
41. Turczyn P, Wojdasiewicz P, Poniatowski ŁA, et al. Omega-3 fatty acids in the treatment of spinal cord injury: untapped potential for therapeutic intervention? *Mol Biol Rep*. 2022;49(11):10797-10809. doi:10.1007/s11033-022-07762-x
42. Huang WL, King VR, Curran OE, et al. A combination of intravenous and dietary docosahexaenoic acid significantly improves outcome after spinal cord injury. *Brain*. 2007;130(Pt 11):3004-3019. doi:10.1093/brain/awm223
43. Ward RE, Huang W, Curran OE, Priestley JV, Michael-Titus AT. Docosahexaenoic acid prevents white matter damage after spinal cord injury. *J Neurotrauma*. 2010;27(10):1769-1780. doi:10.1089/neu.2010.1348
44. Liu ZH, Yip PK, Priestley JV, Michael-Titus AT. A Single Dose of Docosahexaenoic Acid Increases the Functional Recovery Promoted by Rehabilitation after Cervical Spinal Cord Injury in the Rat. *J Neurotrauma*. 2017;34(9):1766-1777. doi:10.1089/neu.2016.4556
45. Arima H, Hanada M, Hayasaka T, et al. Blockade of IL-6 signaling by MR16-1 inhibits reduction of docosahexaenoic acid-containing phosphatidylcholine levels in a mouse model of spinal cord injury. *Neuroscience*. 2014;269:1-10. doi:10.1016/j.neuroscience.2014.03.012
46. Figueroa JD, Serrano-Illan M, Licero J, Cordero K, Miranda JD, De Leon M. Fatty Acid Binding Protein 5 Modulates Docosahexaenoic Acid-Induced Recovery in Rats Undergoing Spinal Cord Injury. *J Neurotrauma*. 2016;33(15):1436-1449. doi:10.1089/neu.2015.4186
47. Lim SN, Huang W, Hall JCE, Ward RE, Priestley JV, Michael-Titus AT. The acute administration of eicosapentaenoic acid is neuroprotective after spinal cord compression injury in rats. *Prostaglandins Leukot Essent Fatty Acids*. 2010;83(4-6):193-201. doi:10.1016/j.plefa.2010.08.003
48. Tas N, Bakar B, Kasimcan MO, et al. Evaluation of protective effects of the alpha lipoic acid after spinal cord injury: an animal study. *Injury*. 2010;41(10):1068-1074. doi:10.1016/j.injury.2010.05.027
49. Ercan S, Aktas A, Kemaloglu MS. Antioxidative effects of alpha-lipoic acid in spinal cord injury An experimental rat model. *Ann Ital Chir*. 2021;92:98-102.
50. Norouzi Javidan A, Sabour H, Latifi S, et al. Does consumption of polyunsaturated fatty acids influence on neurorehabilitation in traumatic spinal cord-injured individuals? A double-blinded clinical trial. *Spinal Cord*. 2014;52(5):378-382. doi:10.1038/sc.2014.30
51. Avila-Martin G, Mata-Roig M, Galán-Arriero I, Taylor JS, Busquets X, Escribá PV. Treatment with albumin-hydroxyoleic acid complex restores sensorimotor function in rats with spinal cord injury: Efficacy and gene expression regulation. *PLoS One*. 2017;12(12):e0189151. doi:10.1371/journal.pone.0189151
52. Wang JL, Ren CH, Feng J, Ou CH, Liu L. Oleanolic acid inhibits mouse spinal cord injury through suppressing inflammation and apoptosis via the blockage of p38 and JNK MAPKs. *Biomed Pharmacother*. 2020;123:109752. doi:10.1016/j.biopha.2019.109752
53. Ghareghani M, Zibara K, Azari H, et al. Safflower Seed Oil, Containing Oleic Acid and Palmitic Acid, Enhances the Stemness of Cultured Embryonic Neural Stem Cells through

Notch1 and Induces Neuronal Differentiation. *Front Neurosci*. 2017;11:446. doi:10.3389/fnins.2017.00446

54. MacIntosh-Smith W a. C, Abdallah A, Cunningham CJ. The potential effects of polyunsaturated ω-3 fatty acids on spinal cord injury: A systematic review & meta-analysis of preclinical evidence. *Prostaglandins Leukot Essent Fatty Acids*. 2023;191:102554. doi:10.1016/j.plefa.2023.102554
55. Torres M, Parets S, Fernández-Díaz J, et al. Lipids in Pathophysiology and Development of the Membrane Lipid Therapy: New Bioactive Lipids. *Membranes (Basel)*. 2021;11(12):919. doi:10.3390/membranes11120919