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Review

Food-Derived Bioactive Peptides Prevent Neurodegenerative Disease by Regulating Renin Angiotensin System (RAS) Related Neurotransmitters and Pathways

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Abstract: Neurodegenerative disease (ND) is a growing global health challenge with limited therapeutic options. Emerging research suggests food-derived bioactive peptides may exhibit neuroprotective activities by regulating the antioxidation, anti-neuroinflammation signaling pathways and the neurotransmitters release in the brain. The regulation is associated with the key components in the renin angiotensin system (RAS). In this paper, we review studies published up to 2025, focusing on the regulation of RAS components and RAS related neurotransmitters by food-derived bioactive peptides. This review describes the crucial role of RAS in the pathophysiology of ND, and discusses how food-derived peptides modulate RAS-mediated neurotransmission and its downstream signaling cascades. Specifically, the structure of peptides affects their penetrability to the blood-brain barrier (BBB), which in turn influences their neuroprotective efficacy. The evidence from animal models indicates that these peptides can affect RAS-related downstream pathways to potentially mitigate the loss of serotonergic and dopaminergic neurons, which are vital for cognition and memory. The findings suggest that food-derived bioactive peptides may hold potential for ameliorating ND symptoms via the regulation of RAS.

Keywords: food-derived bioactive peptides; neurodegenerative disease; renin angiotensin system; neuroinflammation; blood-brain barrier

1. Introduction

Neurodegenerative disease (ND) is the universal problem that affects patients' life and increases the cost of medical care and treatment [1]. Generally, ND is associated with aging, involves the neuron loss and cognitive decline (neurodegeneration), with the common conditions such as Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD), with the syndromes like dementia and movement disorder [2,3]. Globally, over 57 million individuals are affected by ND [4]. According to the data reported from the AD Association and the PD Foundation in 2024, about 1.1 million people in the United States are suffering from PD, and about 6.9 million people may have AD [5,6]. In China, a cross-sectional study revealed that the number of patients with dementia and cognitive impairment has exceeded 15 million and 38 million, respectively [7]. It Europe, the dementia population has increased to 12.2 million in 2025 [8]. Collectively, there will be 152.8 million people of ND worldwide by 2050. Specifically, dementia cases are estimated to reach above 139 million, while PD cases are expected to affect more than 25 million people [9,10]. The prevalence of dementias associated with AD has been rising gradually. About 115.8 million losses would occur by 2050 if the age-specific incidence rate of AD continued to increase at the same rate as in the past decade [11]. PD is a chronic ND marked by motor impairments

and dopaminergic neuron loss. The factors of PD including genetics, environment, diet, and aging [12–14]. People with AD exhibit the accumulation of amyloid-β (Aβ) plaques in the brain, which in turn leads to the deposit in the brain, which cause neurodegeneration. These abnormal proteins lead to the brain inflammation, mitochondrial and bioenergetic disturbances [15]. Moreover, ND gradually damage nerve cells, leading to neurodegeneration and cognitive decline. However, the effective treatments remain elusive.

ND exhibited complicated pathogenesis, which is commonly associated with insulin resistance, hypertension, dyslipidemia, and obesity [16]. These metabolic abnormalities are linked to the dysregulation of the renin-angiotensin system (RAS). The overactivation of RAS contributes to hypertension-induced vascular remodeling, and triggers proinflammatory signaling that causes insulin receptor sensitivity [17,18]. Recent investigations have also suggested that the RAS may be involved in neurodegenerative pathologies [19]. In the RAS, renin promotes the cleavage of angiotensinogen into angiotensin I (Ang I), which serves as a precursor to angiotensin II (Ang II). The angiotensin-converting enzyme (ACE1) cleaves Ang I to create Ang II. Additionally, Ang II converts into angiotensin 1–7 (Ang (1–7)) by angiotensin-converting enzyme 2 (ACE2). Ang II and Ang (1–7) serve as ligands for the angiotensin type 1 receptor (AT1R) and the Mas receptor (MasR), respectively [20]. The Ang II/AT1R axis is considered pro-inflammatory, whereas the Ang II/angiotensin type 2 receptor (AT2R) axis shows anti-inflammatory effects [16]. RAS is also present locally including in the brain. The investigations are justified by the relationship between RAS and many pathways associated with neurodegeneration, such as neuroinflammation, oxidative stress, and changes in neurotransmitter release [21]. A growing body of evidence suggests that the brain's RAS plays a significant role in neuroinflammation and actively contributes to various neurological conditions [19]. For instance, in the hippocampus of AD patients, ACE1 level was increased significantly [22]. A study explored the role of the ACE2/Ang (1–7)/MasR axis in the brain by using ACE2 knockout mice and PD mice model. The RAS axis showed to regulate neuroinflammation and oxidative stress [12]. Genetic evidence showed that ACE1 is a vital factor in AD pathogenesis. Conditional knockout mice lacking neuronal ACE1 exhibited hippocampus-dependent memory impairments and selective dysregulation of the RAS pathway in the hippocampus. These mice also showed age-related capillary loss specifically in the hippocampus [23]. Tayler et al. investigated the dysregulation of the RAS in vascular dementia (VaD), AD, and mixed AD/VaD cases. The findings showed that ACE1, ACE2, Ang II, and Ang III levels were correlated with small vessel disease severity and hypoperfusion markers, suggesting a potential role of RAS in cognitive decline [24]. The components of RAS can activate the expression of neurotransmitter dopamine, which in turn lead to dopaminergic cell death via reactive oxygen species (ROS) activation [25]. However, the current clinical evidence is still limited, and the agonist/antagonist of RAS components may cause side effects. For instance, the ACE inhibitor/AT1R blocker can affect the blood flow, which may lead to hemodynamic insults and kidney damage in fetus [26]. It is necessary to be cautious about directly extrapolating animal/*in vitro* data to humans.

One of the modifiable risk factors that associated with ND is the diet composition [27]. Considering the potential systemic effects of ND drugs, amounting studies investigated that some bioactive compounds in foods, especially food-derived peptides have the potential of alleviating ND [28,29]. These food-derived bioactive peptides act as the RAS modulators, by inhibiting ACE1 or enhancing ACE2 activity, alleviate the downstream oxidation and inflammation pathways in central nervous system (CNS), which were considered as the common pathological mechanisms of ND [30]. Malta et al. [31] identified the bioactive peptides from Brazilian kefir sample, and the higher concentration peptides revealed significant potential to attenuate AD symptoms. Peptide GGPFKSPF from pea protein hydrolysate showed neuroprotective effect on SH-SY5Y cells from Aβ induced apoptosis [32]. A study explored the memory-improving peptides from sea cucumber. One peptide SCP-S alleviated neuroinflammation, while peptide Asp-Ile (SFGDI) reduced oxidative stress and regulated cholinergic system in a scopolamine-induced cell model [33]. A microalgae *Chlorella pyrenoidosa* short-chain anti-AD peptide (CPPs) has also been found to regulate the RAS related neurotransmitters serotonin (5-HT), then prevented neuronal damage by inhibiting downstream inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways [34]. Nonetheless, the pathology of ND involving in multifactorial mechanisms, and the benefits of food-derived peptides on alleviating neurodegeneration still need to be studied.

