

Corrigendum: Edible seaweed-derived constituents: an undisclosed source of neuroprotective compounds

<https://doi.org/10.4103/1673-5374.313070>

In a detailed re-analysis of the published research paper, entitled “Edible seaweed-derived constituents: an undisclosed source of neuroprotective compounds”, published on pages 790–795, Issue 5, Volume 15 of *Neural Regeneration Research*, the authors discovered a shift in the referencing numbering, this results in a substantial number of wrongly cited statements, the full text should be corrected as follows:

Edible seaweed-derived constituents: an undisclosed source of neuroprotective compounds

<https://doi.org/10.4103/1673-5374.268894>

Received: June 25, 2019

Peer review started: June 27, 2019

Accepted: August 7, 2019

Published online: November 8, 2019

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Abstract

Edible marine algae, or seaweeds, are a rich source of several bioactive compounds including phytosterols, carotenoids, and polysaccharides. Over the last decades, seaweed-derived constituents turned out to not only reside in the systemic circulation, but are able to cross the blood-brain barrier to exert neuro-active functions both in homeostatic and pathological conditions. Therefore, seaweed-derived constituents have gained increasing interest for their neuro-immunomodulatory and neuroprotective properties, rendering them interesting candidates for the management of several neurodegenerative disorders. In particular seaweed-derived phytosterols gained interest for the treatment of neurodegenerative disorders as they potentiate neuroplasticity, enhance phagocytic clearance of neurotoxic peptides and have anti-inflammatory properties. Though, the anti-inflammatory and anti-oxidative properties of other constituents including carotenoids, phenols and polysaccharides have recently gained more interest. In this review, we provide an overview of a selection of the described neuro-active properties of seaweed-derived constituents with a focus on phytosterols.

Key Words: algae; carotenoids; neuro-active; phenols; phytosterols; polysaccharides; seaweed

Introduction

The marine ecosystem covers more than 70% of the world's surface and hosts a wide variety of macro- and micro-organisms. Among these organisms, marine algae are of particular interest as they have been attributed medicinal properties due to their distinct nutritional composition. Marine algae are a rich source of bioactive compounds and secondary metabolites, such as peptides, lectins, carotenoids, polysaccharides, fatty acids, flavonoids, and phytosterols, distinguishing them from terrestrial plants (Ngo et al., 2012; Yende et al., 2014). Edible marine algae, also referred to as seaweed, can be classified into three main evolutionary and phylogenetically distinguishable classes that differ in nutritional and chemical composition: brown (Phaeophyceae), red (Rhodophyta) and green (Chlorophyta) algae (Yende

et al., 2014). Since seaweeds require 0.1% photosynthetic light, they can be found in subtidal as well as intertidal waters. Potential medicinal properties of seaweeds have been explored for ages in traditional east Asian medicine, rendering China and Indonesia the two major cultivators and consumers of seaweed nowadays (Dhargalkar and Pereira, 2005; Yende et al., 2014). Interestingly, over the past decades, scientific interest in unravelling the exact pharmacological properties of marine algae and their constituents increased tremendously. Beneficial effects of seaweeds have been studied in the context of anti-inflammatory and anti-oxidant functions in divergent pathological conditions such as cancer, atherosclerosis, skin abnormalities, and neurodegeneration (Liu et al., 2012). In this review we discuss the neuroprotective properties of seaweed and its constituents, focussing on phytosterols in particular (**Table 1** and **Figure 1**).

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Funding: NWO-TTW (Netherlands Organisation for Scientific Research), No. 16437; Alzheimer Nederland, No. WE.03-2018-06.

How to cite this article: Schepers M, Martens N, Tiane A, Vanbrabant K, Liu HB, Lütjohann D, Mulder M, Vanmierlo T (2021) Edible seaweed-derived constituents: an undisclosed source of neuroprotective compounds. *Neural Regen Res* 16(12):2564-2568.

