The Role of Polysaccharide in Treating Neurodegenerative Disorders

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The prevalence of neurodegenerative pathologies increases significantly with growing life expectancy. Neurodegenerative diseases including common diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) impose a global public health burden. In this context, natural products could play a leading role in the search for new drugs for the treatment of neurodegeneration. Of note, more than 80 percent of drugs are of natural origin. Natural polysaccharides (general formula of Cx(H2O)y; where x is number 200_2500) occurs naturally in living matter (on the contrary to polysaccharides combined artificially in the process of organic synthesis) and principally play structural and storage functions. Natural polysaccharides can be classified according to their origin, namely plants (e.g., starch, cellulose), algae (e.g., agar, alginates), animals (e.g., chitin, hyaluronic acid), bacteria (e.g., dextran, polylactosamine), and fungal (e.g., chitosan, elsinan). As one of the most widely distributed biomolecules in nature, natural polysaccharides have received considerable attention because of their diverse pharmacological activity as inhibitors of cellular processes, with their antioxidant, anticoagulant, antithrombotic and anticancer effects.

Keywords: polysaccharides ; neuroprotection

R1. Anti-Amyloidogenic Effects of Polysaccharides

One of the major neuropathological hallmarks of AD is irregular folding and aggregation of amyloid-β protein (Aβ). The discovery of new Aβ aggregation inhibitors, which could be used in prevention and treatment, is however a recent development [1]. Ulvan, an acidic green macroalgal polysaccharide of the genus Ulva, has been documented by Liu et al. [1] to inhibit Aβ fibrillation as measured by fluorescence microscopy. Ulvan was revealed to inhibit Aβ fibrillogenesis in a concentration-dependent manner and to dynamically inhibit the development of A11-reactive Aβ oligomers, the most toxic species of Aβ [1]. Circular dichroism showed that ulvan blocks Aβ40′s conformation transition from the initial random coil to a β-sheet structure, but only delays Aβ42′s conformation transition [1]. Ulvan has also been found to substantially reduce the cytotoxicity of Aβ, measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [1]. It also effectively reduces intracellular ROS levels and protects PC12 cells from the damage caused by Aβ fibrillation [1]. In addition, ulvan disaggregates preformed mature fibrils into off-pathway oligomers and substantially decreases their associated cytotoxicity [1]. The above findings not only thoroughly explain the inhibitory effect of ulvan on Aβ fibrillation and its associated cytotoxicity, but also provide new ideas for the production of usable seaweed food ingredients for the treatment of AD [1].

Different amyloid fibrils are strongly associated with several neurodegenerative conditions and are produced by the accumulation of internally disordered and inappropriately folded proteins [2][3][4]. Therefore, the development of compounds that could bind and prevent amyloid development is important [4]. In this respect, the activity of two sulfated polysaccharides against Aβ40 peptide aggregation has been investigated. Both chitosan (CHT) and its derivative N-trimethyl chitosan chloride (TMC) had specific inhibitory action against the fibrillogenesis of Aβ40 as measured microscopically [4]. Their inhibitory mode consist in formation of electrostatic linkages between the positively charged CHT/TMC compounds and the negatively charged Aβ40 units [4]. Stronger preventative behavior of TMC compared to CHT indicated the importance of the polymeric chain's charge density in the prevention of fibril development [4]. Molecular docking and simulation also showed potential linkages of CHT/TMC with Aβ40 on the atomic level, showing that Aβ40 is a stabilized unit after electrostatic linkages with both charged CHT and TMC amines respectively. The linkage of these polysaccharides with the essential Aβ40 peptide hydrophobic central region might account their ability to prevent nuclear spread of fibrillary structures [4]. Current findings indicate that integration into the polymer structural template of sugars like D-glucosamine and N-trimethyl-D-glucosamine may be a novel method for the production of new anti-amyloid molecules.

