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Food-derived bioactive peptides: Mechanisms of action underlying inflammation and oxidative stress in the central nervous system

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ABSTRACT

There is a great interest in neuroprotective molecules capable of inhibiting the signaling, transduction and amplification of inflammatory and oxidative pathways to reverse or prevent brain cell damage and neurodegeneration. Peptides derived from food proteins represent a potential natural source for this action. Although there are several food sources and amino acid sequences that have shown promising effects, the mechanism of action on brain cells is not fully understood. Food peptides must resist digestion and be absorbed by the gastrointestinal and brain barriers. Its intact form or its metabolites must reach the brain tissue to exert action on a cellular level. It remains unknown which are the main receptors and intracellular pathways through which peptides act in inflammatory and oxidative conditions, and structure-activity relationships. This article reviews the main findings on food-derived peptides with anti-inflammatory and antioxidant bioactivity on brain cell culture and *in vivo* models of neurotoxicity. We highlight the main oxidative and inflammatory pathways by which food peptides interact at cellular level. The evaluation of the interaction/affinity of these food peptides with different brain cellular compounds may provide insight of possible therapeutic use or food supplement development.

1. Introduction

Oxidative and inflammatory damage are one of the main factors associated with neurodegenerative diseases. Foods reach in protein are source of important peptides with preventive or inhibitory action on inflammatory and oxidative pathways (Chakrabarti et al., 2014). Some studies have focused on peptide effect specifically on the central nervous system (CNS) to safely reverse or slow down the course of neurodegenerative disease (Wang et al., 2021). Understanding how these food hydrolysates peptides behave in a biological system and with which re-

Abbreviations: ABAP, 2,2'-azobis(2-amidinopropane)dihydrochloride; ACE, angiotensin-converting enzyme; ACHR, acetylcholine receptors; ACh, acetylcholine; AChE, acetylcholinesterase; AKT, serine-threonine protein kinase; AMP, responsive element-binding protein; ARE, antioxidant response element; Bax, protein pro-apoptotic; Bcl-2, protein anti-apoptotic; BCL-XL, anti-apoptotic gene; BDNF, brain-derived neurotrophic fator (proBDN-precursor and mBDNF-mature), Caspase 3, 7, 8 , cysteine-aspartic proteases; CAT, catalase; CD11B, CD68 and CD86, M1 microglial activation markers; ChAT, choline acetyltransferase; COX-2, cyclooxygenase-2; CREB, transcription factor cyclic; DA, dopamine; eNOS, Endothelial nitric oxide synthase; ERK, phosphorylated substrate of extracellular signal regulated kinase; GABA, γ-aminobutyric acid; GFAP, glial fibrillary acidic protein; Glu, glutamic acid; GSH, glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; GST, glutathione S-transferase; G6PDH, glucose-6-phosphate dehydrogenase; HDL, High-density lipoprotein; HO-1, Heme oxygenase-1; IL-6, IL-10, IL-12 and IL-1ß , interleukine; iNOS, inducible nitric oxide synthase; IκB, complex-associated protein; Keap-1, kelch-like ECH-associated protein 1; LC-PFA, Long Chain Polyunsaturated Fatty Acids; LDL, low-density lipoprotein; MAPK and MAPKs, phosphorylated mitogen-activated protein kinases; MCP-1/CCL2, monocyte chemoattractant protein-1; MDA, malondialdehyde; MIP-1α, macrophage inflammatory protein; MMP, mitochondrial membrane potential; MyD88, myeloid differentiation primary response gene 88; NCAM, neural cell adhesion molecules; NE via CAMKII, noradrenaline via Ca2+/calmodulin-dependent protein kinase; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related fator; NT-3, neurotrophic factor; PARP, Poly (ADP-ribose) polymerase; PGE-2, prostaglandin E2; P13K, phosphatidylinositol 3-kinase; p38, mitogen-activated protein kinases; p53, nuclear protein; p-JNK, phosphorylated c-Jun N-terminal kinase; p-PKA, phosphorylated protein kinase A; PINK1, PTEN-induced putative protein kinase 1; PSD-95, postsynaptic density; p-Tau, Phosphorylated Tau Protein; p47phox, Neutrophil cytosol factor 1; ROS, reactive oxygen species; sAPPß, soluble amyloid precursor protein beta; SOD, superoxide dismutase; SIRT1, Sirtuin 1; T-AOC, total antioxidant capacity; TNFα, Tumor necrosis factor-α; TBARS, thiobarbituric acid reactive substances; TG, triglycerides; TRL4, Toll-like receptor 4; TRKB, tropomycin receptor kinase B; 5HT, 5-hydroxytryptamine.

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ceptor or pathway they interact will elucidate the molecular mechanism and changes at the transcriptional level. This knowledge is essential to evaluate signaling patterns of peptides in relation to their sequence and structure for possible medical applications or therapeutic use.

Peptides are formed and released after the hydrolyzation of proteins that expose previously hidden protein sites. These sites may have a different physiological function from the original protein. Despite unclear signalization, the formation of smaller protein structures may have greater power of penetrability into tissues or greater affinity in interacting with intracellular compounds and transmembrane receptors. This interaction can activate or inhibit signaling pathways that may affect body functions. The biomolecules called Bioactive Peptides (BP) have been studied for their preventive action in several chronic diseases, including the CNS ones, such as Alzheimer's disease (AD), Parkinson's disease (PD) and vascular dementia (Min et al., 2017; Perlikowska, 2021; Wang et al., 2021)

Although there is no clear relationship between structure and function, bioactive peptides present some common characteristics. Most of them have from 2 to 20 amino acids and a molecular weight lower than 6000 Da. Peptide bioactivity is dependent on amino acid composition and sequence. The presence of hydrophobic and positively charged amino acids may be important factors for anti-inflammatory and antioxidant properties (Guha & Majumder, 2018; Lee & Hur, 2019a).

There is great interest in discovering new bioactive compounds that exert effects on the CNS. Bioactive peptides from nutritional sources are unlikely to promote an immune response and are advantageous in terms of absorption, digestion and excretion since they are natural compounds (Mason, 2010). Therefore, they represent an alternative with potentially fewer side effects than synthetic antioxidants and anti-inflammatories. The diversity of proteins and enzymes existing in nature from plants, animals or fungi, provides a wide possibility for the discovery/production of new peptides with pharmacological effects. Their high specificity and low toxicity may offer a safer alternative for therapeutic use. This review gathers studies that have demonstrated the mechanism of anti-inflammatory and antioxidant action of food-derived bioactive peptides either *in vitro* brain cell culture or *in vivo* animal studies with brain pathophysiology simulation.

2. Route of peptide ingestion to the brain

A food bioactive peptide with the potential to exert therapeutic effects on the brain has a long way to reach its target tissue. The peptide may be formed before ingestion by fermentation or *in vitro* enzymatic hydrolysis. After ingestion, the food protein or peptide must go through the entire gastrointestinal tract, where it is highly prone to degradation by acidic stomach conditions and proteolysis by digestive enzymes. Peptide transport 1 (PepT1), highly expressed in enterocytes, has been identified as the main responsible for di/tri peptide transportation across the intestinal epithelial membrane (Smith et al., 2013). Other routes may contribute to the transport of peptides, such as paracellular, transcytosis and transcellular diffusion. Peptide properties may influence the absorption route, including size, hydrophobicity and net charge (Xu et al., 2019).

In the blood stream, peptides have very short half-lives and may only remain intact and functional for short periods (minutes to hours) (Banks, 2016). The peptide passage through the blood-brain barrier (BBB) is not well defined but may occur through receptor-mediated transcytosis or by specific transporters, including the proton-coupled transporters PepT1/SLC15A1 and PepT2/SLC15A2, the peptide histidine transporter (PHT1/2) and the large neutral amino acid transporter 1 (LAT1) (Tanaka et al., 2019). Transport of peptides across the brain barrier may not be static and vary under physiologic or toxic conditions. The mechanisms by which peptides cross the BBB may provide insight for drug delivery to the brain in the treatment of diseases of the central nervous system (Banks, 2016; Matsui et al., 2020).

Positive effects of food peptide intake of preventing inflammation and oxidation in animal models of toxicity suggest peptide entry into the brain (Guidotti et al., 2017; Tanaka et al., 2019). Radioactively labeled tripeptide methionine-lysine-proline from casein hydrolysates was observed in mice brain 15 min after oral administration, followed by anti-inflammatory effects (Min et al., 2017). Through perfusion study, small peptides no larger than two amino acids, such as Tyr-Pro, Gly-Pro and Gly-Ser were able to go through the BBB in intact form (Tanaka et al., 2019). This indicates that at least short peptides may be transported across the BBB in intact form.

Stalmans et al. (2015) classified peptides according to their BBB influx and showed that food peptides have a low influx rate when compared to other classes of peptides (Stalmans et al., 2015). However, a low influx rate does not necessarily mean less biological effect. Modest amounts of the peripherally administration of radioactively His-Pro accumulated in the brain were enough to induce biological effect, including reverse alcohol induced narcosis (Banks et al., 1993).

3. Molecular mechanism of neuroinflammation and peptide potential action

Neuroinflammation is a natural defense process of the CNS, which aims to protect the brain against possible damage and infections. The inflammatory process is regulated by a complex multicellular response (among microglia, astrocytes and neurons) and promotes beneficial effects by eliminating cellular debris, pathogen phagocytosis and repairing damaged tissue. Ongoing environmental and even endogenous factors (e.g. aggregation of proteins, age evolution) may trigger an uncontrolled inflammation. A persistent inflammatory stimulus promotes the production of neurotoxic factors, eventually aggravating the damage and contributing to the pathology of several neurodegenerative diseases, such as AD, PD, narcolepsy and autism (Glass et al., 2010).

Food-derived peptides may avoid neuroinflammation by interacting with immune receptors at the brain membrane cells and/or downstream inflammatory pathways. At pathological condition, immune receptors such as pattern recognition receptors (PRR) recognize pathogen signals or "danger" molecules and activate an inflammatory immune response. PRR are among the first responders to CNS injury, and are highly expressed in neuronal, astrocytes and mainly microglial plasma membrane cells (Kigerl et al., 2014). Five main families of PRR have been identified including Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-like receptors (RLRs), AIM2-like receptors (ALRs), and C-type lectin receptors (Kigerl et al., 2014; Takeuchi & Akira, 2010). Few research groups have studied the interaction of food peptides with inflammatory receptors in the brain. Rice derived peptides prevented endothelial cell damage through TLR-4 interaction, as demonstrated by genetic and biochemical analysis (Liang et al., 2018). In LPS stimulated microglial cell line, the expression of TLR4 was reduced after treatment with a fungus derived peptide, alternaramide, preventing the activation of inflammatory pathways (Ko et al., 2016). More data is needed to understand the potential effect of food peptides on microglial inflammatory receptors.

Peptide anti-inflammatory effect may also act in cell components of the downstream receptor pathway, interacting with transcription factors and inhibiting the expression of genes that amplify the immune response in a pathological way. The inflammatory pathway activated by LPS is one that has been extensively evaluated to study the reversal effect by food hydrolyzed peptides (Fig. 1) (Kigerl et al., 2014). The bacterial endotoxin binds to TLR4 with the help of CD14 (both PRR) and trigger two signaling cascades involving MyD88 and TRIF adaptor proteins; these molecules activates a complex sequence of kinases proteins, including IκB complex and mitogen-activated protein kinase (MAPK). The MAPK cascade is involved in cell proliferation, differentiation, stress response and cell survival through the activation of extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2), c-Jun N-terminal kinases (JNKs), and p38 MAPK (Kaminska, 2005). The activation of MAPK cascade induces the

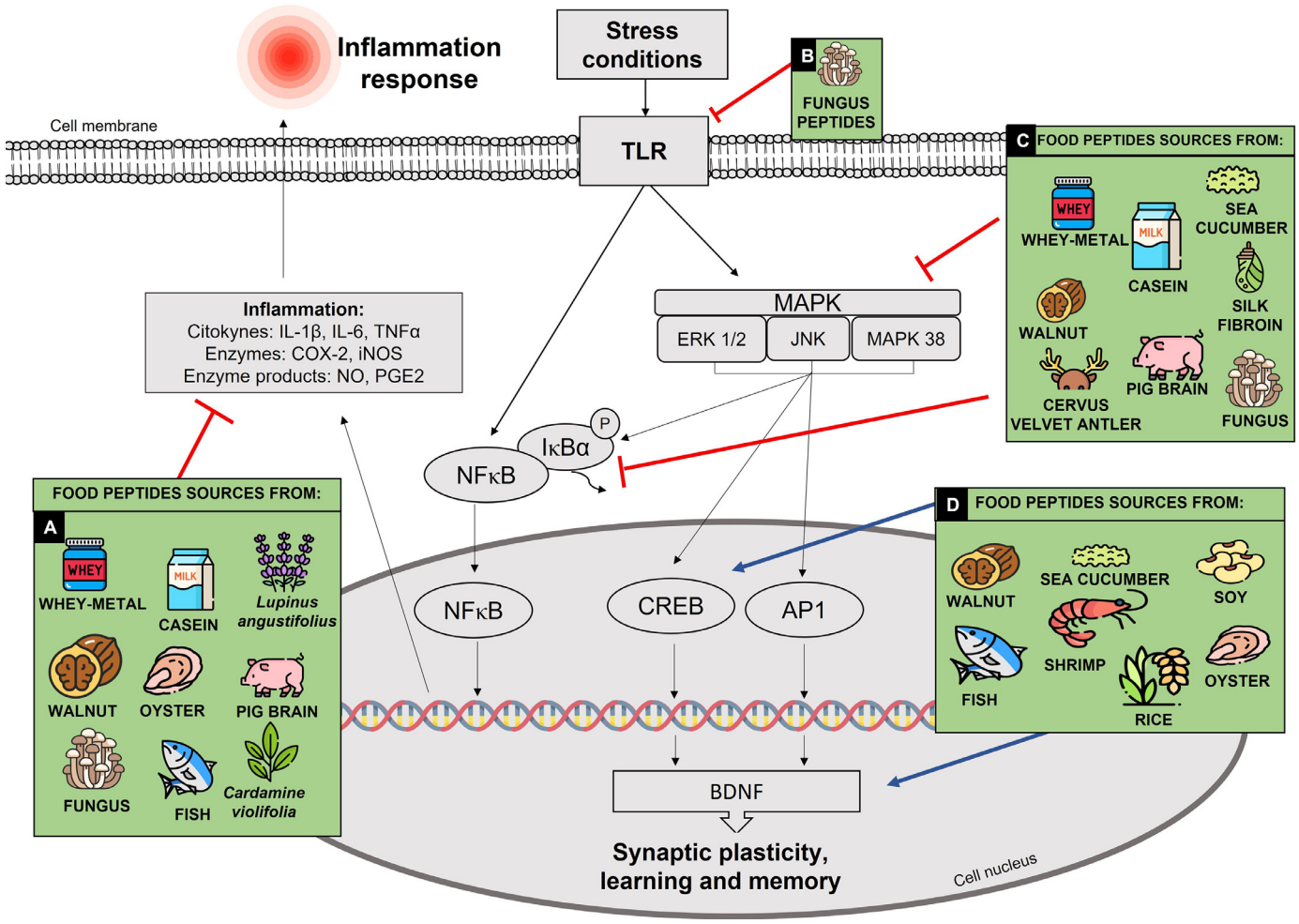

Fig. 1. Mechanism of action of food peptides to prevent inflammation. Representative image of some inflammatory pathways and the preventive action of peptides derived from food in brain cells. Stress conditions, including pathogen and danger molecules, bind to pattern recognition receptors (PRR), such as toll-like receptor (TLR) and activate intracellular downstream inflammatory immune response. Some food peptides may be able to prevent inflammation by reducing TLR4 expression (B box); inhibiting NF-κB and MAPK pathways (C box) or reducing inflammatory cytokines and enzyme expression (A box). Physiological pathways associated with learning and memory are also activated by food peptides, stimulating CREB and BDNF expression (D box). Red arrows inhibit pathways, blue arrows activate pathways. For complete information about characteristics of the evaluated peptide, see Tables 1 and 2.

translocation of transcription factors to the nucleus, such as NFκB, CREB and AP-1 (Ciesielska et al., 2021).

