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Neuroprotective potential of paddy rice: Advancing nutritional and therapeutic strategies for brain health

Bhagyashri Ramesh Shinde * and Amol Navnath Khedkar

Saikrupa Institute of pharmacy, Ghargaon, Shrigonda, A. nagar, Maharashtra, India 413728.

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Abstract

Paddy rice has gained attention beyond its role as a staple food, now recognized for its neuroprotective properties due to its rich phytochemical content. Compounds like tocotrienols, gamma-oryzanol, and phenolic acids in paddy rice exhibit antioxidant, anti-inflammatory, and neuroregenerative properties. These compounds help reduce oxidative stress, manage neuroinflammation, balance neurotransmitter function, and promote neurogenesis, supporting overall brain health and potentially delaying neurodegenerative processes. Components like gamma-oryzanol and ferulic acid show promise in decreasing neuroinflammation and enhancing dopaminergic function, suggesting therapeutic potential for conditions like Parkinson's and Alzheimer's. Research indicates paddy rice bioactives can improve cognitive function and neural resilience, underscoring their therapeutic value for neurological disorders. Further studies are required to validate these findings in clinical settings, explore optimal dosages, and enhance bioavailability. This review summarizes recent research, highlighting the promising effects of paddy rice-derived nutraceuticals and emphasizing the importance of bridging lab discoveries with practical medical applications through comprehensive research efforts.

Keywords: Paddy rice; Neuroprotection; Antioxidants; Neuroinflammation; Cognitive health; Neurological disorders

1. Introduction

1.1. Overview of paddy-rice as a staple crop

Rice is a crucial staple food crop globally, with paddy being the most cultivated crop worldwide. Over 60% of people depend on it as their main food source, particularly in Asia. India follows China in production and has the largest paddy acreage, supporting over half of the world's population.

1.2. Emerging interest in its medicinal properties

Paddy rice byproducts offer both nutritional and therapeutic benefits, with the edible portion being used for potential items while the inedible parts are discarded during processing. Paddy rice is rich in essential vitamins and minerals like iron, zinc, vitamin B6, thiamine, and niacin, which are crucial for brain function. These nutrients play key roles in energy synthesis, nervous system function, neurotransmitter synthesis, immune system support, and oxygen transport to the brain. Additionally, antioxidants found in paddy rice can protect the brain from oxidative stress by neutralizing harmful free radicals. This balance is important for cell health, especially in brain cells, to prevent damage and maintain proper function.

Importance of exploring neuroprotective potential in the context of rising neurological disorder: The global burden of neurological disorders is rising rapidly, with conditions like Alzheimer's and Parkinson's diseases affecting millions worldwide. The World Health Organization predicts a tripling of dementia cases by 2050, with over 10 million

* Corresponding author: Bhagyashri Ramesh Shinde

individuals currently impacted by Parkinson's disease alone. Nutraceutical solutions, such as paddy rice with its neuroprotective bioactives, are being explored to address this crisis. Research has shown that rice bran, rich in antioxidants and nutrients, may have potential neuroprotective properties. A study by Stephanie Hagl et al. in 2013 found that paddy rice extract rich in vitamin E could improve mitochondrial function and mitigate changes in behavior and biochemistry in healthy guinea pigs. This research suggests that paddy rice extract could be a promising treatment for neurological disorders like Huntington's disease.

2. Paddy rice: nutritional and phytochemical composition

Brief overview of the phytochemical profile of paddy-rice including nutritional composition (Table 1):

2.1. Gamma-oryzanol

Gamma-oryzanol improves pituitary function and induces the release of endorphins. It is a safe natural chemical with no significant adverse effects. Anthocyanin, specifically cyanidin-3-glucoside (C3G), is a strong antioxidant with neuroprotective properties. Oryza sativa L has shown potential benefits in a mouse model of Alzheimer's disease.

2.2. Tocotrienols and tocopherols (Vitamin E derivatives)

Various types of whole rice have different levels of vitamin E, with ranges from 36 to 63.

29 mg kg−1. Black-pigmented rice had higher levels of α-tocopherol, β-tocopherol, and γ-tocotrienol compared to red-pigmented and non-pigmented rice. Red-pigmented rice had lower levels of γ-tocotrienol and total vitamin E. γ-tocotrienol was the most common isomer in all species.

2.3. Phenolic compounds

There are various ways that phenolic compounds might demonstrate their antioxidant properties. As chain- breaking antioxidants, they may directly scavenge some reactive species, such as superoxide, peroxyl, and hydroxyl radicals. They might recycle other antioxidants, such α-tocopherol, and inhibit lipid peroxidation.

2.4. Ferulic Acid

Ferulic acid is one of the phenolic acids that has lately been suggested as a possible neuroprotective agent. It has been demonstrated to block Aβ oligomer aggregations and to have antioxidant, anti-inflammatory, and anti-apoptotic properties. In fact, it appears to improve Alzheimer Disease (AD) pathogenesis by avoiding neurodegeneration in several brain regions.

Table 1 Nutritional and Phytochemical Composition of Paddy Rice

Bioactive Compound	Concentration Range	Neuroprotective Effects
Tocotrienols (Vitamin E)	19.36 – 63.29 mg/kg	Antioxidant properties; reduces oxidative stress, protects against cellular damage in neurological disorders likeAlzheimer’s.
Gamma-Oryzanol	1.5 – 2.9 g/kg	Regulates neuroinflammation, enhances hypothalamic function, and may aid in neurotransmitter synthesis.
Phenolic Acids	0.4 – 2.5 g/kg	Scavenges free radicals; helps reduce oxidative stress and lipid peroxidation, protecting against neurodegeneration.
Ferulic Acid	0.5 – 1.0 g/kg	Anti-inflammatory, anti-apoptotic; inhibits amyloid-beta aggregation, reducing risk of Alzheimer’s disease.
Anthocyanins	20 – 500 mg/kg (varies by rice type)	Provides neuroprotection by reducing oxidative stress and neuronal apoptosis; supports memory function.
Flavonoids	0.1 – 0.9 g/kg	Exhibits antioxidant effects; aids in modulating neuroinflammatory pathways, potentially beneficial in cognitive decline.
Zinc	16 – 25 mg/kg	Essential for neurotransmitter function, supports neurogenesis and overall brain health.

