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REVIEW

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Neuroprotective compounds from marine invertebrates

Bachtiar Rivai[1,4] and Abd. Kakhar Umar[2,3,4*]

Abstract

Background Neuroinflammation is a key pathological feature of a wide variety of neurological disorders, including Parkinson's, multiple sclerosis, Alzheimer's, and Huntington's disease. While current treatments for these disorders are primarily symptomatic, there is a growing interest in developing new therapeutics that target the underlying neuroinflammatory processes.

Main body Marine invertebrates, such as coral, sea urchins, starfish, sponges, and sea cucumbers, have been found to contain a wide variety of biologically active compounds that have demonstrated potential therapeutic properties. These compounds are known to target various key proteins and pathways in neuroinflammation, including 6-hydroxydopamine (OHDH), caspase-3 and caspase-9, p-Akt, p-ERK, p-P38, acetylcholinesterase (AChE), amyloid-β (Aβ), HSF-1, α-synuclein, cellular prion protein, advanced glycation end products (AGEs), paraquat (PQ), and mitochondria DJ-1.

Short conclusion This review focuses on the current state of research on the neuroprotective effects of compounds found in marine invertebrates and the potential therapeutic implications of these findings for treating neuroinflammatory disorders. We also discussed the challenges and limitations of using marine-based compounds as therapeutics, such as sourcing and sustainability concerns, and the need for more preclinical and clinical studies to establish their efficacy and safety.

Keywords Immune cell activation, Protein plaque, Neuron apoptosis, Neuronal injury, Marine invertebrate, α-synuclein

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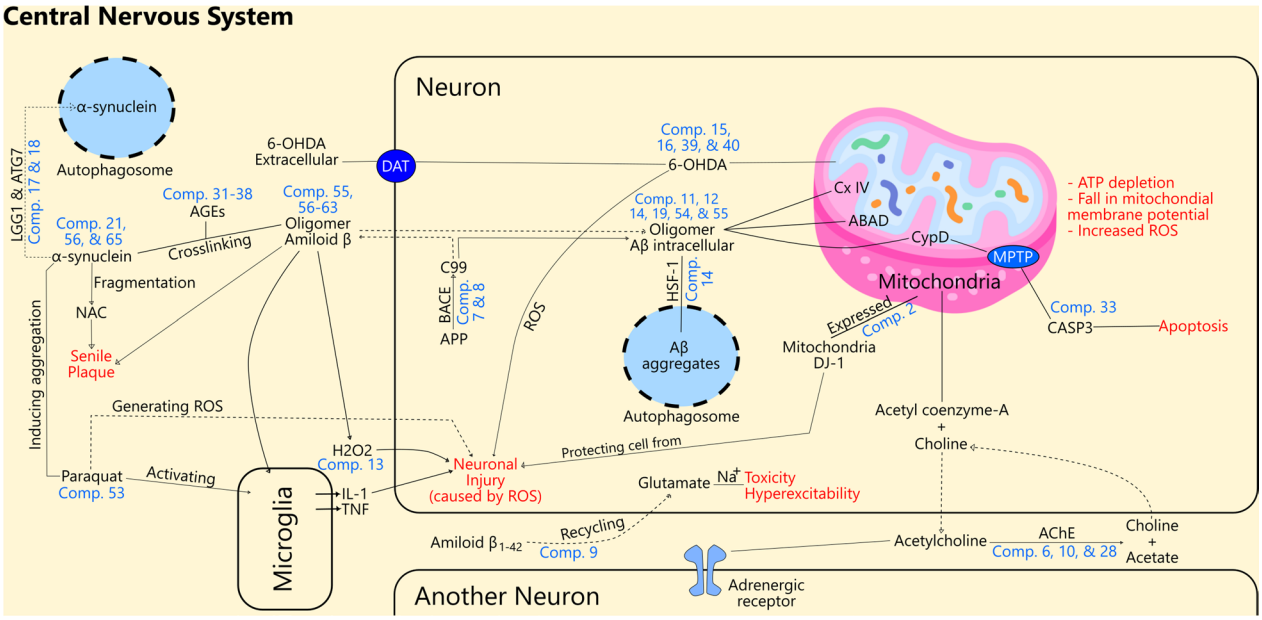
Graphical abstract



1 Background

The process of neuroinflammation is intricate, encompassing the stimulation of immune cells and the discharge of inflammatory substances within the nervous system [1]. This process can destroy neurons and induce the progression of neurodegenerative diseases, such as Parkinson, multiple sclerosis, Alzheimer, and Huntington. Recently, diseases-related neuroinflammatory has become a serious problem. More than 50 million people in the world have been affected, and predicted will increase to triple in 2050 [2]. Studying neuroinflammation presents significant challenges, as it proves not only difficult to study in humans but also presents striking differences when modeled in animal systems. However, ample evidence suggests that neuroinflammation may contribute to various brain disorders, such as Alzheimer's disease, and this area of investigation has been significantly overlooked and inadequately supported, resulting in a shortage of research in the field [3]. While current treatments for these diseases are primarily symptomatic, there is a growing interest in developing therapies that target the underlying neuroinflammatory processes.

Marine drugs have garnered attention as a promising source for developing drugs targeting neuroinflammation [4]. Scientists are exploring marine organisms as a potential source of drugs for neuroinflammatory diseases because these organisms have evolved unique defense mechanisms against pathogens and predators in their aquatic environment. As a result, they produce a wide range of bioactive compounds with potential therapeutic properties, including anti-inflammatory, antioxidant, and neuroprotective effects [5]. Certain marine invertebrate compounds have been found to target essential proteins and pathways in neuroinflammatory therapy, including prions, α-synuclein, and amyloid β, which are known to form plaques and directly activate microglia, contributing to chronic inflammation. According to reports, Lamellosterol C from Lamellodysidea cf. Chlorea exhibited a 3 times more potent anti-prion effect than Guanabenz [6]. Sycosterol A has been found to exert twice the inhibitory effect on α-synuclein compared to Epigallocatechin-3-gallate, a known potent neuroprotective agent [7, 8]. 11-Dehydrosinulariolide regulates several protective pathways by inducing DJ-1 expression and activating Akt/PI3K, Nrf2/HO-1, and p-CREB [9]. In addition to their high medicinal value, cultivating marine invertebrates has economic significance and can be utilized as a food source and daily health supplements.

Different types of compounds and marine invertebrates have distinct mechanisms of action in addressing neuroinflammation. By understanding this topic, researchers can identify the most promising combinations of compounds and marine invertebrates for potent neuroinflammatory therapy. This review focuses on compounds successfully isolated from marine invertebrates as potent anti-neuroinflammatory and anti-neurodegenerative

agents. The mechanisms of action of these compounds are discussed based on the pathophysiology and key pathways of neuroinflammation, providing insight into the development of new natural-based drugs.

2 Main body

2.1 Methodology

To conduct this review, Scopus, PubMed, and Google Scholar were utilized as the primary sources of literature. The search was performed using specific keywords, including 'Marine invertebrates neuroprotection,' 'Sea urchins neuroprotective compounds,' 'Starfish anti-inflammatory properties,' 'Sea cucumbers neurodegenerative disorders,' 'Neuroinflammation marine-derived compounds,' 'Neuroprotection natural compounds,' 'Marine invertebrates Alzheimer's disease,' 'Sea urchins Parkinson's disease,' 'Starfish Huntington's disease,' 'Sea cucumbers neuroinflammation,' 'Neurodegenerative disorders marine-derived compounds.' The first search yielded 171 articles, with 109 research articles, 56 review papers, and 6 book chapters. The initial number of articles selected was only articles labeled research articles by the database ($n=109$). Furthermore, a sum of 28 articles that consisted of research on the efficacy of marine invertebrate isolates as either anti-neuroinflammation or neuroprotection were included. The excluded articles were in the form of reviews, were written non-English, and solely focused on extracts or fractions activity studies. Studies that lack clear explanations and findings regarding the mechanism pathways of the utilized substance were also excluded. A flowchart of the methodology can be seen in Fig. 1.

