Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 5 Issue 8 August 2021

Review Article

Neuroprotective Potential of Bioactive Sulfated Polysaccharides from Algae

Bitarka Bisai and Sirisha L Vavilala*

School of Biological Sciences, University of Mumbai, Kalina Campus, Mumbai, India

***Corresponding Author:** Sirisha L Vavilala, Assistant Professor, School of Biological Sciences, University of Mumbai, Kalina Campus, Mumbai, India.

Received: June 28, 2021

Published: July 31, 2021

Abstract

Neurodegenerative diseases are disorders of the central nervous system and common cause of physiological and economic burden worldwide. Most of the current drugs for treatment of Parkinson's Disease and Alzimer's Disease aren't sufficiently effective in preventing their progress and have multiple adverse side-effects. Hence, there is a need for therapeutics from natural sources. Interest for the use and exploitation of the marine algae is expanding. The marine environment is well known for its rich sources of chemical compounds with numerous beneficial health effects. It is known that many marine algae species contain Sulfated Polysaccharides (SPs) and their lower molecular weight oligosaccharide derivatives which are biocompatible, biodegradable and have been shown to offer numerous health benefits. This review highlights the different types of SPs from different algae, their structures, their bioactive potential particularly their immense potential for prevention of neurodegenerative diseases and provide a scientific basis to the development of new generation of phytopharmaceuticals which can be used alone or in combination with other drugs.

Keywords: Neurodegenerative Diseases; Natural Products; Sulfated Polysaccharides; Algae; Antioxidant Potential; Neuroprotective Agent

Introduction

Neurodegenerative disease are the disorders related to the central nervous system (CNS). Neurodegeneration (ND) is basically related to the loss of function of the neurons which can in turn lead to the death of the neurons. Alzheimer's, Parkinson's, Huntington's are some of the diseases caused due to neurodegeneration. ND are estimated to surpass cancer as the second most common cause of death among elderly by the year 2040 [1]. These diseases are mainly accompanied by the aggregation of the misfolded protein, which trigger the accumulation of certain peptides such as amyloid β (Aβ) [1].

Alzheimer's disease (AD) is one of the ND which results in memory loss and is caused due to the aggregation of misfolded proteins and neurofibrillary tangles in brain. It is one of the progressive irreversible ND of the CNS. It is characterized by decrease in cholinergic transmission, memory loss, personality change and change in the psyche-behavior. The remarkable change in AD patients is the reduction of the acetylcholine (Ach) levels in the brain (hippocampus and cortex region). It is the cause of 60-70% cases of dementia. With disease progression, symptoms like disorientation, problem with language, mood swings, loss of motivation and behavior issues are more prominent [2]. The cause of AD is still unclear but there are multiple factors that play role in the pathogenesis, which includes abnormal protein aggregation, oxidative stress, excessive metal ion, inflammation leading to loss of neurons etc. Apart from this, there are high chances with genetic inheritance of this disease [2].

Parkinson's disease (PD) is a neurodegenerative disease (ND) related with several motor and non-motor features including cognitive dysfunction. It is a long-term disease of the central nervous system which affect the motor function. This is characterized by the aggregation and accumulation of α-synuclein protein of the Lewy bodies and loss of the dopaminergic neurons which results in drastic reduction of the dopamine content in the striatum and corresponding loss of dopamine transporters. The cause of PD is obscure but believed to be mostly hereditary and environmental [3].

Huntington's disease (HD) on the other hand is an autosomal dominant inherited ND characterized by progressive motor, behavioral, and cognitive decline, resulting in death within 15-20 years after diagnosis. The disease progression can be seen as early as 20 years or above 65 years rarely. The pathologic mutation comprises of an extended CAG repeat in the Huntingtin gene (HTT) on chromosome 4, encoding the huntingtin (htt) protein (Dayalu., *et al*. 2015). The clinical set of symptoms in HD is (1) progressive motor disorder; (2) progressive cognitive disturbance culminating in dementia; and (3) psychiatric disturbances including depression, anxiety, apathy, obsessive-compulsive behaviors, outbursts, addictions, and occasionally psychosis. It is a devastating ND affecting the brain through neuronal dysfunction and loss [4].

Type 2 diabetes has previously been established as an independent risk for the development of both cognitive impairment and dementia [5]. It is a profoundly pervasive and chronic metabolic disorder. Recent research proposes that arrangement of toxic aggregates of the islet amyloid polypeptide (IAPP) may add to β-cell dysfunction and infection [6]. However, the component of protein accumulation and related toxic quality remained elusive. Misfolding, aggregation and accumulation of various proteins in various organs is the trademark in the gathering of protein misfolding disorders (PMDs), including very common diseases influencing the CNS [6]. Several research groups are working in understanding the molecular mechanism of ND. Some of the key mechanisms which are associated with ND are discussed subsequently.

Mechanisms of neurodegeneration

NDs are mainly associated with different neurodegeneration like neuroinflammation, damage by reactive oxygen and nitrogen species (ROS, RNS), synaptic loss and other neuronal cell death.

- **Neuroinflammation:** Studies have shown that activation of microglia cells resulted in the production of proinflammatory and nitric oxide, ROS, TNF-α which induced neurodegeneration. Occurrence of excessive pro-inflammatory factors have been activated during the pathogenesis of PD and AD [1].

- **Oxidation/Nitrosative damage:** It is known that the imbalance between pro-oxidant and antioxidant homeostasis leads to the generation of toxic reactive nitrogen and oxygen species that induce pathogenesis of ND. This accumulation of ROS and RNS can results in the degradation of lipids, DNA damage, protein oxidation, and ultimately neuronal cell death [1]. There are several enzymes inside the cell which will try to scavenge these ROS and RNS such as: Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPX), lipid hydroperoxides (LP) [7]. However insufficient scavenging ability of these enzymatic and non-enzymatic machinery of the cell results in the progression of the disease.

- **Synaptic loss:** One of the major hallmarks of ND is the loss of particular subsets of neurons. A decline in the levels of Acetylcholine (Ach) levels was observed in most of the NDs. It is known that two types of cholinesterase (ChE) are found in the CNS: acetylcholinesterase (AChE) and butyl cholinesterase (BuChE). AChE specifically degrade Ach in the cholinergic synapses, while BuChE is a non-specific enzyme which is considered to play role in regulating brain AChE levels [1]. Decline in Ach levels result in neuronal cell death.

Molecular Pathways involved in neurodegeneration

Oxidative and Nitrosative stress are increasingly associated with the pathology of neurodegeneration and aging. Attention is turning towards the modulation of intracellular signaling as a therapeutic approach against neurodegeneration. The various molecular signaling pathways associated with oxidative stress and neurodegeneration has been discussed below.

