Biomed Res Bull 2025;3(3):149-152
doi:10.34172/biomedrb.9077
http://biomedrb.com

Review Article

Shark-Derived Neuroprotective Agents for Neurodegenerative Diseases: From Molecular Pathways to Clinical Evidence

Ali Alipour[1], **Afra Darvishi**[2]

[1]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Article History:
Received: August 2, 2025
Revised: August 20, 2025
Accepted: September 2, 2025
ePublished: September 29, 2025

***Corresponding Author:**
Afra Darvishi,
Email: darvishia@tbzmed.ac.ir

Abstract
Neurodegenerative diseases, such as (but not limited to) Alzheimer's disease and Parkinson's disease, are a serious global health problem. Considering that the current treatments are primarily focused on symptom relief, it is necessary to find novel therapeutic approaches, including target therapies. Sharks have a special biochemical potential, and various neuroprotective agents can be derived from these animals. This review aims to evaluate and summarize the data available on shark-derived compounds in the case of neurodegeneration, explaining the molecular signatures and insights for novel therapies. Squalamine, trodusquemine, and single domain antibodies are the major products discussed in this paper. This review study further provides molecular pathways and clinical and animal data due to date, suggesting promising insights into more investigations in this field.
Keywords: Alzheimer's disease, Parkinson's disease, Shark-derived agents, Squalamine, trodusquemine

Introduction

Neurodegenerative disorders (NDDs), such as Alzheimer's disease (AD) and Parkinson's disease (PD), remain major health issues worldwide. They are marked by progressive neuronal loss caused by convergent mechanisms, including lipid membrane vulnerability, impaired proteostasis, glial/vascular dysregulation, mitochondrial oxidative stress, and lysosomal dysfunction.[1,2] According to classical texts, current treatments merely represent symptomatic relief, along with limited disease-modifying therapies. Marine medicine, with a longstanding historical use, is considered to provide distinct compounds underlying its therapeutic potential in NDDs.[3] Among marine organisms, sharks possess a unique biochemical profile, providing remarkable regenerative capacities, efficient immune systems, and response mechanisms to oxidative stress.[4] The key elements of this profile involved in these processes include aminosterols, such as squalamine, alkylglycerols, and squalene.[5-7]

Squalamine and trodusquemine, first isolated from Squalus acanthias, function by blocking α-synuclein aggregation and its related toxicity, with promising results in NDDs.[8] Squalene, a triterpene lipid, contains strong antioxidants and stabilizes membranes, offering neuroprotection and enhancing drug delivery across the blood-brain barrier (BBB).[9,10] Single-domain shark antibodies (e.g., the T-box 4 brain shuttle) were demonstrated to cross the BBB and deliver neuroprotective agents, such as tropomyosin receptor kinase B (TrkB) receptor agonist antibodies, to the brain.[11] Despite challenges in sustainability and extraction, innovative synthetic methods are driving the development of shark-inspired neuroprotective agents.

Therefore, this review aims to summarize the current evidence from preclinical and clinical studies on shark-derived neuroprotective agents for the management of NDDs. Moreover, it is intended to provide a comprehensive evaluation of their potential as therapeutic agents against neurodegeneration by exploring the molecular pathways.

Neuroprotective Architecture: Molecular Mechanisms

Squalamine, as one of the main aminosterols derived from dogfish sharks, has shown various effects, such as reducing hemangioblastomas and gliomas.[12] It inhibits angiogenesis related to tumors.[13] Moreover, squalamine is known for extensive antibacterial efficacy comparable to colistin.[14] It causes an increase in intracellular adenosine triphosphate, resulting in membrane depolarization. Additionally, this natural aminosterol interacts with the lipid membrane,[15] as it binds to the surface of the membrane, contributing to antifungal and antimicrobial effects. Moreover, it has a role in altering the firing patterns of aged neurons.[16] When applying squalamine in a mouse cortical neuron (ex vivo), the alpha-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid-type glutamate receptors are activated [17], thus regulating the synaptic transmission through

interacting with the lipid membrane.