Table 1 | The neuro-active effects of seaweed derived constituents and their biological effects for the management of neurodegenerative disorders

Constituent family	Individual constituent	Biological impact	Reference
Phytosterol	Fucosterol	Reduction in Aβ-induced ER stress Increases acetylcholine in brain Counteracts memory deficits	Oh et al., 2018 Andrade et al., 2013 Jung et al., 2016; Oh et al., 2018
	24(S)-Saringosterol	Reduces neuronal Aβ release Increases Aβ clearance	Bogje et al., 2019 Bogje et al., 2019
	Sitosterol	Reduces Aβ plaque formation Anti-inflammatory	Wang et al., 2013 Liu et al., 2019
	Stigmasterol	Reduces Aβ plaque formation	Burg et al., 2013; Koivisto et al., 2014
Caretoneoids	Beta-carotene	Anti-oxidant	Sangeetha et al., 2009
	Fucoxanthin	Reduces Aβ plaque formation Anti-oxidant Counteracts memory deficits	Zhao et al., 2015; Jung et al., 2016; Xiang et al., 2017; Alghazwi et al., 2019 Sangeetha et al., 2009; Jang et al., 2018 Jung et al., 2016; Xiang et al., 2017
Phenols	Apo-9'- fucoxanthinone	Anti-inflammatory	Chae et al., 2013
	Phloroglucinol	Anti-oxidant Reduces Aβ-induced dendritic spine reduction Counteracts memory deficits	Yang et al., 2015 Yang et al., 2015 Yang et al., 2015
Polysaccharides	Fucoidan	Counteracts memory deficits	Gao et al., 2012
	<i>Sargassum fusiforme</i> polysaccharide 65	Counteracts memory deficits	Hu et al., 2016

Aβ: Amyloid beta.

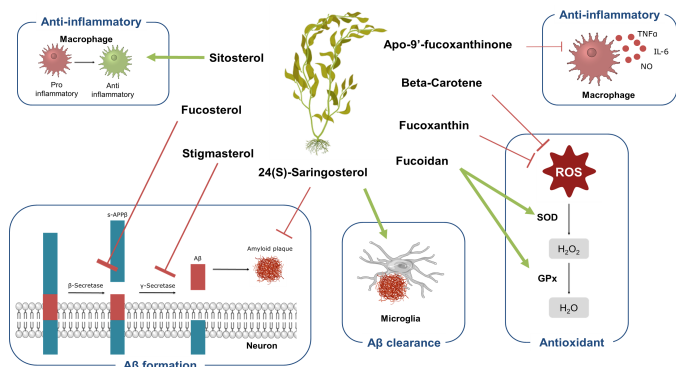


Figure 1 | An overview of the key mechanism underlying bioactive properties of seaweed-derived constituents.

Phytosterols present in seaweed have mainly been described to be anti-inflammatory (sitosterol) and to interfere in neurotoxic peptide formation and clearance (fucosterol, stigmasterol, 24(S)-saringosterol). Especially anti-oxidative (beta-carotene, fucoxanthin) and anti-inflammatory (apo-9'-fucoxanthinone) properties have been attributed to carotenoids although their anti-inflammatory features. The polysaccharides in seaweed called fucoidan have been shown to be able to normalize ROS and GPx levels, essential for preventing ROS accumulation. Images were modified from Reactome icon library and Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Generic License (Sidiropoulos et al., 2017). Aβ: Amyloid beta; GPx: glutathione peroxidase; ROS: reactive oxygen species; SOD: superoxide dismutase.

Search Strategy and Selation Criteria

The approached search strategy was based on a focussed literature review. Databases used for the search included PubMed and Google Scholar. Search terms were combined in different manners and included: "seaweed constituents", "phytosterols", "neuromodulation", "fucoidans", "polysaccharides", "phenols", "caretoneoids", "neuroinflammation", "neurodegeneration", "macroalgae", "memory", "cognition".

Phytosterols as Neuro-Active Constituents

To date, phytosterols (e.g., plant sterols and plant stanols) have been enriched in functional foods to lower circulating levels of cholesterol and thereby reduce the risk of cardiovascular diseases. Yet, up to now, no trials have been conducted (with

