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Original Article

Potential of marine compounds in the treatment of neurodegenerative diseases: a review

Potencial de compostos marinhos no tratamento de doenças neurodegenerativas: uma revisão

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Abstract

Neurodegenerative diseases (ND) are characterized, especially, by the progressive loss of neurons, resulting in neuropsychomotor dysfunctions. Even with a high prevalence, NDs are treated with drugs that alleviate the symptoms of patients, but which develop adverse events and still do not inhibit the progression of the disease. Thus, within a new pharmacological perspective, this review aimed to verify the therapeutic potential of natural compounds of marine origin against ND. For this, an integrative review was carried out, according to the PRISMA methodology, which included steps such as: search, pre-selection and inclusion of articles. The results described revealed species such as Acaudina malpodioides, Holothuria scabra and Xylaria sp., which presented important evidence in relation to Alzheimer's, reducing the generation of ROS, presenting neuroprotective effects and reducing the concentration of Aβ peptide. Regarding Parkinson's disease (PD), another example of ND, the bioactive compounds from Holothuria scabra and Xylaria sp., showed to be able to reduce the degeneration of dopaminergic neurons, reduce the deposition of alpha synuclein and reduce the formation of Mutant Huntingtin protein (Mhtt). The other marine compounds and bioactive substances are also described in this review. In conclusion, the evaluated studies indicate that compounds of marine origin emerge as a promising source of bioactive compounds, revealing an important therapeutic potential for the treatment of ND.

Keywords: marine compound, neurodegenerative diseases, neuroprotective.

Resumo

As doenças neurodegenerativas (ND) são caracterizadas, especialmente, pela perda progressiva de neurônios, resultando em disfunções neuropsicomotoras. Mesmo apresentando uma alta prevalência, as DN são tratadas com medicamentos que aliviam os sintomas dos pacientes, mas que desenvolvem eventos adversos e ainda não inibem a progressão da doença. Assim, dentro de uma nova perspectiva farmacológica, esta revisão teve como objetivo verificar o potencial terapêutico de compostos naturais de origem marinha frente às DN. Para tal, foi realizada uma revisão integrativa, segundo a metodologia PRISMA que compreendeu etapas como: busca, pré-seleção e inclusão dos artigos. Os resultados descritos revelaram espécies como, *Acaudina malpodioides*, *Holothuria scabra* e *Xylaria sp.*, que apresentaram importantes evidências em relação ao Alzheimer, reduzindo a geração de ROS, apresentando efeitos neuroprotetores e reduzindo a concentração de peptídeo Aβ. Sobre a doença de Parkinson (PD), outro exemplo de ND, os compostos bioativos da *Holothuria scabra* e da Xylaria sp., mostraram ser capazes de diminuir a degeneração de neurônios dopaminérgicos, reduzir a deposição de alfa sinucleína e reduzir a formação de agregados da proteína Huntingtina mutante (Mhtt). Os outros compostos marinhos e substâncias bioativas também são descritos nesta revisão. Em conclusão, os estudos avaliados indicam que os compostos de origem marinha despontam como uma promissora fonte de compostos bioativos, revelando um importante potencial terapêutico para o tratamento das ND.

Palavras-chave: composto marinho, doenças neurodegenerativas, neuroprotetor.

1. Introduction

Neurodegenerative diseases (ND) are driven by the progression of neurons, leading to cognitive, motor, and sensory dysfunctions (Bianchi et al., 2021). The World Health Organization (WHO) estimated that 55 million people currently live with dementia worldwide. Alzheimer's disease (AD) accounts for 60%–70% of cases, and its treatment involves the administration of drugs that help with the symptoms of the disease but does not prevent long-term progression, as in Parkinson's disease (PD) and Huntington's disease (HD) (WHO, 2021).

Currently, the treatment of ND basically covers cognitive and motor aspects, combining pharmacological classes,

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which over time trigger numerous adverse events. In addition, current therapy does not prevent disease progression, which can be explained, albeit partially, by the high rate of neuronal death, considerably reducing the effectiveness of the drugs used for this purpose. In this context, AD uses drugs that improve the quality of life of patients, especially at the onset of symptoms and whose mechanisms of action involve an increase in neurotransmitters such as acetylcholine and glutamate in the synaptic cleft (Cummings et al., 2019). Regarding PD, the pharmacological classes used include monoamine oxidase-B (MAO-B) inhibitors and dopaminergic agonists, mainly contributing to the improvement of motor symptoms (Armstrong and Okun, 2020). In relation to HD, the pharmacological combination is used according to the intensity and variety of symptoms, with the most used pharmacological classes being neuroleptics, antidepressants, mood stabilizers, anticonvulsants, hypnotics and amino acid precursors of dopamine (Ross and Tabrizi, 2011).