NF-κB is a transcription factor that controls several cell processes. While it mainly induces survival and plasticity in neurons, it also induces inflammatory response in glial cells (Shabab et al., 2017). In quiescent cells NF-κB remains inhibited by the ligation with IκB protein. After an inflammatory stimulus, IκB is phosphorylated and degraded, allowing the translocation of NF-κB subunits (p50 and p65) to the nucleus thus regulating the expression of several inflammatory, growth control and cell death genes (Dresselhaus & Meffert, 2019). NF-κB activation mediates the production of numerous inflammatory amplifiers such as cytokines (IL-1b, IL-6, IL-8, and TNF-α), the stimulation of inducible nitric oxide synthase (iNOS), and the regulation of cyclooxygenase-2 (COX-2) expression (Guha & Majumder, 2018). Several food peptides have demonstrated to inhibit the NFκB translocation in *in vivo* and *in vitro* brain systems, consequently reducing cytokine levels (see Section 7 and Fig. 1). Interestingly, molecular docking studies revealed interaction of metal chelating whey peptides with NFκB (Caetano-Silva et al., 2021).

4. Oxidative stress in the central nervous system and food peptide potential action

The brain is considered a susceptible organ to oxidative stress (OS) due to its high consumption of oxygen and lipid molecule content. These molecules are prone to lipid peroxidation by the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The brain OS formation has been extensively associated with aging, DA, PD and Huntington disease (HD) (Kim et al., 2015). Although it is not clear if OS plays a causative role or is induced as part of the pathogenesis, many studies has been dedicated to searching natural agents capable of protecting brain cells against oxidative damage and preventing or treating neurodegenerative diseases (van Raamsdonk et al., 2017).

External sources of antioxidants, such as food peptides, are particularly important to avoid an imbalance of ROS production and endogenous antioxidant levels. The accumulation of ROS induces a chain of radical reactions (oxidative stress), damaging cell's lipids, proteins, carbohydrates and nucleic acids (Niedzielska et al., 2016). Using antioxidant peptides is more advantageous than using synthetic antioxidants, as they are of natural origin, less likely to cause an immunoreaction and more stable than enzymatic antioxidants.

Food bioactive peptides may prevent oxidation by donating protons to free radicals, chelating metal ions and lipid peroxyradical trapping (Sarmadi & Ismail, 2010). The peptide metal chelating capacity may be particularly important in the CNS due to highly concentrated metal ions in the brain, such as Fe, Cu and Zn. These favor a redox metal reaction that has been associated with pathogenesis of neurological diseases (Sastre et al., 2015). Whey-hydrolyzed peptides have shown promising

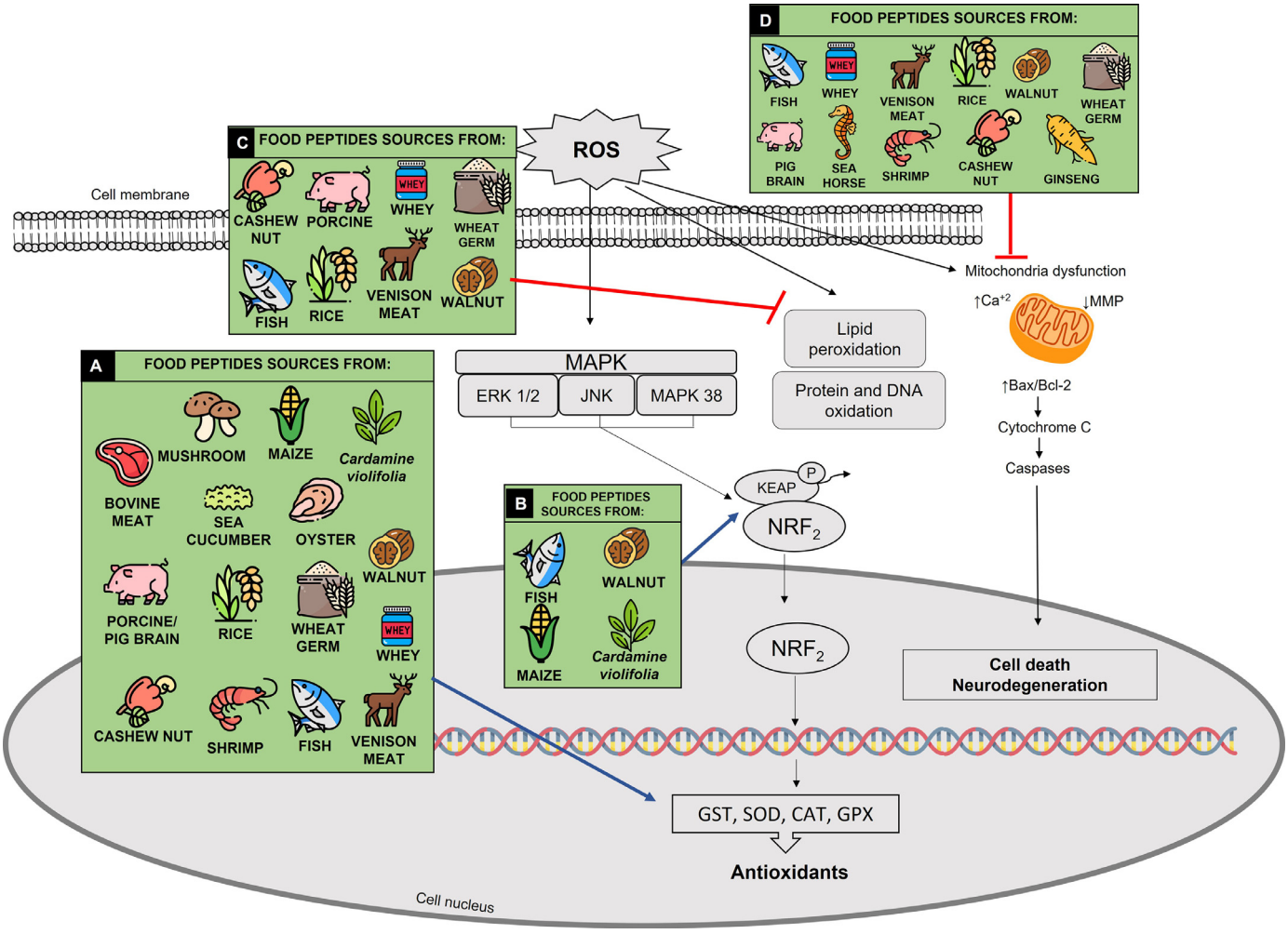

Fig. 2. Mechanism of action of food peptides to prevent oxidation. Representative image of some oxidative pathways and the antioxidant action of peptides derived from food in brain cells. Peptides from animal and plant sources protect cells against oxidation, through the activation of antioxidant Nrf2 signaling pathway (box B) and production of antioxidant enzymes (box A). Mitochondria dysfunction and downstream death pathway was also inhibited by several food peptides (box D). A reduction of lipid peroxidation was observed after food peptide treatment (box C). Red arrows are inhibit pathways, blue arrows activate pathways. For complete information about characteristics of the evaluated peptide, see Tables 1 and 2.

results regarding metal chelating capacity, which may be useful for neuroprotective purposes (Caetano-Silva et al., 2021).

The structure of peptides from food proteins has an important relationship with their antioxidant activity. Various amino acids have been associated with antioxidant properties (His, Trp, Phe, Pro, Gly, lys, Ile and Val) (Zou et al., 2016). Amino acids with aromatic residues can donate protons to electron deficient radicals. The proportion of hydrophobic amino acids may also be important for antioxidant activity, probably because of a better penetrability on cell membranes. Not only the amino acids composition, but also the location of amino acids in the peptide sequence may influence antioxidant activity. For example, the his-his segment was preferred for the antioxidative activity of designed peptides from soybean and the deletion of the C-terminal His decreased the antioxidant activity (Chen et al., 1996).

Some research findings found that food hydrolysates presented better antioxidant activity than purified peptides, showing a synergistic effect between free amino acids and peptides (Chen et al., 1995; Karaś et al., 2014). Furthermore, short chain peptides seem to present better antioxidant potential than their higher molecular weight counterparts (Ngoh & Gan, 2016).

Antioxidant peptide actions are also associated with the modulation of physiological response at the molecular level (Fig. 2, B box). For example, peptides from walnut, fish and maize alleviated oxidative stress by up-regulating the expression of F-E2-related factor 2 (Nrf2) (Gao et al., 2021; Yu et al., 2020; Zhang et al., 2021; Zhang et al., 2020; Zhao et al., 2021). This transcription factor plays an important part in cell redox control. In physiological conditions, Nrf-2 is maintained inactive through Kelch-like ECH associated protein 1 (Keap1) binding. However, increased ROS production disrupts Nrf2/keap1 ligation, allowing the translocation of Nrf-2 to the nucleus to mediate neuroprotection response. In the nucleus, Nrf-2 binds to the ARE sequences and induce the expression of endogenous antioxidant enzymes such as SOD, PRX, GPX, and heme oxygenase-1 (HO-1) which help to control cell oxidation (Lim et al., 2014).

Although oxidative damage is often discussed separately from the inflammatory process, these two pathways are closely related. Increased levels of ROS can promote IκB phosphorylation and subsequent NF-κB translocation to the nucleus to activate the proinflammatory signaling pathways (Michalska & León, 2020). Therefore, a peptide that acts to prevent oxidation may also regulate inflammatory pathways. For instance, the round-scade-derived peptide, WCPFSRSF reduced ROS levels by stimulating not only the Nrf-2/ARE pathway but also as an anti-inflammatory effect (cytokine reduction) on glutamate-stimulated neuronal lineages (Zhang et al., 2021, 2022). The synthetized walnut peptides EVSGPGLSPN and WEKPPVSH were effective against neuronal and microglial toxicity, respectively, increasing antioxidant enzymes

and reducing cytokines inflammatory secretion through NFκB pathway (Liu et al., 2019; Zhao et al., 2021).

5. Food peptide mechanism of action on mitochondrial dysfunction and apoptosis

Food hydrolyzed peptides have shown protection on mitochondrial dysfunction under neurotoxic conditions. Mitochondria is responsible for generating about 90 % of the ROS present in cells through mitochondrial DNA oxidation and mutation, compromising its own functioning (Wang et al., 2019). In addition to the energetic function, mitochondria act as a buffering organelle controlling intracellular Ca^{2+} homeostasis and cell death. Under oxidative and inflammatory stimuli, mitochondria Ca^{2+} overload may increase permeability of the inner mitochondrial membrane leading to the release of certain mitochondrial apoptogenic factors (Bauer & Murphy, 2020; Kriete & Mayo, 2009). Peptides from different food origins were demonstrated to increase mitochondrial membrane potential (MMP) inhibiting cell death (Table 1).

The main inhibitory mechanism described for the action of food peptides in mitochondria mediated apoptosis is the regulation of the Bcl-2 family proteins. The Bcl-2 family is involved in promoting apoptotic signal (Bax, Bad, Bim, Bik, or Bcl-xs) while another group mediates anti-apoptotic effect (Bcl-2, Bcl-xL, Mcl-1, or A1) (Kim et al., 2010). The ratio between pro-apoptotic and anti-apoptotic protein regulates the cell fate towards survival or death and not the concentration of each factor. For example, an increased expression of anti-apoptotic signals, such as Bcl-2, followed by a reduction of pro-apoptotic signals, such as Bax, blocks the ER-Ca^{2+} release into mitochondria, preventing Ca^{2+} induced cell death. The opposite effect, an increased ratio of Bax/Bcl-2, promotes ER-Ca^{2+} release into the mitochondria, impairing MMP and releasing cytochrome *c*, a key mediator of apoptosis (Morris et al., 2021) (Fig. 1). Numerous food peptides have promoted a reduction of Bax/Bcl2 ratio, inhibiting cytochrome *c* mitochondria release, Apaf1 activation (apoptosis-protease activating factor 1) and the consequent apoptosome formation (Table 1). The downstream pathway may be also inhibited, decreasing caspase-9 and caspase 3 activation as well as other caspases that promote cell death. Therefore, natural compounds that decrease mitochondrial damage may be an important target for preventing neurodegenerative diseases (Fig. 2).

6. Peptide reaching the brain: role of neurons, astrocytes and microglia on inflammation and oxidative stress

Once food peptides reach the nervous system, they must be able to interact with cell receptors or be internalized in different brain cell types to mediate anti-inflammatory and/or antioxidant responses. The central nervous system is comprised of neuronal and glial cells (astrocytes, microglia, oligodendrocytes and endothelial cells) that interact with each other to keep brain functions in balance. Different from what was initially proposed, glial cells do not only play a role in neuronal support but also play an active role in maintaining synapses (Linnerbauer et al., 2020). Therefore, any brain cell dysfunction may be the key to the development of neurodegenerative diseases. In this section, we briefly discuss the role of brain cells (microglia, astrocytes and neurons) under inflammatory response related to some food peptide actions.