Iron	3 – 8 mg/kg	Vital for oxygen transport to the brain; supports cognitive function and reduces neurological damage due to hypoxia.
Thiamine (Vitamin B1)	0.2 – 1.0 mg/kg	Critical for nerve function; deficiency linked to memory impairment and neurological conditions like Wernicke's encephalopathy.
Niacin (Vitamin B3)	0.5 – 2.5 mg/kg	Supports brain energy metabolism; reduces neurodegeneration risk by enhancing neuronal survival and

2.4.1. Bioavailability and Metabolic Pathways of Key Compounds

- Tocotrienols: Tocotrienols, a type of vitamin E found in paddy rice, are powerful antioxidants that help protect the brain by reducing oxidative stress and inflammation. However, their absorption is limited due to their fat-soluble nature. They are primarily absorbed in the small intestine and then distributed throughout the body, with some being metabolized in the liver before being excreted. The rapid metabolism and elimination of tocotrienols reduce their effectiveness in reaching target tissues like the brain.
- Gamma-Oryzanol: Gamma-oryzanol is a phytosterol complex with antioxidant and anti-inflammatory properties that offer neuroprotective benefits. It stabilizes neuronal membranes and reduces neuroinflammation. Like tocotrienols, it is lipid-soluble and its absorption depends on dietary fats. However, its bioavailability is typically low.

2.4.2. Enhancing Bioavailability of Tocotrienols and Gamma-Oryzanol

- Lipid-Based Carriers: Encapsulation in lipid-based carriers like liposomes, nanoemulsions, and solid lipid nanoparticles enhances the bioavailability of tocotrienols and gamma-oryzanol. These carriers protect the compounds, enhance stability and solubility, and aid in direct cellular uptake and delivery to the brain. Nanoemulsions improve absorption by increasing surface area for digestion and facilitating lymphatic transport.
- Self-Emulsifying Drug Delivery Systems (SEDDS): SEDDS are a promising approach that involves the use of natural oils, surfactants, and co-solvents to form emulsions upon contact with gastrointestinal fluids. These systems enhance the solubility and absorption of lipid-soluble compounds like tocotrienols and gamma-oryzanol. By promoting a more efficient and consistent release of bioactives into the bloodstream, SEDDS can significantly improve their bioavailability and systemic effects.
- Phospholipid Complexes: Forming phospholipid complexes, such as phytosomes, can also improve the bioavailability of rice-derived bioactives. In these complexes, the bioactive compounds are conjugated with phospholipids, which enhance their solubility and facilitate better interaction with cell membranes, leading to improved uptake and delivery to the brain. This method is particularly advantageous for targeting the central nervous system, as it supports transcellular transport mechanisms that may help tocotrienols and gamma-oryzanol cross the blood-brain barrier.
- Nanoparticle Delivery Systems: Recent advances in nanoparticle technology are improving the bioavailability of bioactives, with polymeric and lipid-based nanoparticles showing promise. These particles can release tocotrienols and gamma-oryzanol in a controlled manner, providing sustained therapeutic effects, particularly beneficial for long-term neuroprotection.

3. Mechanisms of action for neuroprotection

3.1. Antioxidant Properties: Mitigation of Oxidative Damage at the Cellular Level

3.1.1. Role of Antioxidants in Brain Health

Oxidative stress plays a significant role in neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's. The brain's high oxygen consumption and lipid-rich neurons make it vulnerable to damage from reactive oxygen species (ROS). Antioxidants can help neutralize ROS, protecting brain cells from harm.

3.1.2. Specific Antioxidants in Paddy Rice

- Tocotrienols and Tocopherols (Vitamin E Derivatives):Vitamin E derivatives found in paddy rice, such as tocotrienols and tocopherols, are powerful antioxidants that protect against lipid peroxidation. Tocotrienols are especially effective at integrating into neuronal cell membranes, offering neuroprotective benefits and supporting cellular resilience in oxidative conditions.

- Gamma-Oryzanol: Gamma-oryzanol's structure, comprising ferulic acid and phytosterols, enables it to act as a potent antioxidant. It neutralizes free radicals and prevents lipid peroxidation in neuronal cells, thus preserving cell membrane integrity. This compound's dual antioxidant and anti-inflammatory actions provide significant neuroprotection, as it supports both cellular and mitochondrial health.
- Phenolic Compounds: Phenolic acids, including ferulic acid and anthocyanins, exhibit strong antioxidant properties. These compounds directly neutralize reactive species such as superoxide and hydroxyl radicals, which are responsible for neuronal damage in neurodegenerative conditions. Ferulic acid, in particular, has been studied for its role in blocking oxidative pathways that lead to cell death.

3.1.3. Recent Research Findings

Studies on tocotrienols and gamma-oryzanol have shown their potential in reducing oxidative stress in animal models of Alzheimer's disease and neural cell lines, indicating their therapeutic benefits in neurological conditions.

3.2. Anti-inflammatory Effects: Reduction of Neuroinflammatory Pathways

- Mechanism of Neuroinflammation: Chronic neuroinflammation, often driven by the activation of microglia (brain immune cells) and the release of pro-inflammatory cytokines, accelerates neuronal death and contributes to diseases like Alzheimer's and Parkinson's. Persistent inflammation can disrupt normal brain function, leading to a cycle of neuronal damage.

3.2.1. Anti-inflammatory Compounds in Paddy Rice

- Gamma-Oryzanol and Anthocyanins: Gamma-oryzanol and anthocyanins in paddy rice are effective at inhibiting inflammatory enzymes and cytokines, such as IL-1β and TNF-α, which are commonly elevated in neuroinflammatory conditions. Gamma-oryzanol's ability to modulate these inflammatory markers helps to reduce neuroinflammation, potentially preserving neuron health.
- Flavonoids: Flavonoids in paddy rice suppress the NF-κB pathway, a major signaling pathway in inflammation. By inhibiting NF-κB activation, these compounds can reduce inflammation-mediated cell death in brain tissues, thus offering protective effects in chronic neuroinflammatory diseases.

3.2.2. Supporting Studies

Gamma-oryzanol administration in animal models of neuroinflammation has shown a reduction in pro- inflammatory cytokine levels and prevented neuronal apoptosis, suggesting its role in protecting neurons from inflammatory damage.