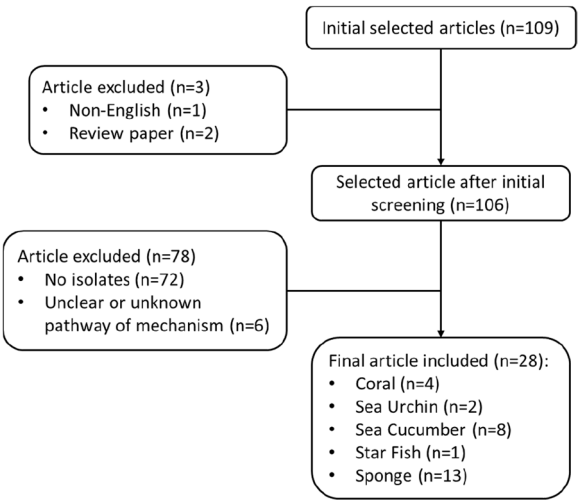


Fig. 1 Flowchart of the methodology

2.2 Pathology of neuroinflammation

2.2.1 Immune cell activation

The activation of immune cells and subsequent release of inflammatory mediators in the central nervous system (CNS) is a multifaceted pathological process known as neuroinflammation [10, 11]. In this process, immune cell activation plays a pivotal role [12]. Upon exposure of the CNS to external stimuli such as injuries or infections, immune cells, such as microglia and astrocytes, get activated and secrete proinflammatory cytokines, chemokines, and reactive oxygen species (ROS) [13, 14]. Microglia are the primary immune cells in the CNS, and they become activated in response to inflammatory stimuli such as proinflammatory cytokines or damage-associated molecular patterns (DAMPs) [15, 16]. Microglia activation is characterized by morphological changes, including an increase in cell size and the development of processes [17]. Similarly, astrocytes, another type of glial cell, become activated in response to inflammatory stimuli and release cytokines, chemokines, and other inflammatory mediators, contributing to the neuroinflammatory response [18, 19].

Activated microglia and astrocytes release proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) [20, 21]. These cytokines can activate other immune cells in the CNS, such as monocytes and neutrophils, which can infiltrate the CNS from the bloodstream [22, 23]. These cytokines can activate neuronal receptors, such as NMDA receptors, and increase calcium influx into the neurons [24, 25]. This can lead to excitotoxicity, a process in which excessive calcium levels can cause damage and even death of neurons [26]. In addition to excitotoxicity, neuroinflammation can cause oxidative stress, leading to neuronal damage [27, 28]. Activated immune cells, particularly microglia, can generate reactive oxygen species (ROS), which contribute to the damage of neuronal and glial cells [29].

If neuroinflammation is left untreated or persists for a prolonged duration, it can cause chronic neurodegeneration, marked by progressive neuronal damage and dysfunction [30, 31]. This can pave the way for various neurodegenerative ailments like Alzheimer's disease, Parkinson's disease, and multiple sclerosis [32]. Therefore, it is critical to comprehend the impact of immune cell activation in neuroinflammation pathology to develop effective therapies for these disorders [33, 34]. One of the proposed therapeutic strategies for neuroinflammatory diseases is inhibiting immune cell activation, particularly that of microglia and astrocytes. Specific inhibitors of these activation pathways [35] or nonsteroidal anti-inflammatory drugs (NSAIDs) [36] can be used to achieve this goal.

Neuroinflammation can also lead to the activation of apoptosis, a programmed cell death pathway [37]. Activated immune cells can release pro-apoptotic factors, such as caspases and Bcl-2 family proteins, which can activate apoptotic pathways in neurons [38, 39]. This can lead to the death of neurons and contribute to the progression of neurodegenerative diseases [40].

2.2.2 Blood–brain barrier dysfunction

The blood–brain barrier (BBB) is a highly selective and tightly regulated barrier that separates the central nervous system (CNS) from the peripheral circulation [41, 42]. The BBB is formed by specialized endothelial cells that line the cerebral microvasculature and pericytes, astrocytes, and extracellular matrix components [43, 44]. The BBB plays a crucial role in maintaining the homeostasis of the CNS by limiting the entry of potentially harmful substances into the brain, including immune cells [45]. The BBB can become dysfunctional and permeable in neuroinflammation, allowing immune cells and inflammatory mediators to infiltrate the CNS [46]. This can occur through several mechanisms. One mechanism is the activation of endothelial cells that form the BBB [47]. The expression of adhesion molecules by endothelial cells is a consequence of activation by inflammatory mediators, including cytokines and chemokines. Such activation enables immune cells to attach and traverse the BBB [48]. Additionally, proinflammatory cytokines can cause changes in the cytoskeleton of endothelial cells, resulting in the formation of gaps between the cells that allow molecules and cells to pass through [49, 50].

Another mechanism is the disruption of tight junctions between endothelial cells [51]. Tight junctions are specialized structures that seal the gaps between endothelial cells and prevent the diffusion of molecules and cells across the BBB [42]. In neuroinflammation, inflammatory mediators can disrupt tight junctions, leading to increased permeability of the BBB [52]. This disruption can also be caused by oxidative stress, which damages the cytoskeleton and leads to the detachment of tight junctions from the endothelial cells [53]. Finally, immune cells themselves can contribute to the disruption of the BBB [45]. When activated, immune cells, like microglia and astrocytes, secrete inflammatory mediators that can harm the endothelial cells comprising the BBB [48]. Additionally, immune cells can physically cross the BBB and infiltrate the CNS, exacerbating the neuroinflammatory response [54, 55].

The dysfunction of the BBB in neuroinflammation has important pathological consequences [47, 56]. The infiltration of immune cells and inflammatory mediators into the CNS can lead to chronic neuroinflammation and neurodegeneration, as seen in diseases such as Alzheimer's and Parkinson's [10, 57]. Additionally, the increased permeability of the BBB can allow the entry of pathogens into the CNS, contributing to the development of infections such as meningitis [58].

2.2.3 Neuronal damage

Another mechanism through which neuroinflammation can cause neuronal damage is through the release of glutamate [59, 60]. Glutamate is a neurotransmitter that plays a key role in excitatory signaling in the CNS. However, excessive levels of glutamate can cause excitotoxicity, leading to neuronal damage and death [60]. In neuroinflammation, immune cells can release glutamate and contribute to the excitotoxicity that damages neurons [61].

2.2.4 Neurodegeneration

Prolonged or severe neuroinflammation may bring about chronic neurodegeneration through several means. Microglia, the CNS's resident immune cells, play a significant role in this process [10, 11]. Upon exposure to inflammatory agents, microglia become activated and release various harmful substances, including reactive oxygen species, nitric oxide, and proinflammatory cytokines, which can directly harm neurons, leading to their demise [20, 21]. Additionally, chronic neuroinflammation can promote the accumulation of misfolded proteins in neurons and glia, a characteristic feature of several neurodegenerative diseases. Misfolded proteins can trigger the innate immune system's activation, leading to chronic inflammation and further protein misfolding and aggregation [62], generating a self-sustaining loop of neuroinflammation and neurodegeneration [63].

In addition, chronic neuroinflammation can impair the brain's ability to clear toxic substances such as amyloid-β in Alzheimer's disease and α-synuclein in Parkinson's disease, leading to their accumulation in the brain and further worsening neuroinflammation, neuronal dysfunction, and death [64, 65]. Moreover, chronic neuroinflammation can interfere with neurotrophic support, which is vital for neuronal survival and function. Neurotrophic factors like brain-derived neurotrophic factor (BDNF) play a crucial role in promoting neuronal growth, differentiation, and survival [66, 67]. However, chronic neuroinflammation can reduce the production and release of neurotrophic factors, leading to neuronal dysfunction and death [68].

In summary, chronic neuroinflammation can contribute to neurodegeneration by activating microglia, accumulating misfolded proteins, impairing clearance of toxic substances, and disrupting neurotrophic support. Gaining knowledge about these mechanisms can offer valuable

information in devising therapeutic interventions for the management of neurodegenerative disorders.

2.3 Marine invertebrate

Marine invertebrates are diverse animals that lack a backbone and inhabit the ocean environment [69]. They include many organisms, from simple forms such as sponges, jellyfish, and sea anemones, to more complex organisms such as crustaceans, molluscs, and echinoderms. Marine invertebrates are found in all ocean habitats, from shallow coral reefs to the deep sea floor, and they play important ecological roles in marine ecosystems [70]. For example, some species of marine invertebrates, such as sea urchins and certain molluscs, are important herbivores, while others, such as crustaceans and cephalopods, are important predators [71]. Marine invertebrates have developed a variety of adaptations that allow them to survive and thrive in the ocean environment [72]. For example, some marine invertebrates have evolved unique structures, such as stinging cells or hard shells for protection, while others have developed specialized appendages for locomotion or feeding.