Likewise, trodusquemine, as a natural aminosterol, attenuates the cytotoxicity of α-synuclein and amyloid β (Aβ) to human neuroblastoma cells.[18] This aminosterol, also known as MSI-1436, was examined on equine hepatic progenitor cells, and it was found to be efficient, as it targeted the protein-tyrosine phosphatase 1B (PTP1B).[19] The PTP1B pathway affects insulin and leptin signaling, leading to diabetes mellitus and obesity, as well as cancer via modulating pro-survival mechanisms.[20] Endoplasmic reticulum stress, which is activated by Aβ oligomers, can upregulate this pathway.[21] This process inhibits tyrosine kinases, resulting in deficits in memory and cognition. Moreover, inhibiting PTP1B cans reduce pro-inflammatory reactions, in part, via the suppression of cyclooxygenase-2 and nuclear factor kappa-light-chain-enhancer of activated B cells.[22] According to Ozek et al, TrkB signaling is a substrate for PTP1B [23] and regulates the brain-derived neurotrophic factor-induced thermogenesis. The distribution of these receptors is widespread in the central nervous system.[24,25] Hypothalamus and hindbrain are major parts of the brain that are affected by PTP1B.[26,27] PTP1B, as an inflammation regulator, is highly overexpressed by microglial cells, so when inhibited, the inflammation is suppressed dramatically.[28] Nitric oxide, interleukin-6, and tumor necrosis factor-α are highly produced in the sinflammatory process. Fuentes et al found that PTP1B modulates the N-cadherin via the dephosphorylation of ß-catenin on Tyr-654.[29] In addition, the downregulation of PTP1B in hippocampus results in improved cognition.

Key Findings From Animal Studies

Squalamine impacts the accumulation of α-synuclein, which is a well-recognized biomarker in PD.[30] This product competes with α-synuclein in binding lipid membranes, leading to a reduction in the oligomer's aggregation in *C. elegans*.[30] West et al [31] explored how squalamine impacts the enteric nervous system in PD mouse models, in which the colonic motility was restored rapidly. Single domain shark antibodies binding to transferrin receptor 1 are other candidates to consider for neurodegeneration treatment. Clarke et al indicated that T-box4-TrkB fusion could provide neuroprotection in a neurotoxin-induced mouse model of PD.[11] Moreover, claramine, an aminosterol that is structurally similar to trodusquemine and squalamine, makes the α-synuclein stable in PD and reduces the aggregation in *C. elegans*.[32]

In AD, trodusquemine could inhibit the PTP1B, a pathway activated by inflammation, thus alleviating the memory deficits and neuronal loss in the hippocampus in a transgenic AD mouse model.[33] Additionally, trodusquemine and related aminosterols could be defensive against the misfolded proteins contributing to aging.[34] Low-density lipoprotein receptor knock-out mice (LDLR-/-) receiving a high-fat diet were reported to have reduced levels of atherosclerosis when receiving trodusquemine.[34,35] The tyrosine phosphorylation of metabotropic glutamate receptor 5 is restored by inhibiting the PTP1B, thereby reducing the anxiety behavior in mice.[36] In addition, low molecular weight chondroitin sulfate derived from shark cartilage is another studied product in AD models suggested by Zhao et al in 5XFAD model.[37] The production of the amyloid precursor protein and presenillin 1 was attenuated, and inflammation and oxidative stress were inhibited. MSI-1436, derived from shark liver oil could cross the BBB. Furthermore, it is possibly effective in central nervous system injuries since it inhibits PTP1B.[38] Further, claramine inhibits the β-secretase 1, which cleaves the insulin receptor, making it a possible candidate for AD.[39]

Focusing on Clinical Evidence

Clinical studies evaluating the efficacy of these neuroprotective factors are still limited in the case of neurodegeneration. ENT-01 is a synthetic squalamine salt (with oral use) that was examined on PD patients and demonstrated improvements in bowel function, with more than 80% of patients reaching an increase of 1 complete spontaneous bowel movement in a week or 3 from the baseline.[40] This study underlines the gastrointestinal benefits of squalamine, along with significant improvements in neurological findings. In a randomized clinical trial, Camilleri et al assessed the ENT-01 for constipation treatment.[41] With no serious side effects, squalamine improved bowel movements. The adverse events mostly included nausea and diarrhea. The preliminary results of these studies suggest that shark-derived compounds could notably enhance constipation, with insights into improving cognitive functions. To the best of our knowledge, no randomized clinical trials have been published primarily concerning the nervous system. A phase I trial (DEMET, NCT03938922) with 40 patients focusing on PD dementia was withdrawn . Marine natural products might provide novel, innovative results with their great pharmaceutical potentials.[42]