Studies on anthocyanins have demonstrated their effectiveness in lowering neuroinflammatory markers in cell cultures and animal models, indicating their value in managing inflammation-associated neurodegeneration.

3.3. Modulation of Neurotransmitters and Synaptic Function

- Importance of Neurotransmitter Balance in Brain Function: Neurotransmitters like dopamine, serotonin, and gamma-aminobutyric acid (GABA) are critical for brain function, influencing mood, cognition, and memory. Imbalances in these neurotransmitters are implicated in neurodegenerative diseases, including Parkinson's and various neuropsychiatric disorders. Supporting the stability of neurotransmitter systems can help maintain cognitive health and reduce the risk of neurodegeneration.

3.3.1. Bioactives Modulating Neurotransmitter Pathways

- Tocotrienols and Tocopherols: These compounds help stabilize neurotransmitter levels by protecting neurons from oxidative and inflammatory stress. By safeguarding synaptic function, tocotrienols and tocopherols ensure neurotransmitters operate optimally, which is crucial for memory, learning, and emotional regulation.
- Gamma-Aminobutyric Acid (GABA): GABA, a key inhibitory neurotransmitter, helps control excitotoxicity, a condition in which neurons are damaged by overstimulation. The presence of GABA in paddy rice bioactives can contribute to neuronal protection, making these compounds relevant for conditions like epilepsy and neuropsychiatric disorders where excitotoxicity is a concern.

3.3.2. Relevant Research

Studies show that tocotrienols improve dopamine levels in Parkinson's disease models, suggesting a therapeutic effect in preserving dopaminergic neurons.

Research on GABA-rich diets demonstrates reduced seizure activity, supporting the potential role of paddy rice bioactives in managing epilepsy .

3.4. Neurogenesis and Neural Plasticity: Stimulation of Neurotrophic Factors and Promotion of Neural Growth

Importance of Neurogenesis and Plasticity in Neuroprotection: Neurogenesis and neural plasticity are essential for brain recovery, particularly in neurodegenerative diseases where neuronal pathways are compromised. Supporting neurogenesis enhances the brain's ability to repair itself, aiding cognitive function, and resilience against progressive neuronal loss.

3.4.1. Compounds That Stimulate Neurotrophic Factors

- Phenolic Compounds (e.g., Ferulic Acid): Phenolic compounds, especially ferulic acid, have been found to stimulate brain-derived neurotrophic factor (BDNF), a molecule that promotes neuronal growth, plasticity, and cognitive function. Increasing BDNF levels can help counteract the cognitive decline associated with aging and neurodegenerative diseases.
- Gamma-Oryzanol: Gamma-oryzanol enhances neurogenesis by supporting synaptic plasticity and promoting the survival of new neurons, which is essential for learning and memory retention.
- Supporting Evidence: Studies indicate that ferulic acid increases hippocampal neurogenesis in animal models, leading to improved spatial memory. Such effects underscore its value in supporting brain health and cognitive resilience.

Research on gamma-oryzanol shows that it supports neurogenesis and synaptic function, suggesting its role in memory enhancement and neuroprotection.

3.5. Mitochondrial Support and Cellular Energy Metabolism

- Role of Mitochondrial Health in Neuroprotection: Neurons rely heavily on mitochondria for energy, and mitochondrial dysfunction is a hallmark of neurodegenerative diseases. Supporting mitochondrial health is essential to ensure that neurons receive adequate energy, maintain cellular function, and resist stress-induced damage.

3.5.1. Compounds Providing Mitochondrial Protection

- Tocotrienols: Tocotrienols support mitochondrial function by stabilizing mitochondrial membranes and reducing oxidative damage within mitochondria, which may improve ATP production and reduce the vulnerability of neurons to degeneration.
- Phenolic Compounds: Phenolic compounds in paddy rice also protect mitochondrial DNA and minimize oxidative stress within mitochondria, which is critical for sustaining cellular energy metabolism and supporting neuronal survival.

3.5.2. Research Support

Studies on tocotrienols in Alzheimer's models have shown improved mitochondrial function and reduced neuronal apoptosis. Such findings underscore the therapeutic potential of tocotrienols in maintaining mitochondrial integrity.

Phenolic compounds have been shown to mitigate mitochondrial oxidative stress, supporting overall cellular health and resilience in neurodegenerative conditions (Table 2)

Table 2 Mechanisms of Neuroprotection by Paddy Rice Components

Mechanism of Neuroprotection	Bioactive Compound	Action/Effect	Neurological Implications
Antioxidant	Gamma-oryzanol	Scavenges free radicals and reduces lipid peroxidation	Protects against oxidative stress, which is a key factor in Alzheimer's and Parkinson's disease
	Tocotrienols (Vitamin E)	Prevents oxidative damage in cell membranes and protects mitochondrial function	May reduce cell death and improve mitochondrial health, beneficial in neurodegenerative diseases

	Phenolic Compounds (e.g., Ferulic Acid)	Inhibits reactive oxygen species (ROS) and prevents neuronal cell damage	Reduces neuronal degeneration, slowing the progression of diseases like Alzheimer's
Anti-inflammatory	Gamma-oryzanol	Modulates cytokine production and reduces inflammatory markers (e.g., IL-1β, TNF-α)	Reduces neuroinflammation associated with multiple sclerosis and Parkinson's disease
	Anthocyanins	Inhibits inflammatory enzymes and reduces pro- inflammatory cytokines	Limits inflammation in brain tissues, which can aid in preventing cognitive decline
Neurotransmitter Modulation	Tocopherols (Vitamin E derivatives)	Supports dopamine and serotonin balance by protecting against oxidative and inflammatory damage	Helps in mood regulation and can reduce symptoms in neuropsychiatric conditions
	Gamma-aminobutyric acid (GABA)	Modulates GABA receptors, which are critical for reducing excitatory neurotransmission	Potentially useful in conditions like epilepsy, where excitotoxicity is a concern
Neurogenesis and	Phenolic	Activates brain-derived	Supports neural growth and

4. Paddy rice in the prevention of neurodegenerative disorders:

The rising number of neurodegenerative disorders like Alzheimer's and Parkinson's is a major global health concern. The World Health Organization reports over 50 million people have dementia, expected to triple by 2050. Parkinson's affects over 10 million worldwide, with rates increasing due to longer lifespans. Both diseases involve neuronal loss, straining healthcare systems and impacting patient and family well-being significantly.