Cultivating and conserving marine invertebrates can be challenging, but several strategies can help promote their growth and survival [73]. Different marine invertebrates have different requirements for survival, so it is important to research the species' specific needs [74]. Factors such as water temperature, salinity, and lighting can all affect their health and growth. To thrive, marine invertebrates need a suitable habitat that mimics their natural environment [73]. This may include a specific type of substrate, such as sand or rocks, or the presence of other organisms that they interact with in the wild. Water quality is also critical for the health of marine invertebrates [75]. Regular testing and maintenance of water parameters such as pH, temperature, and nutrient levels can help ensure a stable environment for your organisms. Many marine invertebrates require specific types of food to thrive [76]. For example, some corals require plankton or other small organisms, while certain sea urchins feed on algae. It is important to research the dietary requirements of the organisms and provide appropriate food sources.

Many marine invertebrates can be cultivated successfully, depending on the location and environmental conditions [77]. Coral reefs are found in many tropical and subtropical regions worldwide, and many different species of coral can be successfully cultivated in aquariums or the wild [78]. Some popular species for cultivation include brain coral, mushroom coral, and stony coral. Oysters are grown commercially in many coastal regions and are an important food source [79, 80]. They are typically grown in mesh bags or cages suspended in the water and are harvested when they reach maturity [81]. Sea urchins are commonly cultivated in aquaculture systems in many regions, particularly in Japan, where they are an important food source [82]. They require specific environmental conditions, including cool water temperatures and high-quality seawater. Clams are another important food source that can be cultivated in many coastal regions [83–85]. They require specific conditions for growth, including a sandy or muddy substrate and high-quality seawater. Lobsters are commercially harvested in many regions, particularly North America and Europe [86, 87]. They require specific environmental conditions, including cool water temperatures and rocky substrate for shelter [88]. Sea cucumbers are cultivated commercially in many regions, particularly in Asia, where they are an important food source [89, 90]. They require specific environmental conditions, including a sandy substrate and high-quality seawater. The specific types of marine invertebrates that can be cultivated successfully depend on the environmental conditions and available resources in a particular region. With proper research and management practices, many different types of marine invertebrates can be grown successfully and sustainably.

Marine invertebrates are important sources of food, medicine, and other resources for humans. For example, many molluscs and crustaceans are commercially harvested for food, while some marine invertebrates, such as sponges and corals, contain compounds with potential medicinal properties. Overall, marine invertebrates are a fascinating and important group of organisms that contribute to the diversity and functioning of marine ecosystems and have significant value to human societies.

2.4 Therapeutic targets of marine invertebrate bioactive compounds

Marine invertebrates have become a fascinating source for discovering bioactive compounds with therapeutic potential. These organisms have evolved a wide range of mechanisms to protect themselves against predators and to interact with their environment. Scientists have discovered that some of these compounds can target specific molecular pathways involved in different diseases, including neuroinflammation and neurodegenerative disorders. Table 1 provides an overview of the therapeutic activities of marine invertebrate bioactive compounds, highlighting their potential as a source of new treatments.

Marine invertebrate bioactive compounds have shown potential therapeutic activities in treating neurological disorders. Table 1 summarizes the therapeutic activities of these compounds, which target essential proteins and pathways involved in neuroinflammatory and neurodegenerative processes. However, a better understanding of the underlying mechanisms is needed to harness

Table 1 Therapeutic activities of marine invertebrate bioactive compounds

No	Species	Compound	Mechanism	Refs
Coral				
1	*Pseudopterogorgia elisabethae*	Pseudopterosin A (**1**)	Modulate synaptic function during oxidative stress	[91]
2	*Sinularia flexibilis*	11-Dehydrosinulariolide (**2**)	Increase the expression of mitochondria DJ-1	[92]
3	*Sinularia polydactyla*	Nebrosteroid A (**3**) 7β-acetoxy-cholest-5-en-3β,19-diol (**4**)	Neuroprotective activity on neuron-like SH-SY5Y cells	[93]
4	*Sarcophyton boettgeri*	Sarboettgerin A-E (**5–9**)	LPS-induced NO release in BV-2 microglial cells	[94]
Sea Urchin				
5	*Scaphechinus mirabilis*	Echinochrome A (**10**)	Reduce acetylcholinesterase (AChE)	[95]
6	*Urechis unicinctus*	Hecogenin (**11**) Cholest-4-en-3-one (**12**)	Inhibit the human β-site amyloid cleaving enzyme (BACE1)	[96]
Sea Cucumber				
7	*Cucumaria frondosa*	Eicosapentaenoic acid (**13**)	Neuroprotective on oxidative stress	[97]
8	*Acaudina molpadioides*	Sea Cucumber cerebrosides (**14**)	Neuroprotective on oxidative stress and inhibit Amyloid-β accumulation	[98–100]
9	*Cucumaria frondosa*	Frondoside A (**15**)	Reduce α-synuclein aggregates and 6-OHDA-induced DAergic neurodegeneration	[101]
10	*Panax notoginseng*	Ginsenoside Rg3 (**16**)	Reduce 6-OHDA-induced DAergic neurodegeneration	
11	*Holothuria scabra*	HSEA-P1 and HSEA-P2 (**17–18**)	Reduce α-synuclein aggregates	[102]
12	*Holothuria scabra*	2-Butoxytetrahydrofuran (**19**)	Inhibit Amyloid-β accumulation	[103]
Star fish				
13	*Asterias amurensis*	Star Fish Cerebrosides (SFC) (**20**)	Neuroprotective on oxidative stress	[100]
Sponge				
14	*Thorectandra sp*	Asterubine (**21**)	Binding activity to α-synuclein	[104]
15	*Spongionella sp*	Gracilin A (**22**) Gracilin H (**23**) Gracilin J (**24**) Gracilin K (**25**) Gracilin L (**26**) Tetrahydroaplysulphurin-1 (**27**)	Neuroprotective on oxidative stress	[105]
16	*Xestospongia testudinaria*	Mutafuran H (**28**) Xestospongic acid (**29**) 29-hydroperoxystigmasta-5,24(28)-dien-3β-ol (**30**)	Reduce acetylcholinesterase (AChE)	[106]
17	*Siliquariaspongia mirabilis* *Stelletta clavosa*	Mirabamides A-H (**31–38**)	Inhibit AGEs formation	[107]
18	*Inflatella sp*	(22E)-24-nor-cholesta-5,22-diene-3β,7β-diol (**39**)	Reduce 6-hydroxydopamine (OHDA) in the cell model of Parkinson's disease	[108]
19	*Jaspis stellifera*	Stellettin B (**40**)	Reduce 6-hydroxydopamine (OHDA)	[109]
20	*Narrabeena nigra*	Narrabeenamine B (**41**) 5,6-Dibromo-7-methoxykynuramine (**42**) 7-bromoquinolin-4(1H)-one (**43**) 5,6-dibromo-N,N-dimethyltryptamine (**44**) 5,6-dibromotryptamine (**45**) 6-bromo-N-methyltryptamine (**46**) 3-bromo-4-methoxytyramine (**47**) 5,6-dibromo-N-methyltryptamine (**48**) 6-bromotryptamine (**49**)	Neuroprotective on oxidative stress	[110]

Table 1 (continued)

No	Species	Compound	Mechanism	Refs
21	*Penares sp*	3β-hydroxy-7β,8β-epoxy-5α-lanost-24-en-30,9α-olide (**50**)	Inhibit Paraquat (PQ) toxicity	[111]
		29-nor-penasterone (**51**)		
		Penasterone (**52**)		
		Acetylpenasterol (**53**)		
22	*Acanthostrongylophora ingens*	Acanthocyclamine A (**54**)	Inhibit Amyloid β	[112]
23	*Fascaplysinopsis sp*	9-methylfascaplysin (**55**)	Inhibit Amyloid β	[113]
24	*Lamellodysidea cf. chlorea*	Lamellosterol A (**56**)	Inhibit prion and α-synuclein	[6]
		Lamellosterol B (**57**)	Inhibit prion	
		Lamellosterol C (**58**)	Inhibit prion	
225	*Polycarpa procera*	Procerolide A-D (**59–62**)	Inhibit prion	[114]
		Procerone A-B (**63–64**)		
26	*Sycozoa cerebriformis*	Sycosterol A (**65**)	Inhibit α-synuclein	[8]