Mitogen Activated Protein Kinase (MAPK) pathway

Nitric oxide may directly influence the intracellular redox-state or can modulate MAPK signaling. Mammals express at least three distinctly regulated groups of MAPKs, which may exist in different isoforms: ERK1/2, c-Jun amino-terminal kinases (JNK1/2/3), and

p38 kinases. All members of the MAPK family require dual phosphorylation of a threonine and tyrosine residue within the catalytic domain by their respective upstream kinase. Once activated they can function as modulators for differentiation, proliferation, cell death, and survival. Mostly, the activation of ERK1/2 has been linked to cell survival, whereas that of JNK and p38 has been associated with apoptosis.

Initiation of ERK1/2 can prompt the phosphorylation of a wide cluster of potential targets in cytosol or nucleus. For instance, active ERK1/2 can initiate transcription factors and thus phosphorylate particular effector kinases i.e., the MAPK-initiated protein kinases (MAPKAPKs), mitogen-and stress-activated kinase-1 (MSK1) or the pp90 ribosomal S6 kinase (RSK). In turn, RSK phosphorylates the Bcl-2 family member i.e., Bad, accordingly restraining its apoptotic movement. RSK and MSK1 are additionally powerful activators of the cyclic Adenosine Mono Phosphate (cAMP) response element binding protein (CREB), a transcription factor for Bcl-2 and, consequently, an essential factor for cell survival. This shows that dynamic ERK1/2 plays a crucial role in pro-survival signal transduction processes. Indeed, different studies that has been done, clearly show that under certain conditions the activation of ERK1/2 is essential to neuronal survival [8].

Another major MAPK that responds to cellular and environmental stress is p38. The p38 pathway can be activated by a variety of extracellular boosts including development factors, for example, Granulocyte-macrophage colony-stimulating factor (GM-CSF), Fibroblast growth factors (FGF), Nerve growth factor (NGF), Insulin-like growth factor (IGF), Vascular endothelial growth factor (VEGF) and Platelet-derived growth factor (PDGF), heat shock, cell extending, proinflammatory cytokines and oxidative anxiety, which can prompt an assortment of cell reactions including cell development, cell cycle, cell death, cell differentiation and inflammation. Another important role of p38 involves neurodegeneration. Inhibition of p38 MAPK has been shown to be neuroprotective following permanent focal stroke in the rat models [9].

MAPKs and Neurodegenerative diseases: Strong evidence showed that active MAPKs increased in AD [10]. Activated MAPK is discovered particularly in intracytoplasmic punctate structures and intracellular Neurofibrillary Tangles (NFTs), for the most part in a subpopulation of neurons. Furthermore, the upstream activators in the ERK pathway, including active Ras and SOS/Grb2, are likewise expanded or modified in AD in contrast with controls. This information proposes that the whole ERK pathway is unusually initiated in AD and a signal got from the cell surface adds to the pathogenesis of AD. Since the ERK pathway transduces signals that control cell cycle movement considering mitogenic stimulus, it is fascinating to take note of that growth factors, for example, NGF, TGF and bFGF, which can fill in as a mitogenic signal from the cell surface, are expanded in AD. As a conceivable outcome of the initiation of ERK pathway, many cell cycle markers are re-expressed in vulnerable neurons in AD, recommending an endeavor of re-entry of the cell cycle, which may add to a definitive cell demise [9].

In relation to AD, increased p38 MAPK activity in human brains was observed [11]. Levels of MKK6, an upstream activator of p38 MAPK, have likewise been observed to be upregulated in AD patients, demonstrating an active part for the p38 MAPK pathway in AD pathogenesis. The positive correlation between p38 MAPK and AD shows various exceptionally distinct parts that this kinase plays in neurodegeneration [12].

C-Jun N-terminal Kinases (JNK) pathway

The JNK belongs to the group of mitogen-activated protein kinases (MAP-kinases) which are activated by exposure of cells to environmental stress. The activation of JNK pathways in general is required for normal cellular activities and was also associated with neurotic demise related with neurodegenerative ailments. Active research on the correlation of JNK signaling cascade with ND has been done. Initial studies concentrated on characterizing the pathway and associated molecules of JNK signaling cascades, however later studies showed that JNK as a target to avoid cell death. A few *in vitro* and *in vivo* studies have detailed adjustments of JNK pathways possibly associated with neuronal demise in PD and AD. So, efforts are currently going on for creating inhibitors of this pathway [13].

JNK activates by dual phosphorylation on the motif Thr-Pro-Tyr, which is mediated by MAP kinase-kinases MKK4 and MKK7. These serve as signaling molecules that integrate a wide array of stimuli into the activation of the JNK signaling pathway. Once JNK is phosphorylated and gets activated, it phosphorylates a variety of nuclear factors such as c-Jun, ATF2 and Elk, as well as cytoplasmic substrates such as cytoskeletal proteins, mitochondrial proteins like Bcl-2 and Bcl-xl, the glucocorticoid receptor, or the amyloid precursor protein (APP) membrane protein leading to neuronal cell

death [13]. JNK1 and JNK2 have a broad tissue distribution, while JNK3 is found mainly in brain and testes thus making this pathway a target for treatment of diseases in which neuronal death must be prevented in the mature CNS. Experimental study has shown that there is positive correlation between JNK signaling pathway activation and neuroinflammation, BBB disruption, and oligodendroglial apoptosis in the white matter injury of the immature rat brain [13].

JNK and Neurodegenerative diseases

At cellular level, major neuropathological scores of AD incorporate extracellular accumulation of Aβ peptides prompting arrangement of decrepit/neurotic plaques and intracellular neurofibrillary tangles (NFTs) which are combined helical fibers (PHFs) of hyperphosphorylated tau proteins. Specifically, JNK3 is exceedingly expressed in brain tissue and cerebrospinal fluid from patients with AD and statistically correlated with the rate of cognitive decline. It has been portrayed that Aβ peptides can initiate JNK activation. JNK3 is the known to be a significant kinase for β-amyloid precursor protein (APP) phosphorylation. JNKs were associated with Aβ activated down control of the counter apoptotic Bcl-w and initiation of Toll-like receptor 4 (TLR4) activation. Neurons from TLR4 mutant mice display lessened JNK and caspase-3 initiation and ensure against Aβ instigated apoptosis. c-Jun N-terminal kinase also modulates the formation of NFTs by the phosphorylation of Tau protein. *In vitro* phosphorylation studies show that the JNK3 isoform can strongly auto phosphorylate itself and contribute to Tau hyperphosphorylation. Apart from this, c-Jun has been identified to play other possible roles in AD, for e.g., phosphorylated c-Jun present within the structure of NFTs may play an indirect regulatory role in tangle maturation in AD, mostly regulated by its phosphorylation by JNK [14].

