

Research

Seabuckthorn Bioactive Compounds in Neuroprotection: Phytochemistry, Pharmacological Mechanisms and Nanotechnology-Based Delivery Approaches

Namrata Singh*

Department of Pharmacy, AMCOP, Gwalior MP

Corresponding Author:

Dr. Namrata Singh

Email: singh.nam8@gmail.com

DOI: 10.62896/ijmsi.2.1.26

Conflict of interest: NIL

Article History

Received: 08/02/2026

Accepted: 27/03/2026

Published: 24/03/2026

Abstract:

Neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), represent major global health challenges associated with progressive neuronal dysfunction, cognitive decline, oxidative stress, mitochondrial impairment, neuroinflammation, protein aggregation and synaptic dysfunction. The complex and multifactorial nature of these disorders has stimulated increasing interest in multi-target therapeutic strategies based on naturally occurring bioactive compounds. Seabuckthorn (*Hippophae rhamnoides* L.), a medicinal and nutritionally important plant belonging to the family Elaeagnaceae, is a rich source of phenolic acids, flavonoids, proanthocyanidins, carotenoids, vitamins, fatty acids, triterpenoids, phytosterols and other secondary metabolites. Among these constituents, phenolic compounds including quercetin, kaempferol, isorhamnetin, gallic acid, ellagic acid, protocatechuic acid and ferulic acid have attracted particular interest because of their antioxidant, anti-inflammatory, anti-apoptotic and neuroprotective properties. Experimental studies indicate that seabuckthorn extracts and selected constituents can attenuate oxidative injury, regulate inflammatory signaling, protect neuronal cells, influence neurotrophic pathways and improve cognitive performance in experimental models. Seabuckthorn flavonoids have been associated with regulation of PI3K/Akt and ERK signaling, while isorhamnetin has demonstrated antioxidant and anti-inflammatory effects in experimental models. However, the therapeutic translation of these compounds is limited by poor aqueous solubility, chemical instability, extensive metabolism, low systemic bioavailability and restricted penetration across the blood-brain barrier (BBB). Nanotechnology-based drug delivery systems, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, phytosomes and exosome-based systems, may provide opportunities to improve stability, pharmacokinetics, cellular uptake and brain delivery. This review summarizes the botanical and phytochemical characteristics of *H. rhamnoides*, with particular emphasis on neuroactive phenolics; discusses potential molecular mechanisms underlying neuroprotection; evaluates available experimental evidence in neurodegenerative and cognitive disorders; and examines nanotechnology-based approaches for improving delivery of seabuckthorn bioactives to the central nervous system. Particular attention is given to liposomal delivery of total phenolics as a prospective strategy for improving bioavailability and therapeutic performance. Although current evidence is promising, systematic characterization, standardized extracts, pharmacokinetic studies, BBB transport studies, toxicological evaluation and well-designed clinical trials are required before seabuckthorn phenolics can be considered established therapeutic agents for neurodegenerative diseases.

Keywords: *Hippophae rhamnoides*; seabuckthorn; polyphenols; flavonoids; phenolic compounds; neuroprotection; Alzheimer's disease; oxidative stress; neuroinflammation; liposomes; nanotechnology; blood-brain barrier.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

1. Introduction

Neurodegenerative diseases are progressive disorders characterized by dysfunction and loss of neuronal populations in the central nervous system. Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis represent major examples [1–3]. Although these disorders differ in their clinical manifestations and pathological characteristics, they share several interconnected mechanisms, including oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, impaired proteostasis, synaptic dysfunction and neuronal apoptosis [2–5].

Alzheimer's disease is particularly important because progressive impairment of memory and cognition substantially affects patients, caregivers and healthcare systems. Amyloid- β accumulation, abnormal tau phosphorylation, synaptic dysfunction, oxidative injury, neuroinflammation and neuronal loss contribute to disease progression [1,3,25]. Because several pathological mechanisms operate simultaneously, the development of multi-target therapeutic approaches has become an important area of pharmaceutical research [4,5].

Natural products provide a large and chemically diverse source of potential therapeutic molecules. Plant polyphenols have attracted considerable interest because they can influence several biological pathways simultaneously [4,5,17]. Their reported activities include free-radical scavenging, modulation of inflammatory pathways, regulation of cellular antioxidant defenses, inhibition of apoptosis and effects on neuronal signaling [5,17,18]. Nevertheless, many polyphenols exhibit poor pharmacokinetic properties, limiting their clinical translation [17–19].

