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REVIEW

Mitochondrial protective potential of fucoxanthin in brain disorders

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Abstract

Mitochondrial dysfunction is a common feature of brain disorders. Mitochondria play a central role in oxidative phosphorylation; thus changes in energy metabolism in the brain have been reported in conditions such as Alzheimer's disease, Parkinson's disease, and stroke. In addition, mitochondria regulate cellular responses associated with neuronal damage such as the production of reactive oxygen species (ROS), opening of the mitochondrial permeability transition pore (mPTP), and apoptosis. Therefore, interventions that aim to protect mitochondria may be effective against brain disorders. Fucoxanthin is a marine carotenoid that has recently gained recognition for its neuroprotective properties. However, the cellular mechanisms of fucoxanthin in brain disorders, particularly its role in mitochondrial function, have not been thoroughly discussed. This review summarises the current literature on the effects of fucoxanthin on oxidative stress, neuroinflammation, and apoptosis using *in vitro* and *in vivo* models of brain disorders. We further present the potential mechanisms by which fucoxanthin protects mitochondria, with the objective of developing dietary interventions for a spectrum of brain disorders. Although the studies reviewed are predominantly preclinical studies, they provide important insights into understanding the cellular and molecular functions of fucoxanthin in the brain. Future studies investigating the mechanisms of action and the molecular targets of fucoxanthin are warranted to develop translational approaches to brain disorders.

Key words: **Antioxidant: Brain: Fucoxanthin: Mitochondria**

Introduction

Brain disorders include a wide range of conditions such as neurodegenerative diseases, stroke, mental illness, epilepsy, traumatic brain injury (TBI), and cancer, and changes in cognition, movement, sense, and personality are commonly associated with these disorders. Data extracted from the Global Burden of Disease 2019 show that stroke is the leading cause of death and disability worldwide and that neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) have increased considerably over the last 20 years.[1] Neurodegenerative diseases are generally correlated with aging. However, a recent study has reported an alarming increase in anxiety and depressive disorders among children and adolescents.[2] Furthermore, researchers predict an increase in the incidence rate of ischaemic stroke in all age groups over the next decade.[3]

Patients with brain disorders often live with symptoms or disabilities for an extended period. In patients with neurodegenerative diseases, structural or functional loss of brain cells can begin years or decades before clinical manifestations are exhibited,[4,5] and this process continues until death. Therefore, long-term interventions that are applicable to a wide range of the population may aid in the prevention or alleviation of the severity of brain disorders.[6] Research suggests that diet is an important factor in the maintenance of brain function.[7,8] Numerous studies have demonstrated the benefits of diets rich in vegetables, fruits, whole grains, and seafood for brain health. However, these dietary pattern studies generally do not include seaweed data.

The major objectives of this review are to introduce the neuroprotective properties of fucoxanthin, a bioactive compound found abundantly in brown seaweed, and to suggest

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potential cellular mechanisms based on recently published articles. In particular, we highlight the role of fucoxanthin in mitochondrial protection since mitochondrial dysfunction is a prominent and recurrent feature of various brain diseases, including AD, PD, and stroke. Here, we synthesise and analyse the existing scientific literature to determine the potential role of fucoxanthin in mitochondrial protection in the context of brain disorders.

Mitochondrial dysfunction in brain disorders

The brain requires a substantial amount of energy to maintain electrophysiological activities; therefore, the generation of ATP through oxidative phosphorylation by mitochondria is critical for brain health. Since the brain lacks sufficient long-term energy storage capacity, neurones are vulnerable to impaired energy metabolism,[9] which commonly occurs in brain disorders that are associated with mitochondrial dysfunction. For example, the lack of blood flow to the brain disrupts the function of the electron transport chain (ETC), leading to energy failure in cases of cerebral ischaemia.[10] Furthermore, impaired energy metabolism has been reported in neurodegeneration models. The aggregation of α-synuclein inhibits the function of complex I in the ETC, which causes ATP depletion.[11] Impaired ETC functioning has been reported in the brains of AD patients.[12]

ATP depletion impairs the ATP-dependent Na^+/K^+ and Ca^{2+} pumps, which leads to ionic imbalance in the cytosol, where increased Ca^{2+} ions activate cellular responses that cause neuronal damage. Ca^{2+} triggers the release of neurotransmitters into the extracellular space, including glutamate, which then activates N-methyl-D-aspartate receptors causing a large influx of Ca^{2+} and excitotoxicity. In addition, Ca^{2+} activates the opening of the mitochondrial permeability transition pore (mPTP),[13,14] which is a large non-selective channel that triggers cell death. Once opened, mitochondrial membrane depolarization, ATP depletion, and mitochondrial swelling occur, ultimately leading to cell death. Research has shown that excitotoxicity triggers the dissociation of the F_1 subcomplex from the Fo component of F_1Fo ATP synthase, which results in the opening of a leak channel.[15,16] A rodent model of focal cerebral ischaemia showed a decreased mitochondrial membrane potential in isolated mitochondria when compared with the control model.[17] An ischaemia-reperfusion model revealed that the loss of mitochondrial membrane potential was prevented by treatment with cyclosporine A, which inhibits mPTP.[18] The neuroprotective properties of cyclosporine A were also observed in rodent TBI models.[19] In addition, amyloid-β (Aβ) peptide can trigger mPTP opening by causing the translocation of cyclophilin D.[20] A deficiency in cyclophilin D could maintain mitochondrial membrane potential and improve cognitive function in AD mice, thereby indicating the involvement of mPTP in AD pathology.[21] In a PD model, α-synuclein aggregates caused the loss of mitochondrial membrane potential and induced the activity of a leak channel similar to mPTP.[22]