Hence, inhibition of JNKs is an attractive therapeutic strategy that has been investigated with considerable recent efforts from both the pharmaceutical industry and academia. In the previous years, couple of small inhibitors of JNKs have entered clinical trials for various signs, however none for the treatment of AD. Current synthetic drugs under assessment are: bentamapimod for the treatment of inflammatory endometriosis, CC-930 (tanzisertib) for the treatment of idiopathic pulmonary fibrosis and discoid lupus erythematous as well as D-JNKi1 for the treatment of inflammation and stroke [14]. All of these are in clinical trials and found to have significant side effects.

AKT pathway and neurodegenerative diseases

Macro-autophagy (autophagy) is an intracellular degradative process in which damaged organelles and perpetual proteins degrade and reused for keeping up normal cell homeostasis. Disruption of autophagy assumes an important part in ND, where insufficient elimination of abnormal and toxic protein aggregates advances cell stress, deformation, and death. Therefore, enlistment of autophagy has been proposed as a sensible technique to enable neurons to clear abnormal protein aggregation and survival. Abnormal protein accumulation is a general characteristic for both AD and PD and is associated with mitochondrial dysfunction and oxidative stress [15].

The kinase mammalian target of rapamycin (mTOR) is a noteworthy modulator of autophagy, and it gets inputs from various signaling pathways. The kinase mTOR is a downstream target of the phosphatidylinositol 3 kinase (PI3K) and kinase (AKT) pathway, which is activated by receptors of neurotrophins, growth factors, and advances cell development, differentiation, and survival, while down regulating apoptotic signals. Therefore, initiation of the PI3K/AKT/mTOR pathway would promote survival, neuronal security, and restraint of autophagy by mTOR enactment [16].

Dysregulation of the PI3K/AKT/mTOR pathway is regularly detailed in brains from AD and PD patients, yet obviously in various ways. Expanded AKT enactment, mTOR phosphorylation at serine buildup 2448, microtubule related protein (tau) phosphorylation at serine deposit 214 and diminished levels of the cyclin dependent kinase inhibitor 1B (p27, kip1), which recommend cell cycle movement to G1, are seen in AD transient cortex neurons contrasted and control neurons. Also, significant loss and altered distribution of the phosphatase and tensin homolog (PTEN), which antagonizes PI3K, were also detected in AD neurons, suggesting altered control of PI3K/AKT/mTOR and PTEN signaling in AD. Alterations in the PI3K/AKT/mTOR pathway are linked to autophagy disruption in the pathology of AD and PD.

Current therapy

The food and drug administration (FDA) has approved the listed medication towards mild and moderate stages of AD (viz. Tacrine, Donepezil, Rivastigmine, Memantine). These drugs function as acetylcholinesterase inhibitor or target the N-methyl D-aspartate receptor. As the reduction in the activity of the cholinergic

neurons is a well-known feature of AD, hence, Acetylcholinesterase inhibitors such as tacrine, donepezil are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons. However, the most common side effects are nausea, loss of appetite, diarrhea, muscle cramps, restlessness, and vomiting.

The motor neuron system in PD is due to the result in reduction in the dopamine production in the brain. Dopamine cannot cross the blood brain barrier (BBB), hence, cannot be taken as the medication for PD. As a result, another precursor of Dopamine i.e., levodopa is being taken as the constitute for this. It can easily pass through the BBB and is easily converted into dopamine. Levodopa has been used for the treatment of PD for the last 40 years. One of the major drawbacks of levodopa is that only 5–10% of levodopa crosses the BBB. Much of the remainder is metabolized to dopamine elsewhere in the body, causing a variety of side effects including nausea, vomiting and orthostatic hypotension. Till now no medication has shown to stop or halt the progression of the disease. Most of the currently available drug in the market are either synthetic or terrestrial based natural products [17].

Many studies show plant polysaccharides exhibit CNS protective function through a variety of mechanisms [18]. Selenylation modification of the polysaccharides of the polysaccharide obtained from *Radix hedysari* showed neuroprotective effect against Aβ- induced oxidative stress and apoptosis of neuroblastoma cells [19]. Cactus polysaccharides also tends to have protected PC12 cells against H2O2 exposure and hence decrease the ROS [18]. Studies with polysaccharides from culinary and medicinal mushroom, *Hericium erinaceushas* showed its ability to accelerate sensory function recovery after peripheral nerve damage. Crude polysaccharides of *L. rhinocerotis* sclerotium could be used as a nerve growth factors activator via MEK/ERK1/2 pathway. *M. charantia* polysaccharide showed to attenuate the neuronal death induced by thrombin in primary hippocampal neurons, and act by inhibited the activation of JNK3/c-Jun/cytochrome c/caspase -3 signaling cascades [18]. Xiang., *et al*. [20] showed that neuronal cells treated with polysaccharides from *Rhizoma Dioscoreae* exhibited improved viability and decreased hypoxia-induced mitochondrial injury and programed cell death.

Due to the growing number of cases as well as the limitation of medication results in the improper therapy for this disease, scientists has been moving towards the marine resources in search of the bioactive molecules. In the recent areas, marine resources have attracted scientist in the search of natural molecules to develop new drugs and healthy food [21].

Marine diversity

The ocean covers nearly 70% of the earth surface, providing a wide range of fascinating biodiversity of nearly 2,210,00 species of which only few are identified. 90% of the world's biomass is found in the marine ecosystem comprising approximately half of the total global diversity. Marine environment exhibits extremely harsh physical and chemical environmental conditions that leads to the production of different molecules with the unique structural features compared to those found in the terrestrial animals. More than 30,000 compounds have been identified from the marine environment with unique structures and pharmaceutical activity. Many medicines are isolated from terrestrial organisms whereas fewer drugs have obtained from marine sources. This contrasts the fact of high level of biodiversity in the marine environment, thus offering a great deal of opportunity for the discovery of potential drugs and therapeutics [22].

Marine ecosystem is known to offer a wide diversity of organisms, which can serve as promising source of beneficial materials [23]. Among them, marine algae have rich source of sulfated polysaccharides which offer varied applications in food, fuel, medical, biotechnological, cosmeceutical, and pharmaceutical industries [22,24]. Sulfated polysaccharides (SPs) are polymers which are anionic in nature and are composed of complex group of macromolecules with enormous useful biological activities. Apart from marine algae, these SPs are widely distributed among animals such as invertebrates and mammals [22]. Marine algae are classified into three types such as red, green, and brown based on their photosynthetic pigments. The major bioactive sulfated polysaccharides found in red algae are carrageenan and agaran from red algae, fucoidan, alginate and laminarin from brown algae and ulvan in green algae. However, green algae produce diverse group of SPs with different sugar residues such as glucuronoxylorhamnans, xyloarabinogalactans and glucuronoxylorhamnogalactans [25-27].