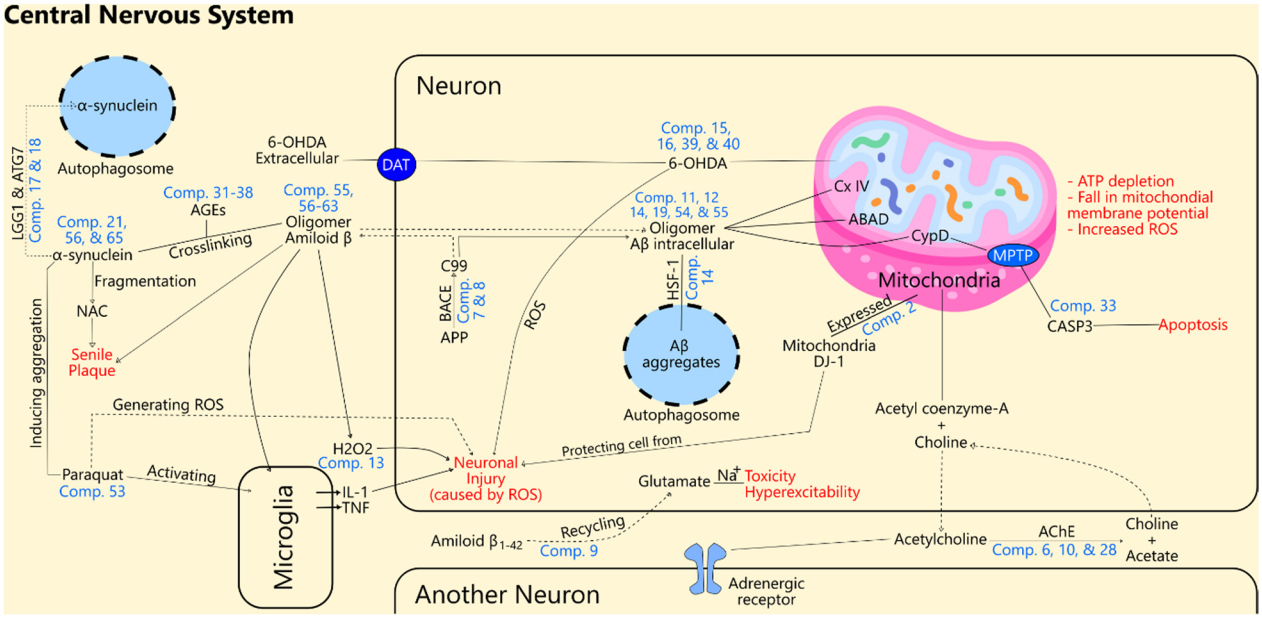


Fig. 2 Anti-neuroinflammation and anti-neurodegenerative mechanism of marine invertebrate compounds. Note: blue text labeled as 'Comp. followed by number' represents the compound responsible for the mechanism. Meanwhile, red text indicates the adverse effects associated with neurological disorders

their potential as natural drug candidates fully. Figure 2 provides an overview of the anti-neuroinflammatory and anti-neurodegenerative mechanisms of these marine invertebrate compounds, highlighting their potential as a source for developing new drugs to combat neurological disorders.

2.4.1 Oxidative stress

Oxidative stress is a condition that arises when the production of reactive oxygen species (ROS) exceeds the cell's capacity to detoxify them [115]. This can harm various parts of cells, such as proteins, lipids, and DNA, causing cells to malfunction or die [116, 117]. Oxidative stress can be triggered by hydrogen peroxide (H_2O_2) and tert-butyl hydroperoxide (t-BHP), both types of ROS that damage mitochondria [118]. The damage to mitochondria can lead to the release of lactate

dehydrogenase (LDH) and a decrease in the overall antioxidant capacity (T-AOC) and activity of superoxide dismutase (SOD) [119].

The cell has two key antioxidant defense systems, namely total antioxidant capacity (T-AOC) and superoxide dismutase (SOD), that help to safeguard it from oxidative harm [120]. The regulation of these antioxidant enzymes is determined by various factors, among which Nrf2 plays a crucial role [121]. Nrf2 binds to the promoter region of the SOD gene, leading to an upsurge in its expression and subsequently, SOD activity [122]. Moreover, Nrf2 also regulates the expression of other genes that participate in the oxidative stress response, such as catalase and glutathione peroxidase [123].

When there is oxidative stress, the mRNA level of Bcl-2 may decrease, which tips the balance in favor of pro-apoptotic proteins like Bax [124]. Bax can cause the release of cytochrome c from the mitochondria, kickstarting the caspase cascade [125]. In the intrinsic pathway of apoptosis, caspase-9 plays the role of the initiator caspase, and its activation leads to the activation of other effector caspases, including caspase-3. The end result of this pathway is cell death [126].

Compound **13** shows potential as a neuroprotective agent by blocking the mitochondrial dysfunction induced by H2O2 or t-BHP, limiting the release of lactate dehydrogenase (LDH) caused by H2O2 or t-BHP, and increasing intracellular total antioxidant capacity (T-AOC) and superoxide dismutase (SOD) activity compared to the H2O2 or t-BHP group [97]. Together with **13**, Sea Cucumber cerebrosides (**14**) and Star Fish Cerebrosides (**20**) have been found to increase the activity of SOD and reduce the content of NO, NOS, 8-OHdG, 8-oxo-G, and MDA. They can also increase the survival rate of PC12 cells, recover cellular morphology, and regulate the expression of caspase-9, cleaved caspase-3, total caspase-3, Bax, and Bcl-2, indicating their potential as neuroprotective agents [98–100].

Compounds **15**, **16**, **39**, and **40** were shown to reduce 6-hydroxydopamine (6-OHDA). 6-OHDA is a neurotoxin commonly used to destroy dopaminergic neurons in the brain selectively. 6-OHDA is often used in animal models of Parkinson's disease to simulate the degeneration of these neurons in human disease [101, 108, 109]. Compound **40** has been discovered to have the ability to reverse the downregulation of the PI3K/Akt signaling pathway induced by 6-OHDA and boost the translocation of Nrf2 to aid downstream protein translation of HO-1 and SOD-1. Moreover, it was observed to impede the cleavage of caspase-3 protein by increasing the levels of p-Akt and p-ERK and reducing the levels of p-P38. These findings suggest that compound **40** might be a promising therapeutic agent for treating neurodegenerative diseases [109]. Marine invertebrate compounds regulating ROS can be seen in Fig. 3.

2.4.2 Acetylcholinesterase

Acetylcholinesterase (AChE) is an enzyme that plays a critical role in regulating cholinergic neurotransmission [127]. This substance is mainly located within the synaptic clefts of cholinergic neurons, and its primary function is to quickly break down the neurotransmitter acetylcholine (ACh) into choline and acetate [128]. In Alzheimer's disease, the activity of AChE is often increased, leading to ACh's breakdown and the depletion of cholinergic neurotransmission [129]. This depletion of cholinergic neurotransmission is thought to contribute to the cognitive deficits seen in Alzheimer's disease. Therefore, AChE is an important enzyme that regulates the activity of the cholinergic system and plays a critical role in normal nervous system function [130]. It is also involved in the pathogenesis of certain neurological disorders, making it an important target for therapeutic interventions.

Previous studies investigated anti-AChE from active compounds of sea urchins, *Scaphechinus mirabilis* (**10**), and sponge, *Xestospongia testudinaria* (**28**) (see Fig. 4) [95, 106]. Compound **28** calculated significant IC_{50} of AChE inhibition (0.64 μM) [106]. Furthermore, compound **10** is a strong acetylcholinesterase (AChE) inhibitor, and its mode of inhibition is both uncompetitive and irreversible [94].

2.4.3 Amyloid-β accumulation

Amyloid beta (Aβ) is a protein that accumulates in the brains of patients with Alzheimer's disease (AD) [131]. Aβ is produced by the cleavage of a larger protein called amyloid precursor protein (APP) by β-secretase 1 (BACE1) and gamma-secretase [132]. The accumulation of Aβ in the brain is thought to play a central role in the pathogenesis of AD. BACE1 is an enzyme that cleaves APP to generate Aβ, and its activity is essential for producing Aβ. Inhibiting BACE1 activity has been proposed as a therapeutic strategy for AD [133]. Neuroprotective effects against Aβ1–42-induced synaptic dysfunction are related to preventing the loss of synaptic function and neuronal damage that occurs in AD [134]. Several studies have demonstrated that certain compounds and interventions can protect against Aβ1–42-induced synaptic dysfunction [99, 135]. For example, resveratrol, a natural compound found in grapes, has been shown to protect against Aβ1–42-induced synaptic dysfunction by reducing oxidative stress and inflammation [136].

The inhibition of Aβ toxicity by preventing its aggregation through an autophagic pathway regulated by HSF-1 involves the activation of heat shock factor 1 (HSF-1).