Pathological Mechanisms: AD and PD share overlapping pathological mechanisms, such as oxidative stress, neuroinflammation, and imbalances in neurotransmitters, which exacerbate the progression of neurodegeneration. Oxidative stress results from an imbalance between free radicals and the body's ability to neutralize them, causing cellular damage, particularly in the brain's lipid-rich tissues. Neuroinflammation, driven by the brain's immune cells, further accelerates neuronal damage and death, creating a cycle that worsens disease outcomes.

- Potential Role of Paddy Rice Bioactives

Compounds derived from paddy rice, such as tocotrienols, gamma-oryzanol, ferulic acid, and phenolic compounds, have antioxidant and anti-inflammatory properties. They can reduce oxidative damage, inflammation, and cellular dysfunction in the brain, supporting cognitive functions and potentially slowing neurodegenerative disorders. This review examines their neuroprotective and brain health potential.

4.1. Detailed Mechanisms of Alzheimer's Disease and Potential Counteraction by Paddy Rice Bioactives

4.1.1. Alzheimer's Disease (AD) Mechanisms

- Amyloid-beta (Aβ) Plaque Formation: Aβ peptides aggregate into plaques in the brain, which disrupts neural cell communication and initiates oxidative stress. These plaques are hallmarks of AD pathology, as they interfere with synaptic function, leading to cognitive decline.
- Tau Protein Hyperphosphorylation: Tau proteins form neurofibrillary tangles within neurons when they become hyperphosphorylated, causing cellular dysfunction and promoting neurodegeneration.
- Neuroinflammation and Oxidative Stress: The accumulation of Aβ plaques and tau tangles triggers inflammatory responses, elevating levels of pro-inflammatory cytokines. This neuroinflammatory state intensifies oxidative stress, further damaging neuronal cells and accelerating the disease's progression.

4.1.2. Potential Role of Paddy Rice Bioactives

- Ferulic Acid: Research indicates that ferulic acid inhibits Aβ aggregation, reducing plaque formation in the brain. As a powerful antioxidant, it scavenges free radicals, helping to mitigate oxidative stress. Ferulic acid also

exhibits anti-inflammatory effects, as it downregulates cytokines like IL-1β and TNF-α, which are typically elevated in AD, thus reducing neuroinflammation and protecting neural integrity.

- Gamma-Oryzanol: Gamma-oryzanol acts as a potent antioxidant that can neutralize free radicals within the brain, decreasing oxidative damage that contributes to AD. Furthermore, it is believed to modulate neuroinflammatory pathways, countering chronic inflammation observed in AD and preserving neuronal health.
- Tocotrienols: These vitamin E derivatives stabilize cellular integrity and protect neuronal cell membranes from lipid peroxidation. By supporting mitochondrial function, tocotrienols prevent mitochondrial dysfunction, a major factor in cell death in AD. This protection aids in maintaining the overall health of neurons impacted by Alzheimer's

4.2. Detailed Mechanisms of Parkinson's Disease and Potential Counteraction by Paddy Rice Bioactives

4.2.1. Parkinson's Disease (PD) Mechanisms

- Dopaminergic Neuron Loss in the Substantia Nigra: PD is primarily marked by the progressive degeneration of dopamine-producing neurons in the substantia nigra, leading to characteristic motor symptoms like tremors and rigidity, as well as cognitive deficits.
- Oxidative Stress and Mitochondrial Dysfunction: Dopaminergic neurons are highly vulnerable to oxidative stress, as dopamine metabolism generates free radicals that further exacerbate oxidative damage. Mitochondrial dysfunction, often accompanying oxidative stress, leads to a lack of cellular energy, accelerating neuron degeneration.
- Protein Aggregation: PD involves the aggregation of the alpha-synuclein protein, forming Lewy bodies within neurons, disrupting normal cell function and contributing to cellular toxicity and neurodegeneration.
- Neuroinflammation: Chronic neuroinflammation exacerbates neuron loss and oxidative stress in PD, worsening disease progression and symptoms.

4.2.2. Potential Role of Paddy Rice Bioactives

- Ferulic Acid: Ferulic acid has been shown to scavenge free radicals, offering protection against oxidative stress and potentially slowing the degeneration of dopaminergic neurons. Its anti- inflammatory effects help counteract the neuroinflammation that aggravates neuron loss in PD.
- Tocotrienols: By stabilizing cell membranes and supporting mitochondrial function, tocotrienols help reduce oxidative damage in dopaminergic neurons. They protect neuronal cells from lipid peroxidation, a significant cause of cellular stress and neuronal death in PD.
- Gamma-Oryzanol: Gamma-oryzanol has shown promise in reducing neuroinflammatory markers and may protect dopaminergic neurons by lowering levels of reactive oxygen species (ROS). Additionally, it supports dopamine production, which is essential for managing PD symptoms.

4.3. Multiple sclerosis and other neuroinflammatory conditions: The impact of anti-inflammatory compounds

Chronic inflammatory autoimmune diseases affecting the central nervous system like multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) result in neurological deficits. Anti- inflammatory drugs, specifically flavonoids found in fruits and vegetables, may help reduce inflammation and severity of MS.