This review summarizes the role of RAS, RAS-related neurotransmitter regulation, and downstream signaling pathways involved in ND. According to the up-to-date information, we discuss the current evidence suggesting that food-derived bioactive peptides may exert neuroprotective effects by regulating the RAS and related pathways. In addition to introducing relevant animal models and mechanisms, this review provides existing knowledge gaps, including insufficient clinical evidence and challenges of peptide bioavailability. Collectively, this review gain insights into the neuroprotective potential of the food-derived bioactive peptides. The findings provide a theoretical foundation for understanding that the peptides interact with RAS in neuroprotection.

2. Effect of the Brain RAS on Neurodegeneration

As the hormonal system in brain, RAS is primarily responsible for maintaining water and ion balance. RAS has shown potential in regulating dopaminergic neurotransmitters and protecting the nerve cells [25]. Altered components (renin; ACE1; ACE2; Ang I; Ang II) in RAS are essential to ND. Some studies established that the down-regulation of Ang II in brain RAS can improve cognitive function. The expression of ACE1 leads to the activation of AT1R, which plays a role in impairing cognitive function and inflammation [35,36]. Therefore, RAS is considered as a vital regulator in the pathophysiology of ND.

2.1. Renin and Neurodegeneration

Renin is an intracellular and secreted substance found in neurons, which is in charge of cleaving angiotensinogen into Ang I. Prorenin, as the secreted version of renin, has a higher affinity when it comes to binding to prorenin receptors in the brain. When the (pro)renin receptors are activated by the binding of renin or prorenin, the resulting signaling facilitate the cleavage of angiotensinogen into Ang I. Through the stimulation of the Ang II/AT1R axis, excessive renin signaling causes cognitive impairment [37].

The expression of renin has been demonstrated in the primary cultures of rat neurons. Research findings also showed up-regulation of renin in the brains of mice with AD and intra-neuronal expression of renin caused by Aβ *in vitro* [38]. According to a recent study, in chronic cerebral circulation insufficiency mice model, the renin inhibitor drug can decrease brain damage and cognitive impairment [39]. However, the increased renin may not translate to functional local angiotensin production. In another study by Shinohara et al., although renin was found in brain, it could be accounted for by the presence of blood that existed in the tissue. It was determined that an isoform of renin produced from a different transcript of the renin gene lacked the signal peptide and did not contribute to the production of brain angiotensin [40]. Despite the fact that renin affects brain RAS activity, the data disproved any involvement of renin or prorenin in the local angiotensin production at the spot in the brain tissue. Therefore, the effect of renin on ND remains to be studied, and the impact of renin in ND may depend more on its intracellular roles or its interaction with systemic RAS components.

2.2. Angiotensin Converting Enzymes ACE1/ACE2 and Neurodegeneration

ACE1 and its homolog ACE2 are two essential enzymes involved in the RAS components. Acetylcholine release from cholinergic neurons was decreased by upregulated ACE1 expression, whereas ACE2 signaling promotes cell survival and enhances cognition [37]. Ang II exerts anti-inflammatory effects after binding to the MasR [19]. ACE2 presents with highest abundance at the mitochondrial membrane, an increase in ACE2 can lead to an increase in the inactivation of AT1R. Therefore, this could be a way to control mitochondrial ROS generation caused by the AT1R, which is possible to promote the conversion of Ang (1–7). Since AT1R is the main contributors to ROS production, the deactivation of AT1R by ACE2 may be the primary regulatory mechanism for limiting oxidative stress in brain. Furthermore, dopaminergic neurons exhibit both pro-inflammatory and anti-inflammatory effects by the regulation of the RAS components, influencing oxidative stress and inflammation [41].

Some ACE1 inhibitors and AT1R antagonists have shown the neuroprotective benefits in PD animal models. The evidence suggested that the neuroprotective effect appear to be mediated by reducing the excessive generation of ROS and Aβ aggregation [42].

It is well-known that ACE1 and ACE2 are the two essential factors in controlling blood pressure. Likewise, hypertension is a major risk factor for cerebrovascular disease, which may aggravate the development of cognition loss. Study has demonstrated that high blood pressure may result in the negative impact on blood-brain barrier (BBB) permeability, and Aβ clearance, which then cause the development of AD and dementia [19]. ACE1 has been recognized as a gene associated with AD vulnerability in recent genomics studies [43]. According to the data collected from a memory clinic cohort, the lower cerebrospinal fluid ACE1 expression were linked to lower cerebrospinal fluid Aβ levels. The results suggested that the inhibition of ACE1 is possibly to retard the progression of AD [44]. The overactivation of ACE1 may contribute to oxidation and pro-inflammation in brain, which is a common pathogenesis of AD. Some bioactive peptides have been found to inhibit ACE1 activity. In the study of Xie et al., four peptides from walnut protein hydrolysate were verified to have high ACE1 inhibitory activity. The walnut peptide also regulated nitric oxide synthase (NOS) secretion in the Ang II-induced endothelial cell model [45]. Result has shown that Ang II can lead to ROS accumulation that aggravate neuronal death [36]. Network pharmacology and molecular docking revealed a hazelnut peptide YYLLVR targeted the RAS, modulating the ACE1/ACE2 axis in human umbilical vein endothelial cell (HUVEC) and HT-22 cells. YYLLVR downregulated ACE1/AT1R while upregulating ACE2/MasR, which alleviated Ang II-induced nerve damage and enhanced neuroprotective markers [46]. ACE1 inhibitory peptides reduced the formation of Ang II, which helps mitigate neuroinflammation and oxidative stress.

2.3. Ang II and Angiotensin Receptors in Neurodegeneration

Renin transforms angiotensinogen into the physiologically inert metabolite Ang I. Ang II then will be created by ACE1 through hydrolyzing the carboxy terminal dipeptide of Ang I [37]. According to the data of quantifying the RAS components in spontaneously hypertensive rats (SHR), Ang I was not detected in the brain tissue, whereas AT1R blockade reduced the Ang II ratio by more than 80% [47]. Thus, the origin of brain Ang II is most likely accumulated by circulating Ang II via binding to AT1R. Study revealed that the increased blood levels of Ang II during hypertension cause the BBB disruption, which allowed circulating Ang II to reach vital brain regions like the hypothalamus. When given the AT1R antagonist, BBB disruption was prevented in the hypertensive rats [48]. Moreover, Ang II has smaller size than renin and angiotensinogen, it may gain access to the brain when BBB is disrupted, and then convert to other metabolites [49]. Therefore, Ang II and AT1R play the significant role of neurodegeneration in brain.

