

Review

Therapeutic Potentials of the Seaweed-Derived Compounds for Alzheimer's Disease

Keanie Ward ¹, Michael H. Cole ^{1,2} , Lyn R. Griffiths ³ , Heidi G. Sutherland ³ , Pia Winberg ^{4,5} ,
Barbara J. Meyer ^{5,6}  and Francesca Fernandez ^{1,2,3,*} 

- ¹ School of Behavioural and Health Sciences, Faculty of Health Sciences, Australian Catholic University, Banyo, QLD 4014, Australia; keanie.ward@myacu.edu.au (K.W.); michael.cole@acu.edu.au (M.H.C.)
² Healthy Brain and Mind Research Centre, Australian Catholic University, Fitzroy, VIC 3065, Australia
³ Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology, 60 Musk Ave, Kelvin Grove, QLD 4059, Australia; lyn.griffiths@qut.edu.au (L.R.G.); heidi.sutherland@qut.edu.au (H.G.S.)
⁴ Venus Shell Systems Pty Ltd., Huskisson, NSW 2540, Australia; pia@venushellsystems.com.au
⁵ School of Medical, Indigenous and Health Science, University of Wollongong, Wollongong, NSW 2522, Australia; bmeyer@uow.edu.au
⁶ Molecular Horizons, University of Wollongong, Wollongong, NSW 2522, Australia
* Correspondence: francesca.fernandez@acu.edu.au

Abstract

Cognitive decline associated with healthy ageing and pathological conditions is driven by multifactorial processes, including oxidative stress, mitochondrial dysfunction and chronic neuroinflammation. Alzheimer's Disease (AD), a progressive neurodegenerative disorder affecting cognition and behaviour, is the leading cause of dementia worldwide. Current pharmacological interventions provide modest and transient benefits, targeting limited molecular pathways with safety and cost concerns, underscoring the need for safe, accessible and multi-targeted strategies. This review explores new avenues of therapy with a focus on bioactive compounds derived from brown, red and green seaweeds and their potential to modulate key mechanisms underlying AD. Preclinical and emerging clinical studies demonstrate that phlorotannins, fucoidans, fucoxanthin, lutein, zeaxanthin, ulvan, and astaxanthin exert antioxidant, anti-inflammatory, cholinergic-modulating and neuroprotective effects. Supplementation with seaweed-derived bioactive compounds has been shown to exert molecular and cellular effects that lead to reduced amyloid burden, preservation of synaptic integrity, and enhanced cognitive performance. Collectively, seaweed-derived compounds represent promising candidates for multi-target therapeutic strategies in cognitive decline prevention in the context of AD and healthy brain ageing.

Keywords: Alzheimer's disease; cognitive decline; seaweeds; neuroinflammation; healthy ageing; oxidative stress; neuroprotection



Academic Editor: Yun-Bae Kim

Received: 23 September 2025

Revised: 7 November 2025

Accepted: 13 November 2025

Published: 19 November 2025

Citation: Ward, K.; Cole, M.H.; Griffiths, L.R.; Sutherland, H.G.; Winberg, P.; Meyer, B.J.; Fernandez, F. Therapeutic Potentials of the Seaweed-Derived Compounds for Alzheimer's Disease. *Molecules* **2025**, *30*, 4456. <https://doi.org/10.3390/molecules30224456>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Cognitive decline, whether age-related or indicative of neurodegenerative disorders such as dementia, is an escalating global health concern. As of 2021, it was estimated that 57 million people worldwide were living with dementia, now the seventh leading cause of death among older adults, with Alzheimer's disease (AD) accounting for 60–70% of cases [1]. While the precise aetiology of AD remains unclear, ongoing research has yielded increasing evidence that disturbance of the biological processes associated with healthy brain ageing contribute to AD. Age is the most prominent risk factor for AD,

and it has been suggested that those aged 65 and over have a 1–2% risk, while those aged 85 and over have an 18–38% risk [2,3]. It is crucial to differentiate pathological cognitive decline, observed in AD, from the cognitive changes associated with physiological ageing [4]. AD is characterised by progressive and irreversible cognitive decline in at least one of the main domains, including executive function, language, learning, memory, complex attention, perceptual–motor or social cognition [5]. An earlier literature review has reported that gender differences in incidence rates were most frequently observed in European and US populations, where women consistently showed higher rates than men, particularly at older ages [6]. Although specific risk factors have been identified, the precise neurobiological mechanisms underlying pathological cognitive decline in AD remain only partially characterised. Evidence suggests that several of the cellular and molecular features associated with dementia-related neurodegeneration are present in the healthy ageing brain, albeit to a lesser extent [7]. Key hallmarks of brain ageing, such as oxidative damage, mitochondrial dysfunction, glial cell activation and inflammation, DNA repair deficits and stem cell exhaustion, compromise neural resilience (Figure 1) [8–10]. These features are also central in dementia, including AD pathogenesis, underscoring a shared biological continuum between physiological ageing and pathological cognitive decline [7]. AD is characterised by extracellular accumulation of amyloid- β ($A\beta$) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau, which impair synaptic communication and leads to neuronal death [11]. While a small proportion of cases may be attributed to genetic mutations, most prevailing models, such as the amyloid cascade and cholinergic hypotheses, offer reductionistic explanations that do not account for the disease's multifactorial and heterogeneous nature [12–15].

Traditional pharmacological approaches to cognitive decline and impairment in the context of AD primarily target $A\beta$ pathology and cholinergic transmission. Acetylcholinesterase inhibitors (AChEIs), including donepezil, galantamine and rivastigmine, aim to improve acetylcholine (ACh) availability in brain by inhibiting cholinesterase activity. These drugs target cholinergic deficits associated with cortical atrophy, particularly in the frontal and temporal lobes, which are essential for memory [16–18]. However, while early studies suggested symptomatic benefits, large randomised controlled trials (RCTs) have shown modest and mixed results [19–21]. In a RCT including 769 individuals with mild cognitive impairment (MCI), a possible precursor to AD for some individuals, reported that donepezil administration for 12 months could delay AD progression; however, these initial benefits diminished over the three-year duration of the study [19]. Similarly, the InDDEX trial found that rivastigmine administration for up to several years during the double-blind phase, depending on disease progression or study closure, demonstrated no significant effect on reducing the risk of developing AD or improving cognitive outcomes [20]. Galantamine administration also demonstrated modest cognitive benefits in patients with severe AD when administered for 26 weeks [21] but was unsuccessful at improving functional outcomes or slowing disease progression and was associated with increased adverse effects in AD patients [21]. Collectively, these findings underscore the ongoing difficulty in developing strategies that reliably mitigate, or slow AD progression. While antipsychotic medications may be used to manage behavioural and psychological symptoms in AD patients, they fail to modify the progression of the disease and have no effect on cognitive decline [22,23]. Additionally, second-generation anti-amyloid monoclonal antibodies (MAB), developed to target $A\beta$ have gained approval as disease-modifying therapies for AD; however, their use remains limited by safety concerns, particularly the risk of amyloid-related imaging abnormalities (ARIA), which include vasogenic oedema (ARIA-E) and microhaemorrhages (ARIA-H) [24]. This therapy also imposes a significant cost, with annual treatment costs often exceeding \$25,000 per patient [25]. Together, the limitation of

current pharmacological approaches, including safety risk, high cost and limited efficacy, highlight the need for safer, more accessible and multifaceted therapeutic strategies.

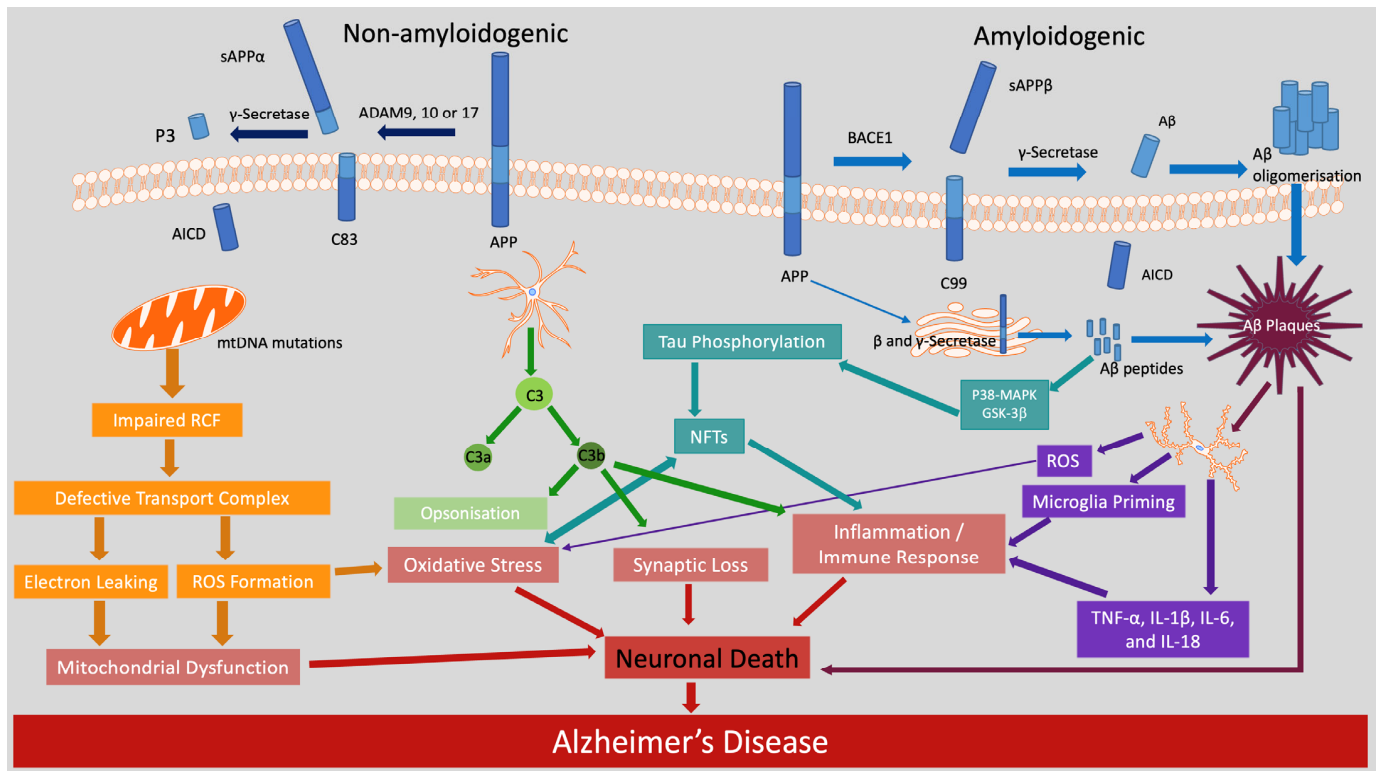


Figure 1. Molecular mechanisms involved in pathophysiology of AD: molecular pathways are colour coded to highlight their contribution to AD pathology. The non-amyloidogenic pathway is dark blue, the amyloidogenic pathway is blue, while mitochondrial dysfunction and oxidative stress are shown in orange, astrocyte and complement activation in green, tau phosphorylation in teal and microglial activation in purple. The colour separation was used to distinguish the overlapping mechanisms and to illustrate how multiple dysregulated pathways converge on neuronal death and AD progression. Abbreviations: ADAM: a disintegrin and metalloproteinase, AICD: APP intracellular domain, APP: amyloid precursor protein, BACE1: β -site APP-cleaving enzyme 1, IL: interleukin, NFTs: neurofibrillary tangles, RCF: respiratory chain function, ROS: reactive oxygen species, sAPP α : soluble APP α , sAPP β : soluble APP β , TNF: tumour necrosis factor.

Marine algae, particularly seaweeds, have gained increasing attention as an emerging area of interest due to their rich composition of bioactive compounds with potential neuroprotective properties that may support brain health and potentially mitigate cognitive decline [26]. The therapeutic potential of bioactive compounds derived from seaweeds will be reviewed here focusing on their application in mitigating cognitive decline in normal ageing and AD. Given the growing recognition that AD arises from a convergence of pathological processes, rather than a single causative pathway, current evidence on the key molecular and cellular mechanisms that underpin neurodegeneration will be synthesised. By establishing this pathophysiological framework, we aim to highlight how the properties of seaweed-derived compounds may offer a more integrative and targeted approach to support cognitive health in ageing populations.

2. Molecular and Cellular Mechanisms Underlying Cognitive Performance in AD

A major factor contributing to cognitive decline in AD involves the processing of amyloid precursor protein (APP), where the balance between amyloidogenic and non-

amyloidogenic pathways influences amyloid deposition, and affects synaptic function, contributing to neurodegeneration.

2.1. Amyloid and Non-Amyloidogenic Pathways in AD

The proteolytic processing of APP, a transmembrane glycoprotein predominantly expressed in neurons, follows two primary pathways, amyloidogenic and non-amyloidogenic, yielding different biological outcomes. The amyloidogenic pathway, long regarded as central to AD pathology, involves the initial cleavage of APP by β -site APP-cleaving enzyme 1 (BACE1), generating a membrane-bound C-terminal fragment (C99) and soluble APP β (sAPP β), a fragment that lacks the neuroprotective properties of its non-amyloidogenic counterpart (sAPP α) (see Figure 1) [11,14,15]. γ -Secretase subsequently cleaves C99, releasing amyloid- β (A β) peptides of varying lengths, most notably the more abundant A β 1–40 and aggregation-prone A β 1–42.

Although A β 40 is the more abundant isoform, A β 42, characterised by two additional C-terminal residues, exhibits markedly greater hydrophobicity and β -sheet forming propensity, attributing a higher aggregation potential [15,27,28]. This structural distinction promotes rapid nucleation kinetics and thermodynamic stability, allowing A β 42 to preferentially accumulate in amyloid plaque deposition in the AD brain despite its lower physiological concentration. While A β 40 can co-aggregate with A β 42, it appears to exert a modulatory rather than inhibitory role, as mixed A β 42/A β 40 oligomers retain comparable neurotoxicity to A β 42-only species [29–31].

Post-mortem studies revealed that AD plaques primarily comprise A β 42 isoforms, and some plaques exclusively contain this isoform of A β peptide [29]. An increased A β 42/A β 40 ratio has been found to shift the balance toward forming A β 42-only aggregates, which have been shown to exert the most detrimental effect on neuronal function [30]. Elevated A β 42 are associated with synaptic plasticity impairments that disrupt calcium homeostasis and initiate oxidative and inflammatory cascades that contribute to synaptic dysfunction and neuronal death; processes associated with cognitive impairment in AD [32–35]. Furthermore, elevated A β 42 levels correlated more closely with cognitive decline than total amyloid burden [36]. Thus, the composition and ratio of A β isoforms, rather than total concentration, appear to determine neurotoxicity levels and AD progression. While neurons have traditionally been considered the principal cell type responsible for APP expression and A β production, recent evidence implicates oligodendrocyte lineage cells (OLGs), including oligodendrocyte precursor cells (OPCs), in this process [37,38]. These glial cells express both β - and α -secretases, supporting their capacity to generate A β species and neuroprotective sAPP α [37,39,40]. This finding broadens the neuron-centric paradigm of amyloidogenesis and underscores the importance of investigating multicellular contribution to AD proteopathy.

This duality of APP cleavage is further demonstrated by the non-amyloidogenic pathway, often described as a neuroprotective counterpart to amyloidogenesis, initiated by the cleavage of APP within the A β domain by α -secretases, most notably a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) [41]. This cleavage precludes the formation of A β peptides. Instead, it releases sAPP α into the extracellular space and membrane-bound C-terminal fragments (C83). Consequent γ -secretase cleavage of C83 yields a truncated non-toxic fragment (P3 peptide) and the APP intracellular domain (AICD) (See dark blue pathway Figure 1) [42]. In contrast to the sAPP β , yielded via the amyloidogenesis pathway, sAPP α mediates neurotrophic, synaptogenic and anti-apoptotic effects, supporting neuronal survival and plasticity [43–46]. Central to these effects is its reaction with the α 7 subtype of nicotinic acetylcholine receptors (α 7 nAChRs), which are

abundantly expressed in the hippocampus and cerebral cortex, regions critical for memory processes and highly susceptible to AD-related degeneration.

Binding of sAPP α to $\alpha 7$ nAChRs facilitates long-term potentiation (LTP) by increasing receptor affinity for endogenous agonists, increasing calcium influx, and activating intracellular signalling cascades, including the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways [47–49]. These molecular mechanisms support synaptic plasticity and neuronal survival [47]. Exogenous administration of sAPP α in aged rat models increased α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor surface expression and restored LTP [50]. This synaptic support is mediated through sAPP α 's high-affinity interaction with $\alpha 7$ nAChRs, receptors that are also targeted by neurotoxic A β oligomers. This dual ligand affinity highlights the complex functional role of the receptor in AD pathology [50]. While sAPP α binding promotes neuroprotective signalling, A β binding induces $\alpha 7$ nAChR de-sensitisation and internalisation, resulting in intracellular A β accumulation and calcium dysregulation [51]. These molecular alterations chronically disrupt downstream signalling pathways including cyclic AMP-responsive element-binding protein (CREB) phosphorylation, attenuate AMPA receptor activity, and ultimately contribute to synaptic dysfunction and cognitive decline [48,52]. Thus, APP's non-amyloidogenic processing averts the formation of neurotoxic A β and promotes synaptic resilience through sAPP α -mediated signalling, suggesting this pathway has an important role in supporting neuronal survival and cognitive integrity in the ageing brain [48,52]. While amyloid- β accumulation has long been regarded as an initiating mechanism in AD, evidence suggests its pathological effects alone are insufficient to fully account for the observed neurodegeneration and clinical symptoms. Amyloid deposition appears to act as a catalyst that triggers downstream processes, among which tau pathology has a critical role [53]. The interaction between these two hallmark pathways is increasingly recognised as a point of convergence, whereby amyloid-induced cellular stress promotes tau hyperphosphorylation and aggregation.