Sulfated polysaccharides present in different types of algae

Red algae

Red algae are phylogenetically the most established and oldest division of marine macrophytes. These algae vary in their polysaccharide composition and mainly contain sulfated galactans as the fundamental basic material of cell dividers and intercellular framework. Some of these polysaccharides known as agar or carrageenans have significant gelling and balancing out properties. Numerous others have no gelling properties but show significant biological activities [28]. The major backbone polysaccharide in red algae is galactose. Agar majorly contain D and L galactose units whereas carrageenans contain only D galactose unit.

Carrageenans are obtained from different species of Rhodophyta: Gigartina, Chondrus crispus, Eucheuma and Hypnea. They are linear sulfated polysaccharides. The average molecular weight of commercially available carrageenan ranges from 100-1000 kDa. These polysaccharides are traditionally split into six basic forms: Iota (ι)-, Kappa (κ)-, Lambda (λ)-, Mu (μ)-, Nu (ν) - and Theta (θ) - carrageenan but mainly there are three main varieties of carrageenan, which differ in their degree of sulfation. Natural carrageenans typically occur as mixtures of different hybrid types, such as κ/β-hybrids,κ/ι-hybrids,κ/μ-hybrids,or ν/ι-hybrid [29].

κ-carrageenan has one sulfate group per disaccharide, ι-carrageenan has two, and λ-carrageenan has three sulfate groups. The repeating units are D galactose units and 3,6 anhydrogalactose (3,6-AG) joined by alternating α-1,3 and β-1,4 glycosidic linkages. κ-carrageenan obtained from red seaweed *Kappaphycus alvarezii* have 3-linked ß-D-galactose 4-sulfate and 4-linked AnGal units. While ι-carrageenans have an additional sulfate group on C2 of the AnGal residue, resulting in two sulfates per disaccharide repeating unit. ι-carrageenans were more homogeneous and flexible than κ-carrageenans. λ-carrageenans have three sulfate groups per disaccharide unit with the third sulfate group of this form at the C6 position. Higher levels of ester sulfate lower the solubility temperature of the carrageenan and produce lower strength gels or contribute to gel inhibition. The chemical structures of carrageenans are, thus, very heterogeneous and are correlated to the algal sources, the life stage of the seaweed and the extraction procedures of the polysaccharide.

Agarans are polysaccharides mixture made up of agarose and agaropectin. It has functional and structural properties like carrageenans. The backbone structure majorly has 4-linked α-galactose residues of the L-series. Agaran from *Acanthophora spicifera*, is highly sulfated at the C-2 position of β-D-galactose units, with a portion of the deposits being 4,6-pyruvylated. This agaran additionally contains little measures of xylose and sulfated xylose deposits [29]. It has also been observed in earlier research that *Gelidium spp*. and *Gracilaria spp* agar extract melts and gels at very high temperature as compared to carrageenans [30]. This enables agar to be used in pastry glazes and fillings to be used before a pastry is baked without melting in the oven.

Brown algae

Fucoidan, laminarin and alginic acid are the major SPs of brown seaweeds.

Fucoidan, was first isolated by Kylin in 1913. Although fucoidan has been know from century but still due to the heterogeneity in its structure, the accurate structure is yet not determined. The backbone is made up of fucose consisting of α-l-fucose units usually referred as α-l-fucopyranose. Studies show that several representatives of the orders Chordariales and Laminariales contain fucoidan with a linear backbone composed of (1→3)-linked α-l-fucose residues. However, fucoidan isolated from algae belonging to the order Fucales mostly display a backbone composed of alternating (1→3)- and (1→4)-linked α-l-fucose residues [29]. Fucoidans are not only highly heterogeneous polysaccharides regarding the sugar composition and sulfate content, but also concerning their molecular weight. This may vary from 10- ~2000 kDa. Structural studies have shown that these SPs have extremely complex highly branched macromolecules. Experimentally 1,2-, 1,3- and 1,4-linked and sulfated fucose units have been obtained [31].

Alginic Acid: The major polysaccharide in brown algae is alginic acid. Structurally Alginate is a high molecular weight polyuronic acid composed of two types of uronic acids distributed as blocks of guluronic acid (GulA or "G") or mannuronic acid (ManA or "M") as well as heteropolymeric mixed sequences. It consists of unbranched chains blocks of continuous ß-l,4-linked D-mannuronic acid and blocks of continuous α-l,4-linked L-guluronic acid. The average length of the block is 20 units. It is exclusively present in brown algae and contributes to the flexibility. Alginates can take either a salt form i.e., alginate or an acid form i.e., alginic acid of this two, both are present in the seaweed. The molecular mass ranges from 20-200 kDa. The bioactive potential of alginates depends on the species and season [32].

Laminarin, a storage β-glucan, is composed of (1,3)-β-D-glucan and some β-(1,6)-intrachain links. It is a food reserve of brown algae. The molecular weight of laminarin is approximately 5 kDa and is dependent upon the degree of polymerization which is in the range of 20–25 glucose moieties. M and G are two types of laminarin chains depending upon the reducing end. M chains end with 1-O-substituted D-mannitol, whereas G chains end with glucose as the reducing end. The arrangement and structure of laminarins are species-specific. For the most part, laminarins comprise of linear (1,3)- glucans and branched (1,6)- glucans (84-94% impartial sugar), with little measures of uronic corrosive (6-9%). Their subatomic weight is typically low (3-6 kDa) and relies upon the level of polymerization. Their solubility relies upon the stretching level, with linear laminarins being more soluble than unbranched ones in aqueous solutions. Their organic properties can be enhanced significantly following sulfation [32].

Green algae

Ulvan is the major water-soluble polysaccharide found in green seaweed. The major repeating disaccharide in the ulvan comprises two different types of aldobiouronic acid. The main repeating disaccharide units reported are ulvanobiouronic acid 3-sulfate types containing either glucuronic or iduronic acid. It has more complex and heterogeneous structure. The sulfate groups are present majorly at C-4 position and minor at C-6. The sugar composition of ulvans is extremely variable, being the most frequent rhamnose (16.8%–45.0%), xylose (2.1%–12.0%), glucose (0.5%–6.4%), glucuronic acid (6.5%–19.0%) and iduronic acid (1.1%–9.1%). Apart from this, Mannose, galactose, and arabinose have also been found in ulvan from some Ulva species. Thus, determining the sugar composition in these algae are extremely difficult. Ulvans obtained from *U. pertusa*, *U. conglobata* and *E. prolifera* have molecular weights ranging from 530 kDa to 3.6 × 103 kDa [29].

Bioactive potential of sulphated polysaccharides from seaweeds

Fucoidans, carrageenans, alginates, agars and ulvans are the economically important seaweed products that are used in various industries including the food and pharmaceuticals [27]. In recent years because of their chemical properties and useful biological effects, algal SPs have been widely investigated. There is a positive correlation between the structural requirements such as composition, position of sulfate group, extent of sulfation of sulfated polysaccharides and their biological activities [24].