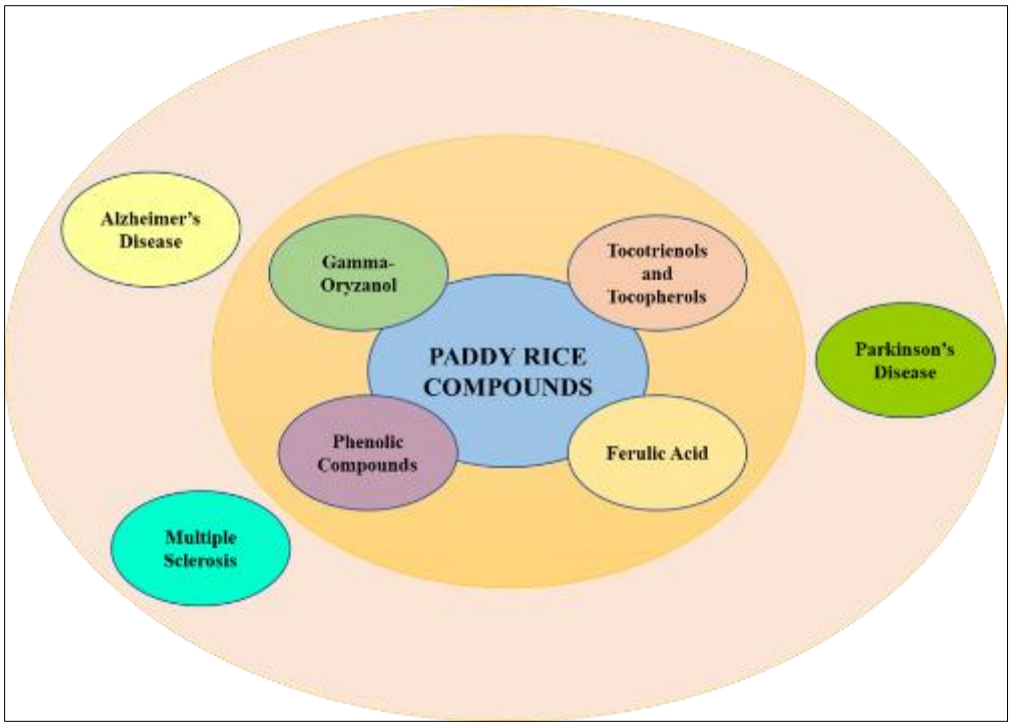

Figure 1 Potential Role of Paddy Rice in Neurological Disorders

5. Cognitive function enhancement

Paddy rice bioactives have shown potential to support cognitive function through various mechanisms, as demonstrated in experimental studies focused on memory and learning. This section explores how compounds like tocotrienols, gamma-oryzanol, ferulic acid, and other phenolic compounds found in paddy rice may enhance cognitive performance, likely through influencing neurotrophic factors, neurotransmitter regulation, and antioxidant properties.

5.1. Mechanisms of Cognitive Enhancement

- Antioxidant Protection: The brain's high metabolic rate and abundant lipid content make it vulnerable to oxidative stress, which contributes to cognitive decline. Paddy rice bioactives, such as tocotrienols and gamma-oryzanol, act as potent antioxidants, scavenging reactive oxygen species (ROS) and protecting neural cells from oxidative damage. By reducing oxidative stress, these bioactives help preserve neuronal integrity, which is crucial for sustaining cognitive functions like memory and attention.

5.2. Experimental Data on Memory and Learning Improvement

Animal studies have shown that extracts from paddy rice can have positive effects on cognitive functions like memory and learning. One study using paddy rice extract on mice with neuroinflammatory conditions found improved memory and spatial learning compared to controls. Another study showed that gamma- oryzanol-enriched rice bran extract improved memory and reduced cognitive deficits in animals under oxidative stress.

5.3. Impact on Neurotrophic Factors

Research suggests that modulating neurotrophic factors like Brain-Derived Neurotrophic Factor (BDNF) can enhance cognitive function. Ferulic acid in paddy rice has been found to stimulate BDNF production, promoting neural growth and resilience. Animal studies show that paddy rice supplementation increases hippocampal BDNF expression, improving spatial memory and learning. These findings highlight the potential benefits of BDNF modulation in combating age-related cognitive decline.

5.4. Neurotransmitter Modulation and Synaptic Function

Paddy rice bioactives, including tocotrienols, influence neurotransmitters like dopamine, serotonin, and GABA, crucial for cognitive function and memory. Tocotrienols protect synaptic health and regulate oxidative reactions.

Supplementing with tocotrienols boosts dopamine levels, enhancing cognitive function and potentially guarding against neurodegenerative changes. GABA in paddy rice balances brain signals, reducing excitotoxicity, and supporting cognition.

5.5. Research Findings on Cognitive Biomarkers

Studies have shown that paddy rice extract supplementation can improve cognitive biomarkers related to memory and learning, such as acetylcholine levels and malondialdehyde. Experimental models have demonstrated that paddy rice bioactives can increase acetylcholine levels, leading to better learning outcomes and memory performance. Reduced MDA levels in supplemented animals indicate a decrease in oxidative stress and improved memory function.

6. Clinical evidence and therapeutic potential

Research on paddy rice bioactives shows promise for use in supplements or treatments for neurodegenerative diseases. Clinical evidence supports their safety and efficacy, underscoring the importance of further research.

6.1. Existing Clinical Studies on Grain-Derived Neuroprotective Compounds

Clinical research on bioactive compounds from grains like rice bran or other cereals reveals their neuroprotective effects. Tocotrienols, gamma-oryzanol, and other phenolic compounds influence cognitive functions, reduce oxidative stress markers, and modulate inflammatory responses in individuals with neurodegenerative conditions or high oxidative stress levels.

6.1.1. Cognitive Performance in Elderly Populations

A study of elderly individuals with mild cognitive impairment found that daily intake of rice bran extract improved cognitive performance, specifically in memory and executive function, while reducing oxidative stress markers.

6.1.2. Gamma-Oryzanol Supplementation in Middle-Aged Adults

A study on middle-aged adults taking gamma-oryzanol-rich rice supplements showed improved memory, verbal fluency, and reduced neuroinflammatory markers, suggesting benefits for age-related cognitive decline.

- Effects on Parkinsonian Symptoms: An open-label trial administered rice bran extract to individuals with Parkinson’s disease, observing reductions in motor symptoms and improvement in dopamine- related biomarkers. This supports the role of rice bioactives in dopaminergic health and symptom management, indicating potential benefits in neurodegenerative diseases like Parkinson's.
- Oxidative Stress Reduction in Healthy Adults: A study showed that gamma-oryzanol and tocotrienol- enriched rice enhanced antioxidants and decreased oxidative stress in healthy adults. These findings suggest paddy rice's benefits extend to those without clinical impairments.