2.2. Tau Phosphorylation and Neurofibrillary Tangles

Tau is a microtubule-associated protein that has a fundamental role in maintaining the structural integrity and dynamic stability of neuronal axons [54]. By binding to and stabilising microtubules, tau supports essential neuronal processes, such as axonal transport and neurite outgrowth [54]. The affinity of tau for microtubules is finely regulated through post-translational modifications, particularly phosphorylation, which influences both its structural conformation and broader cellular functions [55].

Similar to A β , tau exhibits a strong propensity to misfold and form β -sheet-rich aggregates that are associated with neurotoxic effects [56]. This aggregation can occur either through primary nucleation, where tau monomers self-assemble, or secondary nucleation, where existing aggregates accelerate the process [57,58]. Among the various conformations, soluble oligomers and protofibrils are particularly damaging, as they disrupt synaptic signalling and trigger neuronal dysfunction [59]. Importantly, A β and tau aggregates can act synergistically: A β promotes tau misfolding and phosphorylation (see teal pathway Figure 1), while phosphorylated tau can amplify A β -induced mitochondrial damage [59–61]. This bidirectional relationship highlights their complementary involvement in the progression of driving AD pathology [62].

Tau hyperphosphorylation in AD results from a complex interaction between dys-regulated signalling pathways and alterations in tau isoform expression [63]. In the adult human brain, six distinct tau isoforms are expressed from the MAPT gene on chromosome 17q21 [64]. These arise through alternative splicing of exons 2, 3 and 10, producing variants that differ in both their N-terminal inserts (0N, 1N, or 2N) and the number of microtubule-binding repeats (3R or 4R) [64–66]. Isoforms that contain three repeats bind microtubules less tightly than those with four, yet under physiological conditions these two forms are present in roughly equal proportions [64]. In AD, this equilibrium appears to become disturbed, favouring abnormal post-translational modifications, including acetylation, glycosylation, hyperphosphorylation, truncation and conformation changes, which drive self-aggregation and filament assembly [67].

The sequential transformation of tau, from soluble phospho-tau to insoluble fibrillar aggregates forming paired helical filaments, involves converging cellular pathways [68]. The kinases glycogen synthase kinase-3 β (GSK3 β) and p38-MAPK are commonly implicated in this process (Figure 1) [69–71]. Both are abnormally activated in response to oxidative stress, inflammatory cytokines and metabolic dysfunction, further hallmarks of AD [72,73]. Once activated these kinases phosphorylate tau at several disease-associated residues, such as Ser199/202, Tyr 18 and Thr231, reducing its microtubule-binding affinity and contributing to its detachment into the cytosol [74]. Tau hyperphosphorylation decreases its affinity for microtubules and promotes aggregation into NFTs [75]. These aggregates can act as seeds, facilitating further misfolding and prion-like propagation of tau pathology within the brain [76]. The aberrant activation of tau-related kinases such as GSK3 β and p38-MAPK not only drives tau hyperphosphorylation but also amplifies oxidative and metabolic stress within neurons [73]. This reciprocal relationship establishes a feedback loop in which oxidative damage further activates these kinases, perpetuating tau aggregation and NFT formation [73]. Consequently, oxidative stress and mitochondrial damage emerge not merely as parallel features of AD pathology, but also as contributing factors.

2.3. Oxidative Stress and Mitochondrial Dysfunction

Reactive oxygen species (ROS), a subclass of free radicals, are strongly implicated in the progression of age-related cognitive decline and AD [51]. Oxidative stress arises when ROS production exceeds the brain's antioxidant capacity, leading to extensive molecular damage [77]. Neurons are particularly susceptible to oxidative injury due to their high metabolic demand and limited regenerative capacity. Although ROS, including hydroxyl radicals (\bullet OH), superoxide anions ($O_2\bullet^-$), hydrogen peroxide (H_2O_2) and peroxy radicals, are considered harmful by-products, several species serve physiological roles as secondary messengers in cell signalling and homeostasis [78,79]. Under conditions of ageing and AD, this physiological balance is disrupted, and excessive ROS accumulation becomes a key contributor of cellular dysfunction and neurodegeneration [80].

Mitochondria are major producers and primary targets of ROS within the cell. Mitochondrial DNA (mtDNA) becomes increasingly damaged with ageing, impairing respiratory chain function and producing defective electron transport complexes that leak electrons and perpetuating ROS formation, establishing a self-reinforcing cycle of mitochondrial dysfunction and oxidative stress (see orange pathway in Figure 1) [81,82]. Excess ROS leads to the oxidation of critical biomolecules, including lipids, proteins, and nucleic acids [83]. Lipid peroxidation damages neuronal membranes and disrupts membrane fluidity, while protein oxidation alters enzymatic activity and impairs neurotransmitter synthesis in the brain [84]. In neurons, this cumulative burden compromises mitochondrial function, synaptic integrity, and cellular viability, thereby contributing to neuronal death [85,86]. ROS can also disrupt dendritic branching, reduce spine density, impair axonal transport,

and alter the cytoskeleton, compromising synaptic plasticity and connectivity [84,87,88]. Structural changes are also induced across multiple brain cell types. Elevated ROS can inhibit oligodendrocyte precursor cell maturation, alter branching patterns, and promote demyelination, contributing to the white matter loss reported in ageing and cognitive decline [89,90]. These mechanisms are recognised in the progression of AD and other neurodegenerative conditions. Importantly, the oxidative and structural damage associated with ROS, as well as ROS production can trigger innate immune responses that contribute to sustained microglial activation and the neuroinflammatory cascade observed in AD [91].

2.4. Neuroinflammation

Neuroinflammation has a major role in age-related cognitive decline and AD, with the immune cells of the central nervous system serving as key mediators. Astrocytes, the most abundant glial cells in the central nervous system, undergo structural and functional changes with age, contributing to neuroinflammation and cognitive decline [92]. Morphologically, aged astrocytes shift from exhibiting long, slender processes to short, thicker and less ramified extensions; a change observed in humans [93], rodents [94,95], and non-human primates alike [96,97]. Regional differences in astrocyte density have been reported, ranging from reductions in the retina [98] to stability in the hippocampus [99] and increases in the cortex and hypothalamus [100]. Their activation state and molecular signalling appear particularly relevant to age-related neurodegeneration.

One mechanism by which astrocytes contribute to pathological changes in ageing and AD associated with cognitive decline is via the activation of the complement system. Usually dampened in the mature brain, the complement cascade becomes reactivated during ageing and disease, with astrocytes upregulating genes encoding central complement components such as C3 and C4B [101,102]. In particular, C1q and C3 tag synapses for elimination through microglial phagocytosis, a process necessary during development but potentially detrimental when reactivated in the adult brain [103,104]. Astrocytes participate in all three complement pathways, classical, lectin, and alternative, by expressing regulatory proteins and contributing to the cleavage of C3 into C3a and C3b, and facilitating inflammation, and synaptic loss (see green pathway in Figure 1) [104–107]. While overall neuronal loss is not consistently observed in healthy ageing, loss of synaptic connections is more likely to explain cognitive decline. Memory formation and recall depend on strengthening and reactivating specific synaptic connections. Complement-mediated synaptic pruning by reactive astrocytes may disrupt neuronal networks critical for memory [108]. This leads to the hypothesis that excessive complement activation by aged astrocytes may underlie the synaptic and cognitive deficits recognised in ageing and AD [109,110].

Under physiological conditions, microglia regulate the survival of neurons, differentiation and synaptic remodelling [110]. With ageing, however, these cells undergo progressive morphological and functional changes resembling senescence and dystrophy, rather than classic immune activation [111]. Age-related upregulation of MHC II antigens and altered cytoplasmic morphology are associated with reduced surveillance and host defence capacity, rather than increased pro-inflammatory activation [112]. This suggests that age-related microglial dysfunction may stem from cumulative oxidative stress rather than pathogenic triggers.

Microglial activation, measured by ¹¹C-(R)PK11195 PET, was reported to follow a biphasic trajectory, with early elevations observed in people with mild cognitive impairment compared to controls, followed by longitudinal decline, whereas in AD there is a progressive increase consistent with a shift to a pro-inflammatory phenotype [113,114]. Chronic exposure to A β , tau aggregates and neuronal debris is associated with prolonged activation and polarisation towards pro-inflammatory states [115]. Increase in cytokines, including

tumour necrosis factor (TNF), TNF- α , prostaglandins and interleukins (IL), IL-1 β , IL-6, and IL-18, as well as oxidative stress markers (ROS, nitric oxide (NO)) have been reported in AD and ageing [116]. Collectively, these molecules, while initially serving protective roles, become neurotoxic when overproduced (see purple pathway in Figure 1) [117–119]. Notably, microglial-derived TNF and IL-1 β promote apoptosis through signalling cascades involving TNFR1, nuclear factor kappa-light-chain-enhance of activated B cells (NF- κ B), and caspase-3 pathways, which have been the focus of therapeutic interventions for improving cognitive performance and memory [117,120]. As the disease progresses, microglial phenotypes shift along a spectrum from anti-inflammatory, phagocytic M2-like state to pro-inflammatory M1-like profile, characterised by reduced clearance and heightened cytokine release [117,121]. Although the M1/M2 framework has been criticised as overly simplistic, it remains useful in describing this functional transition.

Additionally, with ageing priming of microglia shows a “dark” or dystrophic morphology and exaggerated inflammatory responses [111,118,122]. These morphologically distinct cells observed near amyloid plaques have been implicated in early tau pathology and may represent a maladaptive stress phenotype rather than a reparative response [122,123]. These phenotypic changes coincide with synaptic loss and tau hyperphosphorylation, hallmarks of cognitive decline in AD [124], suggesting that microglial dysfunction contributes to sustained neuroinflammation and neuronal degeneration. Beyond their immune function, however, microglia are also key modulators of synaptic plasticity [125]. Under homeostatic conditions, microglia enhance neuronal communication through the release of neurotrophic factors, most notably brain-derived neurotrophic factor (BDNF), via PI3K/BDNF signalling pathways [126].

2.5. Additional Pathways

BDNF acts as a downstream effector of microglial PI3K, supporting dendritic spine plasticity and synaptic stability in the adult cortex [127]. Reduced expression of BDNF is implicated in the pathogenesis of AD, with mechanistic evidence linking BDNF signalling to neurogenesis and neuronal resilience [128–130]. BDNF supports hippocampal memory consolidation and LTP by regulating the expression of genes through the activation of the transcription factors CREB and CREB-binding protein (CBP), which in turn encode proteins involved in synaptic remodelling, stress tolerance, and neuronal survival [128,130]. BDNF signalling becomes compromised by AD-related processes, including A β accumulation, oxidative stress and mitochondrial dysfunction [131–133]. Reduced BDNF transcription and its downstream TrkB receptor signalling have been linked to disruptions of plasticity-related pathways and accelerating neurodegeneration [134].

Post-mortem analyses indicate that higher BDNF expression levels, as measured in regions such as the dorsolateral prefrontal cortex (DLPFC), are associated with significantly slower rates of cognitive decline and a reduced burden of amyloid and tau pathology across multiple cortical regions [135]. In a longitudinal study assessing memory performance, individuals in the highest decile of BDNF expression showed 48.3% slower rates of cognitive decline than those in the lowest decile, suggesting a potential neuroprotective effect of BDNF [135]. A human study provided further evidence for BDNF’s neuroprotective properties, reporting exogenous administration improved cognitive function, restored signalling pathways, and upregulated genes associated with neuroprotection [129]. As a result, BDNF is an increasing focus of intervention research, with ongoing efforts to identify modulators of its expression to mitigate cognitive decline in AD. Collectively, the pathological mechanisms discussed illustrate the complex multifactorial nature of cognitive decline in AD.

Despite the advances in our understanding of the molecular underpinnings of AD, current pharmacological interventions remain limited in their efficacy. Therapies such as AChE inhibitors and anti-amyloid MABs act on target isolated pathological pathways, without adequately addressing the broader network of molecular disturbances that contribute to disease progression [18,24]. This single-target approach is increasingly recognised as insufficient for addressing the heterogeneity and complexity of AD pathology thereby limiting the overall therapeutic impact of current interventions [136]. These limitations have catalysed a shift in therapeutic focus toward compounds capable of modulating multiple pathways simultaneously, particularly those derived from natural sources.

3. Therapeutic Potential of Seaweed Compounds in Modulating Brain Ageing Pathways

Therapeutically, natural compounds with pleiotropic actions have gained attention for their ability to target multiple pathological processes in complex brain diseases, such as AD. Several plant-derived compounds, such as curcumin [137], resveratrol [138], epigallocatechin gallate (EGCG) [139], and ginkgo biloba [140] have shown the capacity to modulate multiple neurodegenerative pathways simultaneously, including oxidative defence, neuroinflammation, A β oligomerisation and synaptic plasticity. Amid this growing interest in multi-targeted natural therapeutics, marine macroalgae, commonly referred to as seaweeds, have also gained attention due to their biochemical diversity and long-recognised health benefits [141].

Compared to conventional single-target pharmaceuticals, seaweed-derived compounds may offer broader, multi-targeted approaches to intervention, potentially improving safety and efficacy. Marine algae, particularly edible macroalgae (seaweed) and microalgae, contain a wide range of bioactive properties, with biochemical diversity varying significantly across the main phyla: brown (Phaeophyceae), red (Rhodophyta), and green (Chlorophyta). Each group contains distinct metabolites with unique neuroprotective and therapeutic potentials (see Table 1 and Supplementary Materials for methodology for term search) [142]. A defining feature that sets marine algae apart from terrestrial botanicals is their abundance of sulphated glycans, bioactive polysaccharides absent in land plants [143]. While seaweed also contain antioxidant and anti-inflammatory metabolites common to terrestrial species, sulphated glycans such as fucoidans (brown algae), carrageenans (red algae), and ulvans (green algae) introduce a unique therapeutic dimension [144]. These sulphated polysaccharides possess polyanionic characteristics due to their sulphate group, enabling charge-based interactions that can modulate enzymatic activity, immune regulation, and protein aggregation, pathways that are central to AD pathology [145,146]. Although not every effect can be attributed solely to sulfation, this structural hallmark highlights the therapeutic potential of marine algae as multi-target candidates in cognitive decline and AD. Beyond these mechanistic insights, a growing body of preclinical and clinical evidence indicates that several compounds can enhance memory performance, attenuate oxidative stress in neural tissue, and modulate age-related gene expression associated with neurodegenerative pathways (see Table 1) [147].

Table 1. Key Bioactive Compounds in Brown, Red, and Green Seaweeds Relevant to Cognition and AD pathophysiology.

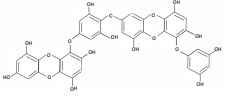
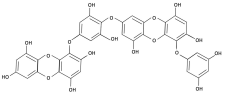
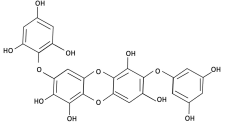
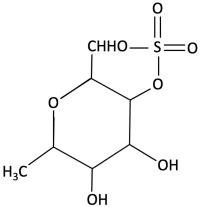
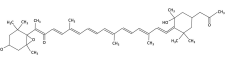
Compound	Chemical Structure	Algal Source	Mechanism	Tested Model	Main Findings	Reference
Dieckol		Ecklonia cava, Brown Seaweed	AChE inhibition, Neurotransmitter modulation	Male ICR mice received oral dieckol (1 or 10 mg/kg/day) for 7 days. Cognitive performance was assessed via passive avoidance test; brain neurotransmitter levels and AChE activity were measured.	Significantly improved memory in ethanol-treated mice, restored hippocampal 5-HT and glutamate levels, reduced elevated GABA and norepinephrine levels, increased brain ACh and inhibited AChE activity (IC ₅₀ ≈ 17.5 μM).	[148]
Dieckol		Ecklonia cava, Brown Seaweed	Antioxidant, Anti-inflammatory, Antiapoptotic, NF-κB and MAPK signalling	<i>In vitro</i> , using PC12 cells treated with Aβ _(25–35) simulating AD-like neurotoxicity. Phlorotannins were administered at varying concentrations 1 h before Aβ.	Dieckol significantly restored PC12 cell viability, reduced Aβ _{25–35} -induced oxidative stress, inflammation, and apoptosis, and modulated NF-κB and MAPK signalling pathways.	[149]
Diphlorethohydroxycarmalol (DPHC)		Ishige okamurae, Brown Algae	Anti-inflammatory, Neuroprotective	AD-like cognitive impairment induced in male C57BL/6 mice via ICV injection of Aβ _{25–35} . <i>In vitro</i> , PC12 neuronal cells used for further investigation of molecular mechanisms related to oxidative stress, apoptosis and MAPK pathway activation.	Significantly attenuated Aβ _(25–35) -induced cognitive impairment, improved maze test performance. IOE reduced neuronal apoptosis, cleaved caspase-3 and PARP, suppressed neuroinflammation (iNOS, COX-2), and decreased ROS overproduction. Both <i>in vivo</i> and PC12 cell models, IOE reversed abnormal phosphorylation of ERK, p38 MAPK, and JNK.	[150]
Fucoidan		Fucus vesiculosi, Brown Algae	Neuroprotective	Male C57BL/6 mice treated with LPS and oral fucoidan (10 mg/kg) daily for three weeks.	Attenuated LPS-induced cognitive impairment by reducing neuroinflammation, oxidative stress, AChE activity. Enhancing BDNF expression and neurogenesis.	[151]
Fucoxanthin		Phaeodactylum tricornutum, Brown Algae	Antioxidant, Anti-inflammatory	D-galactose-induced ageing mouse model using male Swiss mice (n = 72), treated with PT extract for 79 days. Cognitive performance assessed via Y-maze, Morris Water Maze, and Passive Avoidance tests.	Significantly reversed induced cognitive impairment in Y-maze, Morris Water Maze and Passive Avoidance tests, reduced hippocampal lipid peroxidation, and decreased elevated TNF-α and IL-6 levels in brain and plasma, particularly at higher doses.	[152]

Table 1. Cont.