Seabuckthorn, scientifically known as *Hippophae rhamnoides* L., is a medicinal and edible plant distributed widely across Europe and Asia, including the Himalayan region [6–9]. It has a long history of traditional use and is increasingly investigated as a source of nutraceutical and pharmacologically active compounds [6,7]. Comprehensive phytochemical investigations have identified flavonoids, phenolic acids, lignans, tannins, terpenoids, steroids, volatile constituents, organic acids, carotenoids, fatty acids and other bioactive compounds in different plant organs [6–10].

Recent research has strengthened the scientific basis for considering seabuckthorn as a source of

neuroprotective compounds. Seabuckthorn leaf extracts have been reported to protect neuronal PC-12 cells against oxidative stress, whereas flavonoid-rich fractions have demonstrated neurotrophic effects in cultured neuronal models [11,12]. Experimental studies have also reported cognitive and neuroinflammatory benefits associated with seabuckthorn-derived preparations and constituents [13–15].

However, the gap between promising pharmacological activity and practical therapeutic application remains substantial. One of the major challenges is the limited bioavailability of many phenolic compounds and their restricted transport across the BBB [17–20]. Nanotechnology provides a potential solution by enabling encapsulation, protection from degradation, controlled release and, with appropriate formulation and targeting strategies, enhanced brain delivery [19–23].

The present review therefore integrates three interconnected areas: (i) the phytochemistry of seabuckthorn, (ii) the pharmacological mechanisms responsible for potential neuroprotection, and (iii) nanotechnology-based delivery strategies designed to improve the therapeutic potential of seabuckthorn bioactive compounds.

2. Botanical Profile of Seabuckthorn

Seabuckthorn belongs to the genus *Hippophae* and family Elaeagnaceae. *Hippophae rhamnoides* L. is the most extensively investigated species [6–9]. It is a deciduous, thorny shrub or small tree adapted to harsh environmental conditions. The plant can tolerate cold, drought and poor soils and is therefore important not only medicinally but also ecologically for soil stabilization and land restoration [7,8].

The berries are characteristically orange to yellow and possess a distinctive acidic flavor. Different plant parts, including fruits, seeds, leaves, bark and branches, have been investigated for nutritional and pharmacological applications [6–10]. Importantly, the phytochemical composition varies considerably according to plant part, cultivar, geographic origin, maturity, environmental conditions, extraction method and processing conditions [6–9]. This variability is a major consideration when developing standardized pharmaceutical or nutraceutical preparations.



Seabuckthorn Berry



Seabuckthorn Plant

3. Phytochemical Composition of Seabuckthorn

Seabuckthorn represents a chemically complex plant matrix. Its constituents can broadly be divided into phenolic and non-phenolic compounds [6–10].

3.1 Phenolic Acids

Phenolic acids identified in seabuckthorn include gallic acid, protocatechuic acid, p-coumaric acid, ferulic acid and related derivatives [7–10]. These compounds possess hydroxyl groups capable of participating in redox reactions and interacting with cellular signaling pathways.

The concentration of phenolic acids varies among plant parts. Leaves and branches may contain higher concentrations of certain phenolics than edible fruit tissues [7,9]. Gallic acid, p-coumaric acid, protocatechuic acid and ferulic acid have been reported among important phenolic acids in seabuckthorn [7,9].

3.2 Flavonoids

Flavonoids represent one of the most pharmacologically interesting groups in seabuckthorn. Important compounds include quercetin, kaempferol, isorhamnetin and their glycosides [6–12].

Quercetin and isorhamnetin are particularly important because of their antioxidant and anti-inflammatory properties [10,15]. Isorhamnetin has received considerable pharmacological attention because of its antioxidant, anti-inflammatory and potential neuroprotective activities [15].

3.3 Proanthocyanidins and Tannins

Seabuckthorn contains polymeric phenolics, including proanthocyanidins and tannin-related compounds, which may contribute to antioxidant and cellular protective effects [7–10].

3.4 Carotenoids

Seabuckthorn berries contain carotenoids that contribute to their characteristic orange-yellow color. β -Carotene, zeaxanthin and other carotenoids may contribute to antioxidant and membrane-protective activities [7–9].

3.5 Vitamins

The plant contains vitamin C, vitamin E-related compounds and other nutritional antioxidants [6–9]. These constituents may complement polyphenolic antioxidants within cellular redox systems.

3.6 Fatty Acids and Seed Oil

Seabuckthorn seed and fruit oils contain a range of fatty acids, including unsaturated fatty acids [6–9]. These lipids are nutritionally important and may contribute to membrane function and other biological activities.