Neuroprotective effects of marine algal SPs

In recent times the ability of marine organisms especially marine algae as neuroprotective agents have been increased significantly. The various mechanisms by which these algal SPs offer neuroprotection is discussed subsequently.

Antioxidant Ability of Algal SPs and neuroprotection

Oxidative stress results due to the imbalance between the antioxidant concentration and pro-oxidant which leads to the formation of ROS which are toxic for the body specially the CNS. Oxidative stress in the CNS has been shown to include excitotoxicity and apoptosis, the two primary drivers of neuronal death. Moreover, oxidative stress has likewise been implicated in the progression of AD, PD, multiple sclerosis (MS) and other ND. Antioxidants in the CNS may have a positive correlation with neuroprotection, as they can scavenge the excess free radicals and can prevent oxidative damage. Antioxidant activities of marine algal SPs have been researched and reviewed in literature. The antioxidant ability of these SPs mainly depends on the sulfation level, type of major sugar, molecular weight, and branching [33,34] and has been demonstrated by various *in vitro* assays.

The antioxidant activity of these compounds extracted from the algae are mainly contribute to the scavenging activity against superoxide and hydroxyl radicals, chelating ability, quenching singlet and triplet oxygen, and reducing power [35]. The basic antioxidation mechanism by which these antioxidants can delay or prevent the free radical generation are:

- By inhibiting the formation of free radicals.
- By scavenging the free radical thus formed.
- By donating hydrogen and hence terminating the chain reaction of the oxidation reaction.

It was reported that SPs from *Porphyridium* displayed antioxidant activity against the autoxidation of linoleic acid and hindered oxidative harm to 3T3 cells caused by FeSO4. They showed that bioactivity in a dose dependent manner which corresponds with sulfate content of the SPs [36]. Sulfated exopolysaccharide from *Rhodella reticulata* also showed strong ability towards superoxide anion radical scavenging and is dose dependent [37]. Zhang., *et al*. [38] extracted three SPs fractions (F1, F2, and F3) from *Porphyra*

haitanesis, which is an important economic alga in China, through anion-exchange column chromatography and studied their *in vitro* antioxidant ability. The sulfate content of F1, F2 and F3 was found to be 17.4%, 20.5% and 33.5% respectively. It was proven that all three SPs fractions showed antioxidant activities. They had strong scavenging effect on superoxide radical, and much weaker effect on hydroxyl free radical. Lipid peroxide in rat liver microsome was significantly inhibited, and H2O2 induced hemolysis of rat erythrocyte was partly inhibited by F1, F2 and F3 but among them, F3 showed strongest scavenging effect on superoxide radical; F2 had strongest effect on hydroxyl radical and lipid peroxide. Ethanol extracts of *C. japonica* suppressed H2O2-induced cellular apoptosis and activated cellular antioxidant enzymes. Experiments performed with the H1299 cell line showed that treatment with an aqueous extract of *G. tenuistipitata* enhanced the recovery of these cells from H_2O_2-induced DNA damage [39]. It was reported that the reducing power of a polysaccharide has a direct and positive correlation with antioxidant capacity. Natural antioxidants can terminate free radical chain reaction by their capacity to donate an electron or hydrogen atom to free radicals. Studies shows that antioxidant activity of SPs is related to several structural characteristics, such as branch chain, glycosidic linkage, steric conformation, and monosaccharide composition among which, the influence of molecular weight and acid group content are the most noticeable [40]. Free-radical-scavenging assays using green algae revealed antioxidant properties from *Ulva fasciata*. Data obtained from animal model studies has started to shed light on the fact that the free radical scavenging effects of a hot water extract of *Ulva reticulate* reduced hepatic oxidative stress [41]. *In vitro* studies of the antioxidant activities of six SPs: iota, kappa, and lambda carrageenan, fucoidan from *Fucus vesiculosus* and fucans from *Padina gymnospora* one precipitated with 0.5 vol. of acetone and another with 1.1 vol. of acetone, revealed that all the samples had an inhibitory effect on the formation of hydroxyl radicals. Fucoidan and λ-carrageenan were more active in inhibiting superoxide radicals. This shows that the degree of variability in the action of these compounds and also the sulfate content affects the antioxidant action [42]. Similarly experiments with 3 SPs from *Ulva fasciata*, *Gloipeltis furcata*, *Sargassum henslouianum* showed that with relatively higher sulfated content, exhibited excellent antioxidant activities in superoxide radical assay [43]. Studies done by preparing different molecular weight ulvan by H_2O_2 degradation has shown that among all the samples, the lowest molecular weight showed the more potential action. The possible reason for this is that, in case of lower molecular weight, the fragment of the polysaccharide would be small hence there would be more exposure of the sulfate group and less hindrances as a result better activity [44].

Sulfate group present in the SPs is highly nucleophilic. A nucleophile is a chemical species that donates an electron pair to an electrophile to form a chemical bond in relation to a reaction and hence it has negative charge. All molecules or ions with a free pair of electrons or at least one pi bond can act as nucleophiles. Sulfur is very nucleophilic because of its large size, which makes it readily polarizable, and its lone pairs of electrons are readily accessible. Most of the ND are characterized by the accumulation of abnormal protein aggregates or the formation of amyloids due to some cues. These aggregates are supposed to carry positive charge in them. Since the presence of sulfated groups which carry a negative charge, they can interact and help in the disaggregation of the abnormal protein aggregates.

Anti-neuroinflammation

Several studies revealed that NO generated by iNOS causes injury and cell death of neurons hence is involved in the pathogenesis of various ND. Studies with rat models have shown that production of inflammatory responses can also induce production of inflammation [45]. A few cell types have been exhibited as supporters in inflammation-mediated neurodegeneration, yet microglia are ensnared as basic parts of the immunological assault to neurons [46]. Activation of microglia results in the production of proinflammatory factors which in turn results in the neurodegeneration which is seen in the pathogenesis of major ND. *E. cava*- a marine was able to suppress the levels of pro-inflammatory cascades by blocking the nuclear factor- *κB* and MAPK activation [47]. Various investigations have reported anti-inflammatory activities of marine algae *in vitro* and *in vivo* [48]. However, scientific analysis of this activity has been poorly carried out and very few studies are being reported till now. Various studies show that *Ulva conglobata* can suppress the NO production which is another major reason for neuroinflammation and neurodegeneration. The first evidence that fucoidan isolated from *L. japonica* exhibited a potent inhibitory effect against LPS-induced NO production in BV2 cells [49]. Various investigations showed that NO created by iNOS causes damage and cell death of neuron and oligodendrocytes in the CNS, thus NO is embroiled in pathogenesis of different neurodegenera-

tive infection [50]. Experiments with *U. conglobata*, methanolic extracts were able to suppress the expression of pro-inflammatory enzymes, iNOS and cyclooxygenase-2 (COX-2), which accounted for the large production of NO and PGE2, respectively. Among different mediators discharged by microglia, NO and PGE2 are the principal cytotoxic molecules taking part in the intrinsic response in the CNS. Studies also show the application of NSAIDs (non-steroidal anti-inflammatory drugs) can be used for the reduction of the risk and delays the onset of inflammation in the CNS. They act by inhibiting the production of proinflammatory mediators. Hence, attenuation of proinflammatory mediators by marine algae demonstrates its potential neuroprotective effect [33,34].