Some naturally occurring polysaccharides show anti-amyloidogenic effects through their inhibition of protein fibrillation and dissolution of protein fibrils. For example, *Chlamydomonas reinhardtii* sulfated polysaccharides (with a sulfate content of around 29.4%) were examined for their potential inhibition of α-Synuclein fibrillation associated with PD, and could be potentially used in preventive therapy. The isolated sulfated polysaccharides efficiently inhibited α-Synuclein fibrillation. In addition, soluble protein was observed by odium dodecyl sulphate-polyacrylamide gel electrophoresis gel-imaging after complete fibrillation of α-Synuclein [5]. Panigrahi, Gitanjali P., et al. isolated semi-purified sulfated polysaccharides named Cr-SPS from *Chlamydomonas reinhardtii* containing 34% sulfate. The Cr-SPS inhibited fibrillation of α-Synuclein familial mutants A30P, A53T and E35K, and artificial mutants E46K and E57K, and increased solubilized α-Synuclein. The effects of Cr-SPS make them potential therapeutic agents for protein aggregation disorders including PD [6]. Similarly, the disappearance of β-amyloid peptide fibrils has been demonstrated for sulfated polysaccharides isolated from *Ecklonia maxima*, *Gelidium pristoides* and *Ulva rigida* [7]. These sulfated polysaccharides also inhibited the aggregation of amyloid fibrils compared to control untreated peptide [7]. Furthermore, heparan sulfate proteoglycan linear polysaccharides bind to the amyloid structure and to the amyloid precursor protein/peptide [8]. Kisilevsky and Walter synthesized novel glycosaminoglycan anti-amyloid compounds as precursors for heparan sulfate, to alter its structure and inhibit its amyloid precursor protein/peptide-binding and fibril inducing properties [8][9].

Zhou et al., suggested that polysaccharides (LBP1) derived from *Lycium barbarum* can reduce Aβ levels and increase cognitive functions in a APP/PS1 transgenic mouse [10]. Thus, could be used in prevention and therapy of AD. LBP1 can enhance neurogenesis as measured by BrdU/NeuN double labelling [10]. It can also restore synaptic dysfunction in the hippocampal CA3-CA1 pathway. Furthermore, in vitro cell assays show that Aβ processing may be affected by LBP1 [10]. PD is caused by aggregation of the presynaptic protein α-Synuclein. Various medications exist to treat PD but are not very promising in their inhibition of disease progression and have several side effects. Choudhary et al. [5], investigated the effect of sulfated polysaccharides extracted from *Chlamydomonas reinhardtii* on α-Synuclein fibrillation using both microscopic and spectroscopic approaches [5]. By measurement of α-Synuclein fibrillation kinetics, it was demonstrated that these polysaccharides are successful in preventing fibrillation. Electrophoresis revealed the presence of soluble protein in the presence of polysaccharides [5]. Fibrillation-related morphological changes were tracked by microscopy and suggested the polysaccharides attach effectively to α-Synuclein and thus postpone transformation of α-helical structures into β-pleated sheets [5]. These polysaccharides are still effective after the onset of α-Synuclein fibrillation through their ability to relax pre-generated fibrils [5]. These finding suggest that algal polysaccharides could act as alternate preventive treatments for PD and several disorders associated with protein aggregation [5]. PD-associated glutamate and alanine residue mutations of the α-Synuclein protein cause unique tertiary interactions that are important to maintain this protein in a stable native condition and cause more aggregation. Several commonly used medications for the treatment of PD are ineffective and have side effects associated with them [5]. Previous studies on marine algae containing sulfated polysaccharides revealed various medicinal properties. Panigrahi et al. [6] isolated Chlamydomonas reinhardtii sulphated polysaccharides (Cr-SPs) and studied their effects on the suppression of fibrillation/aggregation of α-Synuclein mutants with several microscopic and spectroscopic methods [6]. Measurement of α-Synuclein fibrillation kinetics showed that these polysaccharides can sufficiently suppress α-Synuclein mutant fibrillation [6], and could be potentially used in preventive therapy of PD. Microscopy was used extensively to examine morphological variations associated with fibrillation/aggregation of α-Synuclein. After completion of the fibrillation/aggregation process, electrophoretic results showed these polysaccharides enhance the total quantity of soluble protein [6]. Circular dichroism related techniques revealed that Cr-SPs are slow converters of native protein into accumulated β-sheet structures. Therefore, the referenced work offers insight into why Cr-SPs may prevent PD and other disorders related to protein aggregation, with important medicinal benefits.