3.7 Other Constituents

Other reported classes include triterpenoids, phytosterols, lignans, volatile compounds, organic acids, polysaccharides and minerals [6–10]. The complex chemical profile may help explain the diverse biological activities reported for seabuckthorn preparations.

4. Total Phenolics as a Pharmacological Resource

The term “total phenolics” refers to the collective phenolic fraction of an extract rather than a single

chemically defined compound. From a pharmaceutical perspective, this distinction is important because a total phenolic fraction may contain phenolic acids, flavonoids and their glycosides in different proportions [7–10].

The composition depends strongly on extraction solvent, extraction temperature, extraction time, plant part and geographical origin [7–9]. Conventional extraction using aqueous alcohols remains widely used, whereas ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction and enzyme-assisted extraction may improve recovery and reduce solvent consumption [26,27].

For pharmaceutical development, extraction should ideally be followed by chemical characterization using chromatographic and spectrometric methods. High-performance liquid chromatography coupled with diode-array detection or mass spectrometry can be used to establish a phenolic fingerprint [7,9,10]. LC-MS/MS can provide additional information concerning molecular identity and relative abundance.

Standardization of total phenolic content alone is insufficient for a reproducible therapeutic product. A robust quality-control strategy should include total phenolic content, total flavonoid content, marker-compound quantification, chromatographic fingerprinting, residual-solvent analysis, microbial quality, heavy-metal testing and stability assessment [6–10].

5. Neurodegeneration and Rationale for Natural Polyphenols

Neurodegenerative disorders are characterized by multiple interacting pathological pathways. Oxidative stress occurs when reactive oxygen species exceed endogenous antioxidant capacity [2–5]. Neurons are particularly vulnerable because of their high metabolic activity, high oxygen consumption, abundant membrane lipids and relatively limited regenerative capacity.

Oxidative stress can promote lipid peroxidation, protein oxidation, mitochondrial damage and DNA injury, which may activate inflammatory and apoptotic pathways [2–5]. Neuroinflammation is another major contributor, with activated microglia and astrocytes releasing cytokines and other inflammatory mediators that can exacerbate neuronal damage [3–5].

Mitochondrial dysfunction further increases oxidative stress and reduces ATP generation, while

dysfunctional mitochondria can promote apoptosis [2,3]. Protein misfolding and aggregation are particularly important in AD, where amyloid- β accumulation and abnormal tau phosphorylation are major pathological features [1,25].

The multi-target nature of these mechanisms makes polyphenols attractive candidates because individual compounds can affect several cellular pathways [4,5,17]. Nevertheless, claims of disease modification should be interpreted cautiously because much of the evidence remains preclinical.

6. Antioxidant Mechanisms of Seabuckthorn

The antioxidant activity of seabuckthorn is one of its most extensively investigated biological properties [6–10]. Phenolic compounds can directly interact with reactive oxygen species and may also stimulate endogenous antioxidant systems, including superoxide dismutase, catalase and glutathione peroxidase [5,10].

Seabuckthorn extracts have demonstrated antioxidant activity in chemical assays and cellular systems. In neuronal PC-12 cells, seabuckthorn leaf fractions reduced oxidative stress and apoptosis, supporting a potential neuroprotective role [11].

HPLC analysis of active seabuckthorn leaf fractions identified phenolic constituents including ellagic acid, gallic acid, isorhamnetin, kaempferol and quercetin [11]. The antioxidant mechanism may involve reduction of ROS, protection of membrane lipids and proteins, preservation of mitochondrial function and suppression of oxidative apoptosis [5,11].

However, antioxidant activity measured in chemical assays does not necessarily translate directly into therapeutic antioxidant effects in the human brain. Pharmacokinetic, cellular and in vivo studies are therefore essential.

7. Anti-inflammatory and Immunomodulatory Effects

Chronic neuroinflammation is closely associated with neurodegenerative disease progression [3–5]. Seabuckthorn flavonoids and extracts have demonstrated anti-inflammatory activity through modulation of inflammatory mediators and signaling pathways [6–10].

Reported pathways include NF- κ B and MAPK signaling. Seabuckthorn-derived compounds have been associated with reduced production of inflammatory mediators including nitric oxide and pro-inflammatory cytokines in experimental systems [7,10,15].

Isorhamnetin is of particular interest. Experimental evidence indicates that this flavonoid can modulate inflammatory signaling and oxidative stress [15]. These findings support the hypothesis that seabuckthorn phenolics may contribute to neuroprotection by reducing chronic inflammatory signaling.