Microglial activation plays an important role in the development of ND by producing various proinflammatory cytokines. Microglia-derived nitric oxide is critical for the lipopolysaccharide induced selective loss of dopaminergic neurons. Lipopolysaccharides transformed cells change into amoeboid shape. However, experiments done with fucoidan showed inhibition of this morphological change in the transformed cells. Apart from this, fucoidan also down regulated the expression of the iNOS mRNA and protein by significant amount. It also inhibited microglial NO production to 75%. Studies revealed that, fucoidan also suppressed phosphorylation of p38 and ERK by approximately 50% [49,50].

Cholinesterase inhibitory activity

Reduction of synthesis of acetylcholine is related to the loss of memory and learning which is majorly seen in the pathogenesis of AD. According to the cholinergic hypothesis, serious loss of cholinergic function in CNS contributes to the symptoms associated to AD [51]. AD is related to the decline of neurotransmitter acetylcholine in nerve cells which breaks down the Ach thus leading to disease progression. Hence inhibiting AChE enzyme can lead to cure AD. Currently, studies have shown that a number of marine algae have AChE inhibitory activity [33,34]. Yoon., *et al*. [52] screened ethanolic concentrates of 27 Korean marine algae, for inhibitory action on AChE, and found that the extracts from *Ecklonia stolonifera* showed promising inhibitory activity. Further studies with *Hypnea valentiae* and *Ulva reticulate*, two marine algae species from Tamil Nadu, India, also reported to inhibit both AChE and BChE activity. Taken together, marine algae can possibly be used as useful neuroprotective operators because of their efficiency in inhibiting ChE action. Moreover, a few extracts from marine algae gave mixed type ChE (AChE and BChE) inhibitory biopotential which have been thought to be more viable in the treatment of AD [33,34]. A list of marine algae is presented in the table 1.

Inhibition of neuronal death

A particular hallmark of neurodegeneration is the loss of subset of neurons via apoptosis or necrosis. Caspase-9 and caspase-3 are the responsible components for apoptosis. Fucoidan produced by the marine algae has shown to inhibit the activity of caspase-9 and caspase-3 [53]. Aqueous extracts of *B. triquetrum* have been demonstrated to protect GT1–7 cells death produced by severe (180 min) chemical hypoxia/aglycemia insult, which further reduced the cytotoxicity and early production of free radicals. The protection exerted by *B. triquetrum* extract seems to be linked to its ability to reduce free-radical generation [33,34].

Anti-neurotoxicity

Neurotoxins are compounds, whose impacts on the nervous system of an individual is by interfering with nerve impulse transmission. They can create neuronal damage or neurodegeneration when controlled *in vivo* or *in vitro*. It has been reported that treatment of neuronal cells with fucoidan blocked Aβ neurotoxicity by activating the phosphorylation of protein kinase C. The mechanisms of protection provided by fucoidan may partly relate to its antioxidative activity. Luo., *et al.* [54] demonstrated that fucoidan from *L. japonica* inhibited 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- induced neurotoxicity in animal model of Parkinsonism (C57/BL mice) and dopaminergic (MN9D) cells. Also, marine algae such as *H. incrassata* and B. triquetrum at a concentration of 0.2 mg/mL have offered protection in methyl mercury-induced neurotoxicity in GT1–7 cells [55]. Till now, the neuro-protective properties of marine algae and its compounds were observed only *in vitro* or in mouse models. Moreover, not much work is done related to SPs effect against amyloidosis. These data clearly suggest that marine algae and its sulfated polysaccharides have the potential to develop as a therapeutic agent against protein aggregation related disorders. Hence, in depth characterization of these SPs in terms of structure-function relationship and biophysical parameters are required to understand the molecular mechanism of SPs as neuroprotective agents in human subjects and also large-scale controlled studies [56]. These studies will further help in development of these novel marine algal sulfated polysaccharides as glycol-based mimetics to synthetic drugs against protein aggregation associated disorders by being a part of pharmaceuticals and functional foods [57].

Source	Type of algae and SPs	Application	Effect/type of action	References
B. triquetrum	Red algae (mainly carrageenan)	Potential therapeutics	Antioxidant and ROS scavenging	[35]
Arthrospira/Spirulina	Blue-green *algae*	Health food, potential therapeutics	Antioxidant, Anti-allergic, Anti-inflammatory	[58,59]
Chlorella stigmatophora	Green *algae* (mainly Ulvan)	Potential therapeutics	Anti-inflammatory, Free radical scavenging.	[60]
F.vesiculosus	Brown algae (majorly fucoidans)	Potential therapeutics	Antioxidant, superoxide radical scavenging	[29].
L .japonica	Brown algae (majorly fucoidans)	production of alginates, therapeutics	Antioxidant, Superoxide and hydroxyl radical scavenging, Anti neurotoxic	[29, 35,].
Dunaliella	Green *algae* (majorly ulvan)	Food supplement, potential therapeutics	Anti-inflammatory	[29].
Isochrysis; Pleurochrysis carterae	Microalgae	Food supplement, potential therapeutics	Anti-inflammatory	[61]
Rhodosorus marinus	Red algae (majorly carrageenan)	Potential therapeutics	Anti-inflammatory	[29]
Padina tetrastromatic	Brown algae (majorly fucoidans)	Extraction of alginate, fertilizer, potential therapeutics	Antioxidation	[35]
Ulva conglobata	Green algae (majorly ulvan)	Potential therapeutics	Anti-neuroinflammatory	[35]
Codium capitatum; Amphiora bowerbankii; Dictyota humifusa; U. fasciata	Green algae, Red algae, Green algae	potential therapeutics	Cholinesterase inhibitory	[62]
Capsosiphon fulvescens;Undaria pinnatifida;Callophyllis japonica;Porphyra tenera	Green algae, Brown algae, Red algae	Food supplement, potential therapeutics	Cholinesterase inhibitory	[53]
I. okamurae	Brown algae (majorly fucoidans)	Potential therapeutics	Antioxidant, cholinesterase inhibitory	[53]
Fucus vesiculosus	Brown algae (majorly fucoidans)	Therapeutics, food supplement	Inhibition of neuronal death, Antioxidant	[43]
Sargassum fulvellum	Brown algae (majorly fucoidans)	Potential therapeutics, food supplement, herbal remedy	Potential neurite outgrowth-promoting activity	[35]
H. incrassata; B. triquetrum	Green algae (ulvan), Red algae(carrageenan)	Potential therapeutics	Anti-neurotoxicity	[35]
Padina gymnospora	Brown algae (majorly fucoidans)	Potential therapeutics, traditional medicines	Antioxidant	[43]
Ulva fasciata; Gloiopeltis; Sargassum henslouianum	Green algae (ulvan), Red algae (carrageenan), Brown algae (fucoidans)	Potential therapeutics	Antioxidant	[44]

Table 1: Neuroprotective ability of sulfated polysaccharides extracted from some marine algae.