Some investigations reveal that Ang II caused neuroinflammation by inducing oxidative stress and mitochondrial dysfunction. Along with the hippocampus and basal ganglia, this is linked to abnormalities in neurotransmitters in the neurons [50]. These occurrences cause dopaminergic cell death in the basal ganglia to cause PD and cholinergic cell loss in hippocampus to cause AD. As shown in Figure 1, in RAS, AT1R can result in the activation of NADPH oxidase, which produces ROS and causes oxidative stress in neurons. Vasoconstriction is a known effect of AT1R activation, it reduces cerebral blood flow, resulting in ischemia. Study reported that the activation of AT1R contributes to the neurodegeneration and Aβ aggregation, which exacerbate AD [51]. In a human renin and angiotensinogen transgenic mice model, AT1R activation impaired cognitive function and increased oxidative stress [52].

AT2R activation by Ang II may exert protective effects. In the brain of AT2R knockout mice model, the serious neurological deficit was found in their brain [53]. Additionally, neuroprotection is provided by Ang (1–7), which is produced from Ang II by ACE2. It is believed that MasR are the activator of Ang (1–7), and the two receptors co-localize and are functionally interdependent to exert the same positive effects. The brain's RAS influences cognitive and emotional processes, study reported peptide NVK, acting as an AT2R agonist, showed neuroprotective effects in SHRs [54]. Moreover, the BBB allows circulating angiotensin access to brain receptors, may be necessary for their stimulation.

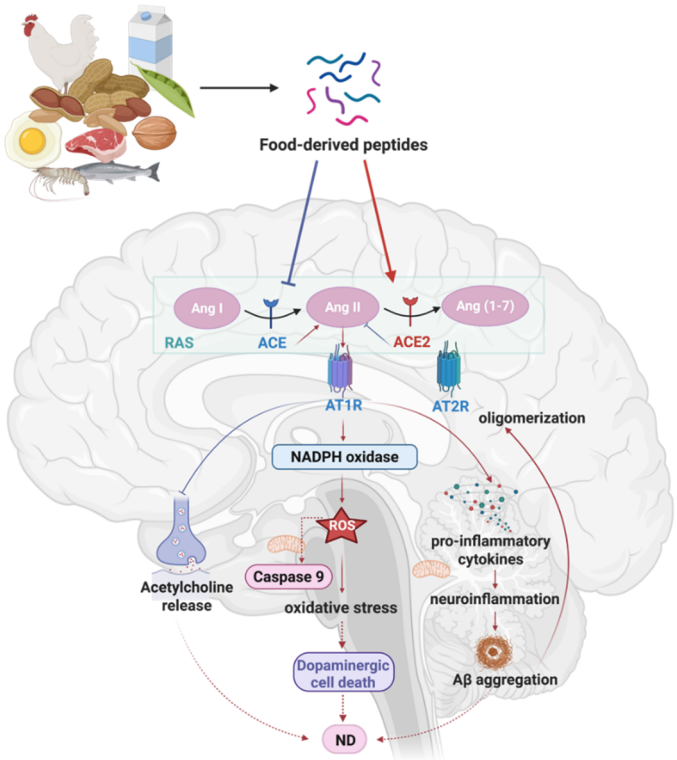

Figure 1. Neuroprotection mechanisms of food-derived peptides regulating RAS in brain. The diagram illustrates the regulatory role of peptides. The activation of AT1R leads to NADPH oxidase activation and downstream oxidative stress/neuroinflammation, which results in Aβ aggregation and AT2R oligomerization. The activated AT1R inhibits acetylcholine release that may causing ND. Peptides inhibit (blue arrows) the ACE1/Ang II/AT1R axis and activate the ACE2/Ang (1–7)/MasR axis (red arrows), thereby inhibiting the harmful effects of AT1R activation. (Created with BioRender) [51,52,55].

Although inhibition of AT1R has frequently been hypothesized to protect cerebrovascular, currently, there is still little clinical support for this idea. Taken together, the regulation of Ang II and the relevant receptors may help to prevent ND.

3. The Role of Neurotransmitters Related to the RAS

Dopamine, 5-HT, and glutamate are the vital neurotransmitters known to interact with the RAS in the CNS. These interactions can influence processes like inflammation, oxidative stress, and neuronal function, all of which are crucial factors of ND. Imbalances or dysregulation in the RAS-neurotransmitter crosstalk can cause neuronal damage, contributing to neurodegeneration. Therefore, the intricate connection between neurotransmitters and the RAS is vital for developing novel strategies to prevent ND, and gaining insights into the complex mechanisms underlying ND.

3.1. Dopamine

Dopamine is a catecholamine neurotransmitter which is produced in the substantia nigra compacta and ventral tegmental region of the brain [56]. Important physiological processes including learning and motivated behavior are regulated by dopamine. A number of processes including mitochondrial failure, oxidative stress, and inflammation, have been linked to dopamine neuron loss in PD. Recent research suggests that peripheral oxidative stress, inflammation, and metabolic abnormalities raise the ND and cause the nigrostriatal dopaminergic pathway to gradually degenerate [57]. ROS overproduction is considered as the main reason of dopamine degradation.

In the pathogenesis of neurodegeneration, dopaminergic neurons gradually degenerate, leading to bradykinesia, tremors, and rigidity [58]. Dopamine depletion can increase the expression of Ang II, which modulates dopamine synthesis through the specific receptors. Ang II interaction with AT1R typically inhibit dopamine synthesis and release, whereas its binding to AT2R can stimulate dopamine production, contributing to neuroprotection. Moreover, Ang II and AT1R can inhibit dopamine1 receptor (D1R) activation through allosteric modulation. Increased level of Ang II may even exacerbate neurodegeneration by activating NADPH oxidase, leading to high ROS production [25].

According to autoradiographic investigations, AT1R were found in dopamine neurons in the striatum of various mammals. Various cytoplasmatic and NADPH complex subunits were presented in mesencephalic dopaminergic neurons. The expression of AT1R, AT2R, and the activity of the NADPH-oxidase complex all increased significantly in response to dopamine depletion and then declined as dopamine function was restored [59]. Evidence has shown a portion of dopamine neurons transporter and co-release glutamate. Buck et al. summarized dopamine neurodegeneration in PD, they found that the dopamine neurons transporter expression may have neuroprotective effects, increasing dopamine neuron resilience in the face of PD neurodegenerative processes [60].

3.2. Glutamate

One of the primary excitatory neurotransmitters in the brain is glutamate, and ND development and occurrence are strongly correlated with glutamate's excitatory neurotoxicity. Nevertheless, mounting data indicates that glutamate plays a role in AD progression beyond its excitotoxicity as a neurotransmitter and is also associated with a disruption in its metabolic homeostasis. One of the key factors influencing the health of the CNS is the balance of glutamate metabolism in the brain, which is mostly determined by glutamate intake, circulation, and mitochondrial metabolism [61].

A sympathetic nerve activity pathway is activated by an increase in Ang II, which leads the increasing neuronal activation. Study revealed that the greater brain mineralocorticoid receptor activation initiates a slow neuromodulator pathway that sustains higher AT1R and glutamate receptor-dependent signaling in the brain [62]. In a hypoxia-induced nerve cell model, the modulation of glutamate can be a potential protective compound for ischemic brain injury [63]. In addition, due to the involvement in inflammation and neuronal damage, excitotoxicity of glutamate may accelerate many neurological diseases. In the study by Xu et al., high concentrations of glutamate dramatically decreased the enzymatic activity of ACE2 in primary cultured cortical neurons. According to the results, the high correlation score was found between the glutamate stimulation level and ACE2 activity, which revealed the possibility that glutamate-induced excitotoxicity interacts with dysregulated RAS [64].