6.1. Microglia

Microglia are the main defense cells of the CNS and of primary importance to regulating inflammation. Under physiological conditions, microglia phenotype remains quiescent and releases anti-inflammatory neurotrophic factors to promote neuron growth and migration (Jeong et al., 2013). Up to a certain threshold, microglia activation helps to control inflammation through phagocytosis of damaged cell debris and secretion of protective cytokines such as IL-10 (M2 phenotype). After a chronic inflammatory stimulus (cellular debris, antigens, aging, etc.) however, these cells assume an activated state (M1 phenotype), which leads to morphologic and biochemical changes: increased soma size, retracted cytoplasmic processes and overexpressed inflammatory marker proteins like Iba-1 and CD11b (Jeong et al., 2013).

It is assumed that compounds that have the ability to inhibit microglial activation could, in theory, limit neuronal damage extension and improve brain functions (Muzio et al., 2021). In fact, a switch from inflammatory (M1) to anti-inflammatory (M2) genes phenotype was observed in microglial cells and in mice brain after the treatment with a peptide isolated from protein hydrolysates of *Lupinus angustifolius L.* (GPETAFLR) (Lemus-Conejo et al., 2022). The downregulation of microglia cytokine expression/secretion, such as IL-6, TNF-α and NO, has been shown after treatment with several bioactive peptides, confirming the capacity of peptide to modulate microglia plasticity and activity. (Table 1-microgia session) (Gao et al., 2021; Muzio et al., 2021).

6.2. Astrocytes

Astrocytes are the most abundant glial cells in the CNS. Astrocytes have a strategic position since they emit processes which are either in contact with endothelial vessel cells (contributing to the BBB permeability) or with synaptic terminals (taking important part on its modulation) (Vasile et al., 2017). Along with microglia, they are an important part of the innate immune response and inflammation. Inflammatory cytokines secreted by microglia play a key role in the activation of A1 astrocyte, a subtype highly present in several neurodegenerative diseases. Astrocyte reactive states can promote inflammation themselves, secreting cytokines, possibly causing the death of neurons and oligodendrocytes (Liddelow et al., 2017).

Astrocytes and neurons take an important role on BDNF and TrkB modulation (Fernández-García et al., 2020). The neurotrophin BDNF and its main receptor TrkB are associated with learning and memory processes, synaptic plasticity and neuronal survival. Dysregulation of BDNF/TrkB signaling has been implicated in multiple neurological and neurodevelopmental disorders (Zuccato & Cattaneo, 2009). Many *in vivo* studies have shown beneficial effects of food peptides on this pathway (Table 2). For example, oyster protein hydrolysates alleviate inflammation and cognitive deficits in mice and zebrafish models of intoxication, through the up-regulation of GFAP (astrocyte marker) and BDNF-TrkB signaling (Wang et al., 2018; Zhu et al., 2021). Therefore, some food-derived peptides may improve astrocytic function, promoting neurogenesis and differentiation.

Despite the importance of astrocytes in the regulation of inflammation, little is known regarding the action of food peptides on specific effects on these cells. To our knowledge, a study on soybean protein hydrolysate (SPH) has been the only one to evaluate the direct effect of food bioactive peptides on astrocytes culture cells over inflammation or oxidation. A SPH fraction of aromatic and positively charged peptides was able to increase the expression of BDNF, mediating neurotrophic effect in astrocytic cell culture (Shimizu et al., 2018).

6.3. Neurons

Neurons were the main CNS cells studied to evaluate bioactive peptides effect (Table 1). Neurons are excitatory cells that conduct and transmit electrical signals inducing motor, sensory and secretory functions (Brady et al., 2012). Neurodegenerative diseases are characterized by a progressive loss of particular subsets of neurons in the brain (Michalska, 2020). Food peptides have shown neuroprotective effects being able to prevent activation of oxidative, inflammatory and apoptotic pathways in neuronal cells (see Section 7).

Many animal models of neurodegeneration have been investigated regarding the capacity of food peptides to improve the neuronal cholinergic system. Acetylcholine (ACh) is the most important neurotransmitter related with memory formation, and its content regulation is made

Table 1
In vitro anti-inflammatory and antioxidants pathways modulated by food peptide in CNS.

Protein Source	Preparation method	Dose(mg/ml)	Injury Model/cell line	Peptide Activated Pathways	Manuscript
NEURONS					
Whey protein	Hydrolysates (pepsin and trypsin)	0.2	H_2O_2/PC12	↑antioxidants (SOD, CAT) ↓ oxid. stress (ROS, MDA) ↓ apoptosis (↑MMP, ↓ intracelular Ca^{2+}, Bax/Bcl-2, caspase 3)	(M. M. Jin et al., 2013)
	Hydrolysates (pepsin and trypsin)	0.1-0.2	H_2O_2/PC12	↑antioxidants (T-AOC, CAT, SOD), cell integrity ↓ lipid peroxidation (MDA)	(Q. X. Zhang et al., 2015)
Bovine meat	Hydrolysates (alcaline-AK and papain)	1.25	H_2O_2/SH-SY5Y	↑ antioxidants (SOD, CAT) ↓ROS, DNA fragmentation	(Lee & Hur, 2019a)
	TQKKVIFC (alkaline-AK)	0.25-0.5	H_2O_2/SH-SY5Y	↑Cell viability, ↓NO, DNA fragmentation, Apoptosis (↑MMP)	(Lee & Hur, 2019b)
Venison meat	Hydrolysate (enzyme not informed)	0.001 - 0.01	H_2O_2/PC12	↑ antioxidants (CAT, GST, GSH-Px), Cell viability ↓ ROS, MDA, NO, iNOS ↓ Apoptosis (Bax/Bcl-2 ratio, citocromo *c*, caspase 3)	(Kim et al., 2010)
Cervus valvet antler	VLSAT DKTNV LAAWG KVGGN APAFG AEALE RM (chemical extraction)	0.01 - 2	MPP^+/SH-SY5Y	↓ROS ↓Apoptosis (↑MMP, ↓Caspase-12 and p-JNK)	(Xin et al., 2017)
Pig brain	Hydrolysate (trypsin)	0.01- 0.05	Corticosterone /PC12	↑ antioxidants (SOD, GSH-Px, GSH), cell integrity ↓ROS, Apoptosis (Bax/Bcl-2, caspase 3) ↓ inflammation (TNF-α, IL-1β, NO, iNOS, PGE-2, COX-2 via NFκB)	(W. Jin et al., 2019)
Fish	FYY and DW of *Benthosema pterotum* (lanternfish) (Protease A and N, Protemex and Prozyme 6)	0.10 -5.0	H_2O_2/SH-SY5Y	↑ antioxidants (SOD, GSH-Px, CAT) ↓ ROS ↑ Cell viability	(Chai et al., 2013, 2016)
	Hydrolysate of *Decapterus maruadsi* (round scad) (protamex and pancreatin)	0–2.5	Glutamate/PC12	↑antioxidants (GSH-Px, SOD via Nrf2/ARE), ↑ Cell integrity ↓ MDA, Apoptosis via Bax/Bcl-2 ratio	(Q. Zhang et al., 2020)
	WCPFSRSF of *Decapterus maruadsi* (round scad) (Chemically synthesized)	0.05–0.5 mM	Glutamate/ SH-SY5Y	↑cell viability and cell integrity ↑antioxidants (SOD, GSH/GSSG, GSH-Px) ↓ROS, MDA ↓NF-kB ↑Nrf2/HO-1 pathways	(Q. Zhang et al., 2021)
	WCPFSRSF of *Decapterus maruadsi* (round scad) (Chemically synthesized)	0.05 - 0.2 mM	Glutamate/ c	↑cell viability and cell integrity ↓ inflammation (TNF-α, IL-1β, IL-6) ↑Akt/mTOR/EIF4E and CREB/TrkB/BDNF pathway	(Q. Zhang et al., 2022)
	PAYCS and CVGSY of *Coilia mystus* (Anchovy) (alcalase, papain and pancreatin)	0.5	Glutamate /PC12	↑ antioxidants (SOD, GSH-Px) ↓ROS, MDA ↑ Cell viability and integrity ↓Apoptosis (Bax/Bcl-2 ratio)	(T. Zhao et al., 2017)
Sea cucumber	YPIEHGIVTNWDDM*EK, IEELEEEIEAER, EYVEETTGDEYVSLK, YPIEHGIVTNWDDMEK (alcalase, a-chymotrypisin, neutrase, papain and trypsin)	0.002-0.05	Control/SH-SY5Y	↓ amyloidogenic pathway (β-secretase, Aβ peptide, sAPPβ) ↓ pJNK, p38 MAPK pathway	(Rathnayake et al., 2021)
	FETLMPLWGNK HEPFYGNEGALR, KMYPVPLN (Synthesized)	0.0005 - 0.5 mM	H_2O_2 or ABAP /SH-SY5Y	↑ antioxidant (GSH) ↓ROS, mitophagy ↑ Cell viability Colocalization of rhodamine B-labelled peptides and lysossome	(M. Lu et al., 2021)
	NDEELNK (Synthesized)	0.05- 0.8	Scopolamine/PC12	↑ antioxidant (SOD), cholinergic system (ACh) ↑ neurotrophin (BDNF and NGF via p-PKA) ↓ ROS, AChE activity Peptide and AChE interaction (molecular docking)	(Y. Zhao et al., 2021)
Shrimp	MTTNI and MTTNL (alcalase)	0.0005 - 1.0	Scopolamine/PC12	↑ antioxidant (SOD)↓ROS ↑Cell viability, pro-survival gene (BCL-XL) ↓Cell apoptosis (P13K, AKT, Bax, Caspase-3, p53)	(D. Wu et al., 2020)

(*continued on next page*)

Table 1 (*continued*)

Protein Source	Preparation method	Dose(mg/ml)	Injury Model/cell line	Peptide Activated Pathways	Manuscript
Sea horse	GTEDELDK (trypsin, a-chymotrypsin, papain and pronase E)	0.01 - 0.1	Ab_{1-42}/PC12	↑Cell viability, pro-survival gene (Bcl-2)	(Pangestuti et al., 2013)
Royal Jelly	Hydrolysate (alcalase, flavourzyme and protamex)	0.1 - 1	H_2O_2 or Glutamate /SH-SY5Y	↑ Cell viability	(Sirinupong et al., 2021)
Silk fibroin	Hydrolysate (alcaline, protease and glucoamylase)	0.1	Ab_{25-35}/SH-SY5Y	↑Cell viability, ↓ROS, p-PP2A, MAPKs, Apoptosis (↑MMP) ↓tau hyperphosphorylation	(Zheng Xu et al., 2018)
Soybean	Hydrolysates (WPK and AYLH) (alcalase and flavorzyme)	0.05 -0.8 mM	H_2O_2/PC12	↑ Cell viability ↓ROS	(Amakye et al., 2021)
Maize	LDYE - anchored gold nanoparticles (synthesized)	0.125-0.75 nM	Glutamate /PC12	↓ ROS	(J. Zhang et al., 2021)
Wheat germ	Hydrolysate (alcalase)	0.25 - 1.00	H_2O_2/PC12	↑antioxidants (SOD, CAT), ↓MDA ↑ Cell integrity ↓Apoptosis (↓intracellular Ca^{2+}, ↑MMP)	(Zhu et al., 2013)
Rice	Hydrolysates enriched with selenium (alcalase, neutrase, trypsin and pepsin)	0,00025 – 0,004	Pb^{2+}/HT22	↑ antioxidants (SOD, GSH-Px) ↑Nrf-2/HO-1 ↑ Cell viability and integrity ↓Apoptosis, NO	(J. Wu, Li, et al., 2020)
	Hydrolysates enriched with selenium (a-amylase glucoamylase and trypsin)	0.1	$Pb^{2+/}$PC12 and RAW264	↓Apoptosis (Caspase-3, 8, 9, Bax/Bcl-2 ratio)	(Fang et al., 2017)
	Hydrolysates enriched with selenium (a-amylase and glucoamylase)	0.02–0.16	Pb2+/ PC12 and RAW264.7	↑antioxidants (SOD, GSH-Px) ↓ROS, MDA, NO ↑ Cell viability and integrity	(Zi Xu et al., 2016)
Walnut	WSREEQEREE and ADIYTEEAGR (pancreatin)	0.10 - 0.50	H_2O_2/PC12	↓ ROS, Apoptosis	(Chen et al., 2015)
	Hydrolysates (pancreatin)	0.10 - 1.00	H_2O_2/PC12	↑ Cell viability	(Gu et al., 2015)
	EVSGPGLSPN (synthesized)	0.0125 - 0.1mM	H_2O_2/PC12	↑ antioxidants (SOD, CAT, GSH-Px) ↓ROS ↑ Cell viability ↓Apoptosis (Caspase-3, 9, cytochrome *c*, PARP) ↓inflammation (IL-1β, TNF-α via NF-kB)	(Liu et al., 2019)
	Hydrolysates (hydrolase and pancreatin)	0.10 mM	Glutamate/PC12	↑ antioxidants (SOD, GSH-Px) ↓ ROS, MDA ↑ Cell viability and integrity ↓ Apoptosis (↑MPP, ↓ intracellular Ca^{2+} and Bax/Bcl-2)	(Wang et al., 2018)
	TWLPLPR, YVLLPSPK, and KVPPLLY (synthesized)	0.05 - 0.2 mM	Ab_{25-35}/PC12	↑ antioxidants (SOD, GSH-Px, ATP) ↓ ROS ↑ Autophagy (Akt/mTOR, LC3-II/LC3-I and Beclin-1)	(F. Zhao et al., 2020)
	YVLLPSPK (synthesized)	0.1 mM	H_2O_2/HT22	↑ NRF2/KEAP1/HO-1, mitophagy-associated proteins (These effects were inhibited by NRF2 inhibitor (ML385)	(F. Zhao et al., 2021)
	WSREEQ, WSREEQE, WSREEQEREE, ADIYTE, ADIYTEEAG and ADIYTEEAGR (Chemically synthesized)	0.10 mM	Glutamate/PC12	↑Cell viability and integrity ↑ antioxidants (SOD, GSH-Px) ↓ROS, MDA ↓Apoptosis (↓intracellular Ca^{2+} and Bax/Bcl-2, ↑MMP,)	(Wang et al., 2022)
	TWLPLPR (synthesized)	0.025 - 0.2 mM	H_2O_2/HT22	↑Cell viability ↑ antioxidants (SOD, GSH-Px, CAT) ↓ROS, MDA ↑ mitochondrial integrity (mPTP, MMP) ↑ Mitophagy (↑PINK,↓JNK, Cyt -C, Caspase 9 and 3)	(Yang et al., 2022)
Hempseed	Hydrolysates (alcalase)	0.001 - 0.1	H_2O_2/PC12	↑Cell viability ↓Apoptosis	(R. R. Lu et al., 2010)
Peanut	Hydrolysate (protease)	0.01 - 1	H_2O_2/PC12	↑Cell viability	(Zheng et al., 2012)
Mushroom	Hydrolysates of *Pleurotus geesteranus* (alcalase, papain, flavourzyme, pepsin and pancreatin)	0.005 - 0.045	H_2O_2/PC12	↑antioxidants (SOD, GSH-Px) ↓ROS	(Liao et al., 2020)