6.2. Comparative Analysis: Clinical vs. Preclinical Data

While preclinical studies provide compelling evidence of the neuroprotective actions of paddy rice compounds (like ferulic acid’s inhibition of amyloid-beta aggregation in Alzheimer’s models), translating these findings into clinical outcomes remains challenging due to variability in bioavailability, dosages, and the complexity of human disease processes. Key areas of comparative analysis include:

6.2.1. Antioxidant and Anti-Inflammatory Actions

Preclinical research shows tocotrienols and gamma-oryzanol can help reduce oxidative stress and neuroinflammation, factors in neurodegeneration. Clinical trials have mixed results due to limited absorption, requiring enhanced delivery methods.

6.2.2. Neurotransmitter Modulation

Experimental data suggest that tocotrienols and gamma-oryzanol have positive effects on neurotransmitter pathways, specifically in Parkinson's disease models. However, clinical evidence is lacking, especially regarding specific markers like dopamine levels and receptor activity in humans. This gap underscores the need for targeted research on bioactive concentrations and their impact on neurotransmission markers.

6.2.3. Cognitive Enhancement and Synaptic Health

Preclinical studies suggest that paddy rice bioactives, such as ferulic acid, may enhance cognitive function and neurogenesis through brain-derived neurotrophic factor (BDNF). Human trials have shown some cognitive benefits, but more research is needed to confirm these effects and determine optimal dosing.

6.3. Identified Gaps and Future Research Directions

Although current studies provide a foundation for the therapeutic potential of paddy rice in neurodegenerative conditions, several gaps warrant attention for effective translation into clinical practice:

- Optimized Delivery Methods: Given the limited bioavailability of key bioactives, novel delivery systems, such as nanoencapsulation, solid lipid nanoparticles, or phospholipid complexes, are essential to ensure these compounds reach target tissues in the brain. Future research should focus on delivery technologies that improve systemic absorption and blood-brain barrier penetration.
- Longitudinal and Large-Scale Trials: Most studies on paddy rice bioactives are short-term and conducted on small sample sizes. Longitudinal studies with larger populations are crucial to determine sustained effects, optimal dosages, and any long-term adverse reactions, providing a comprehensive understanding of paddy rice's role in neuroprotection.
- Biomarker-Based Efficacy Assessments: Incorporating biomarkers (e.g., oxidative stress markers, cytokine levels, neurotransmitter concentrations) in future clinical studies could provide quantitative measures of efficacy. This would bridge preclinical findings with clinical applications, offering a robust method to evaluate bioactive impact in human neurodegenerative pathways (Table 3).

Table 3 Clinical Studies on Paddy Rice and Cognitive Health

Population	Study Design	Intervention	Main Findings	Implications
Elderly adults with mild cognitive impairment	Randomized controlled trial	Daily intake of paddy rice extract	Improved cognitive performance, reduced oxidative stress markers	Suggests paddy rice may support cognitive function in elderly populations by reducing oxidative damage.
Middle-aged adults	Double-blind, placebo-controlled study	Gamma-oryzanol Enriched rice supplement	Significant improvement in memory recall and verbal fluency, with reduced euroinflammatory markers	Highlights anti-inflammatory potential, indicating possible benefits for age-related cognitive decline.
Adults with Parkinson's disease	Open-label clinical trial	Rice bran extract supplement	Reduction in Parkinsonian symptoms and dopamine-related biomarkers improvement	Indicates potential of rice bran bioactives in dopamine modulation and symptom management in neurodegenerative conditions.
Adults with high oxidative stress	Prospective cohort study	Gamma-oryzanol and tocotrienol-rich rice diet	Lower oxidative stress levels, improved antioxidant capacity	Supports antioxidant efficacy in paddy rice for reducing neural oxidative stress, which may aid cognitive health.
Healthy young adults	Cross-over study	Short-term supplementation with tocotrienols	Enhanced focus, attention, and short-term memory after supplementation	Suggests paddy rice's potential in enhancing cognitive function even in healthy populations by supporting neurotransmitter modulation.

7. Challenges and future aspects

7.1. Limitations in current research

Hydrolytic rancidity reduces the quality and restricts the use of paddy rice in cuisine. When lipids and active enzymes come into contact, paddy rice extract experiences hydrolytic rancidity. The hydrolysis of rice bran oil by lipase results in the production of free fatty acids (FFA). The flavor and odor of paddy rice are impacted by this hydrolytic rancidity, which restricts the rice's ability to grow further.

7.2. The need for large-scale trials on neurodegenerative diseases

It's interesting to note that rice by-products have multiple uses, including the manufacture of alternative poultry and the fuel business, in addition to being utilized in the development of functional meals and value- added foods that are currently in great demand. Environmentally friendly, practical, affordable, and easy-to-use extraction technologies are needed to increase the use of paddy-rice processing by-products in developing nations.

7.3. Emerging Biotechnological Approaches for Enhancing Bioavailability of Paddy Rice Bioactives

Paddy rice contains neuroprotective bioactive compounds like tocotrienols, gamma-oryzanol, and phenolic acids. However, their therapeutic effectiveness is limited by poor bioavailability due to their lipid-soluble nature. Biotechnological advancements are being developed to improve delivery and efficacy of these compounds, particularly in reaching the brain for neuroprotection.

7.3.1. Nanoencapsulation

Nanoencapsulation is a promising approach that involves encasing bioactives in nanoparticles to enhance absorption and protect the compounds from degradation in the digestive tract. This technique increases the bioavailability of fat-soluble compounds like tocotrienols and gamma-oryzanol by allowing them to be transported in small, stable particles that can penetrate biological barriers more effectively.

- Mechanism of Action: Nanoencapsulation works by surrounding bioactives with a protective shell, typically made from materials like lipids or biodegradable polymers. When encapsulated, the bioactives are shielded from premature degradation and can reach the bloodstream in a more intact form. Once in the bloodstream, the nanoparticle carriers facilitate the crossing of these compounds through the blood- brain barrier, a key challenge in delivering therapeutic agents to the brain.
- Benefits in Neurological Applications: Nanoencapsulation enhances the stability and solubility of paddy rice bioactives, allowing them to be absorbed more readily and distributed to brain tissues. This technology not only improves the efficacy of paddy rice bioactives for neuroprotection but also provides sustained release, extending their therapeutic effects.

7.3.2. Lipid-Based Carriers

Lipid-based carriers, such as liposomes, nanoemulsions, and solid lipid nanoparticles, are especially effective for enhancing the delivery of lipid-soluble bioactives in paddy rice. These carriers can transport bioactives more efficiently by encapsulating them within lipid molecules that the body can easily absorb and transport across cellular membranes.

