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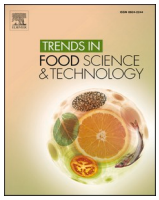

Fucoidans: Exploring its neuroprotective mechanisms and therapeutic applications in brain disorders

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ABSTRACT

Background: Marine-derived natural products have been attracting attention from both the food and pharmaceutical sectors due to their promising therapeutic attributes. Algae and their biomolecules are examples of marine-derived products for ongoing research endeavors. Fucoidan, an algae-derived polysaccharide, has emerged as a recent biomolecule related to a diverse array of beneficial properties, with particular emphasis on its neuroprotective activities.

Scope and approach: This review intended to understand the neuroprotective properties of Fucoidan and its impact on brain disorders. Fucoidan has risen to prominence as one of the most promising neuroprotective agents obtained from macroalgae, with *in vitro* and *in vivo* studies proving its efficiency. Nevertheless, the extant literature underscores the imperative for further clinical trials to substantiate its therapeutic prowess. The neuroprotective effect of fucoidan is related to oxidative stress, mitochondrial function, neuroinflammation, apoptosis, as well as the interaction between gut-brain-microbiota.

Key findings and conclusions: Despite having numerous health benefits being approved by regulatory entities, fucoidan products consumption, and use by industry still needs to be explored. Henceforth, there is a need to search for an efficient method for the successful commercialization of fucoidan, focusing on its suitable dosage for pharmaceutical and nutraceutical applications, but it is also necessary to have clinical studies proving its efficacy in brain disorders. Therefore, this biomolecule has the potential to be exploited by researchers, investors and consumers. In this way, fucoidan could contribute to the promotion and improvement of society's quality of life concerning specific brain pathologies.

1. Introduction

Brain disorders are intensely progressing across the world, compromising health and quality of life. These pathologies involve a broad spectrum from stress, and depression, to other disorders such as autism, and schizophrenia, as well as neurodegenerative diseases and others. Mental disorders are the leading cause of years lived with a disability and consequently poor quality of life. According to the World Health Organization (WHO), the economic consequences of mental health conditions are enormous, since they lead to productivity losses but also have other indirect costs to society, often far outstripping health care costs (World Health Organization, 2022). So, in recent years this topic has been highlighted by governmental entities, being included in the Sustainable Development Goals (SDG) and the WHO has designed an action plan for all countries called "WHO Comprehensive Mental Health Action Plan 2013–2030", to improve mental health and mental health care.

Brain and mental illnesses are constraints on health and well-being, and the use of medication is one of the most widely used strategies. For example, the increase in benzodiazepine prescriptions stands out, namely in Israel, Estern Europe, Japan, North America, and Latin America (Schmitz, 2021). Benzodiazepine consumption has been associated with severe side effects, such as cognitive impairment, falls, abuse, dependence, and mortality (Schmitz, 2021).

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Thus, there is a need to look for alternative strategies, new products, and new molecules with the power to act at the brain level, enabling an improvement in health and well-being. Therefore, the development of natural products has been a growing challenge, with food, nutraceutical and pharmacological industries being more encouraged to exploit natural and promising resources.

In recent years, there has been a growing interest in exploring the potential of marine algae, with algae-derived bioactive compounds studies being reported for application in food and pharmaceuticals. The biological properties of these bioactive compounds, such as antioxidant, neuroprotective, and neuroregenerative properties have been highlighted. Sulfated polysaccharides such as fucoidan or more correctly fucoidans (FUC) are being studied.

FUC belongs to the class of sulfated polysaccharides rich in α-L-fucose (core monomeric module), and other chemical molecules (e.g. sulfate and acetyl groups, monosaccharides (e.g. mannose, galactose, glucose, xylose), uronic acids, protein), with a negative charge, and soluble in water and acidic solutions (Alghazwi, Smid, Karpiniec, & Zhang, 2019; Xing et al., 2023). This biomolecule can be derived from different species such as brown seaweeds and some marine invertebrates (Hu et al., 2023; Takahashi et al., 2018). Its structure is complex, consisting mainly of L-fucose and sulfate ester groups, however, the literature reports the inconsistence and the complexity of categorizing and predicting their structure, because of their different compositions (Fig. 1) (Jayawardena et al., 2022; Wen et al., 2021). Despite the main structure being mainly the same, (1–3)-linked α-*l*-fucopyranose, there might be different sulfates substitutions, molecular weights, branching, and sugar residues, each extract is an individual molecule with different biological properties (Oliveira, Neves, Reis, Martins, & Silva, 2020; Weelden et al., 2019). For example, the structure of fucoidan from *Fucus vesiculosus* is the best studied. It is a relatively simple structure consisting mainly of a backbone of α-(1–3)-linked fucose and α-(1–4) linked fucose residues (Weelden et al., 2019).

The structure depends on the species used (the origin), geographic location (environmental influences), molecular weight, functional groups, the extraction process, time and purification method, and will condition the biological properties of FUC (Fig. 1) (Takahashi et al., 2018; Wang et al., 2019; Xing et al., 2023). So, the FUC structure can condition its characteristics, and bioactivities. However, by removing or adding functional groups, FUC's molecular structure can be modified to improve its bioactive and functional properties.several health benefits related to FUC biological activities have been reported, such as anti-inflammatory, antioxidant, antibacterial, anti-coagulant, anti-cancer, neuroprotective and proapoptotic activities, and immunomodulating effects (Anisha, Padmakumari, Patel, Pandey, & Singhania, 2022; Li et al., 2022; Luthuli et al., 2019; Wang et al., 2019; Xing et al., 2023). These biological activities are beneficial for different therapeutical applications, however, in this review, we will focus on FUC's

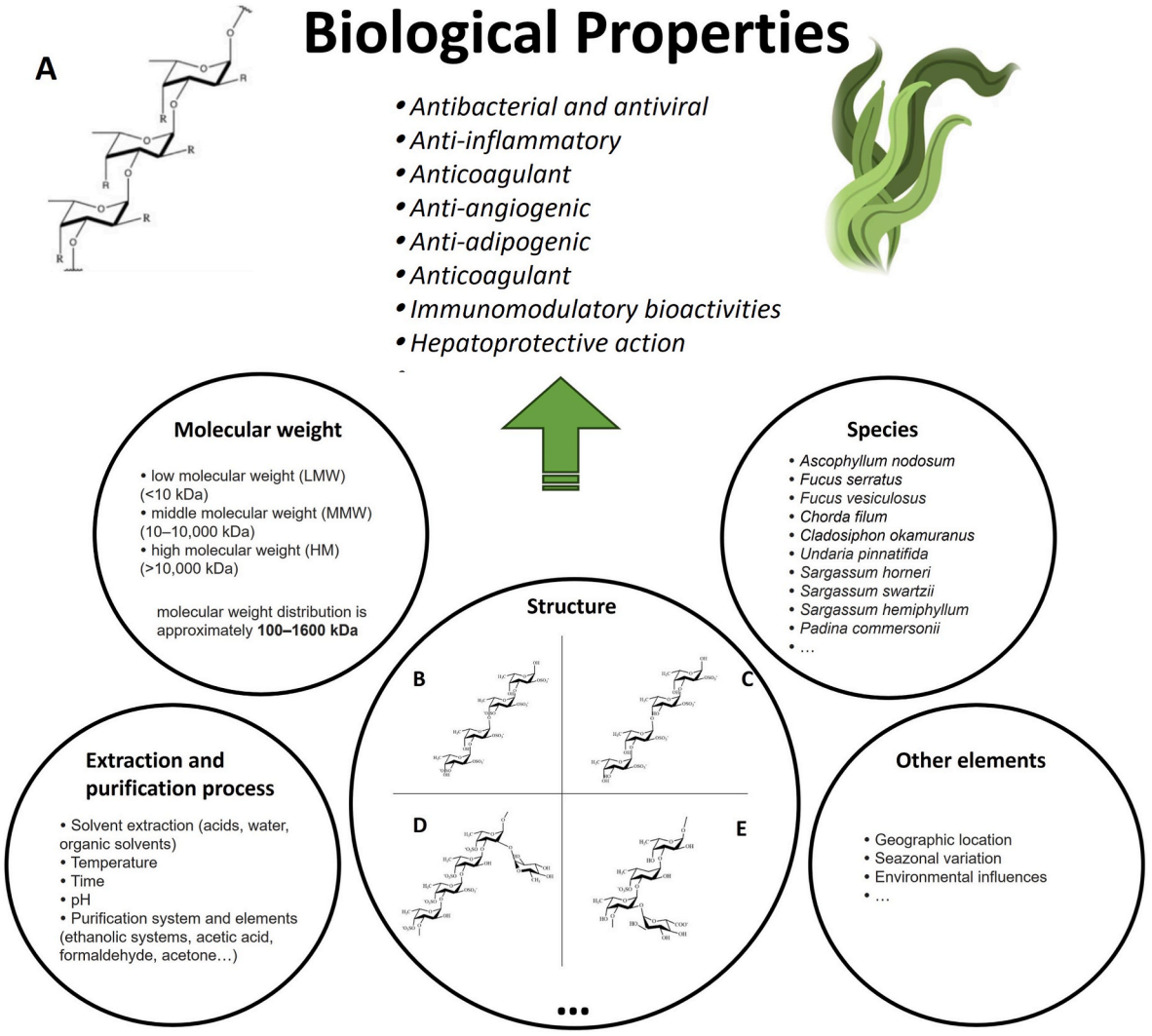

Fig. 1. Several factors affect the biological properties of fucoidan: structure (Simplified fucoidan structure (A), Structural models derived from: *Ascophyllum nodosum* (B), *Fucus serratus* (C), *Chorda filum* (D), *Cladosiphon okamuranus* (E)), molecular weight, types of species, extraction and purification process, and other elements.

neuroprotective activities, with an emphasis on brain disorders.

2. Fucoidan and brain impact

The literature reported an increasing number of studies about FUC's impact on brain disorders (Wang, Zhou, et al., 2021). Recent studies have indicated that FUC could slow down the neurodegenerative processes, protect against brain injury events, decrease the degree of cerebrovascular damage and senile dementia, prevent neuronal apoptosis, improve mitochondrial dysfunction, depression-like behaviours, learning, and memory processes, reduce stress, and promote neurogenesis (Li et al., 2022; Wang et al., 2019, 2021).