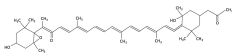
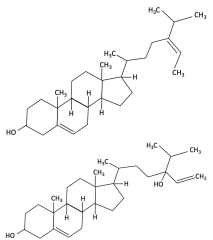
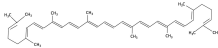
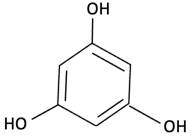
Compound	Chemical Structure	Algal Source	Mechanism	Tested Model	Main Findings	Reference
Fucoxanthin		Phaeodactylum tricornutum, Brown Algae	Antioxidant, Anti-inflammatory	12-week double-blind, randomised, placebo-controlled clinical trial involving older adults (55–75 years) with age-associated memory impairment. Assessing 8.8 mg/day supplementation on cognitive performance and inflammatory biomarkers	Improved working and episodic memory, attention, vigilance and executive function. Inflammatory cytokines showed minimal changes, a slight increase in IL-1 β and stable TNF- α and IL-6 levels.	[153]
Fucoesterol and Saringosterol		Himantalia elongate, Sargassum fusiforme, Brown Seaweed	Anti-inflammatory	<i>In vitro</i> testing using LXR luciferase reporter assays and <i>in vivo</i> via 12-week dietary supplementation in APPswePS1 Δ E9 mice.	Significantly prevented cognitive decline in APPswePS1 Δ E9 mice across object, spatial, and working memory tasks. Both <i>H. elongata</i> and <i>S. fusiforme</i> extracts reduced cortical GFAP expression, suggesting attenuation of astrocyte activation.	[154]
Lycopene		Dictyota spiralis, Brown Seaweed	Neuroprotective	Male C57Bl/6J mice (3-month) administered lycopene-supplemented diet (0.3% w/w) for five weeks. 9 days of LPS induction of neuroinflammation.	Alleviated LPS-induced amyloidogenesis and memory loss, through inhibited microglial activation, reduced inflammatory mediators and enhances antioxidant enzymes, partly via modulating MAPK, NF- κ B, PI3K/Akt, and Keap1/Nrf2 pathways.	[155]
Phloroglucinol		Ecklonia cava, family Laminariaceae, Brown Seaweed	Antioxidant, Anti-inflammatory, A β metabolism	5XFAD transgenic mouse model of Alzheimer's disease used to assess the neuroprotective effects of orally administered phloroglucinol (100 mg/kg/day) over 2 months.	Significantly improved cognitive performance in 5XFAD mice (T-maze and Y-maze), reduced A β protein levels and plaque burden, lowered oxidative stress (\downarrow 4-HNE), and suppressed glial activation (\downarrow GFAP, \downarrow Iba-1). Additionally, decreased pro-inflammatory cytokines (TNF- α , IL-6), reduced BACE1 expression, and restored dendritic spine density and mature spine morphology in the hippocampus.	[156]

Table 1. Cont.

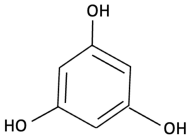
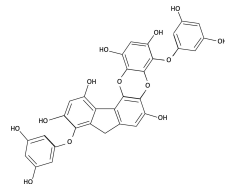
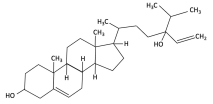
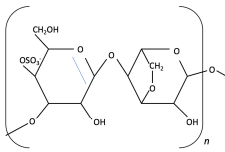
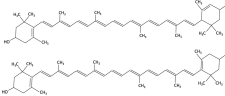
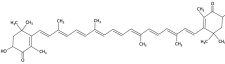
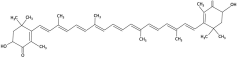
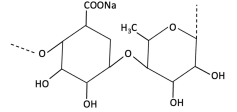
Compound	Chemical Structure	Algal Source	Mechanism	Tested Model	Main Findings	Reference
Phloroglucinol		Brown Seaweed	Neuroprotective	<i>In vitro</i> assays using HT-22 and primary hippocampal neurons were conducted against A β 1–42-induced cytotoxicity, oxidative stress, and synaptic damage, supported by <i>in vivo</i> stereotaxic hippocampal injection and behavioural testing in 5XFAD mice.	Phloroglucinol significantly reduced A β -induced ROS accumulation and synaptic loss <i>in vitro</i> and improved spatial learning and working memory in 5XFAD mice.	[157]
PFF-A (Phlorotannin-s)		Ecklonia cava, Brown Seaweed	AChE inhibition, Neurotransmitter modulation	Male ICR mice received oral PFF (0.2 or 2 mg/kg/day) for 7 days. Memory was evaluated using passive avoidance; neurotransmitter analysis and AChE inhibition were also conducted.	Improved cognitive performance in memory-impaired mice, normalised hippocampal norepinephrine and glutamate, decreased GABA, increased 5-HT and Ach and inhibited AChE (IC ₅₀ \approx 27.4 μ M).	[148]
Saringosterol		Sargassum fusiforme, Brown Seaweed	Anti-inflammatory	Male APP ^{swe} PS1 Δ E9 and WT mice received daily oral gavage of 24(S)-saringosterol (0.5 mg/25 g) for 10 weeks to assess cognitive effects.	Significantly prevented cognitive decline in APP ^{swe} PS1 Δ E9 mice, improving spatial and object memory (OLT and ORT), likely via LXR-mediated microglial modulation.	[158]
k-carrageenan		Kappaphycus alvarezii, Red Algae	Anti-inflammatory, Neuroprotective	<i>In vitro</i> LPS stimulated neuroinflammation in Murine microglial N9 cell. Treated with KOS or desulphated derivatives (DSK)	Attenuated neuroinflammation by reducing NO, TNF-, and IL-10 release, inhibited microglial over proliferation and preserved resting microglial morphology.	[159]
Lutein and Zeaxanthin		Porphyra (Nori), Red Seaweed	Neuroprotective	6-month randomised, double-blind, placebo-controlled trial in adults (40–75 years) assessing daily supplementation of lutein (10 mg) and zeaxanthin (2 mg).	Improvements in visual episodic memory compared to placebo and visual learning.	[160]
Astaxanthin (Ax-Hp)		Haematococcus pluvialis, Green Algae	Antioxidant, Anti-inflammatory	A 12-week randomised, double-blind, placebo-controlled trial in healthy middle-aged adults (aged 45–64 years) with age-related subjective cognitive complaints.	High-dose supplementation improved one CogHealth task, response time and accuracy, with trends in three others. GMLT total errors significantly decreased by week 4, suggesting cognitive benefits.	[161]

Table 1. Cont.

Compound	Chemical Structure	Algal Source	Mechanism	Tested Model	Main Findings	Reference
Astaxanthin (Ax-Hp)		Haematococcus pluvialis, Green Algae	Antioxidant	12-week randomised, double-blind, placebo-controlled trial ($n = 30$) healthy adults (50–69 years), receiving 0 mg, 6 mg or 12 mg/day.	Significantly increased erythrocyte Ax-Hp levels and reduced PLOOH, indicating antioxidant activity.	[162]
Macular Xanthophylls		Chlorella and Dunaliella species, Green Algae	Antioxidant, Anti-inflammatory, Neurotrophic Modulation	6-month randomised, double-blind, placebo-controlled trial in healthy young adults (18–25 years), assessing dose-dependent effects of macular xanthophyll supplementation (13 mg or 27 mg/day) on cognitive and biochemical outcomes.	Supplementation improved composite and verbal memory, attention and processing speeds. BDNF, AOC, MPOD, lutein and zeaxanthin increased; IL-1 β decreased. Cognitive gains correlated with BDNF and MPOD changes.	[163]
Ulvan		Ulva lactuca, Green Seaweed	Neuroprotective	<i>In vitro</i> study using SH-SY5Y neuroblastoma cells of Ulva against BPA-induced toxicity.	Strong antioxidant, anticholinesterase and neuroprotective effects by restoring cell viability, inhibiting capase-3 activation.	[164]
Mixed Compounds, not explicitly recorded		Mixed Edible Algae	Not directly assessed	Cross-sectional analysis of 2018 CLHLS data from older Chinese adults (≥ 65 years), examining associations between edible mushroom/algae intake and cognitive impairment.	In the fully adjusted model, cognitive impairment risk was reduced by 29% (OR: 0.710) for daily intake and 25.3% (OR: 0.747) for occasional intake.	[165]

The arrow represents a decrease level. Abbreviations: AOC: Antioxidant capacity, COX-2: cyclooxygenase-2, GFAP: glial fibrillary acidic protein, GABA: gamma-aminobutyric acid, GMLT: Groton maze learning test, Iba-1: allograft inflammatory factor 1, ICV: intracerebral ventricular, IL: interleukin, iNOS: inducible nitric oxide synthase, IOE: *I. Okamurae* extracts, JNK: c-Jun N-terminus kinase, KOS: κ -carrageenan oligosaccharides, LPS: lipopolysaccharide, LXR: liver X receptor, MAPK: mitogen-activated protein kinase, MPOD: macular pigment optic density, OLT: object location test, ORT: object recognition test, PARP: poly (ADP-ribose) polymerase, PLOOH: phospholipid hydroperoxide, PT: *Phaeodactylum tricornutum*, 4-HNE: 4-hydroxynoneal, 5-HT: serotonin.

3.1. Phaeophyceae (Brown Seaweed)

Brown seaweed, varying in pigmentation from yellow to dark brown, represents one of the largest groups of marine macroalgae and accounts for approximately 66.5% of global seaweed consumption [166]. It has attracted scientific interest due to its diverse array of bioactive compounds and its broad range of biological properties. Its unique biochemical composition, comprising up to 70% of tissue mass, containing polysaccharides and other functional constituents, has enabled its application across the nutraceutical, pharmaceutical and cosmetic industries [167]. Brown seaweed is particularly rich in sulphated and non-sulphated polysaccharides, with fucoidan and its derivatives being among the most studied. In addition, they are a primary source of marine carotenoids, which display notable antioxidant, anti-inflammatory, and immunomodulatory properties (see Table 1) [168].

Phlorotannins, such as dieckol, have been shown to exert multifaceted neuroprotective effects by targeting oxidative stress, neuroinflammation, and synaptic dysfunction [148,149]. Dieckol inhibits AChE and restores hippocampal neurotransmitter balance, increasing serotonin and glutamate while reducing GABA and norepinephrine, thereby alleviating memory deficits in ethanol-treated mice [148]. Administration of dieckol has been reported to exert preventive effects by inhibiting oxidative damage and apoptosis through the suppression of caspase activation and mitochondrial dysfunction, while concurrently countering neuroinflammation by inhibiting the NF- κ B and MAPK pathways [149,169–171]. Dieckol's antioxidant efficacy is thought to occur via scavenging free radicals (DPPH, ABTS) and reducing intracellular ROS in oxidatively stressed neurons, while activating the Nrf2/HO-1 pathway to bolster endogenous antioxidant defences [169,172,173]. It also mitigates microglia-mediated neurotoxicity by suppressing the release of pro-inflammatory cytokines (TNF- α , IL-1 β), responsible for neuronal death (see Figure 1) and by inhibiting NADPH oxidase-driven ROS production in neuronal cell lines [171,174]. In addition, to its antioxidant and anti-inflammatory effects, dieckol has been shown to influence APP processing by enhancing α -secretase (ADAM10) activity while downregulating β - and γ -secretase, promoting the non-amyloidogenic pathway and reducing A β accumulation [175]. Dieckol also activates the PI3K/Akt signalling cascade, leading to inhibitory phosphorylation of GSk-3 β , a key enzyme in tau phosphorylation and NFT formation (refer to teal pathway Figure 1) [175]. Although there is no direct evidence that dieckol acts directly on tau, preliminary findings indicate potential effects on downstream tau-related pathology [175].

Fucoidans have attracted increasing attention for their neuroprotective and cognition-enhancing properties. Extensive preclinical research demonstrates that fucoidan can ameliorate cognitive impairment across various models of brain dysfunction, including those induced by A β infusion, lipopolysaccharide (LPS) exposure and D-galactose administration [151,159,176]. Mechanistically, fucoidans appear to act by reducing oxidative stress and neuroinflammation, restoring mitochondrial function, and modulating key neuroprotective pathways, such as the APN-AMOK-SIRT1 signalling pathway and BDNF expression [151,159]. Emerging evidence also suggests that fucoidans may also interact with molecular processes linked to tau pathology. Preliminary *in vitro* findings indicate that certain sulphated fucoidan fractions, such as galactofucans and heteropolysaccharides, may compete with cell-surface heparan sulphate for tau bindings sites, potentially reducing tau attachment and internalisation [177]. By interfering with this receptor-mediated uptake, fucoidan may theoretically limit the cell-to-cell propagation of tau aggregates and the subsequent formation of NFTs [177].

In animal studies, fucoidan improved performance in learning and memory tasks and ameliorated biochemical markers of neuronal damage [152]. Specifically, it has been shown

to restore ACh levels and enhance biochemical markers of neuronal health, including reducing markers of apoptosis in the hippocampus [152]. These effects are attributed to decreased lipid peroxidation, inhibition of AChE activity, and suppression of caspase-mediated apoptosis, collectively indicating a broad mechanism of action involving oxidative stress reduction, mitochondrial protection, and anti-apoptotic effects [26]. Additionally, *Sargassum muticum*, including fucoidan compounds, has been shown to protect cells from oxidative stress induced by neurotoxins, such as 6-hydroxydopamine (6-OHDA) in *in vitro* studies [178]. Emerging evidence also suggests that fucoidan may exert its neuroprotective effects through epigenetic mechanisms. In a human clinical study, a single oral dose of *Undaria pinnatifida* fucoidan significantly altered the expression of 53 circulating microRNAs and modulated 31 cellular pathways, several of which are associated with neurotrophic signalling, including BDNF, MAPK, EGFR, and insulin receptor pathways [179].

Another brown seaweed-derived compound phloroglucinol, a polyphenolic compound, has demonstrated neuroprotective activity in both *in vitro* and *in vivo* models of AD. In studies using the 5XFAD transgenic mouse model, which recapitulates key features of AD, oral administration of phloroglucinol reduced A β plaque burden and lowered protein levels of BACE1, a key enzyme in A β production (see blue pathway Figure 1) [156,157]. Additionally, it markedly decreased oxidative stress markers, including 4-hydroxynonenal (4-HNE) and suppressed glial activation as evident by reduced levels of GFAP, an astrocyte marker, and Iba-1, a microglia marker [156,157]. These molecular changes were accompanied by restoration of dendritic spine density in the hippocampus and improvements in spatial learning and memory in 5XFAD mice when compared to controls [156,157]. Phloroglucinol exerts its effects through potent antioxidant activity, scavenging ROS and enhancing endogenous antioxidant enzyme levels, likely via upregulation of the Nrf2 pathway [157,180]. These findings suggest that phloroglucinol may mitigate key neuropathological features of AD and improve cognitive function.

Seaweed-derived carotenoids, such as fucoxanthin, have been explored in both pre-clinical and clinical studies. In D-galactose-induced ageing mouse models, fucoxanthin supplementation attenuated cognitive deficits by reducing lipid peroxidation and lowering pro-inflammatory cytokines, specifically TNF- α and IL-6 [152]. In addition to its effects on oxidative and inflammatory pathways, oral administration of fucoxanthin has also been shown to reduce tau accumulation in the brains of treated mice [181]. However, it is speculated that this is likely secondary to the antioxidant and anti-inflammatory properties rather than a direct effect on tau [181]. Clinical trials in older adults with self-perceived cognitive decline reinforce these findings. For example, in a 12-week randomised, placebo-controlled trial, adults ($n = 22$) receiving 8.8 mg/day fucoxanthin supplementation demonstrated significant within-group improvements in delayed recall (+1.2 words), executive function (Stroop reaction time -42 ms), attention (digital vigilance error -13%), and vigilance (choice reaction time -46 ms), although most between-group differences compared with placebo ($n = 21$) were not statistically significant [153]. Furthermore, six months of daily supplementation with a lower dose, 4.4 mg/day, resulted in significant gains in both immediate and delayed word recall [182]; further emphasising enhancements in both working and episodic memory in an intervention study with an elderly cohort.

Brown seaweed-derived phytosterols, particularly fucosterol and 24(S)-saringosterol from *Himantalia elongata* and *Sargassum fusiforme*, have been shown to activate the liver X receptor beta (LXR β) selectively, a nuclear receptor critical for cholesterol homeostasis and amyloid clearance in the brain [183–185]. Importantly activation of LXR β is achieved with minimal activation of LXR α , thereby reducing the risk of hepatic side effects that are commonly associated with non-selective LXR agonists [183–185]. *In vitro* studies confirm that extracts from these seaweeds, especially those from *Sargassum fusiforme*, robustly activate

LXR β , but not LXR α , with this activation selectively attributed to 24(S)-saringosterol [183]. Dietary supplementation of *Sargassum fusiforme* for 12 weeks has led to an accumulation of 24(S)-saringosterol in the brain, upregulating LXR target genes, decreasing astrocyte activation and improving performance in object and spatial memory in APPswePS1 Δ E9 mouse model (see Table 1) [154]. Collectively these studies suggest that brown seaweed phytosterols represent a potential therapeutic strategy without the adverse hepatic effects seen with pan-LXR agonists.

The range of neuroprotective actions attributed to brown seaweed bioactive compounds illustrates their potential therapeutic relevance across multiple molecular targets involved in AD pathology. By addressing several interconnected mechanisms, these compounds offer the potential for a multifaceted intervention strategy that is not achieved by conventional single-target therapies. Given this emerging evidence, research has begun to explore red seaweeds, which offer a distinct phytochemical composition in comparison to brown seaweed.

3.2. Rhodophyta (Red Seaweed)

Red seaweeds, or red algae, are a diverse group of marine macroalgae recognised for their rich bioactive compounds and pigments, including carotenoids, chlorophyll a and d, phycoerythrin, phycocyanin, and allophycocyanin [186]. These pigments not only impart the characteristic red hue, but also contribute to antioxidant capacity, supporting their relevance in nutritional and therapeutic contexts [187]. A hallmark of red seaweeds is their abundant cell wall polysaccharides, particularly agar, carrageenan and sulphated galactan, that exhibit antioxidant, anti-inflammatory and neuroprotective properties [188].