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Table 1 (*continued*)

Protein Source	Preparation method	Dose(mg/ml)	Injury Model/cell line	Peptide Activated Pathways	Manuscript
MICROGLIA					
Protein Source	**Peptide**		**Injury Model**	**Activated Pathways**	**DOI**
Whey	Whey metal-binding peptides (alcalase and isolation of metal-binding peptides)	0.1 and 1	LPS/BV-2	↓inflammation (TNF-α, NO) ↓ NF-κB downregulation	(Caetano-Silva et al., 2021)
Milk (casein)	WY, WM (synthesized)	0,025-0,25 mM	LPS/BV-2	↓ inflammation (TNF-α) ↑ Phagocytosis of Aß	(Ano et al., 2019)
	Hydrolysates (bromelain)	0,01-0,1	LPS/BV-2	↓PGE2, COX-2 via NF-κB and ERK/ JNK/ p38 MAPK pathways	(Hou et al., 2006)
Fish	DPALATEPDPMPF (alcalase, Pronase E, pepsin, and trypsin)	0.005,0.01,0.02, 0.2,0.5,1 and 2	H_20_2/BV-2	↓ROS	(Vo et al., 2011)
	Hydrolysates containing n-3 LC-PFA	0.27	LPS/BV-2/ HT22	↑ BDNF, NGF	(Chataigner et al., 2021)
Frog	WYFITPYIPDK (synthesized)	0.0125 - 0.4	Hypoxia/CHME3	↓ROS	(Barbosa et al., 2018)
Walnut	LPF, GVYY, and APTLW (Viscozyme L and pancreatin)	0.10 mM	LPS/BV-2	↓ inflammation (TNF-α) ↓ PGE2 via COX-2 ↓ NO via iNOS	(Wang et al., 2020)
	WEKPPVSH (neutrase and alcalase)	12.5 - 200 mM	LPS/BV-2	↑ antioxidants (SOD, CAT via Nrf2/HO-1) ↓ ROS ↓ inflammation (NO, iNOS, TNF-α, IL-1β, IL-6, COX-2 ↓ NF-κB/p38 MAPK pathway	(Gao et al., 2021)
Lupinus angustifolius L.	GPETAFLR (synthesized)	0.01-0.5	LPS/BV-2	↓Microglia M1/M2 ↓ inflammation (TNF-α, IL-6 and IL-ß) ↑ anti-inflammation (IL-10)	(Lemus-Conejo et al., 2022)
Fungus *Alternaria sp*	Alternaramide (synthesized)	0.005 - 0.04 mM	LPS/BV-2	↓NO via iNOS, PGE2 via COX-2 ↓Expression of TLR-4 and MyD88 ↓ inflammation (TNF-α, IL-1ß, IL-6 and IL-12 via NF-κB/MAPK	(Ko et al., 2016)
ASTROCYTES					
Soybean	SPH mixture of dipeptides and tripeptides derived of soybean (synthesized)	0.5 and 1	Control/Primary Astrocyte culture	↑ neurotrophin (proBDNF and mBDNF) ↑CREB phosphorylation	(Shimizu et al., 2018)

by acetylcholinesterase (AChE), an enzyme responsible for the breakdown of ACh. According to the cholinergic hypothesis, an increase in AChE activity and the consequent reduction of the ACh content is associated with many neurodegenerative diseases (Tata et al., 2014). In fact, peptides with AChE inhibition capacity in neuronal cells were effective on improving memory and learning functions in *in vivo* animal model (Table 2). The specific sequence derived from sea cucumber peptide NDEELNK was able to positively modulate ACh levels in PC12. The authors confirmed by molecular docking studies that NDEELNK backbone and AChE interacted through hydrophobic and hydrogen bonds in contact with the amino acid residues of the cavity wall (Zhao et al., 2021).

7. Antioxidative and anti-inflammatory action of food peptides in brain

In this section, we will present the latest studies on food peptides bioactivity in the central nervous system. The section is separated *in vitro* studies conducted in brain cells from *in vivo* studies conducted in animal models of neurodegeneration. We focused on studies that evaluated potential signaling pathways inhibited or activated by animal or plant derived peptides in inflammatory or oxidative stimulus. A summary of the results is presented in Tables 1 and 2.

7.1. In vitro *brain peptide bioactivity*

Cell culture is a valuable biological system to evaluate the protective effect of food peptide hydrolysates against inflammatory and antioxidant stressors. The use of brain cells in culture represents an important technique to study the underlying mechanisms of natural compounds considering specific characteristics of the cells, including receptors and intracellular pathways activation. In addition, it is faster and more economical than *in vivo* studies. With cell culture, it is possible to study intrinsic characteristics of each cell under various stressors and simulate model systems for a specific disease, as well as it is a good screening to evaluate peptide concentration toxicity (Niki, 2010).

Table 1 presents a summary of the main studies carried out with neurons, microglia and astrocytes cell culture focusing the underlying anti-inflammatory and antioxidant mechanism of action mediated by food hydrolysates peptides of several sources. The results are organized by cell type and food protein source. Several injury models have been used for the evaluation of inflammatory and oxidative pathways, such as H_2O_2, glutamate, LPS and scopolamine. Table 1 highlights the main activated pathways modulated by food peptide as a protector route against stimulus. It is possible to observe that despite the inflammatory response being mainly led by microglial cells and astrocytes, most studies on cultured cells have been carried out with neuronal lineages. Peptides generated by hydrolysis have been studied mainly as antioxidant actions on neurons and anti-inflammatory effects on microglia. Only one study has been conducted on astroglia cells.

7.1.1. In vitro effect of bioactive peptide derived from animal sources

The bioactivity of peptides derived from milk or whey has received great attention in recent years (Power et al., 2013). Regarding its effect in the CNS, some studies show antioxidant activity on neurons and anti-inflammatory effect on microglia. Whey protein hydrolysate (WPH) exerted oxidative protection on neuronal PC12 cells by suppressing ROS elevation and lipid peroxidation, and increasing antioxidant enzymes, including SOD and CAT (Zhang et al., 2015). One of the mechanisms by which WPH exerts its protective effect against oxidative stress is by reg-

Table 2
In vivo anti-inflammatory and antioxidants pathways modulated by food peptide in CNS.

Protein Source	Preparation method	Injury Model	Peptide administration	Peptide activated Pathways	Reference
Milk (casein)	Hydrolysates (Bioprase, pepsin and trypsin)	Ab_{1-42}	Oral, 23 days (0.5 mg/kg mice)	↑ Memory and learning ↓inflammation (TNF-α, IL-6, MCP-1, iNOS, eNOS, $p47^{phox}$ and $gp91^{phox}$, ACE)	(Min et al., 2017)
	Synthesized (WY)	LPS/aged mice	Oral, 14 days, in mice (10 mg/kg mice)	↑ Memory and learning ↑ dendritic spines ↓ inflammation (MIP-1α, IL-1β, and TNF-α)	(Ano et al., 2019)
Porcine	Hydrolysates (Protease and pepsin)	Scopolamine	Oral, 35 days, (105 mg/kg mice)	↑ Memory and learning Improve cholinergic system (↓AChE activity) ↓excitotoxicity (Glu/GABA ratio) ↑antioxidants (SOD, Na^+-K^+-ATPase) ↓MDA	(An et al., 2016)
	Hydrolysates (Alcalase)	Pb^{2+}	Oral, 21 days, (10 and 200 mg/kg mice)	↑ Memory and learning ↑ antioxidants (GSH, GSH-Px, CAT, SOD) ↓ ROS, MDA	(Zou et al., 2015)
Fish	Synthesized (Hydrolysates containing n-3 LC-PFA)	LPS	Oral, 18 days, (150 mg/ mice)	↓inflammation (IL-6, IL-1 and TNF-α, CCL2, COX-2) ↑ IκB (NF-κB inhibitor) ↑ microglial activation: CD68, CD11b, CD86	(Mathilde Chataigner et al., 2021a)
	Synthesized (Hydrolysates containing n-3 LC-PFA)	Aged mice (18 month)	Oral, 77 days, (280 µg/day mice)	↑ short-term memory, spatial learning and long-term memory ↓ anxiety-like behaviour ↓microglia activation (Iba-1, CD11b)	(Chataigner et al., 2021b)
	Hydrolysates (Protease N)	D-galactose	Oral, 84 days, (500,2500,5000 mg/kg mice)	↑ Memory and learning ↓ ROS, TBARS, eNOS ↑ G6PDH, BDNF	(Chai et al., 2016)
	Hydrolysates (Protamex and pancreatin)	Sleep deprivation	Oral, 20 days, (333 and 666 mg/kg rats)	↑ Memory and learning ↑ antioxidants (SOD, CAT, GPx, GSH/GSSG via p-AKT/Nrf-2/HO-1 pathway) ↑ CREB/BDNF/TrkB Cholinergic system (↑Ach, AchR ↓ AchE)	(Zhang et al., 2019)
	Hydrolysates (pancreatin)	scopolamine	Oral, 20 days, (0.2 mmol/Kg mice)	↑ Memory and learning ↑ antioxidants (SOD) ↑Cholinergic system (Ach, AchR) ↑ Nrf-2/ARE and CREB/BDNF	(Zhao et al., 2019)
	Hydrolysates (trypsin, papain and alkaline proteinase)	Aged C57BL/6 mice	Oral, (0.22, 0.44 or 1.32% wt/wt mice)	↑ Memory and learning ↑ antioxidants (SOD, GSH-px), ↓ TBARS ↑ neurotrophic pathways (BDNF, PSD95)	(Pei et al., 2010)
Shrimp	Synthesized (QMDDQ, KMDDQ)	scopolamine	Oral, 47 days (30 mg/kg mice)	↑ Memory and learning ↑ neurotrophic pathways (PKA/CREB/BNDF) Cholinergic system (↑Ach ↓ AchE)	(Wu et al., 2020)
Sea cucumber	Hydrolysate (protamex)	D-galactose	Oral, 56 days, (200,500 and 1000 mg/kg mice)	↑ Memory and learning of aging mice ↑ antioxidants (SOD, GPx) ↓lipid and protein oxidation Cholinergic system (↓AChE) Prolonged the lifespan of fruit flies	(Lin et al., 2018)
	Synthesized (FYDWPK)	scopolamine	Oral, 35 days, (0,3;0,6 and 1.2 mg/day/mouse)	↑ Memory and learning ↑Cholinergic system (↑Ach, ↓AchE) ↑antioxidants (SOD ↓MDA) ↓ neuronal loss, blurred caryotheca, and pyknotic nuclei	(Zhao et al., 2022)
Oyster (*Crassostrea hongkongensis*)	Hydrolysate (Neutral protease)	Aged zebrafish (18 month)	Oral, 30 days, (1.5 g/kg zebrafish)	↑ Memory and learning in zebrafish ↑ antioxidants (SOD, CAT) ↓lipid peroxidation ↓ inflammation (IL-1β, TNF-α and CD11b) ↑ neurotrophic pathways (BDNF-TrkB, GFAP and psd-95)	(Zhu et al., 2021)
	Hydrolysates (Compound proteinase, trypsin, papain, neutrase and favourzyme))	Huperzine	Oral, 45 days, (150,500 and 1500 mg/kg mice)	↑Spacial memory and learning ↑ antioxidants (SOD, CAT) Cholinergic system (↑ChAT ↓ AchE) ↓ inflammation (IL-1 β, IL-6, TNF-α) ↑ neurotrophic pathways (BDNF and NCAM)	(Wang et al., 2018)

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Table 2 (*continued*)

Protein Source	Preparation method	Injury Model	Peptide administration	Peptide activated Pathways	Reference
Neptunea arthritica cumingii (marine snail)	Synthesized (YIAEDAER)	MPTP	Zebrafish, (2 μg/mL, 10 μg/mL, and 50 μg/mL)	↓ locomotor impairment ↑DA neurons, vasculature and loss of cerebral vessels ↑ autophagy (*α-syn, pink1, parkin, atg5, atg7, beclin1, ulk1b, ulk2, and ambra1a*) oxidative stress (*sod1, sod2, gss, gpx4a, gsto2, and cat)*	(Ren et al., 2022)
Soy	Mixture Peptide (di- and tripeptides)	SAMP8 and SAMR1 mice	Oral, 182 days, (70 g/Kg mice)	↑cognitive abilities ↑ neurotrophic pathways (NGF, BDNF, NT-3, SIRT1 CREB/ERK1/2)	(Katayama et al., 2014)
	Peptides synthesized (KGRKG, KGRK, GRKG, KRG, KGR, GRK, RKG, KG, GR, and RK)	Basal	Intraperitoneal administration, 14 days, (15 mg/kg 100 mg/kg mice)	↑ neurotrophic pathways (proBDNF and mBDNF cerebral cortex and number of neurons in hippocampus and cerebral cortex)	(Shimizu et al., 2018)
Maize	Maize tetrapeptide anchored gold nanoparticle	D-galactose/ $AlCl_3$	Oral, 16 days, 0,5;0,7; 1 mg/kg mice	↑ Memory and learning Cholinergic system (↑Ach, ChaT ↓ AchE) ↑ antioxidants (SOD and GSH-Px in sera and hypothalamic, via Nrf-2/Keap/HO-1 pathway)	(Zhang et al., 2021)
Rice	Fermented	scopolamine	Intraperitoneal administration, 7 days, (25 and 100 mg/ Kg mice)	↑ Memory and learning Cholinergic system (↑Ach, AchR ↓ AchE) ↑ neurotrophic pathways (ERK/CREB/BDNF) ↑ antioxidants (SOD) serum levels ↓ MDA and NO serum levels	(Corpuz et al., 2019)
Walnut	te (Protease and alkaline protease)	Scopolamine	Oral, 30 days, (400 mg/kg mice)	↑ Memory and learning Pharmacokinetic Parameters of P1 and P2 Combined treatments (walnut + polyphenols) were more effective than either subject alone	(Sheng et al., 2020)
	Ácid Hydrolysis	D-galactose/ $AlCl_3$	Oral, 90 days, (1 g/kg mice)	↑ Memory and learning ↑ antioxidants (SOD, GSH-Px) ↓ MDA Cholinergic system (↑Ach, ChAT, ↓ AchE) ↓ inflammation (IL-1 β, TNF- α)	(Feng et al., 2018)
	Peptides (not informed)	$A\beta_{25\text{-}35}$	Oral, 35 days, (200, 400 and 800 mg/kg mice)	↑ Memory and learning ↑ antioxidants (SOD, GSH) ↓ MDA, AchE ↓ inflammation (IL-1 β, IL-6,TNF- α, 8-OHdG, NO via iNOS ↓NF-κB	(Zou et al., 2016)
	Hydrolysate (Neutrase and Alcalase)	Scopolamine	Oral, 30 days, (200,400,800 mg/Kg mice)	↑ Memory and learning ↑ antioxidants (SOD, GSH-Px) ↓MDA Cholinergic system (↑Ach, ChAT, ↓ AchE) ↑ Monoamines neurotransmitters (5-HT, DA, and NE via CaMK II)	(Ren et al., 2018)
	Hydrolysate (complex plant hydrolyze and pancreatin)	sleep deprivation	Oral, 20 days, (666 mg/kg rats)	↑ Memory and learning ↑ antioxidants (SOD, CAT, GSH, GSH-px, GSH/GSSG) ↓MDA	(Wang et al., 2018)
	Hydrolysate (Viscozyme L and pancreatin)	LPS	Oral, 21 days, (666 mg/kg mice)	↑ Memory and learning ↑ antioxidants (SOD, GSH-Px, CAT) ↓ MDA ↓ inflammation (IL-1 β, IL-6, TNF- α, PGE2)	(Wang et al., 2020)
	Hydrolysate (neutrase, papain, bromelain, alcalase, pepsin, and pancreatin)	mycophenolate mofetil (zebrafish), scopolamine (mice)	Oral, 24 h, (222, 667, 2000 μg/mL zebrafish) Oral, 7 days (30,100,300 mg/kg mice)	↑ GSH ↑BDNF ↓GDNF ↓ apoptosis (bcl2 , caspase 3/7/8 in zebrafish) ↑ Memory and learning in mice	(Liu et al., 2019)
	Synthesized (YVLLPSPK)	scopolamine	Oral, 28 days (60 mg/kg mice)	↑ Memory and learning ↓ DNA and protein oxidation, lipid peroxidation, DNA fragmentation, mitochondria damaged ↑ ATP levels, mitophagy, PINK1, Nrf-2/Keap-1/HO-1	(Zhao et al., 2021)