2. Antioxidant Activity of Polysaccharides

The exact mechanisms by which polysaccharides have antioxidant activity are unestablished yet, however some hypotheses have been suggested in the literature [11][12][13][14][15]. Various factors could be important in natural polysaccharide antioxidant potency; including structural properties, chemical composition, type of the molecular linkages and molecular weight, as well as the extraction process used to obtain the polysaccharides form its natural source [11][12][13].

The antioxidant activity of natural polysaccharides is influenced by factors including; the number of hydroxyl groups and presence of carboxylic acids, sulfate content, sulfate attachment position, and molecular weight [16][14][15]. For example, low molecular weight chitosan (9 kDa) scavenges superoxide radicals better than high molecular weight chitosan (760 kDa), with 85.8% and 35.5% inhibition respectively [17]. Higher sulfate content is regularly associated with higher antioxidant activity in polysaccharides [18][19], as shown by Shao et al., in natural marine derived polysaccharides [20].

Additionally, sulfated lower molecular weight polysaccharides of Ulva pertusa show stronger antioxidant activity than the sulfated higher molecular weighted plant polysaccharides [15]. Lower molecular weight and higher uronic acid content was associated with better antioxidant activity in *Chimonobambusa quadrangularis* freeze-dried polysaccharide residue [21].

One proposed polysaccharide antioxidant mechanism for glycone is that it is usually present in natural sources, which contain other non-sugar aglycone moieties, such as polyphenols, flavonoids, lipids, amino acids, and nucleic acids. However, the aglycone (non-sugar part) has the primary antioxidant activity of sugar-aglycone combinations. Evidence for this comes from tea leaf polysaccharides, whereby crude tea leaf polysaccharides show more antioxidant activity than semi-purified tea polysaccharides, due to the presence of epigallocatechin gallate polyphenol in the crude tea leaf mixture [22]. The ratio of polysaccharides to aglycone in polysaccharides aglycone mixtures could be a parameter influencing their activity [23][24][25]. For example, polysaccharide:protein ratio was found to affect free radical scavenging activity, and higher protein:polysaccharide ratio has better free radical scavenging activity for polysaccharide-protein complexes obtained from Ganoderma and Grifola. Studies have also confirmed that protein free samples of polysaccharide show no antioxidant activity [25]. The nature of the aglycone part of the polysaccharide non-sugar conjugations plays a significant role in the antioxidant potential of the whole mixture. Protein-free and protonated phenolic acid arabinoxylan polysaccharide mixtures have been evaluated for free radical scavenging activity. They showed higher antioxidant activity of the free protein phenolic acid arabinoxylan mixture over the protein containing mixture, indicating a role for phenolic acids in the antioxidant activity of sugar mixtures [26].

According to Bai et al. [27] the edible and curative mushroom, Maitake, is highly nutritious and contains a large amount of biologically active and health-promoting compounds [27]. A Maitake-derived polysaccharide called proteo-β-glucan (PGM), was reported to be a strong immunomodulator [27]. However, it remained uncertain if this polysaccharide could have immunomodulatory and neuroprotective effects on transgenic APP/PS1 mice, a common model for AD [27]. This study showed PGM-enhanced learning and memory, with reduced histopathological irregularities and neuronal loss in APP/PS1 mice [27]. Treatment with PGM might stimulate microglial cells and encourage the stability of microglial cells in Aβ-related plaques. Furthermore, PGM might strengthen Aβ phagocytosis, thus alleviating the strain of Aβ and the pathological changes in these experimental mice in the hippocampus and cortex [27]. In addition, PGM had no important impact on the body mass of the mice. Conclusively, this work suggests that PGM intake ameliorates memory decline through immunomodulation. Thus, dietary intake of PGM could be beneficial to ameliorate the effects of brain aging. In addition, Aβ can, through mitochondrial dysfunction, induce oxidative neuronal cell death [27]. Sirin et al. [28] investigated the possibility that exopolysaccharides (EPSs) originating from the *Lactobacillus delbrueckii subsp. bulgaricus* B3 and *Lactobacillus plantarum* GD2, protect SH-SY5Y cells from the apoptotic activity of Aβ1-42. EPSs depolarized mitochondrial membrane potential and decreased the apoptotic activity of Aβ1-42 in a concentration-dependent manner. These results led to the addition of EPSs to traditional medicine recommendations for different neurological disorders [28].