So, despite FUC's beneficial biological properties and its inherent interconnectedness, in this review, we will focus on the neuroprotective activities. However, neuroprotective property depends on FUC's structure and purification methods (Alghazwi et al., 2019; Fitton, Stringer, Park, & Karpiniec, 2019; Xing et al., 2023). Several studies showed that sulfate and benzoyl groups in FUC, condition the neuroprotective activity (Liu, Wang, Zhang, & Zhang, 2018; Xu, Li, Zhang, & Le, 2022). For example, sulfate and benzoyl group derivatives in high molecular weight FUC had better neuroprotective activity than low molecular weight FUC (Liu et al., 2018).

2.1. Neuroprotective activities of fucoidan against brain disorders

The literature has reported that FUC has several neuroprotective activities that include inhibiting reactive oxygen species (ROS) and apoptosis, displaying antioxidant and anti-inflammatory activity, and promoting neurotrophic factor release (NTF) (Alghazwi et al., 2019). FUC's positive impact on brain disorders seems to be related to the way it act in several pathways related to its preventive/protective effects on neuroinflammation (NI), oxidative stress (OS), apoptosis (AP), mitochondrial dysfunction and microglial activation (Fig. 2). Furthermore, FUC shows ability to activate neurite outgrowth and the cholinergic system.

2.1.1. Reactive oxygen species inhibition

Recent studies have reported that several brain pathologies, namely epilepsy, stroke, ataxia, dementia, and neurodegenerative disorders (ND) are significantly influenced by oxidative stress (OS) and mitochondrial dysfunction (Don, Chang, Jheng, Huang, & Chuang, 2021; Han et al., 2021; Khotimchenko, Silachev, & Katanaev, 2022; Li et al., 2023; Manikandan et al., 2023).

The brain and the central nervous system (CNS) are biological structures highly sensitive to ROS. On the one hand, it is known that brain cells need high levels of oxygen, which increases the incidence of developing active forms of oxygen. On the other hand, there are polyunsaturated fatty acids molecules in the brain, which are easily oxidized, thus leading to the development of toxic molecules (Khotimchenko et al., 2022; Li et al., 2023; Manikandan et al., 2023). So, ROS are produced from the cells (in particular in mitochondria structure) or from external sources. The mitochondrial structure is the main source of ROS and their dysfunction increases the ROS levels (Han et al., 2021; Xing et al., 2023). Mitochondrial dysfunction is involved in the pathogenesis of AD and PD, since mitochondria are essential for maintaining normal cellular functions (intracellular metabolic activities and signaling pathways) (Wang, Zhou, et al., 2021). FUC can maintain the mitochondrial function by protecting mitochondrial respiratory function against rotenone; acting protectively on mitochondrial oxidative phosphorylation; increasing AMPK-PGC 1α signaling; up-regulating Sirt3 expression after brain injury.

ROS accumulate in cells, from either excessive production or insufficient neutralization, due to an imbalance between antioxidant defense systems. The production of ROS induces OS, and may cause biomolecules destruction, cells damage, necrosis, apoptosis, and it is a high contributing factor to neurodegenerative pathogenesis (Manikandan et al., 2023; Moratilla-Rivera, Sánchez, Valdés-González, & Gómez-Serranillos, 2023; Park et al., 2022; Xing et al., 2023; Xu et al., 2022).

Thus, there has been a growing demand for the development of antioxidant solutions to remove excessive ROS and/or inhibit ROS production (Khotimchenko et al., 2022; Li et al., 2023). Several natural compounds have received much attention as potent antioxidants. Polyphenols have been highlighted, such as flavonoids, rosmarinic acid, ferulic, caffeinic, chlorogenic, vanillic, p-hydroxybenzoic acid, and others. Additionally, the presence of some enzymes and biomolecules, such as superoxide dismutase-1, heme oxygenase-1, nicotinamide adenine dinucleotide phosphate (NADP), peroxidase, coenzyme Q, vitamins, are also searched since they can break down ROS (Moratilla-Rivera et al., 2023). So, natural antioxidants enhance the

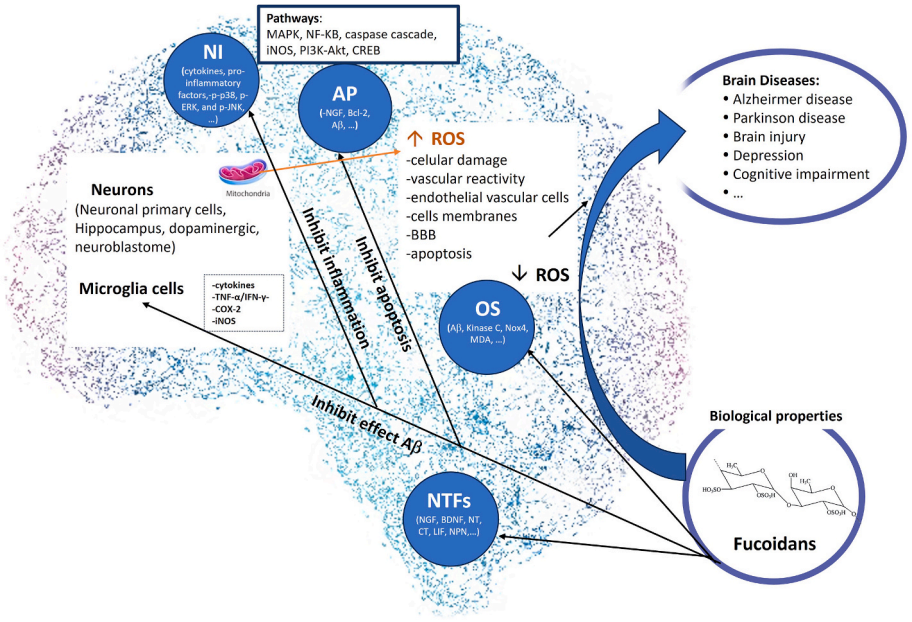

Fig. 2. Fucoidan and its neuroprotective impact on brain disorders and pathways/mechanisms involved.

efficiency of antioxidant gene regulation and impart mechanisms of action, such as hydrogen atom transfer, electron donation, direct radical scavenging, metal chelation, restoration of endogenous antioxidant levels, and activation of antioxidant enzymes (Bagli, Goussia, Moschos, Agnantis, & Kitsos, 2016).

Therefore, there is a growing need for the discovery of new bioactive compounds and new neuroprotective natural products. Nowadays, the demand for marine algae-based bioactive compounds has increased. For example, according to Olasehinde and collaborators (2020), the sulfated polysaccharides from seaweed (*Ecklonia maxima, Gelidium pristoides*, *Ulva lactuca*, *Ulva rigida*, and *Gracilaria gracilis*) exhibited neuroprotective effects against neuronal damage and this may be assigned to inhibition of apoptosis, oxidative damage and acetylcholinesterase activity. So, the biological properties of these polysaccharides may differentiate as good therapeutic agents to protect neuronal cells in Alzheimer's Disease (AD) (Olasehinde, Olaniran, & Okoh, 2020).

FUC are polysaccharides that have shown to be a promising biomolecules due to its anti-oxidant potential (Silva et al., 2022). Several AD-related studies have reported FUC's role in the protection against amyloid-β protein (Aβ) in the brain (Han et al., 2021; Ito et al., 2021; Xing et al., 2023). Aβ induces neuronal toxicity, OS, mitochondrial dysfunction, and apoptosis, while FUC is reported to have an inhibitory effect on Aβ accumulation within microglia, and inhibit or attenuated Aβ-induced OS in the cell membranes and mitochondria (Han et al., 2021; Ito et al., 2021). This evidence is promising data to improve therapies for AD.

A previous study by Jhamandas, Wie, Harris, MacTavish, and Kar (2005) had already reported FUC's ability to block Aβ neurotoxicity in primary neuronal cultures, and attenuat Aβ-induced down-regulation of phosphorylated protein kinase C. Furthermore, Aβ activation of caspases 9 and 3 (signaling pathways related to apoptotic cell death) is blocked by pretreatment of cultures with FUC (Jhamandas et al., 2005).

On the other hand, FUC's impact on other neurodegenerative diseases, such as Parkinson's disease (PD), is reported. According to Liu and collaborators (2020), FUC from Saccharina japonica exhibited a neuroprotective effect in PD. In this study, they demonstrated that FUC could act on the extracellular nerve growth factor (NGF), which can increase the tolerance of cells under oxidative stress and consequently cause progressive activation of the PI3K–Akt pathway (that has an important role in the neuronal functions, namely memory) (Liu et al., 2020). Additionally, Xing et al. (2023) reported that FUC acts on mitochondrial dysfunction preventing excessive mitochondrial ROS and contributing to the recovery of abnormalities in the mitochondrial membrane (Xing et al., 2023). These results are promising in the FUC neuroprotective effect by improving mitochondrial function.

Therefore, biochemical processes such as OS and mitochondrial dysfunction play an important role in the progression and pathogenesis of brain disorders, such as ND (Don et al., 2021).

In other brain-related pathologies, there is a large amount of ROS produced, for example in cerebral ischemia and reperfusion. The brain is very sensitive to hypoxia, and consequently, the production of ROS may change vascular reactivity, damage vascular endothelial cells, destroy the blood-brain barrier (BBB), and cause degeneration and disability of cell membranes (inducing lipid peroxidation of unsaturated fatty acids). These pathologies are associated with brain edema, inflammation, and neuronal cell apoptosis.

The study carried out by Zahan et al. (2022) showed that FUC attenuates oxidative stress by reducing ROS production, malondialdehyde (MDA) levels and downregulating the Nox4 expression, while increasing the activity of antioxidant enzymes (glutathione (GSH), superoxide dismutase (SOD)) (Zahan et al., 2022). This also suggested that FUC has protective effects against OS-mediated cellular damage *in vivo* (Yuan et al., 2021).

2.1.2. Neuroinflammation

In addition to OS, neuroinflammation is another factor related to ND, and often OS is a precursor of neuroinflammation or vice versa. Neuroinflammation is a complex biological reaction of the CNS to protect the brain and ensure brain homeostasis to damaging factors, such as infection, trauma, toxins, endogenous proteins, degeneration or neuronal death (Elbandy, 2023; Xu et al., 2022). However, excessive, prolonged and uncontrolled neuroinflammation in neuronal cells or neuronal cells death are pathological factors reported on ND (Khotimchenko et al., 2022; Silva et al., 2022; Xanthos & Sandkühler, 2014). During the neuroinflammatory process, several cells are activated (in several physiological and pathological conditions), such as immune cells, oligodendrocytes, astrocytes, and microglia in the CNS, and satellite glial cells and Schwann cells in the peripheral nervous system (Elbandy, 2023; Xu et al., 2022).