Mitochondria are critical for the functioning of apoptotic pathways. Oligomerization of pro-apoptotic Bcl-2 family proteins such as Bax and Bak in the mitochondrial membrane promotes the release of cytochrome c from the mitochondria. This cytochrome c then binds to apoptotic protease-activating factor-1 and activates caspases,[23] which causes the proteolysis of structural and functional proteins, leading to cell death. This apoptotic pathway can be inhibited by anti-apoptotic Bcl-2 family members, such as Bcl-2 and Bcl-xL, which sequester pro-apoptotic proteins. Maintaining a balance between pro- and anti-apoptotic Bcl-2 family proteins is critical for cell survival, and alterations in these protein levels are evident in brain tissues of humans and animals with brain disorders. Postmortem studies have identified increased levels of pro-apoptotic Bax proteins in the brain tissues of PD patients.[24] Similarly, mouse PD models have shown increased pro-apoptotic Bax protein and mRNA levels and decreased anti-apoptotic Bcl-2 protein levels in dopaminergic neurones.[25] In addition, genetically modified Bax-deficient PD mice were revealed to be resistant to the loss of dopaminergic neurones.[25] The Aβ peptide, which is a hallmark of AD, can decrease Bcl-2 and increase Bax, thereby potentially contributing to neuronal apoptosis and neurodegeneration.[26] Increased levels of Bax and decreased levels of Bcl-2 and Bcl-xL have been observed in a rodent model of cerebral ischaemia,[27] and treatment with pro-apoptotic protein inhibitors reversed excitotoxicity-associated neuronal death.[28]

Mitochondria are major contributors to cellular ROS, which are by-products of oxidative phosphorylation.[29] ETC impairment can cause excessive ROS production, which overwhelms the antioxidant defence system and promotes oxidative stress. Increases in oxidative stress markers that indicate lipid peroxidation and DNA oxidation have been observed in the brain during neurodegeneration[30,31] and the depletion of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase (SOD) has been identified in neurodegenerative diseases. In AD, Aβ plaques accumulate in the brain and disrupt the activities of ETC complexes, which causes an overproduction of ROS.[12] Moreover, oligomeric or fibrillar α-synuclein inhibits the function of the mitochondrial respiratory chain, resulting in increased ROS production in PD cases.[11] Oxidative stress can activate the NLRP3 inflammasome, which is a multiprotein complex that triggers the processing and secretion of pro-inflammatory cytokines.[32] Elevated levels of ROS and ROS-mediated cellular damage in neurodegenerative diseases trigger inflammatory responses that cause immune cell recruitment and additional ROS production. Extracellular accumulation of Aβ plaques can activate microglia, which release pro-inflammatory cytokines.[33] In cerebral ischaemia, both hypoxia and reperfusion trigger inflammatory responses that activate macrophages and release pro-inflammatory cytokines, including TNF alpha (TNF-α), IL-1, IL-6, and IL-8.[10] These inflammatory cytokines induce the production of adhesion molecules on endothelial cells that promote neutrophil adhesion; these activated neutrophils then generate additional ROS.[34]

Mitochondrial DNA has been implicated in the pathogenesis of neurodegenerative disorders because of its predisposition to oxidative damage due to its proximity to the ETC and the lack of a proper DNA repair mechanism.[35] Furthermore, mutations in genes associated with mitochondrial function

have been linked to neurodegeneration, such as the PARK genes, which are critical for mitochondrial function and have been implicated in the pathogenesis of PD. Mutations in the PINK1 and Parkin genes have been associated with decreased ETC enzyme activity and ATP depletion.[35] These mutations disrupt the balance of mitochondrial fission, fusion, and mitophagy, leading to an increased number of fragmented mitochondria. Mutations in the DJ1 and LRRK2 genes are associated with decreased mitochondrial membrane potential, increased oxidative stress, decreased complex I function, and increased mitochondrial fragmentation.[36,37]

Neuroprotective effects of fucoxanthin

Fucoxanthin ($C_{42}H_{58}O_6$) is a carotenoid marine xanthophyll that is found in brown seaweed such as *Undaria pinnatifida* and *Laminaria japonica*.[38,39] It has a strong antioxidant capacity because of the presence of multiple double bonds, including a conjugated carbonyl group. Fucoxanthin has a radical scavenging effect when treated with 1,1-diphenyl-2-picrylhydrazyl and 2,2′-Azinobis-3-ethylbenzo thiazoline-6-sulfonate[40–43] and exhibits a stronger hydroxyl radical quenching activity than other antioxidants.[43] In addition to its direct scavenging effect, fucoxanthin regulates the gene expression of antioxidant enzymes such as SOD and catalase to help support cellular redox homeostasis.[44]