A source of study for new therapeutic potentials, natural products have always been present in various pharmacological discoveries that have impacted humanity. Notable examples that are still used today are penicillin, derived from a fungus of the genus *Penicillium*, and morphine, a constituent of opium and present in the bulbs of *Papaver somniferum*. Therefore, natural products become important sources of research to obtain new therapeutic alternatives for the treatment and prevention of ND (Viegas Junior et al., 2006).

In view of the above and due to the limitations observed in the conventional treatment of AD, PD and HD, new horizons must be reached in an attempt to obtain new therapeutic agents. As in the examples cited above, natural products of marine origin emerge as a source of pharmacological investigation in the face of the challenge of seeking new bioactive compounds to be used in the treatment of ND. Thus, compounds such as Xylocetal B (Xyl-B), one of the metabolites of the fungus *Xylaria sp, Aspergillus sp* and sea cucumbers *Holothuria scabra* (Jaeger, 1833) and *Cucumaria frondosa* (Gunnerus, 1767), are presented as candidates compounds with therapeutic application, since they have antioxidant mechanisms, promote neuroprotective effect and reduce harmful effects of proteins that accumulate in neurons.

Considering such needs and the importance of seeking new treatment perspectives, this integrative review aimed to organize and describe the potential of natural compounds of marine origin that may be presented as options for pharmacological investigation, in addition to being able to be used in the treatment of ND.

2. Methodology

The present work is an integrative literature review that aims to gather and analyze studies that demonstrated the use of marine components in the treatment of neurodegenerative diseases. This review was based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PubMed and Virtual Health Library databases were searched for eligible articles using the following keywords and their combinations in English: *Holothuria scabra*, sea drugs and neurodegenerative diseases, sea compounds and neurodegenerative diseases, *Xylaria sp* and neurodegenerative diseases, *Aspergillus sp* and neurodegenerative diseases, *Holothuria* and neurodegenerative disease, and Xyloktal B. Two reviewers independently performed the literature search and selection of studies. The inclusion criteria for the selection of relevant studies included those that addressed the use of marine components in neurodegenerative diseases, use of Xylocetal B compound, Xylocetal B composition, use of *Hippocampus kuda Bleeker* (Bleeker, 1852), use of *Holothuria scabra* and *Holothuria leucospilota* (Brandt, 1835), and *Aspergillus sp*. from the sea. Publications in English and Russian were also included, whereas systematic reviews, letters, conference abstracts, case reports or series, and comments were excluded. The articles were pre-selected by preliminary reading of the titles and abstracts. The pre-selected studies were read in full for the final selection of articles for the analysis. Two reviewers independently performed the literature search and selection of studies, and they evaluated the articles using the Scientific Journal Rankings (SJR) too.

3. Results

To conduct this review, 469 records were collected. After analyzing the data, 407 studies were excluded. Eventually, 26 studies met the inclusion and quality assessment criteria. Figure 1 shows the flow diagram of the research.

3.1. Marine animals

3.1.1. Sea cucumber

Wu et al. (2014) evaluated PC12 cells subjected to the stressing agents hydrogen peroxide (H_2O_2) and tert-butyl hydroperoxide (t-BHP). After stress induction, PC12 cells were treated with phospholipids enriched with eicosapentaenoic acid (EPA) extracted from the sea cucumber *C. frondosa*, resulting in increased survival owing to the antioxidant effect. Regarding deficits in learning, memory, anxiety, and cognitive decline, this enriched phospholipid showed significant improvement in behavioral tests in mice (Wu et al., 2014).

Another sea cucumber, *Acaudina molpadioides* (Semper, 1867), was evaluated by Li et al. (2018) where a pre-clinical study with a murine model induced AD through a diet containing beta-amyloid peptide (Aβ). The animals treated with cerebrosides from *Acaudina molpadioides* (Figure 2) showed improvement in induced cognitive dysfunction, in addition to significantly increasing the number of normal neurons in the hippocampus of rats with AD (Li et al., 2018). In an *in vitro* study by Li et al. (2018) showed that cerebrosides obtained from *Acaudina molpadioides* have a neuroprotective effect by increasing cell viability and positively modulating the expression of the BCL-2 protein, revealing an inhibition of cellular apoptosis. Furthermore, the authors observed improvements in