When microglia are activated, they initiate their phagocytic function, and release pro-inflammatory factors, such as cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factor α (TNF-α)), ROS, expression of inflammatory enzymes like cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS) and others (Xu et al., 2022; Yuan et al., 2021; Zahan et al., 2022). These pro-inflammatory factors increase OS and can potentially lead to death by apoptosis of neuronal cells, due to vasomotor contraction, obstruction of microvessels, and release of cytotoxic enzymes, destroying the integrity of the BBB, and promoting ROS production (Yuan et al., 2021).

The pro-inflammatory cytokines promote Aβ and tau-protein accumulation in neurons. Neurons damage or necrosis/apoptosis can occur, which leads to the production of more pro-inflammatory cytokines and initiates the release of neurotoxic Aβ (Khotimchenko et al., 2022). On the other hand, cell damage and death can be caused by tau phosphorylation in neurons (Han et al., 2021). This process is cyclic and reflects chronic irreversible neuroinflammation as a predominant element in the neurodegenerative process (AD, PD). For example, in the early stages of AD, the microglial response is neuroprotective, however, in the late stage, the prolonged activation of microglia can result in potential neurotoxicity. Thus, it is necessary to search for molecules that inhibit microglial activation, control systemic inflammation, and protect neuronal cells (Khotimchenko et al., 2022).

Natural algae-derived polysaccharides have shown an important role in several pharmaceutical applications, including neurodegenerative diseases (AD, PD, Huntington disease) and ischemia-reperfusion injury (IRI), due to their potent immunomodulatory and anti-inflammatory properties (Che, Ma, & Xin, 2017; Elbandy, 2023). These compounds are involved in three important biochemical processes such as, inhibiting the over-activation of microglia, reducing the pro-inflammatory molecules, and regulating signaling pathways (Xu et al., 2022).

The literature shows that FUC can protect against inflammation both *in vitro* and *in vivo* because it attenuates inflammation by inhibiting the expression of brain inflammatory cytokines. Treatments with FUC reduced IL-1β, IL-6, iNOS, COX-2, and NO levels (Kang et al., 2012; Yuan et al., 2021). The activity of FUC against inflammation is associated with the phosphorylation of mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) signaling pathways (Zahan et al., 2022). Some studies have reported that FUC treatment decreased TNF-α/IFN-γ-induced NF-κB, and can inhibit the NF-kB signaling pathway microglial activation (Meenakshi, Umayaparvathi, Saravanan, Manivasagam, & Balasubramanian, 2014; Ryu & Chung, 2015; Wang, Zhou, et al., 2021).

2.1.3. Apoptosis inhibition

The apoptosis process has an important role in the nervous system, and it is a main pathway of neuronal death in ND and other brain diseases, for example, stroke. During normal physiological conditions, neurons resist apoptosis, however, in adverse conditions, such as chronic neuroinflammatory processes and OS, the expression levels of some apoptosis-related proteins are changed (Xu et al., 2022). For example, when ROS are accumulated in brain tissue induced by brain diseases, they activate mitochondria, lead to receptors death and induce

neuronal apoptosis. Additionally, as mentioned before, the inflammatory response induced by OS will activate the MAPK and NF-κB signaling pathways, produce the pro-inflammatory factors (protein, enzymes, polysaccharides, and others), and activate the Caspase cascade, that induce neuronal apoptosis (Yuan et al., 2021).

Another important pathway is the PI3K-Akt, which plays an important role in neuronal survival (e.g., long-term potentiation and memory formation) and death (Liu et al., 2020). The activation of this pathway can inhibit the activity of downstream caspase-3 and inhibit the apoptosis of neurons. Some studies showed the potential of the nerve growth factor (NGF) to activate the PI3K-Akt pathway to inhibit neuronal apoptosis. In the study conducted by Liu and collaborators (2020) reported the impact of FCU in the prevention of cells apoptosis and cell death, and the increased phosphorylation of NGF to activate the PI3K-Akt pathway to inhibit neuronal apoptosis (Liu et al., 2020). This fact can be a new strategy for the prevention and treatment of PD.

On the other hand, certain protein families such as the Bcl-2 protein family play an essential role in the regulation of the intrinsic pathway via monitoring mitochondrial membrane permeability and the release of the pro-apoptotic factor, cytochrome *c*, which promotes the caspase-9 activation (Han et al., 2021). Bcl-2 proteins can inhibit or promote apoptosis. So, the homeostasis of these protein contents determines the apoptosis cell situation. Another protein that there is concerned is the Aβ-protein. The literature has reported the role of this protein in brain functions, since it can cause cognitive impairment due to neuroinflammation, neuronal apoptosis, cholinergic dysfunction, and OS in the brain (Han et al., 2021). However, other bioactive biomolecules, such as polysaccharides, can inhibit nerve cells apoptosis, granting a protective role. These biomolecules block the mitochondria-mediated apoptotic pathway (inhibiting the expression of a related apoptotic protein, promoting the expression of anti-apoptotic protein and maintaining the mitochondrial homeostasis), and blocking the Caspase cascade reaction (Yuan et al., 2021). In this way, the fundamental role of the mitochondrial is once again emphasized, as it is not only responsible for the reduction-oxidation balance mentioned above, but has also functions such as regulation of intracellular calcium ions (Ca^{2+}) and caspase-mediated apoptosis (Han et al., 2021). Additionally, they inhibit the expression of related pro-apoptotic proteins, promote the expression of anti-apoptotic proteins, and consequently inhibit autophagy and apoptosis (Xu et al., 2022).

The literature reports that FUC can reduce the neurotoxicity of β-amyloid protein and prevent the death of dopaminergic neurons *in vivo* and *in vitro* models (Hu et al., 2023). It was found that FUC could reduce neuronal damage in the AD mouse model because it can raise mitochondrial activity and reduce the release of lactate dehydrogenase (LDH) and ROS (Hu et al., 2023). Additionally, studies showed that FUC could inhibit neuronal apoptosis by stabilizing the mitochondrial membrane potential, inhibiting the CytC release and intracellular Ca^{2+} overload, increasing the level of Bcl-2 by inhibiting the MAPK signaling pathway, including reducing the levels of p-p38, p-ERK, and p-JNK (Yuan et al., 2021).

2.1.4. Neurotrophic factors

Compounds with neurogenic potentials are promising to reconstruct a damaged neuronal network, for example, due to neurodegenerative pathologies (Hannan et al., 2020).

Neurotrophic factors (NTFs) are small proteins with important roles in the development and maintenance of structures of both the central and peripheral nervous systems, regulating the growth, differentiation, protection of neurons, and prevention of progressive cell loss (Khotimchenko et al., 2022; Nasrolahi et al., 2022). Additionally, these biomolecules present an important function in mental processes, such as controlling memory and cognition. Several types of NTFs can be organized into 4 categories: neurotrophins (NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), neurotrophin 4/5 (NT-4/5)), neuropoietic cytokines (ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), leukemia inhibitory factor (LIF), neuropoietin (NPN), oncostatin M (OSM), cardiotrophin-like cytokine (CLC), interleukin 6 (IL-6), IL-11 and IL-27)), the glial cell line-derived NTF family (glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), artemin (ARTN), and persephin (PSPN)), and the cerebral dopamine neuropthophic factor (CDNF)/mesencephalic astrocyte-derived neurotrophic factor (MANF) family (Nasrolahi et al., 2022).

The most studied NTFs are BDNF, NGF, NT-3, NT-4/5, and GDNF (Khotimchenko et al., 2022). These NTFs are considered important pharmacological targets in ND (Khotimchenko et al., 2022). The literature describes that many NTFs are synthesized in the brain and are related to neurological diseases, especially at an early disease stage. For example, Nasrolahi and collaborators (2022) stated that AD may be caused by a deficiency of expression of NTFs or their receptors (Nasrolahi et al., 2022). Additionally, some studies reported that AD patients have high levels of NGF and decreased BDNF in the hippocampus and the neocortex (Lübke et al., 2021). NTF signaling in AD patients may be associated with cognitive decline (Nasrolahi et al., 2022). Low levels of BDNF, NGF, and GDNF were also found in patients with moderate AD and mild cognitive impairment (Forlenza et al., 2015).

As the literature evidences, these factors are extremely important. They are related to the prevention of OS (GDNF), neuroinflammation, and neurodegeneration. However, their use as therapeutic agents is complex due to their poor ability to penetrate the BBB. It is, therefore, necessary to look for solutions to solve this problem. It is necessary to develop effective delivery systems and pharmacological agents that can induce the synthesis and release of endogenous NFTs in the corresponding areas of the brain or activate certain NTF receptors.

Some studies have been reported that after treatments with FUCs, the depression-like behaviors were improved, and BDNF levels were increased both in serum and brain tissue (Xue et al., 2021). According to the literature, BDNF plays a critical role in synaptic plasticity, neurogenesis and other physiological processes (learning and memory). So, disruption of BDNF has been compromise some pathologies (Gao, Zhang, Sterling, & Song, 2022; Li et al., 2020). For example, AD, depression and oxidative stress are influenced by the inflammatory process, while an increase in pro-inflammatory cytokines reduces BDNF levels and impairs BDNF-dependent synaptic plasticity. The level of BDNF is abnormally low in depressed or Alzheimer patients (Gao et al., 2022; Li et al., 2020). According the study developed by Li and collaborators (2020) treatment with fucoidan not only reversed the levels of the BDNF-CREB pathway in the hippocampus, but also restored BDNF-dependent synaptic plasticity in stressed mice. On the other hand, neurotrophic factors, such as BDNF, and nerve growth factors, play crucial roles in protecting neurons and improving memory (Zhang, Wu, Yuan, Huang, & Park, 2022). So, the BDNF, a well-known neutrophic factor synthesized in cell bodies of neurons and glial cells and then transported to presynaptic terminals and postsynaptic dendrites; mediates the link between inflammation and neuroplasticity by regulating the release of neurotransmitters (such as glutamate and gamma-aminobutyric acid) following NF-κB activation, and can be used as a biomarker (Gao et al., 2022). BDNF levels in the hippocampus serve as biochemical markers to monitor the development and therapeutic response to depression. Therefore, FUC can comprise the levels of BDNF, and although large FUC molecules are unlikely to cross the BBB, systemic administration of FUC can be effective in protecting neuronal function.