Although epidemiological data demonstrating the direct effect of fucoxanthin on brain disorders are limited, a high intake of seaweed has been reported to lower the risk of PD[45] and stroke-mediated mortality in humans.[46] Pharmacokinetic studies using human plasma detected fucoxanthinol, a metabolite of fucoxanthin, after a single oral administration of kombu (*Laminaria japonica*) extract containing fucoxanthin (31 mg)[47] or a 1-week dose of dried wakame (*Undaria pinnatifida*) containing 6.1 mg of fucoxanthin.[48] Quantitative analyses of fucoxanthin in human tissues other than blood have not been conducted; however, Hashimoto *et al.* observed its distribution and that of its metabolites such as fucoxanthinol and amarouciaxanthin A in tissues after oral administration in a mouse model.[49] Although the brain was not analysed in that study, fucoxanthin was present in other lipid-rich organs such as the adipose and liver. While the neuroprotective potential of fucoxanthin has been documented in *in vivo* animal models, its ability to cross the blood-brain barrier (BBB) remains unconfirmed. However, since other carotenoids from the xanthophyll family, such as astaxanthin, lutein, and zeaxanthin, can permeate the BBB, fucoxanthin has the potential for uptake into brain tissue.[50,51]

Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder that is characterised by cognitive impairment, memory decline, and behavioral and personality changes. It is the most common cause of dementia in older adults and affects one in nine US residents aged 65 and older.[52] The complex neuropathology of AD involves the extracellular aggregation of Aβ into plaques and the intracellular accumulation of hyperphosphorylated tau protein into neurofibrillary tangles. These processes accompany and affect significant mitochondrial dysfunction in AD models. Aβ can impair the functioning of ETC, cause the loss of mitochondrial membrane potential, increase ROS production, and disrupt Ca^{2+} homeostasis.[53–56] In addition to mitochondrial dysfunction, Aβ induces neuroinflammation and impairs neurotransmission.

Fucoxanthin has been suggested to protect mitochondria against AD-associated pathologies.[44,57,58] Treatment with fucoxanthin prevents the loss of cell viability against Aβ-induced cytotoxicity.[57,58] In particular, fucoxanthin-treated cells were resistant to apoptotic death, thereby indicating mitochondrial protection,[57,58] and fucoxanthin-modified Aβ1-42 oligomers have been reported to be less toxic than Aβ1-42 oligomers to SH-SY5Y cells.[44] Furthermore, fucoxanthin may directly prevent the formation of Aβ plaques and neurofibrillary tangles. Xiang *et al.* showed the binding of fucoxanthin to Aβ1-42 peptides, where it inhibited the formation of Aβ fibrils and oligomers[44] and prevented Aβ-mediated mitochondrial dysfunction.[59–62] Similarly, Jung *et al.* reported the binding of fucoxanthin and inhibition of β-site amyloid precursor protein cleaving enzyme 1, which cleaves the amyloid precursor protein to produce Aβ.[63] Fucoxanthin may inhibit the production and aggregation of Aβ through interaction with two hydroxyl groups.[63] In addition, co-incubation of Aβ monomers with fucoxanthin resulted in a dose-dependent decrease in Aβ oligomer formation through hydrophobic interactions. Lee *et al.* reported that fucoxanthin reversed the loss of mitochondrial membrane potential in Aβ-treated PC12 cells.[58] In that study, 5 μM fucoxanthin was as effective as 50 μM resveratrol, an antioxidant with neuroprotective function, indicating a strong mitochondrial protection capacity. Fucoxanthin inhibits Aβ-mediated upregulation of Bax, thereby helping to maintain the integrity of the mitochondrial membrane.[58] Those authors also showed that treatment with fucoxanthin prevented the increase of intracellular Ca^{2+}, as measured by fluo3-AM. Although mPTP was not primarily discussed in that study, the data suggests that fucoxanthin has a role in inhibiting the opening of the mPTP.

Fucoxanthin protects cells from oxidative damage associated with AD.[57,58] Treatment with fucoxanthin was shown to increase nuclear Nrf2 expression, whereas co-treatment with a PI3K inhibitor attenuated this increase, suggesting that fucoxanthin mediated this increased expression through the Akt/GS3K signalling pathway.[58] Similarly, treatment with fucoxanthin increased the activation of the pro-survival PI3K/Akt pathway in Aβ SH-SY5Y cells.[57] Nrf2 is an important regulator of cellular antioxidants that is normally sequestered in the cytosol by Keap1.[59] Oxidative stress induces the translocation of Nrf2 to the nucleus, where pFyn eventually stimulates its export. Fucoxanthin may increase nuclear Nrf2 by preventing the phosphorylation of Fyn and Nrf2 by GS3K, thereby decreasing the degradation and export of Nrf2 from the nucleus.[58] Similarly, fucoxanthin regulated redox homeostasis in *in vivo* models of AD and was shown to attenuate the decrease in SOD, catalase, and glutathione in AD mice.[44] The BV2 cells treated with the poly lactic-*co*-glycolic acid-*block*-polyethylene

glycol (PLGA-PEG)-fucoxanthin nanoparticle prevented Aβ-induced NF-κB, TNF-α, and IL-1β induction compared with the BV2 cells treated with only Aβ oligomers, indicating that fucoxanthin prevented Aβ-induced neuroinflammation.[60] Furthermore, fucoxanthin has anticholinesterase and antibutyrylcholinesterasic activity,[61] and since acetylcholine is considerably depleted in the AD pathology, fucoxanthin may help maintain acetylcholine levels in the brain.[61]

Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder caused by the loss of dopaminergic neurones in the *substantia nigra* that leads to a deficiency of dopamine, which is a neurotransmitter that controls movement, pleasure, and motivation.[62] The common symptoms of PD include tremors, rigidity, akinesia, and postural instability,[62] while non-motor symptoms such as depression, anxiety, and cognitive impairments can also occur.[62] In 2019, over 8.5 million individuals worldwide were estimated to be living with PD.[64] A 2022 study stated that close to 90,000 people are diagnosed with PD every year in the United States, representing a 50% increase from the previously estimated number of 60,000 annually.[65] Currently, patients with PD are treated with levodopa (L-DA) to alleviate symptoms, although this treatment may cause neurotoxicity in the long term.[66]

The degradation of dopaminergic neurones is associated with the accumulation of misfolded α-synuclein proteins. Oligomeric and fibrillar α-synucleins inhibit the function of ETC and impair ATP production. Postmortem studies have shown decreases in complexes I and II in the PD brain.[67] Furthermore, the α-synuclein aggregate interacts with F_1Fo ATP synthase in the respiratory chain, which causes the opening of the mPTP,[22] and disruption of the respiratory chain leads to the overproduction of ROS that damages the mitochondria. Increased oxidative stress also impairs the function of the ubiquitin-proteasome system, thereby inhibiting the clearance of these misfolded proteins and leading to their accumulation in neurones.[68] Degradation of dysfunctional mitochondria is important for maintaining a healthy pool of neuronal mitochondria. Mutations in the PINK1 and Parkin genes in the PD brain impair the mitophagy process resulting in the accumulation of dysfunctional mitochondria.[69] Similarly, DJ1 and LRRK2 gene mutations are associated with loss of mitochondrial membrane potential and morphology.[36,37] DJ1 binds to the β-subunit of the F1Fo ATP synthase enhancing ATP production. In contrast, a DJ1 mutant fails to close the mitochondrial inner membrane leak, thereby altering energy metabolism.[70] The aggregation of α-synuclein can also affect mitochondrial fragmentation[71] and movement, which alters the mitochondrial distribution in axonal regions that have high energy demands.[72]

In vitro and *in vivo* studies have suggested the mitochondrial protective effects of fucoxanthin in PD pathology. Treatment with fucoxanthin prevented the loss of mitochondrial membrane potential in PC12 cells challenged with 6-hydroxydopamine (6-OHDA) or a combination of 6-OHDA and L-DA.[73,74] Although the levels of ATP production and oxygen consumption were not directly measured in those models, maintaining mitochondrial membrane potential is critically important to power F_1Fo ATP synthase. Thus, fucoxanthin may help maintain mitochondrial energy metabolism. In addition, annexin V and propidium iodide co-staining showed that fucoxanthin prevented PD-associated apoptotic cell death,[73,74] suggesting that fucoxanthin is involved in the protection of mitochondrial membrane integrity. The direct role of fucoxanthin on mitochondrial quality control in the PD brain is unknown. Lian *et al.* showed that treatment with fucoxanthin increased the ratio of LC3-II to LC3-I, the protein level of Parkin, and the number of autophagosomes and mitophagosomes in retinal ganglion cells challenged with excitotoxicity,[75] suggesting that fucoxanthin has a role in regulating mitophagy. Those authors further showed that fucoxanthin prevented the loss of mitochondrial membrane potential during excitotoxicity and helped protect from apoptotic death by lowering Bax and increasing Bcl-2.

The loss of mitochondrial membrane integrity and inefficient operation of ETC increases ROS production. PC12 cells challenged with 6-OHDA or a combination of 6-OHDA and L-DA showed increased DCF signals indicating increased intracellular ROS,[73,74] whereas fucoxanthin-treated PC12 cells were resistant to ROS production in a dose-dependent manner. In addition to its radical scavenging properties,[40–42] fucoxanthin increased antioxidant enzyme expression in PD models.[73,74] Fucoxanthin binds to a hydrophobic site on Keap1 where it decreases the affinity of Keap1 to Nrf2-binding in a dose-dependent manner.[73] Therefore, fucoxanthin increased the nuclear expression of Nrf2 and the downstream genes that encode antioxidant enzymes such as haem oxygenase-1, the glutamate-cysteine ligase modifier subunit, and the glutamate-cysteine ligase catalytic subunit in 6-OHDA-treated PC12 cells.[73] In addition, PD mice that underwent intragastric administration of fucoxanthin (50, 100, or 200 mg/kg/day) for 28 d improved pole climbing, swimming, and suspension experiment scores, indicating improved motor function.[74] Similarly, zebrafish larvae treated with different concentrations of fucoxanthin for 4 d showed improved swimming abilities after exposure to 6-OHDA.[73]