Insights Into Future Research in Neurodegeneration

The clinical translation of shark-derived neuroprotective factors is challenging, as the evidence is primarily limited to preclinical studies. More clinical trials, especially concentrating on cognitive outcomes, are required to decide on the plausible implications. The accumulation of α-synuclein is observed in the enteric nervous system of PD patients [43], enabling us to think of conducting more studies, especially on squalamine as it could impact the gut-brain axis. In addition, trial designs should consider longer periods of time for further assessment, as the product was safe with unsignificant adverse events in both recognized clinical trials.[40,41] Marine pharmacology is a promising field to discover novel target therapies and can be more elucidated if more investigation is conducted on these compounds. Other than Aβ or α-synuclein, future studies should further target other mechanisms, in addition to other NDDs, such as Huntington's disease. Furthermore, investigating the synergistic effects of these compounds can be so useful, especially animal studies since the

clinical evidence remains limited. The sustainability and ethical considerations require to be further scrutinized, since the development of these treatments is responsible for ecological outcomes.

Authors' Contribution

A.A: Searching the databases, evaluating the available data, writing the manuscript.
A.D: Writing the manuscript, reviewing the draft.

Competing Interests

None declared.

Consent to Publication

Not applicable. This is a review of current data in the field using online databases.

Consent to Participate

Not applicable. This is a review of current data in the field using online databases.

Data Availability

All supporting data and information are available within the manuscript.

Funding

The Deputy of Research of Tabriz University of Medical Sciences supported this work.