2.2. In vitro and in vivo assays

FUC has been studied regarding its benefits in brain-related diseases, such as PD, AD, cognitive impairment and dysfunction, brain injury, cerebrovascular damage, depression, cerebral ischemic injury (CII), neuronal impairment, and memory dysfunction. *In vitro* and *in vivo* studies are described regarding the effect of FUC on these diseases/problems. *In vitro* assays may be interesting as a first approach to

evaluate the molecule potential and safety (Cunha et al., 2023; Cunha & Pintado, 2022). However, most of the studies are performed *in vivo* with rat models. For the molecules to be able to perform their action on this type of disease, they must reach the brain, thus penetrating the BBB (Cunha et al., 2023). Consequently, an *in vivo* approach appears more promising than the *in vitro* one.

In Table 1 we report 28 *in vivo* studies performed from 2009 to 2023. A higher percentage of studies were published in the last 5 years, 16 of the 28 reported here, which is in accordance with other conclusions regarding the use of algae molecules, such as astaxanthin, for brain-related applications (Cunha et al., 2023).

On the other hand, some *in vitro* studies were performed with specific cell lines, such as mouse hippocampal neuronal HT22 cells, human neuroblastoma SH-Sy5Y cells, PC12 cells and dopaminergic nerve precursor MN9D cells (Table 2). Of the 12 *in vitro* studies reported in Table 2, 7 were published since 2019.

An analysis of the literature find that a great percentage of the research performed with this molecule targets AD and PD, both in the *in vivo* and *in vitro* studies. FUC is one of the most promising polysaccharides isolated from brown algae, namely *Sargassum thunbergi*, *Ascophyllum nodosum*, *Fucus vesiculosus*, *Saccharina japonica* (*Laminaria japonica*), *Fucus evanescens*, and *Saccharina cichorioides* (*Laminaria cichorioides*) (Fletcher, Biller, Ross, & Adams, 2017), and can be around 25–30% of the algae dry weight (Silva et al., 2022). In our search, we found that most of the studies were done with FUC extracted from *Fucus vesiculosus* or *Laminaria japonica*.

In PD studies, FUC was mainly extracted from *Laminaria japonica*/*Saccharina japonica*, but also from *Fucus vesiculosus* and *Turbinaria decurrens*. These studies showed that FUC was able to act on mitochondrial dysfunction, protecting it; prevent neuronal apoptosis; reduce dopaminergic neuron loss; improve motor deficits; and increase the levels of antioxidants and dopamine levels. Different FUC doses were administered, with studies showing efficacy with 10, 20, 25, and 140 mg/kg, thus it seems that FUC can be used in low concentrations.

AD is a worldwide concern that leads to patients' basic cognitive dysfunctions (attention, comprehension, and memory, among others), and FUC showed promising results in improving basic behavioral deficits; increasing important factors expression in the hippocampus; improving glucose tolerance; improving oxidative stress, hyperphosphorylated tau protein and amyloidosis; inhibiting cytochrome *c* release from the mitochondria; acting on the activity of ACh, ChAT and AChE; improving antioxidant activity. The concentrations related in the literature, 100 and 200 mg/kg, seem to be a little higher than the ones necessary for observing positive effects in PD.

FUC at a dose of 40 mg/kg showed promising results in mice with RIBI, acting on neural proliferating cells and immature neurons in the hippocampus, IV collagen, and microglia and also leading to an increase in pro-inflammatory cytokines after radiation (Zhang, Wu, et al., 2022).

Depression is also a condition that seems to benefit from algae-derived molecules, such as astaxanthin and FUC. 300 mg/kg of FUC from *Fucus vesiculosus* showed the ability to improve depression-like symptoms in mice with alcoholism (Xue et al., 2021), while 25–100 mg/kg was enough in a study by Li and collaborators (Li et al., 2020).

Several studies showed that FUC has antioxidant and anti-inflammatory properties, which may be important for its neuroprotective effect since these characteristics have been associated with benefits for several brain diseases in rats, such as AD, epilepsy, ischemic brain injury, depression, and others (Cunha et al., 2023). In fact, some FUC have been described to have higher antioxidant potential than vitamin C (Raposo, Morais, & Morais, 2015).

Brain injury and neurodegenerative diseases have no effective therapies (Wang, Zhou, et al., 2021), thus it is important to find new molecules able to act on these conditions while having few secondary effects. So, FUC appears as a promising natural molecule for the development of new treatments for brain-related diseases. However, more studies are needed, especially in human clinical trials.

Beyond FUC health benefits, some studies also show their potential as an encapsulation material, facilitating the delivery of other molecules to the target site (Silva et al., 2022). Thus, exploring the development of micro- and nano-capsules with FUC and other brain-beneficial molecules may be a promising approach for the pharmaceutical and nutraceutical industries. Some FUC food supplements are already approved by EFSA, but with no proven efficacy (Silva et al., 2022).

Fig. 3 outlines the potential of FUC as compound capable of being incorporated into different oral formulations (tablets, powder, nano-micro structures), also having ability to respond through specific mechanisms to various conditions that compromise the neurological system (either motor, psychiatric or cognitive).

Although the biological potential of FUC is irrefutable, the specific details regarding its digestion, absorption, and metabolism in the context of neurodegenerative diseases are still an area of active research.

Due to FUC's molecular size, few studies *in vivo* were performed regarding its absorption and distribution. Furthermore, other studies defend that humans lack a digestive enzyme, which interferes with FUC's oral absorption (Kadena, Tomori, Iha, & Nagamine, 2018). Research on intestinal absorption of FUC has been hindered by the complexities of its chemical structure and the challenge of determining its method of absorption. Fluorescence detection methods have been used in drug microanalysis recently due to their low detection threshold, sensitivity, and specificity (Bai et al., 2020). Despite the absence of chromogenic groups in FUC, fluorescent reagents could attach to the hemiacetal aldehyde group at the end of the polysaccharide molecule and, under some situations, produce a fluorescent moiety that can absorb ultraviolet light. Some of the performed studies showed that FUC was absorbed in rats and humans gastrointestinal tract (Kadena et al., 2018); FUC extracted from *Cladosiphon okamuranus* was absorbed, *in vivo* and *in vitro*, at the small intestine (Nagamine, Nakazato, Tomioka, Iha, & Nakajima, 2015); and also that it has the ability to pass from the blood to tissues, with kidney and liver being the ones with a higher accumulation, while heart and brain accumulation was not verified (Bai et al., 2020). Despite the absorption and distribution mechanisms not being very well known, it seems that LMWF may be a more promising approach since it showed better absorption and bioavailability when compared to the HMWF. Furthermore, its consumption along with other compounds may enhance FUC's absorption (Luthuli et al., 2019).

On the other hand, enterocytes microvilli and plasma membranes may be important for FUC's digestion and absorption through different mechanisms. Plasma membrane contain enzymes (amylase, protease, and lipase) that may help breaking FUC into monosaccharides, allowing them to be transported into the epithelium by active transport, by endocytosis of IECs or by being absorbed as short-chain fatty acids (SCFAs) (Yang & Lim, 2021).

FUC cannot be digested by gastrointestinal enzymes, however, its fermentation and metabolization by the colonic microbiota lead to SFCAs production (Luthuli et al., 2019; Sun et al., 2021). This is an interesting fact since SFCAs may have a positive impact on the immune system since they increase B cells metabolism by increasing acetyl-CoA and oxidative phosphorylation; increase the intestinal immunoglobulin A antibodies; and have an effect on naïve T cells differentiation into Treg cells (Sun et al., 2021).

The few studies regarding FUC's processing after oral intake showed that FUC from *Cladosiphon okamuranus* was able to be absorbed by intestinal epithelial cells, accumulated by liver macrophages and found, at low levels, in blood and urine; while FUC extracted from Fucus vesiculosus orally administrated to rats highly accumulated in kidneys, spleen, and liver (Yang & Lim, 2021).

In conclusion, even though there have been few investigations on this topic, it is well known that the type and physicochemical characteristics of polysaccharides have a significant influence on their tissue distribution (Zhao et al., 2016). Thus, comprehending the pharmacokinetics and absorption mechanism of FUC would not only support the high-value development of kelp resources but also lay the theoretical

Table 1
Fucoidan *in vivo* studies with impact on brain diseases.