3.3. Serotonin (5-HT)

5-HT is a monoamine neurotransmitter that controlled several physiological processes. A functional change in the neuroregulatory system could potentially result from the presence of a 5-HT dysfunction [65]. Study suggested that ACE2 in RAS plays an important role in regulating 5-HT production. L-tryptophan, an essential amino acid that can cross the BBB via the major neutral amino acid transporter, was reduced by 70% due to the absence of ACE2. Considering that tryptophan is the precursor of 5-HT, RAS components may indirectly influence 5-HT levels, which are known to influence adult neurogenesis [66].

AD cognitive decline and neuropsychiatric disorders have been related to extracellular 5-HT deficiency. Study evaluated the effect of mitochondrial dysfunction on reduced release of 5-HT from the hippocampus in AD amyloidosis mice. The hippocampus area of AD animals showed decreased 5-HT content and a downregulation of serotonergic fiber density and release. The results also revealed that the release of 5-HT from the hippocampus was inhibited by the pharmacological uncoupling of mitochondrial oxidative phosphorylation [67]. In the study of Szapacs et al., the constitutive reductions mice model had either the serotonin transporter or brain neurotrophic factor reduction. The results showed accelerated age-related degeneration of 5-HT forebrain innervation [68]. Therefore, the neurotransmitter 5-HT is closely related to the pathogenesis of neurodegeneration, and the function is mainly regulated by ACE2.

4. Neuroprotective Peptide: Food Sources, Bioavailability and Safety

4.1. Major Dietary Sources and Processing of Neuroprotective Peptides

Food-derived neuroprotective peptides are widely distributed in protein-rich dietary sources. Peptides are typically inactive within the proteins, yet some of them can be released by enzymatic hydrolysis and fermentation [69]. The major dietary sources of the neuroprotective peptides are illustrated in Figure 2. In the dairy products, the tripeptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) from milk products, acting as the ACE1 inhibitor, have shown the neuroprotective potential [70]. By inhibiting ACE1 activity, VPP and IPP enhanced the cognitive function in a human study [71]. In Swiss cheese varieties such as Appenzeller and Emmental, these peptides can accumulate during fermentation, reaching concentrations of 90–180 mg/kg [72]. In the other products such as liquid yogurt, the effective doses were reported as 1.12 mg of VPP and 0.79 mg of IPP [73]. The peptides were also found to be effective at the dosages of 2.5 mg VPP and 3.7 mg IPP in the daily tablet intake (8 weeks) [74]. Recent structural analyses have confirmed that these lactotripeptides inhibited ACE1 activity by altering polar interactions distal to the catalytic zinc ion [75]. Study on casein hydrolysates CH-3 demonstrated that the specific fractions tripeptide Met-Lys-Pro (MKP) could inhibit cellular ACE1 activity at concentrations of 5 mg/mL in SHRs [76]. By regulating the ACE1/Ang II/AT1R axis, the peptide from casein enzymatic hydrolysates lowered the hemorrhage areas in the cerebral cortex in the hypertensive rats model [77].

Recent studies also show that the bioactive peptides from plant revealed the neuroprotective effects. Soybean peptides such as Lunasin and Val-His-Val-Val (VHVV), are generated during traditional fermentation (e.g., Natto, Miso) or industrial enzymatic hydrolysis. Fermentation of soybean with *Bacillus subtilis* significantly increased the diversity of neuroprotective peptides compared to unfermented soy [78]. These peptides have shown potential in maintain neuronal survival by influencing gene expression related to oxidative stress and inflammation. In the SHR model, VHVV regulated ACE1 level and reduced long-term memory loss after 24 weeks of treatment [79,80]. The short peptide from hazelnut hydrolysate Tyr-Leu-Val-Arg (YLVR) and Tyr-Tyr-Leu-Leu-Val-Arg (YYLLVR) modulated ACE1 and ACE2 expression, respectively. The effects on RAS regulation ameliorated Ang II-induced nerve injury in the HUVECs and HT-22 cells [46,81]. Walnuts constitute a nutrient-dense food with a high content of polyunsaturated fatty acids and proteins. Following enzymatic hydrolysis, specific walnut-derived peptide fractions have been demonstrated to exert neuroprotective effects [82]. In the study by Zheng et al. [83], the ACE1 inhibitory peptides from walnut were produced after *Bacillus subtilis* hydrolysis. Moreover, the walnut peptides potentially preventing cognitive decline by regulating oxidative stress pathways which closely linked with the RAS [84,85].