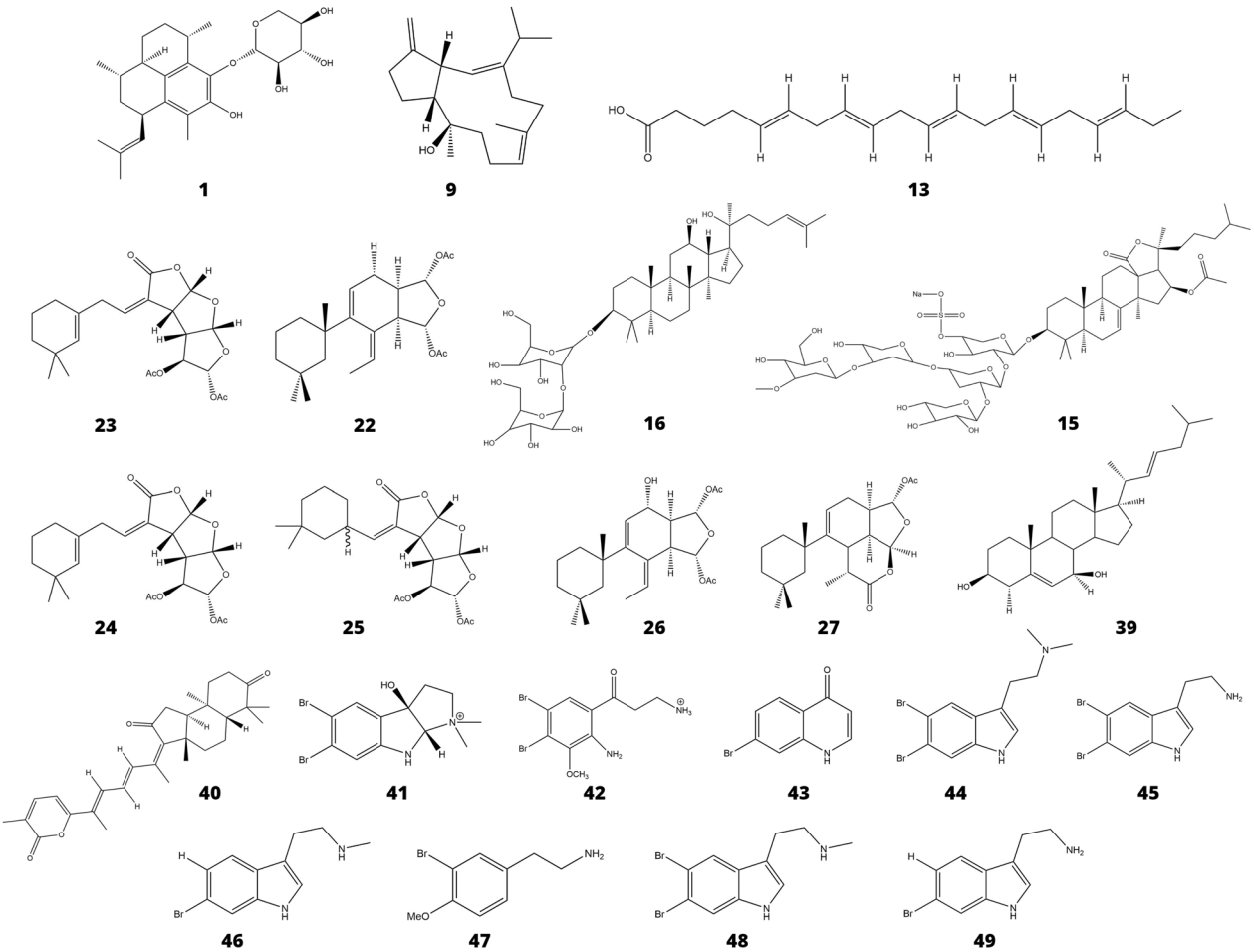


Fig. 3 Marine invertebrate compounds regulating reactive oxygen species. Pseudopterosin A (**1**); Sarboettgerin E (**9**); Eicosapentaenoic acid (**13**); Frondoside A (**15**); Ginsenoside Rg3 (**16**); Gracilin A (**22**); Gracilin H (**23**); Gracilin J (**24**); Gracilin K (**25**); Tetrahydroaplysulphurin-1 (**27**); (22E)-24-norcholesta-5,22-diene-3β,7β-diol (**39**); Stellettin B (**40**); Narrabeenamine B (**41**); 5,6-Dibromo-7-methoxykynuramine (**42**); 7-bromoquinolin-4(1H)-one (**43**); 5,6-dibromo-N,N-dimethyltryptamine (**44**); 5,6-dibromotryptamine (**45**); 6-bromo-N-methyltryptamine (**46**); 3-bromo-4-methoxytyramine (**47**); 5,6-dibromo-N-methyltryptamine (**48**); and 6-bromotryptamine (**49**)

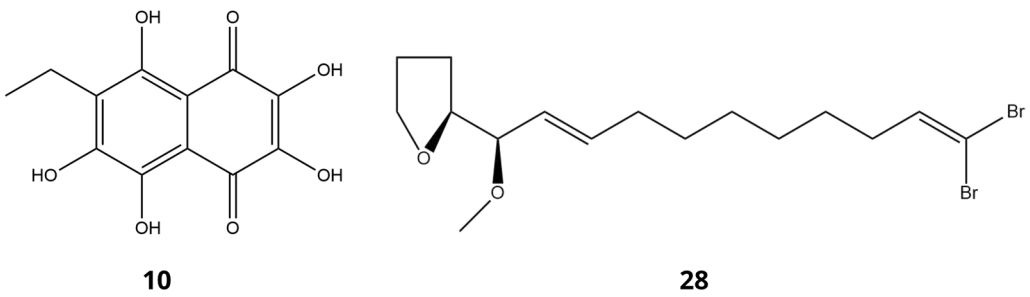


Fig. 4 Structure of Echinochrome A (**10**) and Mutafuran H (**28**) as acetylcholinesterase inhibitors

HSF-1 is a transcription factor that controls the expression of genes involved in the cellular stress response [103]. Studies have demonstrated that activating HSF-1 can enhance the clearance of Aβ aggregates through autophagy, leading to a decrease in Aβ toxicity. Some active compounds from marine invertebrates were investigated for inhibitors of Aβ, including **11**, **12**, **14**, **19**, **54**, and **55** [96, 98–100, 103, 112, 113]. Compound **14** has

been found to have neuroprotective effects against Aβ1–42-induced synaptic dysfunction in the rat hippocampus, possibly by promoting synaptic function and protecting against neuronal damage through the upregulation of proteins involved in synaptic plasticity and neuronal survival [98–100]. Compound **54** inhibits amyloid β-42 production induced by aftin-5 [112]. Compound **19**, conversely, demonstrated that can safeguard C. elegans from the harmful effects of Aβ by inhibiting its aggregation through an autophagic pathway regulated by HSF-1. As a result, this compound could be a potentially valuable therapeutic option for Alzheimer's disease [103].

Finally, compounds **11** and **12** from *Urechis unicinctus* were studied for anti-BECE-1 in vitro [96]. Compound **55** has been found to directly reduce Aβ oligomer formation and produce less neuronal toxicity in SH-SY5Y cells, indicating its potential as a therapeutic agent for AD [113]. Despite different mechanisms of action, all compounds have demonstrated potential as treatments for Alzheimer's (Fig. 5).

2.4.4 α-synuclein aggregations

The involvement of α-synuclein in the degeneration of dopaminergic neurons within the substantia nigra is believed to contribute to the motor-related symptoms seen in Parkinson's disease [137]. α-synuclein aggregation is believed to cause neuronal dysfunction and death by disrupting normal cellular processes, including mitochondrial function, vesicle trafficking, and protein degradation [138]. On the other hand, reducing α-synuclein levels has been shown to improve dopamine-dependent behavioral functions. Dopamine is a neurotransmitter critical in regulating movement and reward, and its depletion is a hallmark of PD [139]. Studies have suggested that reducing α-synuclein levels may increase dopamine release and improve dopaminergic neuron function, thereby improving movement and other dopamine-dependent behaviors [140, 141].

Reduction of α-synuclein levels can be achieved through various mechanisms, including the activation of autophagy [142]. Autophagy is critical in maintaining cellular homeostasis and is essential for neuronal survival. Autophagic signaling mediated through lgg-1 and atg-7 activity has been shown to reduce α-synuclein levels and protect dopaminergic neurons in animal models of PD [143]. The activation of autophagy promotes the clearance of misfolded or aggregated proteins, including α-synuclein, thereby reducing their toxicity.