Sulphated polysaccharides derived from red seaweeds, such as those isolated from *Gelidium pristoides*, have been shown to disrupt A β fibril formation in *in vitro* studies, indicating a direct anti-aggregation effect that targets a pathological feature of AD (see Figure 1) [189]. In addition to this anti-amyloidogenic action, enzymatically digested κ -carrageenan oligosaccharides (KOS), another class of red seaweed polysaccharides, have been found to attenuate neuroinflammation by inhibiting microglial hyperactivation and reducing the expression of pro-inflammatory cytokines, specifically IL-1 β , TNF- α , and IL-6, in *in vivo* and *in vitro* AD models [26]. KOS, significantly attenuated hydrogen peroxide-induced cytotoxicity in PC12 cells, reducing intracellular ROS and preserving mitochondrial membrane potential, indicating protection against oxidative-stress-induced apoptosis [190]. Derivatives of KOS, pentasaccharides, were found to protect neurons from A β -induced apoptosis by suppressing the overactivation of the c-Jun N-terminal kinase (JNK) signalling pathway, a mediator of A β neurotoxicity [191].

Lutein and zeaxanthin, xanthophyll carotenoids found in both red and green algae, have attracted increasing research interest in the context of AD, compared to other red algae bioactive compounds. Supplementation with these carotenoids in pre-clinical studies has been reported to mitigate memory deficits, reducing A β deposition and neuroinflammation [192–194]. Lutein and zeaxanthin are thought to exert their effects through multiple pathways, involved in oxidative stress, AChE activity, and downregulation of pro-inflammatory cytokines such as TNF- α and IL-1 β [192]. Furthermore, neuronal health is supported by increasing neurotrophic factors such as BDNF and ciliary neurotrophic factor (CNTF), and by maintaining glucose homeostasis in the brain [192]. Epidemiological studies and clinical trials found that a higher dietary intake and serum levels of lutein and zeaxanthin were associated with improved episodic memory, visual learning and a reduced risk of cognitive decline and dementia [160,193–195].

Together, the bioactive profile of red seaweeds appears to confer neuroprotective effects through multiple mechanisms. These effects, while overlapping with those of other

phyla, arise from compounds unique to red algae, underscoring the importance of phylum-specific profiles and research in targeting multiple facets of AD pathology. Although red and green seaweeds share broad classes of bioactive compounds, such as polysaccharides, their specific molecular constituents differ considerably.

3.3. Chlorophyta (Green Seaweed)

Green algae are primarily distinguished by their high content of chlorophyll, a green, lipid soluble pigment that is ubiquitous among plants, algae and cyanobacteria [196]. Beyond the chlorophyll content, green seaweeds, like the other phyla contain a rich reservoir of bioactive compounds with potential therapeutic relevance for AD. Although green seaweeds exhibit a lower total polysaccharide content relevant to brown and red seaweeds, they are particularly enriched in ulvan, a sulphated polysaccharide [197].

In vitro research has shown that ulvan-rich extract, derived from *Ulva lactuca*, exhibits notable antioxidant and anticholinesterase activity, restoring cell viability and inhibiting caspase-3 activation in BPA-challenged SH-SY5Y neuroblastoma cells, findings that directly address oxidative stress and apoptosis [164]. Beyond cell studies, ulvan's antioxidant effects have been demonstrated *in vivo* to increase superoxide dismutase and glutathione peroxidase activity, reducing lipid peroxidation and decreasing cytokines such as TNF- α and IL-6 in pre-clinical studies [198]. Ulvan extracts were found to lower markers of biomolecular damage, including protein carbonylation and DNA oxidative lesions, and protected against apoptosis by downregulating caspase-3 expression in animal model [198]. Ulvan anti-inflammatory and immunomodulatory properties have been confirmed in additional studies, which suggests that its biological activity depends on factors such as molecular weight, sulphate content and carbohydrate composition [199]. Ulvan broader therapeutic potential also supports its modulation of immune response [200].

Astaxanthin, a xanthophyll carotenoid belonging to the terpene family, is widely distributed in marine organisms. The microalgae *Haematococcus pluvialis*, can accumulate astaxanthin up to 3.8% of its dry weight, with evidence suggesting potential neuroprotective effects [201]. Preclinical studies in AD have shown that astaxanthin supplementation results in the amelioration of memory deficits, reduction in A β deposition in the hippocampus and cortex, decreased tau phosphorylation and parvalbumin-positive neuron density in the hippocampus of AD model mice compared to control mice [202–204]. In these pre-clinical studies, enhanced antioxidant capacity and modulation of microglia and pro-inflammatory marker expression were reported in the hippocampus of AD mice models [205,206]. Astaxanthin appears to exert its neuroprotective actions by attenuating oxidative stress, reducing neuronal apoptosis, and suppressing neuroinflammatory processes via SIRT1/PGC-1 α signalling pathway [179]. Furthermore, upregulation of anti-apoptotic proteins (Bcl-2), and downregulation of pro-apoptotic proteins (like Bax), were also reported in these AD mice models, inhibiting potentially neuronal senescence and apoptosis induced by A β toxicity [206].

Clinical evidence regarding the effects of astaxanthin on cognitive function in humans remains limited but is gradually emerging, with several randomised, double-blind, placebo-controlled trials offering preliminary insights into its potential therapeutic benefits as well as its limitations (see Table 1). Supplementation of astaxanthin in a human cohort supports preclinical findings as phospholipid hydroperoxide levels in erythrocytes significantly decreased, indicating a reduction in lipid peroxidation and systemic oxidative damage [162]. In a study by Katagiri et al. (2012), supplementation with astaxanthin-rich *H. pluvialis* extract led to significant improvements in cognitive performance, particularly psychomotor and processing speeds in middle-aged and older adults (see Table 1) [161]. Similarly, a systematic review of clinical trials found that astaxanthin supplementation was associated with subjective and objective improvements in cognitive function among older adults,

although not all studies reached statistical significance [207]. Subgroup analyses have indicated that younger participants, aged 45–54 years, may experience more pronounced cognitive benefits, especially in memory tasks, in comparison to older cohorts [208].

These findings underscore the potential of green seaweed-derived compounds in mitigating the neurodegenerative processes associated with AD. Ulvan's potent antioxidant, anti-apoptotic, and anti-inflammatory activity, alongside astaxanthin's capacity to modulate mitochondrial function, position green algae as another promising source of neuroprotective agents. Although green seaweeds possess a comparatively narrower diversity of characterised bioactive compounds than its brown and red counterparts, emerging preclinical and early clinical evidence indicate their continued investigation within a multifaceted, integrative framework for AD intervention.

4. Discussion

Evaluation of the therapeutic potential of brown, red and green seaweeds provides a strong rationale for their consideration in strategies addressing neurodegeneration and cognitive decline in AD. Bioactive compounds from brown, red and green algae share convergent mechanisms that influence key molecular processes involved in AD. Across all phyla, antioxidant activity represents a recurrent characteristic; compounds such as dieckol and fucoxanthin (brown), carrageenans and xanthophylls like lutein and zeaxanthin (red), and ulvan (green) have been reported to reduce intracellular ROS, enhance mitochondrial stability, and activate the Nrf2/HO-1 antioxidant defence pathway [164,172,192]. Anti-inflammatory effects are also frequently observed, with these compounds downregulating NF- κ B and MAPK signalling, suppressing microglial overactivation, and reducing pro-inflammatory cytokine expression [171,198,205]. Additionally, seaweed compounds have been reported to modulate neurotrophic and cholinergic pathways by upregulating BDNF and CTNF, inhibiting AChE activity, and reducing caspase-3-mediated apoptosis, mechanisms supporting synaptic plasticity, neuronal survival and cognitive performance [151,194,198]. Together, these pleiotropic actions suggest the therapeutic potential of seaweed in addressing the multifactorial pathology of AD.

Importantly, these molecular effects are paralleled by reported improvements in cognitive function (see Figure 2). Across both preclinical and clinical models, seaweed-derived compounds have associated with improvements in memory, learning, and attention. In animal models of AD, brown seaweed constituents such as dieckol, fucoxanthin, and phloroglucinol improved memory performance [148,151,161]. Similar effects were observed with LXR-activating compounds like saringosterol, which improved spatial and object memory in transgenic AD mice [154,184]. While human trials remain limited, early evidence suggests cognitive benefits in domains such as memory and processing speed following supplementation with astaxanthin, lutein and zeaxanthin, and fucoxanthin [153,160,161]. This evidence supports the potential of specific seaweed-derived compounds in addressing cognitive decline. While clinical trials remain limited, these early findings suggest cognitive benefits in humans, supporting the potential role of seaweed compounds as multi-target interventions for cognitive impairment associated with ageing and AD. Notably, related effects are not exclusive to age-related and pathological decline, as macular xanthophylls, a green seaweed-derivative demonstrated efficacy in improving cognitive outcomes in young adults [163].

Available studies to date indicate favourable safety and tolerability. Clinical trials involving *Ulva lactuca* and brown seaweed extracts have reported no notable adverse effects over several weeks to months of supplementation [209,210]. Given the convergence of mechanisms across different seaweed species and bioactive compounds, the translational potential of this research appears encouraging. These compounds which target multiple

hallmarks of cognitive decline and AD, position them as potential candidates for future adjunctive or preventative strategies.

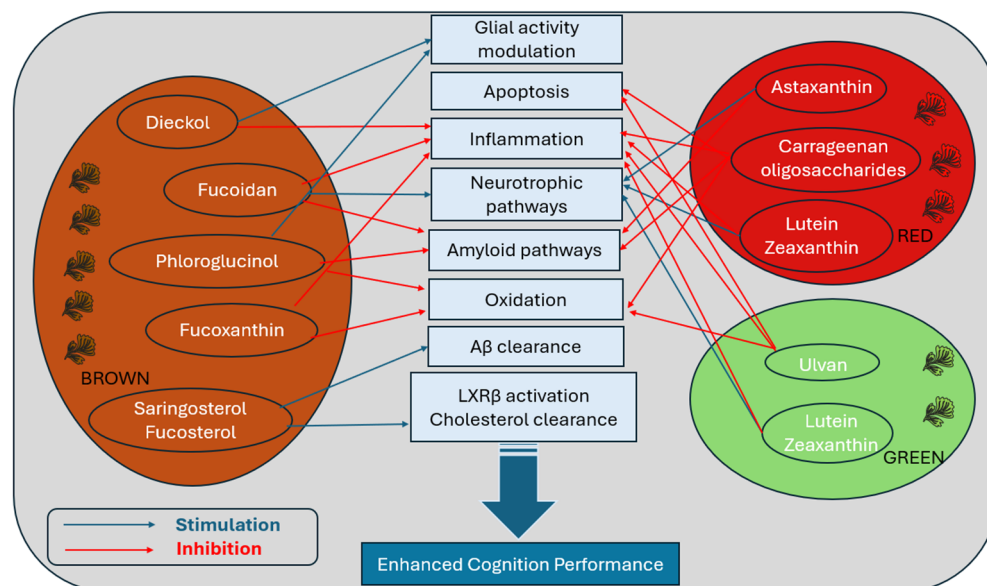


Figure 2. Summary of seaweed derived compounds from brown, red and green algae on major AD molecular pathways. The red arrow represents an inhibition effect while the blue arrow illustrates stimulation. Abbreviations: LXRβ: liver X receptor beta; Aβ: amyloid beta.

Despite promising early findings, current clinical research remains constrained by methodological limitations that restrict the generalisability and strength of conclusions. For example, within green seaweed-derived compounds, Katagiri et al. (2012) conducted a 12-week randomised, double-blind, placebo-controlled trial examining astaxanthin supplementation (6 or 12 mg/day) in 96 middle-aged and older adults [161]. While the results indicated cognitive benefits, the relatively low dosage and short intervention period limit conclusions regarding long-term efficacy or optimal dosing.

Similarly, Lopresti et al. (2022) evaluated the effects of lutein (10 mg/day) and zeaxanthin (2 mg/day), red seaweed-derived compounds, over six months in 51 adults; however, the modest sample-size, limited follow-up and inclusion of a generally healthy middle-aged population may limit the applicability of these findings to older adults experiencing cognitive decline or at risk of AD [160]. While 10 mg of lutein and 2 mg of zeaxanthin fall within the range commonly used in seaweed-related nutritional neuroscience studies, evidence suggests these doses may be lower than those producing stronger cognitive effects from other studies, as a dose equivalent to 10 g of dried brown seaweed has shown greater efficacy in enhancing acute cognitive performance in humans [210]. It also remains unclear whether longer exposure, higher doses, or trials in more clinically relevant populations would yield more robust or translatable outcomes. Potential adverse effects may remain undetected in short-term studies involving healthy individuals but may occur at a later stage. Furthermore, red seaweed compounds, like sulphated polysaccharides, lutein and zeaxanthin, remain understudied in human trials, with most evidence deriving from pre-clinical animal models. The long-term safety and efficacy of high-dose supplementation in humans remains limited.

In a brown seaweed compounds focused study, Yoo et al. (2024) administered fucoxanthin (8.8 mg/day) to a population of adults between 55 and 75 years with subjective cognitive decline, but this study was limited by the cohort age and size ($n = 43$), brief follow-up duration (12 weeks) and low dosage [153]. In contrast to the modest clinical studies, pre-clinical studies in animal models often report greater improvements at higher per-body-weight

doses, such as dieckol (20 mg/kg/day) [148], fucoidan (100 mg/kg/day) [151], fucoxanthin (50 mg/kg/day) and phloroglucinol [156], and saringosterol (10 mg/kg/day) [154]. However, it is recognised that these doses often exceed those that would be considered safe or practical in humans [211].

When integrating current findings across seaweed phyla, evident disparities emerge in the scope, quality, and translational progress of the evidence base. Brown seaweeds remain the most extensively studied, with a growing body of both preclinical and early clinical data supporting the potential for cognitive benefits via antioxidant, anti-inflammatory, and neurotrophic mechanisms. However, existing human trials are often constrained by small sample sizes, brief intervention durations, and subtherapeutic dosing, highlighting the need for larger, well-powered studies targeting AD-relevant populations. In contrast, red seaweed, despite being rich in bioactive xanthophylls and sulphated polysaccharides, remains predominantly explored in preclinical models, with limited human data. Green seaweeds similarly show promising neuroprotective potential *in vitro* and *in vivo*, particularly through ulvan and astaxanthin-mediated antioxidant and anti-apoptotic effects. Yet, clinical evidence remains minimal.

Seaweed-derived bioactive compounds present several physicochemical and pharmacokinetic limitations that challenge their translation into AD therapeutic agents. Brown seaweed-derived compounds, such as phlorotannins and fucoxanthin, have shown poor solubility in aqueous solution (such as plasma) and chemical instability under physiological pH and temperature, leading to their degradation in preclinical studies [212]. Oral administration of phlorotannins compared to IV administration in rats demonstrated the extensive first-pass metabolism in liver, resulting in a low systemic bioavailability [212]. In contrast, sulphated polysaccharides such as fucoidan and laminarin are more water-soluble and their absorption varies according to their molecular weight (differing with sulfation pattern) [213]. High digestion and absorption efficiency was reported with the lower molecular weight of fucoidan [214] while the higher molecular weight fucoidan is often more viscous than laminarin, affecting its absorption and permeability to brain blood barrier (BBB) [215,216].

These physicochemical and pharmacokinetic constraints may limit the concentrations of ingested seaweed-derived compounds in the systemic circulation and, consequently, in the brain. Improving the bioavailability of seaweed-derived compounds remains a key challenge, however novel delivery strategies such as nanoparticle encapsulation, phytosome delivery, and conjugation with carrier molecules have recently emerged and show potential for improving bioavailability [215,217,218].

Nanoencapsulation of fucoxanthin increased its bioavailability when compared with administration of the same non-encapsulated seaweed-derived compound in animal model (encapsulation efficiency of fucoxanthin over 78%), which may open new avenues for effective delivery of seaweed-derived compounds in the human body [217].

Similarly, fucoidan's biological versatility and its gel-forming properties for nanogel preparation, alongside of red seaweed polysaccharides such as carrageenan, offer biocompatible and sustained matrices for controlled drug release, potentially enhancing intestinal or BBB transport [218]. Phytosomes, phospholipid-based nanocarriers that mimic cell membranes, can protect seaweed-derived compounds from degradation from digestive system, improve their bioavailability and increase their transport via BBB [219]. Conjugation of seaweed compounds with negatively charged carbon dot molecules such as fucoidan-derived carbon dots, may enhance BBB transport through their small size and negatively charged surface [220]. With the presence of sulphate and hydroxyl groups derived from fucoidan further facilitating uptake and conferring neuroprotective effects in neuronal cells and animal models of Parkinson disease [220].

These emerging delivery systems, which improve biocompatibility and stability, may enhance the therapeutic potential of seaweed compounds, although further validation in human trials is required to optimise compound efficacy and ensure safety.

To advance clinical translation, future research should prioritise phylum-specific investigations, dose–response relationships, and longer intervention durations in at-risk older adults. Carefully designed pilot trials are warranted to assess the safety, feasibility and preliminary efficacy, followed by larger rigorously controlled studies, to evaluate long-term outcomes and identify any delayed or dose-dependent adverse effects that may not be apparent in short-term trials involving healthy individuals.

5. Conclusions

Existing research proposes seaweed-derived bioactive compounds as potential multi-targeted approaches to target the complex pathology of AD, addressing interconnected mechanisms such as oxidative stress, neuroinflammation, amyloid- β aggregation and synaptic dysfunction. Preclinical studies have reported some neuroprotective effects across brown, red and green algae, with early clinical trials indicating safety and potential cognitive benefits. However, at this point translation to clinical settings is limited by small sample sizes, low dosages, short intervention periods and under-representation of at-risk populations. Advancement in this field will benefit from well-designed and adequately powered human studies that evaluate long-term efficacy, optimal dosing, and potential synergistic effects of combined bioactive compounds. Nonetheless, emerging evidence indicates that integrating these natural compounds into prevention or adjunctive treatment strategies, offers the potential to improve cognitive outcomes in ageing populations and those at risk of AD. Given the global ageing population, the exploration of natural compounds as cognitive support interventions is increasingly relevant for both healthy individuals and people living with pathological conditions such as AD.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules30224456/s1>.