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Table 2 (*continued*)

Protein Source	Preparation method	Injury Model	Peptide administration	Peptide activated Pathways	Reference
Cashew-nut	Hydrolysate (alcalase)	cerebral ischemic rats	Oral, 14 days, 2, 10, and 50 mg/kg rats	↑ improvement of spatial memory ↓ brain infarction in cortex, hippocampus, and striatum ↑ antioxidants (SOD, CAT, GSH-px) ↓ MDA ↓ serum C-reactive protein ↓ serum cholesterol, TG, and LDL ↑ HDL	(Wattanathorn et al., 2017)
Ginseng	Protein Extraction	D-galactose/ $AlCl_3$	Oral, 30 days, (twice daily 0.1g/kg rats)	↑ Memory and learning ↓$A\beta_{1\text{-}42}$ and p-tau ↑ Bcl-2/Bax, PI3K/Akt pathway in hippocampus	(Li et al., 2016)
Cardamine violifolia	Hydrolysate (Protease Alkaline)	D-galactose	Oral, 56 days, (3.55; 14.2 and 56.8 mg/kg.bw rats)	↑ Memory and learning ↓ dysglycemia, dyslipidemia, and hepatic dysfunction ↓ neuronal loss, AchE activity ↑ antioxidants (SOD, GSH-Px, CAT, TAOC) ↓ ROS, MDA ↑ Nrf-2/HO-1 ↓inflammation (IL-6, TNFα via NF-κB)	(Yu et al., 2020)
Cordyceps militaris	Hydrolysate (Pepsin and pancreatin)	LPS	Oral, 28 days (30 and 10 mg/kg/mice)	↑ antioxidants (SOD, CAT,↓MDA) ↓inflammation (IL-β, IL-10, TNFα) ↑gut microbiota	(Wu et al., 2022)

ulating mitochondrial signaling, reducing Ca^{2+} levels, stabilizing MMP and increasing the expression of anti-apoptotic Bcl-2 (Fig. 2)(Jin et al., 2013).

On microglial cells, the observed effect was regarding anti-inflammatory action of whey metal-binding peptides in BV-2 and primary microglial cells. Copper binding peptide (Cu-bp) reduced NO production and TNF-α expression in LPS stimulated cells (Caetano-Silva et al., 2021). A reduction of COX-2 activity and its main product prostaglandin E2 (PGE_2) was also reduced by casein hydrolysates via downregulation of NFκB and ERK/ JNK/ p38 MAPK pathways (Fig. 1) (Hou et al., 2006). Microglia activation was specifically prevented by dipeptide tryptophan-tyrosine (WY) and tryptophan-methionine from digested milk protein increasing amyloid-β phagocytosis by these cells (Ano et al., 2019). Hydrophobicity of whey peptides was associated with the antioxidant and anti-inflammatory ability observed in neuronal and microglia cells (Caetano-Silva et al., 2021; Zhang et al., 2015). Interestingly, specific sequences identified in whey Cu-bp (KIPAVF, KVLVL, FNPT) showed high affinity to bind NFκB p65 by molecular docking studies, suggesting that the bioactive peptide may exert a direct effect by interacting with important inflammatory pathways (Caetano-Silva et al., 2021).

Peptides derived from animal meat have shown bioactive effects on neuronal cells mainly by preventing oxidation. Low fraction of beef protein hydrolysate reduced DNA fragmentation and ROS production, increasing SOD and CAT levels in H_2O_2 treated SH-SY5Y neuronal cells (Lee & Hur, 2019a, 2019b). Polypeptide from venison hydrolysis and velvet antler polypeptides (VAPs) prevented oxidative stress and cell death by downregulation of Bax/Bcl-2 ratio and suppressed the release of apoptosis inducing factors, such as cytochrome *c* and caspase 12 (Kim et al., 2010; Xin et al., 2017). An anti-inflammatory effect was observed with pig brain hydrolysate (PBH) which induced a reduction in cytokines expression by a downregulation of NF-κB signaling in PC12 stimulated neuronal cells. PBH also prevented NO and PGE2 production through a reduction of its respective enzymes iNOS and COX2 (Jin et al., 2019). The studies with beef and pig hydrolysates showed that smaller fraction (< 3 kDa and 5-10 KDa, respectively) and greater amount of hydrophobic amino acids presented better protective activity, probably due increased lipo-solubility and permeability in cell membrane and interaction with target molecules (Jin et al., 2019; Lee & Hur, 2019a).

Fish hydrolysates presented important effects on oxidative neuroprotection (Chai et al., 2013, 2016; Vo et al., 2011). Hydrolysate of lantern fish containing FYY and DW peptide, activated the intracellular antioxidant defense system in H_2O_2 treated neuroblastoma SH-SY5Y cell line (Chai et al., 2013, 2016). The activation of Nrf2-mediated oxidative stress response was observed in PC12 cells against glutamate excitotoxicity after treatment with round scad (WCPFSRSF) and anchovy (PAYCS and CVGSY) peptides (Fig. 2) (Zhang et al., 2020, 2021; Zhao et al., 2017). Interestingly, Tyr- and Trp-containing peptides were associated with an antioxidant potential, and molecular docking studies indicate that these peptides might directly bind to Keap1 to modulate Nrf2 pathway (Zhang et al., 2020). Recently, it has been shown that round scad peptide (WCPFSRSF) ameliorates excitotoxicity, activating neurotrophic pathways such as Akt/mTOR/EIF4E and CREB/TrkB/BDNF (Zhang et al., 2022).

Bioactive peptides from sea cucumber hydrolysates showed promising therapeutic effects on preventing neurodegeneration. Sea cucumbers are echinoderms traditionally used in China as a food supplement. Under oxidative stress, three synthetic peptides from cucumber hydrolysates (FETLMPLWGNK, HEPFYGNEGALR, KMYPVPLN) were able to compensate for glutathione depletion, decrease mitochondrial superoxide levels and alleviate mitophagy in human neuroblastoma cells (Lu et al., 2021). The colocalization of these peptides with lysosome markers suggest that they might be internalized into the endocytosis route. Another cucumber peptide, EELEEEIEAER, inhibited the amyloidogenic pathway via inhibition of MAPk signaling in SH-SY5Y neuronal cells (Rathnayake et al., 2021). The amyloidogenic route is considered the main hypothesis for the development of AD.

Shrimp-derived peptides (QMDDQ and KMDDQ) have demonstrated neuroprotective ability by activating the anti-apoptosis and PKA/CREB/BNDF signaling pathway (Wu, Wu, et al., 2020). Special conformation and charge of peptides played an important role on bioactivity, since QMDDQ sequence presents a superior effect than KMDDQ (change of lysine to glutamine). The authors suggested that this was probably due to a wider spatial conformation, which allows better interactions with membranes and receptors and more stability due to its neutral charged N-terminal glutamine (Wu, Wu, et al., 2020).

7.1.2. In vitro effect of bioactive peptide derived from plant sources

Several sources of plant-based peptides were shown to have bioactivity in brain cells. Hydrolysates from cereal grains such as the maize tetrapeptide anchored gold nanoparticles (LDYE) and wheat germ presented antioxidant effect on PC12 cells by reducing intracellular ROS accumulation and lipid peroxidation, and increasing antioxidant enzymes and neuronal differentiation (Zhang et al., 2021; Zhu et al., 2013). Mitochondria mediated apoptosis in PC12 cells was prevented by rice protein hydrolysates enriched with selenium (SePHR). Two sequences (TSeMMM and SeMDPGQQ) mediated neuroprotection through Nrf2/HO-1 signaling (Wu, Wu, et al., 2020). Selenium is an essential micronutrient, a component of glutathione peroxidase and important for balancing the redox system (Fang et al., 2017; Xu et al., 2016). These studies show that in addition to the natural physiological properties of peptides as electron/hydrogen donor, they are excellent chelators and can be combined with compounds to increase their bioavailability and biological effects.

Walnut hydrolysates have been extensively studied in the mediation of protective effect against oxidative and inflammatory stress in neuronal and microglial cells (Chen et al., 2015; Gu et al., 2015; Liu et al., 2019; Wang et al., 2018). Numerous sequences have been identified (EVSGPGLSPN, YVLLPSPK, WEKPPVSH, LPF, GVYY and APTLW) as able to induce cytokine downregulation (TNFα, IL-1β, IL-6) in neurons and microglial cells, via inhibition of inflammatory route (NF-κB/p38 MAPK) and activation of protective pathway (Nrf2/HO-1) (Gao et al., 2021; Liu et al., 2019; Wang et al., 2020; Zhao et al., 2021). In agreement, molecular docking studies revealed that two walnut peptides (WSREEQEREE and ADIYTEEAGR) have strong interaction with Keap1, the main Nrf-2 inhibitor. In comparison with other peptides, arginine seemed to be decisive for this neuroprotective effect (Wang et al., 2022). However, long peptides must not resist digestive enzymes, indicating that encapsulation may be required to maintain bioactivity in the target tissue.

Shorter walnut peptides (LPF, GVYY, and APTLW) more prone to resist digestion have attenuated leakage of inflammatory mediators, including NO and PGE2, followed by a decrease on its respective enzyme expression, iNOS and COX-2 in LPS stimulated microglia cell line (Wang, 2020; Gao, 2021). The anti-inflammatory activity has been attributed to hydrophobic amino acids content, such as Leu (L), Pro (P), Val (V), Ala (A) and aromatic amino acids Phe (F), Tyr (Y), and Trp (W) (Wang et al., 2020).

7.2. In vivo peptide brain bioactivity

In vivo studies of food peptides allow us to evaluate the systemic effects of the compound, and especially whether they are able to resist gastrointestinal digestion through oral administration and induce effects on the CNS. It is important to mention that *in vivo* tests with bioactive peptides administered orally do not always assess the direct impact of the peptide on the CNS. Part of their effects may be mediated by post-digestion metabolites or even by the effects of secondary products. Therefore, the response observed after food peptide administration *in vivo* may be a consequence of either its direct effect and/or its bioproducts effect in the target tissue.

Most *in vivo* studies have evaluated the antioxidant and anti-inflammatory activity of peptides in human neurodegenerative disease models. These models mostly generate inflammation, oxidation, neurotransmitter imbalance and memory impairment. The most used models to study peptide bioactivity in the brain are those that simulate age progression and dementia, such as AD with scopolamine hydrobromide, A$\beta_{1\pm42}$, LPS and glutamate toxicity (Table 2). In this section, we will highlight the changes observed after food peptide administration in relation to the progression of inflammation and oxidation as well as the involved signaling pathways.

7.2.1. In vivo brain bioactive peptide from animal proteins

Similar to *in vitro* studies, milk-derived peptides have shown anti-inflammatory effects in different models of dementia when administered orally in rats, including LPS, aging brain and A$\beta_{1\text{-}42}$ toxicity (Table 2). The milk peptide containing methionine-lysine-proline (MKP) and the dipeptide tryptophan-tyrosine (WY) reduced cytokine content in the brain, changes that were followed by memory improvement in rats (Ano et al., 2019; Min et al., 2017). Additionally, WY peptide administration prevented dendritic atrophy of pyramidal neurons in the hippocampus of LPS treated rats (Ano et al., 2019). In fact, a reduction of neuron branches is related with less synapses and memory impairment. The same peptide prevented A$\beta_{1\text{-}42}$ accumulation in aging rats, and microglia played an essential role in the absorption of this agent (Ano et al., 2019). Remarkably, the radioactivity label of WY and MKP peptides were detected in several brain areas after oral administration, which indicates that the peptide or its metabolites penetrated the brain and directly affected cognitive functions (Ano et al., 2019; Min et al., 2017). These data corroborate clinical studies that evaluated fermented milk drink containing NIPPLTQTPVVVPPFLQPE peptide sequence, supplemented for 8 weeks. The healthy middle-aged adults treated with the test drink presented higher attention scores and less delayed memory than the placebo group (Ohsawa et al., 2018).

Porcine cerebral hydrolysate peptides (PCHPs) have been shown to improve learning and memory functions after Pb^{2+} and scopolamine neurotoxicity (An et al., 2016; Zou et al., 2015). This effect was accompanied by biochemical changes regarding antioxidant recovery factors, including SOD, CAT and GSH levels and neurotransmitter balance. PCHPs decreased AChE activity and glutamate/GABA ratio levels in the hippocampus of treated mice. These results reinforce that food peptides may be important players on memory modulation by improving function of cholinergic neurons and balancing excitation and inhibition neurotransmitters in the CNS (Holzgrabe et al., 2007).