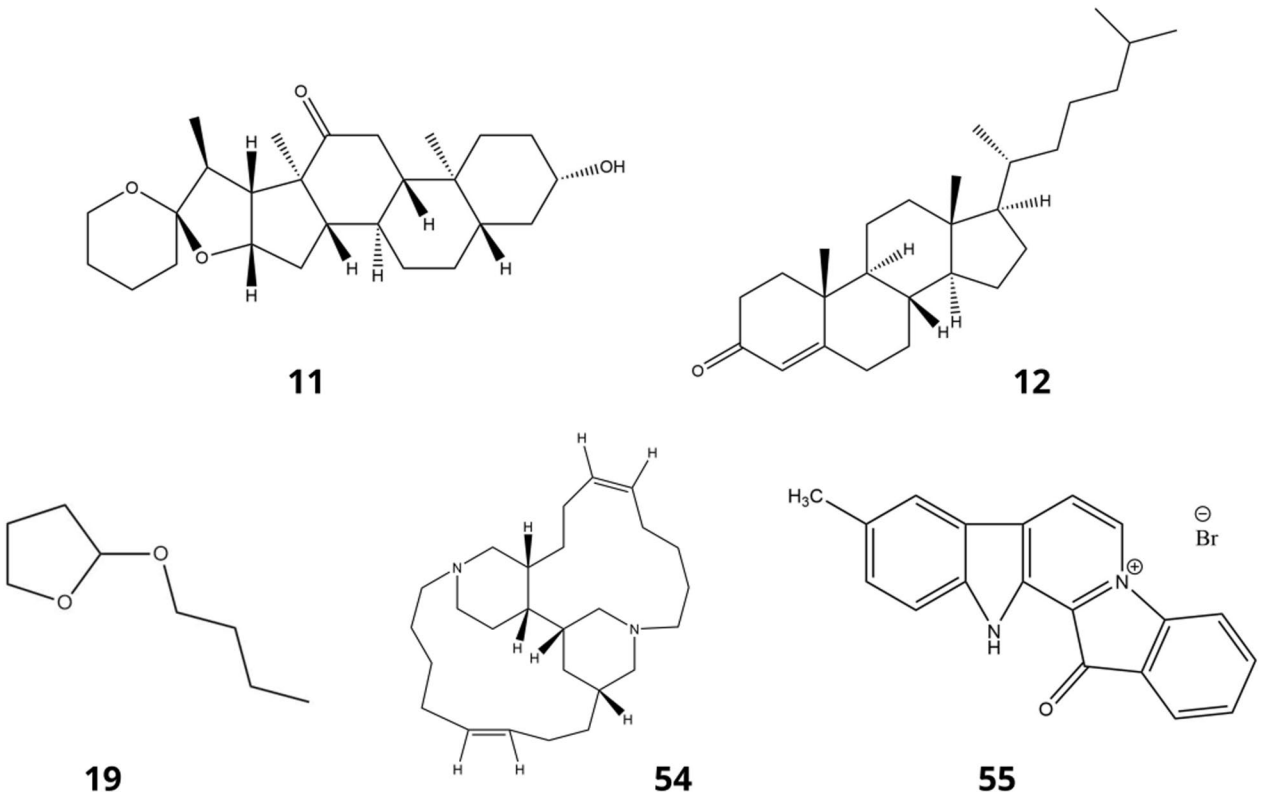


Fig. 5 Marine invertebrate compounds inhibiting Amyloid-β aggregation. Hecogenin (**11**); Cholest-4-en-3-one (**12**); 2-Butoxytetrahydrofuran (**19**); Acanthocyclamine A (**54**); and 9-methylfascaplysin (**55**)

Compounds from *Holothuria scabra* (**17** and **18**) may have therapeutic potential through their effects on autophagic signaling mediated through lgg-1 and atg-7 activity [102], while compounds like **21**, **56,** and **65** have been investigated for the treatment and monitoring of α-synuclein-mediated neurodegeneration and suggested potential strategies.

These compounds have been tested for α-synuclein aggregation inhibitory activity using the Thioflavin T (ThT) dye assay method and demonstrated significant α-synuclein aggregation inhibitory activity [6, 8, 104]. Compound **15** was able to decrease the aggregation of α-synuclein, increase the lifespan in NL5901, and promote the upregulation of regulators of protein degradation, such as ubh-4, hsp-16.2, hsp-16.1, and hsf-1 [101]. Structure of these compounds can be seen in Fig. 6.

2.4.5 Prion aggregations

The activity of prions in the brain can lead to the formation of protein aggregates, which are toxic to neurons and can cause neurodegeneration [144, 145]. These protein aggregates can disrupt the brain's normal function and lead to symptoms such as cognitive impairment, motor dysfunction, and behavioral changes [146]. This enzyme is usually linked to the transformation of regular cellular prion protein (PrPc) into the abnormal and infectious form (PrPSc) [147]. PrPSc is resistant to degradation by cellular machinery and can accumulate in the brain over time [148]. The aggregation of PrPSc results in the formation of plaques and fibrils, which are believed to be responsible for the damage to neurons and subsequent neurodegeneration [149].

Prion diseases can be transmitted through ingestion, contact with infected tissue or blood, or genetic inheritance [150]. Prion diseases have no cure, and treatment options are limited [151]. Therapeutic approaches focus on reducing prion activity, such as inhibiting the conversion of PrPc to PrPSc or promoting the clearance of PrPSc from the brain [152].

Lamellosterols A-C (**56–58**) were examined for their ability to inhibit prion activity and were found to be more effective than the known anti-prion compound guanabenz. The EC_{50} values for these compounds as anti-prion agents against the [PSI+] yeast prion were 12.7, 13.8, and 9.8 μM, respectively [6]. Similarly, procerolide A (**59**) and procerone A (**63**), isolated from the Ascidian Polycarpa procera, showed potential anti-prion activity against the [PSI+] yeast prion with EC_{50} values of 23 and 29 μM, respectively [114]. PrPSc can form protein aggregates in the yeast *S. cerevisiae*, including Sup35, related to the [*PSI*$^{+}$] phenotype. Several studies have also shown that PrPSc can interact with Sup35 in the yeast *S. cerevisiae* and can influence the formation of protein aggregates caused by Sup35 [153]. However, the exact connection between PrPSc and [PSI+] remains unclear, and additional investigation is necessary. Structure of these compounds can be seen in Fig. 7.

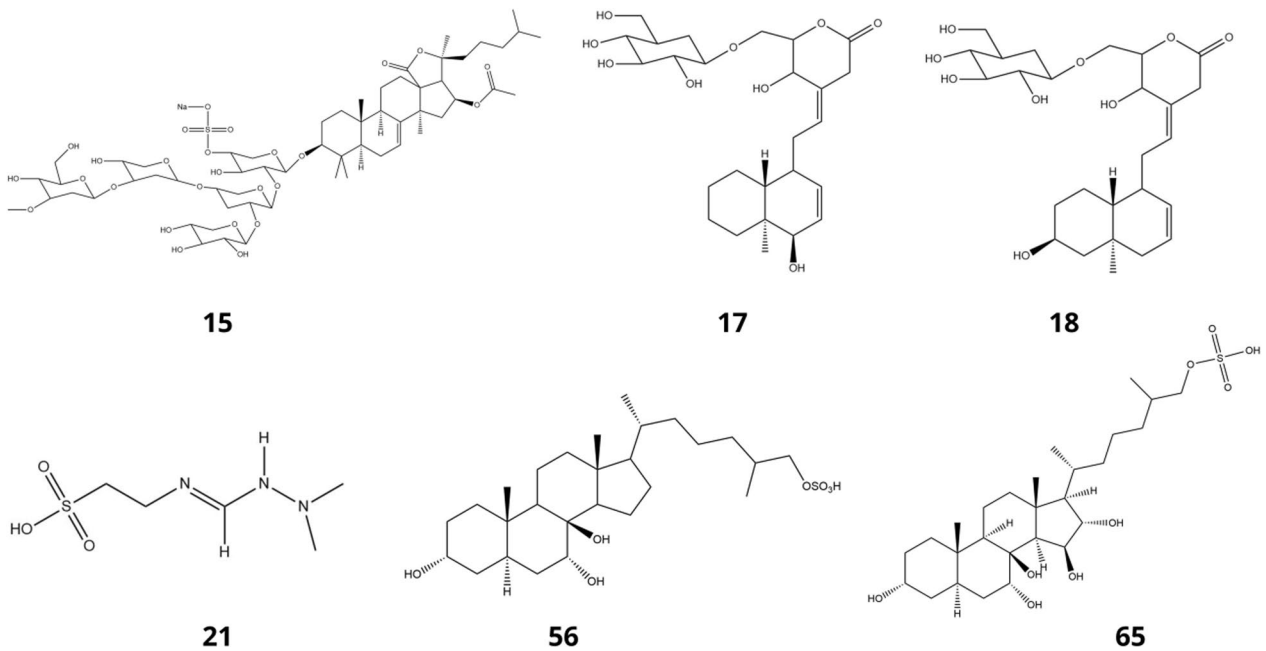


Fig. 6 α-synuclein regulators from marine invertebrate. Frondoside A (**15**); HSEA-P1 (**17**); HSEA-P2 (**18**); Asterubine (**21**); Lamellosterol A (**56**); and Sycosterol A (**65**)