Author Contributions: Conceptualisation, K.W. and F.F. Writing—original draft preparation, K.W.; writing—review and editing, K.W., L.R.G., H.G.S., M.H.C., P.W., B.J.M. and F.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analysed in this study.

Conflicts of Interest: P.W. is employed by Venus Shell Systems Pty Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

A β	Amyloid-beta
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEIs	Acetylcholinesterase inhibitors
ADAM10	a disintegrin and metalloproteinase domain-containing protein 10
AICD	APP intracellular domain
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AOC	Antioxidant capacity

APP	Amyloid precursor protein
ARIAs	amyloid-related imaging abnormalities
ARIA-E	vasogenic oedema
BACE1	β -site APP-cleaving enzyme 1
BDNF	brain-derived neurotrophic factor
COX-2	cyclooxygenase-2
CREB	Cyclic AMP-responsive element-binding protein
CTNF	ciliary neurotrophic factor
DLPFC	dorsolateral prefrontal cortex
EGCG	epigallocatechin gallate
GFAP	Glial fibrillary acidic protein
GABA	Gamma-aminobutyric acid
GMLT	Groton maze learning test
GSK3 β	Glycogen synthase kinase-3 beta
Iba-1	allograft inflammatory factor 1
ICV	intracerebral ventricular
IL	interleukin
iNOS	inducible nitric oxide synthase
IOE	<i>I. Okamurae</i> extracts
JNK	c-Jun N-terminus kinase
KOS	κ -carrageenan oligosaccharides
LPS	lipopolysaccharide
LTP	long-term potentiation
LXR	liver X receptor
MAB	monoclonal antibodies
MAPK	mitogen-activated protein kinase
MAPK/ERK	mitogen-activated protein kinase/extracellular signal-regulated kinase
MCI	Mild cognitive impairment
MDA	malondialdehyde
MPOD	macular pigment optic density
mtDNA	Mitochondrial DNA
NF- κ B	nuclear factor kappa-light-chain-enhance of activated B cells
NFTs	Neurofibrillary tangles
NO	nitric oxide
OLGs	oligodendrocyte lineage cells
OLT	object location test
OPCs	oligodendrocyte precursor cells
ORT	object recognition test
PARP	poly (ADP-ribose) polymerase
PI3K/Akt	phosphatidylinositol 3-kinase/protein kinase B
PLOOH	phospholipid hydroperoxide
PT	<i>Phaeodactylum tricornutum</i>
P38-MAPK	P38 mitogen-activated protein kinase
RCF	Respiratory chain function
RCTs	Randomised controlled trials
ROS	Reactive oxygen species
sAPP	Soluble
TNF	tumour necrosis factor
4-HNE	4-hydroxynoneal
5-HT	serotonin
6-OHDA	6-hydroxydopamine
α 7 nAChRs	α 7 subtype of nicotinic acetylcholine receptors

References

1. World Health Organisation. Dementia. 2025. Available online: <https://www.who.int/news-room/fact-sheets/detail/dementia> (accessed on 6 June 2025).
2. Gardner, R.C.; Valcour, V.; Yaffe, K. Dementia in the oldest old: A multi-factorial and growing public health issue. *Alzheimer's Res. Ther.* **2013**, *5*, 27. [CrossRef]
3. Welberry, H.J.; Brodaty, H.; Hsu, B.; Barbieri, S.; Jorm, L.R. Measuring dementia incidence within a cohort of 267,153 older Australians using routinely collected linked administrative data. *Sci. Rep.* **2020**, *10*, 8781. [CrossRef]
4. Lee, J.; Kim, H.J. Normal Aging Induces Changes in the Brain and Neurodegeneration Progress: Review of the Structural, Biochemical, Metabolic, Cellular, and Molecular Changes. *Front. Aging Neurosci.* **2022**, *14*, 931536. [CrossRef]
5. Emmady, P.D.; Schoo, C.; Tadi, P. Major Neurocognitive Disorder (Dementia). In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: <http://www.ncbi.nlm.nih.gov/books/NBK557444/> (accessed on 24 June 2025).
6. Beam, C.R.; Kaneshiro, C.; Jang, J.Y.; Reynolds, C.A.; Pedersen, N.L.; Gatz, M. Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease. *J. Alzheimer's Dis. JAD* **2018**, *64*, 1077–1083. [CrossRef]
7. Azam, S.; Haque, M.E.; Balakrishnan, R.; Kim, I.S.; Choi, D.K. The Ageing Brain: Molecular and Cellular Basis of Neurodegeneration. *Front. Cell Dev. Biol.* **2021**, *9*, 683459. [CrossRef] [PubMed]
8. Bartman, S.; Coppotelli, G.; Ross, J.M. Mitochondrial Dysfunction: A Key Player in Brain Aging and Diseases. *Curr. Issues Mol. Biol.* **2024**, *46*, 1987–2026. [CrossRef] [PubMed]
9. Latham, A.S.; Moreno, J.A.; Geer, C.E. Biological agents and the aging brain: Glial inflammation and neurotoxic signaling. *Front. Aging* **2023**, *4*, 1244149. [CrossRef]
10. Mattson, M.P.; Arumugam, T.V. Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States. *Cell Metab.* **2018**, *27*, 1176–1199. [CrossRef] [PubMed]
11. Lye, S.; Aust, C.E.; Griffiths, L.R.; Fernandez, F. Exploring New Avenues for Modifying Course of Progression of Alzheimer's Disease: The Rise of Natural Medicine. *J. Neurol. Sci.* **2021**, *422*, 117332. [CrossRef]
12. Castellani, R.J.; Jamshidi, P.; Plascencia-Villa, G.; Perry, G. The Amyloid Cascade Hypothesis: A Conclusion in Search of Support. *Am. J. Pathol.* **2024**, *195*, 1988–1997. [CrossRef]
13. Chen, Z.R.; Huang, J.B.; Yang, S.L.; Hong, F.F. Role of Cholinergic Signaling in Alzheimer's Disease. *Molecules* **2022**, *27*, 1816. [CrossRef]
14. Hampel, H.; Mesulam, M.M.; Cuello, A.C.; Farlow, M.R.; Giacobini, E.; Grossberg, G.T.; Khachaturian, Z.S.; Vergallo, A.; Cavado, E.; Snyder, P.J.; et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain* **2018**, *141*, 1917–1933. [CrossRef]
15. Long, J.M.; Holtzman, D.M. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell* **2019**, *179*, 312–339. [CrossRef] [PubMed]
16. Lyo, M.; Namba, H.; Fukushi, K.; Shinotoh, H.; Nagatsuka, S.; Suhara, T.; Sudo, Y.; Suzuki, K.; Irie, T. Measurement of acetylcholinesterase by positron emission tomography in the brains of healthy controls and patients with Alzheimer's disease. *Lancet* **1997**, *349*, 1805–1809. [CrossRef]
17. Whitehouse, P.J.; Price, D.L.; Clark, A.W.; Coyle, J.T.; DeLong, M.R. Alzheimer disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann. Neurol.* **1981**, *10*, 122–126. [CrossRef]
18. Muth, K.; Schönmeier, R.; Matura, S.; Haenschel, C.; Schröder, J.; Pantel, J. Mild Cognitive Impairment in the Elderly is Associated with Volume Loss of the Cholinergic Basal Forebrain Region. *Biol. Psychiatry* **2010**, *67*, 588–591. [CrossRef]
19. Petersen, R.C.; Thomas, R.G.; Grundman, M.; Bennett, D.; Doody, R.; Ferris, S.; Galasko, D.; Jin, S.; Kaye, J.; Levey, A.; et al. Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment. *N. Engl. J. Med.* **2005**, *352*, 2379–2388. [CrossRef]
20. Feldman, H.H.; Ferris, S.; Winblad, B.; Sfikas, N.; Mancione, L.; He, Y.; Tekin, S.; Burns, A.; Cummings, J.; del Ser, T.; et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: The InDDEX study. *Lancet Neurol.* **2007**, *6*, 501–512. [CrossRef] [PubMed]
21. Burns, A.; Bernabei, R.; Bullock, R.; Jentoft, A.J.C.; Frölich, L.; Hock, C.; Raivio, M.; Triau, E.; Vandewoude, M.; Wimo, A.; et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): A randomised, placebo-controlled, double-blind trial. *Lancet Neurol.* **2009**, *8*, 39–47. [CrossRef] [PubMed]
22. Ferri, C.P.; Prince, M.; Brayne, C.; Brodaty, H.; Fratiglioni, L.; Ganguli, M.; Hall, K.; Hasegawa, K.; Hendrie, H.; Huang, Y.; et al. Global prevalence of dementia: A Delphi consensus study. *Lancet* **2005**, *366*, 2112–2117. [CrossRef]
23. Delrieu, J.; Piau, A.; Caillaud, C.; Voisin, T.; Vellas, B. Managing Cognitive Dysfunction through the Continuum of Alzheimer's Disease. *CNS Drugs* **2011**, *25*, 213–226. [CrossRef] [PubMed]
24. Kim, B.H.; Kim, S.; Nam, Y.; Park, Y.H.; Shin, S.M.; Moon, M. Second-generation anti-amyloid monoclonal antibodies for Alzheimer's disease: Current landscape and future perspectives. *Transl. Neurodegener.* **2025**, *14*, 6. [CrossRef] [PubMed]

25. Brockmann, R.; Nixon, J.; Love, B.L.; Yunusa, I. Impacts of FDA Approval and Medicare Restriction on Antiamyloid Therapies for Alzheimer's Disease: Patient Outcomes, Healthcare Costs, and Drug Development. *Lancet Reg. Health–Am.* **2023**, *20*, 100467. [[CrossRef](#)]
26. Jannat, K.; Balakrishnan, R.; Han, J.H.; Yu, Y.J.; Kim, G.W.; Choi, D.K. The Neuropharmacological Evaluation of Seaweed: A Potential Therapeutic Source. *Cells* **2023**, *12*, 2652. [[CrossRef](#)]
27. Lin, Y.; Im, H.; Diem, L.T.; Ham, S. Characterizing the structural and thermodynamic properties of A β 42 and A β 40. *Biochem. Biophys. Res. Commun.* **2019**, *510*, 442–448. [[CrossRef](#)]
28. Meisl, G.; Yang, X.; Hellstrand, E.; Frohm, B.; Kirkegaard, J.B.; Cohen, S.I.A.; Dobson, C.M.; Linse, S.; Knowles, T.P.J. Differences in nucleation behavior underlie the contrasting aggregation kinetics of the A β 40 and A β 42 peptides. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 9384–9389. [[CrossRef](#)]
29. Gu, L.; Guo, Z. Alzheimer's A β 42 and A β 40 peptides form interlaced amyloid fibrils. *J. Neurochem.* **2013**, *126*, 305–311. [[CrossRef](#)] [[PubMed](#)]
30. Haessler, A.; Gier, S.; Jung, N.; Windbergs, M. The A β 42:A β 40 ratio modulates aggregation in beta-amyloid oligomers and drives metabolic changes and cellular dysfunction. *Front. Cell Neurosci.* **2024**, *18*, 1516093. [[CrossRef](#)]
31. Pauwels, K.; Williams, T.L.; Morris, K.L.; Jonckheere, W.; Vandersteen, A.; Kelly, G.; Schymkowitz, J.; Rousseau, F.; Pastore, A.; Serpell, L.C.; et al. Structural Basis for Increased Toxicity of Pathological A β 42:A β 40 Ratios in Alzheimer Disease. *J. Biol. Chem.* **2012**, *287*, 5650–5660. [[CrossRef](#)]
32. Jensen, L.E.; Bultynck, G.; Luyten, T.; Amijee, H.; Bootman, M.D.; Roderick, H.L. Alzheimer's disease-associated peptide A β 42 mobilizes ER Ca²⁺ via InsP3R-dependent and -independent mechanisms. *Front. Mol. Neurosci.* **2013**, *6*, 36. [[CrossRef](#)]
33. Li, S.; Selkoe, D.J. A mechanistic hypothesis for the impairment of synaptic plasticity by soluble A β oligomers from Alzheimer brain. *J. Neurochem.* **2020**, *154*, 583–597. [[CrossRef](#)]
34. Marsh, J.; Alifragis, P. Synaptic dysfunction in Alzheimer's disease: The effects of amyloid beta on synaptic vesicle dynamics as a novel target for therapeutic intervention. *Neural Regen. Res.* **2018**, *13*, 616–623. [[CrossRef](#)]
35. Shankar, G.M.; Walsh, D.M. Alzheimer's disease: Synaptic dysfunction and A β . *Mol. Neurodegener.* **2009**, *4*, 48. [[CrossRef](#)]
36. Abanto, J.T.; Dwivedi, A.K.; Imbimbo, B.P.; Espay, A.J. Association between amyloid- β 42 levels and neuropsychiatric symptoms in Alzheimer's disease trials. *Brain Commun.* **2025**, *7*, fcdf089. [[CrossRef](#)] [[PubMed](#)]
37. Liu, X.; Lv, Z.; Huang, Q.; Lei, Y.; Liu, H.; Xu, P. The Role of Oligodendrocyte Lineage Cells in the Pathogenesis of Alzheimer's Disease. *Neurochem. Res.* **2025**, *50*, 72. [[CrossRef](#)]
38. Ziar, R.; Tesar, P.J.; Clayton, B.L.L. Astrocyte and oligodendrocyte pathology in Alzheimer's disease. *Neurotherapeutics* **2025**, *22*, e00540. [[PubMed](#)]
39. Sasmita, A.O.; Depp, C.; Nazarenko, T.; Sun, T.; Siems, S.B.; Ong, E.C.; Nkeh, Y.B.; Böhler, C.; Yu, X.; Bues, B.; et al. Oligodendrocytes produce amyloid- β and contribute to plaque formation alongside neurons in Alzheimer's disease model mice. *Nat. Neurosci.* **2024**, *27*, 1668–1674. [[CrossRef](#)] [[PubMed](#)]
40. Spieth, L.; Simons, M. Remember oligodendrocytes: Uncovering their overlooked role in Alzheimer's disease. *PLoS Biol.* **2024**, *22*, e3002798. [[CrossRef](#)]
41. Elsworth, R.J.; Dunleavy, C.; Whitham, M.; Aldred, S. Exercise for the prevention of Alzheimer's disease: Multiple pathways to promote non-amyloidogenic A β PP processing. *Aging Health Res.* **2022**, *2*, 100093. [[CrossRef](#)]
42. Al-kuraishy, H.M.; Jabir, M.S.; Al-Gareeb, A.I.; Albuhadily, A.K.; Albukhaty, S.; Sulaiman, G.M.; Batiha, G.E. Evaluation and targeting of amyloid precursor protein (APP)/amyloid beta (A β) axis in amyloidogenic and non-amyloidogenic pathways: A time outside the tunnel. *Ageing Res. Rev.* **2023**, *92*, 102119. [[CrossRef](#)] [[PubMed](#)]
43. Chasseigneaux, S.; Allinquant, B. Functions of A β , sAPP α and sAPP β : Similarities and differences. *J. Neurochem.* **2012**, *120* (Suppl. 1), 99–108. [[CrossRef](#)]
44. Habib, A.; Sawmiller, D.; Tan, J. Restoring sAPP α functions as a potential treatment for Alzheimer's disease. *J. Neurosci. Res.* **2017**, *95*, 973–991. [[CrossRef](#)] [[PubMed](#)]
45. Hefter, D.; Draguhn, A. APP as a Protective Factor in Acute Neuronal Insults. *Front. Mol. Neurosci.* **2017**, *10*, 22. [[CrossRef](#)]
46. Mockett, B.G.; Ryan, M.M. The therapeutic potential of the neuroactive peptides of soluble amyloid precursor protein-alpha in Alzheimer's disease and related neurological disorders. *Semin. Cell Dev. Biol.* **2023**, *139*, 93–101. [[CrossRef](#)]
47. Dar, N.J.; Glazner, G.W. Deciphering the neuroprotective and neurogenic potential of soluble amyloid precursor protein alpha (sAPP α). *Cell. Mol. Life Sci.* **2020**, *77*, 2315–2330. [[CrossRef](#)]
48. Dineley, K.T.; Bell, K.A.; Bui, D.; Sweatt, J.D. β -Amyloid Peptide Activates α 7 Nicotinic Acetylcholine Receptors Expressed in *Xenopus* Oocytes *. *J. Biol. Chem.* **2002**, *277*, 25056–25061. [[CrossRef](#)]
49. Sharma, K.; Pradhan, S.; Duffy, L.K.; Yeasmin, S.; Bhattarai, N.; Schulte, M.K. Role of Receptors in Relation to Plaques and Tangles in Alzheimer's Disease Pathology. *Int. J. Mol. Sci.* **2021**, *22*, 12987. [[CrossRef](#)] [[PubMed](#)]