Conclusion and Future Perspectives

Algal sulfated polysaccharides hold significant bioactive potential that can potentially hold the key to unlocking a variety of therapeutic benefits. However, the presence of structurally diverse and heterogeneous structures makes studying them challenging. One of the key requirements to overcome neurodegenerative diseases in particular is to identify therapies that delay the onset and even reverse the symptoms of ND. The neuroprotective potential of algal polysaccharides is found to be promising but in detail mechanisms and potential pathways should be observed *in vitro* and model organisms. Moreover, the correlation between antioxidation and prevention of neurodegeneration by algal SPs *in vivo* has to be elucidated. Furthermore, the safety of the sulfated polysaccharides consumption or ingestion need to be studied extensively. Therefore, the current literature survey about algal SPs will provide directions to the development of new generation natural products.

Acknowledgements

This work is supported by UM DAE CEBS, Mumbai, India.

Conflict of Interest

There is no conflict among authors in publishing this manuscript.

Bibliography

1. Barbosa M., *et al*. "Bioactive Compounds from Macroalgae in the New Millennium: Implications for Neurodegenerative Diseases". *Marine Drugs* 12 (2014): 4934-4972.
2. Burns A and Iliffe S. "Clinical Review Alzheimer's disease". *BMJ* 338 (2009): 1-5.
3. Sveinbjornsdottir S. "The clinical symptoms of Parkinson's disease". *Journal of Neurochemistry* 1 (2016): 318-324.
4. Bogaard S., *et al*. "MRI biomarkers in Huntington's disease". *Frontiers in Bioscience* 4 (2012): 1910-1925.
5. Seedevi V., *et al*. "A review on type 2 diabetes mellitus associated with cognitive dysfunction and dementia and future perspective". *World Journal of Pharmacy and Pharmaceutical Sciences* 6 (2017): 579-600.
6. Mukherjee A., *et al*. "Type 2 Diabetes as a Protein Misfolding Disease". *Trends in Molecular Medicine* 21 (2015): 439-449.
7. Dansette PM., *et al*. "Sulfur Containing Compounds as Antioxidants". *Advances in Experimental Medicine and Biology* 264 (1990): 209-215.
8. Schroeter H., *et al*. "MAPK signaling in neurodegeneration: influences of flavonoids and of nitric oxide". *Neurobiology Aging* 23 (2002): 861-880.
9. Zhu X., *et al*. "The role of mitogen-activated protein kinase pathways in Alzheimer's disease". *Neurosignals* 11 (2002): 270-281.
10. Perry G., *et al*. "Activation of neuronal extracellular receptor kinase (ERK) in Alzheimer disease links oxidative stress to abnormal phosphorylation". *Neuroreport* 10 (1999): 2411-2415.
11. Hensley K., *et al*. "p38 Kinase Is Activated in the Alzheimer's Disease Brain". *Journal of Neurochemistry* 72 (1999): 2053-2058.
12. Munoz L and Ammit AJ. "Targeting p38 MAPK pathway for the treatment of Alzheimer's disease". *Neuropharmacology* 58 (2010): 561-8.
13. Borsello T and Forloni G. "JNK Signalling: A Possible Target to Prevent Neurodegeneration". *Current Pharmaceutical Design* 13 (2017): 1875-1886.
14. Yarza R., *et al*. "c-Jun N-terminal Kinase (JNK) Signaling as a Therapeutic Target for Alzheimer's Disease". *Frontiers in Pharmacy* 6 (2016): 321.
15. Sandoval D., *et al*. "The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration". *Cell Signal* 26 (2014): 2694-2701.
16. Datta SR., *et al*. "Cellular survival: a play in three Akts". *Genes and Development* 13 (1999): 2905-2927.
17. Manigandan V., *et al*. "Marine carbohydrate-based therapeutics for Alzheimer's disease - mini review". *Journal of Neuroscience* (2015).

18. Gao Q-H., *et al*. "Neuroprotective effects of plant polysaccharides: A review of the mechanism". *International Journal of Biological Macromolecules* (2017): S0141-8130 (17): 31360-0.

19. Wei D., *et al*. "Synthesis, characterization, antioxidant activity and neuroprotective effects of Selenium polysaccharide from Radix hedysari". *Carbohydrate Polymer* 125 (2015): 161-168.

20. Xiang Q., *et al*. "Neuroprotective effects of Rhizoma Dioscoreae polysaccharides against neuronal apoptosis induced by in vitro hypoxia". *Experimental and Therapeutic Medicine* 10 (2015): 2063-2070.

21. Shao P., *et al*. "In vitro antioxidant and antitumor activities of different sulfated polysaccharides isolated from three algae". *International Journal of Biological Macromolecules* 62 (2013): 155-161.

22. Cunha L and Grenha A. "Sulfated seaweed polysaccharides as multifunctional materials in drug delivery applications". *Marine Drugs* 14 (2016): 1-41.

23. Souza RB., *et al*. "Neuroprotective effects of sulfated agaran from marine alga Gracilaria cornea in Rat 6- hydroxydopamine parkinson's disease model: Behavioral, neurochemical and transcriptional alterations". *Basic and Clinical Pharmacology and Toxicology* (2016).

24. Patel S. "Therapeutic importance of sulfated polysaccharides from seaweeds: Updating the recent findings". *3Biotech* 2 (2012): 171-185.

25. Na YS., *et al*. "Purification, characterization and immune stimulating activity of water-soluble polysaccharide isolated from Capsosiphon fulvescens". *International Immunopharmacology* 10 (2010): 364-370.

26. Costa LS., *et al*. "Biological activities of sulphated polysaccharides from tropical seaweeds". *Biomedicine and Pharmacotherapy* 64 (2010): 21-28.

27. Monteiro VS., *et al*. "Involvement of the GABAergic system in the anxiolytic effect of sulfated polysaccharides from the red seaweed Gracilaria cornea". *Journal of Applied Phycology* 28 (2016): 1997-2004.