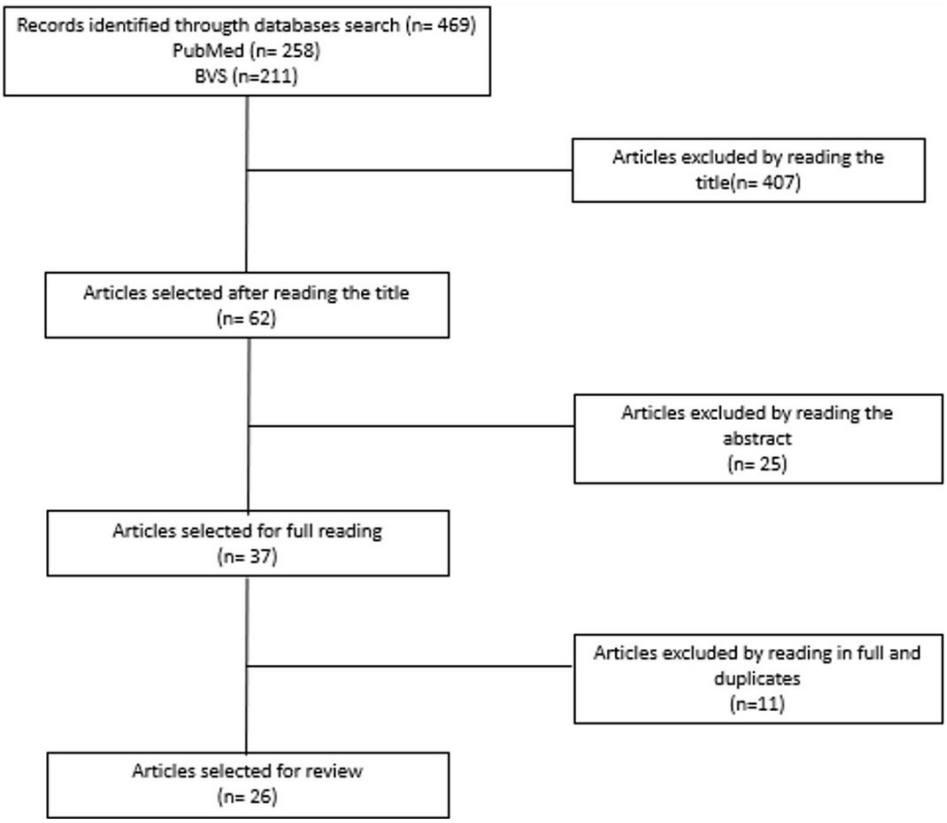

Figure 1. Flow chart of search strategy results.

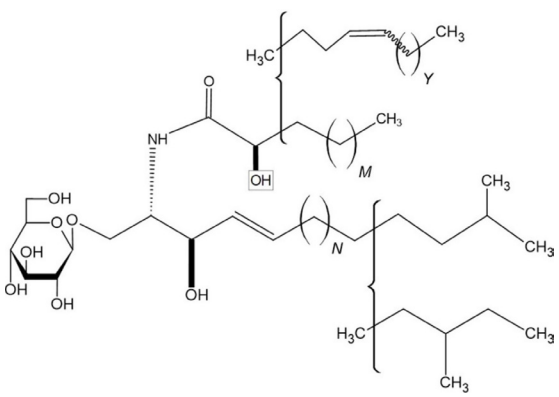

Figure 2. Cerebrosides from *Acaudina molpadioides*.

learning and memory deficits in a murine model of dementia (Che et al., 2017). However, on the sea cucumber *Acaudina molpadioides*, Wu et al. (2013) described not only the effects of cucumber cerebrosides *Acaudina molpadioides*, but also from the starfish *Asterias amurensis* (Lütken, 1871) *in vitro*, indicating the neuroprotective action by preventing cell death and reactive oxygen species (ROS) formation (Wu et al., 2013).