Cerebral ischaemia

Cerebral ischaemia is a condition that commonly occurs during cardiovascular events such as stroke or cardiac arrest and involves reduced blood flow to the brain. This condition impairs mitochondrial energy metabolism through the deprivation of oxygen and essential nutrients to the brain.[76,77] Dysfunctional mitochondria cause the production of excessive ROS, which damage various cellular components and trigger apoptotic pathways, including the oligomerization of pro-apoptotic proteins in the mitochondrial membrane and the release of cytochrome c, leading to programmed cell death.[78] In addition, ischaemia-mediated energy depletion causes the failure of the ATP-dependent ionic pump, thereby altering intracellular ionic homeostasis. Furthermore, excessive cellular Ca^{2+} concentrations cause the opening of mPTP,[79,80] which exacerbates the energy crisis and leads to neuronal death.

Ikeda *et al.* showed that treatment with fucoxanthin isolated from wakame (*Undaria pinnatifida*) promoted the release of

lactate dehydrogenase in hypoxia-exposed primary cortical neurones,[81] which suggests that fucoxanthin reduces cytotoxicity during oxygen depletion. Those authors performed an *in vivo* study using stroke-prone spontaneously hypertensive rats, which were characterised by severe spontaneous hypertension and the development of cerebrovascular diseases. Supplementation with 5% wakame powder delayed the development of stroke and increased the lifespan of the rats. Hu *et al.* further investigated the cellular mechanisms of fucoxanthin-mediated neuroprotection[82] by intragastrically administering 30, 60, and 90 mg/kg of fucoxanthin to Wistar rats 1 h before middle cerebral artery occlusion (MCAO). The results showed that rats treated with fucoxanthin exhibited a dose-dependent reduction of MCAO-induced brain injury. Treatment with fucoxanthin increased the ratio of Bcl-2/Bax and decreased the cleaved caspase 3 protein level, indicating inhibition of mitochondria-mediated apoptosis during cerebral ischaemia. Consistent with *in vivo* data, rat cortical neurones treated with fucoxanthin showed anti-apoptotic properties in response to oxygen-glucose deprivation and reoxygenation challenges.[82] Furthermore, the study suggested that fucoxanthin increased antioxidant proteins such as SOD[82] via the activation of Nrf2,[83] thereby protecting neurones from oxidative stress. Wang *et al.* used PLGA-PEG nanoparticles to increase fucoxanthin bioavailability in the brains of MCAO-induced rats.[83] PLGA-PEG encapsulation improves fucoxanthin stability in the body and allows for its extended release and enhanced penetration into the central nervous system. The results of that study showed that the intravenous administration of PLGA-PEG fucoxanthin nanoparticles (20 and 40 mg/kg) half an hour before MCAO reduced the behavioural deficits associated with cerebral ischaemia in the rats. In addition, the infarct volumes and brain oedema extents were decreased in rats receiving the nanoparticle treatment.[83] Furthermore, PLGA-PEG fucoxanthin nanoparticles prevented the loss of glutathione peroxidase, SOD, and catalase activity in the ischaemic brain indicating the roles of these compounds in regulating antioxidant defence. Fucoxanthin nanoparticles exhibit anti-inflammatory properties through the inactivation of the NF-κB pathway.

Depression and anxiety

Depression is characterised by a pervasive lack of interest in daily activities that can lead to a profound sense of hopelessness or self-harm, while anxiety involves excessive worry and enduring fear. Depression and anxiety frequently co-occur, possibly due to overlapping cellular mechanisms, with 41.6% of individuals diagnosed with a depressive episode presenting with anxiety within 12 months of the diagnosis,[84] demonstrating a substantial comorbidity between the two conditions. Although the neurological pathways that affect these disorders are not fully understood, a growing body of studies suggests an association with mitochondrial dysfunction.[85,86] Cellular energy metabolism is dysregulated in patients with depression.[87] Similarly, a proteomic analysis of mice challenged with chronic corticosterone, a stress hormone associated with depression and anxiety, showed that oxidative phosphorylation-related protein expression was decreased in these mice.[88] Treatment with ATP reversed the impaired synaptic transmission and excitability in neurones in depression mouse models.[89] Moreover, repeated unpredictable stress downregulated anti-apoptotic genes such as Bcl-2 and Bcl-xL in rat brains,[90] whereas approaches that improved the anti-apoptotic/pro-apoptotic Bcl-2 protein ratio alleviated the depression-associated behaviours.[91]