The oral administration of fish hydrolysates were able to prevent memory deficits and anxiety-like behaviors in various neurodegenerative models in mice and rats (Chai et al., 2016; Zhang et al., 2019; Zhao et al., 2019). Similar to *in vitro* results, the main mechanisms associated with memory improvement were the reestablishment of Nrf-2/antioxidant enzymes and activation of the cholinergic system. The presence of positively charged amino acids were associated with the inhibitory effect of AchE activity via the formation of a stable complex with the peripheral anionic site of AChE (Zhang et al., 2019). The reestablishment of neurotrophic pathways in the hippocampus of rodents through CREB/BDNF activation were also associated with fish peptide action. Therefore, in addition to neurotransmission reestablishments, fish peptides may promote pro-survival neurotrophins, which are important mediators of neuronal vitality and major player underlying learning and memory (Chai et al., 2016; Pei et al., 2010; Zhang et al., 2019; Zhao et al., 2019).

Similar to the effects observed *in vitro,* shrimp and sea-cucumber derived peptides prevented oxidation and cholinergic dysfunction when administered orally in mice. In addition to these effects, the shrimp-derived peptides QMDDQ and the sea cucumber peptide FYDWPK improved the performance of mice in the Morris water maze memory experiment (Lin et al., 2018; Wu, Wu, et al., 2020; Zhao et al., 2022). (Lin et al., 2018).

7.2.2. In vivo brain bioactive peptide from plant proteins

Soybean protein hydrolysate (SPH) diet and fermented rice peptides prevented memory impairment in mice models of dementia. This effect was dependent on the induction of neurotrophic factors such as BDNF, NGF and NT-3 via activation of the transcription factor CREB (Katayama et al., 2014; Shimizu et al., 2018). (Corpuz et al., 2019). The reestablishment of the cholinergic system and decline of oxidative stress were also considered fundamental for cognitive improvements in mice models of neurodegeneration after rice peptide and maize

tetrapeptide anchored microparticles administration. (Corpuz et al., 2019; Zhang et al., 2021).

The protein content and its derivative peptides from *Juglans regia* walnuts have been extensively studied and proven to have diverse *in vitro* and *in vivo* effects in an animal model of neurodegeneration, remodulating inflammatory and oxidative pathways (Feng et al., 2018; Ren et al., 2018; Sheng et al., 2020; Wang et al., 2020; Zou et al., 2016). The administration of walnut sequence YVLLPSPK proved to activate autophagy through the AKT/mTOR signaling and mitophagy dependent on the Nrf-2/Keap1/HO-1 pathway (Zhao et al., 2020, 2021). Autophagy and mitophagy has a pivotal protective function in the pathogenesis of neurological disorders. The bioactivity of walnut peptides with tea polyphenols was more effective than the subject alone, suggesting a better permeation on the BBB (Sheng et al., 2020). Interestingly, the biosynthesis and exocytosis of neurotransmitters is largely regulated by CaM-dependent protein kinase II (CaMK II), which was found activated in mice brain tissue after the supplementation with walnut hydrolysates (Ren et al., 2018). This result suggests a possible action route of walnut peptides affecting important regulatory enzymes responsible for synapse and memory formation. The strong anti-inflammatory effects were related with hydrophobic and aromatic amino acid residues (Wang et al., 2020; Zou et al., 2016).

Two plant species from China region commonly used to treat nervous system disorders, Ginseng (*Panaxginseng C.A.Meyer*) and *Cardamine violifolia*, have significantly improved memory abilities of AD rats model and D-galactose toxicity, respectively (Li et al., 2016; Yu et al., 2020). Ginseng peptides reduced the content of $A\beta_{1\text{-}42}$ and p-tau (related to AD dysfunction) via activation of PI3K/Akt signaling and down regulation of apoptotic factor Bcl-2 and Bax. PI3K triggering and the downstream phosphorylation of Akt is associated with cell survival and play a significant role on oxidative stress modulation in AD (Li et al., 2016). The oxidative stress was prevented by Selenium-enriched peptides from *Cardamine violifolia* (CSP) via Nrf2 pathway, which probably represents an anti-aging mechanism (Yu et al., 2020). Furthermore, CSP reduced the neuro-inflammation by inhibiting the NF-κB pathway in D-gal induced aging rats and suppressed RAGE and P-JNK signaling pathway.

8. Conclusion and perspectives

In this review, we presented the main inflammatory and oxidative pathway modulated by food bioactive peptides reported in neurobiological *in vitro* and *in vivo* studies. Cell culture studies have been carried out preferentially in a cell lineage model while very few were carried out in primary culture, which would imply a more physiological response. Although food peptides are shown to exert bioactivity on neuronal cells and microglia, very few studies evaluated this effect in astrocyte culture. Cell brain culture studies showed that bioactive peptides are able to prevent neuroinflammation by the inhibition of important transcription factors, such as NF-κB and MAPK pathway in neuron and microglia, reducing production of cytokines and inhibiting inflammatory propagation. Few studies determine the interaction of peptides with cell receptors and forms of cell internalization. Several sources of food peptides were able to promote defense against oxidative stress by the activation of protective pathways, such as Nrf-2 signaling (which promotes an increased expression of antioxidants) and inhibition of mitochondria apoptosis pathway. Oral administration of food bioactive peptides in animal studies demonstrate that they may resist gastric metabolism and pass through gastrointestinal and brain barriers, promoting protective effects and preventing behavioral and memory losses. More studies on bioavailability would further explain whether the effect is mediated by integral peptide or by its metabolites. Studies that evaluated the amino acid sequence of peptides showed that the presence of hydrophobic and aromatic peptides can be extremely important for the observed neurobiological effects. However, further studies regarding the molecular interaction of peptides with the main cell regulatory factors of oxidative and inflammatory pathways may clarify the specific peptide sequences capable of interaction. Understanding the molecular mechanisms by which peptides act on the central nervous system contribute to the development of new pharmaceutical drugs and dietary supplements that could help prevent neurodegeneration.

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Declaration of Competing Interest

The authors declare there was no conflict of interest to declare.

References

Banks, W. A., Kastin, A. J., Akerstrom, V., & Jaspan, J. B. (1993). Radioactively iodinated cyclo(His-Pro) crosses the blood-brain barrier and reverses ethanol-induced narcosis. *American Journal of Physiology - Endocrinology and Metabolism, 264*(5 27-5), 723–729. doi:10.1152/ajpendo.1993.264.5.e723.

Chen, H. M., Muramoto, K., & Yamauchi, F. (1995). Structural analysis of antioxidative peptides from soybean β-conglycinin. *Journal of Agricultural and Food Chemistry, 43*(3), 574–578. doi:10.1021/jf00051a004.

Chen, H. M., Muramoto, K., Yamauchi, F., & Nokihara, K. (1996). Antioxidant activity of designed peptides based on the antioxidative peptide isolated from digests of a soybean protein. *Journal of Agricultural and Food Chemistry, 44*(9), 2619–2623. doi:10.1021/jf950833m.

Kaminska, B. (2005). MAPK signalling pathways as molecular targets for anti-inflammatory therapy - From molecular mechanisms to therapeutic benefits. *Biochimica et Biophysica Acta - Proteins and Proteomics, 1754*(1–2), 253–262. doi:10.1016/j.bbapap.2005.08.017.

Hou, R. C. W., Chen, Y. S., Huang, J. R., & Jeng, K. C. G. (2006). Cross-linked bromelain inhibits lipopolysaccharide-induced cytokine production involving cellular signaling suppression in rats. *Journal of Agricultural and Food Chemistry, 54*(6), 2193–2198. doi:10.1021/jf052390k.

Holzgrabe, U., Kapková, P., Alptüzün, V., Scheiber, J., & Kugelmann, E. (2007). Targeting acetylcholinesterase to treat neurodegeneration. *Expert Opinion on Therapeutic Targets, 11*(2), 161–179. doi:10.1517/14728222.11.2.161.

Zuccato, C., & Cattaneo, E. (2009). Brain-derived neurotrophic factor in neurodegenerative diseases. *Nature Reviews Neurology, 5*(6), 311–322. doi:10.1038/nrneurol.2009.54.

Kriete, A., & Mayo, K. L. (2009). Atypical pathways of NF-κB activation and aging. *Experimental Gerontology, 44*(4), 250–255. doi:10.1016/j.exger.2008.12.005.

Takeuchi, O., & Akira, S. (2010). Pattern recognition receptors and inflammation. *Cell, 140*(6), 805–820. doi:10.1016/j.cell.2010.01.022.

Sarmadi, B. H., & Ismail, A. (2010). Antioxidative peptides from food proteins: A review. *Peptides, 31*(10), 1949–1956. doi:10.1016/j.peptides.2010.06.020.

Pei, X., Yang, R., Zhang, Z., Gao, L., Wang, J., Xu, Y., Zhao, M., Han, X., Liu, Z., & Li, Y. (2010). Marine collagen peptide isolated from Chum Salmon (Oncorhynchus keta) skin facilitates learning and memory in aged C57BL/6J mice. *Food Chemistry, 118*(2), 333–340. doi:10.1016/j.foodchem.2009.04.120.

Niki, E. (2010). Assessment of antioxidant capacity in vitro and in vivo. *Free Radical Biology and Medicine*. doi:10.1016/j.freeradbiomed.2010.04.016.

Mason, J. M. (2010). Design and development of peptides and peptide mimetics as antagonists for therapeutic intervention. *Future Medicinal Chemistry, 2*(12), 1813–1822. doi:10.4155/fmc.10.259.

Kim, E. K., Lee, S. J., Moon, S. H., Jeon, B. T., Kim, B., Park, T. K., Han, J. S., & Park, P. J. (2010). Neuroprotective effects of a novel peptide purified from venison protein. *Journal of Microbiology and Biotechnology, 20*(4), 700–707. doi:10.4014/jmb.0909.09033.

Glass, C. K., Saijo, K., Winner, B., Marchetto, M. C., & Gage, F. H. (2010). Mechanisms underlying inflammation in neurodegeneration. *Cell, 140*(6), 918–934. doi:10.1016/j.cell.2010.02.016.

Vo, T. S., Ngo, D. H., Kim, J. A., Ryu, B., & Kim, S. K. (2011). An antihypertensive peptide from tilapia gelatin diminishes free radical formation in murine microglial cells. *Journal of Agricultural and Food Chemistry, 59*(22), 12193–12197. doi:10.1021/jf202837g.

Zheng, L., Su, G., Ren, J., Gu, L., You, L., & Zhao, M. (2012). Isolation and characterization of an oxygen radical absorbance activity peptide from defatted peanut meal hydrolysate and its antioxidant properties. *Journal of Agricultural and Food Chemistry, 60*(21), 5431–5437. doi:10.1021/jf3017173.

Brady, S. T., Siegel, G. J., Albers, R. W., & Price, D. L. (2012). Basic neurochemistry. *Basic Neurochemistry*. doi:10.1016/C2009-0-00066-X.

Zhu, K. X., Guo, X., Guo, X. N., Peng, W., & Zhou, H. M. (2013). Protective effects of wheat germ protein isolate hydrolysates (WGPIH) against hydrogen peroxide-induced oxidative stress in PC12 cells. *Food Research International, 53*(1), 297–303. doi:10.1016/j.foodres.2013.05.007.

Smith, DE., Clémençon, B., & Hediger, M. A. (2013). Proton-coupled oligopeptide transporter family SLC15: Physiological, pharmacological and pathological implications. *Molecular Aspects of Medicine, 34*(2–3), 323–336. doi:10.1016/j.mam.2012.11.003.

Power, O., Jakeman, P., & Fitzgerald, R. J. (2013). Antioxidative peptides: Enzymatic production, in vitro and in vivo antioxidant activity and potential applications of milk-derived antioxidative peptides. *Amino Acids*. doi:10.1007/s00726-012-1393-9.

Pangestuti, R., Ryu, B., Himaya, S., & Kim, S. K. (2013). Optimization of hydrolysis conditions, isolation, and identification of neuroprotective peptides derived from seahorse Hippocampus trimaculatus. *Amino Acids, 45*(2), 369–381. doi:10.1007/s00726-013-1510-4.

Jin, M. M., Zhang, L., Yu, H. X., Meng, J., Sun, Z., & Lu, R. R. (2013). Protective effect of whey protein hydrolysates on H2O 2-induced PC12 cells oxidative stress via a mitochondria-mediated pathway. *Food Chemistry, 141*(2), 847–852. doi:10.1016/j.foodchem.2013.03.076.

Jeong, H.-K., Ji, K., Min, K., & Joe, E.-H. (2013). Brain inflammation and microglia: Facts and misconceptions. *Experimental Neurobiology, 22*(2), 59–67. doi:10.5607/en.2013.22.2.59.

Chai, H. J., Chan, Y. L., Li, T. L., Shiau, C. Y., & Wu, C. J. (2013). Evaluation of lanternfish (Benthosema pterotum) hydrolysates as antioxidants against hydrogen peroxide induced oxidative injury. *Food Research International, 54*(2), 1409–1418. doi:10.1016/j.foodres.2013.09.052.

Tata, A., Velluto, L., D'Angelo, C., & Reale, M. (2014). Cholinergic system dysfunction and neurodegenerative diseases: Cause or effect? *CNS & Neurological Disorders - Drug Targets*. doi:10.2174/18715273136661409171211132.

Lim, J. L., Wilhelmus, M. M. M., de Vries, H. E., Drukarch, B., Hoozemans, J. J. M., & van Horssen, J. (2014). Antioxidative defense mechanisms controlled by Nrf2: state-of-the-art and clinical perspectives in neurodegenerative diseases. *Archives of Toxicology, 88*(10), 1773–1786. doi:10.1007/s00204-014-1338-z.

Kigerl, K. A., de Rivero Vaccari, J. P., Dietrich, W. D., Popovich, P. G., & Keane, R. W. (2014). Pattern recognition receptors and central nervous system repair. *Experimental Neurology, 258*, 5–16. doi:10.1016/j.expneurol.2014.01.001.

Katayama, S., Imai, R., Sugiyama, H., & Nakamura, S. (2014). Oral administration of soy peptides suppresses cognitive decline by induction of neurotrophic factors in SAMP8 mice. *Journal of Agricultural and Food Chemistry, 62*(16), 3563–3569. doi:10.1021/jf405416s.

Karaś, M., Jakubczyk, A., Szymanowska, U., Materska, M., & Zielińska, E. (2014). Antioxidant activity of protein hydrolysates from raw and heat-treated yellow string beans (Phaseolus vulgaris L.). *Acta Scientiarum Polonorum Technologia Alimentaria, 13*(4), 385–391. doi:10.17306/J.AFS.2014.4.5.