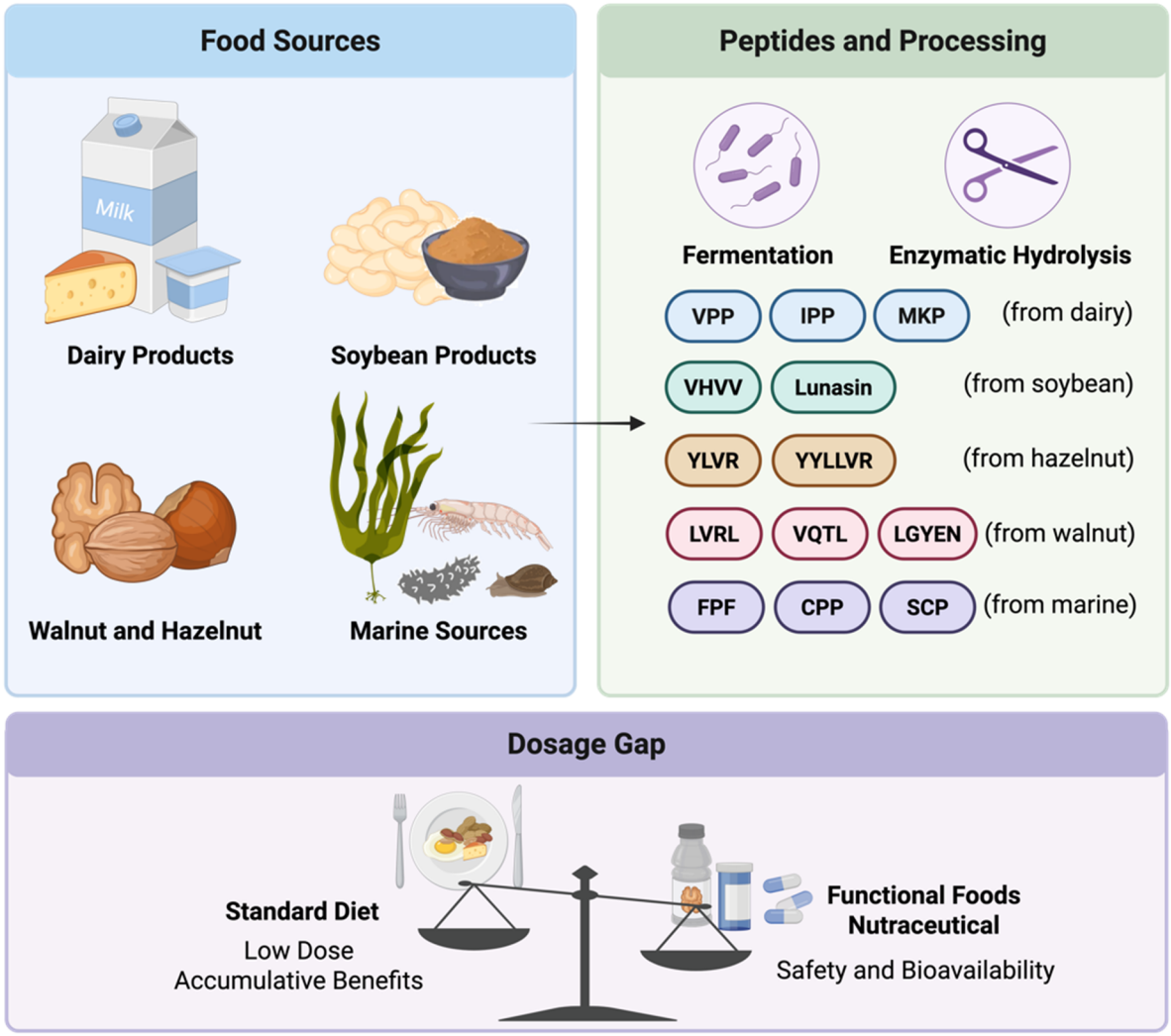

Figure 2. Summary of neuroprotective food-derived peptides sources, processing, and dosage gap between standard diet and nutraceutical (Created with BioRender).

Similarly, marine source peptides are gaining attention for their high bioavailability and BBB crossing ability. Li et al. [86] highlighted the marine-derived proline-rich peptides possess unique structural stability that protects them from gastrointestinal degradation, allowing them to reach the CNS and exert neuroprotective effects. Increasingly studies revealed the peptides from marine source, especially seaweed, sea cucumber and Antarctic krill (shown in Table 1) are associated with RAS related neurotransmitters to exert neuroprotective function [87]. The bioactive peptide isolated from the visceral of a marine snail modulated the neurotransmitter dopamine, which ameliorated the degenerating of dopamine neurons and prevented the cerebral vessels loss *in vivo* [88]. CPP, as the enzymatic extracts of *Chlorella pyrenoidosa*, suppressed the neuroinflammation in AD mice model at the concentration of 100 mg/kg [34]. Enzymatic digestion is the typical method used In Antarctic krill peptide extraction. A tripeptide Phe-Pro-Phe (FPF) from Antarctic krill survived from the digestion and crossed the BBB to exhibit the potential in preventing the memory impairment of scopolamine-induced mice [89]. Similarly, the memory improving peptide Pro-Pro-Trp (PPW) from round scad can stay intact and transported across the intestinal cells [90].

Table 1. Summary of neuroprotective food-derived peptides.

Peptide Sequence	Food Source	Experimental Model	Dose	Mechanism of Action	Key Findings	Evidence Level	Ref.
GGPFKSPF	Flavourzyme®-pea	Aβ-induced SH-SY5Y cells	1 ppm	Downstream pathway: Nrf2/HO-1	Antioxidant effect via Nrf2/HO-1 signaling pathway by activating Nrf2	+	[32]
SCP-S, SFGDI	sea cucumber	male SPF C57BL/6 mice, *n* = 15	Oral, 30 days, 160 mg/kg.bw	Downstream pathway: Sirt3/Ac-SOD pathways	Reducing inflammation levels and oxidative stress levels by modulating the Sirt3/Ac-SOD pathways	++	[33]
CPPs	*Chlorella pyrenoidosa*	male ICR mice, *n* = 6 per group	Oral, 14 days, 100 mg/kg.bw	Neurotransmitter: 5-HT	Inhibiting inflammatory cytokines to improve spatial cognition	++	[34]
YYLLVR	hazelnut	Ang II induced HT-22 cells	25, 50, 100 and 200 μmol/L	ACE1 and ACE2 regulation	Regulation of RAS and pro-inflammatory factors to exert neuroprotection	+	[46]
LVRL	walnut	male C57BL/6 HFD mice, *n* = 8	Oral, 4 weeks, 60 mg/kg.bw	Downstream pathway: Wnt3a/β-Catenin/GSK-3β	Enhancing synaptic plasticity through the Wnt3a/ β-Catenin/GSK-3β pathway	++	[82]
LVRL	walnut	Glucose induced PC12 cells	100 μM	Downstream pathway: Wnt3a/β-Catenin/GSK-3β		+	
YVLLPSPK	walnut	scopolamine-induced C57BL/6 mice, *n* = 10 per group	Oral, 4 weeks, 60 mg/kg.bw	Downstream pathway: Nrf2/Keap-1/HO-1	Inhibition of mitochondrial oxidative stress-related neuronal apoptosis through the NRF-2/Keap-1/ HO-1 pathway	++	[84]
YVLLPSPK	walnut	H_2O_2-induced HT22 cells	100 μM	Downstream pathway: Nrf2/Keap-1/HO-1		+	
YIAEDAER	*Neptunea arthritica cumingii* (marine snail)	MPTP-induced locomotor impairment in zebrafish, *n* = 32 per group	2, 10, 50 μg/mL	Neurotransmitter: dopamine	Ameliorating the degenerating of dopamine neurons, inhibiting the loss of cerebral vessels	++	[88]
FPF	Antarctic krill	Male SPF C57BL/6 mice, *n* = 8–12	Gavage, 40 mg/kg.bw, 50 days	Neurotransmitter: ACh and AChE	Regulation of Ach, AchE, and neurodegeneration proteins level in the hippocampus	+++	[89]
SCP	sea cucumber	scopolamine-induced C57BL/6 mice, *n* = 10 per group	Oral, 7 days, 162.5, 325, 650 mg/kg.bw	Neurotransmitter: 5-HT, dopamine	Improving synapse plasticity and regulating dopamine/ 5-HT metabolization via TH/VMAT2 pathway	++	[91]
GPETAFLR	*Lupinus angustifolius* L.	HFD-induced C57BL/6J male mice, *n* = 10 per group	Oral, 8 weeks, 0.5 and 1 mg/kg.bw	Downstream pathway: NF-κB	Downregulation of IL-10 and upregulation of pro-inflammatory markers in the mouse brain	++	[92]
GPETAFLR	*Lupinus angustifolius* L.	LPS-induced BV-2 cells	50 and 100 μg/mL	Downstream pathway: TNF-α	Upregulation of pro-inflammatory	+	
HCE	chicken	male C57BL/6 mice, *n* = 8–10 per group	Oral, 4 weeks, 300 mg/kg.bw	Downstream pathway: NF-κB; MAPK	Alleviation of hippocampal neuroinflammation and oxidative stress	++	[93]
PIYAG	Annona squamosa	LPS-induced ICR mice, *n* = 10 per group	Gavage, 6 weeks, 0.1g/kg.bw	Downstream pathway: TNF-α	Regulation of inflammation cytokines	++	[94]
MKP	milk	Aβ-induced adult male ddY mice, *n* = 18–20 per group	Oral, 2 days before Aβ1–42 injection, 0.5 mg/kg.bw	ACE1 regulation; downstream pathway: TNF- *α*	ACE1 inhibitory effect and alleviation of inflammatory cytokines expression	+++	[95]
EWH	egg	mercury-induced male Wistar rats, *n* = 8 per group	Gavage, 60 days, 1 g/kg.bw	Downstream pathway: TNF-*α*	Attenuating oxidative damage and expressions of proinflammatory cytokines in brain	+++	[96]
CSP	*Cardamine violifolia*	D-Galactose-induced male Sprague Dawley rats, *n* = 10	Oral gavage, 8 weeks, 3.55; 14.2; 56.8 mg/kg.bw	Downstream pathway: NF-κB; MAPK; Nrf2	Reducing the neuro-inflammation by inhibiting the NF-κB pathway JNK phosphorylation	++	[97]