8. Anti-apoptotic and Mitochondrial Protection

Neuronal apoptosis is a final common pathway in several neurodegenerative conditions. Oxidative stress and inflammatory signaling can activate mitochondrial permeability changes, caspases and pro-apoptotic proteins [2–5].

Experimental work with seabuckthorn leaf fractions in neuronal PC-12 cells demonstrated reduced early and late apoptotic cell populations together with improved cell viability and membrane integrity [11]. Potential mechanisms include reduction of oxidative stress, preservation of mitochondrial membrane integrity, improvement of endogenous antioxidant defenses, suppression of inflammatory signaling and reduction of caspase-mediated apoptosis [5,11].

9. Neurotrophic Effects of Seabuckthorn Flavonoids

Neuronal survival and plasticity depend on neurotrophic signaling. Brain-derived neurotrophic factor (BDNF), ERK, PI3K/Akt and CREB are important components of neuronal growth, differentiation and plasticity [12].

Experimental research has demonstrated that flavonoid-enriched seabuckthorn fractions can stimulate neurite outgrowth in PC12 cells, SH-SY5Y cells and primary cortical and hippocampal neurons [12]. These effects have been associated with PI3K/Akt and ERK signaling [12].

Isorhamnetin, quercetin and kaempferol have been identified as important flavonoids within investigated seabuckthorn fractions [12]. This observation is significant because neurodegenerative disease involves not only neuronal death but also loss of neuronal connectivity and synaptic function.

10. Cholinergic and Cognitive Effects

The cholinergic system plays an important role in learning and memory, and reduced cholinergic function is associated with Alzheimer's disease [1,25].

Experimental studies have indicated that seabuckthorn preparations may exert protective effects in cognitive-impairment models, potentially

involving acetylcholinesterase activity, oxidative stress and inflammatory pathways [13,14].

These findings suggest another possible mechanism through which seabuckthorn-derived compounds may influence cognitive function. However, available evidence should not be interpreted as demonstrating that seabuckthorn is equivalent to established cholinesterase inhibitors or approved AD therapies.

11. Seabuckthorn and Alzheimer's Disease

Alzheimer's disease is characterized by complex interactions among amyloid pathology, tau pathology, oxidative stress, neuroinflammation, synaptic dysfunction and neuronal loss [1,25].

Evidence directly linking seabuckthorn phenolics with AD remains less extensive than evidence for some other plant polyphenols. Nevertheless, several observations provide a mechanistic basis for further investigation [11–15].

Seabuckthorn-derived preparations have demonstrated antioxidant and anti-inflammatory effects, while specific flavonoids such as isorhamnetin have shown cognitive and neuroinflammatory benefits in experimental models [12–15].

Seabuckthorn polysaccharide preparations have also been investigated in AD-like mouse models, where improvements in cognition were associated with reduced oxidative stress and inflammation and modulation of pathways related to Nrf2 and TLR4/MyD88 signaling [14]. Importantly, polysaccharide evidence should not be directly attributed to phenolics.

A plausible neuroprotective framework for seabuckthorn phenolics is therefore:

Phenolic compounds → reduction of oxidative stress → modulation of Nrf2/antioxidant defenses → suppression of NF- κ B/MAPK-associated inflammation → reduced microglial activation → improved neuronal survival and synaptic function → potential cognitive benefit.

This model requires confirmation through targeted mechanistic studies.

12. Evidence from Experimental Models

Experimental evidence for seabuckthorn-associated neuroprotection has been generated using cellular and animal models [11–15].

12.1 Neuronal Cell Models

PC-12 and SH-SY5Y cells are frequently used to study neuronal oxidative injury, differentiation and neuroprotection. Seabuckthorn leaf extracts have

demonstrated protective effects against oxidative injury and apoptosis in PC-12 cells [11].

12.2 Primary Neuronal Cultures

Seabuckthorn flavonoid fractions have demonstrated neurite-promoting activity in primary cortical and hippocampal neurons [12].

12.3 Cognitive-Impairment Models

Animal models involving pharmacological or dietary induction of cognitive impairment have provided evidence of potential cognitive benefits from seabuckthorn-related preparations and constituents [13,14].

12.4 Alzheimer's Disease Models

Polysaccharide fractions of *H. rhamnoides* have demonstrated effects on cognition, oxidative stress and inflammatory responses in experimental AD models [14].

Collectively, these studies support further investigation but do not yet establish clinical efficacy in humans.

13. Major Limitations of Seabuckthorn Phenolics

Despite promising biological effects, several pharmaceutical limitations exist [17–20].

13.1 Poor Aqueous Solubility

Several flavonoids have limited water solubility, which can restrict dissolution and absorption [17,18].