Chakrabarti, S., Jahandideh, F., & Wu, J. (2014). Food-derived bioactive peptides on inflammation and oxidative stress. *BioMed Research International, 2014*. doi:10.1155/2014/608979.

Zou, Y., Feng, W., Wang, W., Chen, Y., Zhou, Z., Li, Q., Zhao, T., Mao, G., Wu, X., & Yang, L. (2015). Protective effect of porcine cerebral hydrolysate peptides on learning and memory deficits and oxidative stress in lead-exposed mice. *Biological Trace Element Research, 168*(2), 429–440. doi:10.1007/s12011-015-0329-0.

Zhang, Q. X., Jin, M. M., Zhang, L., Yu, H. X., Sun, Z., & Lu, R. R. (2015). Hydrophobicity of whey protein hydrolysates enhances the protective effect against oxidative damage on PC 12 cells. *Journal of Dairy Research, 82*(1), 1–7. doi:10.1017/S0022029914000405.

Stalmans, S., Gevaert, B., Wynendaele, E., Nielandt, J., De Tre, G., Peremans, K., Burvenich, C., & De Spiegeleer, B. (2015). Classification of peptides according to their blood-brain barrier influx. *Protein & Peptide Letters, 22*(9), 768–775. doi:10.2174/0929866522666150622101223.

Sastre, M., Ritchie, C. W., & Hajji, N. (2015). JSM Alzheimer's disease and related dementia metal ions in Alzheimer's disease brain. *JSM Alzheimer's Dis Related Dementia, 2*(1), 1014.

Kim, G. H., Kim, J. E., Rhie, S. J., & Yoon, S. (2015). The role of oxidative stress in neurodegenerative diseases. *Experimental Neurobiology, 24*(4), 325–340. doi:10.5607/en.2015.24.4.325.

Gu, M., Chen, H. P., Zhao, M. M., Wang, X., Yang, B., Ren, J. Y., & Su, G. W. (2015). Identification of antioxidant peptides released from defatted walnut (Juglans Sigillata Dode) meal proteins with pancreatin. *LWT - Food Science and Technology, 60*(1), 213–220. doi:10.1016/j.lwt.2014.07.052.

Chen, H., Zhao, M., Lin, L., Wang, J., Sun-Waterhouse, D., Dong, Y., Zhuang, M., & Su, G. (2015). Identification of antioxidative peptides from defatted walnut meal hydrolysate with potential for improving learning and memory. *Food Research International, 78*, 216–223. doi:10.1016/j.foodres.2015.10.008.

Zou, T. B., He, T. P., Li, H. B., Tang, H. W., & Xia, E. Q. (2016). The structure-activity relationship of the antioxidant peptides from natural proteins. *Molecules*. doi:10.3390/molecules21010072.

Xu, Zi, Fang, Y., Chen, Y., Yang, W., Ma, N., Pei, F., Kimatu, B. M., Hu, Q., & Qiu, W. (2016). Protective effects of Se-containing protein hydrolysates from Se-enriched rice against Pb2+-induced cytotoxicity in PC12 and RAW264.7 cells. *Food Chemistry, 202*, 396–403. doi:10.1016/j.foodchem.2016.02.021.

Niedzielska, E., Smaga, I., Gawlik, M., Moniczewski, A., Stankowicz, P., Pera, J., & Filip, M. (2016). Oxidative stress in neurodegenerative diseases. *Molecular Neurobiology, 53*(6), 4094–4125. doi:10.1007/s12035-015-9337-5.

Ngoh, Y.-Y., & Gan, C.-Y. (2016). Enzyme-assisted extraction and identification of antioxidative and α-amylase inhibitory peptides from Pinto beans (Phaseolus vulgaris cv. Pinto). *Food Chemistry, 190*, 331–337. doi:10.1016/j.foodchem.2015.05.120.

Li, H., Kang, T., Qi, B., Kong, L., Jiao, Y., Cao, Y., Zhang, J., & Yang, J. (2016). Neuroprotective effects of ginseng protein on PI3K/Akt signaling pathway in the hippocampus of D-galactose/AlCl3 inducing rats model of Alzheimer's disease. *Journal of Ethnopharmacology, 179*, 162–169. doi:10.1016/j.jep.2015.12.020.

Ko, W., Sohn, J. H., Jang, J. H., Ahn, J. S., Kang, D. G., Lee, H. S., Kim, J. S., Kim, Y. C., & Oh, H. (2016). Inhibitory effects of alternaramide on inflammatory mediator expression through TLR4-MyD88-mediated inhibition of NF-kB and MAPK pathway signaling in lipopolysaccharide-stimulated RAW264.7 and BV2 cells. *Chemico-Biological Interactions*. doi:10.1016/j.cbi.2015.11.024.

Chai, H. J., Wu, C. J., Yang, S. H., Li, T. L., & Sun Pan, B. (2016). Peptides from hydrolysate of lantern fish (Benthosema pterotum) proved neuroprotective in vitro and in vivo. *Journal of Functional Foods, 24*, 438–449. doi:10.1016/j.jff.2016.04.009.

Banks, W. A. (2016). From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. *Nature Reviews Drug Discovery, 15*(4), 275–292. doi:10.1038/nrd.2015.21.

An, L., Han, X., Li, H., Ma, Y., Shi, L., Xu, G., Yuan, G., Sun, J., Zhao, N., Sheng, Y., Wang, M., & Du, P. (2016). Effects and mechanism of cerebroprotein hydrolysate on learning and memory ability in mice. *Genetics and Molecular Research, 15*(3). doi:10.4238/gmr.15038804.

Zhao, T., Su, G., Wang, S., Zhang, Q., Zhang, J., Zheng, L., Sun, B., & Zhao, M. (2017). Neuroprotective effects of acetylcholinesterase inhibitory peptides from anchovy (Coilia mystus) against glutamate-induced toxicity in PC12 cells. *Journal of Agricultural and Food Chemistry, 65*(51), 11192–11201. doi:10.1021/acs.jafc.7b03945.

Xin, J. L., Zhang, Y., Li, Y., Zhang, L. Z., Lin, Y., & Zheng, L. W. (2017). Protective effects of cervus nippon temminck velvet antler polypeptides against MPP+-induced cytotoxicity in SH-SY5Y neuroblastoma cells. *Molecular Medicine Reports, 16*(4), 5143–5150. doi:10.3892/mmr.2017.7303.

Vasile, F., Dossi, E., & Rouach, N. (2017). Human astrocytes: structure and functions in the healthy brain. *Brain Structure & Function*. doi:10.1007/s00429-017-1383-5.

van Raamsdonk, J. M., Vega, I. E., & Brundin, P. (2017). Oxidative stress in neurodegenerative disease: Causation or association? *Oncotarget, 8*(7), 10777–10778. doi:10.18632/oncotarget.14650.

Shabab, T., Khanabdali, R., Moghadamtousi, S. Z., Kadir, H. A., & Mohan, G. (2017). Neuroinflammation pathways: A general review. *International Journal of Neuroscience, 127*(7), 624–633. doi:10.1080/00207454.2016.1212854.

Min, L. J., Kobayashi, Y., Mogi, M., Tsukuda, K., Yamada, A., Yamauchi, K., Abe, F., Iwanami, J., Xiao, J. Z., & Horiuchi, M. (2017). Administration of bovine casein-derived peptide prevents cognitive decline in Alzheimer disease model mice. *PLoS ONE, 12*(2), 1–14. doi:10.1371/journal.pone.0171515.

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature, 541*(7638), 481–487. doi:10.1038/nature21029.

Guidotti, G., Brambilla, L., & Rossi, D. (2017). Cell-penetrating peptides: From basic research to clinics. *Trends in Pharmacological Sciences, 38*(4), 406–424. doi:10.1016/j.tips.2017.01.003.

Fang, Y., Xu, Z., Shi, Y., Pei, F., Yang, W., Ma, N., Kimatu, B. M., Liu, K., Qiu, W., & Hu, Q. (2017). Protection mechanism of Se-containing protein hydrolysates from Se-enriched rice on Pb2+-induced apoptosis in PC12 and RAW264.7 cells. *Food Chemistry, 219*, 391–398. doi:10.1016/j.foodchem.2016.09.131.

Xu, Z., Chen, S., Wang, Y., Chen, S., Yao, W., & Gao, X. (2018). Neuroprotective effects of silk fibroin hydrolysate against Aβ25–35 induced cytotoxicity in SH-SY5Y cells and primary hippocampal neurons by regulating ROS inactivation of PP2A. *Journal of Functional Foods, 45*(November 2017), 100–109. doi:10.1016/j.jff.2018.03.032.

Wang, X., Yu, H., Xing, R., Liu, S., Chen, X., & Li, P. (2018). Effect and mechanism of oyster hydrolytic peptides on spatial learning and memory in mice. *RSC Advances, 8*(11), 6125–6135. doi:10.1039/c7ra13139a.

Wang, S., Su, G., Zhang, Q., Zhao, T., Liu, Y., Zheng, L., & Zhao, M. (2018). Walnut (Juglans regia) peptides reverse sleep deprivation-induced memory impairment in rat via alleviating oxidative stress. *Journal of Agricultural and Food Chemistry, 66*(40), 10617–10627. doi:10.1021/acs.jafc.8b03884.

Shimizu, A., Mitani, T., Tanaka, S., Fujii, H., Maebuchi, M., Amiya, Y., Tanaka, M., Matsui, T., Nakamura, S., & Katayama, S. (2018). Soybean-derived glycine-arginine dipeptide administration promotes neurotrophic factor expression in the mouse brain. *Journal of Agricultural and Food Chemistry, 66*(30), 7935–7941. doi:10.1021/acs.jafc.8b01581.

Ren, D., Zhao, F., Liu, C., Wang, J., Guo, Y., Liu, J., & Min, W. (2018). Antioxidant hydrolyzed peptides from Manchurian walnut (Juglans mandshurica Maxim.) attenuate scopolamine-induced memory impairment in mice. *Journal of the Science of Food and Agriculture, 98*(13), 5142–5152. doi:10.1002/jsfa.9060.

Ohsawa, K., Nakamura, F., Uchida, N., Mizuno, S., & Yokogoshi, H. (2018). Lactobacillus helveticus-fermented milk containing lactononadecapeptide (NIPPLTQTPVVVPPFLQPE) improves cognitive function in healthy middle-aged adults: A randomised, double-blind, placebo-controlled trial. *International Journal of Food Sciences and Nutrition, 69*(3), 369–376. doi:10.1080/09637486.2017.1365824.

Lin, L., Yang, K., Zheng, L., Zhao, M., Sun, W., Zhu, Q., & Liu, S. (2018). Anti-aging effect of sea cucumber (Cucumaria frondosa) hydrolysate on fruit flies and D-galactose-induced aging mice. *Journal of Functional Foods, 47*(May), 11–18. doi:10.1016/j.jff.2018.05.033.

Liang, Y., Lin, Q., Huang, P., Wang, Y., Li, J., Zhang, L., & Cao, J. (2018). Rice bioactive peptide binding with TLR4 to overcome H2O2-induced injury in human umbilical vein endothelial cells through NF-κB signaling. *Journal of Agricultural and Food Chemistry, 66*(2), 440–448. doi:10.1021/acs.jafc.7b04036.

Guha, S., & Majumder, K. (2018). Structural-features of food-derived bioactive peptides with anti-inflammatory activity: A brief review. *Journal of Food Biochemistry* February. doi:10.1111/jfbc.12531.

Feng, L., Wang, X., Peng, F., Liao, J., Nai, Y., Lei, H., Li, M., & Xu, H. (2018). Walnut protein hydrolysates play a protective role on neurotoxicity induced by D-galactose and aluminum chloride in mice. *Molecules, 23*(9). doi:10.3390/molecules23092308.

Barbosa, E. A., Oliveira, A., Plácido, A., Socodato, R., Portugal, C. C., Mafud, A. C., Om-

bredane, A. S., Moreira, D. C., Vale, N., Bessa, L. J., Joanitti, G. A., Alves, C., Gomes, P., Delerue-Matos, C., Mascarenhas, Y. P., Marani, M. M., Relvas, J. B., Pintado, M., & Leite, J. R. S. A. (2018). Structure and function of a novel antioxidant peptide from the skin of tropical frogs. *Free Radical Biology and Medicine, 115*(September 2017), 68–79. doi:10.1016/j.freeradbiomed.2017.11.001.

Zhao, T., Zheng, L., Zhang, Q., Wang, S., Zhao, Q., Su, G., & Zhao, M. (2019). Stability towards the gastrointestinal simulated digestion and bioactivity of PAYCS and its digestive product PAY with cognitive improving properties. *Food and Function, 10*(5), 2439–2449. doi:10.1039/c8fo02314j.

Zhang, Q., Su, G., Zhao, T., Wang, S., Sun, B., Zheng, L., & Zhao, M. (2019). The memory improving effects of round scad (Decapterus maruadsi) hydrolysates on sleep deprivation-induced memory deficits in rats via antioxidant and neurotrophic pathways. *Food and Function, 10*(12), 7733–7744. doi:10.1039/c9fo00855a.

Xu, Q., Yan, X., Zhang, Y., & Wu, J. (2019). Current understanding of transport and bioavailability of bioactive peptides derived from dairy proteins: A review. *International Journal of Food Science and Technology, 54*(6), 1930–1941. doi:10.1111/ijfs.14055.

Wang, Y., Xu, E., Musich, P. R., & Lin, F. (2019). Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure. *CNS Neuroscience and Therapeutics, 25*(7), 816–824. doi:10.1111/cns.13116.

Tanaka, M., Dohgu, S., Komabayashi, G., Kiyohara, H., Takata, F., Kataoka, Y., Nirasawa, T., Maebuchi, M., & Matsui, T. (2019). Brain-transportable dipeptides across the blood-brain barrier in mice. *Scientific Reports, 9*(1), 1–10. doi:10.1038/s41598-019-42099-9.

Liu, C., Guo, Y., Zhao, F., Qin, H., Lu, H., Fang, L., Wang, J., & Min, W. (2019). Potential mechanisms mediating the protective effects of a peptide from walnut (: Juglans mandshurica Maxim.) against hydrogen peroxide induced neurotoxicity in PC12 cells. *Food and Function, 10*(6), 3491–3501. doi:10.1039/c8fo02557f.

Jin, W., Xu, X., Chen, X., Qi, W., Lu, J., Yan, X., Zhao, D., Cong, D., Li, X., & Sun, L. (2019). Protective effect of pig brain polypeptides against corticosterone-induced oxidative stress, inflammatory response, and apoptosis in PC12 cells. *Biomedicine and Pharmacotherapy, 115*(April), Article 108890. doi:10.1016/j.biopha.2019.108890.