Several substances were extracted from the sea cucumber *Holothuria scabras*, followed by tests on strains of *Caenorhabditis elegans*. Chalorak et al. (2021) observed that the accumulation of a-synuclein is linked to PD and worms treated with fractions extracted from *Holothuria scabras* (FHS-whole body-ethyl acetate [WBEA], body wall-[BWEA], viscera-ethyl acetate [VIEA], whole body-butanol [WBBU], body wall-butanol [BWBU], and viscera-butanol [VIBU]) obtained a significant decrease in this accumulation. In addition, they significantly attenuated the degeneration of dopaminergic neurons induced by a neurotoxin, demonstrating its neuroprotective potentials that were also observed in fractions extracted from *Holothuria leucospilota* (FHL- Ethanol extracts from body wall and cuvierian tubules) (Malaiwong et al., 2019; Chalorak et al., 2018). In another study, Chalorak et al. (2021) showed reduced a-synuclein accumulation in dopaminergic neurons after treatment with diterpene glycosides extracted from *Holothuria Scabra* (Figure 3A and 3B) (Chalorak et al., 2021). Noonong et al. (2020) also evaluated the neuroprotective effect of *Holothuria scabras* metabolites (MHS-Friedelina, 3-hydroxybenzaldehyde, and 4-hydroxybenzaldehyde) in mice that were induced in PD by 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine, and showed neurorestorative effects in motor deficiencies, in addition to a significant increase in the cell viability of dopaminergic neurons, promoting the synthesis of tyrosine hydroxylase (TH) and suppressing the formation of α-synuclein protein (Noonong et al., 2020). Finally, the study by Tangrodchanapong et al. (2021) demonstrated the effect of the cyclic ether 2-butoxytetrahydrofuran (2-BTHF), which presented a neuroprotective action by

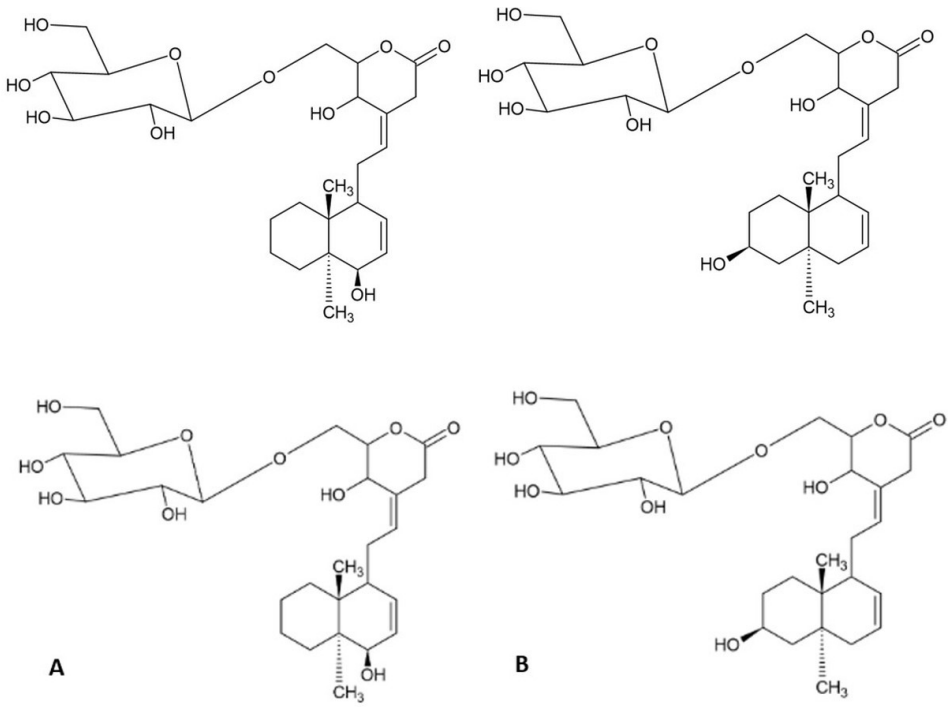

Figure 3. Diterpene glycosides. (A) HSEA-p1 and (B) HSEA-p2.

reducing the level of Aβ oligomers, possibly interrupting their deposition, in addition to reducing oxidative stress (Tangrodchanapong et al., 2021). The Table 1 summarizes the action of sea cucumbers on ND

3.1.2. Seahorse

Himaya et al. (2012) used *Hippocampus kuda Bleeker* in *in vitro* assays, and they observed the anti-inflammatory effect of paeonol, one of the compounds isolated from this species, using BV-2 and RAW264.7 cells challenged with lipopolysaccharide (LPS) as an inducer of the inflammation process. Among the results obtained, a reduction in the gene and protein expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines was observed due to blocking of the pathway of transcriptional factors (Himaya et al., 2012). Himaya et al. (2011) also evaluated 1-(5-bromo-2-hydroxy-4-methoxyphenyl) ethanone (SE1) extracted from the same species (Figure 4), which was also tested in BV-2 cells challenged with LPS. The results indicated an inhibition of the production of inflammatory cytokines, nitric oxide, and prostaglandins, thereby attenuating neuroinflammation (Himaya et al., 2011).