13.2 Chemical Instability

Phenolics may undergo oxidation, photodegradation or degradation during processing and storage [17].

13.3 Extensive Metabolism

After oral administration, polyphenols may undergo intestinal and hepatic metabolism, resulting in metabolites that may differ substantially from the parent compounds [17–19].

13.4 Low Systemic Bioavailability

Only a fraction of orally administered polyphenols may reach systemic circulation in intact form [17–19].

13.5 Blood–Brain Barrier

Even compounds achieving systemic exposure may not achieve adequate concentrations in the brain. The BBB therefore represents a major obstacle to neurotherapeutic delivery [18–20].

13.6 Extract Variability

Different cultivars, plant parts, extraction procedures and storage conditions can produce markedly different phytochemical profiles [6–10]. These limitations provide a strong rationale for pharmaceutical nanotechnology.

14. Nanotechnology-Based Drug Delivery

Nanotechnology provides a range of approaches for improving delivery of natural bioactive compounds. Nanocarriers can potentially improve aqueous dispersibility, protect compounds from degradation, increase apparent solubility, modify pharmacokinetics, increase cellular uptake and provide controlled release [19–23].

Current literature on phytochemical delivery for AD highlights liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, exosomes and other engineered platforms as potential approaches for overcoming BBB-related delivery limitations [19–23].

Lipid-based systems are particularly attractive for poorly soluble natural products because their composition can be modified to improve drug loading, stability and interaction with biological membranes [19,20].

15. Liposomes as a Delivery System for Seabuckthorn Phenolics

Liposomes are spherical vesicular systems consisting primarily of phospholipid bilayers surrounding an aqueous core. Their major advantage is the ability to incorporate both hydrophilic and lipophilic molecules [20,21].

For phenolic-rich seabuckthorn fractions, liposomal formulation may protect phenolics from environmental degradation, improve aqueous dispersion, enhance absorption, alter pharmacokinetic behavior, facilitate cellular uptake and provide controlled release [20–23].

Recent literature examining polyphenol delivery to the CNS supports liposomes as promising carriers because polyphenol bioavailability is frequently limited by instability, metabolism and restricted BBB penetration [19–21].

16. Design Considerations for a Seabuckthorn Total-Phenolic Liposome

A rational formulation strategy should begin with authenticated and standardized *H. rhamnoides* material [6–10].

An optimized extraction procedure may be followed by concentration and fractionation of the phenolic-rich extract. HPLC-DAD and LC-MS/MS should then be used to characterize the phenolic profile [7,9].

Potential marker compounds may include gallic acid, ellagic acid, quercetin, kaempferol, isorhamnetin, ferulic acid and p-coumaric acid [7,9,10].

Liposomes can be prepared using methods such as thin-film hydration, ethanol injection, reverse-phase evaporation, high-pressure homogenization or microfluidic techniques [20,21].

Critical formulation variables include phospholipid concentration, cholesterol concentration, phenolic-to-lipid ratio, hydration conditions, particle size, surface characteristics and processing conditions.

17. Characterization of Liposomal Seabuckthorn Phenolics

A pharmaceutical-quality liposomal formulation should be characterized comprehensively.

Particle size and polydispersity: Dynamic light scattering can determine mean particle size and polydispersity index.

Zeta potential: Zeta potential provides information about surface charge and colloidal stability.

Encapsulation efficiency: Free and encapsulated phenolics should be separated and quantified to determine encapsulation efficiency.

Morphology: Transmission electron microscopy or cryo-TEM can provide information about vesicular morphology.

Chemical stability: HPLC or LC-MS should be used to determine whether the phenolic profile remains stable following formulation.

In vitro release: Release studies can determine whether the formulation provides immediate, sustained or controlled release.

Storage stability: Formulations should be evaluated under appropriate temperature and humidity conditions according to accepted pharmaceutical stability principles.

18. Brain-Targeted Liposomal Delivery

Conventional liposomes do not automatically guarantee BBB penetration. Brain targeting therefore requires rational formulation design [19–23].

Potential strategies include surface functionalization with ligands capable of interacting with BBB transport systems. Examples include transferrin, lactoferrin, receptor-targeting peptides, cell-penetrating peptides and other targeting ligands [19,22,23].

Recent AD nanomedicine literature describes receptor-mediated targeting and peptide-functionalized systems as potential approaches for enhancing BBB transport [19,22].

Intranasal administration represents another promising strategy because it may facilitate nose-to-

brain transport and reduce dependence on conventional systemic BBB crossing [18,20].