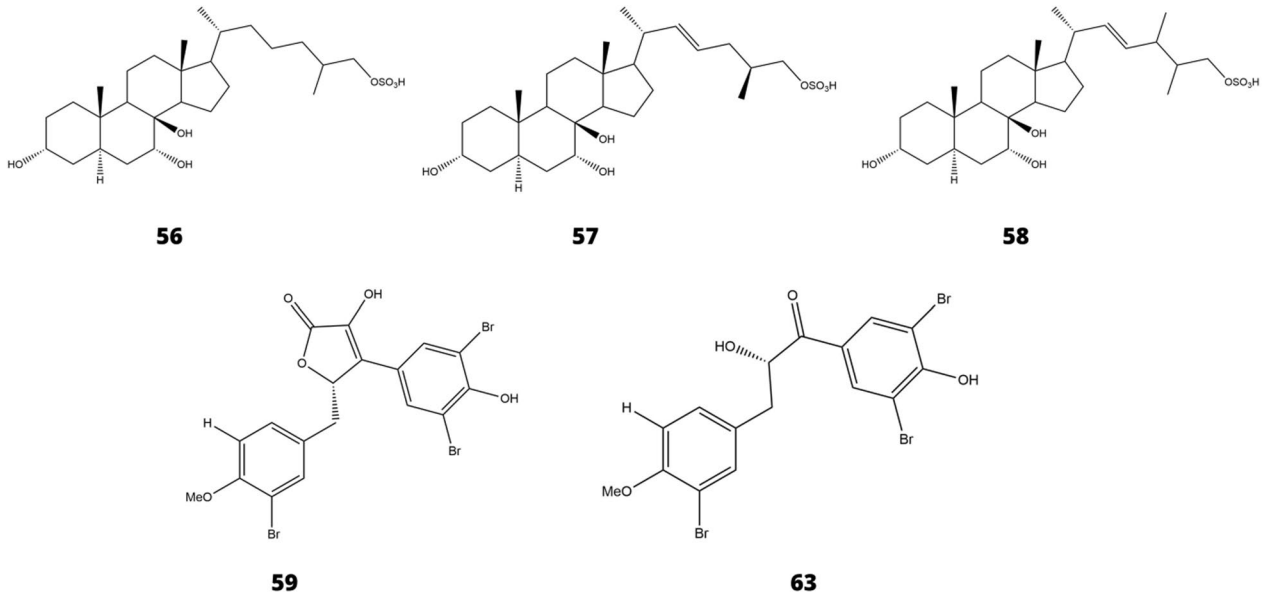


Fig. 7 Anti-prion agents from marine invertebrate. Lamellosterol A (**56**); Lamellosterol B (**57**); Lamellosterol C (**58**); Procerolide A (**59**); and Procerone A (**63**)

2.4.6 Advanced glycation end products (AGEs) formation

Advanced glycation end products (AGEs) refer to a cluster of molecule created by the reaction of amino groups of proteins, lipids, and nucleic acids with reducing sugars, independent of enzymatic activity [154, 155]. These molecules can accumulate in tissues over time and are believed to play a role in the development of chronic illnesses, including neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease (PD) [156]. AGEs can have several deleterious effects on the brain, including increased oxidative stress, inflammation, and disruption of normal cellular function [157]. In neurodegenerative disorders, AGEs can contribute to the aggregation of misfolded proteins, such as amyloid β in AD and α-synuclein in PD [158]. AGEs can also impair the clearance of these proteins, leading to their accumulation and subsequent neurodegeneration [159].

Furthermore, AGEs have the ability to activate a variety of signaling pathways, including RAGE and NF-kB, which are implicated in inflammation and cell death processes [160]. The activation of these pathways can result in the discharge of harmful substances such as proinflammatory cytokines and reactive oxygen species, intensifying the progression of neurodegenerative disorders [161]. Compounds **31**–**38** are mirabamides isolated from *Siliquariaspongia mirabilis* and *Stelletta clavosa*. These compounds have shown calculations via Conceptual Density Functional Theory (DFT) to generate information about the reactive nature of these compounds and the active points for electrophilic, nucleophilic, and radical attacks and the Solvation Model based on the Density (SMD) for the molecular and structural properties of compounds [107]. The computational results accurately predict the compounds' ability to inhibit the formation of AGEs, which could be valuable in developing drugs for combating diseases like Parkinson's and Alzheimer's [162, 163]. Structure of these compounds can be seen in Fig. 8.

2.4.7 Paraquat activity

Paraquat is an herbicide commonly used that has been linked to the occurrence of Parkinson's disease and other neurodegenerative diseases [164]. The compound is extremely harmful and induces oxidative stress by generating reactive oxygen species (ROS), resulting in neuronal damage and ultimately leading to neurodegeneration [165]. The mechanisms by which PQ induces neurodegeneration are complex and multifaceted. PQ can accumulate in the brain and cause damage to dopaminergic neurons, which are particularly vulnerable to oxidative stress [166]. PQ can also induce the formation of protein aggregates, such as α-synuclein, a hallmark of PD pathology [167]. In addition to its direct effects on neurons, PQ can induce inflammation and activate microglia, immune cells in the brain [168]. Microglia that have been activated can secrete cytokines that promote inflammation, as well as molecules that are neurotoxic and reactive oxygen species, all of which can worsen neurodegeneration. Compound **53** increased the survival of Neuro-2a cells when exposed to PQ and decreased the number of harmful ROS within these cells. Additionally,

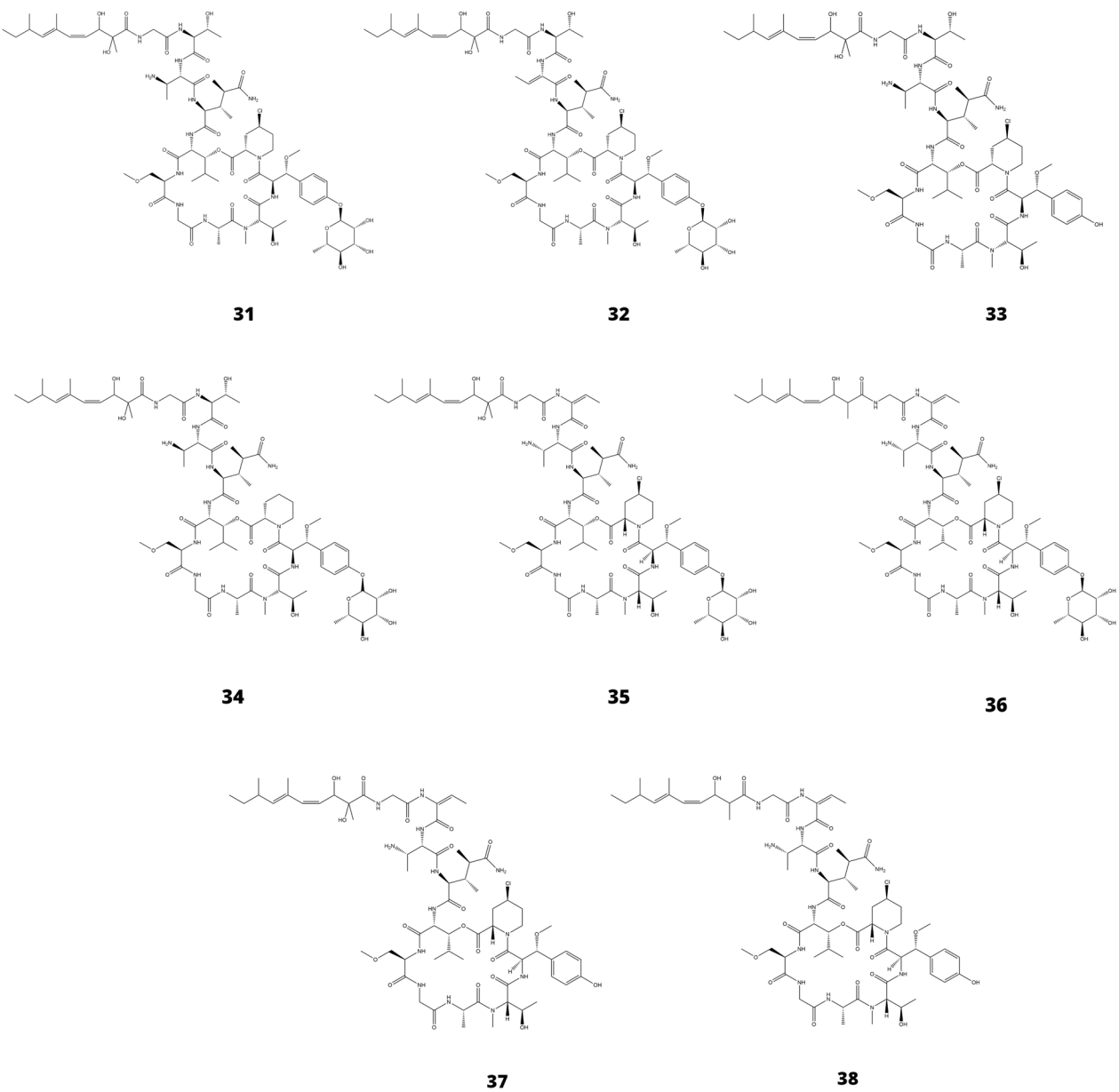
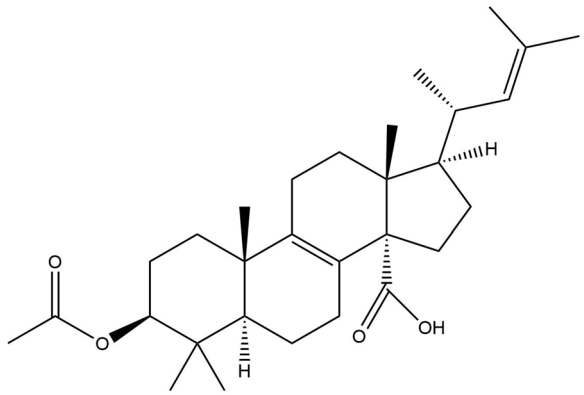