Park et al. [29] examined the impact of fucoidan and polyphenol extracts from *Ecklonia cava*, a brown marine algae, on cognitive function. Fucoidan and its polyphenol—in a specific ratio—enhanced learning and memory as compared to polyphenolic extract in various cognitive tests such as the Y-maze and the Morris water maze [29]. Tau hyper phosphorylation and amyloid-β were also down regulated [29]. In view of these outcomes, fucoidan-rich substances in macroalgae could be a potential material for improving cognitive function compared to polyphenol extract [29]. Alghazwi et al. [30] investigated the chemical composition of extracts from the brown macroalgae *Ecklonia radiata* in several in vitro neuroprotective assays. A total of six fractions were investigated to determine their action against oxidative stress and Aβ1-42 in neuronal cells [30]. These fractions were: crude extract (CE), polysaccharide (PS), phlorotannin (PT), high molecular weight (HM), low molecular weight (LM) and free sugar (FS). All fractions except HM prevented Aβ1-42 aggregation. They also displayed antioxidant properties against hydrogen peroxide-induced toxic effects. This study highlights the potential for enhancing neuroprotective effects with E. radiata brown seaweed components [30]. To enhance neurological function, these extracts may possibly be used as functional food or dietary supplements [30].

Habaike et al. [31] aimed to identify the protective roles of various components in Fomes officinalis Ames polysaccharides (FOAPs) in neuronal cells. Various concentrations of FOAPs were applied to neuronal cells two hours prior to direct exposure to a β-amyloid protein fragment 25–35 (Aβ25-35). The AD disease model of neuronal cells was developed at cellular level using Aβ25-35 [31]. Polysaccharide fractions significantly inhibited the over accumulation of ROS induced by Aβ25-35 and the release of LDH and MDA, dependent on their intake [31]. FOAPs may also prevent cell apoptosis [31]. Translocation of cytochrome C from mitochondria to the cytosol was decreased, and the Bcl-2/Bax ratio was raised in neuronal cells in response to FOAPs. Moreover, polysaccharide fractions had a neuroprotective effect against Aβ25–35-stimulated cytotoxicity in neuronal cells [31].

3. Anti-Neuroinflammation Activity of Polysaccharides

Neuroinflammation initiates and enhances neurodegenerative ailments like PD and AD [32]. Microglia and astrocytes protect the brain from infectious agents, while their prolonged activation causes neuroinflammation that can promote neurodegeneration [32]. Currently, there are no treatments to stop the progression of neurodegeneration. Therefore, work is focused on identifying natural compounds that are protective against these diseases [32]. Given that neuroinflammation significantly initiates and enhances neurodegenerative pathology, natural anti-inflammatory compounds may be good candidates for the development of successful therapeutic strategies [32].

Polysaccharides derived from natural sources contain various monosaccharide units joined with each other by several glycoside linkages with a complex molecular arrangement [33]. Polysaccharides have significant pharmaceutical importance due their strong anti-inflammatory and immunomodulatory properties [33]. A raw polysaccharide extracted from *Acorus tatatinowii*, AT50 [34], substantially enhances learning and memory in mice with amnesia caused by scopolamine and inhibits the release of inflammatory mediators, thus could be potentially used in therapy of neurodegenerative disorders. ATP50-3 decreased high levels of inflammatory mediators in lipopolysaccharide (LPS)-induced pro-inflammatory BV2 cells in vitro, as well as inhibiting the stimulation of nuclear factor kappa B (NF-κB) [34]. Furthermore, LPS-induced protein levels of Toll-like receptor 4 (TLR4), protein kinase B (p-Akt), phosphoinositide 3-kinase (p-PI3K) and myeloid differentiation primary response protein (MyD88) were down-regulated by ATP50-3. ATP50-3 protected against neuroinflammation mediated neurological impairment in primary cortical and hippocampal neurons, by alleviating ROS levels and loss of the mitochondrial membrane potential (MMP) [34]. Taken together, these findings indicate that the anti-neuroinflammatory and neuroprotective effects of ATP50-3 are through the TLR4-mediated MyD88/NF-kB and PI3K/Akt signaling pathways [34].