Dresselhaus, E. C., & Meffert, M. K. (2019). Cellular specificity of NF-κB function in the nervous system. *Frontiers in Immunology, 10*(MAY). doi:10.3389/fimmu.2019.01043.

Corpuz, H. M., Fujii, H., Nakamura, S., & Katayama, S. (2019). Fermented rice peptides attenuate scopolamine-induced memory impairment in mice by regulating neurotrophic signaling pathways in the hippocampus. *Brain Research, 1720*(April), Article 146322. doi:10.1016/j.brainres.2019.146322.

Ano, Y., Yoshino, Y., Kutsukake, T., Ohya, R., Fukuda, T., Uchida, K., Takashima, A., & Nakayama, H. (2019). Tryptophan-related dipeptides in fermented dairy products suppress microglial activation and prevent cognitive decline. *Aging, 11*(10), 2949–2967. doi:10.18632/aging.101909.

Lee, S. Y., & Hur, S. J. (2019a). Neuroprotective effects of different molecular weight peptide fractions obtained from beef by hydrolysis with commercial enzymes in SH-SY5Y cells. *Food Research International, 121*(March), 176–184. doi:10.1016/j.foodres.2019.03.039.

Lee, S. Y., & Hur, S. J. (2019b). Protective effect of a 3 kDa peptide obtained from beef myofibrillar protein using alkaline-AK on neuronal cells. *Neurochemistry International, 129*(April), Article 104459. doi:10.1016/j.neuint.2019.05.003.

Zhao, F., Wang, J., Lu, H., Fang, L., Qin, H., Liu, C., & Min, W. (2020). Neuroprotection by walnut-derived peptides through autophagy promotion via Akt/mTOR signaling pathway against oxidative stress in PC12 cells. *Journal of Agricultural and Food Chemistry, 68*(11), 3638–3648. doi:10.1021/acs.jafc.9b08252.

Zhang, Q., Su, G., Zhao, T., Sun, B., Zheng, L., & Zhao, M. (2020). Neuroprotection of round scad (Decapterus maruadsi) hydrolysate in glutamate-damaged PC12 cells: Possible involved signaling pathways and potential bioactive peptides. *Journal of Functional Foods, 64*(November 2019). doi:10.1016/j.jff.2019.103690.

Yu, T., Guo, J., Zhu, S., Zhang, X., Zhu, Z. Z., Cheng, S., & Cong, X. (2020). Protective effects of selenium-enriched peptides from Cardamine violifolia on D-galactose-induced brain aging by alleviating oxidative stress, neuroinflammation, and neuron apoptosis. *Journal of Functional Foods, 75*, Article 104277. doi:10.1016/j.jff.2020.104277.

Wu, D., Wu, D., Zhang, S., Sun, N., Zhu, B., & Lin, S. (2020). Neuroprotective function of a novel hexapeptide QMDDQ from shrimp via activation of the PKA/CREB/BNDF signaling pathway and its structure-activity relationship. *Journal of Agricultural and Food Chemistry, 68*(24), 6759–6769. doi:10.1021/acs.jafc.0c02689.

Wu, D., Li, M., Ding, J., Zheng, J., Zhu, B. W., & Lin, S. (2020). Structure-activity relationship and pathway of antioxidant shrimp peptides in a PC12 cell model. *Journal of Functional Foods, 70*(April), Article 103978. doi:10.1016/j.jff.2020.103978.

Wang, S., Zheng, L., Zhao, T., Zhang, Q., Liu, Y., Sun, B., Su, G., & Zhao, M. (2020). Inhibitory effects of walnut (Juglans regia) peptides on neuroinflammation and oxidative stress in lipopolysaccharide-induced cognitive impairment mice. *Journal of Agricultural and Food Chemistry, 68*(8), 2381–2392. doi:10.1021/acs.jafc.9b07670.

Sheng, J., Yang, X., Liu, Q., Luo, H., Yin, X., Liang, M., Liu, W., Lan, X., Wan, J., & Yang, X. (2020). Coadministration with tea polyphenols enhances the neuroprotective effect of defatted walnut meal hydrolysate against scopolamine-induced learning and memory deficits in mice. *Journal of Agricultural and Food Chemistry, 68*(3), 751–758. doi:10.1021/acs.jafc.9b05081.

Michalska, P., & León, R. (2020). When it comes to an end: Oxidative stress crosstalk with protein aggregation and neuroinflammation induce neurodegeneration. *Antioxidants, 9*(8), 1–34. doi:10.3390/antiox9080740.

Matsui, T., Yoshino, A., & Tanaka, M. (2020). A trip of peptides to the brain. *Food Production, Processing and Nutrition, 2*(1). doi:10.1186/s43014-020-00044-8.

Linnerbauer, M., Wheeler, M. A., & Quintana, F. J. (2020). Astrocyte crosstalk in CNS inflammation. *Neuron, 108*(4), 608–622. doi:10.1016/j.neuron.2020.08.012.

Liao, X., Zhu, Z., Wu, S., Chen, M., Huang, R., Wang, J., Wu, Q., & Ding, Y. (2020). Preparation of antioxidant protein hydrolysates from pleurotus geesteranus and their protective effects on H2O2 oxidative damaged PC12 cells. *Molecules, 25*(22) Basel, Switzerland. doi:10.3390/molecules25225408.

Fernández-García, S., Sancho-Balsells, A., Longueville, S., Hervé, D., Gruart, A., Delgado-García, J. M., Alberch, J., & Giralt, A. (2020). Astrocytic BDNF and TrkB regulate severity and neuronal activity in mouse models of temporal lobe epilepsy. *Cell Death & Disease, 11*(6), 411. doi:10.1038/s41419-020-2615-9.

Bauer, T. M., & Murphy, E. (2020). Role of mitochondrial calcium and the permeability transition pore in regulating cell death. *Circulation Research*, 280–293. doi:10.1161/CIRCRESAHA.119.316306.

Zhu, G. P., Zhang, C. H., Qin, X. M., Cao, W. H., Zheng, H. N., & Gao, J. L. (2021). Ameliorative effects of oyster (Crassostrea hongkongensis) protein hydrolysate on age-induced cognitive impairment via restoring glia cell dysfunction and neuronal injured in zebrafish. *Journal of Functional Foods, 85*(September 2020), Article 104607. doi:10.1016/j.jff.2021.104607.

Zhao, Y., Dong, Y., Ge, Q., Cui, P., Sun, N., & Lin, S. (2021). Neuroprotective effects of NDEELNK from sea cucumber ovum against scopolamine-induced PC12 cell damage through enhancing energy metabolism and upregulation of the PKA/BDNF/NGF signaling pathway. *Food and Function, 12*(17), 7676–7687. doi:10.1039/d1fo00631b.

Zhao, F., Liu, C., Fang, L., Lu, H., Wang, J., Gao, Y., Gabbianelli, R., & Min, W. (2021). Walnut-derived peptide activates PINK1 via the NRF2/KEAP1/HO-1 pathway, promotes mitophagy, and alleviates learning and memory impairments in a mice model. *Journal of Agricultural and Food Chemistry, 69*(9), 2758–2772. doi:10.1021/acs.jafc.0c07546.

Zhang, Q., Su, G., Yang, Q., Wei, Z., Wang, J., Zheng, L., & Zhao, M. (2021). Round Scad-derived octapeptide WCPFSRSF confers neuroprotection by regulating Akt/Nrf2/NFκB signaling. *Journal of Agricultural and Food Chemistry, 69*(36), 10606–10616. doi:10.1021/acs.jafc.1c04774.

Zhang, J., Liu, R., Zhang, D., Zhang, Z., Zhu, J., Xu, L., & Guo, Y. (2021). Neuroprotective effects of maize tetrapeptide-anchored gold nanoparticles in Alzheimer's disease. *Colloids and Surfaces B: Biointerfaces, 200*(January). doi:10.1016/j.colsurfb.2021.111584.

Wang, S., Sun-Waterhouse, D., Neil Waterhouse, G. I., Zheng, L., Su, G., & Zhao, M. (2021). Effects of food-derived bioactive peptides on cognitive deficits and memory decline in neurodegenerative diseases: A review. *Trends in Food Science and Technology, 116*(March), 712–732. doi:10.1016/j.tifs.2021.04.056.

Sirinupong, N., Chansuwan, W., & Kaewkaen, P. (2021). Hydrolase-treated royal jelly attenuates H2O2- and glutamate-induced SH-SY5Y cell damage and promotes cognitive enhancement in a rat model of vascular dementia. *International Journal of Food Science, 2021*, 1–11. doi:10.1155/2021/2213814.

Rathnayake, A. U., Abuine, R., Palanisamy, S., Lee, J. K., & Byun, H. G. (2021). Characterization and purification of β−secretase inhibitory peptides fraction from sea cucumber (Holothuria spinifera) enzymatic hydrolysates. *Process Biochemistry*. doi:10.1016/j.procbio.2021.10.007.

Perlikowska, R. (2021). Whether short peptides are good candidates for future neuroprotective therapeutics? *Peptides, 140*(March). doi:10.1016/j.peptides.2021.170528.

Muzio, L., Viotti, A., & Martino, G. (2021). Microglia in neuroinflammation and neurodegeneration: From understanding to therapy. *Frontiers in Neuroscience, 15*(September). doi:10.3389/fnins.2021.742065.

Morris, J. L., Gillet, G., Prudent, J., & Popgeorgiev, N. (2021). Bcl-2 family of proteins in the control of mitochondrial calcium signalling: An old chap with new roles. *International Journal of Molecular Sciences, 22*(7). doi:10.3390/ijms22073730.

Lu, M., Mishra, A., Boschetti, C., Lin, J., Liu, Y., Huang, H., Kaminski, C. F., Huang, Z., Tunnacliffe, A., & Kaminski Schierle, G. S. (2021). Sea cucumber-derived peptides alleviate oxidative stress in neuroblastoma cells and improve survival in C. elegans exposed to neurotoxic paraquat. *Oxidative Medicine and Cellular Longevity, 2021*. doi:10.1155/2021/8842926.

Gao, Y., Qin, H., Wu, D., Liu, C., Fang, L., Wang, J., Liu, X., & Min, W. (2021). Walnut peptide WEKPPVSH in alleviating oxidative stress and inflammation in lipopolysaccharide-activated BV-2 microglia via the Nrf2/HO-1 and NF-κB/p38 MAPK pathways. *Journal of Bioscience and Bioengineering, 132*(5), 496–504. doi:10.1016/j.jbiosc.2021.07.009.

Ciesielska, A., Matyjek, M., & Kwiatkowska, K. (2021). TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. *Cellular and Molecular Life Sciences, 78*(4), 1233–1261. doi:10.1007/s00018-020-03656-y.

Chataigner, M., Martin, M., Lucas, C., Pallet, V., Layé, S., Mehaignerie, A., Bouvret, E., Dinel, A. L., & Joffre, C. (2021). Fish hydrolysate supplementation containing n-3 long chain polyunsaturated fatty acids and peptides prevents lps-induced neuroinflammation. *Nutrients, 13*(3), 1–24. doi:10.3390/nu13030824.

Chataigner, M., Mortessagne, P., Lucas, C., Pallet, V., Layé, S., Mehaignerie, A., Bouvret, E., Dinel, A. L., & Joffre, C. (2021). Dietary fish hydrolysate supplementation containing n-3 LC-PUFAs and peptides prevents short-term memory and stress response deficits in aged mice. *Brain, Behavior, and Immunity, 91*(April 2020), 716–730. doi:10.1016/j.bbi.2020.09.022.

Caetano-Silva, M. E., Rund, L. A., Vailati-Riboni, M., Pacheco, M. T. B., & Johnson, R. W. (2021). Copper-binding peptides attenuate microglia inflammation through suppression of NF-kB Pathway. *Molecular Nutrition and Food Research, 65*(22), 1–11. doi:10.1002/mnfr.202100153.

Zhao, Y., Lu, Z., Xu, X., Sun, N., & Lin, S. (2022). Sea cucumber-derived peptide attenuates scopolamine-induced cognitive impairment by preventing hippocampal cholinergic dysfunction and neuronal cell death. *Journal of Agricultural and Food Chemistry, 70*(2), 567–576. doi:10.1021/acs.jafc.1c07232.

Zhang, Q., Zheng, L., Su, G., Luo, D., Huang, M., Feng, Y., & Zhao, M. (2022). Peptide WCPFSRSF ameliorates excitotoxicity and elevates synaptic plasticity in glutamate-damaged SH-SY5Y cells by modulating the PI3K/mTOR/EIF4E and BDNF/CREB/TrkB pathways. *Food Bioscience, 47*(October 2021), Article 101696. doi:10.1016/j.fbio.2022.101696.

Yang, J., Fang, L., Lu, H., Liu, C., Wang, J., Wu, D., & Min, W. (2022). Walnut-derived

peptide enhances mitophagy via JNK-Mediated PINK1 activation to reduce oxidative stress in HT-22 cells. *Journal of Agricultural and Food Chemistry, 70*(8), 2630–2642. doi:10.1021/acs.jafc.2c00005.

Wang, S., Zheng, L., Zhao, T., Zhang, Q., Su, G., & Zhao, M. (2022). Food Science and Human Wellness The neuroprotective effect of walnut-derived peptides against glutamate-induced damage in PC12 cells : mechanism and bioavailability. *Food Science and Human Wellness, 11*(4), 933–942. doi:10.1016/j.fshw.2022.03.021.

Amakye, W. K., Hou, C., Xie, L., Lin, X., Gou, N., Yuan, E., & Ren, J. (2021). Bioactive anti-aging agents and the identification of new anti-oxidant soybean peptides. *Food Bioscience, 42*(June), Article 101194. doi:10.1016/j.fbio.2021.101194.

Zou, J., Cai, P. S., Xiong, C. M., & Ruan, J. L. (2016). Neuroprotective effect of peptides extracted from walnut (Juglans Sigilata Dode) proteins on Aβ25-35-induced memory impairment in mice. *Journal of Huazhong University of Science and Technology - Medical Science, 36*(1), 21–30. doi:10.1007/s11596-016-1536-4.

Lemus-Conejo, A., Millan-Linares, M. D. C., Toscano, R., Millan, F., Pedroche, J., Muriana, F. J. G., & Montserrat-de la Paz, S. (2022). GPETAFLR, a peptide from Lupinus angustifolius L. prevents inflammation in microglial cells and confers neuroprotection in brain. *Nutritional Neuroscience*. doi:10.1080/1028415X.2020.1763058.