References

1. De Strooper B, Karran E. The Cellular Phase of Alzheimer's Disease. Cell 2016;164(4):603–15. doi:10.1016/j.cell.2015.12.056
2. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers 2017;3:17013. doi:10.1038/nrdp.2017.13
3. Catanesi M, Caioni G, Castelli V, Benedetti E, d'Angelo M, Cimini A. Benefits under the Sea: The Role of Marine Compounds in Neurodegenerative Disorders. Mar Drugs 2021;19(1):24. doi:10.3390/md19010024
4. Moore KS, Wehrli S, Roder H, Rogers M, Forrest JN, Jr., McCrimmon D, et al. Squalamine: an aminosterol antibiotic from the shark. Proc Natl Acad Sci U S A 1993;90(4):1354–8. doi:10.1073/pnas.90.4.1354
5. Khodadadi M, Javadi B. A Review of the Protective Effects of Alkaloids against Alpha-synuclein Toxicity in Parkinson's Disease. Mini Rev Med Chem 2025;25(2):112–27. doi:10.2174/0113895575306884240604065754
6. Shrestha RLS, M CS, Tamang A, Poudel M, Parajuli N, Shrestha A, et al. Evaluating the inhibitory efficacy of Oxalis phytocompounds on monoamine oxidase B: An integrated approach targeting age related neurodegenerative diseases through molecular docking and dynamics simulations. PLoS One 2025;20(7):e0329168. doi:10.1371/journal.pone.0329168
7. Spears LD, Adak S, Dong G, Wei X, Spyropoulos G, Zhang Q, et al. Endothelial ether lipids link the vasculature to blood pressure, behavior, and neurodegeneration. J Lipid Res 2021;62:100079. doi:10.1016/j.jlr.2021.100079
8. Limbocker R, Errico S, Barbut D, Knowles TPJ, Vendruscolo M, Chiti F, et al. Squalamine and trodusquemine: two natural products for neurodegenerative diseases, from physical chemistry to the clinic. Nat Prod Rep 2022;39(4):742–53. doi:10.1039/d1np00042j
9. Reddy LH, Couvreur P. Squalene: A natural triterpene for use in disease management and therapy. Adv Drug Deliv Rev 2009;61(15):1412–26. doi:10.1016/j.addr.2009.09.005
10. Kim SK, Karadeniz F. Biological importance and applications of squalene and squalane. Adv Food Nutr Res 2012;65:223–33. doi:10.1016/b978-0-12-416003-3.00014-7
11. Clarke E, Stocki P, Sinclair EH, Gauhar A, Fletcher EJR, Krawczun-Rygmaczewska A, et al. A Single Domain Shark Antibody Targeting the Transferrin Receptor 1 Delivers a TrkB Agonist Antibody to the Brain and Provides Full Neuroprotection in a Mouse Model of Parkinson's Disease. Pharmaceutics 2022;14(7):1335. doi:10.3390/pharmaceutics14071335
12. Sills AK, Jr., Williams JI, Tyler BM, Epstein DS, Sipos EP, Davis JD, et al. Squalamine inhibits angiogenesis and solid tumor growth in vivo and perturbs embryonic vasculature. Cancer Res 1998;58(13):2784–92.
13. Márquez-Garbán DC, Gorrín-Rivas M, Chen HW, Sterling C, Jr., Elashoff D, Hamilton N, et al. Squalamine blocks tumor-associated angiogenesis and growth of human breast cancer cells with or without HER-2/neu overexpression. Cancer Lett 2019;449:66–75. doi:10.1016/j.canlet.2019.02.009
14. Alhanout K, Malesinki S, Vidal N, Peyrot V, Rolain JM, Brunel JM. New insights into the antibacterial mechanism of action of squalamine. J Antimicrob Chemother 2010;65(8):1688–93. doi:10.1093/jac/dkq213
15. Grage SL, Guschtschin-Schmidt N, Meng B, Kohlmeyer A, Afonin S, Ulrich AS. Interaction of Squalamine with Lipid Membranes. J Phys Chem B 2025;129(6):1760–73. doi:10.1021/acs.jpcb.4c06576
16. McVey Neufeld KA, Mao YK, West CL, Ahn M, Hameed H, Iwashita E, et al. Squalamine reverses age-associated changes of firing patterns of myenteric sensory neurons and vagal fibres. Commun Biol 2024;7(1):80. doi:10.1038/s42003-023-05623-2
17. Sumioka A, Yan D, Tomita S. TARP phosphorylation regulates synaptic AMPA receptors through lipid bilayers. Neuron 2010;66(5):755–67. doi:10.1016/j.neuron.2010.04.035
18. Limbocker R, Mannini B, Ruggeri FS, Cascella R, Xu CK, Perni M, et al. Trodusquemine displaces protein misfolded oligomers from cell membranes and abrogates their cytotoxicity through a generic mechanism. Commun Biol 2020;3(1):435. doi:10.1038/s42003-020-01140-8
19. Qasem B, Dąbrowska A, Króliczewski J, Łyczko J, Marycz K. Trodusquemine (MSI-1436) Restores Metabolic Flexibility and Mitochondrial Dynamics in Insulin-Resistant Equine Hepatic Progenitor Cells (HPCs). Cells 2024;13(2):152. doi:10.3390/cells13020152
20. Villamar-Cruz O, Loza-Mejía MA, Arias-Romero LE, Camacho-Arroyo I. Recent advances in PTP1B signaling in metabolism and cancer. Biosci Rep 2021;41(11):BSR20211994. doi:10.1042/bsr20211994
21. Vieira MN, Lyra ESNM, Ferreira ST, De Felice FG. Protein Tyrosine Phosphatase 1B (PTP1B): A Potential Target for Alzheimer's Therapy? Front Aging Neurosci 2017;9:7. doi:10.3389/fnagi.2017.00007
22. Feng CW, Chen NF, Chan TF, Chen WF. Therapeutic Role of Protein Tyrosine Phosphatase 1B in Parkinson's Disease via Antineuroinflammation and Neuroprotection In Vitro and In Vivo. Parkinsons Dis 2020;2020:8814236. doi:10.1155/2020/8814236
23. Ozek C, Kanoski SE, Zhang ZY, Grill HJ, Bence KK. Protein-tyrosine phosphatase 1B (PTP1B) is a novel regulator of central brain-derived neurotrophic factor and tropomyosin receptor kinase B (TrkB) signaling. J Biol Chem 2014;289(46):31682–92. doi:10.1074/jbc.M114.603621
24. Yan Q, Radeke MJ, Matheson CR, Talvenheimo J, Welcher AA, Feinstein SC. Immunocytochemical localization of TrkB in the central nervous system of the adult rat. J Comp Neurol 1997;378(1):135–57.
25. Ohira K, Hayashi M. A new aspect of the TrkB signaling pathway in neural plasticity. Curr Neuropharmacol 2009;7(4):276–85. doi:10.2174/157015909790031210
26. Tsou RC, Rak KS, Zimmer DJ, Bence KK. Improved metabolic