Mediesse et al., investigated polysaccharide *Khaya grandifoliola* fractions (KGF) and *Cymbopogon citratus* fractions (CCF), isolated respectively [35] from stem bark and leaves, for their effect on CNS depression, systemic LPS-induced brain inflammation and hyperalgesia in BALB/c mice. Firstly, the depressant effects of polysaccharide fractions were measured in BALB/c mice weighing around 25–35 g, using the rotarod performance test and an actophotometer [35]. Secondly, one hour after oral administration of polysaccharide fractions (100 mg/kg test dose) or distilled water, LPS or saline solution (5 mg/kg) was intraperitoneally administered. Then, to assess thermal hyperalgesia and brain inflammation, hot plate and tail-flick models were performed one hour post LPS intake and examined by Luminex assay three hours post LPS intake [35]. A complete LPS dose caused a decrease in pain response latency and increased expression of interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) genes, pro-inflammatory cytokines and NF-κB in the brain after 24 h [35]. Treatment with KGF and CCF (100 mg/kg) decreased LPS-induced hyperalgesia and overexpression of IL-1β, IL-6 and TNF-α genes in the brain dependent on NF-κB signaling [35]. These results suggest that KGF and CCF may have potential as treatments of neuroinflammatory diseases, and that further investigation is required to unravel their exact mechanism of action and dose requirements [35].

Crude polysaccharide AOP70 from *Alpinia oxyphylla* of the ginger family was tested in murine models with induced AD, where it significantly enhanced learning and memory [36], and could be potentially used in therapy of AD. AOP70 decreased the production of NO, prostaglandin E-2 (PGE-2), Interleukin 1 beta (IL-1β), and Tumor necrosis factor (TNF-α) to normal concentrations in the serum of AD affected mice, indicating that polysaccharide considerably enhances memory and learning in diseased mice by anti-neuroinflammation [36]. This crude polysaccharide was purified further to isolate the major constituent, a novel heteropolysaccharide (AOP70-2-1) having a molecular weight of about 76.6 kDa [36]. AOP70-2-1 is a novel acidic polysaccharide with an irregular sheet structure and no triple helical arrangement, with wrinkles on the top surface. After its addition to LPS-modulated BV2 cells, the concentrations of NO, IL-6 and TNF-α decreased significantly [36]. These findings indicate that by preventing the development of pro-inflammatory factors, this polysaccharide could be an active constituent responsible for the anti-neuroinflammatory activities of AOP70. Further clarity is needed to understand the structure-activity relationship, along with mechanistic analyses to understand its anti-neuroinflammatory action [36].

Schisandra chinensis whose fruit is called magnolia berry, has been used since ancient times as a medicinal formula for recovery from weak memory or insanity [37]. Xu et al. investigated the action of *Schisandra chinensis* fruit (SCP) polysaccharides on animal models of AD [37]. Immunohistochemistry (IHC) was applied to detect the deposition of Aβ [37]. Certain immune mediators including TNF-α, IL-1β and IL-6 were identified in a specific part of the brain by ELISA [37]. Activation of CNS cells was evaluated via immunofluorescence microscopy. Histopathological modifications were detected by hematoxylin and eosin staining (H&E) [37]. SCP was found to substantially decrease the cognitive and histopathological changes of AD mice, including Aβ accumulation, pro-inflammatory cytokine expression, and activity in brain cells [37].