28. Usov AI. "Structural analysis of red seaweed galactans of agar and carrageenan groups". *Food Hydrocolloids* 12 (1998): 3301-3308.

29. Jiao G., *et al*. "Chemical structures and bioactivities of sulfated polysaccharides from marine algae". *Marine Drugs* 9.2 (2011): 196-223.

30. Jeon YJ., *et al*. "Characterization of agarose product from agar using DMSO". *Algae* 20 (2005): 61-67.

31. Percival E. "The polysaccharides of green, red and brown seaweeds: Their basic structure, biosynthesis and function". *British Phycological Journal* 14 (2007): 103-117.

32. Ruperez P., *et al*. "Biological activities of algal sulfated and non-sulfated polysaccharide". In: (Eds Blanca Hernández-Ledesma, Miguel Herrero). Bioactive Compounds from Marine Foods: Plant and Animal Sources. John Wiley and Sons (2013).

33. Wijesekara I., *et al*. "Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae". *Carbohydrate Polymers* 84.1 (2011): 14-21.

34. Pangestuti R., *et al*. "Neuroprotective Effects of Marine Algae". *Marine Drugs* 9 (2011): 803-818.

35. Vadlapudi V. "Antioxidant activities of marine algae: a review". In: Medicinal Plants as Antioxidant Agents: Understanding Their Mechanism of Action and Therapeutic Efficacy Research Signpost, edited by Capasso, A., 189-203. Kerala, India (2012).

36. Raposo MFJ., *et al*. "Bioactivity and application of sulfated polysaccharides from marine microalgae". *Marine Drugs* 11 (2013): 233-252.

37. Chen B., *et al*. "Isolation and antioxidant property of the extracellular polysaccharide from Rhodella reticulata". *World Journal of Microbiology and Biotechnology* 26 (2010): 833-840.

38. Zhang Q., *et al*. "Antioxidant activities of sulfated polysaccharide fractions from Porphyra haitanesis". *Journal of Applied Phycology* 15 (2003): 305-310.

39. Yang JI., *et al*. "Aqueous extracts of the edible Gracilaria tenuistipitata are protective against H_2O_2-induced DNA damage, growth inhibition, and cell cycle arrest". *Molecules* 17.6 (2012): 7241-7254.

40. Ma X-T., *et al*. "Effect of Content of Sulfate Groups in Seaweed Polysaccharides on Antioxidant Activity and Repair Effect of Subcellular Organelles in Injured HK-2 Cells". *Oxidative Medicine and Cellular Longevity* (2017).

41. Lee JC., *et al*. "Marine algal natural products with anti-oxidative, anti-inflammatory, and anti-cancer properties". *Cancer Cell International* 13 (2013): 55.

42. Rocha de Souza MC., *et al*. "Antioxidant activities of sulfated polysaccharides from brown and red seaweeds". *Journal of Applied Phycology* 19.2 (2007): 153-160.

43. Shao P., *et al*. "In vitro antioxidant and antitumor activities of different sulfated polysaccharides isolated from three algae". *International Journal of Biological Macromolecules* 62 (2013): 155-161.

44. Qi H., *et al*. "Antioxidant activity of different molecular weight sulfated polysaccharides from Ulva pertusa Kjellm (Chlorophyta)". *Journal of Applied Phycology* 17 (2005): 527-534.

45. Liu B and Hong JS. "Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention". *Journal of Pharmacology and Experimental Therapeutics* 304 (2003): 1-7.

46. Block ML., *et al*. "Microglia-mediated neurotoxicity: uncovering the molecular mechanisms". *Nature Reviews Neuroscience* 8 (2007): 57-69.

47. Lull ME and Block ML. "Microglial activation and chronic neurodegeneration". *Neurotherapeutics* 7.4 (2010): 354-365.

48. Abad MJ., *et al*. "Natural marine anti-inflammatory products". *Mini-Reviews in Medicinal Chemistry* 8.8 (2008): 740-754.

49. Cui YQ., *et al*. "Inhibitory effect of fucoidan on nitric oxide production in lipopolysaccharide-activated primary microglia". *Clinical and Experimental Pharmacology and Physiology* 37.4 (2010): 422-428.

50. Heales SJ., *et al*. "Nitric oxide, mitochondria and neurological disease". *Biochimica et Biophysica Acta* 1410.1 (1999): 215-228.

51. Bartus RT. "On neurodegenerative diseases, models, and treatment strategies". *Experimental Neurology* 163.2 (2010): 495-529.

52. Yoon NY., *et al*. "Phlorotannins from Ishige okamurae and their acetyl- and butyrylcholinesterase inhibitory effects". *Journal of Functional Foods* 1 (2009): 331-335.

53. Cowan CM., *et al*. "Caspases 3 and 9 send a pro-apoptotic signal from synapse to cell body in olfactory receptor neurons". *Journal of Neuroscience* 21 (2001): 7099-7109.

54. Luo M., *et al*. "Antitumor and Adjuvant Activity of λ-carrageenan by Stimulating Immune Response in Cancer Immunotherapy". *Scientific Report* 5 (2015): 11062.

55. Fallarero A., *et al*. "Effects of the aqueous extract of Bryothamnion triquetrum on chemical hypoxia and aglycemia-induced damage in GT1-7 mouse hypothalamic immortalized cells". *Phytomedicine* 13 (2006): 240-245.

56. Jin D-Q., *et al*. "Ulva conglobata, a marine alga, has neuroprotective and anti-inflammatory effects in murine hippocampal and microglial cells". *Neuroscience Letter* 402 (2006): 154-158.

57. Robic A., *et al*. "Structure and interactions of ulvan in the cell wall of the marine green algae Ulva rotundata (Ulvales, Chlorophyta)". *Carbohydrate Polymer* 77 (2009): 206-216.

58. Blinkova LP., *et al*. "Biological activity of Spirulina". *Zhurnal Mikrobiologii, Epidemiologii, I Immunobiologii* 2 (2001): 114-118.

59. Fujitani N., *et al*. "Inhibitory effects of microalgae on the activation of hyaluronidase". *Journal of Applied Phycology* 13 (2001): 489-492.

60. Guzman S., *et al*. "Anti-inflammatory, analgesic and free radical scavenging activities of the marine microalgae Chlorella stigmatophora and Phaeodactylum tricornutum". *Phytotherapy Research* 15 (2001): 224-230.

61. Pulz O and Gross W. "Valuable products from biotechnology of microalgae". *Applied Microbiology and Biotechnology* 65.6 (2004): 635-648.

62. Stirk WA and van Staden J. "Comparison of Cytokinin-and Auxin-Like Activity in Some Commercially Used Seaweed Extracts". *Journal of Applied Phycology* 8 (1997): 503-508.

Volume 5 Issue 8 August 2021