Abbreviations: RAS: Renin angiotensin system; CPPs: *Chlorella pyrenoidosa* peptides; EWH: egg white hydrolysate; HCE: hydrolyzed chicken extract; Nrf2: Nuclear factor erythroid 2-related factor 2; Keap-1: Kelch-like ECH-associated protein 1; HO-1: Heme Oxygenase-1; 5-HT: 5-hydroxytryptamine/serotonin; TNF-*α*: Tumor necrosis factor alpha; IL-10: Interleukin-10; NF-κB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase; TH/VMAT2: Tyrosine hydroxylase/ Vesicular monoamine transporter 2; GSK-3β: Glycogen Synthase Kinase 3 Beta; Sirt3/Ac-SOD: Sirtuin 3/ Acetylated superoxide dismutase; Ach: Acetylcholine; AChE: Acetylcholinesterase; ACE: Angiotensin-Converting Enzyme; Ang II: Angiotensin II; Aβ: Amyloid-beta; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ICR mice: Institute of cancer research mice; HFD: High-fat diet; LPS: Lipopolysaccharide; SPF: Specific pathogen-free. Annotation: kg·bw (dose based on animal body weight, Daily dose = animal weight (kg) × Dosage for one day (mg or g)). Evidence level: "+" = *in vitro* only; "++" = *in vivo* animal; "+++" = *in vivo* with pharmacokinetics /BBB penetration evidence.

4.2. Safety and Bioavailability of Food-Derived Neuroprotective Peptides

Although the regulation of peptides on RAS has neuroprotective potential, systemic modulation like ACE inhibition or AT1R blocking may lead to side effects such as hypotension or renal function impact [98,99]. Food-derived peptides are generally considered safer than synthetic ACE inhibitors, the risk of hypotension still exists in high doses consumption [100]. The high intake of animal protein, especially rich in leucine, might increase the risk of cardiovascular diseases [101]. A high-dose of peptide diet may also overload peptidases, potentially affects gastrointestinal function and gut microbiota [57].

Significant differences exist among various food sources regarding the type, concentration, and bioavailability of neuroprotective peptides. Dairy products are considered a readily available source where bioactive peptides may benefit from protection of the dairy matrix. The protein riches in the dairy such as casein, prevents the peptide degradation from digestive enzymes [102]. The neuroprotective peptides from plant sources are frequently contained in the plant fibrous. With the processing method like fermentation, the peptide bioavailability is significantly improved [103,104]. Most peptides are easily degraded by gastrointestinal proteases (pepsin, trypsin) and peptidases before they can be absorbed. During gastrointestinal digestion, many peptides with unknown actions may be produced at the same time, which increase the risk of allergic reactions [105]. Marine source peptides characterized by a high content of proline showed greater resistance to gastrointestinal proteases [106]. However, those bioactive peptides without proline still face bioavailability challenges before reaching the CNS [106].

While the *in vitro* and *in vivo* studies suggest that these bioactive peptides from various protein sources may offer accumulative benefits, the acute neuroprotective effects observed in animal models are difficult to achieve through the diet alone. The lack of consistency in peptide production at the industrial level also makes it difficult to guarantee specific concentrations in final food products [69]. Therefore, effective dietary strategies for neuroprotection may require the incorporation of functional foods specifically enriched with these bioactive peptides or the use of targeted nutraceutical to ensure the adequate intake levels and avoid high-dose side effects [107,108]. In order to lessen systemic effects and increase the specificity of food-derived peptides, the targeted delivery systems like liposomes and nanoparticles can be used in the future research [109]. Some studies used receptor-mediated transcytosis process to deliver the peptides into the brain, which achieve the brain-targeted delivery and solve the challenges due to the BBB [110].

5. Food-Derived Peptides: Potential Candidate to Prevent Neurodegenerative Diseases through the Modulation of RAS Related Neurotransmitters and the Downstream Pathways Regulated ND

5.1. Modulation of Food-Derived Peptides on RAS-Related Neurotransmission Signaling Pathways

Two main pathways that are up-regulated for cognition and memory systems are the serotonergic and dopaminergic synapses. These pathways support synaptic plasticity, vesicle transport, and the synthesis of dopamine and 5-HT. Food-derived peptides exert these neuroprotective effects on neurotransmission by balancing RAS axes in the brain. For the dopaminergic system, peptides that inhibit the ACE1/Ang II/AT1R axis alleviate the inhibition of D1R by Ang II [25]. The reduced Ang II levels prevents the overactivation of NADPH oxidase, that lead to the apoptosis of dopaminergic neurons in the substantia nigra [55]. Since L-tryptophan is the essential precursor for 5-HT synthesis, a decrease in ACE2 activity in neurodegenerative pathologies can lead to reduced 5-HT levels [66]. A study determined the neuroprotection activity of bioactive peptide SVHRSP, which mitigated the loss of dopaminergic neuron, and decreased rotenone-induced proinflammatory neurotoxicity [111]. In the study by Lu et al., sea cucumber peptide SCP influenced the secretion of dopamine and 5-HT, thereby preventing memory impairment in the animals. The proteomics findings showed that the dopaminergic synaptic pathway was responsible for the marked up-regulation of tyrosine hydroxylase (TH) expression level [91]. Considering exogenous dopamine was blocked from passing across the BBB, the memory function was heavily relied on the self-synthesis by dopaminergic neurons. Consuming Camembert cheese has been demonstrated to prevent AD in animal models. Some whey peptides were also proven to improve memory impairment. The KEMPFPKYPVEP peptide derived from beta-casein, administered at 0.5 mg/kg and 2 mg/kg, improved dopamine and norepinephrine levels in the mice brain and ameliorated memory impairment compared to the control group [112]. As a result, peptides found in fermented dairy products can prevent cognitive aging. According to some earlier research, the activity is often related to the regulation of dopamine.