19. Other Nanocarrier Systems

19.1 Solid Lipid Nanoparticles

Solid lipid nanoparticles consist of solid lipids stabilized by surfactants. They can improve the stability and controlled delivery of lipophilic bioactives [19,21].

19.2 Nanostructured Lipid Carriers

Nanostructured lipid carriers combine solid and liquid lipids to create a less ordered lipid matrix that may improve loading capacity [19,21].

19.3 Polymeric Nanoparticles

Polymers such as PLGA can provide controlled release and protection from degradation [19,22].

19.4 Nanoemulsions

Nanoemulsions can improve the dispersibility of poorly water-soluble compounds and are particularly useful for lipophilic constituents [20,21].

19.5 Phytosomes

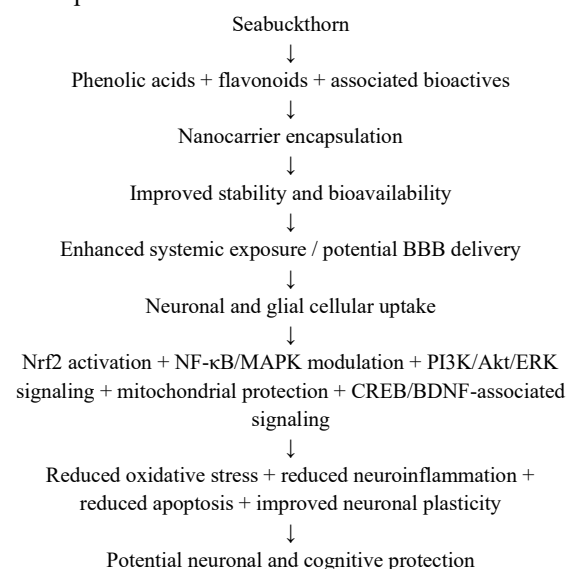
Phytosomes form complexes between phospholipids and plant constituents and can improve membrane interaction and bioavailability [20].

19.6 Exosomes and Biomimetic Systems

Extracellular vesicles and biomimetic nanocarriers are emerging systems for CNS delivery. However, manufacturing, characterization, loading consistency, reproducibility and regulatory standardization remain important challenges [19,22,23].

20. Proposed Mechanistic Model

A conceptual model for seabuckthorn phenolic neuroprotection can be described as:



This mechanistic model should be regarded as a research framework rather than proof of clinical efficacy.

21. Safety and Toxicological Considerations

Seabuckthorn has a long history of dietary and traditional use, and published reviews generally describe favorable safety profiles for commonly investigated preparations [6–10]. Nevertheless, safety cannot be assumed for concentrated extracts or novel nanocarriers.

Potential safety considerations include dose-dependent toxicity, extract-specific contaminants, heavy metals, pesticide residues, residual extraction solvents, batch-to-batch variability, nanoparticle-related toxicity, long-term accumulation, immunological responses, hepatic and renal effects and interactions with conventional medicines.

Future pharmaceutical development should therefore include acute, subacute and chronic toxicity studies, appropriate genotoxicity assessment, hematological and biochemical analyses, histopathology and pharmacokinetic evaluation.

For brain-targeted nanocarriers, additional studies should assess BBB integrity, microglial activation and long-term brain accumulation [19,22,23].

22. Challenges in Translation

Several barriers must be addressed before seabuckthorn phenolic nanomedicines can progress toward clinical development.

These include lack of standardized extracts, insufficient pharmacokinetic information, limited human studies, complexity of total phenolic fractions, uncertainty regarding the dominant active constituents, nanocarrier scalability, regulatory requirements and limited long-term safety data [6,19–23].

Standardization is particularly important because variations in plant source, extraction procedure and processing can substantially influence phytochemical composition and biological activity [6–10].

23. Future Perspectives

Future research should move from simple antioxidant screening toward standardized, mechanism-driven pharmaceutical development.

First, geographically authenticated *H. rhamnoides* material should be subjected to standardized extraction. Second, the total phenolic fraction should be chemically fingerprinted using HPLC-DAD and

LC-MS/MS. Third, individual marker compounds should be quantified [7,9].

The next stage should involve development and optimization of a liposomal formulation. Formulation variables should be optimized using a quality-by-design approach.

The optimized formulation should undergo physicochemical characterization, in vitro antioxidant evaluation, cellular neuroprotection studies, neuroinflammatory assays, mitochondrial-function studies, BBB permeability studies, cellular uptake studies, pharmacokinetic analysis, brain-distribution studies, animal efficacy studies and toxicological evaluation [19–23].

An especially important research direction is comparison of:

Free total phenolics vs. conventional liposomes vs. brain-targeted liposomes.