Fig. 8 Advanced glycation end products inhibitors from marine invertebrate. Mirabamides A (**31**); Mirabamides B (**32**); Mirabamides C (**33**); Mirabamides D (**34**); Mirabamides E (**35**); Mirabamides F (**36**); Mirabamides G (**37**); and Mirabamides H (**38**)

acetylpenasterol induced the expression of Hsp70, a protein that helps protect cells from stress, in PQ-treated cells. Furthermore, it was observed that acetylpenasterol prevented the loss of neurites and increased the number of cells with neurites in PQ-exposed cells [111] (Fig. 9).

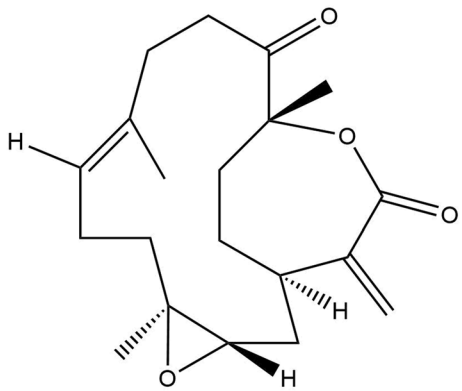
2.4.8 Mitochondria DJ-1 expression

The protein DJ-1 is present in both the cytoplasm and mitochondria of cells [169] and plays a crucial role in maintaining mitochondrial function and safeguarding cells against oxidative stress and mitochondrial dysfunction [170]. Its dysfunction or loss may cause neurodegenerative diseases like PD by compromising mitochondrial function and elevating oxidative stress. In addition to its role in maintaining mitochondrial function, DJ-1 is also involved in the Akt signaling pathway, which is essential for cell survival and growth [171]. Research has shown that DJ-1 is capable of activating the PI3K/Akt pathway, which promotes cell survival and reduces cell death [172]. Conversely, the



53

Fig. 9 Acetylpenasterol (**53**) as a potent anti-paraquat agent



2

Fig. 10 Structure of 11-dehydrosinulariolide (**2**) as a mitochondria DJ-1 inductor

loss or dysfunction of DJ-1 can lead to a decrease in Akt activity and an increase in susceptibility to oxidative stress and apoptosis [173]. These findings suggest that the interaction between DJ-1 and the Akt pathway is crucial for the neuroprotective effects of DJ-1. Further exploration of this relationship could potentially uncover new targets for the treatment of neurodegenerative diseases.

11-Dehydrosinulariolide (compound **2,** see Fig. 10) is a natural compound that has been extracted from the soft coral *Sinularia leptoclados* and has been found to have multiple biological effects. One of its mechanisms for providing neuroprotection is its ability to increase DJ-1 expression. According to one research, the treatment of SH-SY5Y human neuroblastoma cells with 2 increased the expression of DJ-1 in a dose-dependent manner and also stimulated mitochondrial complex I activity [92]. Another study reported that **2** could activate p-CREB and the downstream of Akt/PI3K and promote Nrf2/HO-1 translocation in SH-SY5Y cells [9].

2.5 Author perspective

From our perspective, this review article on using marine invertebrate compounds for anti-neuroinflammation and anti-neurodegenerative purposes provides an opportunity to shed light on an emerging area of drug discovery research. The potential benefits of marine invertebrates as a source of novel therapeutic agents for neurodegenerative diseases are increasingly recognized by researchers [174]. However, several challenges must be addressed to harness the potential of marine invertebrate compounds fully. One of the main challenges is optimizing the bioavailability and activity of these compounds. Many marine invertebrate compounds have poor solubility and bioavailability, which can limit their effectiveness as therapeutic agents [175]. Targeted delivery systems that can improve these compounds' bioavailability and therapeutic efficacy could solve this problem.

Moreover, combining several compounds with different action mechanisms may result in a more potent, efficient, and low side-effect therapy. Implementing a multicompartment delivery system would be beneficial to regulate the release and maintain the stability of the biomolecular mixture during storage. For instance, liposomes, novasomes, and polymers could also be an option for multidelivery synergistic drug biomolecules [176–182]. As derived from marine sources, invertebrate extracts or isolates typically have a less appealing aroma and taste. Instant granule technology and practical dosage forms must also be implemented to mask the unpleasant aroma and taste [115, 183].

Another challenge is identifying more effective and selective compounds that target specific neuroinflammatory and neurodegenerative pathways. While several promising compounds have been identified from marine invertebrates, further research is needed to understand their mechanisms of action and potential clinical applications fully. There is also a need for more extensive in vitro and in vivo studies to evaluate the safety, efficacy, and pharmacokinetic properties of marine invertebrate compounds. This could involve investigating the effects of these compounds on animal models of neurodegenerative diseases and conducting clinical trials to evaluate their potential as therapeutic agents.

3 Conclusion

Based on the reviewed literature, it is evident that compounds isolated from marine invertebrates have shown potential therapeutic mechanisms in inhibiting neuroinflammation caused by amyloid β, paraquat,

α-synuclein, AGEs, prion activity, and oxidative stress. These bioactive compounds have demonstrated promising anti-neuroinflammatory and anti-neurodegenerative properties through various pathways and proteins such as DJ-1, Akt/PI3K, p-CREB, Nrf2/HO-1, Nrf-1, and HSF-1. Therefore, marine invertebrates can serve as a valuable source for developing natural compounds that could be utilized to treat neuroinflammatory disorders. Further research and investigation are needed to explore these bioactive compounds' full potential and underlying mechanisms for developing novel therapeutic drugs.

Abbreviations

CNS	Central nervous system
AZ	Alzheimer's disease
ROS	Reactive oxygen species
DAMPs	Damage-associated molecular patterns
IL	Interleukin
TNF-α	Tumor necrosis factor-α
PD	Parkinson's disease
MS	Multiple sclerosis
NSAIDs	Nonsteroidal anti-inflammatory drugs
BBB	Blood–brain barrier
BDNF	Like brain-derived neurotrophic factor
NO	Nitric oxide
BACE1	Beta-site amyloid cleaving enzyme
PQ	Paraquat
AChE	Acetylcholinesterase
t-BHP	Tert-butyl hydroperoxide
LDH	Lactate dehydrogenase
SOD	Superoxide dismutase
T-AOC	Total antioxidant capacity
ThT	Thioflavin T
PrP	Prion protein
AGEs	Advanced glycation end products
DFT	Conceptual Density Functional Theory
SMD	Solvation Model based on the Density

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