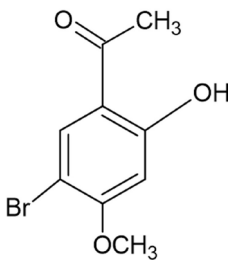

Figure 4. Seahorse.

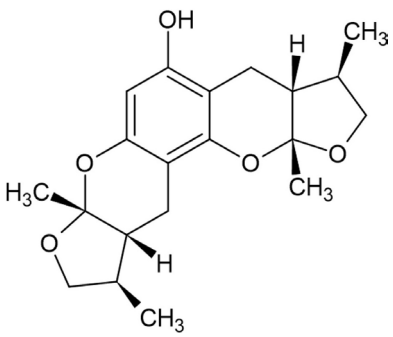

Figure 5. Xylocetal B.

3.2. Marine fungi

Li et al. (2013) showed the antioxidant ability of the compound Xyl-B (Figure 5) and its derivatives because of their ability to reduce the synthesis of ROS in zebrafish models after the induction of neurotoxicity by phorbol myristate acetate (PMA) (Li et al., 2013). In addition, the use of Xyl-B and its compounds in toxicity induced by juglone C and 1-methyl-4-phenylpyridinium (MPP+) in *Caenorhabditis elegans* was analyzed, demonstrating that these compounds increased The survival rate of *Caenorhabditis elegans*, probably due to their antioxidant action (Li et al., 2013). Furthermore, in an MPP+-induced toxicity model, the authors observed a reduced degeneration of dopaminergic neurons and promotion of neuroprotective action in a murine model (Li et al., 2013).

Table 1. Action of sea cucumbers in ND.

Sea cucumbers	Metabolites	Mechanism of action	Intervention	Reference
Cucumaria frondosa	Phospholipids enriched with eicosapentaenoic acid	Antioxidant effect	PC12 cells	Wu et al., 2014
		Improvement of memory deficits, learning, anxiety, and cognitive decline	Murine model	
Acaudina molpadioides	cerebrosides	Improvement of cognitive dysfunctions and increase in the number of normal neurons in the hippocampus	Murine model	Li et al., 2018
		Increased cell survival rate and BCL-2 protein level	*In vitro*	Che et al., 2017
		Improvement in learning and memory deficits	Murine model	
Acaudina molpadioides	cerebrosides	Prevention of cell death and ROS formation	Cells PC12	Wu et al., 2013
Holothuria scabra	FHS*	Decreased a-synuclein accumulation and attenuation of dopaminergic neuron degeneration	*C. elegans*	Chalorak et al., 2018
Holothuria leucospilota	FHL**			Malaiwong et al., 2019
Holothuria scabra	Diterpene Glycosides	Decreased a-synuclein accumulation and rescue of neurodegeneration of dopaminergic neurons	*C. elegans*	Chalorak et al., 2021
Holothuria scabra	MHS***	Improved prevention and restoration of motor function	Murine model	Noonong et al., 2020
		Restore and protect dopaminergic neurons and fibers	Cells SH-SY5Y	
		TH synthesis and suppression of a-synuclein protein formation		
Holothuria Scabra	cyclic ether 2-BTHF****	Decreased level of (Aβ) oligomer	*C. elegans*	Tangrodchanapong et al., 2021
		Antioxidant effect		

*FHS: whole-body ethyl acetate (WBEA), body wall ethyl acetate (BWEA), viscera-ethyl acetate (VIEA), whole-body butanol (WBBU), body wall-butanol (BWBU), and viscera-butanol (VIBU); **FHL: ethanol extracts from body wall and cuvierian tubules; ***MHS: Friedelina, 3-hydroxybenzaldehyde, and 4- hydroxybenzaldehyde; ****2-BTHF: 2-butoxytetrahydrofuran.

Similar results were also obtained in the study by Lu et al. (2010) where in vitro PC12 and *Caenorhabditis elegans* cells were used (Lu et al., 2010).

Zeng et al. (2016) verified that *Caenorhabditis elegans* exposed to mutant Huntingtin protein aggregates and Xyloketal derivatives showed improved motility and survival; when added to mHtt, this forms a stable trimeric complex responsible for attenuating the aggregation of the mutant protein, thus proving a neuroprotective effect (Zeng et al., 2016).