Reference	Fucoidan source	Fucoidan administration			Outcome	Target brain disease
		Model	Dose	Delivery		
Xing et al. (2023)	*Fucus vesiculosus*	Male C57BL/6 mice	n.a.	• Daily injection for 5 days	• Improvement of mitochondrial dysfunction • Preventions of neuronal apoptosis • Reduction of dopaminergic neuron loss • Improvement of motor deficits	PD
Zhang, Wu, et al. (2022)	n.a.	Male Sprague-Dawley rats	1%	• Foods intake with a high-fat diet containing fucoidan for 42 days	• Improvement of memory function • Potentiated hippocampal insulin signaling • Increasing of ciliary neurotrophic factor and BDNF expression in the hippocampus. • Improvement of glucose tolerance	AD
Wang et al. (2022)	*Fucus vesiculosus*	Male C57BL/6 mice	10 mg/kg	• Intragastric injection for 3 weeks	• Improvement of neuroinflammation – neurogenesis promotion and reduced blood-brain barrier and intestinal barrier permeability	Cognitive impairment
Ramu, Anbu, Ammunje, and Krishnaraj (2022)	*Sargassum wightii*	Male and female Wistar rats	100 and 200 mg/kg	• Oral gavage for 30 days	• Improvement of behavioural deficits • Improvement of oxidative stress, hyperphosphorylated tau protein and amyloidosis	AD
Ma et al. (2022)	*Laminaria japonica*	Male ICR mice	100 and 200 mg/kg	• Oral gavage for 4 weeks	• Reversion of adenine-induced high expression of urea, uric acid in urine, and creatinine in serum, • Inhibition of the oxidative stress via GSK3β-Nrf2-HO-1 signaling • Improvement of inflammatory response	Cognitive dysfunction
Zhang, Wu, Yuan, Huang, and Park (2022)	*Laminaria japonica*	Male mice	40 mg/kg	• Intraperitoneal injection for 7 days	• Reduction of the escape latency and increase in the times of crossing platform • Decrease of the neural proliferating cells and immature neurons in the hippocampus • Attenuation of IV collagen degradation • Activation of microglia • Increase of pro-inflammatory cytokines (TNF-α and IL-1β) levels in the neurogenic microenvironment of the hippocampus after radiation	RIBI
Li et al. (2022)	*Saccharina japonica*	Male C57BL/6J mice Zebrafishes	80 or 40 mg/kg	• Treatment during 5 weeks	• Decrease of the degree of cerebrovascular damage, the number of apoptotic neuronal cells and the inflammation • Up-regulated CD34 and vascular endothelial growth factor expression in mice brain • Up-regulated the sub intestinal vessel angiogenesis in zebrafish	Cerebrovascular damage (in type 2 diabetes patients)
Han et al. (2021)	*Ecklonia cava*	Male ICR mice	5, 10 and 20 mg/kg	• Oral gavage for 4 weeks	• Improvement of the effect on Aβ-induced learning and memory impairment • Attenuation of Aβ-induced oxidative stress • Enhancement of mitochondrial function • Regulated tau hyperphosphorylation • Improvement of the ACh content	Cognitive function
Benli, Kaya, and Coskun (2021)	*Fucus vesiculosus*	Swiss albino mice (*Mus musculus*)	50 mg/kg	• Oral gavage for 7 days	• Decrease of the sulfoxaflor-induced up-regulation of caspase-3 mRNA expression • Modulated alterations in the brain of mice • Antioxidant effects	Oxidative Stress and Caspase-3 mRNA Expression
Ramu, Anbu, and Krishnaraj (2021)	*Sargassum wightii*	Male and female Wistar rats	100 and 200 mg/kg	• Oral administration for 30 days	• Reduced behavioral deficits, oxidative stress and amyloid burden	Cognitive dysfunction
Xue et al. (2021)	*Fucus vesiculosus*	Male C57BL/6J mice	300 mg/kg	• Oral gavage for 3 weeks	• Improvement of depression-like behaviors in mice with alcoholism • Increase in 5-hydroxytryptamine and brain derived neurotrophic factor levels in serum and brain tissue • Attenuation of the increase of lipopolysaccharide induced by alcohol, • Decrease of tumor necrosis factor-α and interleukin-1β levels • Inhibition of microglia cell activation in the hippocampus	Depression

(*continued on next page*)

Table 1 (*continued*)

Reference	Fucoidan source	Fucoidan administration			Outcome	Target brain disease
		Model	Dose	Delivery		
					• Down-regulation of the levels of Toll-like receptor 4 and its downstream protein factors • Regulation of the structure of gut flora	
Liu, Jin, Deng, Zhang, and Wang (2021)	*Saccharina japonica*	Male C57BL/6 mice	10 and 20 mg/kg	• Intraperitoneal injection for 5 days	• Reduction of the loss of dopaminergic neurons • Protection of mitochondria	PD
Li et al. (2020)	*Fucus vesiculosus*	Male C57BL/6J mice	25, 50 and 100 mg/kg	• Oral administration for 2 weeks	• Reduction of the stress-induced depressive-like behaviors • Alleviation of the downregulation of BDNF-dependent synaptic plasticity • Attenuation of the behavioral and synaptic plasticity abnormalities in the overexpression of caspase-1 in the hippocampus	Depression
Kim et al. (2019)	*Fucus vesiculosus*	Male Mongolian gerbils (*Meriones unguiculatus*)	50 mg/kg	• Intraperitoneal injection for 5 days	• Attenuation of tGCI-induced hyperactivity • Protection of CA1 pyramidal neurons from tGCI • Inhibition of the activation of astrocytes and microglia in the ischemic CA1 area • Reduction of the increased 4-hydroxy-2-noneal and superoxide anion radical production in the ischemic CA1 area • Increase of SOD1 and SOD2 expression in the CA1 pyramidal neurons before and after tGCI	Cerebral ischemic injury
Park et al. (2019)	*Ecklonia cava*	Male ICR mice	20 mg/kg	• Oral administration for 3 weeks	• Increased learning and memory function effect • Inhibition of lipid peroxidation and cholinergic system activity • Down-regulation of amyloid-β production and tau hyperphosphorylation	Cognitive function
Ahn et al. (2019)	*Fucus vesiculosus*	Male Mongolian gerbils	50 mg/kg	• Intraperitoneal injection for 5 days	• Attenuation of the acceleration and exacerbation of tGCI-induced neuronal death in the CA1–3 – Reduction on the oxidative stress, increase on the antioxidant enzymes	tGCI
(Wang, Yi, & Zhao, 2018)	n.a.	*transgenic Caenorhabditis elegans (C. elegans) rats*	0–2500 ng/ml	• n.a.	• The supplementation of fucoidan alleviated the paralyzed phenotype induced by Abeta. • Fucoidan might exert its protective effects against Abeta-induced toxicity in transgenic AD *C. elegans* by reducing the accumulation of toxic Abeta and decreasing Abeta-induced production of ROS, thus ameliorating the progression of the AD phenotype.	AD
Zhang et al. (2018)	*Laminaria japonica*	Male Sprague–Dawley rats	140 mg/kg	• Oral gavage for 38 days	• Reversion of the loss of nigral dopaminergic neurons and striatal dopaminergic fibers • Reduction of striatal dopamine levels • Alleviation of the rotenone-induced behavioral deficits	PD
Wei et al. (2017)	n.a.	Male ICR mice	50, 100 or 200 mg/kg	• Oral administration for 21 days	• Inhibition of the release of cytochrome *c* from the mitochondria to cytosol • Activation of caspases • Increase in the expression of apoptosis inhibitor proteins • Reversion of the decreased activity of ACh and ChAT, as well as the increased activity of AChE • Improvement of the antioxidant activity	AD
Maclean et al. (2017)	Marinova Pty Ltd	C57 BL/6 mice	2 or 5 mg/mL	• Injected into the stab injury, in increments of 0.5 μL/0.5 mm	• Attenuation of the primary glial scar • Increase in the organization of astrocytes within the glial scar • Change of the morphology of astrocytes distal from the administered hydrogel and further into the parenchyma. • Change in astrocyte phenotype post-injury attenuating "reactive" astrocytosis	Traumatic brain injury

(*continued on next page*)

Table 1 (*continued*)

Reference	Fucoidan source	Fucoidan administration			Outcome	Target brain disease
		Model	Dose	Delivery		
(Che et al., 2017)	*Fucus vesiculosus*	Male Sprague-Dawley rats	80 or 160 mg/kg	• Intraperitoneal injection for 7 days	• Reduction of the neurological deficits and infarct volume • Decrease in the levels of inflammation-associated cytokines and oxidative stress-related proteins • Inhibition of apoptosis • Suppression of the MAPK pathway	IRI
Meenakshi, Umayaparvathi, Saravanan, Manivasagam, and Balasubramanian (2016)	*Turbinaria decurrens*	Male C57BL/6 mice (*Mus musculus*)	25 mg/kg	• Intraperitoneal injection for 7 days	• Increase of the antioxidants and dopamine levels	PD
Hu et al. (2016)	*Sargassum fusiforme*	Male ICR mice	250 mg/kg	• Oral administration for 21 days	• Increase of the cognitive abilities of scopolamine, ethanol, and sodium nitrite-treated mice against memory deficits	AD
Wang, Zhu, and He (2016)	n.a.	Male C57BL/6 mice	1, 10 and 50 mg/kg	• Intraperitoneal injection after traumatic brain injury	• Reduction of cortical and hippocampal lesion volume – reduced neuronal apoptosis • Improvement of long-term neuro-behavioral outcomes - sensorimotor function, hippocampus-associated spatial learning and memory. • Suppression of protein carbonyl, lipid peroxidation, ROS generation and mitochondrial dysfunction	Traumatic brain injury
Zhang et al. (2014)	*Laminaria japonica*	Male Sprague–Dawley rats	20 mg/kg	• Intraperitoneal injection for 3 weeks	• Mitigation of the motor dysfunction induced by 6-OHDA. • Reduction of the loss of DA neurons • Inhibition of the 6-OHDA-stimulating expression of Nox1, preventing Nox1-sensitive oxidative stress and cell damage in substantia nigra pars compacta neurons	PD
Lee, Shim, Lee, and Hahm (2013)	*Fucus vesiculosus*	Male Sprague–Dawley rats	10, 20, or 50 mg/kg	• Intraperitoneal injection for 14 days	• Inhibition of the stress-induced behavioral deficits in this behavioral test • Blocked the increase in TH expression in the locus coeruleus and the basolateral nucleus of the amygdala, and the decrease in BDNF mRNA expression in the hippocampus	Depression
Cui, Jia, Zhang, Zhang, and Wang (2012)	n.a.	Male Sprague–Dawley rats	7.5 and 15 mg/kg	• Intraperitoneal injection for 3 days	• Improved the behavioral manifestation, prevented the loss of dopaminergic neurons and inhibited the deleterious activation of microglia in the substantia nigra pars compacta of LPS-treated rats. • *in vitro* experiments indicated that the excessive production of TNF-α and ROS in LPS-induced primary microglia were significantly inhibited by fucoidan administration.	PD
Gao et al. (2012)	*Laminaria japonica*	Sprague–Dawley rats	100 and 200 mg/kg	• Oral administration for 14 days	• Attenuation of learning and memory impairment in animal behavioral tests • Reverse of the decreased activity of ChAT, SOD, GSH-Px and content of Ach, as well as the increased activity of AchE and content of MDA in hippocampal tissue	Cognitive impairment
Lee et al. (2012)	*Fucus vesiculosus*	Male Sprague-Dawley rats	10, 20, and 50 mg/kg	• Intraperitoneal injection for 14 days	• Relief of memory-associated decreases in cholinergic immuno- reactivity • Restored the expression level of BDNF and cAMP-response element binding protein mRNAs in the hippocampus • Decreased the expression of pro-inflammatory cytokines (IL-1β and TNF-α) mRNAs in the hippocampus	Neuronal Impairment and Memory Dysfunction
Luo et al. (2009)	*Laminaria japonica*	Male C57BL/6 mice	12.5 or 25 mg/kg	• Intraperitoneal injection for 18 days	• Reduction of the behavioral deficits • Increase of the striatal dopamine and its metabolites levels • Reduced on cell death • Increase in tyrosine hydroxylase expression	PD

(*continued on next page*)

Table 1 (*continued*)

Reference	Fucoidan source	Fucoidan administration			Outcome	Target brain disease
		Model	Dose	Delivery		
					• Inhibition of MPTP-induced lipid peroxidation • Reduction of antioxidant enzyme activity	

Abbreviations: not applicable (n.a.), Parkinson disease (PD), Alzheimer disease (AD), Brain-derived neurotrophic factor (BDNF), Radiation-induced brain injury (RIBI), Acetylcholine (ACh), Transient global cerebral ischemia (tGCI), Reactive oxygen species (ROS), Choline acetyl transferase (ChAT), Acetylcholine esterase (AChE), Cerebral ischemia-reperfusion injury (IRI), Tyrosine hydroxylase (TH), Lipopolysaccharide (LPS), Superoxide dismutase (SOD), Glutathione peroxidase (GSH-Px), Malondialdehyde (MDA).