phenotype of hypothalamic PTP1B-deficiency is dependent upon the leptin receptor. Mol Metab 2014;3(3):301–12. doi:10.1016/j.molmet.2014.01.008
27. De Jonghe BC, Hayes MR, Zimmer DJ, Kanoski SE, Grill HJ, Bence KK. Food intake reductions and increases in energetic responses by hindbrain leptin and melanotan II are enhanced in mice with POMC-specific PTP1B deficiency. Am J Physiol Endocrinol Metab 2012;303(5):E644–51. doi:10.1152/ajpendo.00009.2012
28. Song GJ, Jung M, Kim JH, Park H, Rahman MH, Zhang S, et al. A novel role for protein tyrosine phosphatase 1B as a positive regulator of neuroinflammation. J Neuroinflammation 2016;13(1):86. doi:10.1186/s12974-016-0545-3
29. Fuentes F, Zimmer D, Atienza M, Schottenfeld J, Penkala I, Bale T, et al. Protein tyrosine phosphatase PTP1B is involved in hippocampal synapse formation and learning. PLoS One 2012;7(7):e41536. doi:10.1371/journal.pone.0041536
30. Perni M, Galvagnion C, Maltsev A, Meisl G, Müller MB, Challa PK, et al. A natural product inhibits the initiation of α-synuclein aggregation and suppresses its toxicity. Proc Natl Acad Sci U S A 2017;114(6):E1009–e17. doi:10.1073/pnas.1610586114
31. West CL, Mao YK, Delungahawatta T, Amin JY, Farhin S, McQuade RM, et al. Squalamine Restores the Function of the Enteric Nervous System in Mouse Models of Parkinson's Disease. J Parkinsons Dis 2020;10(4):1477–91. doi:10.3233/jpd-202076
32. Dada ST, Toprakcioglu Z, Cali MP, Röntgen A, Hardenberg MC, Morris OM, et al. Pharmacological inhibition of α-synuclein aggregation within liquid condensates. Nat Commun 2024;15(1):3835. doi:10.1038/s41467-024-47585-x
33. Ricke KM, Cruz SA, Qin Z, Farrokhi K, Sharmin F, Zhang L, et al. Neuronal Protein Tyrosine Phosphatase 1B Hastens Amyloid β-Associated Alzheimer's Disease in Mice. J Neurosci 2020;40(7):1581–93. doi:10.1523/jneurosci.2120-19.2019
34. Barbut D, Perni M, Zasloff M. Anti-aging properties of the aminosterols of the dogfish shark. NPJ Aging 2024;10(1):62. doi:10.1038/s41514-024-00188-8
35. Thompson D, Morrice N, Grant L, Le Sommer S, Lees EK, Mody N, et al. Pharmacological inhibition of protein tyrosine phosphatase 1B protects against atherosclerotic plaque formation in the LDLR(-/-) mouse model of atherosclerosis. Clin Sci (Lond) 2017;131(20):2489–501. doi:10.1042/cs20171066
36. Qin Z, Zhou X, Pandey NR, Vecchiarelli HA, Stewart CA, Zhang X, et al. Chronic stress induces anxiety via an amygdalar intracellular cascade that impairs endocannabinoid signaling. Neuron 2015;85(6):1319–31. doi:10.1016/j.neuron.2015.02.015
37. Zhao N, Wu L, Zhang X, Jiang W, Wang F. Low molecular weight chondroitin sulfate ameliorates pathological changes in 5XFAD mice by improving various functions in the brain. Neuropharmacology 2021;199:108796. doi:10.1016/j.neuropharm.2021.108796
38. Smith AM, Maguire-Nguyen KK, Rando TA, Zasloff MA, Strange KB, Yin VP. The protein tyrosine phosphatase 1B inhibitor MSI-1436 stimulates regeneration of heart and multiple other tissues. NPJ Regen Med 2017;2:4. doi:10.1038/s41536-017-0008-1
39. Gaborit B, Govers R, Altié A, Brunel JM, Morange P, Peiretti F. The aminosterol Claramine inhibits β-secretase 1-mediated insulin receptor cleavage. J Biol Chem 2021;297(1):100818. doi:10.1016/j.jbc.2021.100818
40. Hauser RA, Sutherland D, Madrid JA, Rol MA, Frucht S, Isaacson S, et al. Targeting neurons in the gastrointestinal tract to treat Parkinson's disease. Clin Park Relat Disord 2019;1:2–7. doi:10.1016/j.prdoa.2019.06.001
41. Camilleri M, Subramanian T, Pagan F, Isaacson S, Gil R, Hauser RA, et al. Oral ENT-01 Targets Enteric Neurons to Treat Constipation in Parkinson Disease : A Randomized Controlled Trial. Ann Intern Med 2022;175(12):1666–74. doi:10.7326/m22-1438
42. Ayyappan V, Ekambaram Y. Analyzing the Role of Natural Marine Compounds in Developing Biomedical Applications and Pharmaceuticals. Natural and Engineering Sciences 2025;10(2):37–47. doi:10.28978/nesciences.1714379
43. Chen M, Mor DE. Gut-to-Brain α-Synuclein Transmission in Parkinson's Disease: Evidence for Prion-like Mechanisms. Int J Mol Sci 2023;24(8):7205. doi:10.3390/ijms24087205