clinical endpoints) that evaluate the health effects of plant sterols or stanols in cardiovascular disorders. However, given that phytosterols would be capable of lowering cholesterol levels, they would not only reduce the risk of cardiovascular events, but could also be beneficial in central nervous system (CNS) disorders. While phytosterols can solely be derived from the diet, in the CNS, cholesterol is almost entirely synthesized locally (Hijmans et al., 2015; Vanmierlo et al., 2015). We and others have previously shown that phytosterols are able to cross the blood-brain barrier (BBB) and accumulate in the CNS where they can be incorporated in lipid rafts of CNS-resident cells and subsequently modify protein-protein interactions (Jansen et al., 2006; Vanmierlo et al., 2012). Phytosterols may therefore exert neuromodulatory properties. However, most studies thus far focussed on phytosterols present in terrestrial plants such as sitosterol, campesterol, and stigmasterol. Interestingly, seaweed is enriched in other specific phytosterols such as fucosterol and saringosterol which have been shown to exert neuromodulatory effects on synapse integrity and cognition, in health and disease. Importantly, mainly Phaeophyceae seaweed species could be considered a developable resource for phytosterols as all Rhodophyceae species are featured by cholesterol as dominant sterol (Al Easa et al., 1995). Chlorophyceae differs from the other classes because the dominant sterol seems to vary within the order or, for the same order, within the family (Al Easa et al., 1995). Phaeophyceae enriched with phytosterols may therefore offer a promising therapeutic strategy in the prevention or treatment of neurodegenerative disorders.

Neurodegenerative disorders are often featured by a wide range of diverse and intertwined neuro-inflammatory processes, leading to primary or secondary CNS damage. Neuro-inflammation is not only a central mediator of neurodegeneration, it also plays a pivotal role in permitting, facilitating, and orchestrating CNS repair. Therefore, modulating neuro-inflammatory processes can hold the key for treating multiple neurodegenerative disorders such as Alzheimer's disease (AD) and multiple sclerosis (MS). Recently, it has been shown that the phytosterol sitosterol is able to modulate macrophage functions by augmenting the polarization of macrophages towards an anti-inflammatory phenotype, suggesting an interesting strategy for neurodegenerative disease management (Liu et al., 2019). Furthermore, emerging evidence indicates that

Corrigendum

phytosterols exert anti-inflammatory functions by activating nuclear liver X receptors (LXRs). LXRs are key transcription factors essential for modulating the sterol metabolism and homeostasis, and regulating immunomodulatory processes. The anti-inflammatory properties of phytosterols via LXRs can mainly be attributed to a mechanism of transrepression of toll-like receptor activation (Ghisletti et al., 2007). Although phytosterols such as stigmasterol, fucosterol, brassicasterol, and sitosterol have been reported to activate LXRs, it has recently been shown that these phytosterols were unable to activate LXRs at physiological concentrations that can be reached through dietary supplementation (Bogie et al., 2019). Interestingly, the seaweed-derived phytosterol 24(S)-saringosterol was able to activate LXRs at these physiological concentrations (Chen et al., 2014; Bogie et al., 2019). In contrast with full synthetic LXR agonists, both pure 24(S)-saringosterol and a 24(S)-saringosterol-containing seaweed extract of *Sargassum fusiforme* did not induce typical LXR-dependent side effects (e.g. hypertriglyceridemia and hepatic steatosis) likely because 24(S)-saringosterol predominantly activates LXR β (Plat et al., 2005; Bogie et al., 2019). For that reason, seaweed-derived 24(S)-saringosterol may provide an attractive strategy for ceasing and modulating neuro-inflammation in neurodegenerative disorders.

Synaptic loss is an early characteristic of aging and multiple neurodegenerative disorders (e.g., AD, schizophrenia, amyotrophic lateral sclerosis). During disease progression, synaptic loss is prominent and coincides with cognitive decline, sensory disturbances, and motor impairments. Newly formed synapses are often formed as a compensatory mechanism for coping with the pathological consequences (Jansen et al., 2012). In order to maintain synaptic integrity and to support synapse remodelling, distal axons require additional sterols that cannot be supplied sufficiently from the distant nerve cell body. LXRs act as cholesterol metabolite sensors that induce LXR-responsive genes required for maintaining cellular cholesterol turnover from astrocytes to neurons. Activation of LXRs may therefore enhance synaptic integrity and cognitive function. The LXR agonist T0901317 has been shown to stimulate the formation of new synapses in aged AD mice by enhancing cerebral cholesterol turnover (Vanmierlo et al., 2011). Seaweed-derived phytosterols may consequently also offer an interesting therapeutic strategy for enhancing synapse remodelling due to the activation of LXRs.