50. Xiong, M.; Jones, O.D.; Peppercorn, K.; Ohline, S.M.; Tate, W.P.; Abraham, W.C. Secreted amyloid precursor protein-alpha can restore novel object location memory and hippocampal LTP in aged rats. *Neurobiol. Learn. Mem.* **2017**, *138*, 291–299. [[CrossRef](#)] [[PubMed](#)]
51. Singh, A.; Kukreti, R.; Saso, L.; Kukreti, S. Oxidative Stress: A Key Modulator in Neurodegenerative Diseases. *Molecules* **2019**, *24*, 1583. [[CrossRef](#)]
52. Hullinger, R.; Puglielli, L. Molecular and cellular aspects of age-related cognitive decline and Alzheimer's disease. *Behav. Brain Res.* **2017**, *322 Pt B*, 191–205. [[CrossRef](#)]
53. Bloom, G.S. Amyloid- β and Tau: The Trigger and Bullet in Alzheimer Disease Pathogenesis. *JAMA Neurol.* **2014**, *71*, 505–508. [[CrossRef](#)] [[PubMed](#)]
54. Barbier, P.; Zejneli, O.; Martinho, M.; Lasorsa, A.; Belle, V.; Smet-Nocca, C.; Tsvetkov, P.O.; Devred, F.; Landrieu, I. Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects. *Front. Aging Neurosci.* **2019**, *11*, 204. [[CrossRef](#)]
55. Ye, H.; Han, Y.; Li, P.; Su, Z.; Huang, Y. The Role of Post-Translational Modifications on the Structure and Function of Tau Protein. *J. Mol. Neurosci.* **2022**, *72*, 1557–1571. [[CrossRef](#)]
56. Malafaia, D.; Albuquerque, H.M.T.; Silva, A.M.S. Amyloid- β and tau aggregation dual-inhibitors: A synthetic and structure-activity relationship focused review. *Eur. J. Med. Chem.* **2021**, *214*, 113209. [[CrossRef](#)]
57. Rodriguez Camargo, D.C.; Sileikis, E.; Chia, S.; Axell, E.; Bernfur, K.; Cataldi, R.L.; Cohen, S.I.A.; Miesl, G.; Habchi, J.; Knowles, T.P.J.; et al. Proliferation of Tau 304–380 Fragment Aggregates through Autocatalytic Secondary Nucleation. *ACS Chem. Neurosci.* **2021**, *12*, 4406–4415. [[CrossRef](#)]
58. Thacker, D.; Barghouth, M.; Bless, M.; Zhang, E.; Linse, S. Direct observation of secondary nucleation along the fibril surface of the amyloid β 42 peptide. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2220664120. [[CrossRef](#)]
59. Nam, Y.; Shin, S.J.; Kumar, V.; Won, J.; Kim, S.; Moon, M. Dual modulation of amyloid beta and tau aggregation and dissociation in Alzheimer's disease: A comprehensive review of the characteristics and therapeutic strategies. *Transl. Neurodegener.* **2025**, *14*, 15. [[CrossRef](#)]
60. Gulisano, W.; Maugeri, D.; Baltrons, M.A.; Fà, M.; Amato, A.; Palmeri, A.; D'Adamio, L.; Grassi, C.; Devanand, D.P.; Honig, L.S.; et al. Role of Amyloid- β and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. *J. Alzheimer's Dis. JAD* **2018**, *64* (Suppl 1), S611–S631. [[CrossRef](#)]
61. Zhang, H.; Wei, W.; Zhao, M.; Ma, L.; Jiang, X.; Pei, H.; Cao, Y.; Li, H. Interaction between A β and Tau in the Pathogenesis of Alzheimer's Disease. *Int. J. Biol. Sci.* **2021**, *17*, 2181–2192. [[CrossRef](#)] [[PubMed](#)]
62. Zhang, Y.; Chen, H.; Li, R.; Sterling, K.; Song, W. Amyloid β -based therapy for Alzheimer's disease: Challenges, successes and future. *Signal Transduct. Target. Ther.* **2023**, *8*, 248. [[CrossRef](#)] [[PubMed](#)]
63. Rawat, P.; Sehar, U.; Bisht, J.; Selman, A.; Culberson, J.; Reddy, P.H. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. *Int. J. Mol. Sci.* **2022**, *23*, 12841. [[CrossRef](#)]
64. Buchholz, S.; Zempel, H. The six brain-specific TAU isoforms and their role in Alzheimer's disease and related neurodegenerative dementia syndromes. *Alzheimer's Dement.* **2024**, *20*, 3606–3628. [[CrossRef](#)]
65. Park, S.A.; Ahn, S.I.; Gallo, J.M. Tau mis-splicing in the pathogenesis of neurodegenerative disorders. *BMB Rep.* **2016**, *49*, 405–413. [[CrossRef](#)]
66. Zhang, C.C.; Xing, A.; Tan, M.S.; Tan, L.; Yu, J.T. The Role of MAPT in Neurodegenerative Diseases: Genetics, Mechanisms and Therapy. *Mol. Neurobiol.* **2016**, *53*, 4893–4904. [[CrossRef](#)] [[PubMed](#)]
67. Hong, X.; Huang, L.; Lei, F.; Li, T.; Luo, Y.; Zeng, M.; Wang, Z. The Role and Pathogenesis of Tau Protein in Alzheimer's Disease. *Biomolecules* **2025**, *15*, 824. [[CrossRef](#)] [[PubMed](#)]
68. Zheng, H.; Sun, H.; Cai, Q.; Tai, H.C. The Enigma of Tau Protein Aggregation: Mechanistic Insights and Future Challenges. *Int. J. Mol. Sci.* **2024**, *25*, 4969. [[CrossRef](#)]
69. Sayas, C.L.; Ávila, J. GSK-3 and Tau: A Key Duet in Alzheimer's Disease. *Cells* **2021**, *10*, 721. [[CrossRef](#)] [[PubMed](#)]
70. Hernández, F.; de Barreda, E.G.; Fuster-Matanzo, A.; Lucas, J.J.; Avila, J. GSK3: A possible link between beta amyloid peptide and tau protein. *Exp. Neurol.* **2010**, *223*, 322–325. [[CrossRef](#)]
71. Almasoudi, S.H.; Al-kuraishy, H.M.; Al-Gareeb, A.I.; Eliwa, D.; Alexiou, A.; Papadakis, M.; Batiha, G.E. Role of mitogen-activated protein kinase inhibitors in Alzheimer's disease: Rouge of brain kinases. *Brain Res. Bull.* **2025**, *224*, 111296. [[CrossRef](#)]
72. Son, S.H.; Lee, N.R.; Gee, M.S.; Song, C.W.; Lee, S.J.; Lee, S.K.; Lee, Y.; Kim, H.J.; Lee, J.K.; Inn, K.S.; et al. Chemical Knockdown of Phosphorylated p38 Mitogen-Activated Protein Kinase (MAPK) as a Novel Approach for the Treatment of Alzheimer's Disease. *ACS Cent. Sci.* **2023**, *9*, 417–426. [[CrossRef](#)]
73. Wu, X.; Yang, Z.; Zou, J.; Gao, H.; Shao, Z.; Li, C.; Lei, P. Protein kinases in neurodegenerative diseases: Current understandings and implications for drug discovery. *Signal Transduct. Target. Ther.* **2025**, *10*, 146. [[CrossRef](#)] [[PubMed](#)]
74. Neddens, J.; Temmel, M.; Flunkert, S.; Kerschbaumer, B.; Hoeller, C.; Loeffler, T.; Niederkofler, V.; Daum, G.; Attems, J.; Hutter-Paier, B. Phosphorylation of different tau sites during progression of Alzheimer's disease. *Acta Neuropathol. Commun.* **2018**, *6*, 52. [[CrossRef](#)] [[PubMed](#)]

75. Gong, C.X.; Iqbal, K. Hyperphosphorylation of Microtubule-Associated Protein Tau: A Promising Therapeutic Target for Alzheimer Disease. *Curr. Med. Chem.* **2008**, *15*, 2321–2328. [[CrossRef](#)]
76. Hallinan, G.I.; Vargas-Caballero, M.; West, J.; Deinhardt, K. Tau Misfolding Efficiently Propagates between Individual Intact Hippocampal Neurons. *J. Neurosci.* **2019**, *39*, 9623–9632. [[CrossRef](#)]
77. Cassidy, L.; Fernandez, F.; Johnson, J.B.; Naiker, M.; Owoola, A.G.; Broszczak, D.A. Oxidative stress in alzheimer’s disease: A review on emergent natural polyphenolic therapeutics. *Complement. Ther. Med.* **2020**, *49*, 102294. [[CrossRef](#)] [[PubMed](#)]
78. Sies, H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: Oxidative eustress. *Redox Biol.* **2017**, *11*, 613–619. [[CrossRef](#)]
79. D’Aur aux, B.; Toledano, M.B. ROS as signalling molecules: Mechanisms that generate specificity in ROS homeostasis. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 813–824. [[CrossRef](#)]
80. Korovesis, D.; Rubio-Tom as, T.; Tavernarakis, N. Oxidative Stress in Age-Related Neurodegenerative Diseases: An Overview of Recent Tools and Findings. *Antioxidants* **2023**, *12*, 131. [[CrossRef](#)]
81. Harman, D. Aging: Overview. *Ann. N. Y. Acad. Sci.* **2001**, *928*, 1–21. [[CrossRef](#)]
82. Swerdlow, R.H. Mitochondria and Mitochondrial Cascades in Alzheimer’s Disease. *J. Alzheimer’s Dis.* **2018**, *62*, 1403–1416. [[CrossRef](#)]
83. Kowalczyk, P.; Sulejczak, D.; Kleczkowska, P.; Bukowska-O sko, I.; Kucia, M.; Popiel, M.; Wietrak, E.; Kramkowski, K.; Wrzosek, K.; Kaczyńska, K. Mitochondrial Oxidative Stress—A Causative Factor and Therapeutic Target in Many Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 13384. [[CrossRef](#)] [[PubMed](#)]
84. Musgrove, R.E.; Helwig, M.; Bae, E.J.; Aboutalebi, H.; Lee, S.J.; Ulusoy, A.; Di Monte, D.A. Oxidative stress in vagal neurons promotes parkinsonian pathology and intercellular α -synuclein transfer. *J. Clin. Investig.* **2019**, *129*, 3738–3753. [[CrossRef](#)]
85. Kamat, P.K.; Kalani, A.; Rai, S.; Swarnkar, S.; Tota, S.; Nath, C.; Tyagi, N. Mechanism of Oxidative Stress and Synapse Dysfunction in the Pathogenesis of Alzheimer’s Disease: Understanding the Therapeutics Strategies. *Mol. Neurobiol.* **2016**, *53*, 648–661.
86. Sastry, P.S.; Rao, K.S. Apoptosis and the Nervous System. *J. Neurochem.* **2000**, *74*, 1–20. [[CrossRef](#)]
87. Millecamps, S.; Julien, J.P. Axonal transport deficits and neurodegenerative diseases. *Nat. Rev. Neurosci.* **2013**, *14*, 161–176. [[CrossRef](#)]
88. T nnies, E.; Trushina, E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer’s Disease. *J. Alzheimer’s Dis.* **2017**, *57*, 1105–1121. [[CrossRef](#)]
89. Lim, J.L.; van der Pol, S.M.A.; Baron, W.; McCord, J.M.; de Vries, H.E.; van Horssen, J. Protandim Protects Oligodendrocytes against an Oxidative Insult. *Antioxidants* **2016**, *5*, 30. [[CrossRef](#)]
90. Nasrabad, S.E.; Rizvi, B.; Goldman, J.E.; Brickman, A.M. White matter changes in Alzheimer’s disease: A focus on myelin and oligodendrocytes. *Acta Neuropathol. Commun.* **2018**, *6*, 22. [[CrossRef](#)]
91. Bona, D.; Scapagnini, G.; Candore, G.; Castiglia, L.; Colonna-Romano, G.; Duro, G.; Nuzzo, D.; Lemolo, F.; Lio, D.; Pellicano, M.; et al. Immune-Inflammatory Responses and Oxidative Stress in Alzheimers Disease: Therapeutic Implications. *Curr. Pharm. Des.* **2010**, *16*, 684–691. [[CrossRef](#)] [[PubMed](#)]
92. Deng, Q.; Wu, C.; Parker, E.; Liu, T.C.Y.; Duan, R.; Yang, L. Microglia and Astrocytes in Alzheimer’s Disease: Significance and Summary of Recent Advances. *Aging Dis.* **2024**, *15*, 1537–1564. [[CrossRef](#)] [[PubMed](#)]
93. Jyothi, H.J.; Vidyadhara, D.J.; Mahadevan, A.; Philip, M.; Parmar, S.K.; Manohari, S.G.; Shankar, S.K.; Raju, T.R.; Alladi, P.A. Aging causes morphological alterations in astrocytes and microglia in human substantia nigra pars compacta. *Neurobiol. Aging* **2015**, *36*, 3321–3333. [[CrossRef](#)] [[PubMed](#)]
94. Amenta, F.; Bronzetti, E.; Sabbatini, M.; Vega, J.A. Astrocyte changes in aging cerebral cortex and hippocampus: A quantitative immunohistochemical study. *Microsc. Res. Tech.* **1998**, *43*, 29–33. [[CrossRef](#)]
95. Cerbai, F.; Lana, D.; Nosi, D.; Petkova-Kirova, P.; Zecchi, S.; Brothers, H.M.; Wenk, G.L.; Giovannini, M.G. The Neuron-Astrocyte-Microglia Triad in Normal Brain Ageing and in a Model of Neuroinflammation in the Rat Hippocampus. *PLoS ONE* **2012**, *7*, e45250. [[CrossRef](#)]
96. Kanaan, N.M.; Kordower, J.H.; Collier, T.J. Age-related changes in glial cells of dopamine midbrain subregions in rhesus monkeys. *Neurobiol. Aging* **2010**, *31*, 937–952. [[CrossRef](#)] [[PubMed](#)]
97. Robillard, K.N.; Lee, K.M.; Chiu, K.B.; MacLean, A.G. Glial Cell Morphological and Density Changes Through the Lifespan of Rhesus Macaques. *Brain Behav. Immun.* **2016**, *55*, 60–69. [[CrossRef](#)]
98. Mansour, H.; Chamberlain, C.G.; Weible, I.I.M.W.; Hughes, S.; Chu, Y.; Chan-Ling, T. Aging-related changes in astrocytes in the rat retina: Imbalance between cell proliferation and cell death reduces astrocyte availability. *Aging Cell.* **2008**, *7*, 526–540. [[CrossRef](#)]
99. Jinno, S. Regional and laminar differences in antigen profiles and spatial distributions of astrocytes in the mouse hippocampus, with reference to aging. *Neuroscience* **2011**, *180*, 41–52. [[CrossRef](#)]

100. Xiaoli, W.; Yun, X.; Fang, W.; Lihua, T.; Zhilong, L.; Honglian, L.; Shenhong, L. Aging-related changes of microglia and astrocytes in hypothalamus after intraperitoneal injection of hypertonic saline in rats. *J. Huazhong Univ. Sci. Technol. Med. Sci.* **2006**, *26*, 231–234. [[CrossRef](#)]
101. Clarke, L.E.; Liddelov, S.A.; Chakraborty, C.; Münch, A.E.; Heiman, M.; Barres, B.A. Normal aging induces A1-like astrocyte reactivity. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E1896–E1905. [[CrossRef](#)] [[PubMed](#)]
102. Boisvert, M.M.; Erikson, G.A.; Shokhirev, M.N.; Allen, N.J. The Aging Astrocyte Transcriptome from Multiple Regions of the Mouse Brain. *Cell Rep.* **2018**, *22*, 269–285. [[CrossRef](#)]
103. Stephan, A.H.; Barres, B.A.; Stevens, B. The Complement System: An Unexpected Role in Synaptic Pruning During Development and Disease. *Annu. Rev. Neurosci.* **2012**, *35*, 369–389. [[CrossRef](#)] [[PubMed](#)]
104. Stevens, B.; Allen, N.J.; Vazquez, L.E.; Howell, G.R.; Christopherson, K.S.; Nouri, N.; Micheva, K.D.; Mehalow, A.K.; Huberman, A.D.; Stafford, B.; et al. The Classical Complement Cascade Mediates CNS Synapse Elimination. *Cell* **2007**, *131*, 1164–1178. [[CrossRef](#)] [[PubMed](#)]
105. Lian, H.; Litvinchuk, A.; Chiang, A.C.A.; Aithmitti, N.; Jankowsky, J.L.; Zheng, H. Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer’s Disease. *J. Neurosci.* **2016**, *36*, 577–589. [[CrossRef](#)] [[PubMed](#)]
106. Dejanovic, B.; Wu, T.; Tsai, M.C.; Graykowski, D.; Gandham, V.D.; Rose, C.M.; Bakalarski, C.E.; Ngu, H.; Wang, Y.; Pandey, S.; et al. Complement C1q-dependent excitatory and inhibitory synapse elimination by astrocytes and microglia in Alzheimer’s disease mouse models. *Nat. Aging* **2022**, *2*, 837–850. [[CrossRef](#)]
107. Chen, Y.; Chu, J.M.T.; Wong, G.T.C.; Chang, R.C.C. Complement C3 from Astrocytes Plays Significant Roles in Sustained Activation of Microglia and Cognitive Dysfunctions Triggered by Systemic Inflammation After Laparotomy in Adult Male Mice. *J. Neuroimmune Pharmacol.* **2024**, *19*, 8. [[CrossRef](#)]
108. Gomez-Arboledas, A.; Acharya, M.M.; Tenner, A.J. The Role of Complement in Synaptic Pruning and Neurodegeneration. *ImmunoTargets Ther.* **2021**, *10*, 373–386. [[CrossRef](#)]
109. Choi, J.H.; Sim, S.E.; Kim, J.I.; Choi, D.I.; Oh, J.; Ye, S.; Lee, J.; Kim, T.H.; Ko, H.G.; Lim, C.S.; et al. Interregional synaptic maps among engram cells underlie memory formation. *Science* **2018**, *360*, 430–435. [[CrossRef](#)]
110. Salter, M.W.; Stevens, B. Microglia Emerge as Central Players in Brain Disease—ProQuest. 2017. Available online: <https://www.proquest.com/docview/1936797057?pq-origsite=primo&accountid=8194&sourcetype=Scholarly%20Journals> (accessed on 26 June 2025).
111. Streit, W.J.; Sammons, N.W.; Kuhns, A.J.; Sparks, D.L. Dystrophic microglia in the aging human brain. *Glia* **2004**, *45*, 208–212. [[CrossRef](#)]
112. Harry, G.J.; Kraft, A.D. Neuroinflammation and Microglia: Considerations and approaches for neurotoxicity assessment. *Expert Opin. Drug Metab. Toxicol.* **2008**, *4*, 1265–1277. [[CrossRef](#)]
113. Fan, Z.; Brooks, D.J.; Okello, A.; Edison, P. An early and late peak in microglial activation in Alzheimer’s disease trajectory. *Brain* **2017**, *140*, 792–803. [[CrossRef](#)] [[PubMed](#)]
114. Okello, A.; Edison, P.; Archer, H.A.; Turkheimer, F.E.; Kennedy, J.; Bullock, R.; Walker, Z.; Kennedy, A.; Fox, N.; Rossor, M.; et al. Microglial activation and amyloid deposition in mild cognitive impairment. *Neurology* **2009**, *72*, 56–62. [[CrossRef](#)]
115. Wang, Q.; Xie, C. Microglia activation linking amyloid- β drive tau spatial propagation in Alzheimer’s disease. *Front. Neurosci.* **2022**, *16*, 951128. [[CrossRef](#)]
116. Rea, I.M.; Gibson, D.S.; McGilligan, V.; McNerlan, S.E.; Alexander, H.D.; Ross, O.A. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Front. Immunol.* **2018**, *9*, 586. [[CrossRef](#)]
117. Calsolaro, V.; Edison, P. Neuroinflammation in Alzheimer’s disease: Current evidence and future directions. *Alzheimer’s Dement.* **2016**, *12*, 719–732. [[CrossRef](#)]
118. Heneka, M.T.; Kummer, M.P.; Latz, E. Innate immune activation in neurodegenerative disease. *Nat. Rev. Immunol.* **2014**, *14*, 463–477. [[CrossRef](#)] [[PubMed](#)]
119. Heppner, F.L.; Ransohoff, R.M.; Becher, B. Immune attack: The role of inflammation in Alzheimer disease. *Nat. Rev. Neurosci.* **2015**, *16*, 358–372. [[CrossRef](#)] [[PubMed](#)]
120. Kitazawa, M.; Yamasaki, T.R.; Laferla, F.M. Microglia as a Potential Bridge between the Amyloid β -Peptide and Tau. *Ann. N. Y. Acad. Sci.* **2004**, *1035*, 85–103. [[CrossRef](#)] [[PubMed](#)]
121. Tang, Y.; Le, W. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. *Mol. Neurobiol.* **2016**, *53*, 1181–1194. [[CrossRef](#)] [[PubMed](#)]
122. Bisht, K.; Sharma, K.P.; Lecours, C.; Sánchez, M.G.; El Hajj, H.; Milior, G.; Olmos-Alonso, A.; Gómez-Nicola, D.; Luheshi, G.; Vallières, L.; et al. Dark microglia: A new phenotype predominantly associated with pathological states. *Glia* **2016**, *64*, 826–839. [[CrossRef](#)]
123. Streit, W.J.; Xue, Q.S.; Tischer, J.; Bechmann, I. Microglial pathology. *Acta Neuropathol. Commun.* **2014**, *2*, 142. [[CrossRef](#)]