Wang et al. (2020) evaluated the effects of the *Aspergillus* genus on LPS-stimulated RAW264.7 cells, where inhibition of the synthesis of inflammatory cytokines was observed with the treatment of the compounds cyclopenol and cyclopenine, obtained from an *Aspergillus* strain, in addition to an improvement in learning deficits with cyclopenine similar to memantine (Wang et al., 2020). Kim et al. (2018) also identified three metabolites, 6,8,1'-tri-O-methylaverantine (Figure 6), which showed the best anti-inflammatory effect, supplying the synthesis of pro-inflammatory mediators.

In studies by Ingham et al. (2021) and Paranjape et al. (2014), the effects of isoquinoline compounds (ANTC-15) and the metabolites asperbenzaldehyde, asperthecin, and 2,3-dihydroxyemodine, all obtained from *Aspergillus nidulans*, were evaluated. Thus, inhibition of arachidonic

acid-induced tau protein filaments was observed in addition to reducing preformed fibrils (Paranjape et al., 2014; Ingham et al., 2021). *Aspergillus terreus* was evaluated in a study by Qi et al. (2018), where terreusterpene extracts showed anti-Alzheimer activity by simultaneously inhibiting the action of the Aβ-1 precursor protein and acetylcholinesterase (AchE). In an article by Yang et al. (2018), *Asperterethal f.* was isolated, a ring-opened butenolide from the fungus *Aspergillus terreus*, which showed the ability to inhibit TNF-α in BV2 microglial cells *in vitro*, suggesting an anti-neuroprotective effect. Finally, Girich et al. (2020) observed that the metabolites of *Aspergillus terreus*, *Aspergillus flocculosus,* and *Penicillium sp.* showed inhibitory action on ROS and reduced oxidative stress. The Table 2 summarizes the action of marine fungi on ND.

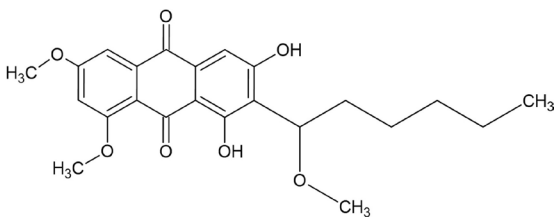

Figure 6. *Aspergillus* sp.

3.2.1. Seaweed

Jin et al. (2006) demonstrated that the seaweed *Ulva conglobata* (Kjellman, F.R.), which has neuroprotective effects through the inhibition of IFN-induced nitric oxide synthesis in BV2 cells, has an almost complete suppression of COX-2 and iNOS expression from the use of a methanol extract of this alga, and significantly attenuated glutamate-induced neurotoxicity in murine hippocampal HT22 cells. Table 3 summarizes the action of other marine compounds on ND.

4. Discussion

The results obtained in this review indicate that compounds of marine origin may represent an important therapeutic interest in neuroprotection, inflammatory modulation, and improvement of neurocognitive deficits, suggesting their potential use in neurodegenerative diseases.

Thus, in relation to neurodegenerative pathologies, AD has a pathophysiological basis associated with the progressive accumulation of Aβ peptides in the brain, leading to the formation of plaques that alter neurotransmission and provoke an inflammatory response, in addition to generating hyperphosphorylation of the

Table 2. Action of marine fungi on ND.

Fungi	Metabolites	Mechanism of action	Intervention	Reference
Xylaria sp.	Xylocetal-Band and derivatives	Reduction of ROS synthesis	Zebrafish and PC12 cells	Li et al., 2013; Lu et al., 2010
		Decreased degeneration of dopaminergic neurons	Murine model *C. elegans*	
		Increased worm survival	*C. elegans*	
		Attenuates mHtt protein aggregation	*C. elegans*	Zeng et al., 2016
Aspergillus sp.	Cyclopenol and cyclopenin	Inhibits the synthesis of pro-inflammatory cytokines and improves learning deficits	RAW-264.7 and *Drosophila sp.*	Wang et al., 2020
	6,8,1'-tri-O-metilaverantin	Suppresses the synthesis of pro-inflammatory mediators	Cells BV2	Kim et al., 2018
Aspergillusw nidulans	asperbenzaldehyde, asperthecin, 2,ω-dihydroxyemodin	Inhibits the aggregation of tau filaments	*In vitro*	Paranjape et al., 2014
	Isoquinoline			Ingham et al., 2021
Aspergillus terreus	extracts terreusterpenes	Inhibits the action of the enzyme BACE-1 and AchE	BACE-1 fluorescence resonance energy transfer and Ellman method, respectively	Qi et al., 2018
	Asperteretal F	Inhibits TNF-a	Cells BV-2	Yang et al., 2018
Aspergillus terreus, Aspergillus flocculosus, Penicillium sp.	4-Hydroxyscytalon, 4-hydroxy-6-dehydroxyscytalone and demethylcitreoviranol	Inhibits ROS synthesis	Cells neuro-2A	Girich et al., 2020

Table 3. Other marine compounds for ND.