Furthermore, SCP decreased the phosphorylation of some kinases by displacement to the nucleus [37]. For these reasons SCP could be a potential candidate for the therapy of AD.

Polymannuronate (PM) is an alginate-separated acidic polymer. It is an edible brown algae linear block polysaccharide that is commonly used in the production of food [38]. Seleno-polymannuronate (Se-PM) is a seleno-derivative of PM prepared in the laboratory. The anti-neuroinflammatory role of Se-PM was investigated by Bi et al. [38] in LPS-modulated microglial cells and in an acute inflammatory mouse model. Their findings indicate that this modified polysaccharide could significantly moderate the development of NO and PGE-2 expression and the secretion of interleukins in microglial cells treated with LPS [38]. In addition, Se-PM was attenuated by the LPS-modulated activation of signaling molecules. Furthermore, in vivo, microglial activation induced by LPS was significantly controlled by this PM derivatives [38]. These findings indicate that Se-PM is worthy of further exploration as a functional food to relieve neuroinflammation [38].

Liang et al., investigated the medicinal action of *Dendrobium officinale* polysaccharides (DOPS) on two standard animal models with learning problems and weak memory [39]. Ovariectomy can be triggered by low production of estrogen in mice, and it also causes learning and memory problems [39]. In murine models, D-galactose was subcutaneously provided to induce cognitive impairment [39]. Different techniques such as H&E staining and Nissl staining were applied to investigate the impact of these polysaccharides on hippocampal neurons. Various analytical experiments were performed to explore the impact of polysaccharides on two impaired mice models [39]. In both models, the intake of these polysaccharides substantially ameliorated impaired learning and memory. Additional analyses showed that the polysaccharides control the initiation of Nrf2/HO-1, preventing stimulation of microglia in ovariectomy, D-galactose-stimulated weak cognition, and oxidative damage and neuroinflammation [39]. These results indicate that DOPS has important restorative action on weak learning and memory, and its mode of action may be related to the activation of the Nrf2/HO-1 system, to alleviate oxidative damage and neuroinflammation.

Xu et al. [40] assessed structural features of SCP2-1 polysaccharides obtained from *Schisandra chinensis* (Turcz.) Baill plants and evaluated its anti-neuroinflammatory activity. SCP2-1 had a molar ratio of 8.78:1.23 of glucose to galactose. Evaluation of behavioral pharmacology and biochemical markers indicated that SCP2-1 might ameliorate the cognitive impairment produced by LPS in mice and reduce inflammation [40]. SCP2-1 was shown to decrease the examination period of animals in a novel arm of the Y maze test, reduce the escape latency in the Morris water maze test, and increase the exploration time of the new objects in the NOR test [40]. Treated mice showed improved LPS-induced histopathological changes. They suppressed glial cell over activation, had decreased pro-inflammatory cytokine expression, increased anti-inflammatory cytokine levels, and decreased NLRP3 and M-caspases-1 levels, which can decrease deposition of Aβ [40]. Additionally, the over-activation of NF-κB and hyper-phosphorylation of the P38 MAPK pathway was repressed by SCP2-1. Thus, SCP2-1 should be examined as a potential therapy of AD.

Polygala tenuifolia is an industrial-export plant in Southeast Asia, particularly in China [41]. Rhizomes obtained from *P. tenuifolia* are well-known for their cognition enhancing and inotropic properties. They are frequently consumed in traditional Chinese medicine. The functional constituents that account for *P. tenuifolia's* natural benefits remain elusive. Li et al. [41] used the hot water method to isolate P. tenuifolia rhizomes and purification was performed with Sephacryl S-100 and diethylaminoethyl cellulose (DEAE-C) 52 chromatographic columns. Homogeneous heteropolysaccharide PTP70-2 was obtained with a molecular weight of 65.2 kDa [41]. The pharmacological assessment showed that PTP70-2 repressed nitric oxide production in LPS-induced pro-inflammatory BV2 microglial cells, and the suppressive action of 3.08 μM PTP70-2 was more than that of a positive control (12.5 μM minocycline) [41]. In addition to the inhibition of nitric oxide, the production of pro-inflammatory cytokines such as TNF-α and IL-6 was inhibited by PTP70-2. Based on these observations, the investigators conclude that PTP70-2 is a novel anti-neuroinflammatory agent with the possible capability to ameliorate AD [41].