124. Hong, S.; Beja-Glasser, V.F.; Nfonoyim, B.M.; Frouin, A.; Li, S.; Ramakrishnan, S.; Merry, K.M.; Shi, Q.; Rosenthal, A.; Barres, B.A.; et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **2016**, *352*, 712–716. [[CrossRef](#)] [[PubMed](#)]
125. Wu, Y.; Dissing-Olesen, L.; MacVicar, B.A.; Stevens, B. Microglia: Dynamic Mediators of Synapse Development and Plasticity. *Trends Immunol.* **2015**, *36*, 605–613. [[CrossRef](#)] [[PubMed](#)]
126. Gao, C.; Jiang, J.; Tan, Y.; Chen, S. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets. *Signal Transduct. Target. Ther.* **2023**, *8*, 359. [[CrossRef](#)]
127. Rauti, R.; Cellot, G.; D’Andrea, P.; Colliva, A.; Scaini, D.; Tongiorgi, E.; Ballerini, L. BDNF impact on synaptic dynamics: Extra or intracellular long-term release differently regulates cultured hippocampal synapses. *Mol. Brain* **2020**, *13*, 43. [[CrossRef](#)]
128. Alqahtani, S.M.; Al-kuraishy, H.M.; Al Gareeb, A.I.; Albuhadily, A.K.; Alexiou, A.; Papadakis, M.; Hemeda, L.R.; Feheem, S.A.; El-Saber Batiha, G. Unlocking Alzheimer’s Disease: The Role of BDNF Signaling in Neuropathology and Treatment. *Neuromol. Med.* **2025**, *27*, 36. [[CrossRef](#)]
129. Laske, C.; Stellos, K.; Hoffmann, N.; Stransky, E.; Straten, G.; Eschweiler, G.W.; Leyhe, T. Higher BDNF serum levels predict slower cognitive decline in Alzheimer’s disease patients. *Int. J. Neuropsychopharmacol.* **2011**, *14*, 399–404. [[CrossRef](#)]
130. Miranda, M.; Morici, J.F.; Zanoni, M.B.; Bekinschtein, P. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Front. Cell. Neurosci.* **2019**, *13*, 363. [[CrossRef](#)]
131. Xue, B.; Waseem, S.M.A.; Zhu, Z.; Alshahrani, M.A.; Nazam, N.; Anjum, F.; Habib, A.H.; Rafeeq, M.M.; Nazam, F.; Sharma, M. Brain-Derived Neurotrophic Factor: A Connecting Link Between Nutrition, Lifestyle, and Alzheimer’s Disease. *Front. Neurosci.* **2022**, *16*, 925991. [[CrossRef](#)]
132. Shen, R.; Ardianto, C.; Celia, C.; Sidharta, V.M.; Sasmita, P.K.; Satriotomo, I.; Turana, Y. Brain-derived neurotrophic factor interplay with oxidative stress: Neuropathology approach in potential biomarker of Alzheimer’s disease. *Dement Neuropsychol.* **2023**, *17*, e20230012. [[CrossRef](#)]
133. Ye, X.; Tai, W.; Zhang, D. The early events of Alzheimer’s disease pathology: From mitochondrial dysfunction to BDNF axonal transport deficits. *Neurobiol. Aging* **2012**, *33*, 1122.e1–1122.e10. [[CrossRef](#)] [[PubMed](#)]
134. Gao, L.; Zhang, Y.; Sterling, K.; Song, W. Brain-derived neurotrophic factor in Alzheimer’s disease and its pharmaceutical potential. *Transl. Neurodegener.* **2022**, *11*, 4. [[CrossRef](#)]
135. Buchman, A.S.; Yu, L.; Boyle, P.A.; Schneider, J.A.; De Jager, P.L.; Bennett, D.A. Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. *Neurology* **2016**, *86*, 735–741. [[CrossRef](#)] [[PubMed](#)]
136. Cummings, J.; Zhou, Y.; Lee, G.; Zhong, K.; Fonseca, J.; Cheng, F. Alzheimer’s disease drug development pipeline: 2023. *Alzheimer’s Dement. Transl. Res. Clin. Interv.* **2023**, *9*, e12385. [[CrossRef](#)] [[PubMed](#)]
137. Moldoveanu, C.A.; Tomoaia-Cotisel, M.; Sevastre-Berghian, A.; Tomoaia, G.; Mocanu, A.; Pal-Racz, C.; Toma, V.A.; Roman, I.; Ujica, M.A.; Pop, L.C. A Review on Current Aspects of Curcumin-Based Effects in Relation to Neurodegenerative, Neuroinflammatory and Cerebrovascular Diseases. *Molecules* **2025**, *30*, 43. [[CrossRef](#)] [[PubMed](#)]
138. Azargoonjahromi, A.; Abutalebian, F. Unraveling the therapeutic efficacy of resveratrol in Alzheimer’s disease: An umbrella review of systematic evidence. *Nutr. Metab.* **2024**, *21*, 15. [[CrossRef](#)]
139. Fernandes, L.; Cardim-Pires, T.R.; Foguel, D.; Palhano, F.L. Green Tea Polyphenol Epigallocatechin-Gallate in Amyloid Aggregation and Neurodegenerative Diseases. *Front. Neurosci.* **2021**, *15*, 718188. [[CrossRef](#)]
140. Singh, S.K.; Srivastav, S.; Castellani, R.J.; Plascencia-Villa, G.; Perry, G. Neuroprotective and Antioxidant Effect of Ginkgo biloba Extract Against AD and Other Neurological Disorders. *Neurotherapeutics* **2019**, *16*, 666–674. [[CrossRef](#)]
141. Lee, J.Y.; Wong, C.Y.; Koh, R.Y.; Lim, C.L.; Kok, Y.Y.; Chye, S.M. Natural Bioactive Compounds from Macroalgae and Microalgae for the Treatment of Alzheimer’s Disease: A Review. *Yale J. Biol. Med.* **2024**, *97*, 205–224. [[CrossRef](#)]
142. El-Beltagi, H.S.; Mohamed, A.A.; Mohamed, H.I.; Ramadan, K.M.A.; Barqawi, A.A.; Mansour, A.T. Phytochemical and Potential Properties of Seaweeds and Their Recent Applications: A Review. *Mar. Drugs* **2022**, *20*, 342. [[CrossRef](#)]
143. Ciancia, M.; Fernández, P.V.; Leliaert, F. Diversity of Sulfated Polysaccharides from Cell Walls of Coenocytic Green Algae and Their Structural Relationships in View of Green Algal Evolution. *Front. Plant Sci.* **2020**, *11*, 554585. [[CrossRef](#)]
144. Patel, S. Therapeutic importance of sulfated polysaccharides from seaweeds: Updating the recent findings. *3 Biotech* **2012**, *2*, 171–185. [[CrossRef](#)]
145. Liyanage, N.M.; Nagahawatta, D.P.; Jayawardena, T.U.; Sanjeewa, K.K.A.; Jayawrdhana, H.H.A.C.K.; Kim, J.I.; Jeon, Y.J. Sulfated Polysaccharides from Seaweeds: A Promising Strategy for Combatting Viral Diseases—A Review. *Mar. Drugs* **2023**, *21*, 461. [[CrossRef](#)] [[PubMed](#)]
146. Aluta, U.P.; Aderolu, A.Z.; Ishola, I.O.; Alyassin, M.; Morris, G.A.; Olajide, O.A. Chemical characterisation of sulfated polysaccharides from the red seaweed *Centroceras clavulatum* and their *in vitro* immunostimulatory and antioxidant properties. *Food Hydrocoll. Health* **2023**, *3*, 100135. [[CrossRef](#)]
147. Pereira, L.; Valado, A. From the ocean to the brain: Harnessing the power of marine algae for neuroprotection and therapeutic advances. *Explor. Neuroprot. Ther.* **2023**, *3*, 409–428. [[CrossRef](#)]

148. Myung, C.S.; Shin, H.C.; Bao, H.Y.; Yeo, S.J.; Lee, B.H.; Kang, J.S. Improvement of memory by dieckol and phlorofuocufuroeckol in ethanol-treated mice: Possible involvement of the inhibition of acetylcholinesterase. *Arch. Pharm. Res.* **2005**, *28*, 691–698. [[CrossRef](#)] [[PubMed](#)]
149. Lee, S.; Youn, K.; Kim, D.H.; Ahn, M.R.; Yoon, E.; Kim, O.Y.; Jun, M. Anti-Neuroinflammatory Property of Phlorotannins from *Ecklonia cava* on A β 25-35-Induced Damage in PC12 Cells. *Mar. Drugs* **2018**, *17*, 7. [[CrossRef](#)]
150. Kwon, O.Y.; Lee, S.H. Ameliorating Activity of *Ishige okamurae* on the Amyloid Beta-Induced Cognitive Deficits and Neurotoxicity through Regulating ERK, p38 MAPK, and JNK Signaling in Alzheimer's Disease-Like Mice Model. *Mol. Nutr. Food Res.* **2020**, *64*, e1901220. [[CrossRef](#)]
151. Wang, Y.; Wang, Q.; Duan, L.; Li, X.; Yang, W.; Huang, T.; Kong, M.; Guan, F.; Ma, S. Fucoidan ameliorates LPS-induced neuronal cell damage and cognitive impairment in mice. *Int. J. Biol. Macromol.* **2022**, *222*, 759–771. [[CrossRef](#)]
152. Maury, J.; Delbrut, A.; Villard, V.; Pradelles, R. A Standardized Extract of Microalgae *Phaeodactylum tricornutum* (Mi136) Inhibit D-Gal Induced Cognitive Dysfunction in Mice. *Mar. Drugs* **2024**, *22*, 99. [[CrossRef](#)]
153. Yoo, C.; Maury, J.; Gonzalez, D.E.; Ko, J.; Xing, D.; Jenkins, V.; Dickerson, B.; Leonard, M.; Estes, L.; Johnson, S.; et al. Effects of Supplementation with a Microalgae Extract from *Phaeodactylum tricornutum* Containing Fucoxanthin on Cognition and Markers of Health in Older Individuals with Perceptions of Cognitive Decline. *Nutrients* **2024**, *16*, 2999. [[CrossRef](#)]
154. Martens, N.; Zhan, N.; Yam, S.C.; Leijten, F.P.J.; Palumbo, M.; Caspers, M.; Tiane, A.; Friedrichs, S.; Li, Y.; van Vark-van der Zee, L.; et al. Supplementation of Seaweed Extracts to the Diet Reduces Symptoms of Alzheimer's Disease in the APPswePS1 Δ E9 Mouse Model. *Nutrients* **2024**, *16*, 1614. [[CrossRef](#)] [[PubMed](#)]
155. Crowe-White, K.M.; Phillips, T.A.; Ellis, A.C. Lycopene and cognitive function. *J. Nutr. Sci.* **2019**, *8*, e20. [[CrossRef](#)]
156. Yang, E.J.; Mahmood, U.; Kim, H.; Choi, M.; Choi, Y.; Lee, J.P.; Cho, J.Y.; Hyun, J.W.; Kim, Y.S.; Chang, M.J.; et al. Phloroglucinol ameliorates cognitive impairments by reducing the amyloid β peptide burden and pro-inflammatory cytokines in the hippocampus of 5XFAD mice. *Free Radic. Biol. Med.* **2018**, *126*, 221–234. [[CrossRef](#)]
157. Yang, E.J.; Ahn, S.; Ryu, J.; Choi, M.S.; Choi, S.; Chong, Y.H.; Hyun, J.W.; Chang, M.J.; Kim, H.S. Phloroglucinol Attenuates the Cognitive Deficits of the 5XFAD Mouse Model of Alzheimer's Disease. *PLoS ONE* **2015**, *10*, e0135686. [[CrossRef](#)] [[PubMed](#)]
158. Martens, N.; Schepers, M.; Zhan, N.; Leijten, F.; Voortman, G.; Tiane, A.; Rombaut, B.; Poisquet, J.; van de Sande, N.; Kerkisiek, A.; et al. 24(S)-Saringosterol Prevents Cognitive Decline in a Mouse Model for Alzheimer's Disease. *Mar. Drugs* **2021**, *19*, 190. [[CrossRef](#)] [[PubMed](#)]
159. Xu, Y.; Xue, M.; Li, J.; Ma, Y.; Wang, Y.; Zhang, H.; Liang, H. Fucoidan Improves D-Galactose-Induced Cognitive Dysfunction by Promoting Mitochondrial Biogenesis and Maintaining Gut Microbiome Homeostasis. *Nutrients* **2024**, *16*, 1512. [[CrossRef](#)]
160. Lopresti, A.L.; Smith, S.J.; Drummond, P.D. The Effects of Lutein and Zeaxanthin Supplementation on Cognitive Function in Adults with Self-Reported Mild Cognitive Complaints: A Randomized, Double-Blind, Placebo-Controlled Study. *Front. Nutr.* **2022**, *9*, 843512. [[CrossRef](#)]
161. Katagiri, M.; Satoh, A.; Tsuji, S.; Shirasawa, T. Effects of astaxanthin-rich *Haematococcus pluvialis* extract on cognitive function: A randomised, double-blind, placebo-controlled study. *J. Clin. Biochem. Nutr.* **2012**, *51*, 102–107. [[CrossRef](#)]
162. Nakagawa, K.; Kiko, T.; Miyazawa, T.; Burdeos, G.C.; Kimura, F.; Satoh, A.; Miyazawa, T. Antioxidant effect of astaxanthin on phospholipid peroxidation in human erythrocytes. *Br. J. Nutr.* **2011**, *105*, 1563–1571. [[CrossRef](#)]
163. Stringham, N.T.; Holmes, P.V.; Stringham, J.M. Effects of macular xanthophyll supplementation on brain-derived neurotrophic factor, pro-inflammatory cytokines, and cognitive performance. *Physiol. Behav.* **2019**, *211*, 112650. [[CrossRef](#)]
164. Kumari, K.N.; Jeyabalan, S.; Rajangam, J.; Gopinathan, N.; Ramakrishnan, S.R.; Reddy, V.J. Neuroprotective Potential of Total Extract of *Ulva Lactuca*: An *In vitro* study. *Res. J. Pharm. Technol.* **2023**, *16*, 5948–5953. [[CrossRef](#)]
165. Yang, Y.; Zhu, D.; Qi, R.; Chen, Y.; Sheng, B.; Zhang, X. Association between Intake of Edible Mushrooms and Algae and the Risk of Cognitive Impairment in Chinese Older Adults. *Nutrients* **2024**, *16*, 637. [[CrossRef](#)] [[PubMed](#)]
166. Park, J.S.; Han, J.M.; Shin, Y.N.; Park, Y.S.; Shin, Y.R.; Park, S.W.; Roy, V.C.; Lee, H.J.; Kumagai, H.; Kishimura, H.; et al. Exploring Bioactive Compounds in Brown Seaweeds Using Subcritical Water: A Comprehensive Analysis. *Mar. Drugs* **2023**, *21*, 328. [[CrossRef](#)] [[PubMed](#)]
167. Shannon, E.; Abu-Ghannam, N. Seaweeds as nutraceuticals for health and nutrition. *Phycologia* **2019**, *58*, 563–577. [[CrossRef](#)]
168. Tagliapietra, B.L.; Clerici, M.T.P.S. Brown algae and their multiple applications as functional ingredient in food production. *Food Res. Int.* **2023**, *167*, 112655. [[CrossRef](#)]
169. Nho, J.A.; Shin, Y.S.; Jeong, H.R.; Cho, S.; Heo, H.J.; Kim, G.H.; Kim, D.O. Neuroprotective Effects of Phlorotannin-Rich Extract from Brown Seaweed *Ecklonia cava* on Neuronal PC-12 and SH-SY5Y Cells with Oxidative Stress. *J. Microbiol. Biotechnol.* **2020**, *30*, 359–367. [[CrossRef](#)]
170. Kwon, Y.J.; Kwon, O.I.; Hwang, H.J.; Shin, H.C.; Yang, S. Therapeutic effects of phlorotannins in the treatment of neurodegenerative disorders. *Front. Mol. Neurosci.* **2023**, *16*, 1193590. [[CrossRef](#)]