Although the risk factors for behavioural disorders are complex, studies have demonstrated that the consumption of a healthy diet lowers the risk of depression.[92,93] A prospective cohort study with Japanese adults, which was adjusted for biological, socio-economic, and dietary factors, reported that high seaweed intake was negatively associated with depressive symptoms.[94] In animal models, treatment with extract from the brown seaweed *Sargassum horneri* (500 mg/kg) for 3 weeks prevented the loss of neurotransmitters such as serotonin, dopamine, and norepinephrine in the mouse brain, as well as improvements in depressive-live behaviours caused by an intraperitoneal injection of corticosterone.[95] The authors performed a quantitative analysis and verified the presence of fucoxanthin in the extract. That study further revealed that the underlying mechanism involved the activation of the ERK-CREB-BDNF pathways by the brown seaweed extract. Although the role of *Sargassum horneri* in mitochondrial protection was not intensively featured in that study, the BDNF has been previously shown to increase anti-apoptotic Bcl-xL[96] where the depletion of Bcl-xL impairs the maturity of BDNF.[97] Thus, treatment with fucoxanthin may promote the development and growth of neurones by preventing the mitochondrial dysfunction associated with depression. In addition, the intragastric administration of fucoxanthin (0, 50, 100, and 200 mg/kg) improved Lipopolysaccharide (LPS)-induced anxiety behaviours in mice.[98] Treatment with fucoxanthin regulates the AMPK-NF-κB pathways and prevents the accumulation of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and iNOS and COX-2 in the hippocampus, cortex, and hypothalamus.

Brain aging

The cumulative impact of oxidative damage on neurones contributes to the process of brain aging.[99,100] This oxidative damage results from the generation of free radicals through environmental exposure, inflammation, immune responses, and infection.[99,100] Postmortem analyses of aged human brain tissues, particularly in the hippocampus and cortical regions, revealed elevated ROS levels and a decrease in antioxidant enzymes such as SOD and catalase.[101] The accumulation of dysfunctional mitochondria in aged brains is associated with brain atrophy and neuronal apoptosis,[102] and the mitochondria isolated from the brains and other tissues of aged rodents demonstrated decreased ETC activity. Specifically, ETC complexes I and IV exhibit reduced activity in the aging brain, which can be attributed to increased oxidative stress.[102]

The diet patterns in Okinawa, a blue zone region with a high life expectancy, include nutrient-dense foods such as lean meat, fish, and vegetables, including seaweed.[103] Fucoxanthin is abundant in brown seaweed, which is a common part of the Okinawan diet. In the 1990s, Okinawan people had the lowest

mortality rate from age-associated diseases in the Japanese and US populations.[104] Research investigating the direct role of fucoxanthin in brain aging is still limited; however, oxidative stress and inflammation are the main risk factors for age-associated cognitive decline,[105,106] and the antioxidant effects of fucoxanthin have been determined.[40–42] Chen *et al.* reported that the administration of 100–200 mg/kg of fucoxanthin for 7 d post-laparotomy surgery improved cognitive function in 12–14-month-old mice.[107] This treatment also decreased neuroinflammation and oxidative stress by activating the Akt and Nrf2 pathways, decreasing the levels of pro-inflammatory cytokines such as TNF-α and IL-1β, and increasing the antioxidant enzymes in the hippocampal tissue.[107]

Fucoxanthin increased the lifespan and resilience of *Caenorhabditis elegans (C. elegans)* and *Drosophila melanogaster* models to starvation and thermal and oxidative stress. Two carotenoids, fucoxanthin and β-carotene, were tested in that study, and lifespan extensions in *C. elegans* were only observed in the fucoxanthin-treated group.[108] Additionally, transcriptome analysis showed that fucoxanthin regulates the pathways involved in longevity, Wnt, and autophagy.[109] In particular, the Wnt signalling pathway controls mitochondrial function, including metabolism, biogenesis, and dynamics in cancer and non-transformed cells. Increased Wnt signalling activates mitophagy by increasing ROS production, which in turn decreases the number of damaged mitochondria and increases the quantity of working mitochondria through biogenesis. The Wnt signalling pathway is important for maintaining mitochondrial homeostasis; therefore, fucoxanthin-mediated upregulation of genes associated with the Wnt pathway could lead to mitochondrial protection. In addition, autophagy is an important quality control mechanism to remove damaged organelles such as dysfunctional mitochondria. Dysregulated autophagy promotes protein aggregation, which is associated with neurodegeneration such as that of PD. Furthermore, this study also showed that oxidative phosphorylation and apoptosis were one of the major targets of fucoxanthin, suggesting its role in regulating mitochondrial function.