AD is featured by the accumulation of the toxic amyloid- β (A β) peptide. Although physiological levels of A β may be crucial for synaptic plasticity and neuronal survival, high concentrations eventually causes neurotoxicity and cell death (Cárdenas-Aguayo Mdel et al., 2014). The seaweed-derived fucosterol has been shown to be a non-competitive inhibitor of the β -secretase, an enzyme crucial in the formation of the toxic A β monomers (Jung et al., 2016). Furthermore, 24(S)-saringosterol has been found to reduce neuronal A β secretion while stimulating microglia-mediated clearance of A β . In line, dietary supplementation with either the brown seaweed *Sargassum fusiforme*, which contains high levels of 24(S)-saringosterol, or its lipid extract reduced A β plaque load and improved cognition in a mouse model for AD (Bogie et al., 2019). However, besides 24(S)-saringosterol, also fucosterol, fucoidan, and fucoxanthin present in seaweed have been reported to counteract memory deficits and can therefore at least partially contribute to the therapeutic effects seen upon *Sargassum fusiforme* and its extract supplementation (Hu et al., 2016; Xiang et al., 2017; Oh et al., 2018). For instance, fucosterol showed to be not only a selective inhibitor of cholinesterases and therefore subsequently increased the levels of the neurotransmitter acetylcholine in the brain, but also reduced and prevented the formation of A β peptides (Andrade et al., 2013; Oh et al., 2018). Furthermore, fucosterol alleviates A β -induced endoplasmic reticulum (ER)

stress and cognitive impairment suggesting that fucosterol can attenuate ER stress-induced ageing-associated cognitive decline (Oh et al., 2018). Since 24(S)-saringosterol is an auto-oxidation product of fucosterol, a contribution of 24(S)-saringosterol to these described health benefits of fucosterol cannot be ruled out yet (Volkman et al., 1994).

Not only seaweed-derived phytosterols, but also phytosterols highly present in terrestrial plants have been reported to modulate AD pathology. Substitution of membrane cholesterol with sitosterol modulates the non-amyloidogenic processing of the amyloid precursor protein and may therefore reduce A β formation (Wang et al., 2013). In accordance with this, *in vitro* experiments showed that stigmasterol suppresses the activity of the lipid-raft associated γ -secretase thereby reducing A β generation and modulating AD pathogenesis (Burg et al., 2013; Koivisto et al., 2014).

Seaweed-derived phytosterols have been shown to be neuro-active modulators in the CNS. By ameliorating neuro-inflammation, stimulating synapse remodelling, diminishing neurotoxic protein accumulation and improving cognitive functioning in the CNS, seaweed-enriched phytosterols can be considered an interesting therapeutic strategy for the treatment of neurodegenerative disorders.

Non-Sterol Constituents as Neuro-Active Compounds

Besides phytosterols, numerous other seaweed-derived constituents have been reported to possess neuromodulating effects, rendering them interesting therapeutic molecules in strategies to modulate neuro-inflammatory and neuro-degenerative processes.

Carotenoids have often been investigated for their anti-oxidative properties. Although beta-carotene has been described as the most important anti-oxidant, fucoxanthin, highly present in Phaeophyceae, has gained interest for modulating CNS-related processes. In AD, accumulation of reactive oxygen species (ROS) leads to oxidative stress which negatively affects synaptic plasticity and causes neuronal death, leading to memory deficits and cognitive impairments. Beta-carotene and fucoxanthin act antioxidative and prevent ROS formation (Sangeetha et al., 2009; Jang et al., 2018). Reducing ROS accumulation may therefore ameliorate the AD-associated deficiencies in memory and cognitive functions. Additionally, in cerebral cortical neurons, SH-SY5Y-, and PC12 cells, fucoxanthin inhibited the formation and aggregation of A β peptides, indicating a potential role for fucoxanthin in the treatment of AD (Zhao et al., 2015; Xiang et al., 2017; Alghazwi et al., 2019). Besides anti-oxidative properties, carotenoids have been shown to exhibit anti-inflammatory features such as inhibiting the inflammatory response in macrophages. Apo-9'-fucoxanthinone isolated from brown alga *Sargassum muticum* suppressed NO and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. Furthermore, in bone marrow-derived phagocytes, apo-9'-fucoxanthinone attenuated nuclear factor-kB-induced inducible nitric oxide synthase and cyclooxygenase-2 expression and suppresses CpG-induced production of pro-inflammatory cytokines interleukin-12 p40, interleukin-6 and tumor necrosis factor- α (Chae et al., 2013).