171. Cui, Y.; Park, J.Y.; Wu, J.; Lee, J.H.; Yang, Y.S.; Kang, M.S.; Jung, S.C.; Park, J.M.; Yoo, E.S.; Kim, S.H.; et al. Dieckol Attenuates Microglia-mediated Neuronal Cell Death via ERK, Akt and NADPH Oxidase-mediated Pathways. *Korean J. Physiol. Pharmacol. Off. J. Korean Physiol. Soc. Korean Soc. Pharmacol.* **2015**, *19*, 219–228. [[CrossRef](#)]
172. Cui, Y.; Amarsanaa, K.; Lee, J.H.; Rhim, J.K.; Kwon, J.M.; Kim, S.H.; Park, J.M.; Jung, S.M.; Eun, S.Y. Neuroprotective mechanisms of dieckol against glutamate toxicity through reactive oxygen species scavenging and nuclear factor-like 2/heme oxygenase-1 pathway. *Korean J. Physiol. Pharmacol. Off. J. Korean Physiol. Soc. Korean Soc. Pharmacol.* **2019**, *23*, 121–130. [[CrossRef](#)] [[PubMed](#)]
173. Shin, Y.S.; Kim, K.J.; Park, H.; Lee, M.G.; Cho, S.; Choi, S.I.; Heo, H.J.; Kim, D.O.; Kim, G.H. Effects of Ecklonia cava Extract on Neuronal Damage and Apoptosis in PC-12 Cells against Oxidative Stress. *J. Microbiol. Biotechnol.* **2021**, *31*, 584–591. [[CrossRef](#)]
174. Rajan, D.K.; Mohan, K.; Zhang, S.; Ganesan, A.R. Dieckol: A brown algal phlorotannin with biological potential. *Biomed. Pharmacother.* **2021**, *142*, 111988. [[CrossRef](#)]
175. Yoon, J.H.; Lee, N.; Youn, K.; Jo, M.R.; Kim, H.R.; Lee, D.S.; Ho, C.T.; Jun, M. Dieckol Ameliorates A β Production via PI3K/Akt/GSK-3 β Regulated APP Processing in SweAPP N2a Cell. *Mar. Drugs* **2021**, *19*, 152. [[CrossRef](#)]
176. Gao, Y.; Li, C.; Yin, J.; Shen, J.; Wang, H.; Wu, Y.; Jin, H. Fucoidan, a sulfated polysaccharide from brown algae, improves cognitive impairment induced by infusion of A β peptide in rats. *Environ. Toxicol. Pharmacol.* **2012**, *33*, 304–311. [[CrossRef](#)]
177. Jin, W.; Lu, C.; Zhu, Y.; Zhao, J.; Zhang, W.; Wang, L.; Linhardt, R.J.; Wang, C.; Zhang, F. Fucoidans inhibited tau interaction and cellular uptake. *Carbohydr. Polym.* **2023**, *299*, 120176. [[CrossRef](#)]
178. Bauer, S.; Jin, W.; Zhang, F.; Linhardt, R.J. The Application of Seaweed Polysaccharides and Their Derived Products with Potential for the Treatment of Alzheimer’s Disease. *Mar. Drugs* **2021**, *19*, 89. [[CrossRef](#)]
179. Gueven, N.; Spring, K.J.; Holmes, S.; Ahuja, K.; Eri, R.; Park, A.Y.; Fitton, H.J. Micro RNA Expression after Ingestion of Fucoidan: A Clinical Study. *Mar. Drugs* **2020**, *18*, 143. [[CrossRef](#)]
180. So, M.J.; Cho, E.J. Phloroglucinol Attenuates Free Radical-induced Oxidative Stress. *Prev. Nutr. Food Sci.* **2014**, *19*, 129–135. [[CrossRef](#)]
181. Li, N.; Gao, X.; Zheng, L.; Huang, Q.; Zeng, F.; Chen, H.; Farag, M.A.; Zhao, C. Advances in fucoxanthin chemistry and management of neurodegenerative diseases. *Phytomedicine* **2022**, *105*, 154352. [[CrossRef](#)] [[PubMed](#)]
182. Goodbody, E.; Maury, J.; Doolan, A.; DunnGalvin, G.; Kakilla, C.; Pradelles, R.; Dinan, T.G. Promising Benefits of Six-Month *Phaeodactylum tricornutum* Microalgae Supplementation on Cognitive Function and Inflammation in Healthy Older Adults with Age-associated Memory Impairment. *Front. Aging.* **2025**, *6*, 1540115. [[CrossRef](#)] [[PubMed](#)]
183. Bogie, J.; Hoeks, C.; Schepers, M.; Tiane, A.; Cuypers, A.; Leijten, F.; Chintapakorn, Y.; Suttiyut, T.; Pornpakakul, S.; Struik, D.; et al. Dietary Sargassum fusiforme improves memory and reduces amyloid plaque load in an Alzheimer’s disease mouse model. *Sci. Rep.* **2019**, *9*, 4908. [[CrossRef](#)] [[PubMed](#)]
184. Martens, N.; Zhan, N.; Voortman, G.; Leijten, F.P.J.; van Rheenen, C.; van Leerdam, S.; Geng, X.; Huybrechts, M.; Liu, H.; Jonker, J.W.; et al. Activation of Liver X Receptors and Peroxisome Proliferator-Activated Receptors by Lipid Extracts of Brown Seaweeds: A Potential Application in Alzheimer’s Disease? *Nutrients* **2023**, *15*, 3004. [[CrossRef](#)] [[PubMed](#)]
185. Yan, Y.; Niu, Z.; Wang, B.; Zhao, S.; Sun, C.; Wu, Y.; Li, Y.; Ying, H.; Liu, H. Saringosterol from Sargassum fusiforme Modulates Cholesterol Metabolism and Alleviates Atherosclerosis in ApoE-Deficient Mice. *Mar. Drugs* **2021**, *19*, 485. [[CrossRef](#)]
186. Freitas, M.V.; Pacheco, D.; Cotas, J.; Mouga, T.; Afonso, C.; Pereira, L. Red Seaweed Pigments from a Biotechnological Perspective. *Phycology* **2022**, *2*, 1–29. [[CrossRef](#)]
187. Yanshin, N.; Kushnareva, A.; Lemesheva, V.; Birkemeyer, C.; Tarakhovskaya, E. Chemical Composition and Potential Practical Application of 15 Red Algal Species from the White Sea Coast (the Arctic Ocean). *Molecules* **2021**, *26*, 2489. [[CrossRef](#)]
188. Ismail, Z.; Ahmad, W.I.W.; Hamjah, S.H.; Astina, I.K. The Impact of Population Ageing: A Review. *Iran. J. Public Health* **2021**, *50*, 2451–2460. [[CrossRef](#)]
189. Olasehinde, T.A.; Mabinya, L.V.; Olaniran, A.O.; Okoh, A.I. Chemical characterization, antioxidant properties, cholinesterase inhibitory and anti-amyloidogenic activities of sulfated polysaccharides from some seaweeds. *Bioact. Carbohydr. Diet. Fibre* **2019**, *18*, 100182. [[CrossRef](#)]
190. Souza, R.B.; Frota, A.F.; Silva, J.; Alves, C.; Neugebauer, A.Z.; Pinteus, S.; Rodrigues, J.A.G.; Cordero, E.M.S.; de Almeida, R.R.; Pedrosa, R.; et al. *In vitro* activities of kappa-carrageenan isolated from red marine alga *Hypnea musciformis*: Antimicrobial, anticancer and neuroprotective potential. *Int. J. Biol. Macromol.* **2018**, *112*, 1248–1256. [[CrossRef](#)]
191. Liu, Y.; Jiang, L.; Li, X. κ -carrageenan-derived pentasaccharide attenuates A β 25-35-induced apoptosis in SH-SY5Y cells via suppression of the JNK signaling pathway. *Mol. Med. Rep.* **2017**, *15*, 285–290. [[CrossRef](#)] [[PubMed](#)]
192. Kim, D.S.; Kang, S.; Moon, N.R.; Shin, B.K.; Park, S. Zeaxanthin and Lutein Ameliorate Alzheimer’s Disease-like Pathology: Modulation of Insulin Resistance, Neuroinflammation, and Acetylcholinesterase Activity in an Amyloid- β Rat Model. *Int. J. Mol. Sci.* **2024**, *25*, 9828. [[CrossRef](#)]
193. Li, X.; Zhang, P.; Li, H.; Yu, H.; Xi, Y. The Protective Effects of Zeaxanthin on Amyloid- β Peptide 1–42-Induced Impairment of Learning and Memory Ability in Rats. *Front. Behav. Neurosci.* **2022**, *16*, 912896. [[CrossRef](#)]

194. Nazari, L.; Komaki, S.; Salehi, I.; Raoufi, S.; Golipoor, Z.; Kourosh-Arami, M.; Komaki, A. Investigation of the protective effects of lutein on memory and learning using behavioral methods in a male rat model of Alzheimer's disease. *J. Funct. Foods* **2022**, *99*, 105319. [[CrossRef](#)]
195. Johnson, E.J. A possible role for lutein and zeaxanthin in cognitive function in the elderly. *Am. J. Clin. Nutr.* **2012**, *96*, 1161S–1165S. [[CrossRef](#)]
196. Sun, D.; Wu, S.; Li, X.; Ge, B.; Zhou, C.; Yan, X.; Ruan, R.; Cheng, P. The Structure, Functions and Potential Medicinal Effects of Chlorophylls Derived from Microalgae. *Mar. Drugs* **2024**, *22*, 65. [[CrossRef](#)] [[PubMed](#)]
197. Kidgell, J.T.; Magnusson, M.; de Nys, R.; Glasson, C.R.K. Ulvan: A systematic review of extraction, composition and function. *Algal Res.* **2019**, *39*, 101422. [[CrossRef](#)]
198. Yang, Q.; Jiang, Y.; Fu, S.; Shen, Z.; Zong, W.; Xia, Z.; Zhan, Z.; Jiang, X. Protective Effects of Ulva lactuca Polysaccharide Extract on Oxidative Stress and Kidney Injury Induced by D-Galactose in Mice. *Mar. Drugs* **2021**, *19*, 539. [[CrossRef](#)]
199. Flórez-Fernández, N.; Rodríguez-Coello, A.; Latire, T.; Bourgougnon, N.; Torres, M.D.; Buján, M.; Muñíos, A.; Muñíos, A.; Meijide-Faílde, R.; Blanco, F.J.; et al. Anti-inflammatory potential of ulvan. *Int. J. Biol. Macromol.* **2023**, *253*, 126936. [[CrossRef](#)]
200. Pradhan, B.; Bhuyan, P.P.; Ki, J.S. Immunomodulatory, Antioxidant, Anticancer, and Pharmacokinetic Activity of Ulvan, a Seaweed-Derived Sulfated Polysaccharide: An Updated Comprehensive Review. *Mar. Drugs* **2023**, *21*, 300. [[CrossRef](#)]
201. Ambati, R.R.; Siew Moi, P.; Ravi, S.; Aswathanarayana, R.G. Astaxanthin: Sources, Extraction, Stability, Biological Activities and Its Commercial Applications—A Review. *Mar. Drugs* **2014**, *12*, 128–152. [[CrossRef](#)] [[PubMed](#)]
202. Hongo, N.; Takamura, Y.; Nishimaru, H.; Matsumoto, J.; Tobe, K.; Saito, T.; Saido, T.C.; Nishijo, H. Astaxanthin Ameliorated Parvalbumin-Positive Neuron Deficits and Alzheimer's Disease-Related Pathological Progression in the Hippocampus of APPNL-G-F/NL-G-F Mice. *Front Pharmacol.* **2020**, *11*, 307. [[CrossRef](#)] [[PubMed](#)]
203. Huang, C.; Wen, C.; Yang, M.; Li, A.; Fan, C.; Gan, D.; Li, Q.; Zhao, J.; Zhu, L.; Lu, D. Astaxanthin Improved the Cognitive Deficits in APP/PS1 Transgenic Mice Via Selective Activation of mTOR. *J. Neuroimmune Pharmacol.* **2021**, *16*, 609–619. [[CrossRef](#)]
204. Wu, H.; Niu, H.; Shao, A.; Wu, C.; Dixon, B.J.; Zhang, J.; Yang, S.; Wang, Y. Astaxanthin as a Potential Neuroprotective Agent for Neurological Diseases. *Mar. Drugs* **2015**, *13*, 5750–5766. [[CrossRef](#)]
205. Grimmig, B.; Kim, S.H.; Nash, K.; Bickford, P.C.; Douglas Shytle, R. Neuroprotective mechanisms of astaxanthin: A potential therapeutic role in preserving cognitive function in age and neurodegeneration. *GeroScience* **2017**, *39*, 19–32. [[CrossRef](#)]
206. Liu, N.; Lyu, X.; Zhang, X.; Zhang, F.; Chen, Y.; Li, G. Astaxanthin attenuates cognitive deficits in Alzheimer's disease models by reducing oxidative stress via the SIRT1/PGC-1 α signaling pathway. *Cell Biosci.* **2023**, *13*, 173. [[CrossRef](#)]
207. Queen, C.J.J.; Sparks, S.A.; Marchant, D.C.; McNaughton, L.R. The Effects of Astaxanthin on Cognitive Function and Neurodegeneration in Humans: A Critical Review. *Nutrients* **2024**, *16*, 826. [[CrossRef](#)]
208. Hayashi, M.; Ishibashi, T.; Maoka, T. Effect of astaxanthin-rich extract derived from *Paracoccus carotinifaciens* on cognitive function in middle-aged and older individuals. *J. Clin. Biochem. Nutr.* **2018**, *62*, 195–205. [[CrossRef](#)]
209. Allaert, F.A.; Demais, H.; Collén, P.N. A randomized controlled double-blind clinical trial comparing versus placebo the effect of an edible algal extract (Ulva Lactuca) on the component of depression in healthy volunteers with anhedonia. *BMC Psychiatry* **2018**, *18*, 215. [[CrossRef](#)] [[PubMed](#)]
210. Haskell-Ramsay, C.F.; Jackson, P.A.; Dodd, F.L.; Forster, J.S.; Bérubé, J.; Levinton, C.; Kennedy, D.O. Acute Post-Prandial Cognitive Effects of Brown Seaweed Extract in Humans. *Nutrients* **2018**, *10*, 85. [[CrossRef](#)]
211. Nair, A.B.; Jacob, S. A simple practice guide for dose conversion between animals and human. *J. Basic Clin. Pharm.* **2016**, *7*, 27–31. [[CrossRef](#)]
212. Shin, H.C.; Rosenfeld, C.; Guttendorf, R.J.; Wade, S.B.; Park, Y.J.; Kim, J.H.; Kim, S.H.; Lee, B.H.; Hwang, H.J. A Pharmacokinetic and Bioavailability Study of *Ecklonia cava* Phlorotannins Following Intravenous and Oral Administration in Sprague–Dawley Rats. *Mar. Drugs* **2024**, *22*, 500. [[CrossRef](#)] [[PubMed](#)]
213. Yao, W.; Kong, Q.; You, L.; Zhong, S.; Hileuskaya, K. Polysaccharides from brown seaweed: Physicochemical properties, absorption in the intestine, and beneficial effects on intestinal barrier. *Food Front.* **2023**, *4*, 1547–1560. [[CrossRef](#)]
214. Tan, J.; Song, Y.; Wang, J.; Wu, N.; Yue, Y.; Zhang, Q. Pharmacokinetics of fucoidan and low molecular weight fucoidan from *Saccharina japonica* after oral administration to mice. *J. Oceanol. Limnol.* **2023**, *41*, 1900–1909. [[CrossRef](#)]
215. You, L.; Gong, Y.; Li, L.; Hu, X.; Brennan, C.; Kulikouskaya, V. Beneficial effects of three brown seaweed polysaccharides on gut microbiota and their structural characteristics: An overview. *Int. J. Food Sci. Technol.* **2020**, *55*, 1199–1206. [[CrossRef](#)]
216. Komersová, A.; Svoboda, R.; Skalická, B.; Bartoš, M.; Šnejdrová, E.; Mužíková, J.; Matzick, K. Matrix Tablets Based on Chitosan–Carrageenan Polyelectrolyte Complex: Unique Matrices for Drug Targeting in the Intestine. *Pharmaceuticals* **2022**, *15*, 980. [[CrossRef](#)] [[PubMed](#)]
217. Koo, S.Y.; Hwang, K.T.; Hwang, S.; Choi, K.Y.; Park, Y.J.; Choi, J.H.; Truong, T.Q.; Kim, S.M. Nanoencapsulation enhances the bioavailability of fucoxanthin in microalga *Phaeodactylum tricornutum* extract. *Food Chem.* **2023**, *403*, 134348. [[CrossRef](#)] [[PubMed](#)]
218. Ramos-de-la-Peña, A.M.; Contreras-Esquivel, J.C.; Aguilar, O.; González-Valdez, J. Structural and bioactive roles of fucoidan in nanogel delivery systems. *A review. Carbohydr. Polym. Technol. Appl.* **2022**, *4*, 100235. [[CrossRef](#)]

219. Portela, M.; Silva, A.; Carpena, M.; Grosso, C.; Barroso, M.F.; Oliveira, A.I.; Martins, C.; Ribeiro, C.; Prieto, M.A. Phytosomes-Based Nanocarriers Enhanced with Seaweed Extracts: Overcoming the Blood–Brain Barrier. *Eng. Proc.* **2025**, *87*, 75. [[CrossRef](#)]
220. Han, M.; Yi, B.; Song, R.; Wang, D.; Huang, N.; Ma, Y.; Zhao, L.; Liu, S.; Zhang, H.; Xu, R.; et al. Fucoidan-derived carbon dots as nanopenetrants of blood-brain barrier for Parkinson’s disease treatment. *J. Colloid. Interface Sci.* **2025**, *680*, 516–527. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.