For hundreds of years, *Ganoderma lucidum* (GL) has been commonly recommended to boost health and longevity in Asian countries [42]. Putative pharmacological functions include the stimulation of innate immunity, cell proliferative control and cancer suppression [42]. Key components of polysaccharides isolated from *Ganoderma lucidum* (GLP) have been suggested previously in the literature to regulate the immune system. A contribution of GLP to neuroinflammation mediated by microglia has not been elucidated [42], and GLP's effect on microglial behavior is still to be unraveled [42]. Cai et al. [42] thoroughly studied the influence of GLP on BV2 microglia and primary mouse microglia. This quantitative study was performed to find the impact of GLP on microglial pro- and anti-inflammatory cytokine responses, along with behavioral variations such as morphology, movement, and phagocytosis. In the zebrafish brain, study of microglial morphology and modulation of phagocytosis has been verified. GLP downregulated pro-inflammatory cytokines induced by LPS or Aβ and stimulated anti-inflammatory expression of cytokines in BV-2 and primary microglial cells [42]. Furthermore, GLP reduced inflammation-associated microglial movement, variations in morphology, and phagocytosis.

The expression of MCP-1 and C1q were also observed in correlation with modulations of microglial behavioral responses [42]. Cai et al. provided insight into GLP-mediated control of neuroinflammation prompted by LPS and Aβ and proposes that the neuroprotective effects of GLP might be provided by modulating inflammatory and behavioral microglial responses.

Moringa oleifera is a multi-functional herbal plant used in traditional medicine. Cui et al. [43] obtained a new polysaccharide, known as MRP-1 from Moringa oleifera roots. GC-MS based estimation of monosaccharide configuration found that MRP-1 contained mostly 1.5:2.0:3.1:6.0:5.3:1.1. molar ratios of rhamnose, fructose, arabinose, mannose, xylose, and galactose [43]. Various spectral studies indicated that MRP-1 contained carbohydrate features such as alpha-Araf, β-Galp, α-Gly, β-Gly and α-GalpA [43]. LPS-induced RAW264.7 macrophage cells were selected to determine whether MRP-1 has anti-inflammatory properties. Various doses of MRP-1 stopped LPS-induced TNF-α and NO production [43]. In addition, LPS-induced mRNA expression levels of Inducible nitric oxide synthase (iNOS) were decreased with treatment of multidrug resistance protein 1 (MRP-1), while having no prominent impact on the expression level of COX-2 mRNA [43].

4. Anticholinesterase Activity of Polysaccharides

Currently, four AChE inhibitors (AChEi) or anti-AChEs, namely donepezil, rivastigmine, galantamine, and memantine, are available for the prevention of dementia and for improving the cognitive deficits of neurodegenerative disorders. AChEi increase the levels of ACh at the synapse and enhance cholinergic activity in the brain [44][45]. The only naturally occurring AChEi with clinical significance is galantamine, an alkaloidal derivative from the *Amaryllidaceae* family of herbal plants [46] [47]. Galantamine inhibits ACh reversibly and competitively, and modulates nicotinic ACh receptors allosterically [48][49].

Acetylcholinesterase inhibitors have been used to combat AD [50]. Even so, most of these drugs have undesirable side effects, including dizziness, liver toxicity, bradycardia, and bowel disturbances [50]. As a result, the development of effective anticholinesterase compounds derived from nature is highly anticipated and sought-after.

Natural AChEi have additional pharmacological properties, especially antioxidant properties, making them a multifunctional therapeutic strategy for preventing the occurrence and progression of AD [51][52][53]. Several studies have isolated and identified natural molecules with potential AChEi activity that have shown positive outcomes as novel anti-AD drugs [54]. Natural polysaccharides isolated from natural sources ranging from rice bran to edible mushrooms have shown potential AChEi activity and could be formulated as novel drugs to treat drug-resistant AD.