Such a comparative design would establish whether nanoencapsulation provides a meaningful pharmacological advantage.

24. Research Gaps

Important research gaps include:

1. Lack of standardized seabuckthorn phenolic preparations [6–10].
2. Limited direct evidence in validated AD models [14].
3. Insufficient information on brain pharmacokinetics [18–20].
4. Limited BBB permeability studies.
5. Inadequate comparison between individual phenolics and total phenolic fractions.
6. Limited information regarding phenolic–lipid interactions during liposome formulation.
7. Lack of long-term safety data for brain-targeted formulations.
8. Limited clinical evidence.
9. Lack of standardized quality markers for neuroprotective preparations.
10. Limited information on pharmacokinetic metabolites.
11. Need for mechanistic studies involving microglia, astrocytes and neurons simultaneously.
12. Need for scalable manufacturing processes [19–23].

25. Proposed Experimental Framework for Future Development

A translational research program may be divided into five stages.

Stage I: Plant material and extraction.

Authenticated *H. rhamnoides* material should be collected and processed under controlled conditions. Total phenolics should be extracted using an optimized extraction technique.

Stage II: Phytochemical characterization. Total phenolic and flavonoid contents should be determined, followed by HPLC-DAD and LC-MS/MS characterization [7,9].

Stage III: Liposomal formulation. The total phenolic fraction should be encapsulated in phospholipid-based liposomes. Formulation optimization should target particle size, PDI, zeta potential, encapsulation efficiency and stability [20,21].

Stage IV: Neuroprotective evaluation. Free and liposomal preparations should be compared using neuronal cell models under oxidative and inflammatory stress. Parameters may include ROS, MDA, GSH, SOD, mitochondrial membrane potential, inflammatory cytokines and apoptosis markers.

Stage V: In vivo evaluation. The optimized formulation can subsequently be investigated in appropriate cognitive-impairment or AD models. Behavioral assessment should be complemented by biochemical, histopathological and molecular investigations.

26. Conclusion

Seabuckthorn (*Hippophae rhamnoides* L.) represents a promising medicinal and nutraceutical resource containing a diverse spectrum of phenolic and non-phenolic bioactive compounds [6–10]. Phenolic acids and flavonoids, particularly quercetin, kaempferol and isorhamnetin, have attracted significant attention because of their antioxidant, anti-inflammatory and neurotrophic properties [10–12,15].

Experimental evidence demonstrates that seabuckthorn extracts and selected constituents can protect neuronal cells against oxidative injury, influence inflammatory pathways and support neuronal differentiation and cognitive function in experimental models [11–15]. Nevertheless, the current evidence does not justify considering seabuckthorn phenolics as clinically established treatments for Alzheimer's disease. The majority of evidence remains preclinical, and significant gaps exist concerning standardized preparations, pharmacokinetics, BBB penetration, long-term safety and clinical efficacy.

Nanotechnology offers a potentially important solution to some of these limitations [19–23]. Liposomes are particularly attractive because they can encapsulate diverse phytochemicals, improve stability and modify delivery characteristics [20,21]. Current literature supports the broader concept of lipid-based nanodelivery for polyphenols and neurodegenerative disease, including approaches aimed at improving BBB transport [19–23].

Therefore, the development of a standardized **seabuckthorn total-phenolic liposomal formulation** represents a scientifically rational research direction. Future investigations should integrate advanced extraction, comprehensive phytochemical characterization, quality-by-design formulation, BBB models, pharmacokinetic studies, mechanistic neuroprotection assays and appropriate animal models. Such an integrated strategy may facilitate the transition of seabuckthorn from a traditional medicinal and nutraceutical resource toward a scientifically standardized neuroprotective formulation.

References

1. Knopman DS, Amieva H, Petersen RC, Ch  telat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primers. 2021;7(1):33. doi:10.1038/s41572-021-00269-4.
2. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. J Alzheimers Dis. 2018;62(3):1403-1416. doi:10.3233/JAD-170585.
3. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405. doi:10.1016/S1474-4422(15)70016-1.
4. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep. 2015;67(2):195-203. doi:10.1016/j.pharep.2014.09.004.
5. Vauzour D. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. Oxid Med Cell Longev. 2012;2012:914273. doi:10.1155/2012/914273.
6. Liu M, Yu T, Nurlan U, Wu Z, Zhao J. Ethnopharmacology, phytochemistry, and