Compounds	Metabolites	Mechanism of action	Intervention	Reference
Hippocampus kuda Bleeker	Paeonol	Attenuates gene and protein expression of iNOS, COX-2, and pro-inflammatory cytokines	Cells BV2 and RAW-264.7	Himaya et al., 2012
	1-(5-bromo-2-hydroxy-4-methoxyphenyl) ethanone	Reduced synthesis of pro-inflammatory cytokines, NO, and prostaglandins	Cells BV-2	Himaya et al., 2011
Ulva conglobata	*Ulva conglobata* + methanol extract	Reduction of NO synthesis and suppression of COX-2 and iNOS expression	Cells BV2	Jin et al., 2006
		Attenuates murine neurofield toxicity	Cells HT22	
Asterias amurensis	Cerebrosides	Prevention of cell death and ROS formation	Cells PC12	Wu et al., 2013

microtubule-binding protein tau, which contributes to neuronal cell death (Kumar et al., 2010). In relation to HD, its pathophysiological mechanism is related to the accumulation of mHtt that leads to the progressive loss of neurons in the brain, especially the striatum (caudate and putamen) (Kumar et al., 2010). Finally, PD, another neurodegenerative pathology, is characterized by the accumulation of a-synuclein protein in dopaminergic neurons of the substantia nigra of the midbrain, which can cause neurotoxicity by increasing the synthesis of ROS, resulting in neuronal death (Chalorak et al., 2018).

The inflammatory response, a common feature of neurodegenerative diseases, contributes to their progression (Himaya et al., 2012). Thus, metabolites mentioned in this review such as Xyl-B (Li et al., 2013; Lu et al., 2010); PL enriched with EPA 6, cerebrosides of *Acaudina molpadioides* and *Asterias amurensis* (Che et al., 2017; Wu et al., 2013); 2-BTHF (Tangrodchanapong et al., 2021); 4-hydroxyscitalone, 4-hydroxy-6-dehydroxycitalone, and demethylcitreoviranol (Girich et al., 2020); paeonol and SE-1 (Himaya et al., 2012; Himaya et al., 2011); cyclopenol and cyclopenine (Wang et al., 2020); 6,8,1'-tri-O-methylaveranthine (Kim et al., 2018); *Asperterectal f.* (Yang et al., 2018); and methanol extract (Jin et al., 2006), are characterized by having inhibitory mechanisms of inflammatory pathways, such as ROS synthesis, reduction of pro-inflammatory cytokines, and modulation of iNOS and COX-2 expression.

In addition to a reduction in the inflammatory response, other beneficial effects were observed for these metabolites. For example, in relation to the accumulation of Aβ peptide, which is strongly associated with the pathophysiology of AD, 2-BTHF extracted from *Holothuria scabra* has a protective potential, as it indirectly reduces the aggregation of Aβ oligomers from metabolic pathways observed in specific genes related to neurotoxicity and reduction of Aβ (Tangrodchanapong et al., 2021).

Terreusterpenes extracted from *Aspergillus terreus* showed inhibition of the BACE-1 enzyme, which is responsible for the cleavage of the amyloid precursor protein at the β site, resulting in a reduction in the formation of Aβ peptide and *in vitro* inhibition of acetylcholinesterase, which then increases the availability of acetylcholine in the synaptic cleft and improves cognitive deficits (Qi et al., 2018). Metabolites such as PL enriched with EPA extracted from *Cucumaria frondosa*, cerebrosides extracted from *Acaudina molpadioides*, cyclopenol, and cyclopenine have also shown effects on AD, improving deficits in learning, memory, and cognitive decline in murine models, and decreased neuronal apoptosis induced by Aβ in the hippocampus (Wu et al., 2014; Li et al., 2018; Che et al., 2017; Wang et al., 2020). In relation to AD, an important therapeutic strategy is the reversal of Tau protein aggregation. The results showed that the metabolites 2,3-dihydroxyemodine, asperthecin, and asperbenzaldehyde can interact with the β structure, which characterizes the conformations of the Tau protein. This is responsible for aggregation and prevention of the polymerization of filaments (Paranjape et al., 2014), in addition to isoquinoline interferring with the metabolism of Tau protein filaments (Ingham et al., 2021).