Next, seaweed-derived phenols have been described to possess neuroprotective properties. The polyphenol phloroglucinol, which is plentiful in the brown alga specie *Ecklonia cava*, was found to attenuate A β -induced ROS accumulation in the hippocampal neuronal cell line HT-22 (Yang et al., 2015). Potentially by acting as an anti-oxidant, phloroglucinol ameliorated the A β -induced reduction in dendritic spine density in primary rat hippocampal neurons and attenuated cognitive impairment *in vivo* in an animal

model of AD (Yang et al., 2015).

The family of homo- and heteropolysaccharides called fucoidans, are widely distributed in brown algae. Biological effects of fucoidans have been extensively described and include mainly antitumor, antiviral and anticoagulant activities. Recently the neuro-active properties of fucoidans have been investigated in the context of AD. Fucoidans have been shown to normalize the levels of superoxide dismutase, glutathione peroxidase, choline acetyltransferase and acetylcholinesterase in the hippocampus of rats injected with A β (Gao et al., 2012). Cognitive impairments observed upon the A β infusion in these animals were ameliorated upon fucoidan treatment, suggesting a therapeutic potential of fucoidans in the context of AD (Gao et al., 2012). Additionally, *Sargassum fusiforme* polysaccharide 65 (SFPS65), a fucoidan, has been shown to ameliorate spatial learning and memory deficits in Swiss Albino mice (Hu et al., 2016). Further studies are however required to elucidate the underlying mechanisms of SFPS65-induced cognitive improvement.

Besides individual non-sterol constituents, the combination of multiple constituents to modulate cognitive processes, such as depression, anxiety and memory have been extensively investigated. A cross-sectional study conducted in Japan, where seaweed is largely being consumed, reported that depressive-like symptoms during pregnancy were reduced upon increased seaweed consumption, independent of the seaweed taxonomy (Miyake et al., 2014). Interestingly, a hydrophilic extract made from the green seaweed *Ulva sp.* reduced depressive-like behaviour in rodents. Although the exact underlying mechanisms remain unknown, the neuro-active compound is thought to be a family of sulphated polysaccharides, the ulvanse, which are highly present in the extract (Violle et al., 2018). The hypothesis of polysaccharides being involved in the observed anti-depressive actions is further strengthened by the finding that a water-soluble extract derived from the green seaweed *Ulva Lactuca* improved depressive symptoms in humans who experience a reduced feeling of motivation and pleasure (Allaert et al., 2018). A hexane extract of brown algae, containing a high amount of hydrocarbons, made from *Sargassum plagyophyllum* acted as an antidepressant in a mouse model of despair (Mesripour et al., 2019). However, not only hydrocarbons of brown seaweed but also plant phenols present in the methanolic extracts of *Sargassum swartzii*, *Sargassum plagyophyllum*, *Stoechospermum marginatum* and *Nizamuddiniana zanardinii* exhibited an antidepressant-like activity potentially by acting and modulating the monoaminergic system in rodents (Siddiqui et al., 2017; Mesripour et al., 2019).

Since the glucose stores in the brain are limited, a steady supply of glucose is required to maintain optimal cognitive function (Haskell-Ramsay et al., 2018). Several studies have shown that consumption of foods low on the glycemic index (GI) scale, which tend to release glucose slowly and steadily, have beneficial effects on cognition compared to high GI foods (Philippou and Constantinou, 2014). The drawback of a low GI diet is the limiting types of food that can be consumed. An alternative approach to slow the carbohydrate absorption is inhibiting carbohydrate digestion (Haskell-Ramsay et al., 2018). Although the anti-diabetic drug acarbose inhibits the key enzymes of carbohydrate digestion and absorption, α -amylase and α -glucosidase (Haskell-Ramsay et al., 2018), it induces side effects including gas accumulation and abdominal distention (Bischoff, 1994). A natural alternative to this anti-diabetic drug could be seaweed. The brown algae *Ascophyllum nodosum* (Apostolidis and Lee, 2010; Lordan et al., 2013; Pantidos et al., 2014) and *Fucus vesiculosus* (Lordan et al., 2013) have been shown to inhibit α -glucosidase to a greater extent than acarbose and α -amylase to a lesser extent

(Haskell-Ramsay et al., 2018), an effect that has been shown to correlate with the seaweed phenol content (Apostolidis and Lee, 2010). Importantly, no side effects have been observed yet (Paradis et al., 2011). Seaweeds may therefore improve glucoregulation without side effects, which is suggested to have cognitive benefits. Nevertheless, it needs to be kept in mind that several studies showed the presence of toxic elements, such as radioactive isotopes and toxic metals (e.g., As, Cd, Pb and Al) in multiple seaweed species potentially entailing health risks (Rubio et al., 2017). Similar to the composition of bioactive constituents, the concentrations of toxic metals and traces differs upon seaweed taxonomy and cultivation conditions (Rubio et al., 2017). Although there are exceptions, toxic metals found in seaweed have not been reported to exceed the reference value (< 5%) upon consumption of 4 g seaweed per day, the average amount of seaweed the Japanese consume, indicating a negligible safety hazard (Rubio et al., 2017).