Discussion

Mitochondrial protection is critically important to prevent the ATP depletion that occurs as an effect of brain disorders. In addition to cellular energy metabolism, targeting mitochondria can prevent pathological cell damage associated with ROS, apoptosis, and mPTP opening.[110] Fucoxanthin demonstrates neuroprotective effects towards a range of brain disorders including AD, PD, cerebral ischaemia, depression, and anxiety (Table 1). Although limited studies have focused on the direct mechanisms of fucoxanthin-mediated mitochondrial function, fucoxanthin has been implicated in mitochondrial protection in several reports (Fig. 1). In particular, mitochondria-mediated apoptosis under fucoxanthin treatment has been tested in various brain disorder models. It was found that this treatment prevented the loss of the Bcl-2/Bax ratio and the cleavage of caspase-3 in ischaemia-induced brain infarct.[82] Similar results have been reported in cells challenged with Aβ and 6-OHDA, in which the anti-apoptotic Bcl-2 family protein was maintained while pro-apoptotic proteins were suppressed.[58,74] Treatment with fucoxanthin has also been shown to prevent Aβ-induced intracellular Ca^{+2} increase in PC12 cells,[58] suggesting the potential role of this compound in halting the opening of the mPTP. Despite promising data regarding the mitochondrial protective roles of fucoxanthin, the measurements that show the effects on cellular energy metabolism, such as those of ATP production and oxygen consumption, have not been performed in brain disorder models. However, cells treated with fucoxanthin have been shown to maintain rhodamine 123 and JC-1 fluorescent signals in neurodegenerative disease models, indicating the presence of the mitochondrial membrane potential.[58,74] Since the mitochondrial membrane potential drives the operation of F_1Fo ATP synthase, fucoxanthin may help alleviate the neuronal dysfunction that is associated with energy depletion in brain disorders.

Oxidative stress and inflammation, which commonly occur in brain disorders during pathological processes, can damage intracellular organelles including mitochondria; therefore, the antioxidant and anti-inflammatory effects of fucoxanthin (Fig. 1) have been studied with various models. In particular, treatment with fucoxanthin has been shown to activate Nrf-2 signalling and upregulate genes that encode antioxidant enzymes such as SOD, catalase, and haem oxygenase-1 in conditions with neurotoxic challenges induced by Aβ, 6-OHDA, and ischaemia.[58,60,73] Mitochondria are the major sources of ROS, and the fucoxanthin-mediated transcriptional regulation of antioxidants may protect mitochondria from oxidative stress. In addition, fucoxanthin has been shown to alleviate neuroinflammation in the hippocampus and cortex of Aβ-treated mice.[60] This study showed that fucoxanthin decreased the NF-κB activity and its downstream targets such as TNF-α and IL-1β. Similarly, treatment with fucoxanthin prevented NF-κB p65 expression in the hippocampus, cortex, and hypothalamus of LPS-injected depressive mice[98] and the production of TNF-α in MCAO-induced rats.[83]

In this review, we discuss the existing literature on the potential of fucoxanthin to protect mitochondria in brain disorders. However, we acknowledge limitations. First, the existing body of literature investigating the mechanism of fucoxanthin on mitochondrial function in the context of brain diseases is limited. This scarcity of dedicated studies hinders a comprehensive understanding of the specific effects of fucoxanthin on mitochondrial function in the brain. In addition, the majority of the discussed evidence was derived from preclinical studies. While the results from these experimental studies provide valuable insights into the cellular and molecular aspects, the findings must be adaptable to clinical applications in humans. Moreover, the bioavailability of fucoxanthin could pose a challenge since the absorption, distribution, metabolism, and excretion in the human body may influence its efficacy; therefore, these aspects should be explored.

Conclusion

Fucoxanthin has been shown to protect the brain against challenges associated with brain disorders. Here, we discuss the potential roles of fucoxanthin in cellular responses associated

Table 1. The effects of fucoxanthin on *in vitro* and *in vivo* brain disorder models