There are various neurodegenerative illnesses that have been linked to the glutamate-induced toxicity pathway. In these conditions, neuronal cell death can be reduced by molecules that either activate glutamate receptors or block glutamate release. Shah et al. studied the neuroprotective effects of osmotin, a plant protein derived from *Nicotiana tabacum*, it ameliorated the neurodegeneration and synaptic dysfunction caused by glutamate in the rat brain. According to the findings, glutamate therapy overactivated glutamate receptors,

resulting in toxicity in the hippocampus of rats, caused synaptic dysfunction and cell apoptosis. Moreover, osmotin therapy reversed the effects of glutamate-induced DNA damage and cell death, while also establishing the distribution and localization of p53, phosphorylated protein kinase (p-Akt), and caspase-3 in the rats' brain hippocampus [113].

5.2. Regulation of Food-Derived Peptides on RAS Downstream Antioxidation and Anti-Neuroinflammation Signaling Pathways

In RAS, the activation of AT1R triggers a cascade of oxidative signaling events that involve mitogen-activated protein kinase p44/42 and JNK, which are responsible for neurotoxicity. AT1R's role in the brain injuries is to increase the phosphorylation of apoptotic signal mitogen activated protein kinase (MAPK) [114].

Foodborne bioactive peptides can act as antioxidants, scavenging free radicals and protecting neurons from oxidative damage associated with RAS. Chickpea seed bioactive peptide was demonstrated to be effective on suppressing ACE1 to show the inhibition of amyloid fibril formation in rats [115]. Pulse crops peptides also showed similar effect as ACE1 inhibitors to exert neuroprotective activity both *in vitro* and *in vivo* [116]. Study obtained tryptic hydrolysates of protein fractions from *Cicer arietinum* L. seeds, and the peptide was interacted with zinc ions. The results revealed that the regulation of zinc-chelating peptides on Aβ was associated with the ACE2 level [117]. Suwanangul et al. separated peptide SPH in sacha inchi protein. Their results suggested that SPH had strong ACE1 inhibitory efficiency, associated with the potential utility as a functional foods and nutraceuticals with the ability to protect vascular and brain health [118]. The antioxidant peptide SVDGKEDLIW purified from buffalo milk protein was evaluated in aging Kunming mice. The findings in high-dose peptide treatment group revealed the highest antioxidase activity in mice brain and blood [119]. Similarly, study investigated the neuroprotective effects of whey protein peptide WHP in aging mice model. The results revealed that WHP significantly resisted oxidative stress injury, which the prevented hippocampal nerve cells. Moreover, the down-regulation of inflammatory factors tumor necrosis factor-alpha (TNF-α) and Interleukin IL-1β was also found in brain tissue. Three peptide fractions were extracted from *Salvia hispanica* seeds following hydrolysis. Results indicated that peptides neuroprotection functions were linked to a reduction in the generation of ROS. Similarly, the peptides showed the significant decrease of IL-6 and TNF-α. The plant-derived peptides demonstrated a neuroprotective impact with the anti-inflammatory and antioxidant properties [120]. These results indicated that many food-derived peptides suppress the activation of oxidation pathways to prevent neurodegeneration. The regulation is also related to neuroinflammation pathways.

The localized brain RAS activation is linked to neuroinflammation response associated with Ang II. The increasing level of Ang II can cause the release of pro-inflammatory cytokines, results in neuroinflammation in brain [121]. In the study by Lemus-Conejo, peptide extracted from *Lupinus angustifolius* L. downregulated the expression of inflammation cytokines in lipopolysaccharides-induced microglial BV-2 cells. The *in vivo* results also revealed that lupine peptide decreased the pro-inflammatory markers in the mouse brain [92]. The tilapia skin peptides were found to decrease inflammation cytokines levels in the hippocampus of mice. The peptides reversed the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway, which indicated the amelioration of neuroinflammatory response in the mice brain [122]. Peptides SLPY, QYPPMQY and EYEA form Antarctic krill hydrolysate inhibited ACE1 activity and upregulated Nrf2 protein level in HUVECs. The oxidation level was subsequently reduced by the peptide [123]. Hydrolysate of chicken meat could ameliorate neuroinflammation and memory loss in male C57BL/6 mice. The hydrolysate treatment significantly down regulation in the NF-κB and p38 MAPK signaling pathways, which were associated with the neurotransmission related to inflammation [93]. A neuroprotective peptide from *Flammulina velutipes* protein hydrolysates regulated the Keap1/Nrf2/HO-1 pathway *in vitro* [124]. The peptide PIYAG, derived from Annona squamosa, demonstrated significant anti-inflammatory and neuroprotective effects. In LPS-induced mice, it enhanced spatial memory and suppressed key inflammatory markers such as iNOS and TNF-α. PIYAG (0.01–0.2 μM) also dose-dependently reduced inflammation in BV2 microglial cells [94]. As summarized in Table 1, food peptides have demonstrated to reduce neuroinflammation *in vivo* and *in vitro*. The result is considered that the antioxidation and anti-neuroinflammation mechanisms are framed as RAS downstream regulation. However, there is few studies discussed the peptide stability after animal oral administration. And the results found in cell models still need to be verified on dosage effects [32].

5.3. Peptide Structure and ND

Molecular structure of peptides is a vital factor that affects peptide bioactive functions. Study revealed that the hydrophobicity of peptides allowed them to get into cells and act on their specific targets. According to the examination results of the amino acid compositions of neuroprotective peptides, 92% of the peptides contained hydrophobic amino acids [125]. It has been found that the neuroprotective potential of peptides can be influenced by aromatic amino acids. In neurodegeneration condition, the presence of aromatic amino acids like phenylalanine and tyrosine demonstrated better anti-inflammatory and antioxidant effects. [126]. Wang et al. summarized the basic amino acids, particularly lysine and arginine could affect the activity of acetylcholinesterase by creating stable complexes with acetylcholinesterase peripheral anionic site. When the neurotransmitter glutamate crosses the BBB, it can aid in neuroprotection through a high-affinity transport system, which includes glutamate transporters on pre-synaptic and astroglia in the CNS [125]. Hence, the development of food derived peptides, including the choice of enzymes and the production procedures benefit from the understanding of the structural properties of neuroprotective peptides. On the other hand, the majority of research continues to focus on how peptide molecular weight, amino acid composition, and sequencing affect their neuroprotective effects, whereas the relationship between the precise binding sites of peptides and their neuroprotective properties need further study.

Some neuroprotective peptides are investigated to crossing the BBB in order to prevent ND. Hydrophobic peptides, especially those containing aromatic amino acids, can cross the BBB via passive diffusion. For example, the tripeptide FPF from Antarctic krill is suggested to utilize this pathway due to its small size and phenylalanine residue [89]. The tripeptide MKP, found in milk protein showed a strong ACE1 inhibitory activity and the ability to cross the BBB. Its specific transport mechanism to CNS is through receptor-mediated transcytosis, a process where peptides bind to specific receptors on the endothelial cells [127]. In the mice brain, MKP was shown to reduce oxidative stress, indicating that it may hold potential in avoiding cognitive decline in AD [95]. Some peptides and the metabolic fragments such as L-tryptophan cross the BBB via the neutral amino acid transporter [128]. Food derived β-casomorphin-5 and the active fragments were reported to pass BBB, reach opioid receptors in the brain and exert their bioactive functions in the CNS [129,130].