Regarding the accumulation of a-synuclein protein, the main hypothesis of the pathophysiological mechanism of PD is that FHS and FHL reduce the accumulation of this protein, suggesting that neuroprotection and FHL show regenerative activity in dopaminergic neurons (Malaiwong et al., 2019; Chalorak et al., 2021). Diterpene glycosides extracted from the species *Holothuria scabra* showed a reduction of a-synuclein in muscle cells in the *Caenorhabditis elegans* model, promoting improved motility due to the degradation of a-synuclein induced by autophagic signaling (Chalorak et al., 2021). The MHS metabolite reduces mitochondrial depolarization and promotes the inhibition of pro-apoptotic substances (BCE-1 and caspase 3), in addition to upregulating BCL-2, preserving neurons, and promoting behavioral and motor improvement in murine models (Noonong et al., 2020). Another therapeutic potential in PD was observed in Xyl-B and its derivatives, which is a probable mechanism of action to restore glutathione levels in PC12 cells and attenuate the loss of mitochondrial potential through the reduction of ROS overproduction (Lu et al., 2010). Such mechanisms may

explain the reduction in the degeneration of dopaminergic neurons evaluated in longevity and thermoregulation assays in *Caenorhabditis elegans* worms and the respiratory burst in zebrafish (Li et al., 2013; Zhou et al., 2018).

On HD, which occurs due to the accumulation of mHtt protein, leading to progressive neuronal loss, Xyloketal-B derivatives showed a significant protective effect from the formation of a complex through hydrogen bonding at the GLN396 site of the protein. Htt, thus prevents the aggregation of mHtt in muscle cells of *Caenorhabditis elegans*. Another hypothesis for the reduction of mHtt aggregates is through the stimulation of proteases, which would stimulate the elimination of mutant proteins (Zeng et al., 2016).

Thus, we can observe that *Acaudina malpodioides, Holothuria scabra and Xylaria sp*. stand out in our study, as they present a greater number of evidence in the literature. The 3 species have, in common, an important antioxidant action, with direct repercussions on biochemical pathways that generate ROS (Wu et al., 2013; Tangrodchanapong et al., 2021; Lu et al., 2010). Regarding ND and with different mechanisms of action, *A. malpodioides* and *Holothuria scabra*, demonstrated in murine models, positive effects on symptoms associated with Alzheimer's, in addition to presenting, respectively, neuroprotective effects and ability to reduce the concentration of Aβ. (Li et al., 2018; Che et al., 2017; Tangrodchanapong et al., 2021). Regarding PD, *Holothuria scabra*, through its bioactive compounds, has shown promise, as well as *Xylaria sp*., since both seem to attenuate the degeneration of dopaminergic neurons (Li et al., 2013; Lu et al., 2010; Chalorak et al., 2018; Chalorak et al., 2021). Furthermore, *Holothuria scabra* was able to reduce alpha synuclein deposition, while *Xylaria sp*., with its metabolite Xyl-B, reduced the formation of Mhtt protein aggregates, suggesting a possible neuroprotective effect for HD (Noonong et al., 2020; Zeng et al., 2016). The other marine compounds present in this study show promising potential in the context of ND, however further studies are needed for a better understanding of the repercussion of these compounds in the course of ND.

5. Limitations

Although research in the field of natural products of marine origin offers an incredible opportunity in the field of therapeutics, the results obtained in this review should be viewed with caution, since most of the analyzed studies were carried out using murine and in vitro models.. Thus, although some studies have described the therapeutic potential of some products of marine origin in relation to neurodegenerative disorders, it should be noted that a more detailed analysis of the repercussions of marine compounds in humans will only be possible with more preclinical evidence and the realization of of clinical studies, so that in this way, it is possible to explore and understand the potential of these substances of marine origin, thus bringing confidence in the applicability of these compounds.

6. Conclusion

The results presented in this review suggest that marine compounds have potential therapeutic mechanisms for ND, which may contribute to neuroprotection, antioxidant, anti-inflammatory, and anti-aging effects, especially to the progression of ND. Thus, the therapeutic action of these compounds has emerged as a possible new approach in the treatment of ND, as they act in pathological processes that are strongly associated with them. However, the reduced number of publications on the subject and the lack of clinical trials are important limitations of this review, especially in relation to long-term therapeutic efficacy and reduction of symptoms.

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