Table 2
Fucoidan *in vitro* studies with impact on brain diseases.

Reference	Fucoidan source	Fucoidan administration		Outcome	Target brain disease
		Model	Dose		
Wang et al. (2022)	*Fucus vesiculosus*	Mouse hippocampal neuronal HT22 cells	100 μg/mL	• Protection from LPS-induced damage by inhibiting the activation of NLRP3 inflammasomes	Cognitive impairment
(Nagata et al., 2021)	*Laminaria japonica*	Human neuroblastoma SH-SY5Y cells (EC-94030304)	5 μg/mL	• Improvement of the Aβ-reduced cell viability • Suppression of the increased ROS, lipid peroxidation, and mitochondrial ROS • Suppression of the decline in mitochondrial permeability transition and ATP caused by Aβ	AD
Liu et al. (2021)	*Saccharina japonica*	PC12 cells	200 and 400 μg/mL	• Improvement on the cell viability and mitochondrial membrane potential • Inhibition of MPP^+ - induced apoptosis and enhanced autophagy	PD
Liang et al. (2019)	n.a.	Dopaminergic nerve precursor cell line	100 μM	• Reduction of cellular expression of Lugh Chain 3-II (LC3-II) and Cat D • Suppression of the induction of B cell lymphoma-2-associated x protein (Bax) • Reversion of the reduction of SOD GSH, decreased cell viability, and apoptosis • Protection of lysosomes • Reduction of the expression of LC3-II • Inhibition of the expression of Cat D-Bax and the oxidative stress response, suppressed apoptosis, • Conferred protective effects for dopaminergic neural cells	PD
Han, Lee, and Lee (2019)	*Fucus vesiculosus*	Human neuroblastoma SH-SY5Y cells	50 μg/mL	• Protection of SH-SY5Y cells from mitochondrial dysfunction and cell death	PD
Alghazwi et al. (2019)	*Fucus vesiculosus and Undaria pinnatifida (Marinova)*	PC-12 cell	12.5 or 100 μg/mL	• Reduction of the cytotoxicity of Aβ1–42 and hydrogen peroxide • Inhibition of apoptosis induced by Aβ1–42	AD
Huang, Kuo, and Chen (2017)	*Sargassum hemiphyllum*	Human dopaminergic neuroblastoma SH-SY5Y Cells	500 μg/mL	• Protection from 6-hydroxydopamine-induced apoptosis	Neuroprotection
Liu et al. (2018)	*Saccharina japonica*	Human neuroblastoma SH-SY5Y cell lines cells	0.1 and 0.5 mg/mL	• Reversion of the decreased mitochondrial activity and decreased LDH and ROS release	Neuroprotection
Wei et al. (2017)	n.a.	PC12 cells	100, 200 and 400 μg/mL	• Inhibition of the release of cytochrome *c* from the mitochondria to cytosol • Activation of caspases • Increase of the expression of apoptosis inhibitor proteins • Reversion of the decreased activity of ACh and ChAT, as well as the increased activity of AChE • Improvement of the antioxidant activity *in vitro* and *in vivo* by activation of SOD and GSH.	AD
Luo et al. (2009)	*Laminaria japonica*	MN9D	0.01, 0.1 and 1.0 mg/ml	• Protection against MPP^+ - induced damage	PD
Jhamandas et al. (2005)	*Fucus vesiculosus*	16- to 17-day-old embryos of time-dependent pregnant Sprague–Dawley rats	n.a.	• Reduction in whole-cell currents in basal forebrain neurons • Neuroprotective effects against Ab-induced neurotoxicity in basal forebrain neuronal cultures	AD

Abbreviations: not applicable (n.a.), Alzheimer disease (AD), Parkinson disease (PD), Reactive oxygen species (ROS), Superoxide dismutase (SOD), Lactate dehydrogenase (LDH), Acetylcholine (ACh), Choline acetyl transferase (ChAT), Acetylcholine esterase (AChE), Glutathione (GSH).

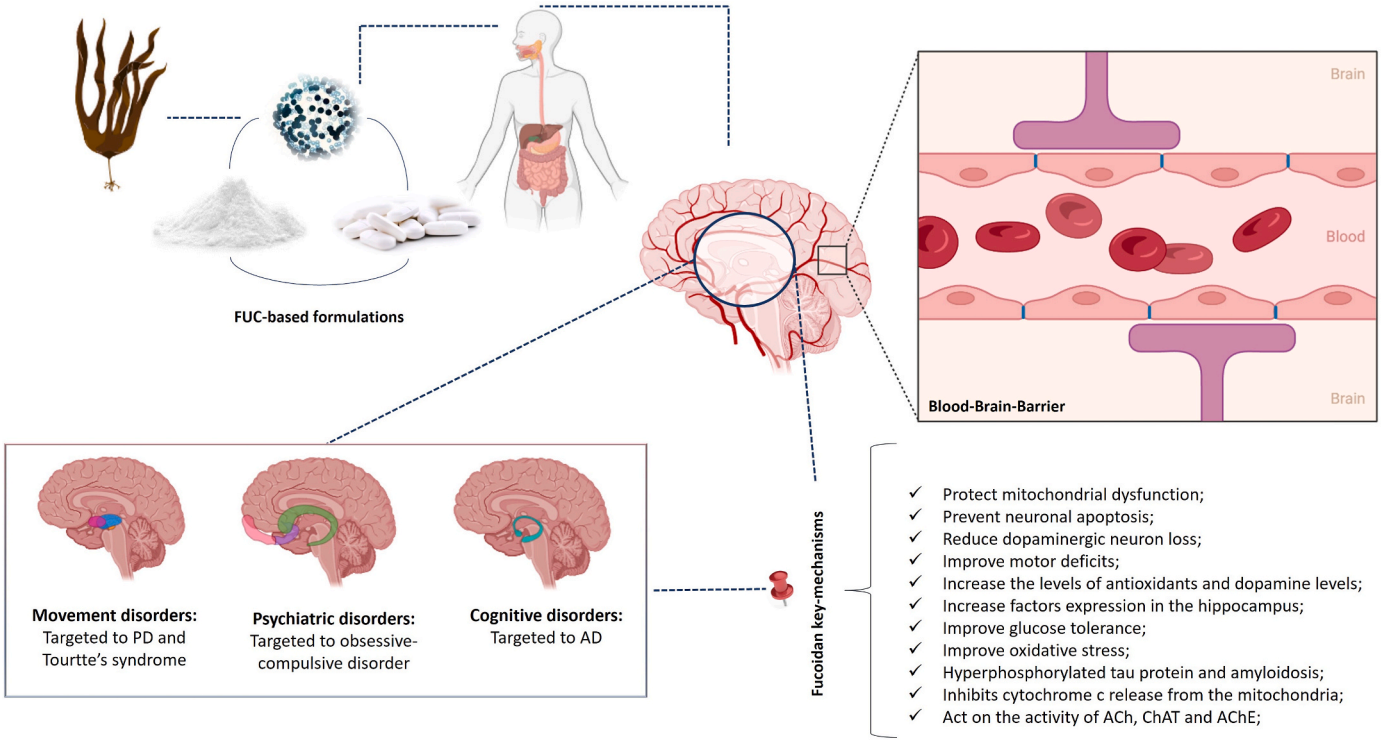

Fig. 3. A general overview of FUC mechanisms and potential upon neurodegenerative diseases. This figure drawn using Biorender (Biorender Co., Toronto, Canada).

groundwork for FUC's use in medicines and healthcare goods. Furthermore, the development of nanoparticle complexes with FUC may be a promising approach for enhancing its absorption and consequent bioavailability.

2.3. *Neuroprotection and delivery systems: opportunities*

The central nervous system is a very complex structure that is separated from but interconnected with the bloodstream, by BBB and blood-cerebrospinal fluid barrier (BSCFB). These barriers exhibit certain properties such as facilitating ions and nutrients diffusion and collection of toxic substances. Therefore, the delivery of drugs to the CNS presents some limitations and there is a lack of appropriate methods to transport these substances. So, developing systems to deliver these molecules is a challenge that needs to be overcome to improve neuroprotection.

Nowadays the search for solutions that positively impact the brain has become urgent due to the increase in average life expectancy and consequent growing ageing effects and mental illnesses. Therefore, the search for new biomolecules in natural matrices has been increasing. Natural compounds have a wide-ranging spectrum of biological activities, such as anti-inflammatory and antioxidant, which make them attractive candidates for the treatment of disorders, like neurodegenerative diseases.

These natural compounds cover several signaling pathways, however, their physicochemical properties can limit their delivery to the target organ and, consequently, their efficiency. For example, some natural molecules show limited stability (sensitivity to degradation or metabolization to inactive derivatives in circulation), solubility, limited brain distribution, and restricted passage across the BBB. Besides, the permitted or desirable concentration is often constrained.

Thus, it is essential to know these biomolecules properties and also comprehend how they act at the brain level, both isolated or together with other elements. It is important to understand how we can transport these biomolecules or devices we can use to ensure appropriate release, stability, and the ability to deliver them to the brain. Therefore, the compound delivery system properties are crucial for achieving an efficient biodistribution.

Nowadays, the research on this topic has increased exponentially, namely in the development of micro and nano delivery systems (Anisha et al., 2022; Gonçalves et al., 2023). The development of microencapsulated systems has proven to be very effective in the bioavailability, controlled release profile, and targeting of specific points. In the development of these microencapsulated systems several factors must be considered such as particle size, specific type of particle, amount of the encapsulated natural compound, and the target.