- pharmacology of sea buckthorn (*Hippophae rhamnoides* L.): a comprehensive review. *Front Pharmacol.* 2026;17:1759697. doi:10.3389/fphar.2026.1759697.
7. Olas B. The bioactive components as well as the nutritional and health effects of sea buckthorn. *Antioxidants* (Basel). 2022;11(6):1089.
 8. Wang Z, Zhao F, Wei P, Chai X, Hou G, Meng Q. Phytochemistry, health benefits, and food applications of sea buckthorn (*Hippophae rhamnoides* L.): a comprehensive review. *Front Nutr.* 2022;9:1036295. doi:10.3389/fnut.2022.1036295.
 9. Ma QG, He NX, Zhu MN, Sang ZP, Shu JC, Wang QY, et al. *Hippophae rhamnoides* L.: a comprehensive review on the botany, traditional uses, phytonutrients, health benefits, quality markers, and applications. *J Agric Food Chem.* 2023;71(12):4769-4788. doi:10.1021/acs.jafc.2c06916.
 10. Singh et al. Phenolic compounds in sea buckthorn (*Hippophae rhamnoides* L.) and their health-promoting activities: a review. *Int J Food Sci Technol.* 2024;59(9):6642-6658.
 11. Cho C, Jang H, Lee M, Kang H, Heo HJ, Kim DO. Sea buckthorn (*Hippophae rhamnoides* L.) leaf extracts protect neuronal PC-12 cells from oxidative stress. *J Microbiol Biotechnol.* 2017;27(7):1257-1265. doi:10.4014/jmb.1704.04033.
 12. Xia CX, Gao AX, Dong TT-X, Tsim KW-K. Flavonoids from seabuckthorn (*Hippophae rhamnoides* L.) mimic neurotrophic functions in inducing neurite outgrowth in cultured neurons: signaling via PI3K/Akt and ERK pathways. *Phytomedicine.* 2023;115:154832. doi:10.1016/j.phymed.2023.154832.
 13. Liu S, Xiao P, Kuang Y, Hao J, Huang T, Liu E. Flavonoids from sea buckthorn: a review on phytochemistry, pharmacokinetics and role in metabolic diseases. *J Food Biochem.* 2021;45(5):e13724. doi:10.1111/jfbc.13724.
 14. Polysaccharides from sea buckthorn (*Hippophae rhamnoides* L.) berries ameliorate cognitive dysfunction in AD mice induced by D-gal and AlCl₃ by suppressing oxidative stress and inflammation. 2023.
 15. Gong G, Guan YY, Zhang ZL, Rahman K, Wang SJ, Zhou S, et al. Isorhamnetin: a review of pharmacological effects. *Biomed Pharmacother.* 2020;128:110301. doi:10.1016/j.biopha.2020.110301.
 16. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.* 2009;2(5):270-278. doi:10.4161/oxim.2.5.9498.
 17. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr.* 2005;81(1 Suppl):230S-242S. doi:10.1093/ajcn/81.1.230S.
 18. D'Archivio M, Filesi C, Vari R, Scazzocchio B, Masella R. Bioavailability of the polyphenols: status and controversies. *Int J Mol Sci.* 2010;11(4):1321-1342. doi:10.3390/ijms11041321.
 19. Paramanick D, Singh VD, Singh VK. Neuroprotective effect of phytoconstituents via nanotechnology for treatment of Alzheimer diseases. *J Control Release.* 2022;351:638-655. doi:10.1016/j.jconrel.2022.09.058.
 20. Khot KB, Gopan G, Bandiwadekar A, Jose J. Current advancements related to phytobioactive compounds based liposomal delivery for neurodegenerative diseases. *Ageing Res Rev.* 2023;83:101806. doi:10.1016/j.arr.2022.101806.
 21. Kaluza M, Ksiazek-Winiarek D, Szpakowski P, Czapkowska J, Fijalkowska J, Glabinski A. Polyphenols in the central nervous system: cellular effects and liposomal delivery approaches. *Int J Mol Sci.* 2025;26(13):6477. doi:10.3390/ijms26136477.
 22. Chen L, Guan Y, Wang S, Han X, Guo F, Wang Y. Engineered nanoplateforms for brain-targeted co-delivery of

phytochemicals in Alzheimer's disease: rational design, blood-brain barrier penetration, and multi-target therapeutic synergy. *Neurotherapeutics*. 2025;22(6):e00722. doi:10.1016/j.neurot.2025.e00722.

23. Yuan X, Tang Q, Wang T. Nanotechnology-based targeted delivery strategies for the treatment of Alzheimer's disease. *Nanoscale Adv*. 2026;8(7):2195-2214. doi:10.1039/D5NA00993F.