- Liposomes: Liposomes are spherical vesicles made of phospholipid bilayers that can encapsulate both water- and fat-soluble bioactives. For paddy rice bioactives, liposomes allow for direct fusion with cell membranes, leading to efficient delivery into cells and enhanced absorption in brain tissues.
- Nanoemulsions: Nanoemulsions consist of extremely small oil-in-water droplets, which provide a large surface area for enhanced digestion and absorption. This improves the solubility of tocotrienols and gamma-oryzanol, facilitating better uptake and transport via lymphatic pathways, bypassing the liver’s first-pass metabolism and thereby increasing the bioavailability in systemic circulation.
- Solid Lipid Nanoparticles (SLNs): SLNs offer a stable, solid structure that can encapsulate and protect the bioactives while controlling the release rate, which is particularly beneficial for maintaining steady therapeutic levels over extended periods.

7.3.3. Self-Emulsifying Drug Delivery Systems (SEDDS)

SEDDS are an advanced technology that combines natural oils, surfactants, and co-solvents to form a fine emulsion in the gastrointestinal tract, which enhances the absorption of fat-soluble compounds like tocotrienols and gamma-oryzanol.

- Mechanism in Improving Absorption: When exposed to gastrointestinal fluids, SEDDS rapidly form microemulsions that dissolve and transport the bioactives. This process significantly enhances the solubility and bioavailability of paddy rice bioactives, promoting a more efficient and consistent release into the bloodstream.
- Impact on Neurological Health: By increasing the bioavailability of neuroprotective compounds, SEDDS support higher concentrations of these bioactives reaching the brain, thereby amplifying their protective effects against oxidative stress, neuroinflammation, and other neurodegenerative processes.

7.3.4. Phospholipid Complexes (Phytosomes)

Phytosomes are phospholipid-based carriers that form complexes with bioactives, increasing their affinity for cell membranes and enhancing cellular uptake. This method improves the solubility and bioavailability of paddy rice bioactives by allowing better interaction with cell membranes.

- Enhanced Cellular Delivery: Phytosomes enable better uptake of paddy rice bioactives by brain cells, supporting neuroprotection by improving the efficiency with which these compounds cross the blood- brain barrier. This is particularly useful for bioactives like tocotrienols and gamma-oryzanol, which require efficient transport into brain tissues to exert their neuroprotective effects.
- Applications in Cognitive Health: Phytosomes have shown promise in delivering bioactives to neural tissues, potentially benefiting cognitive functions such as memory and learning by ensuring sustained delivery of these protective compounds in the brain.

7.3.5. Nanoparticle Delivery Systems

Nanoparticle systems, including polymeric and lipid-based nanoparticles, are versatile carriers designed to deliver bioactives in a controlled manner, offering prolonged release and targeted delivery to specific tissues.

- Controlled Release and Targeting: Nanoparticles can be engineered to release paddy rice bioactives over an extended time frame, providing sustained neuroprotective effects. By controlling the release, nanoparticles minimize the potential for rapid metabolism and excretion, enhancing the therapeutic duration of tocotrienols, gamma-oryzanol, and other neuroprotective compounds.
- Enhanced Stability and Transport: These nanoparticles protect bioactives from enzymatic degradation and improve their transport through cellular barriers, including the blood-brain barrier. This ensures that paddy rice bioactives can effectively reach and impact brain cells, supporting antioxidant, anti- inflammatory, and neurogenesis-promoting functions critical in combating neurodegenerative disorders.

8. Conclusion

The review highlights the neuroprotective benefits of bioactive compounds in paddy rice, such as tocotrienols, gamma-oryzanol, and phenolic acids, in maintaining brain health. These compounds help reduce oxidative stress, inflammation, and support neurotransmitter regulation and neurogenesis, crucial in preventing neurodegenerative diseases. Paddy rice strengthens neural resilience and combats cellular damage through its antioxidative properties, making it a promising candidate for managing conditions like Alzheimer's and Parkinson's disease. Future research should focus on enhancing bioavailability and exploring combination therapies. Integrating paddy rice bioactives into personalized nutrition plans can offer targeted support for cognitive health within integrative medicine practices. Visual aids can further clarify the mechanisms by which these compounds work, aiding in a better understanding of paddy rice's potential for brain health maintenance.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Mohidem NA, Hashim N, Shamsudin R, Che Man H. Rice for food security: Revisiting its production, diversity, rice milling process and nutrient content. Agriculture. 2022 May 24;12(6):741.

[2] Liu Y, Ge T, van Groenigen KJ, Yang Y, Wang P, Cheng K, Zhu Z, Wang J, Li Y, Guggenberger G, Sardans J. Rice paddy soils are a quantitatively important carbon store according to a global synthesis. Communications Earth & Environment. 2021 Aug 6;2(1):154.

[3] Spaggiari M, Dall'Asta C, Galaverna G, del Castillo Bilbao MD. Rice bran by-product: From valorization strategies to nutritional perspectives. Foods. 2021 Jan 4;10(1):85.

[4] Wang N, Cui X, Duan Y, Yang S, Wang P, Saleh AS, Xiao Z. Potential health benefits and food applications of rice bran protein: Research advances and challenges. Food Reviews International. 2023 Aug 18;39(6):3578-601.

[5] Singh R, Patel M. Effective utilization of rice straw in value-added by-products: A systematic review of state of art and future perspectives. Biomass and Bioenergy. 2022 Apr 1;159:106411.

[6] Ciurea, A.V., Mohan, A.G., Covache-Busuioc, R.A., Costin, H.P., Glavan, L.A., Corlatescu, A.D. and Saceleanu, V.M., 2023. Unraveling molecular and genetic insights into neurodegenerative diseases: Advances in understanding Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis. International journal of molecular sciences, 24(13), p.10809.

[7] Kumar A, Sudevan ST, Nair AS, Singh AK, Kumar S, Jose J, Behl T, Mangalathillam S, Mathew B, Kim H. Current and future nano-carrier-based approaches in the treatment of Alzheimer's disease. Brain Sciences. 2023 Jan 27;13(2):213.