Conversely, BBB disruption in the brain is indicated as an early biomarker for AD, since most patients show hippocampus disruption before neuronal destruction. The maintenance of BBB integrity may be another effective target to ameliorate neurodegeneration. The walnut-derived peptide TW-7 improved memory ability in mice by protecting BBB integrity [131]. Taken together, some bioactive peptides exert the targeting neuroprotective effect by the penetrability to BBB and the protection of BBB integrity.

5.4. Animal Models

To evaluate the effects of different peptides on anti-ND, studies have reported various animal models. The establishment of specific animal models is crucial for the pathological mechanisms. However, given the complex pathogenesis of ND, which involves multiple factors and various pathological features, there isn't a single animal model that fully replicates all neurodegeneration pathological characteristics. In the following sections, we provide an overview of several commonly used animal models in the research of neuroprotective food peptides.

Generally, aging animal models and injury-based animal models are the most common animal models in neurodegeneration research. Natural aging models involve the development of ND-like symptoms in animals. The model does not require external stimuli through drugs or procedures, making it more representative of real ND pathology. In this model, the mice exhibit pathological changes such as alterations in cortical microvascular structure, reduced vascular density, and inhibited vascular growth [132]. However, these models have limitations, including high costs, high mortality rate, and the inability to guarantee the pathological characteristics. Senescence Accelerated Mouse-Prone (SAMP) is a rapid aging animal model, which includes nine sub-strains. Among them, SAMP8 is widely used in AD aging model [133]. This animal model shows cognitive impairment, neuronal loss, abnormal neurotransmitter metabolism, and brain atrophy after a 5-month aging period [134]. SAMP mice ensure a higher modeling success rate, whereas they come with disadvantages such as high cost, short lifespan, and unsuitability for long-term studies. Another aging animal model D-galactose-induced aging model, is one of the most commonly used models in ND studies. The mice were induced with D-galactose which in turn cause natural aging characteristics. The intracellular accumulation of galactose can affect protein and lipid metabolism. This model disrupts neuronal cells' normal physiological functions through a series of oxidative damage, resulting in cognitive impairment [135]. As shown in Table 2, these animal models are used in the functional research of various food-derived peptides.

To simulate ND in the animal models, research focused on chemical induced approach such as scopolamine and Aβ-induced model. The models often characterized with the disruptions in the cholinergic system and

impairing their ability to acquire information [136]. Considering that excessive Aβ accumulation is the major pathogenic factor in AD, researchers injected different Aβ fragments into mice hippocampus to mimic AD pathogenesis [137]. The pathological simulation emphases of these models need to correspond with the core mechanisms of action of food-derived peptides to ensure that activity assessment is more targeted.

6. Current Challenges and Future Perspectives

Although food-derived peptides demonstrate potential in alleviating ND in cellular and animal models, the application of food-derived peptides still face significant challenges, primarily regarding bioavailability and metabolic stability. Many peptides are degraded by gastrointestinal proteases before reaching the systemic circulation. Therefore, the BBB crossing ability of peptides remains a major issue. While some peptides can cross via transcytosis or specific transporters, the permeability of long-chain peptides remains limited. Future research should focus on the peptide absorption, safety, dose comparability and translation.

Specifically, few studies reported the relevant dietary recommendations of human equivalent dose of the neuroprotective peptides. The significant difference exists between the high doses used in animal models and realistic dietary intake levels. Although cellular models like Caco-2 cells provide preliminary absorption data, rigorous *in vivo* studies are required to verify the specific mechanisms and the actual concentration of intact peptides that reach the CNS. Although several food-derived peptides exhibit neuroprotective properties, specific fractions such as the RP peptide, showed a significant neuroprotective reduction following digestion [32]. while MKP showed neuroprotective potential, its effect is specifically linked to the regulation of the ACE1/Ang II/AT1R axis, but no significant regulation of ACE2. A reduction in neuroprotective efficacy was also observed at high MKP concentrations [77,95]. As the long-term supplementation of the peptides may be required in the future, the toxicological assessments are necessary to evaluate the potential allergenicity or harmful effects during peptide preparation [138]. Furthermore, most current data depends on short-term animal studies. The clinical study is essential to determine whether the modulation of RAS by dietary peptides has sustained neuroprotective benefits.

Table 2. Animal models used in neuroprotective food peptides research.

Animal Model	Peptide/Hydrolysate	Advantages	Drawbacks	Ref.
Aged mice	protein hydrolysate from fish	no external stimuli through drugs or procedures	high costs; high mortality rate	[132]
Senescence Accelerated Mouse-Prone (SAMP)	soy peptides	no external stimuli through drugs or procedures; higher modeling success rate	short lifespan; unsuitability for long-term studies; high cost	[139]
D-Galactose-induced mice	protein hydrolysate from walnut; protein hydrolysate from *Cardamine violifolia*	cost-effective; high reproducibility; most commonly used model	short lifespan	[97,140]
Scopolamine-induced mice	peptides QMDDQ, KMDDQ from shrimp; peptide FYDWPK from sea cucumber; protein hydrolysate from walnut	cost-effective	scopolamine effects can be reversible	[141–143]
Aβ-induced mice	peptide from walnut; protein hydrolysate from milk	Easy to mimic AD pathology	unpredictable brain injuries during injection	[95,144]

7. Conclusions

An overactive RAS in the brain is increasingly recognized as a critical factor in the pathogenesis of ND. Food-derived bioactive peptides have demonstrated their ability to modulate RAS related neurotransmitters and the downstream pathways within the brain, where they actively participate in processes related to neuroinflammation and oxidative stress. This review elucidated the profound impact of RAS on ND, exploring the effects of RAS on neurotransmitter regulation and neurodegeneration pathways. Moreover, we discussed the effect of food-derived bioactive peptides in mitigating ND by modulating RAS. Specifically, peptides sourced from food have shown the positive effects by engaging with downstream inflammatory pathways and neurotransmitter systems in the brain. Some food bioactive peptides were shown to have the ability of penetrating BBB in the animal model. Furthermore, these peptides have demonstrated their capacity to mitigate the loss of serotonergic and dopaminergic neurons, which are indispensable for cognition and memory functions.

Food-derived bioactive peptides show the protective potential on brain health to ameliorate neurodegeneration. However, further studies still need to assess the bioavailability and metabolic fate of these food peptides following oral administration, ensuring their efficacy in the body, especially when consumed by human. While animal models indicate that some peptides have BBB-penetrating capabilities and neuroprotective efficacy, few human and clinical evidence are reported to support the effects. Therefore, rigorous PK, BBB penetration, and safety studies are required to translate preclinical findings into clinical application. Subsequent studies, especially the integration of advanced multi-omics approaches such as transcriptomics, metabolomics, and metagenomics, are essential to fully understand the underlying mechanisms of food-derived bioactive peptides.

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