Brain Disorder	Model	Pathological challenge	Effect of fucoxanthin	Ref.
Alzheimer's Disease	SH-SY5Y cells	Treatment with Aβ1-42	-Inhibits the formation of Aβ1-42 fibril and oligomer -Prevents Aβ1-42 -mediated cytotoxicity	(44)
	ICR mice	Hippocampal injection of Aβ1-42 oligomers	-Improves recognition performance, spatial learning, and memory -Prevents the reduction of Aβ1-42-mediated antioxidant activities and the downregulation of BDNF and ChAT	
Alzheimer's Disease	SH-SY5Y cells	Treatment with Aβ1-42	-Attenuates Aβ-mediated cell death -Attenuates Aβ-mediated ROS production -Prevents the alteration of PI3K/Akt and ERK pathway	(57)
Alzheimer's Disease	PC12 cells	Treatment with Aβ25-35	-Attenuates Aβ-mediated ROS production -Prevents Aβ-mediated apoptosis -Protects the mitochondrial membrane potential -Prevents Aβ-mediated Ca^{2+} production -Increases nuclear translocation of Nrf2 -Regulates Akt/GSK-3β/Fyn signalling	(58)
Alzheimer's Disease	SH-SY5Y cells BV2 microglial cells	Treatment with Aβ oligomers Treatment with Aβ oligomers	-Prevents Aβ-mediated cell death and ROS production -Prevents Aβ-mediated neuroinflammation	(60)
	ICR mice	Hippocampal injection of Aβ1-42 oligomers	-Improves cognitive performance -Attenuates neuroinflammation and oxidative stress -Activates Nrf2 pathway -Reduces NF-κB pathway	
Parkinson's Disease	PC12 cells	Treatment with 6-OHDA	-Binds to Keap1 and activates Nrf2 pathway -Prevents 6-OHDA-mediated decrease in antioxidant enzymes -Prevents 6-OHDA-mediated cell damage	(73)
	Zebrafish	Treatment with 6-OHDA	-Improves 6-OHDA-mediated locomotor dysfunction -Prevents 6-OHDA-mediated ROS production and cell damage -Upregulates antioxidant genes	
Parkinson's Disease	PC12 cells	Treatment with 6-OHDA and L-DA	-Prevents 6-OHDA and L-DA-mediated apoptosis -Prevents 6-OHDA and L-DA-mediated mitochondrial damage -Inhibits the ERK/JNK-c-Jun pathway	(74)
	C57BL/6 mice	6-OHDA injection	-Improves 6-OHDA-mediated motility dysfunction -Prevents 6-OHDA-mediated dopaminergic neuronal loss	
Cerebral Ischaemia	Primary cortical neurones	Hypoxia	-Attenuates hypoxia and re-oxygenation-mediated cell damage	(81)
	SHRSP rats		-Prevents the incidence of stroke and increases the mean lifespan in SHRSP	
Cerebral Ischaemia	Primary cortical neurones	Oxygen-glucose deprivation and reperfusion (OGD/R)	-Prevents OGD/R-mediated apoptosis -Activates Nrf2/HO-1 signalling	(82)
	Wistar rats	Middle cerebral artery occlusion (MCAO)	-Decreases ischaemia-mediated infarction and neurological deficits -Prevents ischaemia-mediated apoptosis and ROS production	
Cerebral Ischaemia	HT22 cells	Treatment with iodoacetic acid (IAA)	-Prevents IAA-mediated ROS production -Prevents IAA-mediated cell death	(83)
	Sprague-Dawley rats	MCAO	-Prevents MCAO-mediated brain infarct and behavioural deficits -Attenuates MCAO-mediated neuroinflammation and oxidative stress	
Depression and Anxiety	ICR mice	Intraperitoneal injection of corticosterone	-Improves corticosterone-mediated depressive-like behaviours -Prevents corticosterone-mediated dysfunction of HPA axis and neurotransmitters -Activates the ERK-CREB-BDNF pathway	(95)
Depression and Anxiety	ICR mice	Intraperitoneal injection of LPS	-Improves depressive and anxiety-like behaviours -Increases AMPK activation -Prevents LPS-induced inflammation	(98)
Cognitive Impairment	Aged ICR mice	Laparotomy	-Prevents surgery-mediated cognitive impairment in aged mice -Activates the Akt pathway and prevents inflammation -Activates the ERK pathway and increases antioxidant enzymes	(107)
Aging	*Drosophila*	Aging, thermal stress, and paraquat	-Increases lifespan and stress resistance -Regulates the expression of stress resistance genes	(108)
	C. elegans	Aging	-Increases lifespan	
Aging	*Drosophila*	Aging, thermal stress, paraquat, and starvation	-Increases lifespan -Regulates the genes related to longevity, autophagy, apoptosis, and neurogenesis	(109)

HPA, hypothalamic-pituitary-adrenal; ICR, Institute of Cancer Research; ROS, reactive oxygen species; SHRSP, Stroke-prone spontaneously hypertensive.

with mitochondrial dysfunction. The antioxidant and anti-apoptotic effects of fucoxanthin suggesting mitochondrial protection have been evaluated in various brain disorder models. However, future mechanistic studies focusing on the role of fucoxanthin in mitochondrial function, along with clinical studies on its efficacy in alleviating neuronal damage, can aid in the development of dietary recommendations to offset the burden of brain disorders.

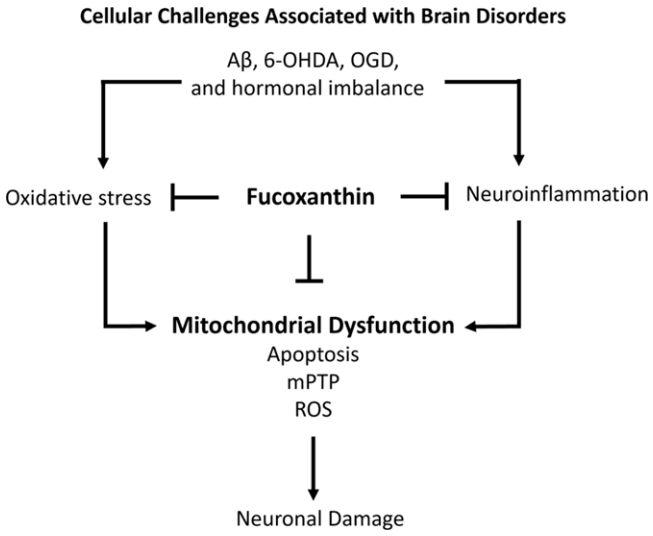

Fig. 1. Mechanism of mitochondrial protection by fucoxanthin in brain disorders.

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Authorship

KAF was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript. JJ was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript. EA was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript. EP was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript. RB was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript. AB was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript. MC was involved in drafting the original manuscript. HP was involved in drafting the original manuscript, interpretation of findings, and editing of the manuscript.

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