[8] Fatima J, Siddique YH. Application of Nanocomposites and Nanoparticles in Treating Neurodegenerative Disorders. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2024.

[9] Salman MM, Al-Obaidi Z, Kitchen P, Loreto A, Bill RM, Wade-Martins R. Advances in applying computer-aided drug design for neurodegenerative diseases. International journal of molecular sciences. 2021 Apr 28;22(9):4688.

[10] Liang S, Wang L, Wu X, Hu X, Wang T, Jin F. The different trends in the burden of neurological and mental disorders following dietary transition in China, the USA, and the world: An extension analysis for the Global Burden of Disease Study 2019. Frontiers in Nutrition. 2023 Jan 9;9:957688.

[11] Singh RB, Horiuchi R, Wilczynska A, Suchday S, Tyagi G, Magomedova A, Fatima G, Smail MM, Isaza A, Jain M, De Meester F. The role of modified Mediterranean neuroprotective diet on emotion, cognition, and depression. InFunctional Foods and Nutraceuticals in Metabolic and Non-Communicable Diseases 2022 Jan 1 (pp. 551-579). Academic Press.

[12] Rahman S, Mathew S, Nair P, Ramadan WS, Vazhappilly CG. Health benefits of cyanidin-3-glucoside as a potent modulator of Nrf2-mediated oxidative stress. Inflammopharmacology. 2021 Aug;29:907-23.

[13] Deepa P, Hong M, Sowndhararajan K, Kim S. A Review of the Role of an Anthocyanin, Cyanidin-3-O- β-glucoside in Obesity-Related Complications. Plants. 2023 Nov 17;12(22):3889.

[14] Yang M, Ahmad N, Hussain M, Lu X, Xu J, Zhong H, Guan R. A review of recent advances on cyanidin- 3-glucoside: the biotransformation, absorption, bioactivity and applications of nano-encapsulation. Food & Function. 2023;14(14):6320-45.

[15] Oumeddour DZ, Al-Dalali S, Zhao L, Zhao L, Wang C. Recent advances on cyanidin-3-O-glucoside in preventing obesity-related metabolic disorders: A comprehensive review. Biochemical and Biophysical Research Communications. 2024 Oct 15;729:150344.

[16] Frountzas M, Karanikki E, Toutouza O, Sotirakis D, Schizas D, Theofilis P, Tousoulis D, Toutouzas KG. Exploring the Impact of Cyanidin-3-Glucoside on Inflammatory Bowel Diseases: Investigating New Mechanisms for Emerging Interventions. International Journal of Molecular Sciences. 2023 May 28;24(11):9399.

[17] Zannou O, Oussou KF, Chabi IB, Awad NM, Aïssi MV, Goksen G, Mortas M, Oz F, Proestos C, Kayodé AP. Nanoencapsulation of Cyanidin 3-O-Glucoside: Purpose, technique, bioavailability, and stability. Nanomaterials. 2023 Feb 3;13(3):617.

[18] Zhong H, Hussain M, Hussain K, Wang L, Abdullah, Qayum A, S. Hamed Y, Guan R. Nanoliposomes a future based delivery vehicle of cyanidin-3-O-glucoside against major chronic disease. Critical Reviews in Food Science and Nutrition. 2024 Jul 24:1-8.

[19] Qian H, Guo F, Xiong H, Zhang H, Jiang L, Sun Y. The interactional characterization of lentil protein isolate (lpi) with cyanidin-3-o-glucoside (C3G) and their effect on the stability and antioxidant activity of C3G. Foods. 2022 Dec 25;12(1):104.

[20] Bartel I, Koszarska M, Strzałkowska N, Tzvetkov NT, Wang D, Horbańczuk JO, Wierzbicka A, Atanasov AG, Jóźwik A. Cyanidin-3-O-glucoside as a nutrigenomic factor in type 2 diabetes and its prominent impact on health. International Journal of Molecular Sciences. 2023 Jun 5;24(11):9765.

[21] Kim TJ, Kim SY, Park YJ, Lim SH, Ha SH, Park SU, Lee B, Kim JK. Metabolite profiling reveals distinct modulation of complex metabolic networks in non-pigmented, black, and red rice (Oryza sativa L.) cultivars. Metabolites. 2021 Jun 9;11(6):367.

[22] Kasote D, Sreenivasulu N, Acuin C, Regina A. Enhancing health benefits of milled rice: current status and future perspectives. Critical Reviews in Food Science and Nutrition. 2022 Oct 17;62(29):8099-119.

[23] Baschieri A, Amorati R. Methods to determine chain-breaking antioxidant activity of nanomaterials beyond DPPH•. A review. Antioxidants. 2021 Sep 29;10(10):1551.

[24] Pisoschi AM, Pop A, Iordache F, Stanca L, Predoi G, Serban AI. Oxidative stress mitigation by antioxidants-an overview on their chemistry and influences on health status. European Journal of Medicinal Chemistry. 2021 Jan 1;209:112891.

[25] Baschieri A, Jin Z, Amorati R. Hydroperoxyl radical (HOO•) as a reducing agent: unexpected synergy with antioxidants. A review. Free Radical Research. 2023 Feb 1;57(2):115-29.

[26] Al-Mamary MA, Moussa Z. Antioxidant activity: The presence and impact of hydroxyl groups in small molecules of natural and synthetic origin. Antioxidants—Benefits, sources, mechanisms of action. 2021 Jan 13:318-77.

[27] Jia W, Wu X, Kang X. Integrated the embedding delivery system and targeted oxygen scavenger enhances free radical scavenging capacity. Food Chemistry: X. 2023 Mar 3;17.

[28] Di Giacomo S, Percaccio E, Gullì M, Romano A, Vitalone A, Mazzanti G, Gaetani S, Di Sotto A. Recent advances in the neuroprotective properties of ferulic acid in Alzheimer's disease: A narrative review. Nutrients. 2022 Sep 8;14(18):3709.

[29] Caruso G, Godos J, Privitera A, Lanza G, Castellano S, Chillemi A, Bruni O, Ferri R, Caraci F, Grosso G. Phenolic acids and prevention of cognitive decline: Polyphenols with a neuroprotective role in cognitive disorders and Alzheimer's disease. Nutrients. 2022 Feb 15;14(4):819.