In 2017, Hafsa and colleagues reported the extraction of some hydrophilic polysaccharides from microalgae such as *Isochrysis galbana* and *Nannochloropsis oculate,* which possessed antimicrobial, anticancer, and anticholinesterase properties [55]. In 2018, Mebrek and colleagues reported that barley-derived beta-glucan, a homopolysaccharide, has moderate antioxidant and enzyme inhibitory activities. In 2017, Pejin and colleagues demonstrated that polysaccharides from two fungal strains, *Coprinus comatus*, and *Coprinellus truncorum*, possessed potential AChEi activity [56]. In 2018, Zhang and colleagues reported that polysaccharides derived from *Flammulina velutipes* had various pharmacological effects, including AChEi activity [57]. In 2019, Deveci and colleagues reported that a polysaccharide obtained from *Pleurotus ostreatus,* a mushroom tree, exhibited significant inhibitory activity against BChE [58]. Badshah and colleagues reported that polysaccharides isolated from a wide range of mushrooms, which contain glucans, krestin, and lentinan, have significant AChE and BChE inhibitory activity and are being regarded as novel drug therapies for the management of AD and PD [59][60]. Also Badshah and colleagues have extracted mushroom polysaccharides from *M. esculenta*. This polysaccharide's deproteinized form has shown moderate free antioxidant activity but exhibited substantial AChE and BChE inhibitory properties. As a result, these polysaccharides are considered new therapeutic candidates for the treatment of AD and PD [60]. Another class of natural polysaccharides obtained from algae include fucoidans and fucose-containing sulfated polysaccharides such as glucose, mannose, galactose, and uronic acids [61]. These polysaccharides are found to have sulfur complexed with polysaccharides, called sulfated polysaccharides, and they possess high molecular weight and are isolated from *Sargassum horneri* [62]. The most extensively studied sulfated polysaccharides are algae's fucoidans and sulfated galactans. These sulfated polysaccharides have various physiological and pharmacological actions, including antithrombotic, anticoagulant, antioxidant, anti-inflammatory, antitumor, and immune-modulating properties [63]. The sulfated polysaccharides derived from *Ecklonia maxima, Gelidium pristoides*, and *Ulva rigida* have shown inhibitory action on AChE, BChE, and β-secretase activity. Sulfated polysaccharides induce the elimination of Aβ (1–42) fibrils, which inhibit fibril accumulation, implying that they could have antioxidant and neuroprotective properties in the treatment of AD [7]. In research published in 2019, Rahmani Nezhad and colleagues demonstrated the AChE and BChE inhibitory activities of a broad variety of polysaccharides isolated from two Iranian and French strains of *Agaricus subrufescens*. Both extracts exhibited selective AChE inhibitory action. Furthermore, these

extracts had anti-aggregation activity comparable to donepezil [64]. Olasehinde and colleagues recently confirmed that sulfated polysaccharides could prevent apoptosis and necrosis caused by Zn-induced neuronal damage in an AD model. According to them, the neuroprotective effects of sulfated polysaccharides strongly correlate with a reduction in apoptosis, oxidative damage, and AChE activity [65].

Zhang et al. [66] investigated a polysaccharide with antioxidant activity, known as porphyran. This polysaccharide was obtained from the red macroalgae *Pyropia haitanensis*. Findings suggested that it acts as a protective compound against neurotoxicity during AD in mice. Colorimetric methods investigated the action of cholinesterases in hippocampal and cortical tissue [66]. Results showed that porphyran greatly enhanced Aβ1-40 mediated learning and memory impairment [66]. Biochemical research found that porphyran increased choline acetyltransferase activity in hippocampal and cortical tissue and decreased acetylcholinesterase activity. The mechanism may be linked to an increase in the acetylcholine content of the brain. Porphyran has potential as an anti-aging drug [66].

In conclusion, natural polysaccharides appear to have a diversity of functions in neurodegenerative disorders. Hence, they can be developed as a novel class of AChE inhibitory drugs with therapeutic efficacy against a wide range of neurodegenerative disorders, including AD and PD.

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