Most of the studies related to FUC's delivery systems report their potential in cancer therapy. For example, reporting the development of immunotherapeutic nanoparticles for breast cancer with doxorubicin prepared using FUC (Pawar et al., 2019), or FUC/chitosan layered PLGA nanoparticles with melatonin loading for inducing intestinal absorption and addressing breast cancer progression (Yen et al., 2023). Other studies focus on anti-inflammatory and antibacterial potential, such as the study of Barbosa and collaborators (2019) that developed FUC/-chitosan nanoparticles for delivering methotrexate in treatments of skin inflammatory diseases (Barbosa, Costa Lima, & Reis, 2019); Shanthi, Arumugam, Murugan, Sudhakar, and Arunkumar (2021). Explored the potential of FUC-coated silver nanoparticles proving a strong antibacterial activity (Shanthi et al., 2021). Recent studies have emerged in the area of brain inflammation, such as the study by Don and collaborators (2021) that developed curcumin-containing chitosan/fucoidan nanocarriers, an improved drug delivery system to brain lesions, which augmented the inhibitory effect against brain inflammation (Don et al., 2021).

It is important to emphasize that FUC can interact with polymers such as collagen, gelatin, alginate, and chitosan, and by electrostatic interaction can form hydrogels. So, the recent investment in the development of new formulations with chitosan is, therefore, noteworthy. Furthermore, there are fucoidan-containing pharmaceutical formulations (powder, tablet, nanoparticles and microparticles, hydrogels) that are dependent on the routes of administration to be used (Haggag, Abd Elrahman, Ulber, & Zayed, 2023).

3. Interaction between fucoidan and gut-brain-microbiota

Numerous studies emphasize the broad influence of the gut microbiota, which goes beyond than only regulating gastrointestinal equilibrium, since it can affect diverse organs actively, including the CNS, and also impact disorders related to it. Production of neurotoxic compounds, including lactic acid, pro-inflammatory cytokines, ammonia, and other substances (e.g., LPS, polyamines, short-chain fatty acids (SCFA)) occurs during microbiota gastrointestinal imbalance. These compounds may lead to memory deficits and other cognitive disorders such as AD and PD (Khotimchenko et al., 2022; Sun et al., 2020). Indeed, AD and PD are often accompanied by abnormal gastrointestinal motility and intestinal microbiota homeostasis disorders (Sun et al., 2020). Table 3 illustrates some of the changes in gut microbiota detected during some neurodegenerative diseases and related pathophysiological outcomes.

Recent evidence suggests that FUC's potential capacity to modulate gut microbiota, improve intestinal health, and protect intestinal barrier integrity was linked to its neuroprotective benefits (Khotimchenko et al., 2022; Wang et al., 2022; Xue et al., 2021; Zhang, Wu, et al., 2022). FUC is, among all the seaweeds-derived polysaccharides, the one with the higher potential prebiotic activity, i.e., FUC is a non-digestible food component with the potential to be utilized as a carbon source, supporting the growth of beneficial gut microbial populations (Okolie, Mason, Mohan, Pitts, & Udenigwe, 2019; Shannon, Conlon, & Hayes, 2021). Like other prebiotics, FUC can not only selectively stimulate the beneficial bacteria growth but also affect the production of their metabolites, exerting diverse biological activities such as suppression of pathogenic microorganisms (for example, *Helicobacter pylori*), mediation of the immune system, facilitation of nutrient absorption, and even prevention of several human diseases (Chen, Fan, Lin, & Zhao, 2023; Fitton et al., 2019; Zhu et al., 2021). Few studies have demonstrated the prebiotic activity of FUC, including *in vitro* (Chen et al., 2023; Hwang, Phan, Lu, Hieu, & Lin, 2016; Okolie et al., 2019; Zhu et al., 2021), *in vivo* (Shang et al., 2016; Takahashi et al., 2018) and clinical studies (Kan et al., 2020).

Regarding *in vitro* studies, Hwang et al. (2016) found that FUC (Hi-Q Oligo-Fucoidans®) stimulated probiotic growth in a lipopolysaccharide (LPS)-induced inflammatory Caco-2 cell line co-culture with *Bifidobacterium lactis* and reduced intestinal epithelial barrier inflammation (Hwang et al., 2016). Besides that, FUC combination with high-stability fucoxanthin has an even more positive effect in the reduction of intestinal epithelial barrier inflammation but also enhances the immune system against the LPS effect by inhibiting IL-1 β and TNF-α, and promoting IL-10 and IFN-γ. This positive effect of fucoidan could potentially be extended to CNS, ameliorating the development of neurodegenerative diseases such as AD by reducing bacterial LPS levels (Lin, Chen, et al., 2019).

The effect of conventional and novel extraction technologies on the prebiotic activity of FUC extracts was also investigated using *in vitro* fermentation studies after their chemical characterization (Okolie et al., 2019). Microwave-assisted extraction revealed better physicochemical characteristics (fucose and galactose, sulfate, molecular weight, and dispersity index). However all four extraction methods (conventional chemical, microwave-assisted, ultrasound-assisted, and enzyme-assisted extraction) significantly increased the growth rates of *Lactobacillus delbruecki* ssp. *bulgaricus* with no significant difference on *in vitro* prebiotic activity between each other, despite their different chemical and structural properties. Moreover, Zhu and collaborators (2021) demonstrated that FUC could modulate the growth and antibacterial activity of *Lactobacillus rhamnosus* (Zhu et al., 2021). FUC's positive effect on *Lactobacillus rhamnosus'* modulation may improve anxiety- and depression-like behaviors. Reduction of anxiety- and depression – symptoms was shown in rodents, oral gavage administrated with *Lactobacillus rhamnosus*. Brain region-specific alterations in $GABA_{A\alpha 2}$

Table 3
Association between Microbiota Gut-brain axis and neurodegenerative diseases.

Reference	Changes on Microbiota	Effects/Outcomes	Neurological Disorder
(Haran et al., 2019; Lin, Chen, et al., 2019; Liu et al., 2019; Wu et al., 2021)	↓ Diversity of gut microbiota, ↑ Dysbiotic bacteria (*Odoribacter splanchnicus, Eggerthella lenta)* ↓ Butyrate-producing bacteria (*Butyrivibrio hungatei, Eubacterium eligens, Roseburia hominis, Faecalibacterium prausnitzii)* ↑ Opportunistic pathogens (*Bacteroides fragilis)* ↓ Firmicutes, *Bifidobacterium bifidum*, Clostridia, Lachnospiraceae Ruminococcaceae ↑Inflammation promoting Proteobacteria ↑ Enterobacteriaceae were associated with patients with AD when compared with predementia stage and healthy subjects	• Dysregulation of the Anti-Inflammatory P-Glycoprotein Pathway • Up-regulation of TLRs, NF-κB, IL-1β, IL-18, Aβ, and caspase-1 • Increase of the accumulation of cerebral Aβ/ neuroinflammation • Increase of bacterial LPS • Dysregulation pathways of tryptophan, SCFAs, and bile acids	AD
Lin, Chen, et al. (2019)	↑ *Enterobacteriaceae, Verrucomicrobiaceae, Lactobacillus, Porphyromonas, Parabacteroides, Mucispirillum,* ↑ *Bacteroides fragilis* in higher levels in patients with non-tremor PD subtype than patients with tremor subtype. ↓ *Prevotellaceae*	• Upregulation of levels of TLR4 • Increase of levels of interleukins: IL-1β, IL-2, IL-4, IL-6, IL-13, IL-18, • Elevated rate of TNF-α, which was correlated with *Bacteroides* • Correlation between Verrucomicrobia abundance and higher plasma concentrations of IFN-γ	PD
(Cheung et al., 2019; Du, Gao, Peng, & Ge, 2020)	↑ *Anaerostipes, Klebsiella, Clostridium, Lachnospiraceae, Parabacteroides, Phascolarctobacterium, Streptococcus* ↓ *Bifidobacterium, Faecalibacterium, Ruminococcus* ↑*Alistipes,*	• Decrease of DOPAC, homovanillic acid, hippocampus 5-HT, BDNF expression, and circulatory IL-10 • Increase plasma stress hormone • Dysregulate levels of GABA • Increase of gut inflammation	Depression
(Erber, Cetin, Berry, & Schernhammer, 2020; Obrenovich et al., 2020)	↑Inflammation-promoting *Ruminococcaceae, Enterobacteria, Escherichia coli* ↓ Butyrate-producing bacteria (*Butyrivibrio fibrisolvens)* ↑ *Bacteroidetes,* ↓ *Firmicutes, Anaerostipes, Lachnospiraceae, Oscillibacter*	• Dysregulated levels of NO, GABA, LPS, AMPA/N-methyl-d-aspartate, and oxidative pathways	ALS

Abbreviations: Alzheimer disease (AD), Parkinson disease (PD), Amyotrophic lateral sclerosis (ALS), toll-like receptors (TLRs), nuclear factor κB (NF-κB), interleukins (IL), amyloid β (Aβ), lipopolysaccharides (LPS), short-chain fatty acids (SCFAs), tumor necrosis factor-α (TNF-α), interferon (IFN)-γ, dopamine (DOPAC), 5-hydroxytryptamine (5-HT), brain-derived neurotrophic factor (BDNF), γ-aminobutyric acid (GABA), nitric oxide (NO).

mRNA expression were also detected by *in situ* hybridization (Cheung et al., 2019).

On the other hand, the combination of FUC with another polysaccharide (*Lycium barbarum* L. polysaccharide (LBP)) was evaluated by Chen et al. (2023). The combination of *Laminaria japonica* polysaccharide (LJP) and LBP from enzyme-assisted acid extraction (50 °C at a specific ratio (1:4)), allowed the optimal compound polysaccharide to achieve the synergistic effect. This optimum effect was noticeable in the proliferation of Bacteroides and the production of hypoglycemic and anti-hypertensive peptides.

However, this positive effect on microbial diversity and in the elevation of levels of *Bacteroides* could be an asset to achieve cognitive improvements in AD patients, like found in high-altitude Tibetan fermented milk that increase microbial diversity and elevate the levels of *Bacteroides* and *Faecalibacterium* in AD mice model (Ling et al., 2021).