Concluding Remarks

The role of seaweed and its constituents as neuro-active compounds have gained tremendous interest in the last decade. Moreover, not only seaweed but also the multiple individual constituents can modify several CNS-related processes for modulating neuro-inflammation and neurodegeneration. Especially phytosterols have been extensively studied for their neuroprotective properties. Phytosterols can be found both in terrestrial plants and in multiple seaweed species with the most promising class being the Phaeophyceae algae. Due to the variety of biological actions, phytosterols offer a promising therapeutic strategy for ceasing the intertwined neuro-inflammatory and neurodegenerative processes featuring multiple CNS disorders. Sitosterol enhances the polarization of bone marrow-derived macrophages towards a more anti-inflammatory phenotype. Both fucosterol and stigmasterol have been described to reduce A β plaque formation by inhibiting β - and γ -secretases respectively. Interestingly, 24(S)-saringosterol not only reduces A β production but additionally increased microglial clearance of A β peptides, providing an attractive strategy for enhancing the clearance of neurotoxic peptides in general. Furthermore, in contrast to phytosterols common in the Western diet, 24(S)-saringosterol recently has been shown to be an LXR β agonist at physiological concentrations. Due to the subsequent transrepression of toll-like receptors upon LXR activation, 24(S)-saringosterol possess a potential anti-inflammatory benefit. Furthermore, carotenoids, phenols and polysaccharides present in seaweed recently gained interest for their potential to treat CNS disorders. The carotenoids beta-carotene and fucoxanthin gained tremendous interest for their anti-oxidative properties, while apo-9'-fucoxanthinone reduced pro-inflammatory cytokine secretion by activated macrophages. Moreover, the seaweed-derived phenol, phloroglucinol, has been shown to harbour neuroprotective properties since it preserves dendritic spine density *in vitro* in primary hippocampal neurons cultured with A β . Finally, fucoidans, the polysaccharides widely distributed in algae, protect mice against cognitive decline, albeit the exact underlying mechanism remains to be elucidated.

By unravelling the neuro-active seaweed-derived constituents, the emerging field of seaweed constituent-based pharma gains more interest. For instance, semi-synthetic phytosterols are being developed and characterised for their potential to activate LXRs (Castro Navas et al., 2018). The semi-synthetic phytosterols have so far been described as positive LXR modulators rendering them interesting therapeutic strategies for modulating neuro-inflammation and enhancing neuroprotection (Castro Navas et al., 2018). As mentioned before, not only separate constituents but seaweed as a whole can be used for their neuroprotective properties. The

Corrigendum

usage of seaweed supplementation in the food industry combines the beneficial properties of multiple nutraceuticals for the application of disease prevention and disease management. Yet, the composition of bioactive constituents in the seaweed is highly variable and dependent on seasonality of sampling, taxonomic entity, location and related growth conditions. By identifying the most promising constituents, seaweed production and harvest can be optimised by utilizing more controlled systems before harvesting the seaweed. Nevertheless, the required amount of seaweed intake to reach neuro-active concentrations of the constituent of interest exceeds the dietary feasibility. Use of crude plant extracts with increased concentrations of its constituents may bypass this limitation and are easily implemented in the diet or as therapeutic intervention. Taken together, further identifying and unravelling the key neuro-active compounds in multiple seaweed species may lead to the development of nutraceutical treatment options for managing several neurodegenerative disorders.

Acknowledgements: *The authors sincerely thank Chuck Ungerman for editing the paper.*

Author contributions: *All authors wrote the manuscript and approved the final manuscript.*

Conflicts of interest: *We declare no conflicts of interest.*

Financial support: *NWO-TTW (Netherlands Organisation for Scientific Research), No. 16437; Alzheimer Nederland, No. WE.03-2018-06.*

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