Animal studies also corroborated that FUC can modulate the gut microbiota. Shang et al. (2016) studied the effects of different FUCs on gut microbiota in mice (dosage of 100 mg/kg/day by gavage), verifying an increased abundance of *Lactobacillus* and *Ruminococcaceae* and a decreased abundance of *Peptococcus*, which supported the FUC prebiotic activity (Shang et al., 2016). Besides that, FUC also significantly reduced the host's antigen load and inflammatory response (decreased serum lipopolysaccharide-binding protein level). Another study using mice revealed a positive effect of FUC from *Cladosiphon okamuranus* on the repair of the intestinal barrier function (increased volumes of mucin and IgA) and microbiota modulation (high relative abundance of Bacteroidetes). More recently, FUC showed potential in positively modulating fibre deficiency-induced dysbiosis of mice (Jia et al., 2023; Zheng, Jia, Tang, Song, & Ai, 2023). According to Jia and collaborators (2023), FUC oral administration (50 g/kg) promoted beneficial bacteria in the gut of mice with fibre deficiency-induced dysbiosis but also protected the intestinal epithelial barrier integrity, inhibited OS and the inflammatory response and regulated lipid metabolism (Jia et al., 2023). Besides that, FUC has been investigated as a prebiotic adjuvant for Bacteroides to enhance colonic inflammation in mice with fibre deficiency-induced dysbiosis alleviating colonic inflammation via modulation of gut microbiota and protection of intestinal barrier integrity (Zheng et al., 2022). Another potentially beneficial effect of FUC was reducing PD symptoms since the non-tremor PD subtype revealed higher *Bacteroides* abundances than patients with the tremor subtype. A correlation between *Bacteroides* and plasma level of TNFα was detected in a fecal microbiota study of AD patients (Lin, Chen, et al., 2019).

Besides the potential neuroprotective activity of FUCs proposed above, some studies evaluate the neuroprotective activity of FUC via the gut-microbiota-brain axis. One of these studies evaluates the effect of FUCs in the treatment of alcohol-linked depressive behaviour using a murine model of chronic alcoholism (C57BL/6J mice). In this study, Xue et al. (2021) evaluate not only the levels of 5-hydroxytryptamine (5-HT), BDNF, LPS-induced by alcohol, tumour necrosis factor-α and interleukin-1β, microglia cell activation, Toll-like receptor 4 and its downstream protein factors but also gut microbiota composition (Xue et al., 2021). FUC positively modulates gut microbiota, making C57BL/6J mice microbiota more similar to the normal control mice with an increased abundance of *Prevotella* and *Alloprevotella* positively correlated with the 5-hydroxytryptamine and brain-derived neurotrophic factor levels. Indeed, FUC seems to increase serum BDNF, and 5-HT levels by regulating gut microbiota, supporting its neuroprotective effect via the gut-microbiota-brain axis.

The gut-microbiota-brain axis was also evaluated on mice's LPS-induced neuronal cell damage and cognitive impairment (Wang et al., 2022). In this study, FUC demonstrated the capacity to protect HT22 cells from LPS-induced damage by inhibiting the activation of NLRP3 inflammasomes. Besides that, correlations among gut microbiota, cognitive function, and SCFAs were detected. The literature also reported that the inclusion of FUC in the diet increases the concentration of gut SCFAs, enriching the gut microbiota with beneficial microorganisms, such as *Akkermansia* (Wang, Zhou, et al., 2021; Zaporozhets et al., 2014). On another study, FUC reversed the abundance of *Akkermansiaceae*, *Enterobacteriaceae*, *Erysipelotrichaceae*, and *Oscillospiraceae* at the family level. *Akkermansiaceae* has been associated with loss of cognitive function and AD disease (Ling et al., 2021). Moreover, *Erysipelotrichaceae* and *Oscillospiraceae* were correlated with anxiety and depression-like behaviour (Wang et al., 2022). In another study, FUC enhanced memory impairment in rats induced with Alzheimer's disease symptoms (Hippocampal Amyloid-β Infused Rats) by modulating glucose metabolism and gut microbiota. FUC boosted hippocampal insulin signaling via pSTAT3→pAkt→pGSK-3β, rectifying cerebral glucose metabolism by increasing acetate and butyrate serum concentrations (Zhang, Wu, et al., 2022).

Until now, FUC studies have not explored the correlation between gut microbiota modulation and neuroinflammation, motor symptoms, and abnormal aggregation of α-synuclein associated with AD and PD diseases (Obata & Pachnis, 2016; Sampson et al., 2016; Sun et al., 2020). However, the potential beneficial effects of FUC in AD and PD diseases are doubtless correlated with gut microbiota modulation (Sun et al., 2020). Nonetheless, recent studies have reported a bidirectional relationship between microbiota-gut-brain and the positive roles in preventing and treating NDs (Sun et al., 2020).

Nevertheless, studies are scarce, particularly at the level of clinical trials. The main focus of clinical studies is related to oncological and other pathologies. For example, Kan and collaborators (2020) developed a clinical study that also disclosed the positive effect of the combination of wheat peptides and FUC on gut microbial (Kan et al., 2020), but a study is currently underway about the effects of FUC on the gut microbiota (Sien-Hung, 2022). Therefore, the results are eagerly awaited since the literature has highlighted the great potential for FUCs to modulate the microbiome. However, more studies are needed, particularly on the FUCs gut-brain-microbiota relationship.

In conclusion, despite the few studies, FUC discloses potential as a prebiotic capable of protecting CNS by modulation of gut microbiota.

4. Challenges of fucoidan in society

Nowadays, the population is more informed, more attentive, and more discerning about their health and well-being. The demand for natural foods/supplements that enhance well-being and promote healthy ageing is growing. Researchers and industries are therefore increasingly interested in finding new biomolecules and developing devices that allow them to be released at specific targets to have the desired impact. In this sense, algae have been increasingly studied and their compounds highlighted as having potential benefits in various health areas. These bioactive compounds have therefore been increasingly exploited by the food and pharmaceutical industries.

This review presents a specific compound, fucoidan, a natural bioproduct obtained from several natural sources as mentioned above. The wide range of FUC biological properties, including antimicrobial, anti-inflammatory, anti-cancer, antioxidant activity, and prebiotic activity, has been shown as an important health promoter and, in this review, we highlighted the neuroprotective potential. Understanding its potential neuroprotective effects is a challenge for researchers, but the existing studies indicates that FUC could be a natural alternative for improving brain disorders. So, this biomolecule can have a positive impact on society since it can to improve wellbeing and decrease brain disorders, such as ND. However, more research is needed to better understand the neuroprotective potential of this biomolecule. There is still a scarcity of clinical studies proving this neuroprotective potential, which could prove crucial in promoting diseases related to the brain and CNS, particularly ND.

The present and previous research findings show FUC's high nutritional and pharmaceutical/medicinal value, with promising expanding market applications. In recent years, FUC has been approved by Food and Drug Administration (FDA) and the European Commission for use in

foods and dietary supplements. The FUC extracts from the algae *Undaria pinnatifida* and *Fucus vesiculosus* have been recognized as insurance, 'Generally Recognized as Safe' (GRAS), by the Australian company, Marinova (Fitton et al., 2019). The FDA and European Commission permitted daily consumption of high-concentration fucoidan extracts from *Undaria pinnatifida* or *Fucus vesiculosus* at rates of up to 250 mg/day (Fitton et al., 2019). In Canada and Australia, the respective agencies have approved several medicines containing FUC extracts.

Therefore, this new biomolecule has attractive characteristics for researchers, investors, and consumers. Nevertheless, there are few industries that are exploring this compound and there is a need to invest in technologies to extract it, to develop new FUC-containing products and new delivery systems. In addition to its biological properties, FUC is much cheaper than other polysaccharides, has low toxicity and few side effects, and has also a low environmental impact since it is sustainable, renewable, and environmentally-friendly (Wen et al., 2021). However, there are some limitations, such as the fact that algae cultivation is not easy, and requires large cultivation areas as well as an improvement in the harvesting and extraction process (Cunha et al., 2023). Furthermore, one of the main challenges facing the industry is the extraction process of these bioactive compounds. The recovery rates of these biomolecules are low, due to the rigidity of the seaweed matrix which hinders the release of bioactive substances (Ummat, Sivagnanam, Rajauria, O'Donnell, & Tiwari, 2021). Thus, it is essential to improve the development of biorefinery to make the exploitation of algae more sustainable and consequently enable a wide range of high-value products to be exploited by the food and pharmaceutical industries.

So, as discussed in the literature, bioactive compounds from algae are a natural alternative with potential application in the food, nutraceutical, and pharmaceutical industries. The high market demand for natural bioactive compounds, has brought new challenges and opportunities for investors, researchers, and consumers. The growing demand for foods and supplements that enhance well-being is a need of today's consumers, so there is a pressing need for more clinical studies to increase the knowledge about FUC mechanisms of action, namely the interaction FUC-gut-brain-microbiome and its potential applications in the prevention, management, and treatment of brain disorders.

5. Conclusion

With life expectancy increasing, society is increasingly concerned with health and well-being. The number of patients with cerebrovascular diseases has been increasing, so the search for solutions is urgent. Thus, the demand for natural biomolecules with neuroprotective properties is urgently needed to prevent and/or treat diseases related to the brain and nervous system, in particular ND. In fact, the extant research reveals a pronounced emphasis on the investigation of FUC's therapeutic potential in those disorders, prominently AD and PD, as substantiated by a multitude of *in vivo* and *in vitro* studies.

Algae-derived compounds have shown possible therapeutic applications in brain disorders. FUC has very interesting biological properties, highlighting its promising neuroprotective activity. These kinds of natural molecules with neuroprotective properties can be used to improve neurodegeneration and neuroinflammation, representing both a challenge and an opportunity for the food and pharmaceutical industries.

FUC is already present on the market as a bioactive oral supplement since it is approved by the FDA, and its commercialization is expected to grow. FUC's potential for ameliorating several pathologies has been described, both as a single molecule or incorporated in a drug delivery system. There is also a need for more research into brain and nervous system pathologies, as well as the gut-brain-microbiota relationship. This review was intended to draw attention to this topic, highlighting the challenges of FUC for researchers, investors, and consumers, aiming to encourage the development of clinical studies as well as the development of new products, and delivery systems.

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Author contributions

Patrícia Batista designed the manuscript. Patrícia Batista, Sara Cunha, and Tânia Ribeiro performed the part of pharmacological experiments, analyzed the data, and wrote the manuscript. Sandra Borges and Sara Baptista-Silva designed and performed the part of chemical experiments and analyzed the data. Patrícia Batista, Manuela Pintado, and Patrícia Oliveira-Silva supervised the project. Manuela Pintado, and Patrícia Oliveira-Silva review the manuscript. All the authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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